Title: The Effect of Controlling the Cardiovascular Risk Factors on the Cognitive Decline Prevention in the Elderly: A Systematic Review

Running Title: Risk Factors of Cognitive Decline

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Abstract

Along with the growing percentage of the elderly population, neurodegenerative diseases including dementia are increasing in the world. Vascular risk factors are considered as a notable goal for cognitive decline prevention. We reviewed the effect of cardiovascular risk factors on cognitive decline prevention in the elderly to evaluate the quantity and quality of evidence in managing the elderly population with cognitive decline. Analysis data were available for 25 studies that examined the effect of controlling cardiovascular risk factors on the risk of cognitive impairment. These risk factors including, diabetes mellitus, high blood pressure, high cholesterol levels, exercise and physical activity. Most positive evidence was available for exercise and physical activity. On the other hand, diabetes mellitus and cholesterol modifications have not positive impact on cognitive function. Hypertension control studies were incongruous. The large-sampled robust Randomized Clinical Trial should be designed to reach sufficient evidence for several cardiovascular risk factors modifications in cognitive decline prevention.

Keyword: Cardiovascular, Risk factors, Cognitive decline, Elderly, Prevention

Introduction

Increased life expectancy throughout the world leads to an increasing number of people affected by chronic diseases that have become major health challenges. (Brown, 2015)Evidence revealed that many chronic diseases in the elderly have the common shared risk factors. In the top of these chronic diseases, dementia and cognitive impairment is the most prevalent cause of morbidity and mortality in elderly. Cognitive decline in older adults is a major public health problem and can diminish independence and quality of life.(Livingston, Huntley *et al.*, 2020) Approximately 47 million people worldwide have dementia in 2015, and that number will triple by 2050.(Patterson & International, 2018) In the absence of a cure for the disease or treatment, reducing the risk of dementia is doubly important.(Cummings, Morstorf *et al.*, 2016) Even when effective treatments are available, reducing the risk of disease occurrence will be a fundamental solution; For many non-communicable diseases with existing treatments (such as diabetes, cancer, and heart disease), risk reduction is an important element of diseases prevention.(Bloom, Schnaider-Beeri *et al.*, 2017)

The main risk factors for the onset of Alzheimer's and other dementias are age, family history, and predisposed genes such as apolipoprotein E allele ε4.(Hsiung & Sadovnick, 2007) But none of these risk factors can be altered or modified by medical interventions or individual behavior. There is sufficient evidence to support the association between multiple variable risk factors and decreased cognitive decline risk and this review discusses these risk factors.(Baumgart, Snyder *et al.*, 2015)

Vascular risk factors are increasingly considered as important causes of dementia and therefore as a goal for future treatments. Middle age vascular risk factors seem to be most associated with cognitive decline in old age.(Whitmer, Sidney *et al.*, 2005)The US National Institutes of Health emphasizes that diabetes mellitus, smoking, depression, mental or physical inactivity, and poor diet are related to the risk of cognitive decline. The list then expanded to include high blood pressure, obesity, and poor education.(Barnes & Yaffe, 2011) Even the association between high blood pressure and AD risk is complex and age-dependent, some evidence showing that in middle-aged, not older population, blood pressure is associated with a 50% increase in AD and dementia risk.(C. J. Lee, Lee *et al.*, 2022) High blood pressure can increase the risk of AD by reducing the vascular integrity of the blood-brain barrier, which leads to extravasation or leakage of protein into brain tissue, which in turn leads to cell damage, apoptosis, and increased Aβ accumulation.

However, the direct causal relationship between blood pressure and subsequent cognitive decline is questionable because there is also growing evidence that blood pressure may be a protective response to cerebral hypoperfusion, which was demonstrated 10 years before the onset of AD.(Corrada, Hayden *et al.*, 2017)According to the obesity epidemic and growing evidence of the relationship between body mass index (BMI) and cognition, several studies have found that being overweight or obese were independent risk factors for cognitive decline (Doruk, Naharci *et al.*, 2010; Y. Lee, Back *et al.*, 2010; Naderali, Ratcliffe *et al.*, 2009; Nilsson & Nilsson, 2009).Obese individuals show smaller whole brain and total gray matter volume than normal. (Gunstad, Paul *et al.*, 2008)

