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ORIGINAL RESEARCH

Lower cognitive function in patients with age-related macular degeneration: a meta-analysis

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Objective: To investigate the cognitive impairment in patients with age-related macular degeneration (AMD).

Methods: Relevant articles were identified through a search of the following electronic databases through October 2015, without language restriction: 1) PubMed; 2) the Cochrane Library; 3) EMBASE; 4) ScienceDirect. Meta-analysis was conducted using STATA 12.0 software. Standardized mean differences with corresponding 95% confidence intervals were calculated. All of the included studies met the following four criteria: 1) the study design was a case–control or randomized controlled trial (RCT) study; 2) the study investigated cognitive function in the patient with AMD; 3) the diagnoses of AMD must be provided; 4) there were sufficient scores data to extract for evaluating cognitive function between cases and controls. The Newcastle–Ottawa Scale criteria were used to assess the methodological quality of the studies.

Results: Of the initial 278 literatures, only six case–control and one RCT studies met all of the inclusion criteria. A total of 794 AMD patients and 1,227 controls were included in this study. Five studies were performed with mini-mental state examination (MMSE), two studies with animal fluency, two studies with trail making test (TMT)-A and -B, one study with Mini-Cog. Results of the meta-analysis revealed lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test ($P \leq 0.001$ for all). The results also showed that differences in the TMT-A (except AMD [total] vs controls) and TMT-B test had no statistical significance ($P > 0.01$). The Newcastle–Ottawa Scale score was ≥5 for all of the included studies. Based on the sensitivity analysis, no single study influenced the overall pooled estimates.

Conclusion: This meta-analysis suggests lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test. The other cognitive impairment screening tests, such as animal fluency test and TMT, need more studies to assess.

Keywords: age-related macular degeneration; cognitive impairment; meta-analysis; mini mental state examination

Introduction

As the aging population grows, an increasing number of people would be affected by age-related diseases, such as age-related macular degeneration (AMD) and Alzheimer's disease. AMDs are increasingly affecting both the society and family. Although they are degenerative diseases of different tissues, as the retina is an integral part of the central nervous system, there may be an association between the two diseases. However, the pathogenesis and etiology of the two diseases are still not very clear.

Recently, several studies have shown amyloid β, the main constituent of senile amyloid plaques in the brains of Alzheimer's disease patients, is also deposited in the drusen of eyes with AMD.[1,2] Several factors, such as complement factor H[3] and angiogenesis-related factors,[4] that may reveal this link have been proposed. Not only the pathology,

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the epidemiology survey also found positive links between two age-related diseases. A cross-sectional study performed by Lindekleiv et al[5] found that large drusen were associated with decreased performance in cognitive function test. The hypothesis of the correlation between the two diseases originated from molecular research in cognitive function tests.[6]

Many studies have shown a significant difference in investigating the cognitive function between AMD and controls.[7,8] However, a few studies reported conflicting results.[9] In view of the fact that the sample size of the study was not large enough and there was some contradiction between studies, we performed a meta-analysis of case–control and randomized controlled trial studies to assess the association between cognitive function and AMD disease. To our knowledge, this is the first meta-analysis to assess cognitive impairment in patients with AMD.

Methods

Search and identification strategy

We searched PubMed, EMBASE, Cochrane and ScienceDirect databases on the last day of October for the published literatures through October 2015. The following search terms were used: ("Mild Cognitive" OR "Mild cognitive impairments" OR "Cognitive impairment" OR "Cognitive impairments" OR "Cognitive deficit" OR "CI") AND ("Macular Degeneration" OR "Wet Macular Degenerations" OR "Wet Macular" OR "Macular Degenerations" OR "Dry Macular Degeneration" OR "Dry Macular Degenerations" OR "Geographic Atrophies" OR "Dry Macular" OR "Age-related macular degeneration" OR "AMD").

Inclusion and exclusion criteria

The study was included without language restriction and sample size limited if it met the following criteria: 1) the study design was a case–control or randomized controlled trial study; 2) the study investigated cognitive function in the patient with AMD; 3) the diagnosis of AMD must be provided; 4) there were sufficient scores data to extract for evaluating cognitive function between cases and controls.

Two investigators, Sun and Lv, independently evaluated the eligibility of all studies retrieved from the database on the basis of the predetermined selection criteria. Studies not designed as case–control, systematic reviews were excluded from this meta-analysis. Disagreements were resolved by discussion or in consultation with the third investigator.

