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Risk Factors Associated with Mild Cognitive Impairment among Apparently Healthy People and the Role of MicroRNAs

Iman I. Salama[1*], Somaia I. Salama[1], Dalia M. Elmosalami[1], Rehan M. Saleh[1], Hanaa Rasmy[2], Mona Hamed Ibrahim[2], Solaf Ahmed Kamel[2], Mona M. F. Ganem[3], Hala M. Raslan[3]

[1]Community Medicine Research Department, National Research Centre, Cairo, Egypt; [2]Clinical and Chemical Pathology Medical Division, Centre of Excellence, Department, National Research Centre, Cairo, Egypt; [3]Internal Medicine Research Department, National Research Centre, Cairo, Egypt

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Keywords: Mild cognitive impairment; Lifestyle style; Family 132 & 134 miRNA

***Correspondence:** Iman I. Salama. Community Medicine Research Department, National Research Centre, Cairo, Egypt. E-mail: salamaiman@yahoo.com

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Abstract

BACKGROUND: Mild cognitive impairment (MCI) is a stage between the expected cognitive decline of normal ageing and the serious decline of dementia.

AIM: To identify risk factors and role of miRNAs associated with mild cognitive impairment (MCI) among employees.

SUBJECTS AND METHOD: A cross-sectional study was carried out on 186 employees aged between 40 and 65 years. Cognitive function was evaluated using ACEIII, MoCA, and Quick cognitive tests. Medical history and lifestyle were assessed. Family 132 & 134 miRNA expressions were assessed by real-time PCR.

RESULTS: MCI was detected among 14 / 186 (7.5%). miRNA 132 expression was the only significant miRNAs to detect MCI with low sensitivity and specificity (70%). The logistic analysis revealed that higher miRNA132 expressions, low monthly intake of; vegetables, unroasted nuts, low education and higher ALT levels were predicting factors for MCI with AOR 1.1 (1.01-3.3), 1.2 (1.04-1.43), 0.8 (0.8-0.98), 2.7 (1.9-7.4) and 1.6 (1.1-2.3) respectively.

CONCLUSION: MiRNAs expression showed low sensitivity and specificity in detecting MCI; only miRNA 132 might be used. Several modifiable factors seem to reduce the risk of MCI.

Introduction

Mild cognitive impairment (MCI) is a stage between the cognitive decline of normal ageing and dementia. MCI involves the onset and evolution of problems related to memory, language, and thinking beyond those expected for age. People with MCI are at greater risk of later developing dementia. However, some of them never get worse, and a few get better [1].

Detecting intervenable risk factors is a key component of preventive strategies for mild cognitive impairment [2]. Medical and lifestyle factors that have been related to an increased risk of cognitive impairment include hypertension, diabetes, elevated cholesterol, depression, infrequent participation in mentally or socially stimulating activities, and smoking [3], [4].

MicroRNA (miRNA), is a small non-coding RNA molecule that functions in the regulation of gene expression. It plays an important role in the pathogenesis of many diseases. It has been reported that miR-132 is linked with cognitive impairment [5]. MiRNAs are actively secreted and expressed in body fluids, such as plasma and cerebrospinal fluid (CSF) [6], [7], [8].

This study aimed to assess the potential risk factors of MCI among employees at the National Research Center (NRC) and the role of family 132 and 134 miRNAs expression.

Subjects and Methods

Study design

A cross-sectional study was carried out on 186 adults aged between 40 and 65 years recruited from NRC employees. Recruitment of participants and data collection was carried out along one year during the period between June 2016 and December 2017. Employees with diabetes, neurological and psychiatric illness, major organ failure and cancer were excluded from the study.

Ethical statement

This work has been carried out by The Code of Ethics of the World Medical Association (Declaration of Helsinki). Each study participant provided informed written consent after acknowledgement about the research and the study was approved by the Ethical Committee of the National Research Centre (registration number 15131).

Methods

Assessment of risk factors for MCI

A closed-ended questionnaire module was designed to cover data on demographic characteristics and full medical history. Data included age, gender and education. Data on tobacco smoking, physical activity, dietary habits were also collected to identify risk factors associated with MCI. The questionnaire was tested for the clarity & flow of the questions, and the time required to complete it. A consent form was also signed by all the participants before the interview.

