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(REVIEW ARTICLE)

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Comparative accuracy of screening instruments for Alzheimer's disease: Systematic review and meta-analysis

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Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline. Early detection and accurate screening of AD are crucial for timely interventions and improved patient outcomes. Various screening instruments have been developed to aid in the identification of individuals at risk of AD. However, the comparative accuracy of these instruments has not been thoroughly assessed.

Aim: This study aims to evaluate and compare the accuracy of different screening instruments used for the detection of AD.

Method: A PRISMA selection was used to identify studies across electronic database such as PubMed and Google scholar from up until February 4, 2023.A total of 5 studies evaluating neuropsychological assessment such as, Mini-mental state examination (MMSE), Montreal cognitive assessment (MoCA), and clinical dementia rate (CDR) between patients with AD, mild cognitive impairment (MCI) and healthy control (HC). Meta-analysis was performed by Rev-Man 5.4.

Result: The studies included a total number of 1,177 individuals, 398 were in the AD group,409 in MCI and 370 in HC group. The cognitive function assessed by the meta-analysis revealed AD with lesser MMSE ($P < 0.00001$), MoCA ($P < 0.00001$), when compared to MCI. But CDR score was decrease with MCI ($P < 0.00001$). In addition, AD showed a lesser MSSE ($P < 0.00001$), CDR ($P < 0.00001$), and MoCA ($P < 0.00001$), scores when compared to HC.

Conclusion: The findings indicate that individuals with AD exhibit lower scores in MMSE, MoCA, and CDR compared to those with MCI and HC.

Keywords: Alzheimer's disease (AD); Mild cognitive impairment (MCI); Mini-Mental State Examination (MMSE); Clinical Dementia Rating (CDR); Montreal Cognitive Assessment (MoCA); Neurological assessment

1. Introduction

One of the most prevalent neurodegenerative illnesses, Alzheimer's disease (AD) affects a variety of processes, including memory loss, emotional disturbances, behavioral issues, and cognitive decline(1, 2). Multi-domain cognitive abilities are fully evaluated in well-organized sequences using structural cognitive tests. Three often used structured tests are used to evaluate cognitive impairment in people with MCI and dementia: the Mini-Mental State Examination (MMSE), the MoCA, and the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog)(3). In order for physicians and researchers to assess the cognitive abilities of the people who are referred for assessment, they need to know the norms of the cognitive tests.

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Brief screening measures, such as the MMSE and MoCA , are easily administered with little training and have demonstrated diagnostic utility , particularly in differentiating dementia from normal cognitive aging (4, 5, 6, 7, 8, 9).For almost 50 years, MMSE has been routinely used to record mental states in an easy-to-use, standardized manner(4). Additionally, the MMSE (sensitivity 85.1%, specificity 85.5%) is a useful and efficient tool for screening for cognitive impairment in community settings as shown in Table 1(10). MoCA was created in 2005 as a mild dementia screening tool for academic and community settings. It was found to be more sensitive than MMSE in detecting MCI (specificity 87 vs. 100%, sensitivity 100 vs. 78%) depicted in Table 2(5). It has been used globally over the past 15 years as a well-accepted cognitive test for the general public. You may access the translated versions of MoCA at www.mocatest.org.Globally, the CDR has been accepted as the gold standard for dementia staging. In a number of clinically relevant areas, including memory, orientation, judgment and problem solving, home and hobbies, and personal care, it evaluates cognitive and functional decline(11). Face validity, correlation to established diagnostic criteria for AD dementia, scoring independent of psychometric ability, absence of practice effects, and low impact of language, educational, and age confounders are some of the qualities of CDRs(12, 13, 14, 15). Strong content and criterion validity, internal consistency, internal responsiveness, and excellent interrater reliability in multicenter studies are among its many positive traits as seen in Table 3(16, 17, 18, 19, 20, 21).

Thus, we perform a meta-analysis to objectively evaluate the accuracies of scoring tools for AD.

