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A summary of the evidence and evaluation of the effectiveness of nonpharmacological interventions for mild cognitive impairment†

Original article

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Abstract: **Objective:** To summarize and evaluate the evidence of guidelines and systematic reviews (SRs) of nonpharmacological interventions for mild cognitive impairment (MCI) to support the development of future guidelines and clinical decisions for MCI patients.
Methods: Scottish Intercollegiate Guideline Network (SIGN), National Institute for Health and Clinical Excellence (NICE), American Academy of Neurology (AAN), Registered Nurses Association of Ontario (RNAO), Web of Science, PubMed, Cochrane Library, CNAHL, VIP, China National Knowledge Infrastructure (CNKI), and Wanfang Database were searched for relevant publications, including guidelines and SRs, from January 2014 to March 2019. Two authors independently screened articles, extracted data, and assessed the publications for adherence to the inclusion criteria. Appraisal of Guidelines for Research and Evaluation (AGREE II) was used to assess the quality of the guidelines, and Assessment of Multiple Systematic Reviews (AMSTAR 2) was used to assess the quality of SRs. In addition, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to evaluate the quality of outcomes.
Results: Thirty-two articles were retrieved, including 1 guideline and 31 SRs. Fourteen SRs of physical exercise for MCI, six articles describing cognitive interventions, four articles describing acupuncture, and seven articles assessing dietary interventions (including four articles employing a Mediterranean diet, one article using vitamin B supplementation, and two articles assessing the effects of tea, coffee, and caffeine) were included. The quality of the articles was very low for 4 (13%), low for 10 (32%), and moderate for 17 (55%).
Conclusions: Based on the evidence available to date, nonpharmacological interventions may improve the current cognitive function of persons with MCI. In particular, physical exercise, cognitive interventions, and acupuncture exerted promising effects. However, due to the limited number and quality of the included publications, additional high-quality reviews are needed to further confirm.

Keywords: *nonpharmacological intervention • mild cognitive impairment • systematic review methodology • evidence evaluation • evidence synthesis*

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1. Introduction

Mild cognitive impairment (MCI), an intermediate stage between normal cognitive aging and dementia, is defined as a cognitive decline greater than expected for a person's age and education level that does not significantly interfere with activities in daily life.[1] The prevalence of MCI has gradually increased over time. The prevalence of MCI is 6.7% for individuals aged 60–64 years and 25.2% for individuals aged 80–84 years, and MCI patients present a significantly greater risk of developing Alzheimer's diseasae (AD). The cumulative incidence of dementia is 14.9% in MCI patients aged greater than 65 years who were followed for 2 years.[2] Additionally, MCI potentially poses a significant burden to individuals, families, and society.[3] Therefore, early interventions and early prevention of the disease are particularly essential. However, the updated guidelines for MCI[2] did not identify high-quality evidence supporting the administration of pharmacological treatments for MCI. In addition, pharmacological interventions may produce adverse side effects.[4]

Thus, more recent researches increasingly have focused on nonpharmacological interventions, such as physical exercise, cognitive interventions, dietary interventions, and among others. An increasing number of systematic reviews (SRs) has indicated that nonpharmacological interventions may be a viable alternative for MCI patient by potentially maintaining cognitive function and reducing dementia risk. However, due to the quality of both the SRs and their studies and diverse methodologies, the quality of evidence supporting these recommendations for improvements on cognitive functions is low and should be improved. Thus, this review is to obtain, summarize, and evaluate the high-level evidence, and hope that this summary is useful to support the development of future guidelines and clinical decisions. A summary of the evidence should follow the "6S" model of evidence, starting from the highest level of evidence. Therefore, this review focuses on summarizing and appraising the results and methodological quality of nonpharmacological interventions that have emerged from the relevant guidelines, SRs, and meta-analyses.

2. Methods

2.1. Inclusion and exclusion criteria

The inclusion criteria were guidelines including nonpharmacological interventions for MCI and SRs examining (1) patients who were diagnosed with MCI (no limitations on diagnostic criteria); (2) nonpharmacological interventions defined as nondrug, focused, and replicable interventions conducted with the patient that potentially improve some domains of cognitive impairment. In this evidence summary, we considered nonpharmacological interventions that were classified into the following four categories: physical exercise, cognitive intervention, nonpharmacological interventions using traditional Chinese medicine, and dietary interventions; and (3) studies reporting the following outcomes were considered for inclusion: the cognitive symptoms of individuals with MCI were rated using a variety of neuropsychological measures. Hence, we recorded measurement scales according to the following domains: (1) global cognition (e.g., Mini-Mental State Examination [MMSE], Alzheimer's Disease Assessment Scale-cognition sub-scale [ADAS-cog], Montreal Cognitive Assessment [MOCA]); (2) executive function; (3) working memory; (4) attention; (5) immediate and delayed memory; and (6) orientation. We excluded studies that did not provide measures for any of the outcomes mentioned above, and duplicate publications were also excluded.

2.2. Search strategy

We searched PubMed, National Institute for Health and Clinical Excellence (NICE), Scottish Intercollegiate Guideline Network (SIGN), American Academy of Neurology (AAN), and Registered Nurses Association of Ontario (RNAO) for guidelines published from January 2014 to March 2019 to identify relevant publications on this topic.

We also searched China National Knowledge Infrastructure (CNKI), VIP, Wanfang Database, Cochrane Library, Web of Science, PubMed, and CINAHL for SRs and meta-analyses published from January 2014 to March 2019. According to the PICO framework, the following keywords were used: "cognitive dysfunction", "mild cognitive impairment*", "mild cognitive disorder", "mild cognitive decline", "MCI", "MCD", "meta-analysis*", "systematic review*", and "meta-analysis and systematic review". We used the following Medical Subjects Headings and free-text words to search the aforementioned databases. In addition, reference sections of the retrieved reviews were also searched. The complete PubMed search strategy is presented in additional Figure 1.

