



**THE EFFECT OF PHYSICAL EXERCISE ON COGNITIVE IMPAIRMENT IN PATIENTS WITH DIABETES MELLITUS**

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**ABSTRACT**

Diabetes mellitus has been proven to be associated with cognitive decline and an increased risk of dementia. Exercise, both physical activity and brain training, as a non-pharmacological intervention, has the potential to improve cognitive function. Objective to investigate the effect of physical activity on cognitive impairment in patients with diabetes mellitus. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method was used to select articles. The JBI critical appraisal checklist was used for quality assessment. Articles were searched through PubMed, Medline, and ScienceDirect databases from 2014 to 2024, using full-text articles. Out of 507 articles identified, 13 articles were included in the review, selected through a screening process based on predefined inclusion and exclusion criteria, and all demonstrated that physical activity, cognitive training, combined training, and training with lifestyle modifications can improve cognitive function in patients with type 2 diabetes mellitus. Exercise programs such as aerobic exercise, combined training, or other more specific exercises have been proven to improve cognitive function and metabolic indicators in patients with diabetes mellitus, such as HbA1c levels and insulin resistance. However, the majority of study participants were older adults.

Keywords: brain gym; cognitive dysfunction; cognitive impairment; diabetes mellitus; physical activity

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**INTRODUCTION**

A study by Roberts et al. identified that diabetes may contribute to both amnesic and non-amnesic cognitive impairment, focusing on brain areas such as the hippocampus and frontal cortex that contain insulin receptors (Roberts et al., 2013). Research shows that impaired amyloid processing in these areas may be influenced by insulin resistance and hyperglycemia, which contribute to cognitive decline (Roberts et al., 2013). In addition, Meloh et al. highlighted that insulin resistance and diabetes-related complications, such as small vessel disease, may further increase the risk of cognitive impairment and dementia (Meloh et al., 2015).

On the other hand, cognitive impairment can also interfere with a patient's ability to manage their diabetes, increasing the risk of further complications such as hypoglycemia or hyperglycemia (Ojo & Brooke, 2015). This highlights the importance of good diabetes management to prevent further cognitive decline. A review is needed to demonstrate the benefits of physical activity on cognitive impairment in patients with diabetes mellitus. This review will summarize recent study findings on the effectiveness of physical activity in addressing cognitive impairment in patients with diabetes mellitus.

Research has shown that diabetes can contribute to both amnesic and non-amnesic cognitive impairment, with a focus on brain areas such as the hippocampus and frontal cortex that

contain insulin receptors. Studies indicate that impaired amyloid processing in these regions may be influenced by insulin resistance and hyperglycemia, contributing to cognitive decline. Furthermore, research highlights that insulin resistance and diabetes-related complications, such as small vessel disease, can increase the risk of cognitive impairment and dementia (Lee & Baek, 2020).

On the other hand, cognitive impairment can interfere with patients' ability to manage their diabetes, increasing the risk of further complications such as hypoglycemia or hyperglycemia. This underscores the importance of good diabetes management to prevent further cognitive decline. Recent studies have shown that chronic hyperglycemia is a major contributor to cognitive impairment in diabetes. This condition induces oxidative stress through the production of reactive oxygen species (ROS), leading to neuronal damage and cognitive deficits. Hyperglycemia also accelerates the formation of advanced glycation end-products (AGEs), which promote neuroinflammation and disrupt insulin signaling. In addition, hyperglycemia impairs cerebral blood flow and blood-brain barrier (BBB) integrity, causing endothelial dysfunction, reduced cerebral perfusion, and increased BBB permeability, allowing neurotoxic substances to enter the brain (Feter et al., 2024).

Insulin resistance and insulin dysregulation also play a critical role in diabetes-related cognitive impairment. Insulin acts as an important neuromodulator in the brain, influencing neuronal survival, synaptic plasticity, and cognitive processes. In diabetes, insulin resistance and dysregulation disrupt brain insulin signaling, impairing neuronal function and cognition. This leads to reduced glucose uptake, increased oxidative stress, and impaired synaptic plasticity (Yu et al., 2025). Neuroinflammation is a key feature of type 2 diabetes mellitus (T2DM), adversely affecting hippocampal neurogenesis. Studies show that diabetes induces microglial activation and increases the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- $\alpha$ ). Microglial activation in the M1 (pro-inflammatory) pattern contributes to neuronal damage and impaired hippocampal neurogenesis. Research also indicates that brain atrophy has consistently been associated with type 2 diabetes, starting from the early stages of glycemic dysregulation, independent of microvascular and macrovascular complications. Cross-sectional studies have shown that physical activity correlates with larger brain volumes, particularly in regions involved in executive function, memory, and motor control (Xu et al., 2024).