Table 1 MMSE scores (Scores on the MMSE range from **0-30**, with scores of 25 or higher being traditionally considered normal. Scores less than 10 generally indicate severe impairment, while scores between 10 and 20 indicate moderate dementia)(22).

Category	Maximum score	Description
Orientation to time	5	From broadest to most narrow. Orientation to time has been correlated with future decline
Orientation to place	5	From broadest to most narrow. This is sometimes narrowed down to streets and sometimes to the floor.
Registration	3	Immediate memory
Attention and calculation	5	It has been suggested that serial sevens may be more appropriated where English is not the first language.
Recall	3	Registration recall
Language	2	Naming a pencil and watch
Repetition	1	Speaking back a phrase
Complex commands	6	Varies can involve drawing figure shown

Table 2 MoCA scores (18–25 points: Mild cognitive impairment, 10–17 points: Moderate cognitive impairment, and Fewer than 10 points: Severe cognitive impairment)(22).

Cognitive domain	maximum score	MoCA index score
Orientation	6	orientation
Attention	6	digit span forward & backward, letter A tapping, serial-7 subtraction, sentence repetition, words recalled in both immediate recall trials
Language	3	naming, sentence repetition, letter fluency
Visuospatial function	5	cube copy, clock drawing, naming
Memory	5	number of words recalled in free recall, delayed recall, category-cued recall, & multiple choice-cued recall multiplied by 3, 2, and 1, respectively

Executive function	5	modified Trail-Making Test Part B, clock drawing, digit span forward & backward, letter A tapping, serial-7 subtraction, letter fluency, abstraction

Table 3 CDR scores (CDR-0: no cognitive impairment, CDR-0.5: questionable or very mild dementia, CDR-1: mild, CDR-2: moderate, and CDR-3: severe). Data source from Morris (1997)(18).

Impairment	**None** **0**	**Questionable** **0.5**	**Mild** **1**	**Moderate** **2**	**Severe** **3**
Memory	No memory loss	Consistently slight, forgetfulness	Moderate loss	Severe loss; new material rapidly lost	Severe loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for time relationships	Oriented only for place at examination	Disoriented with time and place	Oriented to person only
Judgment and problem solving	Solves everyday problems	Slight impairment in judgement	Moderate impairment in judgement	Severely impaired in judgement	Unable to make judgements
Community affairs	Independent function at usual level	Slight impairment in activities	Unable to function at all these activities	No pretense of independent function outside home	No pretense of independent function outside home
Home and hobbies	Life and interests well maintained	Interest slightly impairment	Mild but definite impairment	Only simple chores preserved	No significant function in home
Personal care	Fully capable of self-care	-	Needs prompting	Requires assistance in dressing	Requires much help

2. Materials and Method

2.1. Data source and search

The current meta-analysis followed the PRISMA guidelines(23). This search was executed to identify literature concerning assessment tools in relation with AD. By searching the major medical databases, PubMed and Google scholar, we identified relevant publications up to February 4, 2023. We used the Mesh form strategy for PubMed as follows: (Alzheimer disease) AND assessment score) AND MoCA score) AND (Mental Status and Dementia Tests)) AND Clinical dementia rate) AND (Mental Status and Dementia Tests)) AND Mild cognitive impairment. All articles were checked by title and abstract to decide their importance to the study question. Relevant articles in relations with the study question were successively added. The publication language was limited in English.

2.2. Inclusion criteria

- Patients diagnosed with AD
- Assessment of all enrolled patients within the range of cognitive impairment
- Studies comparing AD, MCI and HC
- Studies that underwent MRI
- Studies with outcome of interest

2.3. Exclusion Criteria

- Intercranial tumors
- Patients who Fail to cooperate
- Non-English papers

- Reviews
- Case reports

2.4. Study selection and data extraction

Data were collected for selected literature. Firstly, data about author, publication year, nationality, total number of patients, assessment scores such as, MMSE scores, MoCA scores, and CDR scores as shown in Table 1.