On the other hand, there is a U-shaped relationship between weight and cognitive function: both low and high weight is associated with a high risk of AD and cognitive impairment. This relationship can also have an age-related element. (Bae & Park, 2021) There are data for the opposite relationship in the years before the onset of the disease; Such as weight loss that may be due to cognitive deficits during the pre-dementia phase of AD.(Luchsinger, Patel *et al.*, 2007)Diabetes has been shown to directly increase dementia risk by affecting Aβ accumulation in the brain. Other studies show that diabetes can increase the risk of cerebrovascular disease, but not the pathology of AD.(Geert Jan Biessels & Despa, 2018) Even though proper diabetes control has been approved and recommended to prevent most diabetes-related diseases, its effect on preventing or delaying the onset of dementia is not known.(Ravona-Springer & Schnaider-Beeri, 2011) In addition to glycemic control, there are several factors associated with diabetes that can interact with the clinical manifestations of dementia and neuropathology, as well as the rate of functional and cognitive decline.(G. J. Biessels, Deary *et al.*, 2008) A review study found that severe hypoglycemia did not benefit the cognitive function of young people with type 1 diabetes, while older people with type 2 diabetes benefited from the treatment in terms of information processing speed and executive function.(Moheet, Mangia *et al.*, 2015)

Systematic reviews and prospective studies on the association between cholesterol levels in middle age, old age, and dementia have yielded combined results, including no association between cholesterol levels and vascular dementia.(Park, Kim *et al.*, 2013) While some observational studies have shown that statin used to control cholesterol levels reduce the risk of dementia, one review

in Cochrane (McGuinness, Craig *et al.*, 2016) and other review studies found no evidence that statin use reduces the risk of dementia.

Materials and Methods

Search strategy

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. (Moher, Liberati *et al.*, 2009)A systematic search of scientific article databases including PubMed, Scopus, Google scholar, SCIELO and Cochrane Central was performed using the appropriate keywords and search protocol for each database. For example, in the PubMed database, based on the MeSH term, the relevant search keywords and search strategy were determined based on this database.

The inclusion criteria were related clinical studies published in English that included elderly population and intervened for modification of at least one of the cardiovascular risk factors (diabetes, dyslipidemia, hypertension, sedentary lifestyle and obesity) and evaluated the cognitive state as an outcome measure.

The general search model was based on the following phrases: Intervent * OR modification OR modify OR control OR change in combination with: vascular OR hypertension OR hyperlipidemia OR dyslipidemia OR diabetes OR obesity OR overweight, in combination with cogniti * OR memory * OR dementi * OR mind with exclusion of non-human studies. The time limit for publishing studies after 2000 was accepted. This search strategy was then adapted to the characteristics of other databases. We described the search strategy in Figure-1 by details. The search terms with similar meanings were combined using the OR logic, and the search terms were coupled using the AND logic. The search syntax was written separately according to any database.