#1. "Cognitive Dysfunction"[Mesh]

#2. ((((“mild cognitive impairment*” [Title/Abstract]) OR “mild cognitive disorder” [Title/Abstract]) OR “mild cognitive decline” [Title/Abstract]) OR MCI[Title/Abstract]) OR MCD[Title/Abstract]

#3. #1 OR #2

#4. "Meta-Analysis" [Publication Type] OR "Meta-Analysis as Topic"[Mesh]

#5. ((“meta-analysis*” [Title/Abstract]) OR “systematic review*” [Title/Abstract]) OR (“meta-analysis [Title/Abstract] AND systematic review” [Title/Abstract])

#6. #4 OR #5

#7. #3 AND #6

Figure 1. Complete PubMed search strategy.

2.3. Study selection and data extraction

All reviews identified in the search were independently assessed by two researchers (first and third authors). When eligibility was unclear, disagreements were resolved by a third reviewer, who approved the final list of included studies. For reviews that fulfilled the inclusion criteria, data were independently extracted from each included review in duplicate, including authors' names, publication year, sample, patients, intervention, comparison, outcomes, and study characteristics.

2.4. Quality appraisal

We used the updated Appraisal of Guidelines for Research and Evaluation (AGREE II)[5,6] assessing the methodological quality of each guideline using which consists of 23 key items organized within 6 domains, to assess the quality of guidelines. Each of the AGREE II items and the two global rating items are rated on a 7-point scale (1—strongly disagree to 7—strongly agree).

We used the Assessment of Multiple Systematic Reviews (AMSTAR 2) tool, to assess the methodological quality of each SR, a 16-item checklist that is widely used to evaluate the methodological quality of quantitative SRs, 6 of which are key items. The evaluation results are divided into high, medium, low, and very low quality.[7]

In addition, we assessed the overall quality of the evidence[8,9] using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which included risk of bias (RoB), consistency, accuracy, indirectness, and risk of publication bias. The evidence level was divided into four grades: high, moderate, low, and very low.

3. Results

3.1. Search outcome

Our search identified one clinical practice guideline (CPG) describing a nonpharmacological intervention for MCI,[2] and the basic characteristics of this guideline are shown in Table 1.

In addition, the search strategy identified 1,600 studies in electronic databases. Five hundred and eleven duplicate records were excluded. After assessing the titles and abstracts, 1,044 SRs were omitted, as they did not meet the criteria of the reviews according to the PICO framework. After reviewing the full-text, another 14 SRs were excluded. Finally, 31 SRs were analyzed in this evidence summary. The PRISMA flow diagram for included reviews is presented in Figure 2. Fourteen SRs of physical exercise for MCI were included, six SRs describing cognitive interventions, four SRs analyzing acupuncture, and seven SRs describing dietary interventions (including four articles examining a Mediterranean diet, one article examining vitamin B supplementation, and two articles describing the effects of tea, coffee, and caffeine).

3.2. Summary and description of the guideline

The 2017 updated AAN guideline[2] for MCI included various nonpharmacological interventions, such as

Study	Nation	Development organization	Published, updated times	Guideline type	References	Recommendation	Grade
AAN, 2017[2]	America	American Academy of Neurology	2017 (update)	clinical practice guideline	103	In patients with MCI, treatment with exercise training for 6 months is likely to improve cognitive function[10,11]	moderate confidence
						There is insufficient evidence to support or refute the use of any individual cognitive intervention [12]	very low confidence
						When various cognitive interventions are considered as a group, for patients with MCI, cognitive interventions may improve select measures of cognitive function [12]	low confidence
						In patients with MCI, there is insufficient evidence to support or refute the use of homocysteine lowering therapies in patients with MCI [13]	very low confidence
						In patients with MCI, use of vitamin E 2,000 IU daily is possibly ineffective for reducing progression to AD [14]	low confidence
						In patients with MCI, combined use of oral vitamin E 300 mg and vitamin C 400 mg daily over 12 months is of uncertain efficacy [15]	very low confidence

Table 1. Basic characteristics of the included guideline.