2.5. Characteristics of Included studies

A search of the database yielded 500 studies in all. After removing duplicate entries, 287 articles remained. After perusing the titles and abstracts of the remaining 213 publications, a comprehensive screening was conducted. Following screening, 188 were disqualified for not meeting the standards. After a thorough screening process, there were only 25 papers left, and of those, 5 were ultimately included in the meta-analysis, as seen in Figure 1. 1,177 patients in all were registered in the five included trials. Of these patients, 409 belonged to the MCI group, 370 to the HC group, and 398 to the AD group. One study was carried out in Taiwan, two in China, and two in Iran. Research revealed the use of neuropsychological tests such the MMSE, MoCA, and CDR as shown in Table 4.

2.6. Statistical analysis

Table 4 Characteristics of included studies

Author	Publication year	Country	Age (AD/MCI/HC)	Number of patients in assessment (AD/MCI/HC)	Assessment score	AD	MCI	HC
Ali Khazaee et al (24)	2017	Iran	72.54 ± 7.02 / 71.77 ± 7.78 / 75.90 ± 6.79	34/89/45	MMSE CDR	21. 24 ± 3.37 0.92 ± 0.31	27.56 ± 2.20 0.49 ± 0.17	28.95 ± 1.56 0.07 ± 0.21
Kai Du et al (25)	2022	China	68.89 ±8.27 /68.56 ± 8.91 /66.93 ± 6.83	295/257/257	MMSE	16.56 ± 6.02	25.14 ± 3.39	28.52 ± 1.64
Min-Chien Tu et al (26)	2020	Taiwan	77.3 ±6.40 / 75.8 ±7.67 / 65.1 ±6.97	32/20/23	MMSE CDR	22.6±3.92 4.2 ±2.71	20.1 ±5.88 5.1 ±4.18	27.9 ±1.60 0.6 ±0.46
Xuanyu Li et al (27)	2018	China	72.25±9.15 / 70.33±8.27 / 67.61±8.86	24/27/31	MMSE MoCA	15.54±5.62 10.67±5.11	23.69±4.71 19.22±5.15	28.26±3.02 25.61±3.77
Fatema Mohammadian (28)	2023	Iran	77.77 ± 7.95/ 72.44 ± 7.11/ 71.57 ± 7.14	13/16/14	MMSE MoCA	18.62 ± 1.39 16.15 ± 3.53	25.06 ± 2.24 22.19 ± 3.94	28.07 ± 0.83 27.29 ± 1.14

Version 5.4 of the Review Manager (RevMan) software, made available by the Cochrane collaboration, was utilized to do statistical analysis. Using mean difference with a 95% CI, continuous variables were aggregated. For OR, the Mantel-Haenszel statistical technique was used to calculate the random effect and fixed effect models. We used the inconsistency statistic (I2) to assess the heterogeneity of the studies. It was decided to adopt the fixed effect model for

the eligible studies if the I^2 value was less than 50%, as this indicated homogeneity. However, if I^2 was more than 50%, the pooled data was considered to be heterogeneous and significant, and the random effect model was substituted.

3. Results

3.1. AD vs. MCI

3.1.1. MSSE scores

MMSE score is by and large utilized for screening patients with dementia and the score ranges between 0-30. Higher MMSE scores show better mental capability's score of 24 following educational correction is suggested for patients with VCI (29). Five studies(24, 25, 26, 27, 28) collected MMSE scores. There was a statistically significant difference between the two groups. The AD (n=398) saw a lesser MMSE score as compared to MCI (n=409). Heterogeneity: $Chi^2 = 57.61$, df = 4 ($P < 0.00001$); $I^2 = 93\%$, Test for overall effect: $Z = 24.66$ ($P < 0.00001$). Figure 2