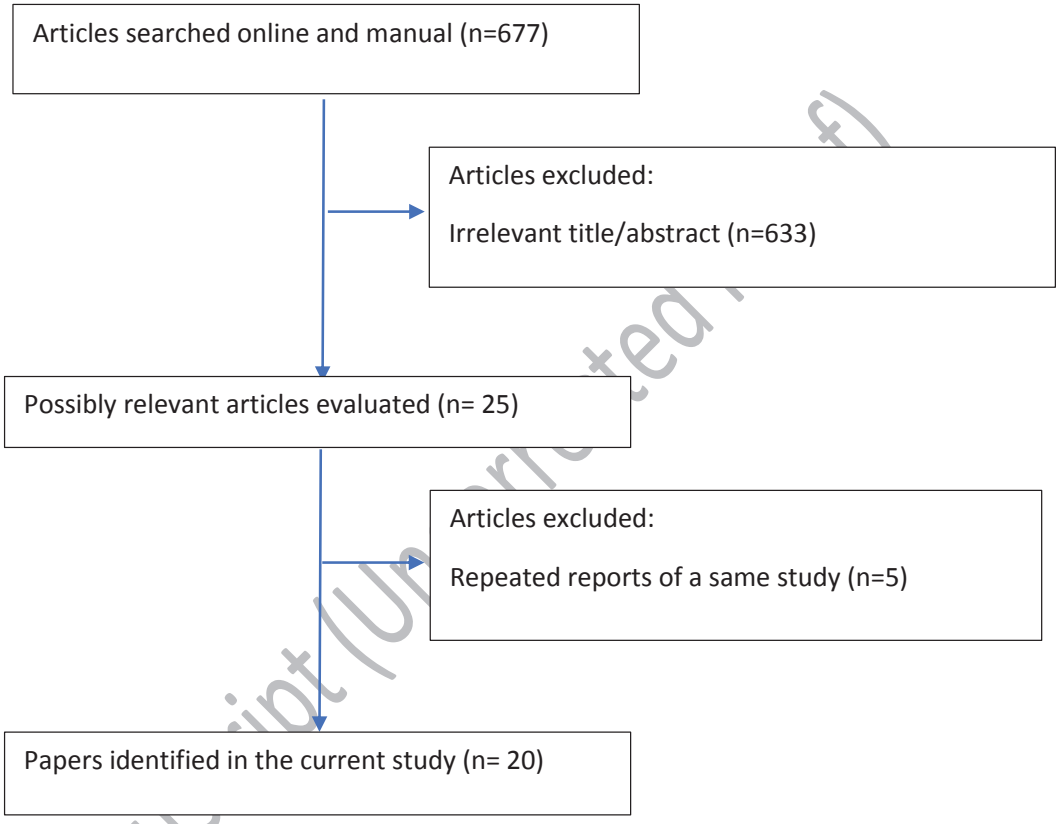

Figure 1- Flowchart: Search and selection of articles to enter the study

Articles found in a total of 4 databases after deleting duplicates included 677 articles. Two researchers blind with each other screened the searched studies and evaluated them based on inclusion criteria, titles, and abstracts of the articles. When there were doubts about the selection of an article, the full text of the article was studied. In cases where there was disagreement, the two researchers consulted with another independent researcher about the paper and ultimately decided whether or not to include the paper. Then, the required data were extracted from qualified articles according to the data collection form for RCT studies.

Study results

The PRISMA flow chart shows the process of identifying, screening, and evaluating selected studies (Figure 1). The initial search resulted in 677 eligible articles, which two independent researchers scrutinized. Of these 677 articles, 633 articles were excluded from further research for various reasons, including duplicate articles. Studies were included in the review if they fulfill the following inclusion and exclusion criteria. Inclusion criteria including, the randomized controlled trial as study design, published as full text in the scientific journal. Exclusion criteria including, reported insufficient data and published only as abstracts for conferences and proceedings.

Finally, 25 articles remained on which data analysis was performed. Studies have examined the effect of controlling cardiovascular risk factors and lifestyle on the risk of cognitive impairment. These risk factors include diabetes mellitus, high blood pressure, high cholesterol levels, and exercise and physical activity have been studied as one of the lifestyle factors affecting cardiovascular disease.

Diabetes

In the articles review, six articles were related to the study of intensive blood-glucose control effect on cognitive function (Table 1). Of these articles, five were related to the results of one study. This study is called Look AHEAD, and its protocol was published in 2003.(Ryan, Espeland *et al.*, 2003)

Table 1 - Articles in which diabetes as a risk factor for cardiovascular disease has been the goal of treatment

Study name-author-publication year	Study population	Sample size	Intervention	Assessment	Follow-up duration	Effect on cognitive function
Look-AHEAD study; Wing, 2011[17]	overweight or obese volunteers with type 2 diabetes	5154	intensive lifestyle intervention (ILI) VS diabetes support and education (DSE)	clinical interview, a standardized neuropsychological assessment of major cognitive domains, assessment of the individual's functional abilities with a knowledgeable proxy	9.8 years	no significant differences of global cognitive function, verbal memory, attention, executive function, or processing speed.
ADVANCE, 2001[36]	Patients with DM-II at age>30 years, age >50 years at the time of the study, history of major macrovascular or microvascular disease or at least one other risk factor for vascular disease	11140	intensive blood glucose control VS standard glucose control	MMSE	4.3 years	No effect on cognitive decline or incident dementia

The primary purpose of this study was evaluation the long-term effects of a severe weight loss program in patients with type 2 diabetes over 4 years. About 5,000 men and women with type 2 diabetes aged 45 to 47 years participated in this study, in which two types of interventions were performed as intensive lifestyle intervention and diabetic support and education.(Look & Wing,

2010) In the ILI intervention, participants had a diet with 1200-1800 calories per day and more than 175 minutes per week of physical activity, with a goal of 7% weight loss. Participants were followed for an average of 9.8 years. In this study, participants were evaluated with cognitive batteries including, Modified Mini-Mental State Examination, Rey Auditory Verbal Learning Test, Digit Symbol Coding, Trail-Making Test, Modified Stroop Color-Word Test, and brain imaging assessments. In this study, no significant difference was seen between the two intervention groups in terms of cognitive function. However, in the ILI group, the rate of brain hyperintensities lesions was lower, which could mean better overall brain health. Negative effects on cognitive function were observed in the subgroup of very obese patients with body mass index above 40, and patients with a positive history of cardiovascular disease.