Studies show that the brain regions most affected by diabetes include the prefrontal cortex, which is essential for executive function and cognitive control. Research using functional Near-Infrared Spectroscopy (fNIRS) found that older adults with diabetes exhibit different patterns of prefrontal cortical activation during challenging cognitive tasks, indicating alterations in cortical control of gait and executive function (Holtzer et al., 2018). This review aims to summarize recent findings on the benefits of physical activity for cognitive impairment in patients with diabetes mellitus.

## **METHOD**

### **Design and Search Method**

The search was conducted using the PubMed, Medline, and ScienceDirect databases, limited to the last 10 years from 2014-2024, full-text articles, and using the keywords “diabetes mellitus”, “physical activity”, and “cognitive dysfunction”. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to select the articles (Pati & Lorusso, 2018).

## Inclusion and Exclusion Criteria

A PICO analysis (Population = patients with diabetes mellitus; Intervention = physical activity; brain gym; Comparison = (-); Outcome = cognitive dysfunction) was used to screen articles. Randomized Controlled Trials (RCTs) involving participants aged >18 years, with physical or cognitive training interventions, were selected. The exclusion criteria were review articles, non-human studies, and pharmacological interventions. If an article was in a language other than English, it was translated using Google Translate.

## Search Results

The search retrieved 159 articles from PubMed, 152 articles from Medline, and 196 articles from ScienceDirect. After removing 143 duplicates, 364 articles were screened according to the inclusion criteria, and 13 articles met the criteria.