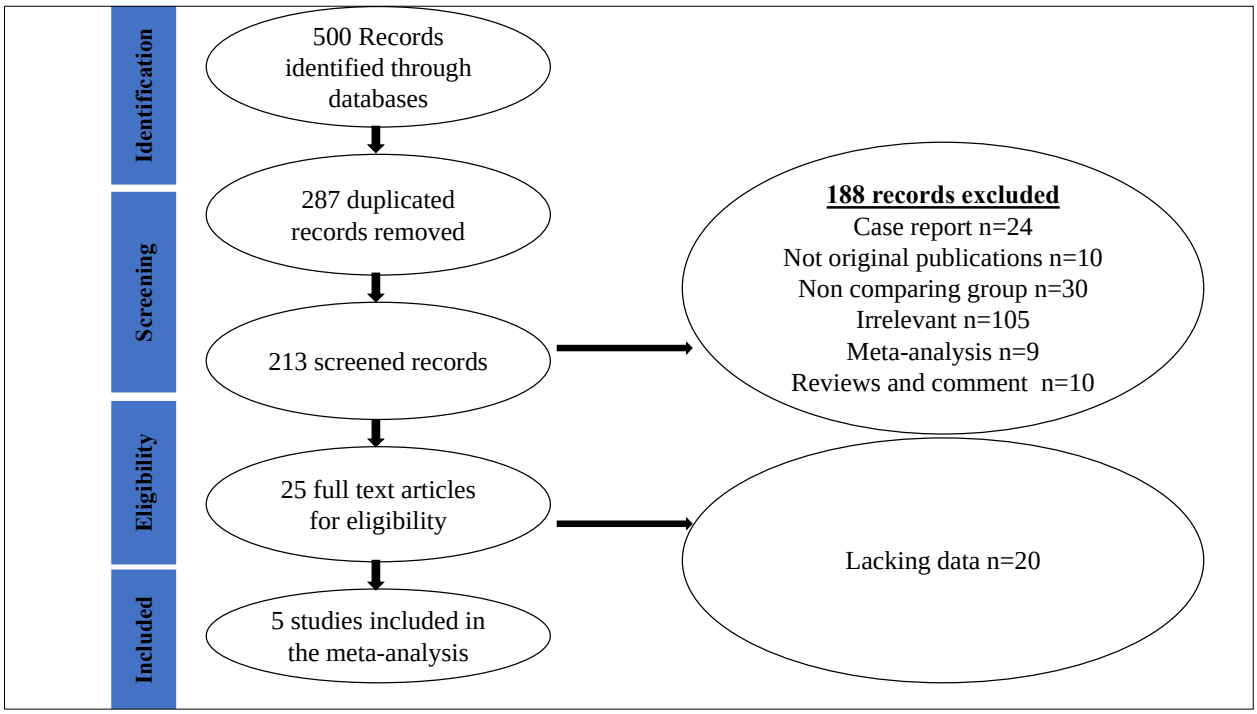

Figure 1 Prisma flow diagram

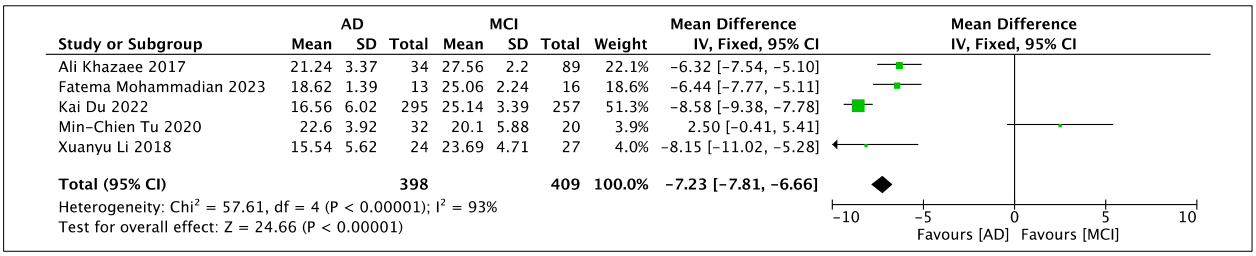

Figure 2 Forest plot of MSSE (AD vs. MCI)

