Caregiver awareness of cerebrovascular risk of patients with dementia due to Alzheimer's disease in São Paulo, Brazil

Conhecimento dos cuidadores acerca do risco cerebrovascular de pacientes com síndrome demencial da doença de Alzheimer em São Paulo, Brasil

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Received: 1/26/2014 – **Accepted:** 6/3/2014
DOI: 10.1590/0101-60830000000015

Abstract

Background: Proper control of cerebrovascular risk is essential to prevent cognitive change in dementia due to Alzheimer's disease (AD). **Objective:** To investigate whether caregiver awareness to control cerebrovascular risk impacts the lifestyles of patients with AD. **Methods:** Consecutive outpatients with AD were assessed for demographic features, Clinical Dementia Rating scores, cerebrovascular risk, pharmacotherapy, dietary therapy and practice of physical activities. Patients and caregivers were inquired on awareness of the importance of measures to control cerebrovascular risk. *Chi*-square test was employed for statistics, significance at $\rho < 0.05$. **Results:** A total of 217 patients were included; whereas 149 caregivers (68.7%) were aware of the need to control cerebrovascular risk, only 11 patients (5.1%) simultaneously practiced physical activities and received pharmacological treatment and dietary therapy. Patients with hypertension and *diabetes mellitus* were more likely to receive dietary therapy ($\rho = 0.007$). Male patients were more engaged in physical activities ($\rho = 0.018$). Patients in earlier AD stages exercised ($\rho = 0.0003$) and received pharmacological treatment more often ($\rho = 0.0072$). Caregiver awareness of the need to control cerebrovascular risk was higher when patients had hypertension ($\rho = 0.024$) and/or hypercholesterolemia ($\rho = 0.006$), and influenced adherence to dietary therapy ($\rho = 0.002$) and to pharmacological treatment ($\rho = 0.001$). **Discussion:** Caregiver awareness of the need to control cerebrovascular risk has positive impacts for patients with AD.

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Keywords: Alzheimer disease, dementia, neurodegenerative diseases, risk factors, caregivers.

Resumo

Contexto: O risco cerebrovascular é fundamental na etiologia da demência da doença de Alzheimer (DA), sendo importante seu controle adequado. **Objetivo:** Investigar se o conhecimento dos cuidadores sobre o controle do risco cerebrovascular tem impacto sobre a saúde de pacientes com DA. **Métodos:** Pacientes consecutivos com DA foram avaliados quanto a dados demográficos, *Clinical Dementia Rating*, risco cerebrovascular, tratamento farmacológico, dietoterapia e prática de atividades físicas. Pacientes e cuidadores foram questionados quanto à importância de medidas para controle do risco cerebrovascular. *Chi*-quadrado foi empregado na análise estatística, significância com $\rho < 0,05$. **Resultados:** No total, 217 pacientes foram incluídos; enquanto 149 cuidadores (68,7%) conheciam a necessidade de controle do risco cerebrovascular, somente 11 pacientes (5,1%) simultaneamente praticavam exercícios e recebiam tratamento farmacológico e dietoterápico. Pacientes com hipertensão arterial e *diabetes mellitus* tinham maiores chances de receber dietotetapia ($\rho = 0,007$). Homens estavam mais engajados em atividades físicas ($\rho = 0,018$). Pacientes em estágios precoces da DA praticavam exercícios ($\rho = 0,0003$) e recebiam farmacoterapia mais frequentemente ($\rho = 0,0072$). O conhecimento dos cuidadores acerca do controle do risco cerebrovascular era maior quando os pacientes tinham hipertensão arterial ($\rho = 0,024$) e/ou dislipidemia ($\rho = 0,006$), e influenciou a adesão à dietoterapia ($\rho = 0,002$) e à farmacoterapia ($\rho = 0,001$). **Conclusão:** O conhecimento dos cuidadores acerca do risco cerebrovascular tem impactos positivos para pacientes com DA.

