

# Effect of exercise on cognitive function in chronic disease patients: a meta-analysis and systematic review of randomized controlled trials

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**Background:** The purpose of this study was to conduct a meta-analysis and systematic review to assess the effect of exercise on cognitive function in people with chronic diseases.

**Methods:** PubMed, Web of Science, Embase, the Cochrane Library, CINAHL, PsycINFO, and three Chinese databases were electronically searched for papers that were published until September 2016. This meta-analysis and systematic review included randomized controlled trials that evaluated the effect of exercise on cognitive function compared with control group for people with chronic diseases.

**Results:** Totally, 35 studies met the inclusion criteria, with 3,113 participants. The main analysis revealed a positive overall random effect of exercise intervention on cognitive function in patients with chronic diseases. The secondary analysis revealed that aerobic exercise interventions and aerobic included exercise interventions had a positive effect on cognition in patients with chronic diseases. The intervention offering low frequency had a positive effect on cognitive function in patients with chronic diseases. Finally, we found that interventions offered at both low exercise intensity and moderate exercise intensity had a positive effect on cognitive function in patients with chronic diseases. The secondary analysis also revealed that exercise interventions were beneficial in Alzheimer's disease patients when grouped by disease type.

**Conclusion:** This meta-analysis and systematic review suggests that exercise interventions positively influence cognitive function in patients with chronic diseases. Beneficial effect was independent of the type of disease, type of exercise, frequency, and the intensity of the exercise intervention.

**Keywords:** exercise, cognitive function, physical activity

## Abbreviations

ACE-R, Addenbrooke's Cognitive Examination-Revised; ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; AIDS, acquired immune deficiency syndrome; BCPT-cog, Breast Cancer Prevention Trial symptom checklist-cognitive problems scale; BDI-cog, Beck Depression Inventory-cognitive subscale; BDNF, brain-derived neurotrophic factor; BOPI-cog, Breast Cancer Prevention Trial Symptom Checklist-Cognitive Problems Scale; CDT, clock drawing test; CI, confidence interval; CINAHL, Cumulative Index to Nursing and Health Literature; CNKI, China National Knowledge Infrastructure; EORTC-cog, European Organization for Research and Treatment of Cancer-cognitive; ERFC, Rapid Evaluation of Cognitive Function; FAB, Frontal Assessment Battery; FACS, functional assessment of communication skills; HR<sub>max</sub>, maximum heart rate; MCI, mild cognitive impairment; IL, interleukin; MD, mean difference; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive

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Assessment; PFS-cog, Piper Fatigue Scale-cognitive; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLCT, six-letter cancellation test; SMD, standardized mean difference; TCD, total cognitive domain; TNF- $\alpha$ , tumor necrosis factor-alpha.

## Introduction

Chronic diseases are long-term conditions with slow disease progression and without an effective cure,<sup>1</sup> and 38 million people die from chronic diseases each year. In addition, 16 million of these deaths occur before the age of 70 years. Chronic diseases may lead to alteration in brain structure and function and are associated with cognitive change.<sup>2–5</sup> Some of these changes may be related to neurodegenerative diseases (such as Alzheimer's disease and other types of dementia), increased dementia incidence, and cognitive decline. Strategies are needed to reduce disease-related cognitive impairment in chronic disease patients.

Exercise, the aim of which is to improve or maintain physical fitness, is a subset of physical activity that is planned, structured, and flexible, in addition to promoting aerobic endurance.<sup>6</sup> Exercise is essential in maintaining physical function and physiological health. The results of animal studies have identified that engagement in physical activity may enhance neurotrophic factor levels,<sup>7,8</sup> neurogenesis,<sup>9,10</sup> and vascularization<sup>11</sup> and may even reduce aggregation of pathogenic proteins,<sup>12,13</sup> mediate neuroinflammation,<sup>13</sup> and inhibit neuronal dysfunction.<sup>14</sup> Exercise also appears to be associated with the maintenance of brain health and cognitive performance in cognitively normal older adults. Most experimental studies have identified increased lifetime physical activity to be associated with reduced risk of suffering from dementia in cognitively normal older persons.<sup>15–17</sup> The results of a meta-analysis of prospective studies on physical activity and the risk of cognitive decline, which included 15 prospective studies (12 cohorts) with 33,816 nondemented subjects followed for 1–12 years, showed that a total of 3,210 patients demonstrated cognitive decline during the follow-up period. The results of the cumulative analysis indicated that subjects who performed high levels of physical activity were significantly less likely to demonstrate cognitive decline during the follow-up period.<sup>18</sup>

The results of a meta-analysis of the effect of physical activity on cognitive function in patients with dementia suggested that physical activity interventions positively influenced cognitive function in patients with dementia.<sup>19</sup> The results of another meta-analysis of aerobic exercise implied that this practice promotes cognitive function in older adults

with mild cognitive impairment, finding that aerobic exercise was associated with an improvement in global cognitive ability.<sup>20</sup> However, a comprehensive evaluation of the effect of exercise interventions on cognitive function in chronic disease patients has not been conducted. We therefore conducted a meta-analysis and systematic review of randomized controlled trials investigating the effect of exercise intervention on cognitive outcomes in chronic disease patients.