3.1.2. CDR scores

Two studies(24, 27), were collected for CDR. AD included n =66 patients and MCI with n=109 patients. The MCI group saw a lesser CDR score as compared to the AD. Heterogeneity: $Chi^2 = 1.60$, df = 1 ($P = 0.21$); $I^2 = 37\%$, Test for overall effect: $Z = 7.60$ ($P < 0.00001$). Figure 3

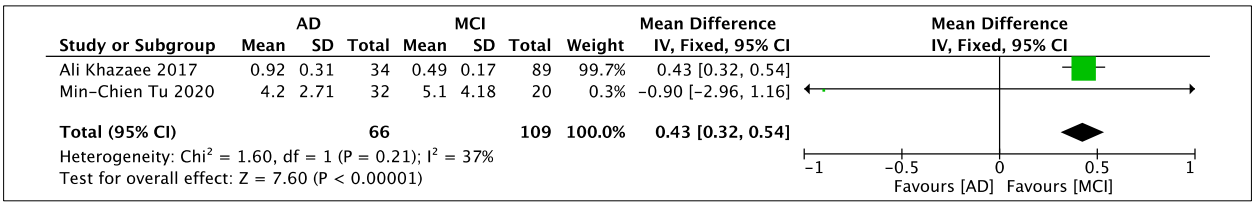

Figure 3 Forest plot of CDR (AD vs. MCI)

3.1.3. MoCA scores

The MoCA is utilized for VCI and mild dementia which has been uncovered in examinations to have high responsiveness and particularity for separating individuals with VCI and the people who do not(30). MoCA scores range from 0-30. Higher MOCA score represents good cognitive function and a cut off of 26 following education is need for people with cognitive disorders. The MoCA score was recorded in two studies (27, 28). The meta-analysis showed a statistically significant difference between the two groups. Patient with AD (n=37) had a lesser MoCA score than those in the MCI group(n=43). Heterogeneity: $Chi^2 = 1.58$, df = 1 (P = 0.21); $I^2 = 37\%$, Test for overall effect: Z = 7.26 (P < 0.00001). Figure 4

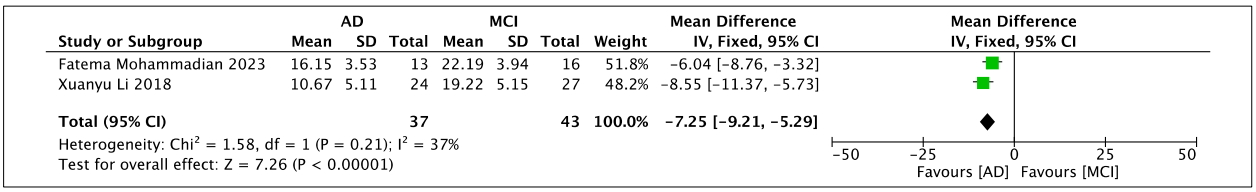

Figure 4 Forest plot MOCA scores (AD vs. MCI)

3.2. AD vs. HC

3.2.1. MSSE scores

Five studies(24, 25, 26, 27, 28) , recorded the number subject that underwent MSSE between AD(n=398) and HC(n=370). The results discovered a significant difference the two groups. MSSE was lower in the AD than the HC. Heterogeneity: $Chi^2 = 83.11$, df = 4 (P < 0.00001); $I^2 = 95\%$, Test for overall effect: Z = 41.86 (P < 0.00001). Figure 5