Assessment of cognitive function with its domains

The case definition of MCI was derived from the National Institute on Aging–Alzheimer's Association recommendations [9]. It includes the following clinical criteria for the diagnosis of MCI.

Subjective Concern as regards the change in cognition

We measured subjective cognitive concerns through two questions, according to Lara et al., [10].

"How would you most describe your memory at present?", with answer options being very good, good, moderate, bad or very bad, and "Compared to 12 months ago, would you say your memory is now better, the same or worse than it was then?".

Participants were evaluated to have memory weakness if they answered "bad" or "very bad" to the former question and / or "worse" to the latter.

Objective Impairment in one or more cognitive domains

Changes can occur in a diversity of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. To assess global and specific cognitive domains, we choose the most reliable and validated Arabic forms scales or easily translated cognitive scales and freely available to be applied to the studied subjects. The following tests were used to assess MCI:

A) Montreal Cognitive Assessment test (MoCA)

It comprises five neurological domains: executive function, attention, short-term memory, language, and visuospatial [11]. It is available in Arabic version [12].

B) Addenbrooke's Cognitive Examination III (ACE III)

It is available in Arabic [13]. It assesses MCI and early stages of dementia [13], [14].

C) The Quick Mild Cognitive Impairment (Quick MCI)

It assesses the five domains of cognitive function: registration, orientation, delayed recall, clock drawing and verbal fluency (VF) [15], [16]. It is easily translatable (linguistically and culturally) and has alternative forms, which allow follow up of cognitive function over time [17].

The recommended cut-off points for each studied cognitive scale were utilized to detect objective cognitive impairment

The cut-off point for ACE III score < 88 [18], for MoCA score < 26 [19] and for Quick MCI score < 67 [20].

Objective MCI was considered if two or all of the three studied cognitive tests were below the cut-off points.

Preservation of independence in daily functional abilities, such as paying bills, preparing a meal, or shopping.

Clinical Assessment

All studied participants were subjected to thorough clinical examination. The anthropometric assessment included weight, height, waist and hip circumference, and body mass index (BMI) was calculated. Blood pressure was measured**.**

Laboratory analysis: - Fasting peripheral blood samples (10 ml) were withdrawn from each participant under complete aseptic conditions and after 10 fasting hrs. Part of the blood sample was anticoagulated with EDTA for assessment of the glycated haemoglobin (HbA1c) using Labona check™ HbA1c analyser and measurement of selected MicroRNAs by real-time PCR. The other part of the blood sample was left to clot and sera were separated immediately for analysis of fasting blood sugar, lipid profile, liver and kidney functions by Erbaxl -300 Mannheim Gmbh Germany; and - MicroRNA isolation and real-time RT-PCR.

MicroRNA was isolated according to the manufacturer's instructions using miRNeasy Mini Kit (Cat. No. 217004) and QIAzol Lysis Reagent supplied by QIAGEN, Germany. Concentration and purity of the yield were determined using Nanodrop 2000, USA. Synthesis of cDNA was performed via thermal cycler (Verity, Applied Biosystems, USA) using the TaqMan® Advanced miRNA-cDNA synthesis kit (cat. No A28007) supplied by Applied Biosystems, Life Technologies, USA.

The relative quantity of (miRNA-128, miRNA-132, miRNA-874) and (miRNA-134, miRNA-323, miRNA-382) in plasma were measured by qRT-PCR via TaqMantechnology using QuantStudio™ 12K Flex real-time PCR system (Applied Biosystems, USA). MicroRNAs' levels were determined by the comparative CT (ΔΔCT) method via the Expression Suite Software using miRNA-491 and miRNA-370 levels, respectively for normalisation.