### DIAGRAM PRISMA

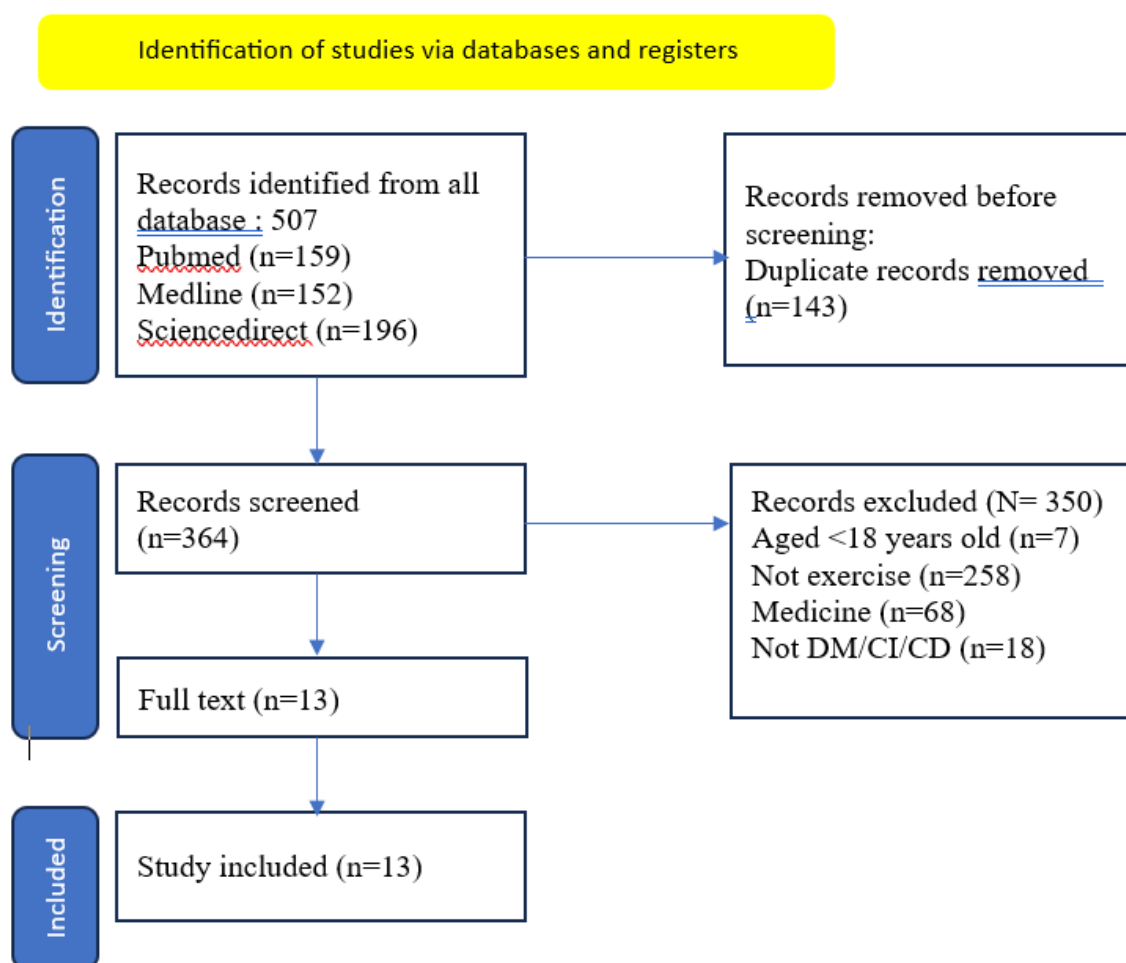


Figure 1. Flowchart of Article Selection

## Quality Assessment

The quality of the articles was assessed using the JBI critical appraisal checklist. This approach consists of 13 questions that must be answered with *yes*, *no*, or *unclear* for each article reviewed, and then categorized as low risk of bias (score  $\geq 70\%$ ), moderate risk of bias (score 50–69%), or high risk of bias ( $\leq 49\%$ ). Of the 13 articles selected, 5 were rated as having a low risk of bias, 6 had a moderate risk of bias, and 2 had a low risk of bias (see Table 1). The studies analyzed were conducted in Japan, the United States, Spain, Thailand, Hong Kong, Iran, China, and Israel, with a total of 7,681 participants, the majority of whom were older adults. Four out of the 13 studies involved middle-aged participants, while the remaining studies focused on older adults. The duration of the studies ranged from several weeks to several years.

Table 1.  
Risk of Bias using JBI Critical Appraisal Checklist for Randomized Controlled Trial










































































































































































No	Writer	Parameters													Raw score and %	Risk of Bias
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13		
1	Oki, Y., et al. (2024)														11/13= 84.61%	Low
2	Matveeva, MV, et al. (2019)														5/13= 34.46%	High
3	Martínez-Velilla, N., et al. (2021)														9/13= 69.23%	Mode rate
4	Wong, C.-W., et al. (2020)														8/13= 61.53%	Mode rate
5	Wang, Y., et al. (2023)														11/13= 84.61%	Low
6	Silverman, JM, et al. (2023)														12/13= 92.30%	Low
7	Ghahfarokhi, MM, et al. (2024)														12/13= 92.30%	Low
8	Espeland, MA, et al. (2017)														8/13= 61.53%	Mode rate
9	Espeland, MA, et al. (2018)														7/13= 53.84%	Mode rate
10	Bahar-Fuchs, A., et al. (2020)														11/13= 84.61%	Low
11	Ploydang, T., et al. (2023)														9/13= 69.23%	Mode rate
12	Chen, Y., et al. (2023)														7/13= 53.84%	Mode rate
13	Silveira Rodrigues, J.G., et al. (2021)														5/13= 38.46%	High

Table 2.  
Summary of Filtered Studies

No	Writer	Design	Duration	Participant	Intervention group	Control Group	Devices	Results
1	Y. Oki, et al (2024) In Japan	RCT	18 months	N=203 Tamba residents with DM and/or hypertension aged 65-85 years	N=101 Multimodal intervention (disease-related lifestyle management, physical activity, nutritional counseling, and cognitive training)	N=102 Written health interventions	DASC-21  Five Times Sit-to-Stand Test (FTSST)  Neuropsychological tests	Multimodal intervention in the elderly showed significant results on global cognition (CI 95% 0.004-0.27; p value=0.009)
2	MV Matveeva, et al(2019) In Russia	RCT Comparative study	6 months intervention 6 months observation of effectiveness and stability of results	N=120 patients with type 2 diabetes age 45-65 years	N=90 Divided into 3 intervention groups. Group 1 computer training twice a week. Group 2 physical activity exercises. Group 3 consumption of acatinol memantine	N=30 without any particular intervention.	<i>Montreal Cognitive Assessment</i> (MoCA) and memory test involving recall of 12 words	Consumption of acatinol memantine is more effective in improving cognitive function compared to other rehabilitation methods (p value=0.001}
3	N. Martinez-Velilla, et al (2021) In Spain	RCT	5-7 days per week training sessions	N=103 Patients aged ≥75 years with type 2 DM who are treated in the acute care unit of the elderly at a tertiary hospital, Barthel Index score ≥60 Able to ambulate (with or without assistance) Able to communicate and collaborate with research team	N=54 Progressive resistance training, balance and walking	N=47 Without intervention	Short Physical Performance Battery (SPPB), Barthel index Mini-Mental State Examination questionnaire (MMSE) Yesavage Geriatric Depression Scale Visual analog scale of the EuroQol-5 Dimension (quality of Life) Incident delirium (Confusion Assessment Method)	There was a significant increase in cognitive function in the intervention group compared to the control group (95% CI, 0.7;2.6, p value 0.001).