## Methods

### Protocol and registration

The meta-analysis was conducted and reported in accordance with the PRISMA guidelines<sup>21</sup> to ensure comprehensive and transparent reporting of our methods and results.

### Search strategy

PubMed, Web of Science, Embase, the Cochrane Library, CINAHL, PsycINFO, and three Chinese databases (CNKI, WanFang Data, and VIP) were electronically searched for papers that were published until September 2016. The search strategy included various combinations of the terms “Cognition”, “Cognitive function”, and “MMSE”, with exercise intervention terms such as “Exercise” or “Muscle Stretching Exercises” or “Resistance Training” or “Running” or “Swimming” or “Walking” or “Cycling” or “Physical activity” or “Aerobic” or “Yoga” or “Tai Chi” or “Qigong”. Randomized controlled trials were specifically targeted using the following search terms: “Randomized controlled trial”, “Controlled clinical trial”, or “Randomized” or “Randomly” or “Trial” or “Group”. The search was limited to human studies.

### Eligibility criteria

#### Types of studies

Only randomized controlled trials were included in this review. No publication date restrictions were imposed on the initial search.

#### Types of participants

The participants were adults ( $\geq 18$  years) who had been diagnosed with a chronic disease (eg, arthritis, asthma, cancer, COPD, diabetes, heart disease, or AIDS).<sup>1</sup> Participants with mental problems were excluded.

#### Types of interventions

The inclusion criteria were as follows: 1) the intervention group underwent exercise intervention. When a study included two or more intervention groups that were found to be eligible criteria, we included all in the meta-analysis; 2) the control

group did not undergo any type of exercise intervention. However, studies in which exercise training was part of an intervention with multiple components (eg, combined with a drug intervention) were excluded.

### Types of outcomes

The studies were required to report global cognitive function as the outcome measure. Any studies reporting only the results for a specific cognition scale, including scales assessing memory, attention, language, verbal fluency, visuospatial ability, or executive ability, were excluded.

### Study selection

The study selection process is outlined in Figure 1. The eligibility assessment was performed by two independent reviewers in a standardized manner. All papers identified using the search strategy were assessed for eligibility, as indicated based on the previously defined inclusion criteria, by reviewing their titles and/or abstracts. If insufficient information was available to evaluate the inclusion or exclusion of an article, then a full-text version was obtained. Full-text versions of all the relevant studies were obtained and reviewed by two independent reviewers to ensure that the studies met the inclusion criteria. Disagreements were resolved by discussion with a third reviewer. When insufficient information or data were available in the included articles, the authors were contacted to obtain additional information if possible.

### Quality assessment

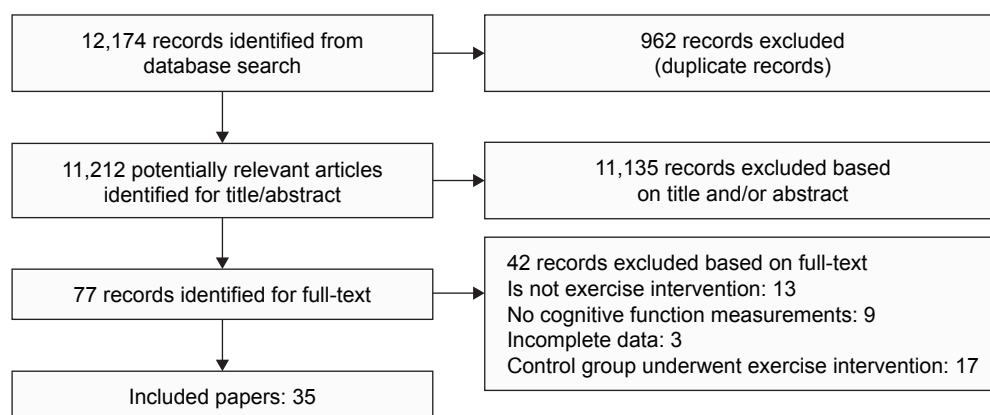
Two reviewers independently assessed the quality of all included studies, using the Downs and Black Quality Index. The scales are designed to assess the methodological quality of randomized studies of health care interventions<sup>22</sup> and include reporting, external validity, bias, confounding, and

power, and their maximum scores are 11, 3, 7, 6, and 5, respectively. The maximum possible total score is 32. Quality was then rated on a four-category scale: poor (<18), moderate (18–23), good (24–29), and excellent ( $\geq 30$ ).