Data extraction and study quality assessment

Two reviewers, Sun and Wei, independently extracted the following data for each eligible study using a standard form including: first author's last name, year of publication, area, design of study, education years, control group selection, sex, age, sample size, measure of cognitive function, mean ± standard deviation (SD) of cognitive function test scores and assessed the methodological quality of the included studies with the Newcastle–Ottawa Scale.[10] Discrepancies were addressed in consultation with the third reviewer.

Statistical analysis

All the data analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA). Standard mean difference (SMD) was used to evaluate the specified relationship. The *Z*-test was used to estimate the statistical significance of the pooled data. The Cochrane's Q-statistic and I^2 test were used to evaluate interstudy heterogeneity. If the *Q*-test showed a $P<0.05$ or I^2 test exhibited $>50\%$, indicating the presence of significant heterogeneity, the random effects model was used; otherwise, the fixed-effects model was used. Subgroup analyses were performed to investigate potential sources of heterogeneity. Sensitivity analysis was performed to evaluate the influence of a single study on the overall estimate. A $P<0.05$ was identified as statistically significant except for the heterogeneity tests where a level of 0.10 was used.

Results

Identification of included studies

Two hundred and seventy-eight studies were identified by our search strategy through PubMed (n=50), EMBASE (n=185), ScienceDirect (n=24), and Cochrane (n=19) library. After duplicate literatures (n=79) were removed, 199 studies were screened with the title or abstract. From the remaining studies (n=50), we excluded cohort study (n=32) and cross-sectional study (n=6). By further screening, five studies were excluded for the following reasons: two meeting abstracts with no detail data, one study on patients with visual impairment, one study investigating depression, and one investigating visual acuity and driving performance among drivers. Finally, seven studies were eligible for inclusion in this meta-analysis. The literature search, selection process, and reasons for exclusion are shown in Figure 1.

Characteristics and quality of included studies

The age, a most critical factor in cognitive impairment, was described in all the included studies. Other related factors, sex, and educational years were investigated by some but not all studies. Due to the different measurement methods, we did a horizontal comparison between different studies