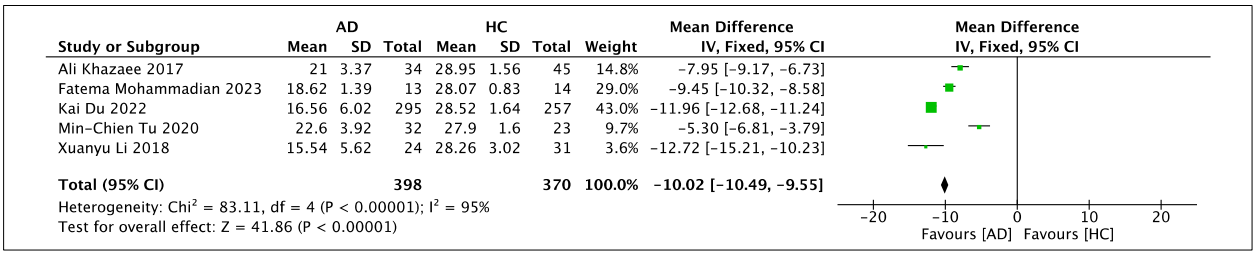

Figure 5 Forest plot of MSSE (AD vs. HC)

3.2.2. CDR scores

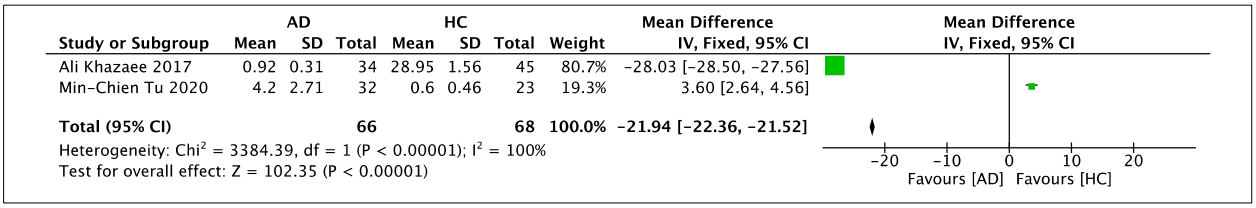

Figure 6 Forest plot of CDR (AD vs. HC)

Two studies(24, 27) , retrieved for CDR showed a significant difference between AD(n=66) and HC(n=68). The patients with AD had lesser CDR. Heterogeneity: $Chi^2 = 3384.39$, df = 1 ($P < 0.00001$); $I^2 = 100\%$, Test for overall effect: Z = 102.35 ($P < 0.00001$). Figure 6.

3.2.3. MoCA scores

MoCA score was lesser with AD (n= 37) than HC(n=45) after two studies(27, 28) was analyzed. Heterogeneity: $Chi^2 = 5.56$, df = 1 ($P = 0.02$); $I^2 = 82\%$, Test for overall effect: Z = 16.03 ($P < 0.00001$). Figure 7

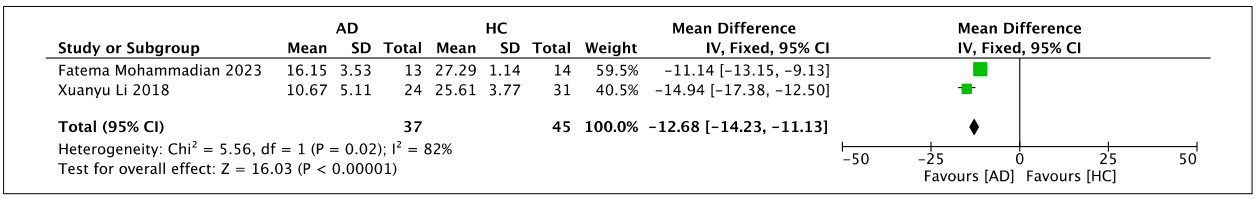

Figure 7 Forest plot of MOCA (AD vs. HC)

3.3. Quality assessment

In this study, we used the Cochrane Handbook for systematic reviews of interventions, version 5.1 on the risk of bias to determine the quality of the trial. We considered possible confounding factors in the following area: 1) sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete data, 5) selective reporting, and other factors. "High risk" trials are those with a risk of bias for one or more domains. A case is considered "low risk" if it has a low risk of bias in all relevant areas. For others, it is considered "unclear", as shown in Figure 8.