### Data extraction and statistical analysis

Data were extracted from the included articles using a data extraction form (Table 1). Sample characteristics were collected, including the sample size, intervention and control group sizes, diagnoses, baseline MMSE scores, and age. Details on exercise interventions were collected, including intervention category, frequency, duration,  $HR_{max}$ , and exercise intensity. The effects of the exercise training interventions, including cognitive function measures and the study results, were extracted. One investigator performed the data extraction, which was checked by a second investigator.

The statistical analyses were performed using version 5.3 of the RevMan meta-analysis software. The intervention effect sizes for continuous variables were measured by determining the SMDs between the intervention and control groups with regard to the change observed between the baseline and follow-up cognitive scores and their corresponding 95% CI. According to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions*, published by Cochrane Collaboration and Wiley, the selection of fixed- or random-effects model is based on the underlying effect of the intervention.<sup>23</sup> Due to the expected heterogeneity across studies (eg, different intervention types and cognitive outcome measurements), we performed random-effects meta-analysis. Additionally, when the heterogeneity identified across studies was high, a subgroup analysis was performed to identify potential causes of heterogeneity, including exercise types, types of disease, exercise frequency, and intensity. Heterogeneity



**Figure 1** Flow diagram of literature search.

Table 1 Patient characteristics of included studies

First author (Year)	Sample characteristics			Intervention characteristics					Outcome			
	Total N	Intervention/ control, n	Diagnosis	Baseline MMSE	Age, years	Intervention category	Frequency, min/wk	Duration, weeks	HR <sub>max</sub>	Exercise intensity	Selected cognitive measurement	Conclusion
Arcoverde (2013) <sup>24</sup>	20	10/10	Alzheimer's disease	21.15	78.75	Aerobic	60	12	60%	Moderate	MMSE	Yes
	81	44/37	Cancer	Unknown	62	Aerobic	180	10	Unknown	Low	EORTC-cog	Yes
	55	28/27	Osteoarthritis knee	25.45	78.91	Aerobic	60–120	20	Unknown	Low	MMSE	No
Moore (2015) <sup>41</sup>	40	20/20	Stroke	28.5	69	Resistance	135–180	19	70%–80%	High	ACE-R	Yes
Derry (2015) <sup>29</sup>	200	100/100	Cancer	Unknown	51.6	Aerobic	90	12	Unknown	Low	BCPT-CPS	Yes
Varela (2011) <sup>51</sup>	32	17/15	MCI	20.77	78.3	Aerobic	90	12	40%	Low	MMSE	No
Varela (2011) <sup>51</sup>	30	15/15	MCI	21.29	77.9	Aerobic	90	12	60%	Moderate	MMSE	No
Hildreth (2015) <sup>33</sup>	53	26/27	MCI	28.7	64.5	Aerobic	180	18	50%–60%	Moderate	ADAS-cog	No
Lindsay (2014) <sup>40</sup>	168	47/121	Heart failure	Unknown	68.98	Aerobic	180	12	Unknown	Moderate	MMSE	No
Vadiraia (2009) <sup>49</sup>	88	44/44	Cancer	Unknown	47.5	Aerobic	180	6	Unknown	Low	EORTC-cog	Yes