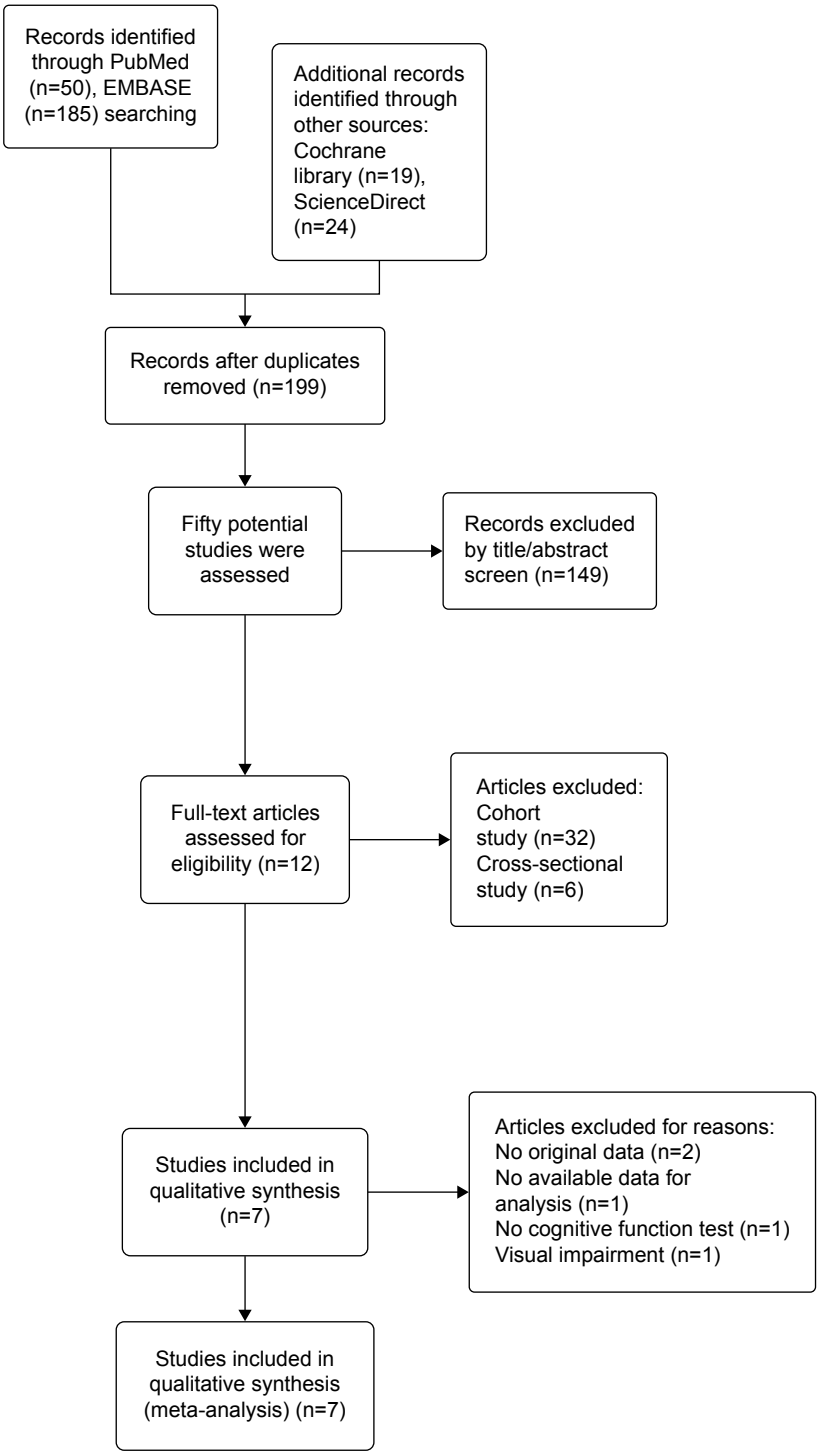

Figure 1 Flow chart of the studies selection process.

to view if they had the same measurement. If the preceding conditions existed, we performed pool analysis of the related studies. On assessing the quality of included studies, we found that no studies had described non-response rate in AMD or control group. All of the included studies gave the age data, while not every study gave the education data. The Newcastle–Ottawa Scale scores were ≥5 for all the included studies. Details of each included study are described in Tables 1 and 2.

Analysis of cognitive test scores between AMD patients and control subjects

Heterogeneity between the results of different studies was conducted by STATA 12.0 and random-effects models were

Table 1 Baseline characteristic and quality of the included studies

Author	Year	Area	Design of study	Cases		Control selection	Sex (female %)		Age (years)		Education (years)		NOS score	Measure of cognitive
				AMD	CON		AMD	CON	AMD	CON	AMD	CON		
Woo[12]	2012	Korea	Case–control	170	190	Community dwelling without AMD	47.1	41.6	72.5±7.6	76.8±6.1	12.0±7.3	9.8±5.2	7	MMSE, DST, TMT, WLT, etc
Rozzini[21]	2014	Italy	Case–control	51	24	Spouses, family member	53	83	73.7±7.2	71.7±6.2	8.4±4.3	7.5±2.8	8	MMSE, MOCA, TMT, etc
Peiretti[22]	2014	Italy	Case–control	136	38	Normal individuals	44.9	55.3	76.5±9.7	75.3±5.5	N		7	MMSE
Mandas[23]	2014	Italy	Case–control	119	730	No vision problem	N		78.4±6.9	78.5±6.7	N		7	MMSE, ADL, CIRS
Al-Salem[6]	2014	US	Case–control	138	91	No retinal disease	52.2	54.9	76.6±8.6	75±8	N		5	Mini-Cog test
Demirci[7]	2015	Turk	Case–control	59	49	Healthy subjects	47	48	74.3±7.3	73.9±5.5	3.5±2.6	3.6±2.8	7	Mini-MMSE, animals, FAB, etc
Kelly[24]	2015	Irish	RCT	121	105	Low MP	66.9	50.5	65±9	47±12.1	$P<0.001$		7	FAS, animals, PAL, etc

Abbreviations: NOS, Newcastle-Ottawa Scale; ADL, activities of daily living; AMD, age-related macular degeneration; CIRS, cumulative illness rating scale; CON, control; DST, digit span test; FAB, frontal assessment battery; FAS, a phonemic fluency score; MMSE, mini-mental state examination; MOCA, Montreal Cognitive Assessment; MP, macular pigment; N, information not provided in this study; PAL, paired associates learning; RCT, randomized controlled clinical trials; TMT, trail making test; WLT, word list memory test.

used. The forest plot (Figure 2) showed heterogeneity test results of included studies on cognitive function in AMD patients and controls. It showed no statistically significant difference among included studies of mini-mental state examination (MMSE) scores, trail making test (TMT)-A and -B. The I^2 and P-value were 50.7%, 0.087; 0.0%, 0.807; and 0.0%, 0.904; respectively. The difference among included studies of animal fluency test (AFT) was statistically significant. The I^2 and P-value were 94.1%, 0.000.

