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The Impact of Tai Chi on Cognitive Performance in Older Adults: A Systematic Review and Meta-Analysis

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Abstract

OBJECTIVES—Summarize and critically evaluate research on the effects of Tai Chi on cognitive function in older adults.

DESIGN—Systematic review with meta-analysis.

SETTING—Community and residential care.

PARTICIPANTS—Individuals aged 60 and over (with the exception of one study) with and without cognitive impairment.

MEASUREMENTS—Cognitive ability using a variety of neuropsychological testing.

RESULTS—Twenty eligible studies with a total of 2,553 participants were identified that met inclusion criteria for the systematic review: 11 of the 20 eligible studies were randomized

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controlled trials (RCTs), 1 was a prospective non-randomized controlled study, 4 were prospective non-controlled observational studies, and 4 were cross-sectional studies. Overall quality of RCTs was modest, with 3 of 11 trials categorized as high risk of bias. Meta-analyses of outcomes related to executive function in RCTs of cognitively healthy adults indicated a large effect size when Tai Chi was compared to non-intervention controls (Hedge's $g=0.90$; $p=0.043$) and moderate effect size when compared to exercise controls (Hedge's $g=0.51$; $p=0.003$). Meta-analyses of outcomes related to global cognitive function in RCTs of cognitively impaired adults, ranging from mild cognitive impairment to dementia, showed smaller but statistically significant effects when Tai Chi was compared to both non-intervention controls (Hedge's $g=0.35$; $p=0.004$) and other active interventions (Hedge's $g=0.30$; $p=0.002$). Findings from non-randomized studies add further evidence that Tai Chi may positively impact these and other domains of cognitive function.

CONCLUSION—Tai Chi shows potential to enhance cognitive function in older adults, particularly in the realm of executive functioning and in those individuals without significant impairment. Larger and methodologically sound trials with longer follow-up periods are needed before more definitive conclusions can be drawn.

Keywords

Tai Chi; cognitive function; executive function; mind-body exercise

INTRODUCTION

Age-related cognitive decline is a burgeoning public health concern worldwide. In the United States alone, approximately 5.4 million people over age 70 have mild cognitive impairment (MCI) and an additional 3.4 million have dementia.¹ Between 2005 and 2009, the worldwide cost of dementia increased by ~34%.² The relative lack of pharmaceutical treatments to halt cognitive decline associated with aging has contributed to a growing interest in low-cost behavioral interventions for improving cognition.

The most well-researched behavioral intervention for cognitive functioning is physical activity.³ A recent meta-analysis of 16 prospective studies found that physical exercise reduced the relative risk of dementia by 28%.⁴ Hypothesized mechanisms for the cognitive benefits of physical exercise include direct effects on the brain, such as increased vasculature and production of neurotrophic factors, which may promote neuronal repair, neuronal growth, and plasticity.^{5,6} Physical exercise may also mitigate risk factors for cognitive decline such as cardiovascular disease. Other behavioral interventions have attempted to harness factors which have been shown to be protective against cognitive decline in epidemiological research such as: high educational achievement ('brain training' interventions), social engagement, and stress reduction interventions (meditation and relaxation).^{7,8} Recent reviews suggest that multimodal interventions that include more than one behavioral or lifestyle intervention may have greater likelihood of influencing neurobiological mechanisms underlying cognitive decline, compared to any one activity alone.⁹

Tai Chi is an increasingly popular multimodal mind-body exercise that incorporates physical, cognitive, social, and meditative components in the same activity.¹⁰ For both

conceptual and practical reasons, Tai Chi might be an effective intervention to slow cognitive decline in both healthy adults as well as in individuals with cognitive impairment. As a physical exercise, Tai Chi provides both moderate aerobic and agility/mobility training, which are each believed to impact cognitive function via unique neurophysiological pathways.¹¹ Tai Chi also involves the learning of choreographed movement patterns, which may support visuospatial processing, processing speed, and episodic memory. As a mind-body exercise, Tai Chi includes training in sustained attentional focus and multi-tasking. One hypothesis for age-related cognitive decline is that the brain's attentional control is reduced and information processing becomes less efficient. Meditation has been shown to impact attention and executive functions by increasing the brain's ability to allocate attentional resources.^{12,13} The meditative component of Tai Chi may have direct benefits on enhancing attention and executive functions; it may also improve cognition indirectly by mitigating the known effects of anxiety and depression on cognition through stress-related pathways.¹⁴ Engaging in Tai Chi in a group setting may have further benefits on cognition by enhancing mood and coping skills through social interactions and support. Because Tai Chi may impact cognitive function via a diverse and potentially synergistic set of mechanistic pathways, it is plausible that it may offer benefits superior to interventions that target only single pathways (e.g., aerobic training or stress reduction alone).

Prior studies support the potential of Tai Chi to attenuate age-related declines in cardiovascular disease,¹⁵ balance,¹⁶ and emotional well-being.¹⁴ Importantly, these studies also suggest that Tai Chi is safe for older adults and an enjoyable activity with the potential for long-term adherence and exercise maintenance. Individual studies have reported on cognitive outcomes in different populations, but to our knowledge, there has not been a comprehensive systematic review examining Tai Chi's impact on age-related cognitive decline in older adults. Our objective was to conduct a systematic review and meta-analysis of research examining Tai Chi as an intervention to attenuate age-related cognitive decline across the spectrum from normal cognition to dementia. Other than Tai Chi, there were no limitations concerning the type or number of comparison groups included in each study or any restrictions on study type or design.

METHODS

Literature search

Electronic literature searches were conducted using PubMed/MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (Embase), and the Cochrane Library from inception through March 2013. The search terms were tai chi, tai ji, tai chi chuan, memory, cognition, cognitive decline, and brain function. Hand searches were performed of retrieved articles for additional references.

Eligibility criteria

We included available randomized controlled trials (RCTs), prospective non-randomized controlled studies (PNRCS), prospective non-controlled observational studies (PNCS), and cross-sectional studies (CSS) published in English, where cognitive measures were examined as outcomes in relation to a Tai Chi intervention in both cognitively impaired and

unimpaired populations. Both because of the limited number of published RCTs to date and because this review is the first attempt to synthesize research evaluating Tai Chi for cognitive function, we have chosen to include a diverse set of study designs. To strike a balance between minimizing bias and being comprehensive, we restrict our meta-analytic methods to RCTs, and use tables and narrative methods to report on additional studies, as well as the degree to which they support or broaden findings from RCTs.

Data extraction and synthesis

Data were extracted by two reviewers (PW, JW) independently in a standardized manner. Data pertinent to: location, study design, duration, subject population, interventions, cognitive outcomes measured and all cognition-related results were summarized in Tables 1 and 2. Inclusion and exclusion of studies were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁷

For RCTs only, we used meta-analytical methods to synthesize a subset of the most commonly reported outcomes. Comprehensive Meta Analysis Version 2.0 software was used to calculate effect sizes (i.e., Hedges' g) and the 95% confidence intervals using random effects models.¹⁸ For studies among adults without cognitive impairment, we calculated the effect size for all executive function outcomes, with separate analyses for comparisons of Tai Chi with active (e.g., walking) and non-active (e.g., usual care) control interventions. No other outcomes in this population were measured as consistently as executive function, thus precluding pooled analyses. For studies among cognitively impaired adults, we calculated the effect size for global cognition, with separate analyses for comparisons of Tai Chi with active and non-active control interventions. Again, no other outcomes in this population were measured as consistently as global cognition, thus precluding pooled analyses.