Schmidt (2015) <sup>45</sup>	98	49/49	Cancer	Unknown	52.7	Resistance	120	12	Unknown	High	EORTC-cog	No
Gowans (2001) <sup>31</sup>	31	15/16	Fibromyalgia	Unknown	47.94	Aerobic	90	23	60%–75%	Moderate	BDI-cog	Yes
Kim (2005) <sup>35</sup>	35	18/17	Cancer	Unknown	33.58	Aerobic	210	6	Unknown	Low	PFS-cog	Yes
Ohman (2016) <sup>43</sup>	140	70/70	Alzheimer's disease	17.75	77.9	Combined	120	48	Unknown	Low	CDT	No
Ohman (2016) <sup>43</sup>	140	70/70	Alzheimer's disease	18.1	78.2	Combined	120	48	Unknown	Moderate	CDT	No
Cancela (2016) <sup>25</sup>	189	73/116	Alzheimer's disease	15.03	82.02	Aerobic	105	60	Unknown	Low	MMSE	Yes
Chattha (2008) <sup>26</sup>	120	59/61	Climacteric syndrome	Unknown	48.5	Aerobic	300	8	Unknown	Low	SLCT	Yes
Cheng (2014) <sup>27</sup>	74	39/35	Alzheimer's disease	18.79	81.38	Aerobic	180	12	Unknown	Low	MMSE	Yes
Christoforetti (2008) <sup>54</sup>	30	17/20	Alzheimer's disease	13.7	76.7	Resistance	180	24	Unknown	Moderate	MMSE	No
Cott (2002) <sup>28</sup>	56	30/26	Alzheimer's disease	5.8	82.5	Aerobic	150	16	Unknown	Low	FACS	No
Hashimoto (2015) <sup>32</sup>	38	19/19	Parkinson's disease	28.25	68.77	Aerobic	60	12	50%–70%	Moderate	FAB	Yes
Hashimoto (2015) <sup>32</sup>	40	21/19	Parkinson's disease	28.41	65.86	Resistance	60	12	50%–70%	Moderate	FAB	Yes
Holthoff (2015) <sup>34</sup>	30	15/15	Alzheimer's disease	20.6	72.4	Combined	90	12	Unknown	Moderate	MMSE	Yes
Lam (2015) <sup>37</sup>	278	147/131	MCI	25.7	75.45	Aerobic	180	48	Unknown	Low	MMSE	No
Lam (2012) <sup>57</sup>	261	171/218	MCI	24.5	77.82	Aerobic	90	48	Unknown	Low	MMSE	No
Lautenschlager (2011) <sup>38</sup>	170	85/85	MCI	Unknown	68.65	Combined	150	24	Unknown	Moderate	ADAS-cog	Yes
Lu (2016) <sup>39</sup>	46	23/23	MCI	26.82	69.73	Resistance	180	12	Unknown	Moderate	ADAS-cog	Yes
Miu (2008) <sup>30</sup>	85	36/49	Alzheimer's disease	18.9	76.66	Aerobic	120	12	Unknown	Moderate	MMSE	No
Nascimento (2014) <sup>58</sup>	37	20/17	MCI	Unknown	67.7	Aerobic	180	16	Unknown	Moderate	MoCA	Yes
Kwak (2008) <sup>56</sup>	30	15/15	Alzheimer's disease	14.0	81.0	Combined	40	48	40%–60%	Moderate	MMSE	Yes
Kemoun (2010) <sup>55</sup>	38	20/18	Alzheimer's disease	12.8	81.8	Aerobic	180	15	Unknown	Moderate	ERFC	Yes
Kim (2011) <sup>36</sup>	44	32/12	Metabolic syndrome	26.18	68.19	Aerobic	120	24	50%–80%	Moderate to high	TCD	No
Stevens (2016) <sup>46</sup>	54	24/30	Alzheimer's disease	Unknown	80.2	Aerobic	90	12	Unknown	Moderate	CDT	Yes
Suzuki (2013) <sup>47</sup>	100	50/50	MCI	26.55	75.3	Combined	180	24	60%	Moderate	MMSE	No
Suzuki (2012) <sup>48</sup>	50	25/25	MCI	26.7	76.05	Combined	180	48	60%	Moderate	MMSE	Yes
Van (2004) <sup>50</sup>	25	15/10	Alzheimer's disease	Unknown	81.65	Combined	210	12	Unknown	Moderate	MMSE	Yes
Vreugdenhil (2011) <sup>52</sup>	40	20/20	Alzheimer's disease	22.00	74.1	Combined	210	17.3	Unknown	Moderate	MMSE	Yes
Wei (2014) <sup>53</sup>	60	30/30	MCI	24.67	66	Aerobic	120	24	Unknown	Moderate	MMSE	Yes