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Palavras-chave: Doença de Alzheimer, demência, transtornos cerebrovasculares, fatores de risco, cuidadores.

Introduction

It has been demonstrated that cerebrovascular risk factors influence the incidence of mild cognitive impairment[1] and its rate of progression to dementia due to Alzheimer's disease[1,2]. Caregivers have an important role in the control of cerebrovascular risk of patients with dementia.

A longitudinal Brazilian study[3] previously described that a decline in the degree of awareness of Alzheimer's disease follows depressive symptoms, cognitive and functional decline. Awareness of the dementia syndrome may be important for its proper treatment; nevertheless, no studies have ever evaluated the impact of awareness of cerebrovascular risk factors over measures to control them.

An earlier preliminary study[4] confirmed that patients were more likely to accept pharmacological therapy or to follow a diet when caregivers were aware of the importance to control cerebrovascular risk, and also that patients who followed a diet were more likely to practice physical activities or to accept pharmacological therapy. In the present study, with a more comprehensive evaluation of a larger sample, we sought to investigate whether caregiver awareness to control cerebrovascular risk has any impact on the lifestyles of patients with dementia due to Alzheimer's disease, as well as to describe any relations between the presence of cerebrovascular risk factors and adherence to dietary therapy or regular practice of physical activities.

Methods

Consecutive outpatients with dementia due to Alzheimer's disease in different stages were recruited from November 2010 to February 2013 (28 months) at the Behavioral Neurology Section of *Hospital São*

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Paulo. After diagnostic confirmation, they were assessed for: gender, schooling, estimated age of onset of dementia due to Alzheimer's disease, estimated length of the dementia syndrome, Clinical Dementia Rating[5] (CDR) scores, marital status, urban living (considering patients who lived in non-rural settings for at least two thirds of their lifetimes), sanitation (considering patients who lived in environments with sanitation for at least two thirds of their lifetimes), body mass index, arterial hypertension, hypercholesterolemia, *diabetes mellitus*, dietary therapy, pharmacological therapy, regular practice of physical activities, family history of Alzheimer's disease or other neuropsychiatric disorders, family history of cardiovascular diseases, and quantification of alcohol consumption or smoking. Family history of neuropsychiatric disorders included only those with non-infectious and non-vascular causes (cerebrovascular diseases were included as family history of cardiovascular diseases), and family history of cardiovascular diseases did not include infectious causes such as Chagas' disease. Patients and caregivers were inquired on awareness of the importance to control cerebrovascular risk factors. The expected answer was that such control would be important for prevention of vascular events or neurodegenerative diseases such as Alzheimer's disease. Caregivers were also inquired whether patients were encouraged to follow any specific diets, to regularly practice any physical activities, or to accept pharmacological treatment. All body mass index measurements and caregiver assessments were conducted on weekdays at morning time, by the same examiner (FFO).

Diagnosis of dementia due to Alzheimer's disease was in accordance with National Institute on Aging – Alzheimer's Association criteria[6]. Obesity was diagnosed when body mass index was over 30 kg/m^2.

For statistical analysis, lifetime drinking in excess of ten liters per year of alcoholic beverages was considered. Lifetime smoking in any quantity was weighted in the analysis. Diagnosis of arterial hypertension was in accordance with the JNC 7 Report[7], diagnosis of *diabetes mellitus* was in accordance with American Diabetes Association criteria[8], and diagnosis of hypercholesterolemia was in accordance with the third report of the National Cholesterol Education Program[9].

Physical activities were considered if they were non-work related, of at least moderate intensity (≥ 3 METS), comprising equivalents to walking or running summing up to at least one km per week, or engaging in other physical activities summing up to at least one hour per week. Any activities in lesser intensity were taken as physical inactivity.

Statistical comparisons for all groups were conducted by way of *Chi*-square test. The threshold of significance was set at $\rho < 0.05$.