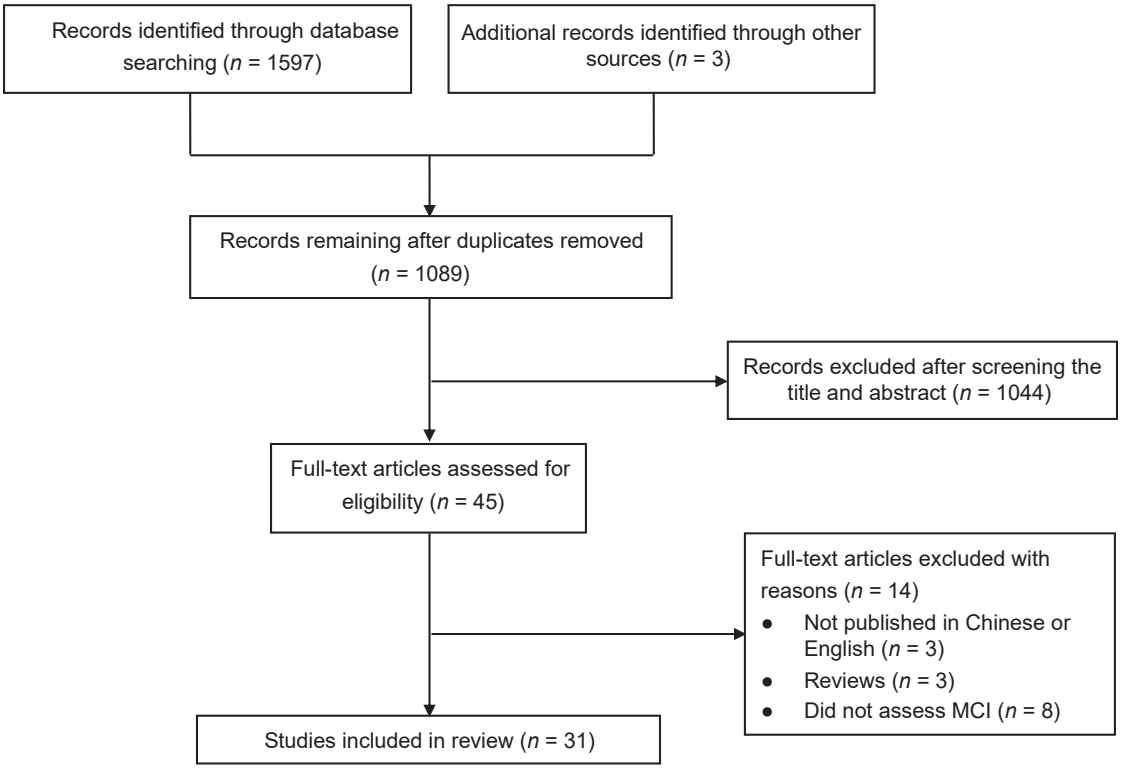


Figure 2. PRISMA flow diagram for included reviews.

cognitive intervention, dietary interventions, and physical exercise, among others. The major recommendations are described as follows: (1) clinicians should recommend regular exercise twice a week (Level B) and encourage patients to engage in meaningful, interesting activities and regular exercise; [10,11] (2) clinicians may recommend cognitive training (Level C); [12] (3) using vitamin E 2,000 IU/day might be ineffective for reducing AD risk (low confidence) and combine use of 300 mg of oral vitamin E and 400 mg of vitamin C daily for 12 months has an uncertain efficacy (very low confidence).[13–15]

We used the AGREE II to independently evaluate this guideline in duplicate (ICC>0.9). The total quality of this CPG was good. For this guideline, the appraisers assigned the highest scores to the clarity (72.2%), followed by the scope and purpose (66.70%), editorial independence (62.50%), and participation (53.30%).

3.3. SRs and meta-analyses

3.3.1. Physical exercise

3.3.1.1. Characteristics of included reviews

Table 2 presents the characteristics of the 14 SRs[16–29] of exercise interventions and included data from 455 to 117,410 participants. All SRs were published in English. One SR was published in 2019, three in 2018, four in 2017, two in 2016, two in 2015 and two in 2014. Most SRs included randomized controlled trials (RCTs) and only two SRs[23,24] included prospective cohort studies. The studies examined various, diverse intervention types. In the case of Tai Chi, aerobic exercise, and walking were the most commonly used interventions. The average duration of the intervention was 30–90 min/session in 1–5 sessions/week for 3–12 months.

3.3.1.2. Methodological quality of the included reviews

The results of the assessment of the methodological quality of the SRs of exercise interventions are presented in Table 3. Eleven of the remaining SRs[16–21,24,25,27–29] were of moderate quality, two SRs[22,23] were considered low quality, and one SR[26] was considered very low quality.

Commonly unreported items were the presence of an a priori design (*n*=11, 78.6%), an explanation of the method used to select the study designs for inclusion in the review (*n*=14, 100%), the lack of a comprehensive literature search strategy and the inclusion of grey literature (*n*=6, 42.9%), and the provision of a list

Articles	Study (sample size)	Research design type	Intervention group/ (exposure section)	Intervention frequency/ time	Control group (unexposed group)	Outcome	Main conclusions
Wang et al. 2019[16]	18 (1364)	RCT	aerobic exercise, resistance exercise, mind-body exercise	30-90 min/time; 1-5 times/ week; 6-12 weeks	health education/ placebo	MMSE, MoCA, ADAS-Cog	Four exercise types all had significant benefits compared to the control, and resistance exercises outperformed mind-body exercises.
Loprinzi et al. 2019[17]	6 (355)	RCT	exercise intervention	30-50 min/time; 2-4 times/ week; 2-6 months	regular exercise	short term memory, long term memory	Exercise may help to improve MCI memory function
Song et al. 2018[18]	13 (956)	RCT	aerobic exercise, resistance exercise, multi-mode exercise	30-60 min/time; 1-4 times/ week; 3-12 months	regular exercise/ placebo	global cognitive function, memory (short term memory, long term memory), executive function	Physical exercise can improve global cognitive function, but there was no significant effect on short-term memory, long-term memory, executive function
Lam et al. 2018[19]	43 (3988)	RCT	aerobic exercise (slow walking)	60 min/time; 2-3 times/ week	regular exercise	physical functions (BMI/strength/ flexibility/stride/balance, walking endurance)	Aerobic exercise can improve physical function (strength/flexibility/stride/balance)
Barreto et al. 2018[20]	5 (2878)	RCT	aerobics, Tai Chi	12/24 months	regular exercise	MMSE	Exercise intervention could not improve MCI cognitive function and reduce the risk of MCI
Cammisuli et al. 2017[21]	9 (768)	RCT	aerobic exercise (slow walking, handball)	30-60 min; 2-4 times/ week; 6-26 weeks	regular exercise/ placebo	global cognitive function (MMSE, ADAS-Cog, MoCA)	Aerobic exercise can improve MCI cognitive function
Zheng et al. 2017[22]	3 (455)	RCT	Tai Chi	24 style of Tai Chi (30 min, 3 times/week), Yang style of Tai Chi (60 min, 2 times/ week), Dao style of Tai Chi (90 min, 2 times/week)	regular exercise	memory	Tai chi can improve MCI cognitive function
Guure et al. 2017[23]	45 (117410)	prospective study	physical exercise	more than once a week	——	——	Physical exercise has positive benefits for improving MCI and AD
Quan et al. 2016[24]	17 (24089)	prospective study	slow walking	——	——	——	Slow walking can improve cognitive function
Zheng et al. 2016[25]	11 (1497)	RCT	aerobic exercises (Tai Chi, walking, jogging)	30-90 min/day; 1-5 times/ week; 3-12 months	regular exercise	global cognitive function (MMSE, ADAS-Cog, MoCA), attention, executive function, memory (short- term, long- term memory)	Aerobic exercise can improve MMSE, MoCA, short-term memory and long-term memory, has no significant effect on ADAS-cog, attention and executive function
Cai and Abrahamson 2015[26]	13 (1171)	RCT	aerobic exercise (walking, Tai Chi)	10 weeks-6/12 months	regular exercise	global cognitive function (MMSE, ADAS-Cog), attention, execution and memory function	Aerobic exercise has an ameliorative effect on MMSE, memory, endurance, attention and executive function
Ströhle et al. 2015[27]	5 (22689)	RCT	western medicine + exercise therapy	6-12 months	western medicine + regular exercise/ western medicine treatment	global cognitive function (ADAS-Cog, MMSE)	Exercise interventions can improve MCI cognitive function
Wang et al. 2014[28]	9 (795)	RCT	aerobic exercise (Tai Chi, walking, stretching)	6 weeks-12 months	regular exercise	global cognitive function (ADAS-Cog, MMSE) attention, executive function, memory (short-term, long-term memory)	Exercise interventions can improve MCI cognitive function
Öhman et al. 2014[29]	22 (1699)	RCT	physical exercise, walking	6 weeks-12 months	regular exercise/ blank control	global cognitive function, executive function, long-term memory, attention	Exercise interventions can improve MCI global cognitive function, executive function, long-term memory and attention