**Abbreviations:** ACE-R, Addenbrooke's Cognitive Examination-Revised; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; BCPT-CPS, Breast Cancer Prevention Trial Symptom Checklist-Cognitive Problems Scale; BDI-cog, Beck Depression Inventory-cognitive; CDT, clock drawing test; EORTC-cog, European Organization for Research and Treatment of Cancer-cognitive; ERFC, Rapid Evaluation of Cognitive Function; FAB, Frontal Assessment Battery; FACS, functional assessment of communication skills; HR<sub>max</sub>, maximum heart rate; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PFS-cog, Piper Fatigue Scale-cognitive; SLCT, six-letter cancellation test; TCD, total cognitive domain.

was assessed using Higgins  $P$  values. The significance level was set at  $P < 0.05$ .

## Results

### Study search and selection

We identified 12,174 studies based on the database searches; 962 articles were excluded because of duplicate records. Based on title and abstract, we excluded 11,135 studies. The full-text papers of 77 studies were reviewed and 42 studies were excluded. These studies were excluded because they did not assess exercise interventions, reported incomplete data, their control group underwent an exercise intervention, or they did not report cognitive function as an outcome measurement. Finally, 35 studies with 3,113 participants were included in the final analysis (Figure 1).<sup>24–58</sup>

### Description of studies

The characteristics of the included articles are stated in Table 1. In the included studies, the sample size ranged from 20<sup>24</sup> to 278<sup>37</sup> participants. Thirteen studies examined the effect of exercise on cognitive function in patients with Alzheimer's disease.<sup>24,25,27,28,30,34,43,46,50,52,54–56</sup> Nine studies examined the effect of exercise on cognitive function in patients with mild cognitive impairment.<sup>33,37–39,47,48,53,57,58</sup> Five studies examined the effect of exercise on cognitive function in patients with cancer.<sup>29,35,42,45,49</sup> One study examined the effect of exercise on cognitive function in patients with Parkinson's disease.<sup>32</sup> One study examined the effect of exercise on cognitive function in patients with heart failure.<sup>40</sup> One study examined the effect of exercise on cognitive function in patients with stroke.<sup>41</sup> One study examined the effect of exercise on cognitive function in patients with metabolic syndrome.<sup>36</sup> One study examined the effect of exercise on cognitive function in patients with osteoarthritic knee.<sup>44</sup> And one study examined the effect of exercise on cognitive function in patients with fibromyalgia.<sup>31</sup> One study examined the effect of exercise on cognitive function in patients with climacteric syndrome.<sup>26</sup> The mean baseline MMSE ranged from 5.8<sup>28</sup> to 28.7,<sup>33</sup> excluding 11 studies that did not report baseline MMSE. The mean age ranged from 47.5 years<sup>49</sup> to 82.5 years.<sup>28</sup> The interventions were then divided into three exercise modes: aerobic, resistance, and a combination of aerobic and resistance, according to the American College of Sports Medicine.<sup>59</sup> The frequency of the exercise intervention varied from 40 min<sup>56</sup> to 300 min<sup>26</sup> per week. The duration of the total training period varied from 6 weeks<sup>35,49</sup> to 60 weeks.<sup>25</sup> Fitness level was divided into three modes: low, moderate, and high, according to the American College of Sports Medicine.<sup>60</sup>

Seventeen studies used the MMSE,<sup>24,25,27,30,34,37,40,44,47,48,50–54,56,57</sup> three studies used the ADAS-cog,<sup>33,38,39</sup> three studies used the EORTC questionnaire,<sup>42,45,49</sup> two studies used the CDT,<sup>43,46</sup> one study used the FAB,<sup>32</sup> one study used the ACE-R,<sup>41</sup> one study used the BOPI-cog,<sup>29</sup> one study used the BDI-cog,<sup>31</sup> one study used the PFS-cog,<sup>35</sup> one study used the FACS,<sup>28</sup> one study used the SLCT,<sup>26</sup> one study used the MoCA,<sup>58</sup> one study used the ERFC,<sup>55</sup> and one study used the TCD assessment tool.<sup>36</sup> These different tools were applied to evaluate the same cognitive domain within a study or between studies.

Among the included studies, three studies compared two intervention types with a control group (Table 1).<sup>32,43,51</sup>

### Quality assessment

Thirty-five studies were included in the quality assessment. The assessment of bias in each domain across the included studies is shown in Table 2. The quality of the majority of the studies was moderate, with a mean score of 22.05. Four studies were rated as of poor quality, 18 studies were deemed to be of moderate quality, and 13 studies were deemed to be of good quality.

### Main analysis: effects of exercise intervention on cognitive function

Thirty-five studies with 3,113 participants evaluated the effect of exercise on cognitive function in patients with chronic diseases.<sup>24–58</sup> The main analysis revealed a positive overall random effect of the exercise interventions on cognitive function in patients with chronic diseases (Table 3).

### Secondary analyses

#### Types of disease

Thirteen studies containing 958 participants examined the effect of exercise on cognitive function in patients with Alzheimer's disease.<sup>24,25,27,28,30,34,43,46,50,52,54–56</sup> We found positive overall random effect of exercise intervention on cognitive function in studies evaluating Alzheimer's disease patients. Nine studies containing 1,117 participants examined the effect of exercise on cognitive function in patients with MCI.<sup>33,37–39,47,48,51,53,57,58</sup> In these studies, the difference observed in postintervention cognitive function did not differ between the exercise group and the control group. Five studies containing 502 participants examined the effect of exercise on cognitive function in patients with cancer.<sup>29,35,42,45,49</sup> In these studies, the difference observed in postintervention cognitive function did not differ between the exercise group and the control group in cancer patients.