This study is part of the research project 1067/10 (CAAE 0540.0.174.000-10) approved by the Ethics Committee of *Hospital São Paulo* on August 2010. All patients and their legal representatives signed the Informed Consent Form before the evaluation. All invited patients and their respective caregivers agreed to participate on the research, with no exceptions.

Results

A total of 217 patients were included, and none were excluded; 147 were female (67.7%) and 70 were male (32.3%); 109 (50.23%) were married, while six (2.76%) were divorced, 19 (8.76%) were single, and 83 (38.25%) were widowers; 56 (25.8%) had history of alcohol use, whereas 11 (5.1%) were regularly drinking at survey time; 79 (36.4%) had smoking history, whereas 14 (6.5%) were regular smokers at survey time. All patients lived in urban environments at evaluation time. Obesity was diagnosed in 36 patients (16.6%). Table 1 shows full demographic data of patients.

Among female patients, 43 (29.3%) followed a diet, ten (6.8%) regularly practiced physical activities, and 103 (70.1%) received pharmacological treatment. Among male patients, 23 (32.9%) followed a diet, 12 (17.1%) regularly practiced physical activities, and 51 (72.9%) received pharmacological treatment. No impact of gender was found over adherence to dietary therapy ($\rho = 0.589$) or to pharmacological therapy ($\rho = 0.672$), but male patients were significantly more engaged in physical activities than female patients ($\rho = 0.018$). Nonetheless, patient gender had no impact over caregiver awareness of the need to control cerebrovascular risk ($\rho = 0.984$).

Regarding CDR scores, 83 patients (38.3%) scored 1.0, 104 patients (47.9%) scored 2.0, and 30 patients (13.8%) scored 3.0. Among mildly impaired patients (CDR = 1.0), 31 (37.3%) followed a diet, 17 (20.5%) regularly practiced physical activities, and 69 (83.1%) received pharmacological treatment. Among moderately impaired patients (CDR = 2.0), 28 (26.9%) followed a diet, five (4.8%) regularly practiced physical activities, and 67 (64.4%) received pharmacological treatment. Among severely impaired patients (CDR = 3.0), seven (23.3%) followed a diet, none were regularly practicing physical activities, and 18 (60.0%) received pharmacological treatment. No impact of CDR scores over dietary therapy was found ($\rho = 0.202$), but patients in the earlier dementia stages would significantly practice more physical activities ($\rho = 0.0003$) and be more prone to receive pharmacological therapy ($\rho = 0.0072$). Nevertheless, CDR scores had no impact over caregiver awareness of the need to control cerebrovascular risk ($\rho = 0.984$).

Table 1. Demographic data of patients

Variable (units), n = 217	Mean	SD*	Range
Age of dementia onset (years-old)	73.19	6.8	52-88
Length of the dementia syndrome (years)	5.4	2.9	0.5-14.5
Schooling (years)	4.21	3.7	0-15
Body mass index (kg/m^2)	25.75	4.3	14.28-41.62
Lifetime alcoholic drinking load (liters per year)	17.26	50.8	0-315
Current alcoholic drinking load (liters per year)	1.67	11.3	0-120
Lifetime smoking load (packs per year)	48.75	103.7	0-700
Current smoking load (packs per year)	14.38	62.1	0-365

* SD: standard deviation.

Table 2 shows relationships between awareness of the need to control cerebrovascular risk and assessed variables. Overall 119 patients (54.8%) had family history neither of Alzheimer's disease nor of other neuropsychiatric syndromes, but 77 patients reported family history of Alzheimer's disease, and 27 reported family history of other neuropsychiatric disorders (sometimes more than once in the same family): nine relatives with epilepsy (eight with onset during childhood), six with parkinsonian syndromes, six with schizophrenia, six with bipolar disorder, three with brain cancer, one cousin with amyotrophic lateral sclerosis, and one daughter with writer's cramp.

Table 3 shows relationships between cerebrovascular risk and adherence to dietary therapy. Table 4 shows relationships between cerebrovascular risk and regular practice of physical activities.