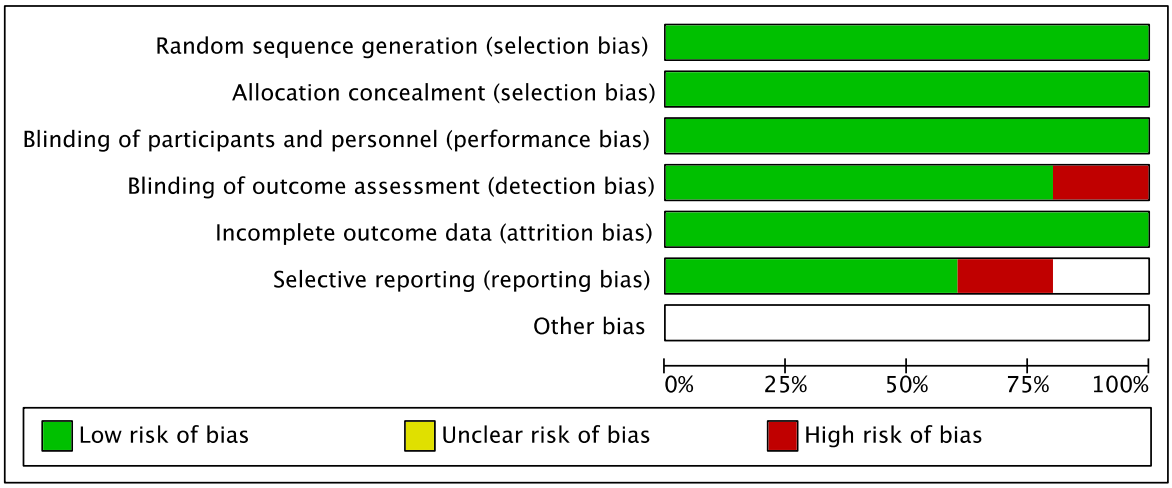

Figure 8 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

4. Discussion

During the past decade, neuroimaging has gained increasing interest as a tool used for predicting mental disorders [30].This systematic review and meta-analysis aimed to evaluate and compare the accuracy of different screening instruments used for the detection of AD. The findings of this study provide valuable insights into the cognitive performance of individuals with AD, MCI, and HC.

The results of the meta-analysis indicate that individuals with AD exhibit significantly lower cognitive function compared to those with MCI and HC. This is evidenced by lower scores on screening instruments such as the MMSE, MoCA, and CDR. These findings highlight the importance of early detection and accurate screening for AD, as it allows for timely interventions and improved patient outcomes. A meta-analysis stated that, both tests (MMSE and MoCA) were shown to be reliable in detecting AD, however MoCA is a better screening tool than MMSE in identifying MCI(31). Additionally, it has been demonstrated that the older group with more formal education had a lower MMSE accuracy.

This is because older people with higher levels of education have a ceiling effect while taking the MMSE. The test's accuracy is decreased as even those with moderate AD and MCI diagnoses can perform on par with older people who are cognitively healthy(32, 33). This was made clearer in the research conducted by Mellor and associates, where the area under curve (AUC) of MMSE fell from 0.85 to 0.72 (accuracy detection of MCI) and from 0.97 to 0.72 (accuracy detection of mild AD) when comparing elderly people with ≤6 to ≥10 years of formal education, respectively(33). Shaowei Zhang and colleagues observed that the MoCA is more appropriate for differentiating MCI in older Chinese people who are younger and better educated than the MMSE. Nonetheless, the MMSE outperforms MoCA in the screening of MCI in older Chinese senior populations and those with lower educational attainment(34). The Yang research employed both MMSE and MOCA on an aged population(35). The Larner research found that the MMSE (index test) had an AUC of 0.64, whereas the MOCA (reference test) had reported AUCs of 0.80 and 0.86, respectively. Owing to the MMSE's limited sensitivity, researchers have determined that it is not an appropriate instrument for screening for cognitive impairment in low prevalence areas. Instead, they have presented more effective alternatives, such MOCA(36).