An overall summary effect was calculated, using a random effects model to estimate the mean of the distribution of effects that could have been observed (e.g., different subjects or intervention protocols). Under the random effects model, the individual study weights are more balanced, thus the summary effect is more conservative. We also calculated the ratio of true heterogeneity to total observed variation using the I^2 statistic, as I^2 is not directly affected by the number of studies in the analysis. I^2 is not scale dependent, but is expressed as a ratio ranging from 0–100% (25%=low, 50%=moderate, 75%=high heterogeneity).

Results from non-RCTs were synthesized and summarized in narrative form.

Risk of bias in individual studies

Quality of methodology reported and associated risk of bias was assessed by two reviewers (PW, GY) independently using the 12 criteria (rating: yes, no, unclear) recommended by the Cochrane Back Review Group.¹⁹ When necessary, discrepancies were rechecked with a third reviewer and consensus achieved by discussion. Studies that met 6 of the 12 criteria and had no serious flaw (such as drop-out rate higher than 50%, and/or statistically significant and clinically important baseline differences that were not accounted for in the analyses) were rated as having low risk of bias. Studies that met fewer than 6 criteria or had

a serious flaw were rated as having high risk of bias. Methodological quality and associated risk of bias for all RCTs are summarized in Table 3.

RESULTS

Literature search

Figure 1 summarizes the flow of our literature search and selection process. Our search resulted in 195 studies. Eighty-three articles were excluded because they were duplicates. Twelve were further excluded: 4 were irrelevant to the search (e.g., author name “Tai”), 5 were not published in English; and 3 were not full text articles. Of the remaining 71 articles, 27 did not report original data, 4 did not utilize Tai Chi as an intervention, and 20 did not report a cognitive function outcome.

Study designs

The 20 eligible studies identified by our search are summarized in Tables 1 and 2. These studies include 11 RCTs, 1 PNRCS, 4 PNCS, and 4 CSS.

Participant characteristics and study setting

Table 1 includes 11 studies that evaluated the impact of Tai Chi on older adults that had no reported cognitive impairment.^{20–30} Table 2 includes 9 studies in populations that reported varying degrees of cognitive impairment, ranging from MCI to irreversible dementia.^{9,31–39} Eight studies were conducted in the United States, 7 in China, 3 in France, and 1 in both Japan and Vietnam. All but one study²² focused on older adults with average ages above 60. These included 12 studies in community dwelling individuals, 4 in residents of assisted living facilities, 1 in healthy volunteers, and 3 in patients from hospital-based settings.

Intervention and control group characteristics

Tai Chi interventions varied greatly in content, dosage, duration and intensity. Of the 16 prospective studies, 8 interventions were described as variations of Yang style Tai Chi,^{27–29,32–34,38,39} 3 of Sun style,^{25,31,37} and 1 of Tai Chi Chih.²³ In all cases, interventions were described as simplified, and/or included a subset of movements typically learned in traditional longer Tai Chi forms. One study integrated Tai Chi exercises within a multi-component intervention including cognitive behavioral therapy and support group.⁹ Two studies did not provide details on the Tai Chi intervention.^{23,26}

Individual sessions varied in duration from 20–60 minutes. The frequency of sessions varied from 1 to 4 times per week, with overall training programs lasting 10 weeks to 1 year. Two studies conducted a year-long observation with an induction or adoption phase and a maintenance phase.^{29,39} Guidelines for practice outside of class were reported in 2 of 3 studies that required and monitored home practice. Instructor qualifications were mentioned in 1 of 20 studies.

Eight of 11 RCTs used active control groups for comparison, including group Western exercise,²⁹ stretching and toning,³⁹ and combination of resistance and non-resistance

training.³⁸ Five studies utilized educational programs.^{9,23,32,34,37} Three studies employed a non-intervention control.^{26,27,33}

Outcomes measured

Outcomes related to cognitive function were broadly categorized into the following cognitive domains: **1) global cognition:** Mini Mental Status Exam (MMSE), Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog); **2) executive functions:** measures of processing speed, attention, and working memory: Trail Making Test (TMT A& B), digit span, digit symbol coding, spatial span forward/backward, Stroop color and word test, rule shift cards test, controlled oral word association test (COWAT), WAIS-R similarities, color trails test (CTT) trail 1–2; **3) language:** verbal fluency (category/semantic), Boston Naming Test (BNT); **4) learning and memory:** list learning tasks: California Verbal Learning Test II (CVLT), Hopkins Verbal Learning Test (HVLT), Hong Kong List Learning Test (HKLLT), Rivermead Behavioral Memory Test (RBMT); and **5) spatial and quantitative:** Rey-Osterrieth complex figure, clock drawing test (CDT), math word problems and calculations. Additional outcomes included neurobiological markers such as P300 amplitude and latency, MRI for whole brain volume, and psychiatric functioning (Neuropsychiatric Inventory; NPI). The three most widely used outcomes across studies were MMSE, TMT, and digit span test.

Methodological quality of randomized clinical trials and bias risk

Quality of reporting of clinical trial features was fair, although this varied considerably across the 11 RCTs (Table 3). Quality scores ranged from 4 to 11 (maximum score =12), with an average of 7.1. No studies were deemed fatally flawed, and 8 of the 11 studies had a score ≥ 6 indicating a low risk of bias.^{9,23,26,29,33,34,37,39}

Synthesis of studies of cognitively healthy adults

Of the 11 studies that evaluated older adults without reported cognitive impairment, 4 were RCTs (total n= 421) (Table 1). These RCTs all reported positive effects of Tai Chi on cognitive function including at least one measure of executive function.^{23,26,27,29} Meta-analyses including these four studies comparing Tai Chi to non-intervention controls for outcomes related to executive function indicated a large effect size, but high heterogeneity (Hedge's $g=0.904$; $p=0.043$, $I^2=92.02\%$; Figure 2a). After excluding the one study with a low quality score indicating bias,²⁷ the effect size was reduced but remained statistically significant and indicated no heterogeneity between studies (Hedge's $g=0.394$; $p=0.004$, $I^2=0\%$). Meta-analyses of the two studies^{26,29} that compared Tai Chi to another exercise intervention (walking and "western exercise") also showed a modest positive effect size (Hedge's $g=0.509$; $p=0.003$, $I^2=0\%$; Figure 2b). Of note, one of these studies including a long-term follow-up reported sustained Tai Chi-related improvements in executive function at 1 year (i.e., 8 months post intervention).²⁹

In addition, measures of learning and memory and semantic fluency (AVLT, CVLT, categories) also improved with Tai Chi in the three higher quality RCTs,^{23,26,29} in one study these improvements were greater relative to aerobic exercise.²⁶ One study also reported

improvements in overall global cognitive function (Mattis DRS) and total brain volume assessed via MRI.²⁶

Findings from 6 of the 7 non-randomized and cross-sectional studies support an effect on cognitive function in healthy adults (Table 1).^{21,22,24,25,28,30} One small PNCs reported that 10 weeks of Tai Chi improved scores on two measures of executive function.²⁵ Another small non-controlled study reported acutely enhanced performance in math computations.²² One CSS reported older adults who regularly trained with Tai Chi had better executive function/attention, learning and memory compared with matched sedentary adults or with conventional exercise.²⁴ A second CSS reported that adults who practiced mind-body exercise (including Tai Chi) or cardiovascular exercise demonstrated similar levels of memory function. Exercise was better than non-exercisers, and those who practiced both mind-body and aerobic exercise cognitively outperformed all other groups.²⁰