Only 11 (5.1%) of the 217 patients were under pharmacological therapy and reported following a diet and regularly practicing physical activities at the same time. Among the 63 patients who reported no pharmacological therapy for control of cerebrovascular risk, ten had neither hypertension nor *diabetes mellitus* nor hypercholesterolemia.

Discussion

Considering the modest effects of cholinesterase inhibitors and memantine over cognition and functionality of patients with dementia due to Alzheimer's disease[10], control of modifiable risk factors is a major therapeutic goal[11]. More than a third of worldwide cases of Alzheimer's disease are attributable to cerebrovascular risk factors[12]. While the burden of dementia is recognizable all around the world, its prevalence seems to be higher in Europe and North America[11], rather than in Latin America, Africa, India or China. Prevalence of dementia due to Alzheimer's disease in people over 65 years-old may vary from 1.3% in India to 2.7% in Brazil, reaching up to 20.5% in Israel (where consanguinity among families is common)[13]; however, these results might be biased by the employment of different diagnostic criteria[13,14] or less access to tertiary health care in poorer countries of the southern hemisphere.

Table 2. Relationships between awareness of the need to control cerebrovascular risk and variables of interest

Assessed variables of patients (n = 217)	*n*	%	Patients' and/or caregivers' awareness of the need to control cerebrovascular risk				ρ-value*
			YES (*n* = 149)		NO (*n* = 68)		
			Variable present	Variable absent	Variable present	Variable absent	
Urban living†	189	87.1	130	19	59	9	0.921
Sanitation‡	190	87.6	133	16	57	11	0.260
Arterial hypertension	173	79.7	125	24	48	20	0.024
Hypercholesterolemia	166	76.5	122	27	44	24	0.006
Diabetes mellitus	56	25.8	44	105	12	56	0.063
Obesity	36	16.6	27	122	9	59	0.369
Lifetime alcohol consumption§	38	17.5	25	124	13	55	0.674
Lifetime smoking	79	36.4	51	98	28	40	0.324
Dietary therapy	66	30.4	55	94	11	57	0.002
Physical activities	22	10.1	18	131	4	64	0.161
Pharmacological therapy	154	70.9	116	33	38	30	0.001
Family history of Alzheimer's disease	77	35.5	58	91	19	49	0.117
Family history of other neuropsychiatric disorders	27	12.4	17	132	10	58	0.495
Family history of cardiovascular diseases	74	34.1	54	95	20	48	0.325

* *Chi*-square test.
† Patients who lived in urban (non-rural) environments for at least two thirds of their lifetimes.
‡ Patients who lived in environments with sanitation for at least two thirds of their lifetimes.
§ More than ten liters of alcoholic beverages per year.

Table 3. Relationships between cerebrovascular risk and adherence to dietary therapy

Variables of cerebrovascular risk or pharmacological treatment of patients	Dietary therapy				ρ-value*
	YES (*n* = 66)		NO (*n* = 151)		
	Variable present	Variable absent	Variable present	Variable absent	
Arterial hypertension	60	6	113	38	0.007
Hypercholesterolemia	55	11	111	40	0.116
Diabetes mellitus	25	41	31	120	0.007
Obesity	11	55	25	126	0.984
Physical inactivity	55	11	140	11	0.035
Pharmacological therapy	63	3	91	60	< 0.001

* *Chi*-square test.

Table 4. Relationships between cerebrovascular risk and regular practice of physical activities

Variables of cerebrovascular risk or pharmacological treatment of patients	Regular physical activities				ρ-value*
	YES (*n* = 22)		NO (*n* = 195)		
	Variable present	Variable absent	Variable present	Variable absent	
Arterial hypertension	20	2	153	42	0.169
Hypercholesterolemia	19	3	147	48	0.250
Diabetes mellitus	5	17	51	144	0.728
Obesity	2	20	34	161	0.319
Dietary therapy	11	11	55	140	0.035
Pharmacological therapy	20	2	134	61	0.030

* *Chi*-square test.