Data analysis

Data entry was carried on excel sheet, and statistical analysis was done using Statistical program for social science (SPSS) version 18 for windows SPSS; Inc, Chicago IL. Continuous data were expressed as mean and standard deviation Number and percent were used to describe categorical data. Chi square test was used for comparing between two qualitative variables. T-test was used for comparing between two means. Non-parametric tests were used in cases of not normally distributed data. The Bivariate correlations procedure (Pearson correlation) was used to calculate the pairwise associations for a group of variables. Receiver-Operating Characteristic (ROC) curves were formed and the area under ROC curves (AUC) was determined to assess sensitivity and specificity of various miRNAs biomarkers. The cutoff points on the ROC curves, where the accuracy of MCI detection is greatest, were determined. P-value was considered statistically significant if $p < 0.05$ and considered statistically highly significant if $p < 0.01$.

Results

Regarding socio-demographic data, there were 73 (36.6%) males and 113 (63.4%) females, their ages ranged from 40 to 65 years with a mean of 51.3 ± 4.1 years. About 41% of the studied individuals had secondary education, 42% had a university education, and 17% had a post-graduate level of education. As regards the subjective complaint of memory impairment, about 60% of all participants complained of frequent forgetfulness. Comparing their current memory to that of the previous year, 31.9% of them reported impaired memory. MCI was detected among 14 / 186 (7.5%) of the studied individuals depending on both subjective complaint and objective detection with at least two positive cognitive tests. The mean score of ACE III (88.14 ± 2.5), MOCA (25.29 ± 2.09) and Quick MCI (63.42 ± 9.78) tests was significantly lower among individuals with confirmed MCI compared to those with normal cognition (94.5 ± 4.5), (27.9 ± 2.2) and (77.6 ± 10.09) respectively, $P < 0.01$.

The percentage of subjects with MCI was significantly higher among current or ex-smokers compared to nonsmokers and among individuals with sedentary life compared to those with physical activities, $P < 0.05$. Mean BMI was significantly higher among individuals with MCI compared to those with normal cognition, $P < 0.01$ (Table 1).

Table 1: Socio-demographic, medical and physical history of the studied participants about MCI

Variable	Total	Cognitive function		Odds Ratio (CI 95%)
		MCI (N = 14) N (%)	Normal (N = 172) N (%)	
Age in years				
< 50	65	5 (7.8)	60 (92.2)	®
50 -< 55	64	6 (9.4)	58 (90.6)	1.2(0.3-4.3)
55 -< 60	42	3 (7.1)	39 (92.9)	0.9(0.2-4.1)
60-65	15	0 (0.0)	15 (100.0)	
Gender		6 (8.2)	67 (91.8)	1.1 (0.3-3.5)
Males	73	8 (7.1)	105 (92.9)	®
Females	113			
Education				2.6 (0.8-8.2)
Secondary	79	9 (11.3)	70 (88.7)	®
University and Master / MD	107	5 (4.7)	102 (95.3)	
Smoking				3.1(0.96-10.1) *
Current or ex-smokers	31	5 (16.1)	26 (83.9)	®
Non-smokers	155	9 (5.8)	146 (94.2)	
Marital status				3.7 (0.5-29.1)
Married	150	14 (9.3)	136 (90.7)	®
Single or widowed	36	1 (2.7)	36 (100.0)	
Family history of dementia				0.8(0.2-3.1)
Yes	45	3 (6.6)	42 (93.4)	®
No	141	11 (7.8)	130 (92.2)	
History of head Trauma				
Yes	44	3 (6.8)	41 (92.3)	0.8(0.2-3.2)
No	142	11 (7.7)	131 (92.3)	®
Physical activities				
No	40	6 (15.0)	34 (85.0)	4.2(1.2-14.5)*
Several times/month	123	5 (4.1)	118 (95.9)	®
Systolic blood pressure (mean ± SD)	186	120 ± 14.1	118 ± 14.9	P > 0.05
Diastolic blood pressure (mean ± SD)	186	78.5 ± 7.7	77.5 ± 10.7	P > 0.05
BMI (mean ± SD)	186	35.5 ± 7.2	30.8 ± 5.6	P < 0.01
Waist/Hip ratio (mean ± SD)	186	0.88 ± 0.08	0.87 ± 0.07	P > 0.05

® Reference group; CI: confidence interval; * Significant P value < 0.05.