Another study was called ADVANCE, in which participants also had type 2 diabetes. A total of 5,571 patients over the age of 55 (mean age 65 years) were included in the study. In the intervention group, treatment with slow-release glycoside at a dose of 120-30 mg plus metformin, thiazolidinediones, acarbose, or insulin was performed to achieve HBA1c less than 6.5%. In this study, no cognitive changes based on MMSE were seen after five years, and a non-significant increase in the dementia incidence was seen in the study group.(Look & Wing, 2010)

Hypertension

There were five articles on the effects of blood pressure control on the incidence of cognitive disorders, and the results of four studies were reported. (Table 2)(Forette, Seux *et al.*, 2002; Lithell, Hansson *et al.*, 2003; Peters, Beckett *et al.*, 2008; Tzourio, Anderson *et al.*, 2003)

Table 2 - Articles in which hypertension as a risk factor for cardiovascular disease has been the goal of treatment

Study name-author-publication year	Study population	Sample size	Intervention	assessment	Follow-up duration	Effect on cognitive function
Syst-Eur study; Forette et al. 2002[18]	SBP>160 mmHg DBP> 95 mmHg Age>60 ys	2418	nitrendipine (10-40 mg/d) with or replaced by enalapril maleate (5-20 mg/d), hydrochlorothiazide (12.5-25 mg/d), or both second-line medications VS placebo	MMSE	2 years in double blind and 3.9 years in total	blood pressure-lowering therapy initiated with a long-acting dihydropyridine protects against dementia
PROGRESS; Tzuorio 2003[19]	Pateints with prior stroke or TIA	6105	Perindopril ± indapamide VS placebo	DSM-IV criteria for diagnosis of dementia	3.9 years	34% risk reduction for dementia or cognitive decline in recurrent stroke and no clear effect for either dementia or cognitive decline in the absence of recurrent stroke
SCOPE; Lithel et al 2003[20]-2008	Pateints with SBP 160-179 mmHg and/or DBP 90-99 mmHg and MMSE score ≥ 24 and age 70-89 years	4964	candesartan or placebo with open-label added antihypertensive therapy as needed	MMSE	3.7 years	Fall in MMSE score in both groups with no difference
HYVET-COG; Peters et al 2008[21]	SBP 160-200 mmHg Age ≥ 80	3336	1.5 mg slow release indapamide ± 2-4 mg perindopril VS placebo	MMSE	2.2 years	no decrease in incidence of dementia

In all these studies, cognitive status assessment has been one of the secondary goals of the study. The primary purpose was to investigate adverse vascular consequences such as stroke, cardiovascular events such as MI, or cardiac death. The sample size was between 2418 and 6105 people. All studies were performed in the elderly group and one (HYVET-COG) in the oldest-old group.(Peters et al., 2008) The MMSE tool was used to assess cognitive function. The follow-up period in these studies was between 2.2 and 3.9 years.

In these studies, a 24% to 42% reduction in stroke incidence was seen. The HYVET-COG study, which targeted the oldest-old, also showed a significant reduction in stroke incidence. In all these studies, no significant effect was seen in cognitive function. A SCOPE study on data reanalysis found an impact on some cognitive domains, including episodic memory.(Lithell et al., 2003)

Lipid-profile disorders

Two studies specifically examined the effect of LDL-reducing therapies on cognitive disorders (Table 3). ("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002; Shepherd, Blauw *et al.*, 2002)The first study was the MRC / BHF Heart Protection Study, which compared simvastatin with placebo. In this study, with a 5-year follow-up, cognitive function as a secondary outcome was assessed by the cognitive assessment telephone interview test("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002). In the second PROSPER study, 5804 people in the two randomized groups received Pravastatin or placebo. Cognitive status in this study was evaluated as a secondary outcome by the MMSE test. Both studies have shown positive effects of treatment on primary outcomes such as all-cause mortality, coronary death, non-vascular death, non-fatal myocardial infarction, and stroke. But in both studies, no effects were seen on cognitive function.(Shepherd et al., 2002)

Table 3 - Articles in which cholesterol as a risk factor for cardiovascular disease has been the target of treatment