**Table 2** Quality of included studies

First author (year)	Reporting (11 points)	External validity (3 points)	Bias (7 points)	Confounding (6 points)	Power (5 points)	Total (32 points)	Quality as per cutoff described
Arcoverde (2013) <sup>24</sup>	10	3	6	3	5	27	Good
Oh (2012) <sup>42</sup>	10	3	5	3	5	26	Good
Tsai (2013) <sup>44</sup>	8	3	5	3	0	19	Moderate
Moore (2015) <sup>41</sup>	9	3	6	1	5	24	Good
Derry (2015) <sup>29</sup>	8	2	5	2	5	17	Poor
Varela (2011) <sup>51</sup>	8	3	5	3	0	19	Moderate
Hildreth (2015) <sup>33</sup>	8	2	5	4	0	16	Poor
Lindsay (2014) <sup>40</sup>	8	3	5	4	0	20	Moderate
Vadiraja (2009) <sup>49</sup>	10	2	5	4	0	21	Moderate
Schmidt (2015) <sup>45</sup>	9	3	5	4	0	21	Moderate
Gowans (2001) <sup>31</sup>	9	3	5	4	5	26	Good
Kim (2005) <sup>35</sup>	9	2	5	3	0	19	Moderate
Ohman (2016) <sup>43</sup>	9	2	5	5	0	21	Moderate
Cancela (2016) <sup>25</sup>	9	3	5	4	5	27	Good
Chattha (2008) <sup>26</sup>	9	3	5	3	5	25	Good
Cheng (2014) <sup>27</sup>	9	3	5	4	5	26	Good
Cott (2002) <sup>28</sup>	9	2	5	3	0	19	Moderate
Christofletti (2008) <sup>54</sup>	7	2	5	2	0	16	Poor
Hashimoto (2015) <sup>32</sup>	9	2	5	1	5	22	Moderate
Holthoff (2015) <sup>34</sup>	9	2	5	2	5	23	Moderate
Lam (2015) <sup>37</sup>	10	2	6	4	0	22	Moderate
Lam (2012) <sup>57</sup>	8	3	5	3	0	19	Moderate
Lautenschlager (2011) <sup>38</sup>	9	2	5	3	5	24	Good
Lu (2016) <sup>39</sup>	9	2	5	3	5	24	Good
Miu (2008) <sup>30</sup>	10	2	6	4	5	27	Good
Nascimento (2014) <sup>58</sup>	8	2	5	2	0	17	Poor
Kwak (2008) <sup>56</sup>	9	1	5	4	5	24	Moderate
Kemoun (2010) <sup>55</sup>	7	3	5	2	5	22	Moderate
Kim (2011) <sup>36</sup>	9	3	6	3	5	26	Good
Stevens (2016) <sup>46</sup>	8	2	5	3	0	18	Moderate
Suzuki (2013) <sup>47</sup>	9	2	5	4	0	20	Moderate
Suzuki (2012) <sup>48</sup>	9	2	5	4	5	25	Good
Van (2004) <sup>50</sup>	8	2	5	3	5	23	Moderate
Vreugdenhil (2011) <sup>52</sup>	9	3	5	4	5	26	Good
Wei (2014) <sup>53</sup>	7	2	5	2	5	21	Moderate

Three studies assessed the effect of exercise intervention on cognitive function in patients with osteoarthritic knee,<sup>44</sup> heart failure,<sup>40</sup> and metabolic syndrome.<sup>36</sup> In these studies, the difference observed in postintervention cognitive function did not differ between the exercise and control groups. Four studies evaluated the effect of exercise on cognitive function in patients with fibromyalgia,<sup>31</sup> stroke,<sup>41</sup> Parkinson's disease,<sup>32</sup> and climacteric syndrome,<sup>26</sup> and the results of these studies indicated that exercise had a positive effect on cognitive function.

### Types of exercise intervention

Twenty-three studies containing 2,120 participants examined the effect of aerobic exercise on cognitive function in patients with chronic disease.<sup>24–33,35–37,40,42,44,46,49,51,53,55,57,58</sup> Five studies containing 261 participants examined the effect of resistance exercise on cognitive function in patients

with chronic disease.<sup>32,39,41,45,54</sup> Eight studies containing 725 participants examined the effect of combined exercise on cognitive function in patients with chronic disease.<sup>34,38,43,47,48,50,52,56</sup> We identified an overall positive random effect for aerobic exercise interventions but not for resistance exercise interventions and combined exercise interventions. Twenty-seven studies containing 2,845 participants examined the effect of interventions including aerobic exercise (both combined exercise and aerobic exercise intervention) on cognitive function in patient with chronic disease.<sup>24–38,40,42–44,46–53,55–58</sup> We identified positive overall random effect for the included aerobic exercise interventions.

### Frequency of exercise intervention

According to the World Health Organization recommendations, a weekly schedule of 150 min exercise was used to distinguish between high- and low-frequency interventions.<sup>61</sup>