Synthesis of studies of cognitively impaired adults

Of the 9 studies that evaluated adults with some form of cognitive impairment, 7 were RCTs (total n= 843)^{9,32–35,37,38} (Table 2). All but one³⁸ of these studies employed MMSE as a measure of global cognitive function. Meta-analyses of the 4 studies that included a non-intervention comparison^{9,32,33,37} indicated a small but statistically significant effect for Tai Chi on MMSE (Hedge's $g=0.346$; $p=0.004$, $I^2=0\%$; Figure 2c). When meta-analyses were limited to the 3 studies with quality scores ≥ 6 ,^{9,33,37} effect sizes remained significant (Hedge's $g=0.304$; $p=0.033$, $I^2=0\%$). Meta-analyses including the 4 studies that compared Tai Chi to another active intervention (western exercise, cognitive behavioral therapy, Mahjong)^{32–34,39} showed a small positive significant effect of Tai Chi on MMSE (Hedge's $g=0.300$; $p=0.002$, $I^2=0\%$; Figure 2d). This effect remained when the one lower quality study³² was removed (Hedge's $g=0.268$; $p=0.010$, $I^2=0\%$).

Other outcomes observed in individual RCTs of cognitively impaired populations include a marked reduction in rates of progression to dementia (4.3% vs. 16.6% in Tai Chi vs. western exercise) in one trial³⁵ and improved executive function in Tai Chi compared with an arts and crafts intervention.³² One larger CSS (n=782) reported the proportion of adults without cognitive impairment was highest in those with regular mind-body practice (including Tai Chi). In addition, participants who regularly practiced aerobic or mind-body exercises for >5 years had higher scores on MMSE, 10 min delayed recall, visual backward span, and CVFT ($p<0.05$).³⁶

Reports of safety and adverse events

Six of the 11 RCTs reported on adverse events (AEs), however no RCTs described a formal protocol for systematically monitoring AEs. Two studies stated that no AEs were reported in either Tai Chi or comparison group. Four studies reported AE's including falls, hospitalization, side-effects of medication, and death; however, none were attributable to Tai Chi.

DISCUSSION

The literature on non-pharmacological behavioral approaches to improve cognitive function in older adults has been growing. Tai Chi shows promise as an alternative multi-modal exercise for attenuating age-related cognitive decline and warrants further research. Our findings add to a growing body of studies evaluating a variety of other mind-body interventions (e.g., yoga, meditation, qigong) on cognitive function and provide further support for the effectiveness of multi-modal behavioral interventions.^{13,40}

Tai Chi for cognitively intact adults

Results of our meta-analyses support small to moderate, but clinically relevant improvements in executive function following 10 weeks to 1 year of Tai Chi training in cognitively intact adults. Effect sizes were equivalent to those reported following other exercise^{3,4} and cognitive training.⁴¹ Benefits were apparent in RCTs that compared Tai Chi to other exercise interventions suggesting that Tai Chi's effects are not simply due to group social support or placebo expectation for improvement. While the positive effects of Tai Chi on executive function persisted when our analyses were limited to studies of higher methodological quality, more definitive conclusions regarding Tai Chi's potential benefits will require results from a greater number of larger, well-designed studies.

Executive function is an umbrella term for cognitive processes that regulate, control, and manage other cognitive processes such as planning, working memory, attention, problem solving, verbal reasoning, inhibition, mental flexibility, task switching, and initiation and monitoring of actions.⁴² Executive function is increasingly appreciated as a key component of healthy balance and postural control.⁴³ Improvement in this domain of cognitive function may thus play a role in mediating Tai Chi's effects on balance and motor control. The link between Tai Chi-associated increases in executive function and motor control is supported by some recent studies.^{25,44}

Evidence for the impact of Tai Chi on other domains of cognitive function in cognitively intact adults is less conclusive. Individual studies reported improvements in outcomes related to learning, memory, language, global cognitive function, as well as total brain volume assessed with MRI. These outcomes, however, were not employed consistently across studies precluding quantitative synthesis.

Tai Chi for cognitively impaired

Tai Chi may benefit cognitive function in cognitively impaired adults. Results of our meta-analyses support small to moderate, but clinically relevant improvements in global cognitive function (MMSE) following 12 weeks to 1 year of Tai Chi training, equivalent to effects reported following other exercise^{3,4} and cognitive training.⁴¹ As in studies of cognitively intact adults, these benefits were apparent in RCTs that compared Tai Chi to other exercise interventions, as well as non-active interventions, and persisted when methodologically biased studies were excluded from analyses. Evidence for the impact of Tai Chi on specific domains of cognitive function in cognitively impaired adults is less conclusive.

Safety

Poor reporting of protocols for systematically monitoring adverse events limits the conclusions that can be drawn regarding the safety of Tai Chi in populations with and without cognitive impairment. However, in the subset of studies that did report adverse events, there were no reports that could be directly attributed to Tai Chi. These observations support other study findings – including populations with serious balance impairments, cardiovascular risk factors, and affective disorders -- that Tai Chi can be safely administered with few serious adverse events.^{14–16} Of note, all studies in this review relied on simplified forms, thereby minimizing potential psychological distress associated with memorizing complex routines. For populations with existing cognitive impairment, interventions based on long and complex choreographies should be contraindicated.

How might Tai Chi positively impact cognitive function?

It has been hypothesized that there are at least six potentially therapeutic elements inherent in Tai Chi training that may underlie its impact on cognitive function.¹⁰ First, Tai Chi is a moderately aerobic exercise, with metabolic equivalents estimated between 1.5 and 4.0. This aerobic intensity overlaps with brisk walking which has been shown to have positive effects on cognitive function.⁴⁵ Importantly, the impact of exercise is supported by studies associating functional changes with neurophysiological changes such as increased brain derived neurotrophic factor and plasticity in brain morphology and function, including processes central to executive function.^{5,46–48} Future studies might evaluate how Tai Chi vs. unimodal exercise programs (e.g., stationary cycling) compare with respect to their impact on brain plasticity and activation of neural networks during functional tasks. Second, Tai Chi trains agility and mobility, which some evidence suggests impacts cognitive function via neurophysiological pathways unique to those associated with aerobic exercise. One study reported that aerobic and muscular fitness were both associated with executive function, where as motor fitness (agility and mobility) was associated with both executive control and perceptual speed tasks. Paralleling these functional changes were distinct patterns of activation assessed using fMRI during the Flanker Task.¹¹ Future studies might use functional imaging paradigms to explore how biomechanically repetitive exercises that target aerobic and muscle fitness (e.g., treadmill walking) compare with exercises like Tai Chi that also train agility and dynamic postural control. Third, Tai Chi involves learning and memorization of new skills and movement patterns; studies of other skill-based learning activities including dance, juggling, and music have shown improvements in cognitive function and underlying neural mechanisms.^{49,50} For example, learning juggling has been associated with increased gray matter in the occipito-temporal cortex⁵¹ and dance training with hippocampal formation.⁵² Better understanding how the learning of Tai Chi routines that vary in choreographical complexity impacts brain structure and function will greatly enhance our mechanistic understanding of Tai Chi on cognitive function. Fourth, Tai Chi includes training in sustained attentional focus, shifting, and multi-tasking which could help train working memory, divided attention, cognitive flexibility, and overall executive function. One study that employed a computerized visual and finger-pointing paradigm reported that compared to age-matched Tai Chi naïve controls, older Tai Chi practitioners have improved hand-eye coordination and movement times during tasks involving cognitive processing.⁴⁴ Fifth, the meditative and relaxation training of Tai Chi have been shown to