Study name-author-publication year	Study population	Sample size	Intervention	Assessment	Follow-up duration	Effect on cognitive function
MRC/BHF Heart protection Study; 2002[22]	UK adults (40-60 years) with coronary artery disease, other occlusive arterial disease, or diabetes	20536	Simvastatin VS placebo	Telephone Interview for Cognitive Status (TICSm)	5 years	No effect on cognition
PROSPER; Shepherd et al 2002[23]	Pateints 70-82 years, with a history of, or risk factors for, vascular disease	5804	pravastatin VS placebo	MMSE	3.2 years	No effect on cognition

Physical activity and exercise

Seven studies have examined the effects of exercise and physical activity on cognitive function (Table 4). (Carles, Curnier *et al.*, 2007; Emery, Hsiao *et al.*, 2003; Fiocco, Scarcello *et al.*, 2013; C. V. Teixeira, Gobbi *et al.*, 2013; Xu, Delmonico *et al.*, 2017; Yamamoto, Yamanaka *et al.*, 2009)In 2013, Fiocco and colleagues measured the effect of exercise and lifestyle intervention programs on the cardiovascular and metabolic status of middle-aged people with type 2 diabetes. In this pilot study, 17 middle-aged patients underwent 24-week exercise intervention and were assessed using CVLT, DSST, and Fluency test cognitive tests. This study showed that despite the improvement of cardiovascular tenacity, BMI decrease, and improvement of depressive symptoms, no change in glucose and fat levels occurred, and contrary to expectations, a decrease occurred after cognitive tests. However, this decrease in CVLT was limited to patients who simultaneously had diabetes and high blood pressure.(Fiocco et al., 2013)

Table 4 - Articles in which exercise and physical activity as a protective factor against cardiovascular disease have been the goal of treatment

Study name-author-publication year	Study population	Sample size	Intervention	Assessment	Follow-up duration	Effect on cognitive function
Teixeira 2017[31]	Patients with HTN and/or DM	13	aerobic VS resistance training three times a week	cognitrone test (Attention and Concentration test)	12 weeks	Significant improvements in attention and concentration levels no significant differences in the reaction time test and selective attention
Fiocco 2013[25]	Middle-aged participants with DM-II	17	Diabetes Exercise and Healthy Lifestyle Service	California Verbal Learning Test (CVLT), Digit Symbol Substitution Tasl (DSST) and fluency test	24 weeks	cognitive performance dec lined. decline on the CVLT was limited to adults with co-morbid T2DM and hypertension
Yamomoto 2009[28]	Elderly people (>75 years) with DM or IFG	129	group exercise program 2–4 times per week	MMSE, revised Hasegawa Dementia Scale (HDSR), and Koh's design block test	2 years	Improvement in delayed recall function MMSE changed in all participants
Emery 2003[27]	patients with coronary artery disease Mean age 62.6 years	33	Two exercise sessions ± music	Verbal Fluency	-	a significant increase in performance associated with the music condition
Carles 2007[29]	Male patients	24	21 day	mental arithmetic test, a Trail Making	-	no significant difference

	with CAD			Test, and two memory tests (COG) a tracking task (TRAC) to measure motor precision		appeared between rest and acute exercise for COG score acute exercise significantly improved the TRAC performance
Xu 2017[26]	Women 50-80 years with BMI 30-50 kg/m^2	25	DASH Dietary Education Intervention Tai Chi Exercise Intervention RT Exercise Intervention for 12 weeks	-	-	improvements in domain specific cognitive function
Espeland MA 2017[30]	individuals with diabetes and 1,061 individuals without diabetes	415	The Lifestyle Interventions and Independence for Elders (LIFE) trial randomized controlled clinical trial of physical activity intervention (walking, resistance training, and flexibility)	Standardized measures of physical and cognitive function average of	2 years post-randomization	No positive effect of the intervention on cognitive function in general cognitive function and recent memory of people with diabetes were better in the intervention group

The Yamamoto study cognitively assessed 129 individuals over the age of 75 with MMSE and HDSR. In this study, three groups of people with diabetes, IGT, NGT participated in an exercise program 2-4 times a week and a nutrition training program. In people with MMSE diabetes, HDSR had a lower baseline than NGT, which returned to NGT after lifestyle intervention.(Yamamoto et al., 2009)

The Carles et al study examined the short-term exercise effect on cognitive function in patients with coronary heart disease and heart failure. In this study, 24 men with a mean age of 51.6 years were cognitively assessed by COG and TRACK after exercise. This study showed that exercise training increases the positive effect of exercise on cognition.(Carles et al., 2007)Overall, aerobic

exercise seems to improve cognitive function. The positive effect of exercise is characterized by increased cerebral blood flow and levels of neurotransmitters.