The results of meta-analysis are showed in Table 3. The results of meta-analysis showed: AMD (total) patients had lower MMSE scores (SMD=−0.32, 95% confidence interval (CI) −0.51 to −0.13, Z=3.28, P=0.001), lower Mini-Cog scores (SMD=−0.70, 95% CI −0.97 to −0.43, Z=5.03, $P<0.001$), and higher TMT-A (SMD=0.32, 95% CI 0.13–0.51, Z=3.27, P=0.001) scores than controls, while differences in the animal fluency (SMD=−0.75, 95% CI −1.73 to 0.23, Z=1.51, P=0.132) and TMT-B (SMD=0.10, 95% CI −0.10 to 0.29, Z=0.98, P=0.326) test were not statistically significant.

Analysis of cognitive test scores of dry and wet AMD patients with control subjects

The forest plot (Figure 3) shows heterogeneity test results of included studies of wet AMD patients and controls. It showed no statistically significant difference among included studies of MMSE scores and TMT-B test. The I^2 and P-value were 0%, 0.463 and 45.3%, 0.176, respectively. The difference among included studies of TMT-A test is statistically significant. The I^2 and P-value were 78.1%, 0.033. The results of meta-analysis are shown in Table 3. It showed AMD (wet) patients had lower MMSE scores (SMD=−0.58, 95% CI −0.77 to −0.38, Z=5.80, $P<0.001$), lower Mini-Cog scores (SMD=−0.56, 95% CI −0.90 to −0.22, Z=3.23, P=0.001), and higher TMT-A scores (SMD=0.76, 95% CI 0.13 to 1.39, Z=2.38, P=0.017) than controls, while differences in the animal fluency (SMD=−0.04, 95% CI −0.45 to 0.36, Z=0.20, P=0.845) and TMT-B test (SMD=0.32, 95% CI −0.04 to 0.69, Z=1.73, P=0.084) were not statistically significant.

The forest plot (Figure 4) shows heterogeneity test results of included studies of dry AMD patients and controls. It showed no statistically significant difference among included studies of MMSE scores and TMT-B test. The I^2 and P-value were 48.6%, 0.143 and 0%, 0.785, respectively. The difference among included studies of TMT-A test was statistically significant. The I^2 and P-value were 91.8%, <0.001.

Table 2 Cognitive function test scores in each AMD subtype and control subject of the included studies

Study	AMD (total)				AMD (wet)				AMD (dry)				Control			Measure
	n	Mean	SD	*P*-value	n	Mean	SD	*P*-value	n	Mean	SD	*P*-value	n	Mean	SD	
Woo[12]	170	24.97	3.30	<0.001	107	24.5	0.26	<0.001	17	23.42	0.62	<0.001	190	25.99	2.79	MMSE
Rozzini[21]	51	26.8	3.2	0.050	31	27.2	2.8	0.081	20	26.2	3.6	0.011	24	28.3	1.3	MMSE
Peiretti[22]	136	27.8	1.5	0.721									38	27.7	1.6	MMSE
Mandas[23]	119	20.9	6.3	0.008									730	22.5	6.0	MMSE
Al-Salem[6]	138	3.68	1.61	<0.001	56	3.95	1.65	0.001	82	3.5	1.59	<0.001	91	4.63	0.85	Mini-Cog test
Demirci[7]	59	24.3	3.88	0.002	45	25.46	2.80	0.071	14	20.71	4.71	<0.001	49	26.59	3.16	MMSE
Demirci[7]	59	13.7	5.50	0.21	45	14.84	5.20	0.845	14	10.14	5.03	0.005	49	15.06	5.66	Animal fluency
Kelly[24]	121	15.5	4.0	<0.001									105	21.6	5.8	Animal fluency
Woo[12]	170	83.49	78.10	0.001	107	96.34	5.35	<0.001	17	135.03	13.09	<0.001	190	64.83	37.61	TMT-A
Rozzini[21]	51	78.4	57.4	0.09	31	80.4	66.4	0.154	20	74.8	37.2	0.104	24	60	20.9	TMT-A
Woo[12]	170	201.22	86.09	0.002	107	222.59	7.39	<0.001	17	213.98	18.04	0.291	190	192.84	81.93	TMT-B
Rozzini[21]	51	131.9	72.5	0.92	31	130.9	88.4	0.856	20	133.7	32.9	0.600	24	127.3	44.9	TMT-B

Abbreviations: AMD, age-related macular degeneration; MMSE, mini-mental state examination; SD, standard deviation; TMT, trail making test.