**Table 3** Meta-analysis of effect of exercise on cognitive function

Parameters	Included studies	N	P-value	I	Z	SMD (95% CI)
Main outcome	35	3,113	0.0007	74%	3.41	0.26 (0.11, 0.41)
<b>Types of disease</b>						
Alzheimer's disease	13	958	0.004	77%	2.88	0.42 (0.14, 0.71)
Mild cognitive impairment	9	1,117	0.21	77%	1.25	0.17 (−0.10, 0.44)
Cancer	5	502	0.66	86%	0.44	0.11 (−0.39, 0.61)
<b>Types of exercise intervention</b>						
Aerobic	23	2,120	0.0008	70%	3.34	0.29 (0.12, 0.47)
Resistance	5	261	0.69	73%	0.40	0.10 (−0.39, 0.59)
Combined	8	725	0.14	83%	1.46	0.29 (−0.10, 0.67)
Aerobic included	31	2,845	0.0005	75%	3.47	0.28 (0.12, 0.45)
<b>Frequency of exercise intervention</b>						
High frequency	18	1,494	0.07	83%	1.82	0.25 (−0.02, 0.52)
High frequency (excluded resistance)	16	1,450	0.02	82%	2.24	0.31 (0.04, 0.57)
Low frequency	16	1,547	0.0008	40%	2.67	0.19 (0.05, 0.33)
Low frequency (excluded resistance)	14	1,409	0.15	60%	1.43	0.13 (−0.05, 0.32)
<b>Intensity of exercise intervention</b>						
Low	13	1,609	0.03	77%	2.12	0.24 (0.02, 0.47)
Moderate	21	1,322	0.03	72%	2.13	0.24 (0.02, 0.46)
Moderate (excluded resistance)	19	1,199	0.008	76%	2.66	0.34 (0.09, 0.59)
High	2	138	0.30	0%	1.04	0.18 (−0.16, 0.51)

**Abbreviations:** CI, confidence interval; SMD, standardized mean difference.

Eighteen studies containing 1,494 participants examined the effect of high-frequency exercise intervention on cognitive function in patients with chronic disease.<sup>26–28,33,35,37–40,42,47–50,52,54,55,58</sup> Sixteen studies containing 1,547 participants examined the effect of low-frequency exercise intervention on cognitive function in patients with chronic disease.<sup>24,25,29–32,34,36,43–46,51,53,56,57</sup> We identified a positive overall random effect for low-frequency interventions but not for high-frequency interventions. Further investigations revealed that after the exclusion of resistance exercise interventions, the effect of low-frequency exercise interventions was not significant. Further investigations revealed that after the exclusion of resistance interventions, the effect of the high-frequency exercise interventions was significant. Moore et al<sup>41</sup> examined the effect of an intervention including 135–180 min of weekly exercise on cognitive function in patients with stroke and found that the exercise intervention did not have an effect on cognitive function.

### Intensity of exercise intervention

Thirteen studies containing 1,609 participants examined the effect of low-intensity exercise intervention on cognitive function in patients with chronic diseases.<sup>25–29,35,37,42–44,49,51,57</sup> Twenty-one studies containing 1,322 participants examined the effect of moderate-intensity exercise intervention on cognitive function in patients with chronic diseases.<sup>24,30–33,38–40,43,46–48,50–56,58</sup> Two studies containing 138 participants examined the effect of high-intensity exercise intervention

on cognitive function in patients with chronic diseases.<sup>41,45</sup> We found positive random effects for low-intensity and moderate-intensity exercise interventions but not for high-intensity exercise interventions. Further investigations revealed that after the exclusion of resistance interventions, the effect of moderate-intensity exercise intervention on the cognitive function was significant.

## Discussion

In this meta-analysis of randomized controlled trials, we identified a positive overall effect of exercise interventions on cognitive function in patients with chronic diseases. Aerobic exercise interventions were found to have a positive effect on cognitive function in patients with chronic disease. In addition, the effect of exercise on cognitive function was independent of the presence of Alzheimer's disease. Furthermore, we found that low-frequency exercise interventions had a positive effect on cognitive function in chronic disease patients. Finally, we observed positive effects of low-intensity and moderate-intensity exercise intervention on cognitive function in chronic disease patients.

In this meta-analysis and systematic review, we found that the exercise interventions were beneficial in the current sample of chronic disease patients. Exercise has been reported to cause physiological state changes that disrupt brain homeostasis.<sup>41</sup> The brain has been found to modify its resource allocation in response to these changes. Studies have suggested that maintenance of physical activity may

be associated with increased neural resources in some brain regions and reduced neural resources in other brain regions.<sup>47,58,62</sup> Exercise affects cognitive function by causing a significant reduction in the peripheral concentrations of IL-6 and TNF- $\alpha$ , as well as a significant increase in peripheral levels of BDNF in individuals with chronic diseases.<sup>58</sup> Exercise also leads to structural changes in the brain, such as increases in dendritic length and branching and hippocampal neurogenesis,<sup>62</sup> as well as maintains the atrophy levels of the whole brain cortex.<sup>47</sup>

Cognition is a complex term that includes various domains. Some studies have proposed relationships between specific exercise regimens and specific cognitive domains in chronic disease patients. Aerobic exercise has been reported to contribute to further beneficial effects on the memory domain.<sup>32,36,48</sup> The results of an animal study investigating the effects of 12 weeks of voluntary running on the restoration of place recognition memory in 20-month-old rats emphasized the unique synaptic effects of exercise on the aged brain and their specific relevance to the hippocampal-based system for place recognition memory.<sup>63</sup> Dancing involves paying attention to music and signals while envisaging the next movement, and these feature may help patients to perform better in the verbal fluency category.<sup>50</sup> Lu et al<sup>39</sup> found that variations in position changes and movement configurations during dumbbell-training sessions were associated with changes in the spatiotemporal orientation, selective attention, and executive control of participants.