Table 2. Summary of the characteristics of systematic reviews (SRs) assessing exercise interventions and detailed characteristics obtained from the full data abstraction.

AMSTAR 2	Wang et al. 2019[16]	Loprinzi et al. 2019[17]	Song et al. 2018[18]	Lam et al. 2017[9]	Barreto et al. 2018[20]	Cammisuli et al. 2017[21]	Zheng et al. 2017[22]	Guure et al. 2017[23]	Quan et al. 2016[24]	Zheng et al. 2016[25]	Cai and Abrahamson 2015 [26]	Ströhle et al. 2015[27]	Wang et al. 2014[28]	Öhman et al. 2014[29]
Q1	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Q2	×	×	×	×	√	×	×	×	×	√	×	√	×	×
Q3	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Q4	√	≠	≠	√	√	√	≠	≠	≠	√	√	√	≠	√
Q5	√	√	√	√	√	√	√	√	√	√	×	√	√	√
Q6	√	√	√	×	√	√	√	√	√	√	×	√	√	√
Q7	√	√	√	√	×	√	×	×	√	√	√	√	√	√
Q8	√	√	√	√	√	√	√	×	√	√	√	√	√	√
Q9	√	√	√	√	√	√	×	√	√	√	×	√	√	√
Q10	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Q11	√	√	√	√	——	——	——	——	√	√	——	√	√	——
Q12	√	√	√	√	——	——	——	——	×	√	——	√	√	——
Q13	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Q14	√	×	√	√	√	√	√	√	√	√	√	√	√	√
Q15	√	√	√	√	——	——	——	——	√	√	——	√	√	——
Q16	√	√	×	√	√	√	×	√	√	√	×	√	√	√
Systematically evaluate the overall quality level	moderate	moderate	moderate	moderate	moderate	moderate	low	low	moderate	moderate	very low	moderate	moderate	moderate

Note: √: yes; ×: no; ≠: partly.

Table 3. Assessment of the methodological quality of systematic reviews (SRs) of exercise interventions.

of excluded studies and justification for the exclusions (*n*=11, 78.6%). Notably, 21.4% reviews did not report any potential sources of conflicts of interest. In addition, six SRs used narrative reviews to describe their findings, whereas eight reviews used meta-analysis methods.

3.3.1.3. Efficacy and benefits

(1) Global cognitive function

Five SRs[16,18,22,27,28] analyzed the effect of physical exercise on cognitive function in MCI patients, as measured using the ADAS-Cog, MMSE, and MoCA. According to three SRs,[18,27,28] aerobic exercise can improve global cognitive function significantly than controls (GRADE: moderate, moderate, and high). In another SR[22] showed that aerobic exercise can significantly increase MoCA scores and MMSE scores, but it did not significantly influence ADAS-Cog scores (GRADE: low, low, and very low). One SR[16] revealed significant beneficial effects of aerobic exercises (*n*=5), mind–body exercises (*n*=7), and resistance exercises (*n*=4) on improving global cognition in MCI patients compared to controls (GRADE: moderate, very low, and low).

(2) Executive ability

Three SRs[18,22,28] analyzed the effects of aerobic exercise on executive ability in MCI patients, and aerobic exercise exerted a significant effect on improving verbal fluency test (VFT) scores compared with controls (GRADE: very low, low, and moderate). One SR[20] did not observe an effect of aerobic exercise on improving TMT scores (GRADE: moderate).

(3) Memory

Three SRs[18,22,28] analyzed the effects of aerobic exercise on memory in MCI patients. Three SRs all included a subgroup analysis, and only one SR[22] showed that aerobic exercise group can significantly improve MCI patients immediate recall and delayed recall ability compared with controls (GRADE: low and low). However, the other two SRs[18,28] did not observe an effect of aerobic exercise on improving immediate recall and delayed recall abilities (GRADE: moderate, moderate, low, and low).

3.3.1.4. GRADE assessment

Nineteen evidences of eight SRs of physical exercise were evaluated according to the GRADE system for the quality of evidence. One of them was high quality, seven of them were moderate quality, eight of them were low quality, and three of them were very low quality, which was downgraded due to the RoB, inconsistencies, and imprecision.

3.3.2. Cognitive intervention

3.3.2.1. Characteristics of included reviews

Table 4 presents the characteristics of the six SRs[30–35] of cognitive intervention. Across the studies, the sample size varied considerably, ranging from 224 participants to 2,177 participants; the average sample size was 945 participants. One SR was published in 2019, one in 2018, two in 2017, and two in 2016. All SRs included RCTs, four SRs[30,31,33,35] used meta-analysis methods, whereas two SRs[32,34] describe their findings by narrative reviews.