The results of meta-analysis are shown in Table 3. It shows AMD (dry) patients had lower MMSE scores (SMD=–1.12, 95% CI –1.59 to –0.64, Z=4.59, P<0.001), lower Mini-Cog scores (SMD=–0.90, 95% CI –1.21 to –0.59, Z=5.63, P<0.001), and lower animal fluency scores (SMD=–0.89, 95% CI –1.50 to –0.27, Z=2.84, P=0.005) than controls, while differences in the TMT-A (SMD=1.23, 95% CI –0.18 to 2.63, Z=1.71, P=0.087)and TMT-B (SMD=0.22, 95% CI –0.16 to 0.61, Z=1.15, P=0.250) test were not statistically significant.

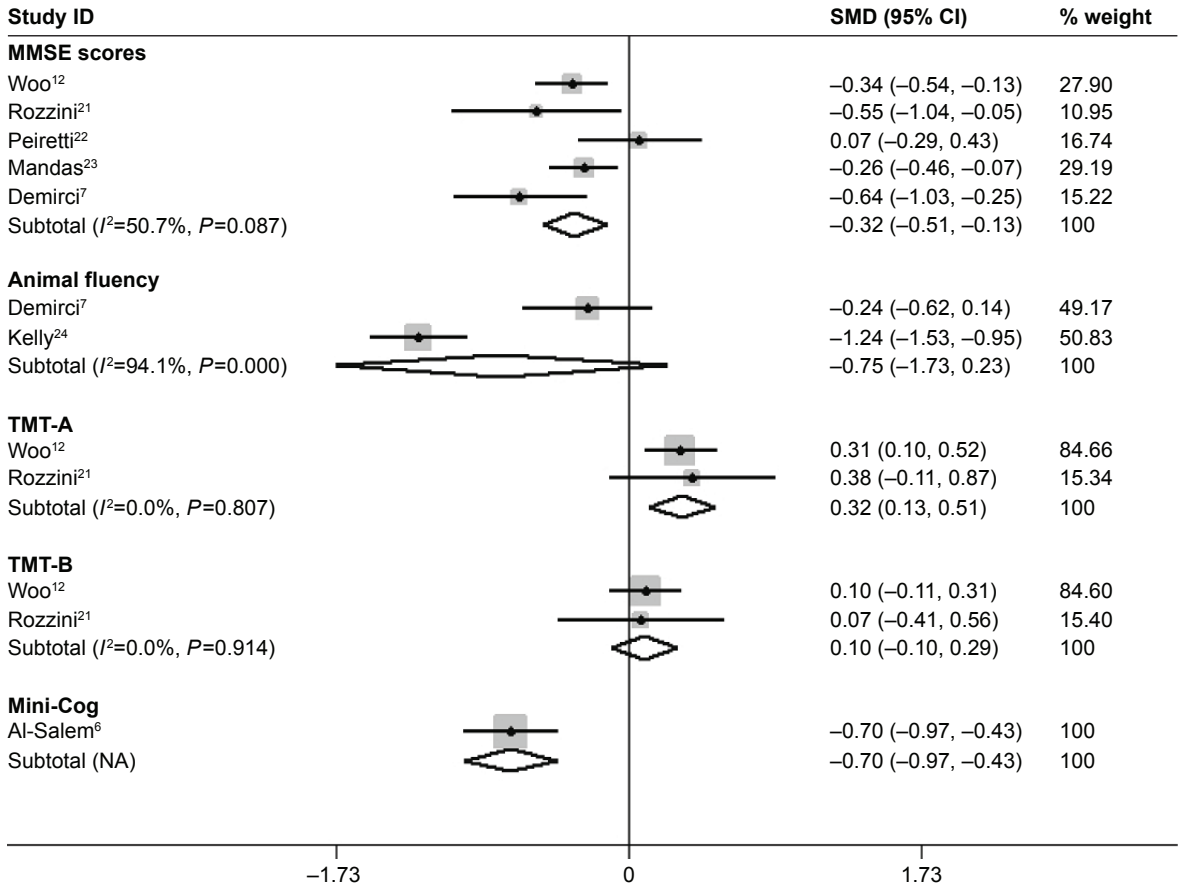

Figure 2 Meta-analysis of the cognitive function in AMD patients and controls by MMSE, Animal fluency, Mini-Cog, TMT-A and -B.
Note: Weights are from random-effects analysis.
Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; NA, not applicable; SMD, standard mean difference; TMT, trail making test.