reduce anxiety and depression,¹⁴ which may impact cortisol and other stress-related pathways of cognitive decline.⁷ The relevance of this component of Tai Chi is supported by studies linking meditation training with improvements in multiple functional and neurophysiological aspects of cognitive performance.¹² Finally, greater time allocated to leisure activities and social support has been associated with improved or preserved cognitive function.⁸ In summary, these six interdependent therapeutic elements of Tai Chi may afford greater effectiveness in enhancing cognitive function, compared to unimodal interventions that target a more limited set of mechanisms and physiological pathways.

Limitations and Suggestions for Future Research

There are a number of limitations to this study. First, our analysis was limited to studies in the English language. Including studies in other languages may have better represented the evidence to date and improved generalizability to other cultures. Second, due to heterogeneity in outcomes employed in trials, we necessarily limited our meta-analyses to only the most commonly measured outcomes. Until more studies are available with common outcomes reflecting other domains, it will be difficult to more broadly evaluate Tai Chi and cognitive function. Some studies with poorer methodological quality were included in this review. In addition to better reporting of key design features (e.g., blinding, randomization, adverse event reporting), future studies should report features specifically relevant to Tai Chi studies (e.g., details, rationale and validity of training protocols). This will enable future reviews to better evaluate protocol-specific effects. Third, our pooling of studies into two broad groups – cognitively healthy and cognitively impaired population – does not capture the diversity and complexity of participants across studies, and thus limits the inferences we can draw regarding the benefits of Tai Chi to specific populations. Future reviews should further stratify results based on more fine-grained classification of levels of cognitive impairment as well as cognition-related comorbidities. Finally, given the unique multi-component nature of Tai Chi, outcomes characterizing complex physiological (e.g. aerobic capacity, neuroendocrine function, motor control) and behavioral measures (e.g. stress, mood, body awareness, perceived social support) should be evaluated and explored as mechanisms or mediators of Tai Chi's effects.

CONCLUSIONS

Our meta-analysis and broader systematic review suggest that Tai Chi may offer a safe, non-pharmacological approach to enhancing cognitive function in older adults. Larger, more robust trials with longer follow-up periods and standardized neuropsychological outcome measures are needed before more definitive conclusions can be drawn. If future research supports the benefits of Tai Chi for cognitive function, this would add to the literature supporting other Tai Chi-associated benefits for older adults, including positive effects on balance and fall prevention, cardiovascular risk, musculoskeletal pain, immune function and psychological well-being.¹⁰ Tai Chi may be an attractive first line intervention for adults interested in integrated long-term strategies for healthy aging.

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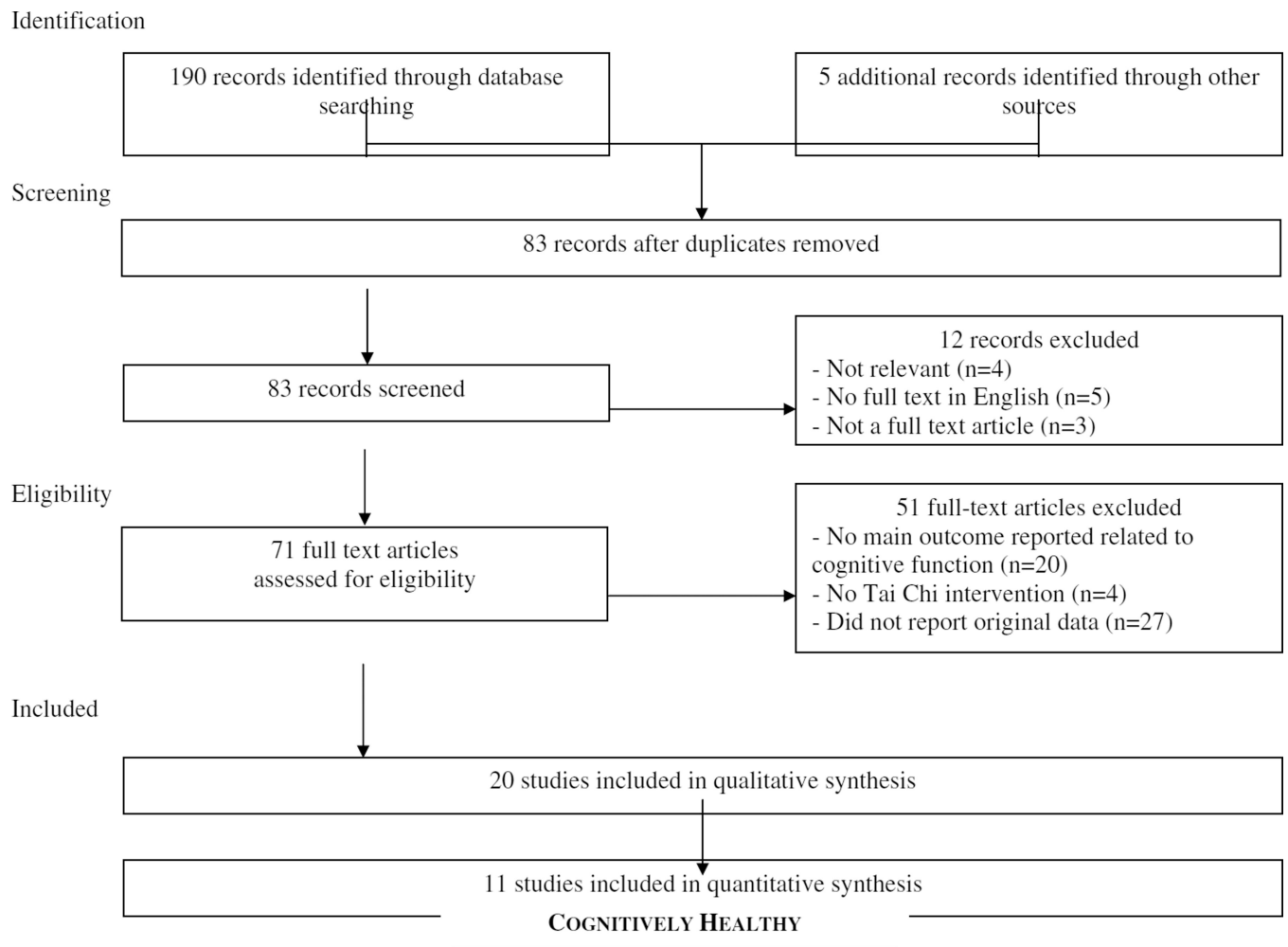
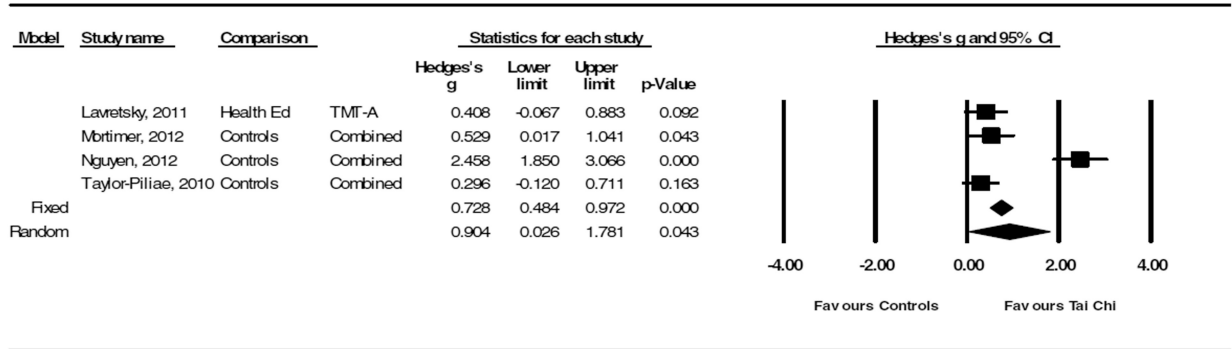