The results of our study showed that aerobic exercise interventions had a positive effect on cognitive function. This result was consistent with the recommendations of the World Health Organization for a weekly minimum of 150 min of moderate-intensity aerobic or 75 min of vigorous-intensity aerobic activity with additional muscle-strengthening exercises.<sup>61</sup> Two meta-analyses of the effect of aerobic exercise on cognitive function found that aerobic exercise improved cognitive function.<sup>19,20</sup> These results were similar to the results of our study. Aerobic exercises improve the maximum oxygen uptake and increase and redistribute cerebral blood flow, enhance antioxidant action via repair enzymes and proinflammatory cytokines, as well as increase beta-amyloid degradation, levels of neurotrophic factors, neurogenesis, and angiogenesis.<sup>24,58</sup> In this meta-analysis, we did not find resistance exercises to have an effect on cognitive function in chronic disease patients, which may be due to the difficulties related to controlling for some methodological and sampling biases and the short follow-up periods.<sup>54</sup>

In this meta-analysis and systematic review, we found that exercise interventions were beneficial for cognitive function in Alzheimer's disease patients. The results of this study were similar to those of previous studies that reported that exercise has a positive effect on cognitive function in Alzheimer disease patients.<sup>19,64,65</sup> These trends may indicate that the practice of regular physical exercise might contribute to slower declines in cognitive function. In our study, the exercise interventions were not found to have a positive effect on cognitive function in patients with MCI. There may be insufficient evidence for an effect of exercise intervention on MCI patients. A meta-analysis and systematic review of the effect of aerobic exercise on cognitive function in older adults with MCI showed that aerobic exercise significantly improved global cognitive ability (MMSE scores: MD=0.98, 95% CI: 0.5–1.45;  $P<0.0001$ ).<sup>20</sup> The cited meta-analysis and systematic review evaluated interventions encompassing the practice of any aerobic exercises regardless of the style (eg, yoga, Tai Chi, or treadmill) for at least 4 weeks, with  $>1$  exercise session per week. In addition, the outcomes assessed included global cognitive ability and any specific domains of cognition assessed in the aforementioned meta-analysis. Our meta-analysis and systematic review was not restricted by type of exercise, and the outcome of interest was global cognitive function. In our study, the exercise intervention was not found to have a positive effect on cognitive function in patients with cancer. The studies that assessed the effects of exercise interventions on cognitive function in cancer patients all provided data for short-term interventions that did not exceed 12 weeks.

In this meta-analysis and systematic review, we found that low-frequency exercise intervention was beneficial in chronic disease patients. The studies providing low-frequency exercise intervention all exceeded 12 weeks' duration, and two studies even exceeded 48 weeks' duration.<sup>25,43</sup> The beneficial effect of low-frequency exercise on cognitive function may be associated with a good performance of the functional capacity.<sup>24</sup> Additionally, all the included studies of low-frequency exercise interventions were of good methodological quality.

The American College of Sports Medicine has suggested that moderate-intensity physical exercise may lead to significant changes in brain health and cognitive performance, with potential effects on a broad range of cognitive domains.<sup>66</sup> In this meta-analysis and systematic review, we found that both low-intensity and moderate-intensity exercise interventions appeared to be effective in improving cognitive function in chronic disease patients. Moderate-intensity exercise might



be an effective alternative to reduce the level of systemic inflammation and decrease cognitive decline.<sup>58</sup> Additionally, most of the studies evaluating moderate-intensity exercise were of good methodological quality. The included studies indicated that low-intensity exercise such as Tai Chi<sup>27,42,44</sup> or yoga<sup>29</sup> exerted positive effects on cognitive function. Patients involved in low-exercise intensity interventions demonstrated more notable changes in physical functioning, contributing to the positive effects observed in psychological well-being.<sup>42</sup> Lower levels of distress and fatigue may have contributed to the beneficial effects of low-intensity exercise interventions on cognitive function.<sup>29</sup>

## Limitations

This study had some limitations. First, the weekly duration of exercise intervention used in the included studies varied from 40 min to 300 min per week, and the overall duration of the exercise intervention used in the included studies varied from 6 weeks to 60 weeks. These differences may have affected the relationship observed between the specific types of exercise and improvements in the evaluated cognitive domains. Second, it was not possible to blind participants to the exercise intervention. Therefore, performance bias may have been unavoidable.

## Conclusion

The findings of this meta-analysis support the efficacy of exercise interventions in improving cognitive function in individuals affected by chronic disease. Beneficial effects were observed independent of the type of clinical disease, type of exercise, frequency, and intensity of the exercise intervention.

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## Disclosure

The authors report no conflicts of interest in this work.

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