Table 3 Stratified analyses according to AMD subtype and different tests

Subgroups	Number of studies	SMD (95% CI)	Meta-analyses		Heterogeneity	
			Z	*P*-value	I^2 (%)	*P*-value
AMD (total)						
MMSE	5	−0.32 (−0.51, −0.13)	3.28	0.001	50.7	0.087
Animal fluency	2	−0.75 (−1.73, 0.23)	1.51	0.132	94.1	<0.001
TMT-A	2	0.32 (0.13, 0.51)	3.27	0.001	0	0.807
TMT-B	2	0.10 (−0.10, 0.29)	0.98	0.326	0	0.914
Mini-Cog	1	−0.70 (−0.97, −0.43)	5.03	<0.001	0	1
AMD (wet)						
MMSE	3	−0.58 (−0.77, −0.38)	5.80	<0.001	0	0.463
Animal fluency	1	−0.04 (−0.45, 0.36)	0.20	0.845	0	1
TMT-A	2	0.76 (0.13, 1.39)	2.38	0.017	78.1	0.033
TMT-B	2	0.32 (−0.04, 0.69)	1.73	0.084	45.3	0.176
Mini-Cog	1	−0.56 (−0.90, −0.22)	3.23	0.001	0	1
AMD (dry)						
MMSE	3	−1.12 (−1.59, −0.64)	4.59	<0.001	48.6	0.143
Animal fluency	1	−0.89 (−1.50, −0.27)	2.84	0.005	0	1
TMT-A	2	1.23 (−0.18, 2.63)	1.71	0.087	91.8	<0.001
TMT-B	2	0.22 (−0.16, 0.61)	1.15	0.250	0	0.785
Mini-Cog	1	−0.90 (−1.21, −0.59)	5.63	<0.001	0	1

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; SMD, standard mean difference; TMT, trail making test.