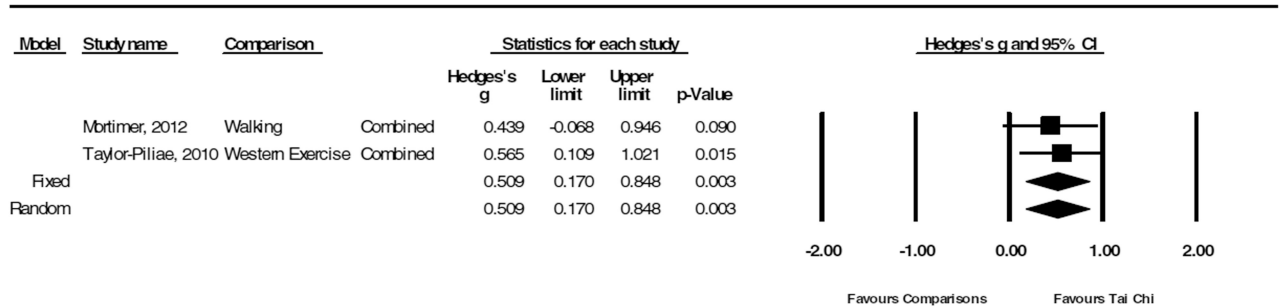
Figure 1. Summary of the flow of our literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Executive Function: Tai Chi vs Controls



a

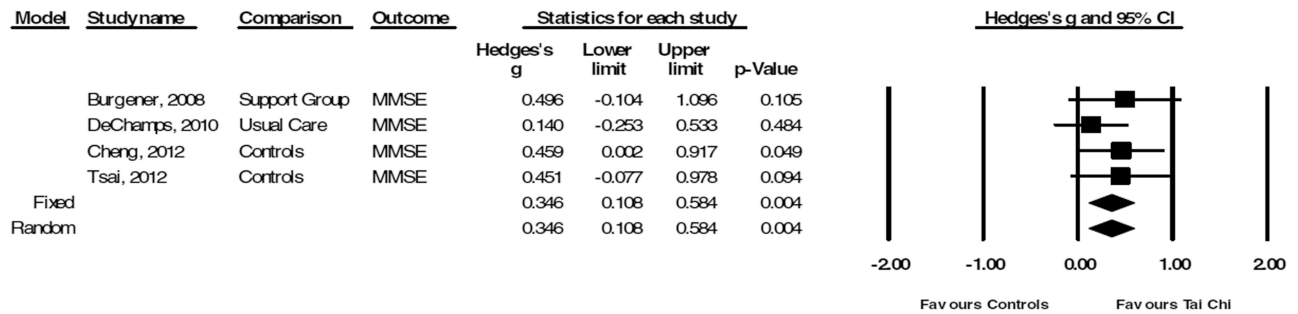
Executive Function: Tai Chi vs Active Comparisons



b

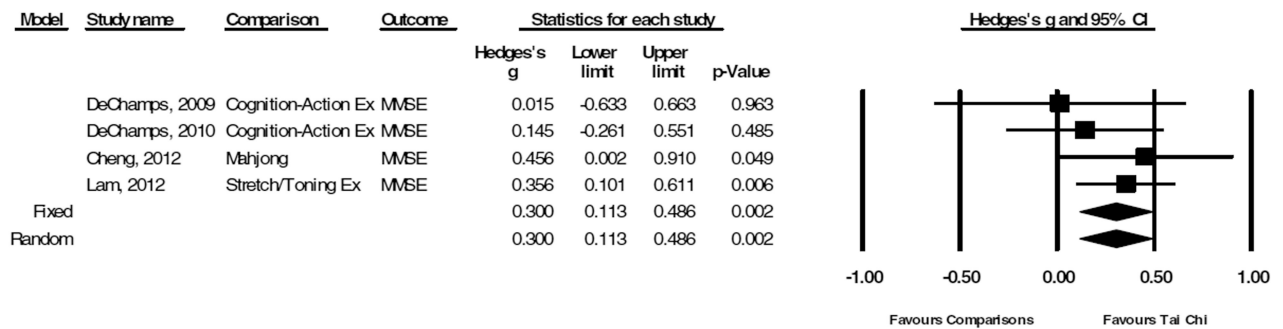
COGNITIVELY IMPAIRED

Global Cognition: Tai Chi vs Controls



c

Global Cognition: Tai Chi vs Active Comparisons



d

Figure 2.

Results of meta-analyses evaluating Tai Chi for cognitive function. 2a and 2b summarize results for comparisons between Tai Chi and non-active and active controls, respectively, for executive function in adults without existing cognitive impairment. 2c and 2d summarize results for comparisons between Tai Chi and non-active and active controls, respectively, for global cognition in cognitively impaired adults.

Table 1

Summary of Tai Chi studies including participants without existing cognitive impairment.

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures**
Nguyen et al (2012) ²⁷ Vinh, Vietnam	RCT (n=96)	Community dwelling adults Mean age 69y MIMSE >25	<ul style="list-style-type: none"> • TC (n=48) • Control: No intervention (n=48) 	<ul style="list-style-type: none"> • 2 (60min) classes per wk for 6 mo 	<ul style="list-style-type: none"> • Executive Function: TMT A&B 	<ul style="list-style-type: none"> • At 6 mo: <ul style="list-style-type: none"> • TC improved TMT A&B compared to control group (p < 0.001)
Mortimer et al (2012) ²⁶ Shanghai, China	RCT (n=120)	Independently living adults Mean age 68y MIMSE >25	<ul style="list-style-type: none"> • TC (n=30) • Aerobic (walking) (n=30) • Social Interaction (n=30) • No intervention control (n=30) 	<ul style="list-style-type: none"> • All groups 3x/wk for 40 wks: - TC, 50min classes - Aerobic (walking), 10min warm-up, 30min brisk walk, 10min cool-down - Social Interaction, 60min classes 	<ul style="list-style-type: none"> • Global Function: Mattis DRS • Executive Function: DS, TMT A&B, Stroop, Wais-R similarities • Language: BNT, Category fluency • Learning and Memory: AVLT, CVLT • Spatial and Quantitative: Rey, CDT • Other: MRI whole brain volume 	<ul style="list-style-type: none"> • TC showed significant improvements from baseline compared to other groups in: <ul style="list-style-type: none"> - Mattis DRS (total score) (p<0.01) - Mattis Attention Score (p<0.05) - Mattis Initiation Score (p<0.01) - Mattis Memory Score (p<0.05) - TMT A&B time (p<0.01) - CVFT (animals) (p<0.05) - AVLT (delayed recall) (p<0.1) - AVLT (delayed recognition) (p<0.01)