No	Writer	Design	Duration	Participant	Intervention group	Control Group	Devices	Results
4	Chit-Wai Wong, et al. (2020) In Hong Kong	Prospective single blinded, randomized controlled study	10 weeks	N=139 Patients with type 2 DM Age $\geq 65$ years with memory/memory complaints and HbA1c 7-9%	N=73 Combination of patient empowerment and cognitive training exercises once a week for 2.5 hours each	N=66 Standard care	Mini-Mental State Examination questionnaire (MMSE) The International Shopping List test Continuous Paired Associate Learning test in the computerized Cogstate Neuropsychological Test Battery Verbal Fluency Test and Controlled Oral Word Association Test General Health Questionnaire (GHO)-Chinese version Morisky Medication Adherence Scale	The results showed that the intervention did not significantly reduce glycosylated hemoglobin levels in the intervention group compared to the control group, but the intervention group showed significant progressive improvement in memory over 12 months, and executive function improved significantly at 12 months (p-value=0.015)
5	Y. Wang, et al. (2023) In China	RCT	12 months	N=100 Patients with type 2 DM Age 60-75 years BMI $\geq 18.5$ - $\leq 35$ kg/m <sup>2</sup> Normal cognitive function (MMSE $\geq 27$ points, MoCA $\geq 26$ points) Elementary school education or above Duration of type 2 DM $> 5$ years	N=50 Aerobic exercise 3x per week 60 minutes each session	N=50 No change in activity	International Physical Activity Questionnaire (IPAQ) MRI Mini-mental State Examination (MMSE) The Montreal Cognitive Assessment scale (MoCA)	In the aerobic exercise group, the total volume of the hippocampus increased compared to baseline (p=0.034), correlation between aerobic exercise and increased total volume of the hippocampus (OR: 1.091, [95%CI 0.969; 1.228] p=0.002).
6	JM Silverman, et al. (2023) In the United States	RCT	8 weeks	N=180 US military veteran at least 55 years with type 2 DM DSMQ score 18 or $< 20$	N=90 Adaptive CCT	N=90 Active control	Diabetes Self-Management Questionnaire (DSMQ)	Adaptive CCT improved DSMQ (p=0.017) and attention/executive function domain changes (p=0.305)
7	MM Ghahfa	RCT	6 weeks	N=48 Elderly aged	N=16 High-	N=16 Not	Mini-Mental State Examination	HIFT showed significant

No	Writer	Design	Duration	Participant	Intervention group	Control Group	Devices	Results
	rrokhi, et al. (2024) In Iran			≥60 years with type 2 DM Cognitive impairment/dementia (MMSE score >23) Fasting blood sugar ≥126 mg/dL HbA1c ≥6.5% Population of Iran	Intensity Functional Training (HIFT)  N=16 Low-intensity functional training (LIFT)	participating in any exercises	(MMSE) The Symbol Digit Modalities Test (SDMT) The California Verbal Learning Test Second Edition (CVLT-II) The Brief Visuospatial Memory Test-Revised (BVMT-R) The Stroop Color and World Test (SCWT)	improvements in cognitive variables such as global cognition, attention, speed, memory, and learning, likely through improvements in metabolic and functional status (all, $p \leq 0.004$ )
8	MA Espeland, et al. (2017) In the United States	RCT	10 years	N=5145 People with type 2 DM Overweight or obesity BMI >25 kg/m <sup>2</sup> or >27 kg/m <sup>2</sup> in patients with insulin injections Age 45-76 years HbA1c <11% BP <160/100 mmHg Triglycerides <600 mg/dL	N=1918 Intensive lifestyle intervention	N=1884 Diabetes support and education	The Paffenbarger Physical Activity Questionnaire The Beck Depression Inventory The Look AHEAD Movement and Memory Study The Look AHEAD Brain MRI study The cognitive battery Modified Mini-Mental State Examination (3MSE)	A long-term intensive lifestyle intervention aimed at reducing body weight and increasing physical activity did not result in significant differences in the prevalence of cognitive impairment among overweight or obese adults with type 2 diabetes ( $p$ value=0.93)
9	MA Espeland, et al (2018) In the United States	RCT	10 years	N=1091 People with type 2 DM Aged 45-76 years BMI>25 kg/m <sup>2</sup> or >27 kg/m <sup>2</sup> if with insulin HbA1c <11% BP 160/100 mmHg Triglycerides <600 mg/dL	N=554 Intensive lifestyle intervention (ILI): diet modification and physical activity	N=537 Diabetes Support and Education (DSE): 3 sessions per year focusing on diet, physical activity and social support	The Rey Auditory Verbal Learning Test (AVLT) The Digit Symbol Coding Test (DSC) The Modified Stroop Color and Word Test (MSCWT) and the Trail Making Test-Part B (TMT-B) The Modified Mini-Mental Status Exam (3MSE)	There was no significant difference in changes in cognitive function between the intervention and control groups in participants with BMI>27 at 4 years of follow-up after the intervention ended ( $p$ -value=0.795). However, in participants with BMI ≤27, the intervention