The mean monthly intake of important food for good memories like vegetables, dark green

vegetables and unroasted nuts were significantly higher among those with normal cognition compared to those with MCI, P < 0.01. The mean monthly hours spent on the internet, playing intellectual games and going to the museum / cinema was significantly lower among participants with MCI (P < 0.01) (Table 2).

Table 2: Monthly frequency intake of some food items, social and mental activities of the studied participants about MCI

Variable	Cognitive function		P-value
	MCI	Normal	
	N = 14 (Mean ± SD)	N = 172 (Mean ± SD)	
Main Meal contain (vegetables- carbohydrates- protein)	11.3 ± 9.4	21.1 ± 27.9	0.249
Red meat	5.0 ± 3.0	5.4 ± 4.5	0.748
Egg	8.5 ± 10.9	12.6 ± 10.0	0.201
Dairy products	23.5 ± 9.3	25.4 ± 12.3	0.603
Fish	5.7 ± 8.3	4.6 ± 7.5	0.623
Canned tuna	0.9 ± 0.8	1.9 ± 4.1	0.446
Bean	8.0 ± 11.3	15.4 ± 12.3	0.059
Whole brown Grain	1.3 ± 2.5	4.3 ± 10.2	0.336
Vegetable	4.2 ± 8.7	19.4 ± 16.1	0.000*
Dark green vegetables	1.0 ± 1.1	4.9 ± 7.7	0.000*
Fruits	12.7 ± 9.6	21.1 ± 14.1	0.055
Unroasted nuts	0.4 ± 0.5	3.6 ± 7.1	0.000*
Dark chocolate	0.4 ± 0.5	2.8 ± 6.5	0.219
Social activities			
Going to Club	1.0 ± 1.6	2.4 ± 6.8	0.520
Going to Museum/ Cinema/ parties	0.0 ± 0.0	0.2 ± 0.5	0.000*
Mental activities (In hours)			
Watching TV	79.1 ± 70.1	51.3 ± 50.4	0.088
Using Internet	21.8 ± 14.0	36.9 ± 33.3	0.007*
Playing intellectual games	0.7 ± 0.3	6.2 ± 14.9	0.000*

P significant at < 0.05.

None of the studied laboratory tests was found to be significantly associated with MCI (P > 0.05) (Table 3).

Table 3: Lipid profile and other laboratory analysis of the studied participants and MCI

Laboratory Test	Cognitive function		P-value
	MCI	Normal	
	N = 14 Mean ± SD	N = 172 Mean ± SD	
Alanine aminotransferase (ALT)	21.4 ±14.1	19.2±10.5	0.467
Albumin (ALB)	4.5 ± 0.2	4.6 ± 0.2	0.128
Creatinine	0.9 ± 0.1	0.9 ± 0.1	0.539
Fasting Blood Glucose (FBG)	117.8 ± 31.2	96.5 ± 31.2	0.134
Glycosylated Hemoglobin (HbA1c)	6.2 ± 1.5	5.5 ± 1.2	0.620
Cholesterol	181.7 ± 16.8	189.5 ± 14.2	0.073
Triglycerides	107.1 ± 81.5	120.7 ± 49.0	0.401
High Density lipoprotein (HDL)	42.3 ± 14.5	46.3 ± 13.6	0.348
Low Density lipoprotein (LDL)	122.7 ± 22.1	125.1 ± 20.3	0.092

P non-significant > 0.05.

ROC curve analysis was done for miRNA 128, miRNA-132, miRNA-874, miRNA-134, miRNA-323 and miRNA-382 expressions in plasma of the studied subjects. Upon analysis, only miRNA-132 can significantly differentiate between MCI and normal cognition with AUC = 0.69 with a 95% confidence interval 0.52 – 0.86 (P = 0.04) (Figure 1).

These biomarker pairs for family miRNA 132 expressions differentiated individuals with MCI from those with normal cognition with 60%-70% sensitivity and 57.9%-68.6% specificity.