3.3.2.2. Methodological quality of the included reviews

The results of the assessment of the methodological quality of the SRs of cognitive intervention are presented in Table 5. Six SRs[30–35] evaluated the efficacy of cognitive interventions, and the SRs were rated as having moderate (*n*=2),[34,35] low (*n*=2),[32,33] and very low quality (*n*=2).[30,31]

None of the SRs reported funding sources for the studies included in the SRs, and the results of industry-funded studies may occasionally favor sponsored products. Only two SRs employed an a priori design. Two SRs used narrative reviews to describe their findings and four SRs used meta-analysis. Commonly unreported items were an explanation of the methods used to select the study designs included in the review (*n*=6, 100%). Three reviews did not assess RoB when interpreting and discussing the results of their reviews.

3.3.2.3. Efficacy and benefits

(1) Global cognitive function

Four SRs[30–32,35] analyzed the effect of cognitive training on cognitive function in MCI patients. One SR[32] showed little effect of memory training on improving global cognitive ability compared with controls, but the other three SRs[30,31,35] reported a moderately significant effect of computerized cognitive training on improving cognitive function among MCI patients (GRADE: very low, very low, and low).

(2) Memory

Four SRs[31–33,35] analyzed the effect of cognitive interventions on memory in MCI patients. Two SRs[32,35] revealed moderate and statistically significant effects of cognitive interventions on working memory. Only one SR[31] described a significant improvement in the delayed recall ability of participants who received

Articles	Study (sample size)	Intervention groups	Control groups	Time	Frequency	Outcome	Main conclusions
Wang 2019[30]	21 (1470)	cognitive Intervention	blank controls/ conventional therapy	——	——	MoCA	Cognitive intervention can effectively improve MCI cognitive function
Zhao et al. 2018[31]	11 (1069)	cognitive training	conventional health education	4-48 weeks	——	MMSE, ADL, MoCA	Cognitive training can effectively improve MCI cognitive function
Yang et al. 2017[32]	27 (2177)	memory training/ rehabilitation is conducted individually or in groups	blank controls/ conventional therapy	4-9 weeks	30-120 min/ time, 3-36 times (70%≤10 times)	learning, memory function, immediate response, delayed response, overall cognitive function	Memory training has medium to high benefits for learning, memory, subjective memory, moderate benefits for delayed response and global cognitive function, low benefit for immediate reaction and no obvious effect for recognition
Le et al. 2017[33]	13 (692)	conventional therapy + + computerized cognitive function training	conventional therapy + conventional cognitive function training	3-12weeks	30-45 min/time, 5-7 times/week	immediate effects, different cognitive domains (memory, orientation, attention)	Short-term computerized cognitive training can improve patients' cognitive function; computerized cognitive function training was better than control group in terms of directional ability and attention improvement in different cognitive domains
Chandler et al. 2016[34]	6 (224)	computerized cognitive function training	conventional therapy / conventional cognitive function training	2-36 weeks an average of 25.5 h (6-130h)	——	memory function	Computerized cognitive training could not improve MCI memory function.
Hill et al. 2016[35]	17 (686)	computerized cognitive training	blank controls/ conventional therapy	4h +	——	global cognition, verbal fluency, working memory, attention	Computer cognitive function training can improve MCI patients' global cognition, and it has significant effects on different cognitive domains (language learning, language memory, working memory, attention)

Table 4. A summary of the characteristics of SRs analyzing cognitive interventions and detailed characteristics obtained from the full data abstraction.

mnemonic training compared with controls (GRADE: moderate). However, another SR[33] did not observe an effect of computer cognitive training on improving memory (GRADE: very low).

(3) Attention

Three SRs[31,33,35] evaluated the efficacy of cognitive training on attention and showed that cognitive training exerted a statistically significant effect on the attention capacity compared with controls (GRADE: low, moderate, and moderate).

(4) Orientation

Two SRs evaluated the efficacy of cognitive training on orientation. One SR[31] reported a statistically significant effect of cognitive training on orientation compared with controls (GRADE: moderate). However, another SR[33] did not observe an effect of cognitive training (GRADE: very low).

3.3.2.4. GRADE assessment

Ten evidences of four SRs of cognitive intervention were evaluated according to the GRADE system for the quality of evidence. Four of them were moderate quality, two of them were low quality, and four of them were very low quality, which was downgraded due to the RoB of the included literatures, inconsistencies, and imprecision of the treatment effect.

3.3.3. Nonpharmacological interventions using traditional Chinese medicine

3.3.3.1. Characteristics of the studies

Table 6 presents the characteristics of the four SRs[36–39] of nonpharmacological interventions using traditional Chinese medicine. The effects of acupuncture were only reported in, and the most recent search included studies published throughout 2016.[36] The SRs included data from 5 to 18 primary prevention trials with 565 to 1,095 participants. All four SRs performed a meta-analysis and reported safety.

3.3.3.2. Methodological quality of the included reviews

The results of the assessment of the methodological quality of the SRs of nonpharmacological interventions using traditional Chinese medicine are presented in Table 7. Only one SR[36] was considered moderate quality and three SRs[37–39] were considered low quality.

None of the SRs reported funding sources for the studies included in the SRs (*n*=4, 100%), the presence of an a priori design (*n*=4, 100%), an explanation of the method used to select the study designs included in the review (*n*=0, 0%), duplication of selected studies

AMSTAR 2	Wang 2019[30]	Zhao et al. 2018[31]	Yang et al. 2017[32]	Le et al. 2017[33]	Chandler et al. 2016[34]	Hill et al. 2016[35]
Q1	√	√	√	√	√	√
Q2	×	×	×	×	√	√
Q3	×	×	×	×	×	×
Q4	≠	≠	√	√	≠	√
Q5	√	√	√	√	√	√
Q6	√	√	√	√	√	√
Q7	√	√	√	√	√	√
Q8	≠	√	√	√	√	√
Q9	√	√	√	√	√	√
Q10	×	×	×	×	×	×
Q11	√	×	——	√	——	√
Q12	×	×	——	×	——	√
Q13	×	×	√	×	√	√
Q14	×	×	√	√	√	√
Q15	×	×	——	√	——	√
Q16	×	×	×	×	√	√
Systematically evaluate the overall quality level	very low	very low	low	low	moderate	moderate

Note: √: yes; ×: no; ≠: partly.