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures**
Lavretsky et al (2011) ²³ California, USA	RCT (n=73)	Community dwelling adults with depression Mean age 71y Mean MMSE 29	Escitalopram (anti-depressant medication) plus <ul style="list-style-type: none"> • TC (n=36) • Control: Health Education (HE) (n=37) 	<ul style="list-style-type: none"> • TC: 1 (120min) session per wk for 10 wks • Control: 1 (120min) per wk for 10 wks 	<ul style="list-style-type: none"> • Global Cognition: MMSE • Executive Function: TMT A (error time), TMT B, Stroop • Learning and Memory: CVLT-DR (cued) 	<ul style="list-style-type: none"> • At 10wks: TC improved CVLT long delayed recall (cued) compared to control (p = 0.05) • TC showed trends towards improvement of TMT-A errors (p=0.07) • No data reported for Stroop and TMT-B
Taylor-Phlax et al (2010) ²⁹ California, USA	RCT (2 phase) (n=132)	Community dwelling adults age 69y	<ul style="list-style-type: none"> • TC (n=37) • Western exercise, WE (n=39) • Attention-control (n=56) 	<ul style="list-style-type: none"> • Adoption phase (0-6mo) = 2 (45-60min) class-based and 3 home-based sessions per wk • Maintenance phase (6-12mo) = 1 class-based and 3 home-based sessions per wk • Control: 90min "healthy aging" classes 1x/wk for 6 mo, adoption phase only 	<ul style="list-style-type: none"> • Executive Function: DS-F, DS-B • Language: Animal naming, category fluency 	<ul style="list-style-type: none"> • At 6mo: TC improved DS-B compared to WE and control (p<.001) • At 12mo: TC maintained improvements in DS-B compared to Western exercise (p=.014) • Both TC and WE improved ANT (both p<0.01), however no differences between groups
Coubard et al (2011) ²¹ Paris, France	PNRCS (n=110)	Adults Mean age 74y Mean MMSE 27	<ul style="list-style-type: none"> • TC (n=27) • Contemporary dance (n=16) • Fall prevention (n=67) 	All groups 1 (60min) session per wk, for 5,7 mo	<ul style="list-style-type: none"> • Executive Function: Stroop, rule shift cards test • Spatial and Quantitative: 	<ul style="list-style-type: none"> • At 6 months: No change in TC compared with contemporary dance in arithmetic word

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Whole brain volume (% of total intracranial volume) (p<0.05)

• No significant change in DS, Stroop, WAIS-R similarities, Rey figure, CDT

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures**
Rein-Amdt et al (2012) ²⁸ Missouri, USA	PNCS (n=23)	Adults with history of cancer, 12 mo post chemotherapy treatment Mean age 62y	<ul style="list-style-type: none"> TC (n=23) 	<ul style="list-style-type: none"> 2 (60min) classes per wk for 10wk 	<ul style="list-style-type: none"> arithmetic word problems arithmetic word problems shift Executive Function: Digit Span, digit symbol, TMT A&B, Stroop Test, COWAT Learning and Memory: RAVLT, LMI, LMII Other: MASQ 	<ul style="list-style-type: none"> At 10 weeks: <ul style="list-style-type: none"> Significant pre-post improvements in: COWAT (p=0.002) TMT A (p=0.002) TMT B (p<0.001) Stroop Test (p=0.019) RAVLT Rey Trial I (p=0.026) RVALT Rey Trials 15 (p=0.035) Logical Memory I (p<0.001) Logical Memory II (p=0.001) MASQ Verbal memory (p = 0.01) MASQ Visual memory (p <0.05)
Field et al (2010) ²² Florida, USA	PNCS (Acute) (n=38)	Medical staff Mean age 41y	TC/Yoga (n=38)	Single 20min TC/yoga session	<ul style="list-style-type: none"> Spatial and Quantitative: math computations 	<ul style="list-style-type: none"> After 1 session: <ul style="list-style-type: none"> Improved performance on math computations; reduced time taken to perform task (p=0.000)

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures
Mathews and Williams (2008) ²⁵ South Carolina, USA	PNGS (n=20)	Adults Mean age 77y	TC (n=20)	30 (50min) classes over 10 wks	<ul style="list-style-type: none"> Executive Function: TMT A&B, Digit symbol substitution Spatial and Quantitative: CDT 	<p>At 10 weeks:</p> <ul style="list-style-type: none"> Significant pre-post improvements in TMT B (p=0.029) and CDT (p=0.029)
Man et al (2010) ²⁴ Hong Kong, China	CSS (n=135)	Community dwelling adults Mean age 68y Mean MMSE 28	<ul style="list-style-type: none"> TC (n=42) Exercise (n=49) Control (n=44) 	<ul style="list-style-type: none"> TC : practice 3 (45min) sessions per wk for 3y (able to perform 108 forms alone) Exercise group: aerobic, flexibility, and stretching exercises, 3 (45min) sessions per wk for 3y, no prior TC experience Control group: no regular exercise 	<p>Executive Function:</p> <ul style="list-style-type: none"> CTT-Trail 1 and 2 Learning and Memory: HKLLT, RBMT 	<p>Baseline:</p> <ul style="list-style-type: none"> Compared to other groups, the TC group performed better on: <ul style="list-style-type: none"> CTT 1 (p=0.03) CTT 2 (p=0.02) RBMT total standard score (p=0.03) and total screening score (p=0.04) HKLLT learning trials 1+2+3 random (p=0.005) and blocked (p=0.00), HKLLT retrieval blocked (p=0.018) HKLLT semantic clustering score blocked (p=0.00) HKLLT subjective

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and increased accuracy (p=0.05)
and increased accuracy (p=0.05)

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures**
Wu et al (2010) ³⁰ Taiwan, China	CSS (n=30)	Community-dwelling adults Mean age 69y	<ul style="list-style-type: none"> Yuanji-Dance (n=15) Control (n=15) 	<ul style="list-style-type: none"> 3y Yuanji-dance experience No Yuanji-dance experience 	<ul style="list-style-type: none"> Executive Function: Button reaction time and accuracy tested under three conditions: <ol style="list-style-type: none"> Single-primary task (walking alone) Single-secondary task (hand pressing button alone) Dual-task (walking plus hand button pressing tasks) 	<p>Baseline:</p> <ul style="list-style-type: none"> Significant group effect on reaction time in the single-secondary task (p = 0.009) and dual-task (p = 0.033)
Chan et al (2005) ²⁰ Hong Kong, China	CSS (n=140)	Community dwelling adults Mean age 66y	<ul style="list-style-type: none"> Mind-body exercise, MB (n=35) Cardiovascular exercise, CV (n=35) CV +MB exercise (n=35) No regular physical exercise (n=35) 	<ul style="list-style-type: none"> One year observation Self-reported frequency and duration of practicing MB, CV, or MB+CV exercise 1x/mo 	<ul style="list-style-type: none"> Global Function: C-Mattis DRS Language: CBNT Learning and Memory: HKLLT 	<p>At 1 year:</p> <ul style="list-style-type: none"> All exercise groups identified more correct responses compared to the no exercise group (MB, p=0.006), (CV, p=0.02), (CV+MB, p=.001) CV committed more false-alarm errors than CV+MB (p=.001) CV+MB had higher discrimination scores than CV (p=.01) and no exercise (p=.001) Less change in memory performance across age was found in MB: 10min DR (p=.008), 30min DR