Espeland et al measured the physical activity effect on the cognitive and physical function of sedentary people. The LIFE study measured the physical activity effect intervention in people aged 70 to 89 years and two years later performed the cognitive and physical evaluation of 415 patients with diabetes and 1061 patients without diabetes. Although there was no positive effect of the intervention on cognitive function in general, it showed that the overall cognitive function and recent memory of people with diabetes were better in the intervention group.(Espeland, Lipska *et al.*, 2017)

In another study, Teixeira et al. Examined the effect of aerobic / resistance training and exercise on diabetic and hypertensive patients over 12 weeks. This study showed that improved attention and concentration occurred in patients without affecting reaction time that could be justified by increasing perfusion and oxygen delivery to the brain due to exercise. In this study, 21 patients were included in the study. After eight patients left, the remaining 13 patients underwent exercise according to the Ramp protocol. A cognitive assessment-based MTTS (Mental test and training system) test was performed. In this study, there was an improvement in attention and concentration, which will be very effective in diabetic patients to manage their various medications and improve social relationships. Limitations of this study: It was a limited period of exercise.(R. B. Teixeira, Marins *et al.*, 2019)

Compared to the studies reviewed in the previous sections, studies examining the effect of exercise often had a smaller sample size (129-13) and a shorter follow-up duration (immediately after two sessions of an exercise program for up to 24 weeks). In these studies, it was found that exercise improves some areas of cognitive activity, such as attention and concentration or accuracy in motor movements. In patients with comorbidity of diabetes and hypertension, an exercise program was even associated with cognitive function decrease.

Weight Loss

One study investigated the effect of weight loss with cognitive rehabilitation on cognitive function. In Beck et al. study, participants were included in two groups of cognitive rehabilitation interventions or weight loss programs. At the end of the study, there was no significant difference between the two groups in cognitive function changes. However, the immediate and delayed Memory index in both groups improved compared to the study beginning.(Beck, Fausett *et al.*, 2013)

Multiple interventions

Four studies performed interventions to control several risk factors for cardiovascular disease. ("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002; A. M. Murray, F.-C. Hsu *et al.*, 2017; Shepherd et al., 2002; Strandberg, Pitkala *et al.*, 2006)(Table 5)

Table 5 - Articles in which multiple factors as a risk factor in cardiovascular disease have been the goal of treatment

Study name-author-publication year	Study population	Sample size	Intervention	Assessment	Follow-up duration	Effect on cognitive function
MRC/BHF Heart protection Study; 2002[22]	UK adults (40-60 years) with coronary artery disease, other occlusive arterial disease, or diabetes	20536	Simvastatin VS placebo	Telephone Interview for Cognitive Status (TICSm)	5 years	No effect on cognition
PROSPER; Shepherd et al 2002[23]	Pateints 70-82 years, with a history of, or risk factors for, vascular disease	5804	pravastatin VS placebo	MMSE	3.2 years	No effect on cognition
ACCORD-MIND; Murray 2017[33]	mean diabetes duration 10 years; mean age 62 years	1328	Intensive VS standard management of hyperglycaemia, BP or lipid levels	Digit Symbol Substitution Test (DSST) and total brain volume (TBV)	80 months	No long-term beneficial or adverse effects on cognitive or brain MRI outcomes
DEBATE study; Strandberg 2006[34]	vascular patients with mean age of 80 years	400	both nonpharmacological and pharmacological cardiovascular treatments VS usual care	MMSE	3.4 years	No significant difference

In (MIND) study, part of the (ACCORD) study, 2977 patients with type 2 diabetes underwent standard or intensive glycemic, lipid, and blood pressure control. In this study, Digit Symbol Substitution Test (DSST) and total brain volume were measured by MRI. At 80-month follow-up, there was no significant difference in DSST test score or brain structure between the two groups.(Anne M. Murray et al., 2017)

The largest sample size in these studies is related to the MRC / BHF study. Although, it had the highest dropout rate, which was significantly related to the participants who had lower scores in the cognitive tests in the baseline assessment.("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002)The two MRC / BHF and ACCORD-MIND studies had long follow-up periods of 5 years or more.

None of these studies, which targeted several cardiovascular risk factors, showed a significant reduction in cognitive impairment or cognitive function improvement. In the only study that examined the effect of weight loss, the cognitive performance improvement was similar to the cognitive rehabilitation program (control group).