Table 5. Assessment of the methodological quality of systematic reviews (SRs) examining cognitive interventions.

(*n*=1, 25%), and three reviews did not assess RoB when interpreting and discussing the results of their reviews (*n*=3, 75%). Additionally, two studies failed to report any potential sources of conflicts of interest (*n*=2, 50%).

3.3.3.3. Efficacy and benefits

(1) MMSE

Three of four SRs[36,37,39] compared the efficacy of Western medicine alone and acupuncture combined with Western medicine on MMSE scores, and showed a significant difference in MMSE scores. The combination of acupuncture combined with Western medicine produced a statistically significant decrease in cognitive decline (GRADE: very low, low, and low). In addition, one SR reported a significant effect on the outcome of MMSE scores between the two study groups that received acupuncture and acupuncture combined with aricept[39] (GRADE: moderate). Two SRs[36,38] revealed a better MMSE score for patients who received acupuncture treatment for MCI than patients who received nimodipine alone (GRADE: moderate and low), as cognitive function was improved to some extent.

(2) MoCA

Only one SR[38] showed an increase in the MoCA score for patients who received acupuncture at multiple sites on the head combined with cognitive training for MCI compared with patients subjected to cognitive training alone (GRADE: low). Importantly, cognitive function was improved to some extent.

3.3.3.4. Safety and adverse effects

All four SRs[37–39] provided detailed descriptions of adverse events. The adverse events of acupuncture may include fainting during treatment, errhysis at the needle sites, and minor hematoma due to a shorter time of applying local pressure at the acupoint, but these adverse effects did not impact the treatment for MCI. Meanwhile, the adverse events of nimodipine therapy may include gastrointestinal reactions and mild headache.

3.3.3.5. GRADE assessment

Seven evidences of four SRs of nonpharmacological interventions using traditional Chinese medicine were evaluated according to the GRADE system for the quality of evidence. Two of them were moderate quality, four of them were low quality, and one of them was very low quality, which was downgraded due to the RoB of the included literatures, inconsistencies, and imprecision of the treatment effect.

Articles	Study (sample size)	Intervention	Control	Treatment time	Frequency	Key findings	Safety
Deng and Wang 2017[36]	5 (568)	Acupuncture	Nimodipine	8 weeks	30 min/time 3 times/week	MMSE (3RCT): MD=0.99, [0.71-1.28], $P<0.01$ Picture cognition (2RCT): MD=2.12, [1.48-2.75], $P<0.01$	3 RCT reported the safety of acupuncture, 2 RCT adverse reactions may occur in the area of acupuncture, 1 RCT may appear megrim; another 1 RCT mention of gastrointestinal reactions and minor headaches in the nimodipine group
		Acupuncture + Nimodipine	Nimodipine	8 weeks	30 min/time 3 times/week	MMSE (2RCT): MD=1.09, [0.29-1.89], $P<0.01$	
Shuai et al. 2016[37]	18 (1095)	Acupuncture + medicine (Nimodipine, Duxil, Donepezil, Aniracetam)	Single medication (Nimodipine, Duxil, Donepezil, Aniracetam)	4-24 weeks	30-50 min/time 4-6 times/week	MMSE (12RCT): MD= 1.73, [1.28-2.18], $P<0.00001$ ADL (6RCT): MD =5.63, [4.40-6.87], $P<0.001$	4 RCT reported security, 3 RCT mentioned bleeding reaction, 1RCT mention that intervention group and control group all vomiting
Mai and Zheng 2015[38]	5 (565)	electric scalp acupuncture	Nimodipine	8 weeks	30 min/time 6 times/week	MMSE (3RCT): MD=1.33, [0.85-1.82], $P<0.0001$	3 RCT mention causing headaches dizziness, bleeding, motion sickness, Subcutaneous ecchymosis, 1 RCT report no reaction, 1RCT unreported
		cluster needling of scalp acupuncture + cognitive training	cognitive training	8 weeks	30 min/time 6 times/week	MoCA (2RCT): MD=2.12, [0.78-3.47], $P=0.0002$	
Hu et al. 2014[39]	14 (1052)	Acupuncture + Nimodipine	Nimodipine	8-9weeks	30 min/ time 3-4 times/week	MMSE (6RCT): MD=1.19, [0.67-1.70], $P<0.00001$	5/14 RCT reported security, there were 240 cases in the acupuncture group, reported a total of 6 cases of fainting during acupunctures ecchymosis and 3 cases of fainting during acupuncture
		Acupuncture + Aricept	Aricept	4-6weeks	30 min/time 6 times/week	MMSE (2RCT): MD=0.70, [0.24-1.17], $P=0.003$	

Table 6. A summary of the characteristics of systematic reviews (SRs) of acupuncture and detailed characteristics derived from the full data abstraction.

3.3.4. Dietary interventions

3.3.4.1. Characteristics of included reviews

Table 8 presents the characteristics of the seven SRs[40–46] of dietary interventions, and included data from 900 to 84,481 participants. Of these SRs, four examined Mediterranean diets; one analyzed vitamin B supplementation; and two assessed tea, coffee, and caffeine. One SR was published in 2017, two in 2016, two in 2015, and two in 2014. Only one SR explicitly included RCTs, three SRs[40,42,46] explicitly included cohort studies, two SRs[41,44] included both cohort studies and longitudinal studies, and one SR[43] included case–control studies, longitudinal and cross-sectional. Four SRs[40,42,45,46] used meta-analysis methods, whereas three SRs[41,43,44] describe their findings by narrative reviews.