It has been shown that the dementia severity as measured by the CDR ratings is stable (37).Our study found that individuals with MCI had decreased CDR scores compared to those with AD. This suggests that the cognitive decline in MCI may be less severe than in AD, indicating a potential transitional phase between normal cognition and AD. According to the findings of other studies, the CDR can identify the very early stages of AD, including the mildest stages that are similar to MCI and even a milder stage of cognitive decline that is similar to pre-MCI (38, 39).These findings emphasize the need for further research to better understand the progression of cognitive decline in MCI and its relationship to AD.

The meta-analysis also revealed that individuals with AD had lower cognitive function scores compared to HC. This indicates that the screening instruments used in this study are effective in differentiating between individuals with AD and those with normal cognitive function. Early detection and accurate screening of AD in individuals without cognitive impairments can help identify those at risk and enable timely interventions to slow down the progression of the disease.

It is worth noting that this study focused on the use of neuropsychological assessment tools in combination with MRI techniques. This highlights the importance of a comprehensive approach to AD screening, which includes both cognitive assessments and neuroimaging techniques. Future research should continue to explore the effectiveness of different screening instruments and their combination with other diagnostic tools to improve the accuracy and early detection of AD.

4.1. Limitations

Despite the valuable insights provided by this study, there are several limitations to consider. Firstly, the included studies were limited to a specific timeframe and databases, which may introduce selection bias and limit the generalizability of the findings. Additionally, the sample size of the included studies was relatively small, which may impact the statistical power and precision of the results. Furthermore, there may be variations in the administration and interpretation of the screening instruments across different settings and healthcare professionals, which could introduce variability in the accuracy of the instruments. It is essential to consider the standardization of these instruments to ensure consistent and reliable results across different settings. Moreover, this study focused on the comparative accuracy of different screening instruments and did not address other important aspects such as the cost-effectiveness and practicality of the instruments in real-world clinical settings. These factors are essential considerations when implementing screening tools for AD in routine clinical practice.

Lastly, this study primarily focused on cognitive assessments and did not consider other potential biomarkers or diagnostic tools for AD, such as cerebrospinal fluid analysis or amyloid positron emission tomography. Future research should explore the integration of multiple diagnostic modalities to enhance the accuracy and reliability of AD screening.

5. Conclusion

The findings indicate that individuals with AD exhibit lower scores in MMSE, MOCA, and CDR compared to those with minimal cognitive impairment (MCI) and healthy controls (HC). Moreover, the cognitive function of AD patients was found to be significantly impaired compared to individuals with MCI and HC. Additionally, the study highlights the importance of incorporating educational factors when evaluating cognitive function using MMSE and MOCA scores. Overall, the findings suggest that the use of neuropsychological scoring systems, in combination with MRI techniques, can aid in the accurate assessment of cognitive performance in individuals with AD. However, it is important to consider

the limitations of this study and further research is needed to address these limitations and improve the accuracy and practicality of AD screening tools.

Abbreviations

AD: Alzheimer's disease, MMSE: Mini-mental state examination, MoCA: Montreal cognitive assessment, CDR: Clinical dementia rate, I^2: inconsistency statistic, CI: Confidence interval,

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare they have no competing interest.

Availability of Data and Material

The studies included were retrieved from PubMed, and Google scholar databases.

Authors' contributions

Hayford Boamah was the main contributor in data collection, statistical analysis, and interpretation of data and text writing. Zakari Shaibu was responsible in data check, critical revision of draft and data analysis. All authors approved and contributed to the research and writing of this manuscript.

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