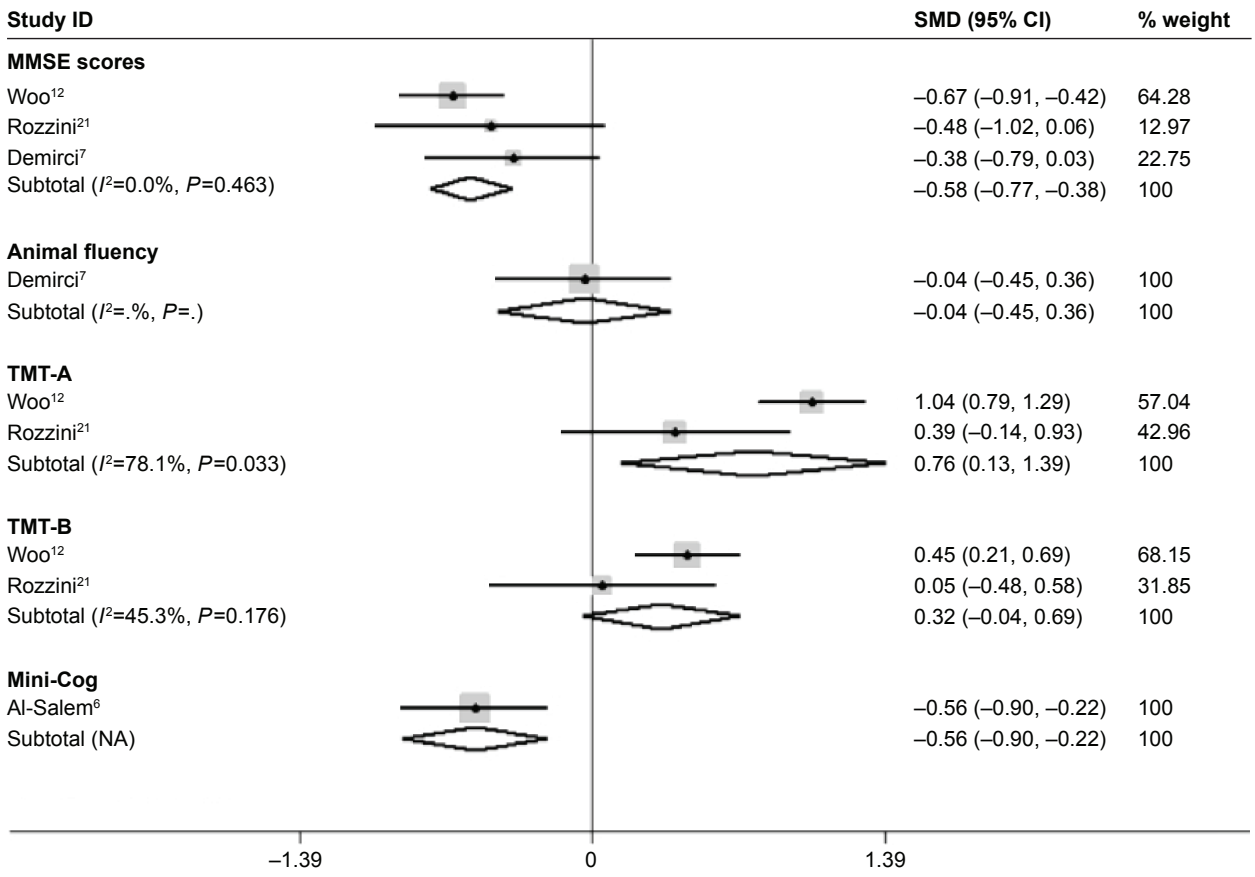

Figure 3 Meta-analysis of the cognitive function in wet-AMD patients and controls by MMSE, Animal fluency, Mini-Cog, TMT-A and -B.
Note: Weights are from random-effects analysis.
Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; NA, not applicable; SMD, standard mean difference; TMT, trail making test.

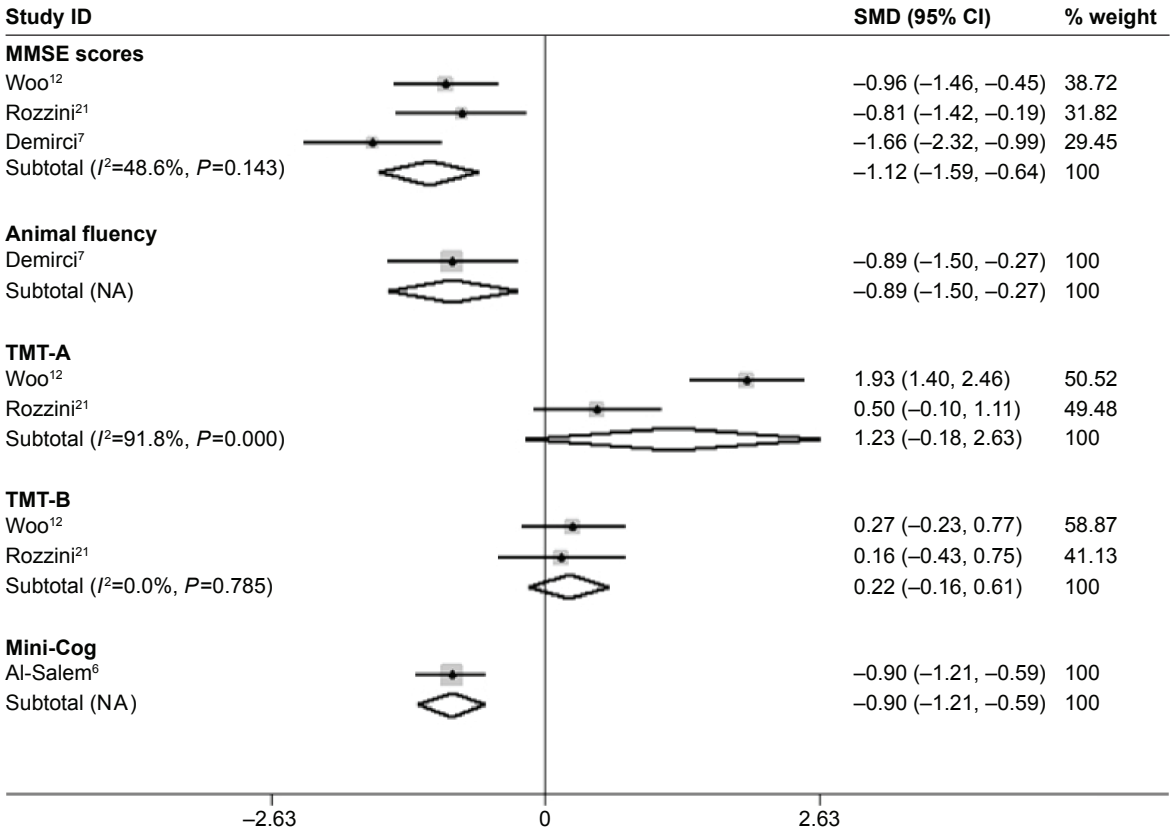

Figure 4 Meta-analysis of the cognitive function in dry-AMD patients and controls by MMSE, Animal fluency, Mini-Cog, TMT-A and -B.
Note: Weights are from random-effects analysis.
Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; MMSE, mini-mental state examination; NA, not applicable; SMD, standard mean difference; TMT, trail making test.

Sensitivity analyses of the included studies for the cognitive function in patients with AMD

The sensitivity analysis results suggest that no single study influenced the overall pooled estimates (Figure 5).