3.3.4.2. Methodological quality of the included reviews

The results of the assessment of the methodological quality of the SRs of dietary interventions are presented in Table 9. Three SRs[40,45,46] were considered to have moderate quality and majority of the included SRs[41–44] were of low and very low quality.

Commonly unreported items were an explanation of the methods used to select the study designs included in the review (*n*=7, 100%), reporting conflicts of interest of included studies (*n*=7, 100%), the presence of an a priori study design (*n*=6, 86%), the lack of a comprehensive literature search strategy and the inclusion of grey literature (*n*=4, 71%), duplication of selected studies or data extraction (*n*=2, 29%), and a satisfactory technique for assessing the RoB was not appropriately performed in four reviews (57%).

3.3.4.3. Efficacy and benefits

(1) Cognitive effects of vitamin B supplementation on patients with MCI

Only one SR[45] analyzed the effects of multivitamin B supplements on people with MCI, and the results showed that had moderate beneficial on memory. However, no significant differences in general cognitive function, executive function, and attention were observed (GRADE: low, moderate, moderate, and low).

(2) Cognitive effects of a Mediterranean diet on patients with MCI

A Mediterranean diet is characterized by the consumption of large amounts of vegetables, fruit, cereals, legumes, and unsaturated fatty acids, small amounts saturated fatty acids and meat, small-to-moderate amounts of dairy products, moderate-to-large amounts of fish and regular but moderate consumption of

AMSTAR 2	Deng and Wang 2017[36]	Shuai et al. 2016[37]	Mai and Zheng 2015[38]	Hu et al. 2014[39]
Q1	√	√	√	√
Q2	×	×	×	×
Q3	×	×	×	×
Q4	√	≠	≠	√
Q5	√	×	×	×
Q6	√	√	√	√
Q7	√	√	√	√
Q8	√	√	√	√
Q9	√	√	√	√
Q10	×	×	×	×
Q11	√	√	√	√
Q12	×	×	×	×
Q13	√	×	×	×
Q14	√	√	√	√
Q15	√	√	√	√
Q16	√	√	×	×
Systematically evaluate the overall quality level	moderate	low	low	low

Note: √: yes; ×: no; ≠: partly.

Table 7. Assessment of the methodological quality of systematic reviews (SRs) evaluating acupuncture.

Articles	Study (sample size)	Exposure group/ intervention group	Unexposed group/ control group	Design	Results
Wu and Sun 2017[40]	9 (34168)	Mediterranean diet	unexposed group	cohort studies	High adherence to the Mediterranean diet can delay cognitive function decline, reduce the risk of AD
Hardman et al. 2016[41]	18 (59928)	Mediterranean diet	unexposed group	cohort, longitudinal studies, RCT	High adherence towards Mediterranean diet can delay cognitive decline and reduce the risk of AD
Liu et al. 2016[42]	11 (29155)	coffee	unexposed group	cohort studies	Moderate coffee intake can delay cognitive decline and reduce the risk of MCI/AD
Panza et al. 2015[43]	28 (56384)	coffee	unexposed group	cross-sectional, longitudinal studies, case control	Moderate coffee intake can delay cognitive decline and reduce the risk of MCI/AD
Van de Rest et al. 2015[44]	26 (84481)	Mediterranean diet	unexposed group	cross-sectional longitudinal studies, RCT	Higher adherence towards Mediterranean diet can delay cognitive decline and reduce the risk of AD
Li et al. 2014[45]	5 (900)	Vitamin B	placebo	RCT	Vitamin B intake had no significant effect on MCI global cognitive function, executive function and attention
Singh et al. 2014[46]	5 (3636)	Mediterranean diet	unexposed group	Cohort studies	Higher adherence towards Mediterranean diet can delay cognitive decline and reduce the risk of AD

Table 8. A summary of the characteristics of systematic reviews (SRs) analyzing dietary interventions and detailed characteristics obtained from the full data abstraction.

alcohol.[40,41] At present, some articles have reported a positive effect of a Mediterranean diet on MCI.

One SR[40] included nine articles, and follow-up period ranged from 2.2 to 12 years. The Mediterranean diet score (category of high vs. low) was significantly associated with the incident risk of cognitive disorders (GRADE: moderate). However, the Mediterranean diet score (category of median vs. low) was not significantly associated with the risk of developing cognitive disorders (GRADE: low). In

AMSTAR 2	Wu and Sun 2017[40]	Hardman et al. 2016[41]	Liu et al. 2016[42]	Panza et al. 2015[43]	Van de Rest et al. 2015[44]	Li et al. 2014[45]	Singh et al. 2014[46]
Q1	√	√	√	√	√	√	√
Q2	×	×	×	×	×	×	√
Q3	×	×	×	×	×	×	×
Q4	≠	√	≠	≠	≠	≠	√
Q5	√	×	√	×	√	√	√
Q6	√	×	√	×	√	√	√
Q7	√	≠	√	√	√	√	√
Q8	√	√	√	√	√	√	√
Q9	√	×	×	×	×	√	√
Q10	×	×	×	×	×	×	×
Q11	√	—	√	—	—	√	√
Q12	√	—	√	—	—	√	√
Q13	√	√	√	×	√	√	√
Q14	√	√	√	×	√	√	√
Q15	√	—	√	—	—	√	√
Q16	√	√	×	√	√	√	√
Systematically evaluate the overall quality level	moderate	low	low	very low	low	moderate	moderate

Note: √: yes; ×: no; ≠: partly.