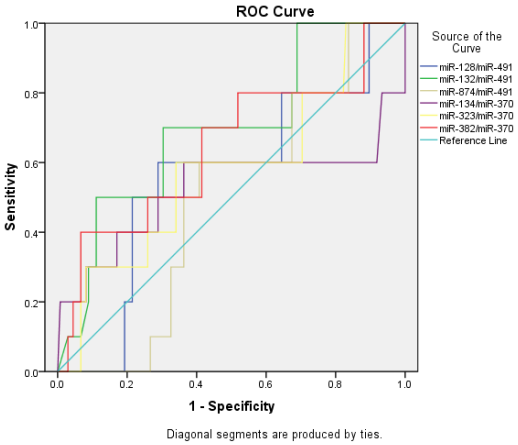

Figure 1: Receiver-Operating Characteristic (ROC) curve for differentiation between MCI and normal cognition among apparently healthy individuals obtained with different miRNAs biomarker pairs

Family miRNA 134 expressions differentiated individuals with MCI from those with normal cognition with 40%-60% sensitivity and 65.2%-83.3% specificity (Table 4).

Table 4: Sensitivity, specificity and ACU of MiRNA biomarker pairs in detecting MCI

Family / normalizer	AUC (95% CI)	Sensitivity	Specificity	Accuracy	P-value
miRNA-128 / miRNA-491	0.56 (0.37-0.74)	60%	68.6%	64.3%	0.5
miRNA-132 / miRNA-491	0.69 (0.52-0.86)	70%	68.6%	69.3%	0.04
miRNA-874 / miRNA-491	0.49 (0.34-0.63)	60%	57.9%	58.9%	0.9
miRNA-134 / miRNA-370	0.52 (0.26-0.78)	40%	83.3%	61.6%	0.8
miRNA-323 / miRNA-370	0.57 (0.38-0.77)	60%	65.2%	62.6%	0.4
miRNA-382 / miRNA-370	0.64 (0.44-0.84)	50%	71.9%	60.9%	0.1

AUC: area under the curve.

Logistic regression analysis revealed higher miRNA132 expressions, little vegetables, little nuts, lower level of education and a higher level of ALT are predicting factors for MCI with AOR 1.1 (1.01-3.3), 1.2 (1.04-1.43), 0.8 (0.8-0.98), 2.7 (1.9-7.4) and 1.6 (1.1-2.3) respectively (Table 5).

Table 5: Logistic regression analysis for predicting the risk of MCI

Variable	Adjusted Odds Ratio	95% confidence interval		P-value
		Lower	Upper	
miRNA132	1.12	1.01	3.387	0.007
no vegetables	1.2	1.04	1.43	0.01
no nuts	0.88	0.80	0.98	0.02
secondary education	2.7	1.96	7.4	0.04
ALT lab	1.586	1.079	2.332	0.019
Constant	1.459E23			0.017

Discussion

The risk of dementia is higher in individuals with MCI (10-15%) compared to others with normal cognition (1-2%) [21], [22], [23].

In the present study, the prevalence of MCI was 7.5%. In a study done among doctors and workers at Zagazig University Hospital, Egypt, with a

similar age group, MCI was found among 9% of them [24]. In China, in Tianjin city, MCI was detected among 9.7% of normal individuals according to the Petersen's criteria of MCI [25]. Ding and Zhao [26] documented MCI prevalence of 20.1% among normal Chinese individuals aged ≤ 60 years in an urban community of Shanghai using Mini-Mental status test. Moreover, Salama et al., [27] found that the prevalence of MCI was 11.6% among non-obese aged 40-60 years. The lack of homogeneity in the reported data about the prevalence of MCI may be due to the differences in the test used for the detection of MCI, the varieties in the application of MCI diagnostic criteria, the demographic characteristics of the shared populations, the education level and the age range of the participants.

The current study aimed to identify the demographic factors associated with cognitive function. The results showed that the prevalence of MCI was insignificantly higher at the age of 50-55 years ($P > 0.05$), which contradicts previous results that showed a trend that the prevalence of MCI increased with increasing age [28]. This could be attributed to the fact that all the participants at higher age group had post-graduate education. We found that all 32 participants with post-graduate education had normal cognition. A previous study found that education was an effective preventive factor against MCI [29]. People with a lower level of education were more likely to develop MCI. Possible reasons may be: high level of education can make changes to the brain metabolism and the degree of biological neural synaptic connections so that the brain can tolerate functional or structural defects in the brain cells to a certain extent. Instead, for people with lower levels of education, there is a lack of knowledge to stimulate the brain, causing massive loss of neurons [30]. Another possible reason is the health; poverty and socio-economic status which are associated with lower education level [31].