No	Writer	Design	Duration	Participant	Intervention group	Control Group	Devices	Results
								group showed significant improvement in cognitive function at 4 years of follow-up (p-value=0.005).
10	Fuchs, et al. (2020) In Israel	<i>Single blind trial</i>	8 weeks	N=84 Diagnosed with type 2 DM without being diagnosed with dementia or Alzheimer's disease	N=44 Tailored and adaptive computerized cognitive training (TA-CCT)	N=40 Generic computerized cognitive training (G-CCT)	Mini-Addenbrooke's Cognitive Evaluation (M-ACE), L'Hermitte Board, Logical Memory test, Rey Auditory Verbal Learning Test (RAVLT), Rey-Ostrich Figure Copy Test (ROFCT), Verbal Fluency, Digit Span, Digit-Symbol Coding, Boston Naming Test, and Trail-Making Task  Diabetes Self Management Questionnaire (DSMQ)	There was a moderate improvement in global cognitive performance immediately after the intervention, with further small improvements observed at 6-month follow-up (p-value=0.007).
11	T. Ploydang, et al. (2023) In Thailand	RCT	12 weeks	N=33 Elderly aged 60-75 years DM type 2	N=16 <i>Aquatic Nordic Walking (ANW)</i> 3x a week for 12 weeks	N=17 Without intervention	Homeostasis of insulin resistance (HOMA-IR) Montreal Cognitive Assessment (MoCA)	The results showed that ANW significantly improved functional physical fitness, reduced plasma glucose and insulin resistance, and improved vascular reactivity. MoCA scores increased in the intervention group (p-value=0.031)
12	Y. Chen, et al (2023) In China	RCT	24 weeks	N=328 Elderly aged ≥60 years DM type 2 Mild cognitive impairment but not	N=107 Tai chi chuan, get 24 simple Tai Chi Chuan forms	N=111 Without intervention	Montreal Cognitive Assessment (MoCA)	The Tai Chi Chuan group had significantly better global cognitive function



No	Writer	Design	Duration	Participant	Intervention group	Control Group	Devices	Results
				dementia Not exercising regularly in the last 3 months	N=110 fitness walking, get fitness walking exercise  Both groups participated in 60 minutes/session training, 3x/week.			scores than the fitness walking group (p-value=0.46)
13	JG Silvera-Rodrigues, et al. (2021) In Brazil	RCT	8 weeks	N=31 DM type 2 with sedentary lifestyle Adults or elderly	N=16 Combined training (aerobic and resistance training)	N=15 Without intervention	Adapted Senior Fitness Test Sit-to-stands and arm-curls movements The 6 min walking test (6MWT) Montreal Cognitive Assessment (MoCA)	The results showed that the CT program significantly improved specific cognitive domains, including inhibitory control (d = 0.89), working memory (d = 0.88), cognitive flexibility (d = 0.67), and attention/concentration (d = 0.64) in T2DM subjects.

## DISCUSSION

Diabetes mellitus, as a chronic disease characterized by impaired glucose metabolism, can negatively impact various body systems, including the cognitive system. A study by Janson et al. (2017) showed that diabetes mellitus, particularly type 2 diabetes, can increase the risk of cognitive decline, including impairments in memory, attention, and executive function. One factor that may exacerbate cognitive decline in diabetic patients is chronic hyperglycemia, which can cause vascular damage and reduced cerebral blood flow (Luchsinger et al., 2013). Cognitive impairment in patients with diabetes mellitus can, in turn, affect their ability to manage their condition, potentially leading to further complications such as hypoglycemia or hyperglycemia. Several approaches to understanding and addressing the impact of type 2 diabetes on cognitive function, particularly in the elderly, include physical exercise and cognitive training.