Table-6: Brief review of RCT in various risk factors modification effect on cognitive function

Risk factor	Number of studies	Result
Diabetes Mellitus	6	No effect on cognitive decline or incident dementia
Hypertension	5	2: No effect 2: protects against dementia
Cholesterol	2	No effect on cognition
Exercise and physical activity	7	4: positive effect on attention/memory +music 1: cognitive decline 1: no effect
Weight Loss	1	No significant difference between the two groups in cognitive function
Multiple factors	4	No effect on cognition

Discussion

The present study reviews the medical treatment of four common cardiovascular risk factors and lifestyle interventions including, physical activity and diet. The aim was to evaluate the results of all randomized trials of appropriate quality to assess dementia as a primary or secondary outcome.

Over the past 20 years, several randomized clinical trials (RCTs) have been conducted on the effect of medical treatment on cardiovascular risk factors on dementia. Most of the studies mentioned in the present review had a large sample size and considerable follow-up time.

These studies evaluate the effect of controlling cardiovascular risk factors on mortality and a range of vascular outcomes including, stroke, myocardial infarction, and peripheral arterial disease, as the core purpose. However, evaluation of cognitive impairment, dementia, or improvement in cognitive function was considered as secondary outcomes. There is only one positive study (Syst-Eur) that shows the protective consequence of hypertension treatment. Because different antihypertensive regimens have been used in these studies, the cognitive effect of a particular class of antihypertensive medications was not obvious.(Forette et al., 2002)

There is no evidence of prophylactic effects on dementia for type 2 diabetes management and statin therapy. The long-term effect of subclinical hypoglycemia and functional disorders on brain autoregulation may be the cause for cognitive function exacerbation in the ILI group. A similar mechanism is seen in tight control in type 1 diabetes. Another reason may be related to the reduced neuroprotective effects of leptin in this group. (27) The effects of physical activity on improving cognitive function were promising. However, these studies often had a smaller sample size and a much shorter setting time than other reviewed studies.(Emery et al., 2003; Espeland et al., 2017; Fiocco et al., 2013; R. B. Teixeira et al., 2019; Xu et al., 2017; Yamamoto et al., 2009)There was no significant reduction in the incidence of cognitive impairment in studies that targeted several risk factors.("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002; A. M. Murray, F. C. Hsu *et al.*, 2017; Shepherd et al., 2002; Strandberg et al., 2006)

The most important bias that may have affected the study results is *the sample exclusion due to cognitive impairment.* Especially if a study is not designed to monitor cognitive function explicitly and cognitive impairment may lead to cessation of informed consent or hospitalization. This

omission of the selected study may reduce the potential effect of treatment and therefore lead to type 2 error. Especially if the intervention is effective and dropout occurs more in the control group. Another limitation of these studies was *treatment in the control group*. In all hypertension studies, further treatment with other antihypertensive medications was allowed in both the intervention and placebo groups if needed to achieve acceptable blood pressure levels. As a result, many patients in the controls received antihypertensive medications, which may reduce experimental differentiation and its effect on cardiovascular outcomes and dementia.(Forette et al., 2002; Lithell et al., 2003; Peters et al., 2008; Tzourio et al., 2003) In cholesterol studies, this additional treatment with statins was performed lower than the study medications. In many cases, placebo-controlled trials are often not possible for ethical reasons.("MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial," 2002; Shepherd et al., 2002)The *age of the participants* can also be another factor in changing the results. The study population is relatively young in most studies, and therefore its effect on cognitive impairment and the incidence of dementia during follow-up was not recognizable. In the age range of 65-69, dementia is still relatively rare, and its incidence is approximately 2.4 cases per 1000 people, which increases sharply with age to 70.2 cases per 1000 people over the age of 90.(Rizzi, Rosset *et al.*, 2014) However, it was expected that the number of participants with dementia or significant cognitive impairment was low in most studies, which limits the study's ability to find such an effect.

Another point is the *effect of mortality* on the probability of disease. Dementia and cognitive disorders are age-related. The incidence of dementia may be increased by preventing cardiovascular disease that reduces mortality. In many studies, interventions have reduced mortality. However, none of the studies has investigated the role of premature mortality in reducing the incidence of dementia.

One of the limitations of this study was the *lack of a basic cognitive assessment*, which makes the changes after the intervention cannot be well interpreted. Another limitation was the cognitive assessment time, which was up to 3 months between the cognitive assessment and the end time of the program, and future studies should reduce this time to less than two weeks. Obviously, clinical dementia is the result of the interaction of brain injuries secondary to various risk factors, and brain resilience and cognitive reserve and the presence of a high cognitive reserve can modify this

damage. Cognitive reserve was not initially measured in many of these studies, then the effectiveness of interventions in people with different cognitive reserves cannot be assured.