Table 9. Assessment of the methodological quality of systematic reviews (SRs) evaluating dietary interventions.

addition, there was no significant linear association between the Mediterranean diet and the incident risk of all types of cognitive disorders[41]. Singh B[46] and colleagues reported that highest MeDi tertile had a 33% lower risk of cognitive impairment than the lowest MeDi score tertile (GRADE: moderate). In addition, another SR[41] also revealed higher adherence to a Mediterranean diet can slower rate of cognitive decline and reduced conversion to Alzheimer's disease. The specific cognitive domains that improved as the MeDi score increased were memory, executive function, and visual constructs. Furthermore, another SRs[44] showed that better adherence to a Mediterranean diet can reduce cognitive decline.

(3) Cognitive effects of coffee, tea, and caffeine on patients with MCI

Eleven prospective studies, including 29,155 participants, were included in the SRs.[42] The dose–response analysis did not show an association between increased coffee intake and cognitive decline (GRADE: low) or cognitive impairment (GRADE: low). In addition, another SR[43] included some cross-sectional, case–control, and longitudinal population-based studies that evaluated the long-term effects on brain function and provided some evidence supporting protective effects of tea, coffee, and caffeine used on late-life cognitive impairment/decline, but the association lacked a distinct dose–response association.

3.3.4.4. GRADE assessment

Nine evidences of four SRs of dietary intervention were evaluated according to the GRADE system for the quality of evidence. Four of them had moderate quality and five of them had low quality. GRADE evidence from observational studies was initially described as low-quality evidence, and observational studies generally had not been upgraded due to lack the upgrade factors.

4. Discussion

This study evaluated and summarized the evidence from a guideline and many SRs of treatments for MCI patients using nonpharmacological interventions to provide the largest amount of data possible. However, some reviews exhibited a lack of inclusion of high-quality studies or SRs.

The updated guideline[22] for mild cognitive impairment (MCI) indicates that clinicians should recommend cognitive training (Level C) and regular exercise (Level B); however, several dietary interventions were not recommended by the guideline. In addition, although the evidence was not robust, the use of

Mediterranean diets may have some benefits, but the effects of tea, coffee, and caffeine remain unclear.

Many SRs of nonpharmacological interventions for changing (or at least maintaining) cognitive function have also been conducted; the impact of these changes on improving cognitive function and reducing the AD incidence has produced mixed results. An in-depth summary of the current SRs suggested that dietary interventions, physical exercise, and cognitive interventions are the most widely studied treatments. In general, nonpharmacological interventions for MCI are very important, some reviews showed that has a good effect and can be used as a supplementary treatment for MCI patients. Meanwhile, these findings were promising, but challenges remain.

High-quality SRs will likely provide less biased and relatively conclusive scientific evidence for clinical practice and health decision-making processes.[47] Therefore, ARs require strict control over the quality of reviews and methodology.[48]

The methodological quality of included SRs was generally low. The most common reason was a lack of reporting of funding source for the studies included in all of the reviews. The quality of some SRs may be limited by the presence of an a priori study design, which may lead to publication bias. Moreover, some SRs lack a comprehensive literature search strategy. In addition, because of the variability and heterogeneity of the intervention methods, and assessment tools, data consolidation is difficult. Generally, the author often cannot subgroup analysis, thus it is difficult to draw strong conclusions about the efficacy of these interventions. Actually, different outcomes were reported by researchers focusing on the same health problems. However, due to the lack of a unified standard intervention and complete outcome description, the data were difficult to merge. Furthermore, one of the other new items was the new supplementary items of AMSTAR 2 assessing whether review authors explained their methods for selecting the study designs included in the review, a very important component RCTs were defined as high-quality evidence. However, observational studies may be the only studies available to answer some questions, for example, determine ethical reasons. Therefore, the assessment of the effects of the Mediterranean diet was better analyzed using observational studies than an RCT. Thus, authors should justify the inclusion of different study designs in SRs.[7]

In addition, based on the conclusions of SRs, we assessed the quality of evidence for outcomes of the meta-analysis, which were downgraded due to (1) RoB: the included studies have major defects in randomization method, allocation concealment and blinding methods. For example, the randomization method is not sufficiently reported, the allocation concealment is unreported or blinding method is not mentioned; (2)imprecision: information included in the study sample size did not meet the optimal sample size (line to a rough estimate, for the dichotomous variable data, if the total number of events of the quality of evidence is less than 300; for the continuous variable data, if some evidence total sample is less than 400, are more likely to consider the inconformity to the OIS); (3) inconsistencies: confidence interval of the overlap between different review is small, heterogeneity of I^2 value is big, there are unexplained heterogeneity. Through analysis, the reason may be that different intervention duration and intervention implementation plan. The conclusion of the above factors can lead to system review have a quite difference with the real situation. Furthermore, among the studies we reviewed, MCI diagnostic criteria were not unified.

5. Conclusions

This review summarized and evaluated the evidence for treatment options utilizing nonpharmacological interventions in patients with MCI. To date, some physical exercise, acupuncture, Mediterranean diet, and cognitive training can significantly improve MCI cognitive function. However, the effects of coffee, tea, and caffeine remain unclear. In addition, due to the limited number and quality of the included publications, further research is necessary.

Strengths and limitations

This review was characterized by various strengths and limitations. Our summary has several strengths. First, we used a comprehensive search strategy to obtain, summarize, and evaluate the guideline, reviews, and meta-analysis of RCTs and cohort studies in order to confirm the effects of nonpharmacological interventions, which were also complemented and identified through other research sources. Second, we performed all title screening, data extraction, and quality assessments by two researchers, which minimized potential bias while preparing this summary.

By contrast, what we concerned most was the uneven quality of the included SRs. In addition, we did not search original publications, only limited to the information provided in guideline and SRs. Furthermore, due to the limitation of number, quality and methodology, there are few reviews performed a quantitative meta-analysis of the study results. Finally, we only searched English and Chinese languages journals, and other conference proceedings, trial registries, and dissertations were not included, which may lead to some literatures being missed. In the future, higher quality reviews are needed to further confirm the effects of specific intervening measures.

Ethical approval

Ethical issues are not involved in this paper.

Conflicts of interest

There is no conflict of interest to be declared.

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