Discussion

In the present analysis, we confirmed that patients with AMD have lower cognitive function test scores and showed that MMSE and TMT test have positive significance in cognitive function assessment. Consistent with the hypothesis

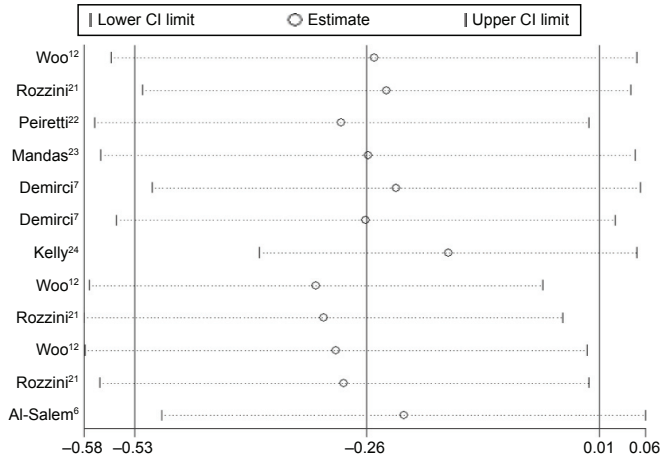

Figure 5 Sensitivity analysis of the included studies for the cognitive function in patients with AMD.
Abbreviations: AMD, age-related macular degeneration; CI, confidence interval.

that patients with sensory dysfunction, vision[11] or hearing impairment, are more likely to have a cognitive impairment and dementia than age-matched people with normal vision and hearing, we showed AMD may be a significant factor for cognitive impairment.

Although the sensitivity of the MMSE is approximately 49%–63%, it is widely used to screen for dementia because of its high specificity. It is also the common examination used in most of the included studies. According to the realistic diversity of different countries, there are different versions. Therefore, Woo et al[12] from Korea used a Korean version for global cognition examination. The boundary value of MMSE screening has been highly controversial, for example, 17,[13] 21,[14] and 24.[13] The differences of age and education year may be the main source of heterogeneity. Of course, the controls' selection and ethnicity may also contribute to the heterogeneity. In spite of the difference of baseline characters listed, the heterogeneity is acceptable (I^2=50.7% in total AMD, 0% in wet-AMD and 48.6% in dry-AMD). Irrespective of the sample size, AMD patients, either wet or dry subtypes, have lower MMSE scores compared with controls, taking into account its high specificity.

Compared with global cognition that MMSE indicated, the AFT mainly represents semantic long-term memory[15] and may suggests neurodegeneration in the frontotemporal lobe.[16] It has a statistically significant correlation with education level, primordial intelligence, current global cognitive and memory function, while having a weak association with age and sex of subjects. In this meta-analysis, only the patients with dry AMD showed a statistically significant difference with the controls (one study).[7] More research is needed to explore the significance of AFT in patients with AMD.

TMT is one of the most popular neuropsychological tests. It provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions.[17] TMT-A and -B reflect the function of the right and left brain hemispheres, respectively. The present meta-analysis shows the different outcomes between TMT-A and -B. Whether poor performance on the TMT-A is caused by longstanding visual deterioration is unclear and should be determined in the future.

Compared with other dementia screening tests, the Mini-Cog test is unique with its acceptable sensitivity of 53.7% and a high specificity of 95.5%.[18] As a replacement test tool of MMSE, the Mini-Cog test has similar sensitivity and specificity, whereas its biggest advantage is that it is a simple test.[19] In addition, the Mini-Cog test is not affected by language or education years.[20] The study performed by Al-Salem and Schaal[6] also showed the same conclusion compared with MMSE scores in our meta-analysis.

As the first meta-analysis on cognitive impairment in patients with AMD, our study has some limitations. First, this meta-analysis included only seven studies. In addition, the meta-analysis is a retrospective study that may lead to subject selection bias. Importantly, the inclusion criteria of cases and controls were not always well defined in the included studies. Diagnostic criteria of AMD are not clear at present, especially the early diagnosis. Considering that not all cognitive function tests are influenced by age factor, we did not take age as an inclusion criterion even though most included studies with subjects over the age of 65 years.

In summary, this meta-analysis suggests lower cognitive function test scores in patients with AMD, especially with MMSE and Mini-Cog test. Other cognitive impairment screening tests, such as AFT and TMT, need more studies to assess. However, due to limitations mentioned above, more studies are still necessary to confirm these findings.

Disclosure

The authors report no conflicts of interest in this work.

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