On the other hand, the cognitive assessment which was performed in the AHEAD study was years *after the initial randomization.* The studies should consider the loss of effective follow-up in a percentage of patients: Due to the time interval between study randomization and cognitive evaluation, many patients with cognitive impairment in the study may have died due to old age.

Some studies have found that weight loss can be a sign of the onset of cognitive impairment. In contrast, some weight loss trials have suggested the obesity paradox that obesity increases the risk of dementia in the middle of life but reduces dementia risk in late life and aging. These studies suggest that neurodegenerative diseases and dementia by affecting hormones, mood and smell sense can lead to reduced oral intake and weight loss. The weight loss caused in these studies should be considered in two categories of desire (due to intervention) and unwanted (due to the onset of dementia). It is difficult to differentiate the effects of weight loss due to intervention from the weight-loss impact due to the inflammatory and neurodegenerative process. Another hypothesis suggests that leptin can have positive effects on neurogenesis and reduce apoptosis, and due to the decrease in leptin in the ILI group, these positive effects are also reduced. It can be suggested that in the ILI group, with a decrease in leptin, a decrease in neurogenesis in the hippocampus probably occurs at the molecular level and infrastructure of the brain.

Overall, *brain structural changes* applied to assess the outcome of cognitive function. Another issue to consider is that the ILI group has fewer microvascular changes and cerebral atrophy. (9% smaller ventricular volume and less global atrophy and 28% less white matter changes). Unexpectedly, there is no association between decreased cognitive function in the ILI group and atrophy and vascular lesions of the brain.(Look & Wing, 2010)As a result, functional imaging techniques may be able to answer our question of why more cognitive decline occurs despite fewer brain changes in the ILI group.

The ACCORD-MIND study also showed that strict control of blood sugar leads to greater overall brain volume despite no difference in cognitive function. On the other hand, it should be borne in mind that ILI can lead to subclinical hypoglycemia and that this hypoglycemia has long-term negative effects on brain function and cognition.(A. M. Murray et al., 2017)In other words, the question of self-regulation of cerebral arteries should be considered whether there is a similar

mechanism for organ damage due to strict control of blood sugar in diabetic patients that can lead to alteration or damage to cerebral arteries in the elderly. Another issue to consider is the *effect of legacy*, which is the lag time between the intervention time that affects the metabolic process in diabetic patients and the benefits that the patient achieves. On the other hand, most of the mentioned studies have designed *short-term interventions*, while the process of dementia and cognitive decline is much longer. From middle age, when risk factors are revealed, to old age, when the dementia process occurs, it takes a long time, and to observe the effect of metabolic disorders, a short period of study can be considered a significant limitation. Although in long-term studies, cost-effectiveness of intervention should also be considered as an important challenge.

In general, it seems that exercise can improve cognitive function by improving glucose metabolism in the elderly with complaints of memory impairment. Exercise may increase the oxidative load already high in type 2 diabetes. Studies have shown that even moderate exercise levels can increase the level of free radicals and lead to oxidative effects. In contrast, regular physical activity can protect against oxidative effects. Diet is another factor that should be considered in relation to cognitive function and physical activity in patients with type 2 diabetes. There must be a control group to determine that cognitive decline can be part of normal aging apart from the intervention.

Finally, we should consider *the method of cognition assessment* and heterogeneous testing when some of these interventions have not been able to affect cognitive function. Although in many studies, the used test is the MMSE, which can help diagnose established dementia, it is not sensitive in cognitively healthy populations and at a young age. We need to use a more sensitive test whenever we cannot find a significant change in clinical trials and prevention studies. Thus, it is recommended, using a more comprehensive battery such as AVLT in future studies.

As with all review studies**,** *publication bias* may affect our search results; Studies usually do not publish negative results in the abstracts section, so some articles may not be included in the initial search.

Conclusion

Based on the studies review, it can be concluded that there is insufficient evidence to suggest that cardiovascular risk factors treatment can prevent dementia. While exercise, and possibly blood

pressure control, have a preventative effect, this is less obvious for statin therapy and serious treatment of type 2 diabetes. Study abandonment, inability to continue the study, competitive risks, or other types of selection or treatment bias may have diminished the potential interventions effects in the mentioned trials. Future RCTs in other populations with different interventions and longer follow-ups, especially to diagnose its effect on cognitive function or dementia, hope to address the key question of whether the relationships in cohort studies can be translated into significant clinical therapeutic effects on cognition.

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