Our findings revealed no difference as regards the prevalence of MCI among males (8.2%) compared to females (7.1%), $P > 0.05$. Similarly, Ferreira et al., [32] reported that there were no sex differences as regards the rates of cognitive decline in the normal ageing process. On the contrary, Caracciolo et al., and Roberts et al., [33], [34] found that the incidence of MCI was higher among men. The pathological mechanisms that could explain these patterns precisely are still concealed. However, the pathophysiological changes regulated by endocrinal transition states, such as the menopause may have a role [35].

Midlife obesity has consistently been considered as a risk factor for the decline of cognitive function [36]. Our findings revealed that the mean BMI was significantly higher among participants having MCI (35.5 ± 7.2) compared to those with normal cognition (30.8 ± 5.6), $P < 0.01$. Similarly, Salama et al., [27] found that the prevalence of objective MCI was 42.6% among obese compared to 11.6% among non-obese. In a population-based study, participants who were obese had twice the risk of developing dementia (OR = 2.10) [36].

In the current study, the prevalence of MCI was significantly higher among smokers (16.1%) compared to non- smokers (5.8%), with OR 3.1 (0.96-10.1). It was reported that cognitive dysfunction accounted for 75.6% among smokers, compared to only 52.5% among nonsmokers, suggesting that smoking is a risk factor for MCI. During smoking, carbon monoxide fumes, as well as tobacco nicotine, tar and other harmful substances are produced, which will cause vascular endothelial damage, myosin contraction, and increase vascular permeability to accelerate atherosclerosis. Smoking may impair cognitive function through its effect on the arterial wall, leading to thickening of arterial plaque, increasing plasma viscosity and fibrinogen levels, platelet aggregation, hypertension and increases the risk of stroke [30].

A history of traumatic brain injury may possess a higher risk of having neurodegenerative diseases such as MCI and dementia across the life span [37]. The relation between traumatic brain injury and the risk of dementia later in life has been repeatedly established [38], [39]. In the present study, the prevalence of MCI was not significantly different between subjects having previous head trauma and those without, $P > 0.05$. May be that the reported head trauma in the current study was mild and did not lead to brain injury.

The present study assessed the effects of lifestyle habits and leisure activities on cognition. Participants with normal cognition were found to be monthly consuming a significantly higher level of vegetables, fruits and unroasted nut compared to MCI subjects, $P < 0.05$. It was found that eating a healthy balanced diet that contains fruits, vegetables, unrefined cereal grains and nuts, and avoiding fatty and high-calorie foods was directly related to normal cognition [40]. The Mediterranean diet was reported as a preventive factor against MCI and AD diseases [41]. A study done by Pasinetti and Eberstein [42] found that polyunsaturated fatty acids, vegetables, and a high Mediterranean-diet score may improve cognitive activity. A balanced diet with fewer calories and low glucose may enhance carbohydrate metabolism and decrease obesity which will effectively reduce the risk of hyperglycemia and thus avoiding Alzheimer's disease [43]. On the other hand, persons with Alzheimer's disease reported high consumption of animal protein and sugar in comparison to healthy controls who consumed more vegetables, fruits and whole grains [44]. Prevention of the deterioration of cognitive functions and dementia is directly related to the intake of certain nutrients or dietary antioxidant supplements [45].

Increased level of engagement in physical

activities is an important factor that increases the cognitive reserves [29]. We found that the prevalence of MCI was significantly higher among inactive subjects (15%) compared to those who were practising physical exercise (4.1%), OR 4.2 (1.2-14.5). In a population-based study, and frequency of moderate-intensity exercise had a protective effect on MCI. Those findings were consonant in both sexes. Light and intense physical activities were not significantly associated with MCI [46].