The literature reviewed indicates that physical activity, including aerobic exercise, resistance training, Tai Chi Chuan, and aquatic walking, can improve cognitive function in individuals with type 2 diabetes (Velilla et al., 2021; Wang et al., 2023; Ploydang, 2023; Chen et al., 2023; Rodrigues, 2021). This is consistent with findings that physical exercise can increase hippocampal volume, where hippocampal atrophy is often used as a parameter for mild cognitive impairment (Wang et al., 2023). The prevalence of cognitive impairment in type 2 diabetes patients with obesity showed no difference between control and intervention groups in an intensive lifestyle intervention study (Espeland et al., 2017). Similarly, no significant cognitive changes were found between intensive lifestyle and control groups with BMI >27, although significant improvements were observed in those with BMI ≤27 (Espeland et al., 2018). Both cognitive training and combined interventions (cognitive training with physical exercise) have also proven effective in improving cognitive function (Wong et al., 2022; Fuchs et al., 2020; Silverman, 2023). However, a study by Matveeva et al. (2019) found that the use of acatinol memantine was more effective in improving cognitive function compared to computer-based training and physical activity.

### **Physical and Cognitive Training**

Physical exercise, as a non-pharmacological intervention strategy, has the potential to enhance cognitive function through several mechanisms, including increased cerebral blood flow, reduction of systemic inflammation, and positive effects on glucose and insulin metabolism (Colberg et al., 2016). Exercise programs such as aerobic training, combined training (CT), and specific activities such as aquatic Nordic walking have been shown to have potential to improve specific cognitive functions and metabolic indicators, such as HbA1c and insulin resistance. This aligns with Barnard et al. (2019), who demonstrated the effectiveness of aerobic exercise, such as walking or cycling, in improving memory and attention in diabetic patients. The underlying mechanisms include various interrelated biological factors. Jeon et al. (2017) reported that physical exercise increases the production of brain-derived neurotrophic factor (BDNF), a protein that supports the growth and maintenance of nerve cells, particularly in memory-related areas such as the hippocampus. A study by Wang et al. (2023) found that moderate aerobic exercise for one year increased hippocampal volume, improving memory and learning ability in type 2 diabetes patients. This is consistent with Liu-Ambrose (2010), who found that physical exercise increases brain volume in memory-related areas. Tai Chi Chuan has also shown significant results in improving cognitive function in elderly patients with type 2 diabetes and mild cognitive impairment. Studies indicate that Tai Chi is particularly effective in improving global cognitive function and memory in women with a BMI of 24 or less, a diabetes duration of more than 10 years, and fewer comorbidities.

### **Computerized Cognitive Training (CCT)**

Computer-based cognitive training has shown mixed results. Some studies found moderate improvements in global cognitive function, but not all reported significant effects on diabetes self-management or cognitive outcomes. Post-hoc analyzes suggested that engaging in computer-related activities could improve diabetes self-management and memory-related cognitive outcomes.

### **Multimodal Interventions**

Interventions combining physical exercise, cognitive training, nutritional counseling, and vascular risk management demonstrated positive results in improving global cognitive function scores in patients at risk of dementia. These programs also improved lower limb muscle strength and respiratory muscle strength, indicating comprehensive benefits beyond cognitive enhancement.

## Intensity and Type of Exercise

Various types of physical exercise have been shown to benefit cognitive function, depending on duration, intensity, and exercise type. High-intensity, low-volume training (HIFT) was found to produce better cognitive and physical improvements compared to low-intensity, high-volume training (LIFT). Baker (2010) also noted that moderate-to-high intensity aerobic exercise yielded better cognitive improvements than low-intensity physical activity.

## CONCLUSION

Based on the literature reviewed, physical and cognitive interventions have substantial potential to improve or maintain cognitive function in patients with type 2 diabetes. However, outcomes vary depending on the type, duration, and intensity of the intervention, as well as individual participant characteristics. Physical exercise not only aids glycemic management but also enhances specific cognitive domains such as memory, attention, and executive function. Multimodal interventions appear to be the most effective for preventing cognitive decline and improving patients' quality of life.

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