Was
organization blocked (p=0.001)
organization blocked (p=0.001)
organization blocked (p=0.001)

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures**
						<p>Wang et al. (p=.049), and recognition scores (p=.049) (p=.004), and recognition scores (p=.049)</p> <ul style="list-style-type: none"> • Post-hoc Tukey HSD analyses showed CV +MB learned more words than no exercise(p=0.02) • CV + MB recalled more words than CV (p=.005) and no exercise (p=.001)

Abbreviations used throughout table

** Results reported are between groups unless otherwise noted

TC = Tai Chi
 RCT = Randomized Controlled Trial
 PNRCS = Prospective Non-Randomized Controlled Trial
 PNCS = Prospective Non-Controlled Trial
 CSS = Cross-Sectional Study
 MMSE = Mini Mental Status Examination
 (C) BNT = (Chinese) Boston Naming Test
 (C) Mattis DRS – (Chinese) Dementia Rating Scale
 ANT = Animal Naming Test
 ADAS-Cog = Alzheimer’s disease Assessment Scale – Cognitive Subscale
 ADL = Activities of Daily Living
 AVLT = Auditory Verbal Learning Test
 CDR –SB = Clinical Dementia Rating – Sum of Boxes
 CDT = Clock Drawing Test
 COWAT = Controlled Oral Word Association Test
 CSDD = Cornell Scale for Depression in Dementia
 CTT (1/2) = Color Trails Test (part 1 and/or part 2)
 CVFT = Category Verbal Fluency Test
 CVLT = California Verbal Learning Test
 DR = Delayed Recall
 DSC = Digit Symbol Coding
 DS-F/DS-B = Digit Span Forward/Digit Span Backward
 Dseq-F/Des-B = Digit sequence Forward/Digit sequence Backward
 HKLLT = Hong Kong List Learning Test
 MASQ = Multiple Abilities Self-Report Questionnaire
 MCS of SF-12 = Mental Component Summary of the SF-12
 NPI = Neuropsychiatric Inventory
 RAVLT = Rey Auditory Verbal Learning Test
 RBMT-CV = Rivermead Behavioral Memory Test – Chinese Version

TMT A&B = Trail Making Test part A and part B
VS-F/B = Visual Span Forward/Backward

Table 2

Summary of Tai Chi studies including participants with cognitive impairment.

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures ^{***}
Cheng et al (2012) ³² Hong Kong, China	RCT (n=110)	Dementia institutionalized Mean MMSE 19 Mean age 82y	<ul style="list-style-type: none"> TC (n=59) Mahjong (n=36) Control: Simple handicrafts (n=35) 	<ul style="list-style-type: none"> All groups: 3 (60min) sessions per wk for 12 wks 	<ul style="list-style-type: none"> Global Cognition: MMSE Executive Function: DS F/B Language: CVFT Learning Memory: DR 	<ul style="list-style-type: none"> At 9 mo: <ul style="list-style-type: none"> TC improved MMSE (+3.7 compared to control (95% CI: 1.4-6.0; d=0.40)) Only intervention groups improved on MMSE (Mahjong +1.5 points (95% CI: -0.0 to 3.0), TC +1.3 points (95% CI: -0.0 to 2.5), control group -2.9 points (95% CI: -4.2 to -1.7)) TC improved DS-F compared to control (difference between means: 0.98; 95% CI: 0.12-1.84; d=0.25) No changes in DR and DSB Main effect of Mahjong (overall mean: 13.4 ± 12.4; 95% CI: 9.3-17.5) over control (overall mean: 9.9 ± 12.7; 95% CI: 5.7-14.2) in CVFT
Tsai et al (2013) ³⁷ Arkansas, USA	RCT (n=55)	Cognitive impairment, community dwelling w/knee osteoarthritis Mean MMSE 25 Mean age 79y	<ul style="list-style-type: none"> TC (n=28) Control: health education and social activities (n=27) 	<ul style="list-style-type: none"> Both groups: 3 (20-40min) sessions per wk for 20 wks 	<ul style="list-style-type: none"> Global Cognition: MMSE 	<ul style="list-style-type: none"> At 21 wks: <ul style="list-style-type: none"> TC improved MMSE (+1.33 at wk 21 (P=0.096))
Lam et al (2012) ³⁹ Hong Kong	RCT (n=389)	Cognitive impairment, community dwelling w/	<ul style="list-style-type: none"> TC (n=171) Control: exercise, 	<ul style="list-style-type: none"> Both groups: <ul style="list-style-type: none"> Initial 1 instructor-led 	<ul style="list-style-type: none"> Clinical progression: incident dementia Global Function: CDR-SB 	<ul style="list-style-type: none"> At 1 yr: <ul style="list-style-type: none"> Fewer progressed to dementia in TC vs.

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures***
Kong, China		amnesic MCI Mean MMSE 25 Mean age 78y	stretching and toning (n=218)	session per week for 8-12 wks After 12 wks, home video, goal 30min/day, 3x/wk; monthly refresher session Total 1 year	<ul style="list-style-type: none"> Global Cognition: MMSE, ADAS-cog Executive Function: DS, VSF/B, TMT Language: CVFT Learning Memory: DR Other: NPI, CSDD 	<ul style="list-style-type: none"> control: 4 (4.3%) vs. 28 (16.6%) Trend for lower risk of developing dementia at 1 year with TC (intention to treat analyses: odds ratio 0.28, 95% confidence interval 0.05-0.92, p=0.06; completer-only analyses: odds ratio 0.21, 95% CI 0.05-0.92, p=.04) TC had better preservation of CDR-SB (p=0.04) TC improved CSDD (completers only, p=0.02) and DR (completers only, p=0.05) No difference in MMSE, DR, CVFT, ADAS-Cog, VSB, NPI
Wang et al (2010) ³⁸ Akitu-Kounoike, Japan	RCT (n=34)	Cognitive impairment w/ cerebral vascular disease Mean MMSE 26 Mean age 77y	<ul style="list-style-type: none"> TC (n=17) Control: Rehabilitation (n=17) 	<ul style="list-style-type: none"> TC: 1 (50min) session per wk for 12 wks Rehabilitation: 1 (80 min) session, non-resistance training (20min) and resistance training (60min), per wk for 12 wks 	<ul style="list-style-type: none"> Other: P300 amplitude and latency 	<ul style="list-style-type: none"> No significant differences between TC and rehabilitation in P300 amplitudes and latencies
Dechamps et al (2010) ³³ Bordeaux, France	RCT (n=160)	Dementia institutionalized Mean MMSE 15 Mean age 82y	<ul style="list-style-type: none"> TC (n=51) Cognition-Action (n=49) Control: Usual care (n=60) 	<ul style="list-style-type: none"> TC: 4 (30min) sessions per wk for 24 wks Cognition-Action: 2 (30-40min) sessions of light-intensity exercises per wk for 24 wks 	<ul style="list-style-type: none"> Global Function: ADL Global Cognition: MMSE Other: NPI 	<ul style="list-style-type: none"> At 1 yr: Significant difference in ADL scores across groups, with no change in TC and Cognition

Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures***
Dechamps et al (2009) ³⁴ Bordeaux, France	<u>RCT</u> (n=52)	Dementia institutionalized Mean MMSE 20 Mean age 81y	<ul style="list-style-type: none"> TC (n=26) Control: Cognition-Action (n=26) 	<ul style="list-style-type: none"> TC: 4 (30min) sessions per wk for 24 wks Cognition-Action: 2 (30-40min) sessions of light intensity exercises (stepping, stretching, deep abdominal breathing) per wk for 24 weeks 	<ul style="list-style-type: none"> Global Cognition: MMSE Other: MCS of SF-12 	<p>Action and decline in cognition, p=0.007) Action and decline in control, p=0.007)</p> <ul style="list-style-type: none"> No difference in NPI between TC group and control; no difference in NPI between TC and Cognition Action No significant changes in MMSE
Burgener et al (2008) ⁹ Illinois, USA	<u>RCT</u> (n=43)	Dementia Mean MMSE 24 Mean age 77y	<ul style="list-style-type: none"> TC plus cognitive behavioral therapy plus support group (n=24) Control: Wait-list, plus attention control classes (n=19) 	<ul style="list-style-type: none"> TC, 1 hour classes 3x/wk for 20 wks, plus 90 min bi-wkly classes of cognitive behavioral therapy or support group Control: Unspecified attention control education classes × 20 wks 	<ul style="list-style-type: none"> Global Function: MMSE 	<ul style="list-style-type: none"> TC improved MMSE compared to control group (+0.4 vs. -0.5, p=.05)
Chang et al (2011) ³¹ Arkansas, USA	<u>PNCS</u> (n=11)	Dementia Mean MMSE 23 Mean age 85y	<ul style="list-style-type: none"> TC (n=11) 	<ul style="list-style-type: none"> 2 (20-40min) sessions per wk for 15 wks 	<ul style="list-style-type: none"> Global Cognition: MMSE Executive Function: DS, DSC, Stroop color word Learning Memory: Hopkins Verbal Learning DR 	<ul style="list-style-type: none"> No significant pre-post differences on MMSE, DSC, DS, Stroop Color and Word, Hopkins Verbal Learning immediate and delayed recall

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Study and Location	Study Design	Study Population	Intervention Groups	Frequency and Duration of Intervention	Cognitive Outcomes Measured	Results related to Cognitive Measures ^{***}
Lam et al (2009) ³⁶ Hong Kong, China	CSS (n=782)	Cognitive impairment Mean MMSE 26 Mean age 72y	<ul style="list-style-type: none"> Mind-body, e.g. TC, yoga (n=90) Stretching (n=346) Aerobic, e.g. swimming, jogging (n=117) No exercise (n=229) 	<ul style="list-style-type: none"> Self-reported regular exercise Duration of practice, >5 years or <5 years CDR = 0 (n=379), CDR = 0.5 (n=403) 	<ul style="list-style-type: none"> Global Cognition: MMSE, ADASCog Executive Function: DS-B, VS-B Language: CVFT Learning Memory: DR 	<ul style="list-style-type: none"> Stratified analysis by TC dose found improvements in MMSE (p<0.05) and DSC (p<0.05) in those attending 24 sessions vs. 4 sessions Among those with regular exercise, lower prevalence of no cognitive impairment (CDR = 0) vs. MCI (CDR = 0.5) Lowest proportion with MCI among mind-body group (p=0.003) Subjects in aerobic and mind-body group practicing >5yrs had higher MMSE, 10-min DR, VS-B and CVFT (p < 0.05) compared to stretching group Cognitive profiles between aerobic and mind-body groups not significantly different

Abbreviations used throughout table

^{***} Results reported are between groups unless otherwise noted

TC = Tai Chi

RCT = Randomized Controlled Trial

PNRCS = Prospective Non-Randomized Controlled Trial

PNCS = Prospective Non-Controlled Trial

CSS = Cross-Sectional Study

MMSE = Mini Mental Status Examination

(C) BNT = (Chinese) Boston Naming Test

(C) Mattis DRS – (Chinese) Dementia Rating Scale

ANT = Animal Naming Test

ADAS-Cog = Alzheimer's disease Assessment Scale – Cognitive Subscale
 ADL = Activities of Daily Living
 AVLT = Auditory Verbal Learning Test
 CDR – SB = Clinical Dementia Rating – Sum of Boxes
 CDT = Clock Drawing Test
 COWAT = Controlled Oral Word Association Test
 CSDD = Cornell Scale for Depression in Dementia
 CTT (1/2) = Color Trails Test (part 1 and/or part 2)
 CVFT = Category Verbal Fluency Test
 CVLT = California Verbal Learning Test
 DR = Delayed Recall
 DSC = Digit Symbol Coding
 DS-F/DS-B = Digit Span Forward/Digit Span Backward
 Dseq-F/Des-B = Digit sequence Forward/Digit sequence Backward
 HKLLT = Hong Kong List Learning Test
 MASQ = Multiple Abilities Self-Report Questionnaire
 MCS of SF-12 = Mental Component Summary of the SF-12
 NPI = Neuropsychiatric Inventory
 RAVLT = Rey Auditory Verbal Learning Test
 RBMT-CV = Rivermead Behavioral Memory Test – Chinese Version
 TMT A&B = Trail Making Test part A and part B
 VS-F/B = Visual Span Forward/Backward

Table 3

Summary of methodological quality and associated risk of bias of all randomized controlled trials.

	Cognitively Healthy Adults										Cognitively Impaired Adults				
	Lavretsky 2011	Taylor- Pillae 2010	Mortimer 2012	Nguyen 2012	Dechamps 2010	Tsai 2013	Lam 2012	Dechamps 2009	Burgener 2008	Cheng 2012	Wang 2010				
1. Method of randomization adequate?	Y	N	N	N	Y	Y	N	N	N	N	N				
2. Treatment allocation concealed? Was the knowledge of the allocated interventions adequately prevented during the study?	Y	N	N	N	Y	Y	Y	N	N	N	N				
3. Was the patient blinded to the intervention?	Y	N	N	N	N	N	N	N	N	N	N				
4. Was the care provider blinded to the intervention?	N	N	N	N	N	N	Y	N	N	N	N				
5. Was the outcome assessor blinded to the intervention? Were incomplete outcome data adequately addressed?	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y				
6. Was the drop-out rate described and acceptable?	Y	Y	Y	N	Y	Y	N	Y	Y	Y	N				
7. Were all randomized participants analyzed in the group to which the were allocated?	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N				
8. Are reports of the study free of suggestion of selective outcome reporting?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				
9. Were the groups similar at baseline regarding the most important prognostic indicators?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				
10. Were co-interventions avoided or similar?	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y				
11. Was the compliance acceptable in all groups?	Y	Y	N	N	N	N	N	Y	Y	N	N				
12. Was the timing of the outcome assessment similar in all groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				
Serious Flow Overall Quality Score	11	8	6	4	9	9	8	7	6	5	5				