There is growing evidence demonstrating that participation in different forms of leisure activities, either mental or social activities have a good effect on well-being, especially for conserving functional capacity during the ageing procedure and decreasing the risk of chronic diseases [47], [49]. In the present study, the mean time in hours/week spent in intellectual games, reading and social activities were significantly higher among participants with normal cognition compared to subjects with MCI, $P < 0.01$. Several studies agreed with the results of the current study and reported that computer activities, reading, dancing, playing games and musical instruments decrease the risk of MCI and dementia [50], [51], [52].

In the present study, there was no significant association between lipid profiles and FBS and the risk of MCI. Similarly, other studies reported that lower concentration of HDL was associated with lower cognitive function, suggesting a positive correlation between HDL and cognitive function [53], [54].

A study done by Mielke and his colleagues [55] concluded that high cholesterol level at old age was associated with reduced risk of dementia. However, Yaffe et al., [56] and He et al., [57] found that cholesterol and triglyceride levels were significantly higher among individuals with MCI subjects compared to those with normal cognition. Increase in serum cholesterol might cause damage to the brain capillary endothelial cells and accelerate atherosclerosis, then reduce cerebral blood flow, leading to the impaired cognitive function [30].

Evolution of reliable and non-invasive procedures for detecting subjects with MCI is important. It could help in increasing the efficiency of existing and new therapies and observing the advancement of disease [58] (Michael-Titus et al., 2010). Sheinerman et al., in 2012 [59] performed a pilot study for selecting promising miRNA biomarkers for detecting MCI. Two sets of biomarkers (the miR-132 and miR-134 families paired with miR-491-5p and miR-370) showed high specificity and sensitivity in recognising MCI subjects. Moreover, Sheinerman et al., [60] validated these two sets of 50 MCI patients and 50 controls. They reported that these two sets could distinguish MCI from normal controls with 84%-94% sensitivity and 96%-98% specificity for miRNA-132 family and 74%-88% sensitivity and 80%-92% specificity for miRNA-134 family.

In the present work, we aimed at validating these two miRNA-132 and miR-134 families (paired with miR-491-5p and miR-370 respectively), as biomarkers for the detection of MCI**.** Surprisingly, these two sets revealed much lower sensitivity and specificity in detecting MCI. Family miRNA 132 expressions differentiated individuals with MCI from those with normal cognition with 60%-70% sensitivity and 57.9%-68.6% specificity**.**

For family miRNA, 134 expressions differentiated individuals with MCI from those with normal cognition with 40%-60% sensitivity and 65.2%-83.3% specificity. However, only miRNA 132 expression was significantly upregulated among individuals with MCI compared to those with normal cognition, with a significant AUC 0.69 (0.52-0.86), 70% sensitivity, 68.6 specificities and accuracy 69.3%.

These results preliminarily indicated that miRNA-132 might be a potential biomarker for the diagnosis of MCI. A significantly upregulated expression of miRNA-132 was reported among patients with MCI (n = 66) in comparison to their age-matched controls (n = 76) [61]. Moreover, Weinberg et al., [62] assessed miRNA 132 in the frontal and inferior temporal cortex of postmortem brains of patients with MCI and normal individuals and found that miR 132 was significantly down-regulated in MCI. Many studies have reported the value of miRNA-132 in managing dendritic morphology. MiR-132 is important for the functional integrity of adult neurons reduces synaptic transmission between neurons in the hippocampus and has a key role in controlling cognitive functions [63], [64], [65]. While, Dhahbi et al., [66] reported that ageing is associated with an increase in the levels of miR-134 and miR-874 expression.

The accuracy of miRNAs as diagnostic and/or prognostic biomarker of MCI is inconsistent among several studies which could be attributed to different factors including different sample collection techniques regarding temperature, freezing and centrifugation of the drawn blood sample, different sample size, difference in selection of the participants as some studies matched cases and controls depending on gender and age while others relied on gender and ethnicity, different analytical methods and publication bias (where negative studies may be difficult to be found when searching on usual databases) which may overestimate the connection between miRNAs and MCI [67], [68].

In conclusion, the risk of MCI could be reduced by targeting modifiable risk factors. MiRNAs showed low sensitivity and specificity. However, miRNA 132 expression might be used as a minimally invasive test for detection of MCI.

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