This sample consisted mostly of patients who were born in the first half of the last century, with low access to formal education, and who were more prone to pharmacological treatment of their comorbidities than to dietary therapy or regular physical activities. More than 80% of the patients who did not receive pharmacological treatment had at least one uncontrolled cerebrovascular risk factor, an information that reflects the need for more patient education with regard to public health policies, even in the largest city in Brazil.

Even though urban living with sanitation was the rule for most patients, it should be considered that this is a sample with access to treatment in an university hospital, and probably does not reflect what happens in the whole country. Considering that recruitment was carried out in a single center, results may not be generalizable to the whole population of São Paulo. Nevertheless, urban living and sanitation did not impact awareness of cerebrovascular risk.

Caregiver awareness of the need to control cerebrovascular risk was significantly higher when patients had arterial hypertension and/or hypercholesterolemia, and had significant impacts over adherence to dietary therapy and to pharmacological treatment. A marginally significant association was also found for such awareness when patients had *diabetes mellitus*, but not when patients regularly practiced physical activities, a fact that could be a result of overall low adherence to such activities for control of cerebrovascular risk.

There is evidence that anti-oxidants[15], polyunsaturated fatty acids (particularly present in fish oil) and a Mediterranean diet can reduce cognitive decline[15,16], while dietary therapy is a major component of the control of cerebrovascular risk. Caregivers of patients with heart failure have reported that the most burdensome aspects of care are enforcing dietary restriction and adherence[17]. Almost 70% of our patients did not follow specific dietary patterns. Patients who received dietary therapy were more likely to also receive pharmacological treatment and to regularly practice physical activities. Patients with arterial hypertension and *diabetes mellitus* were significantly more likely to receive dietary therapy.

Midlife obesity is known to be a risk factor for dementia due to Alzheimer's disease, particularly when associated with other cerebrovascular risk factors[18]; on the other hand, weight loss may be an early symptom of dementia, but patients are expected to lose more weight in later dementia stages[18,19]. In late life, hyperleptinemia as a result of obesity may be protective against cognitive decline[18], and it has been shown that oral nutritional supplementation is more effective compared to nutrition education in improving the nutritional status of patients with dementia due to Alzheimer's disease[19]. Nevertheless, we found no relation of obesity with awareness of cerebrovascular risk or adherence to dietary therapy or physical activities in this sample.

Long-term regular physical activity is associated with positive behavior[20], higher levels of cognitive function and less cognitive decline[16,20], particularly in patients with dementia[15], while increasing brain neurotrophins, perfusion and plasticity[16,21]. Elderly with disabilities usually have lower levels of participation in social activities, but their social engagement tends to be more strongly related to life satisfaction[22]. Exercise reduces the risks of developing both mild cognitive impairment and dementia[23,24]. However, no association has been found so far between physical activity and Alzheimer's disease biomarkers[25]. Little more than 10% of our patients reported regular practice of physical activities, even if we consider the flexible criteria employed for such assessment. Patients who regularly practiced physical activities were more likely to receive dietary therapy and/or pharmacological treatment, while isolated cerebrovascular risk factors such as arterial hypertension, hypercholesterolemia, *diabetes mellitus* and obesity had no significant impacts over engagement in physical activities.

No gender differences were found with regard to adherence to dietary therapy or to pharmacological treatment, but male patients were significantly more likely to regularly practice physical activities than female patients, regardless of caregiver awareness of the need to control cerebrovascular risk. This is an unfortunate result, in view of the fact that rates of arterial hypertension, hypercholesterolemia and *diabetes mellitus* are higher in elderly women than in similarly aged men[26].

With progression of cognitive decline, patients would significantly practice less physical activities and be less prone to receive pharmacological treatment, regardless of caregiver awareness of the need to control cerebrovascular risk. No severely impaired patients would regularly practice physical activities. In spite of the cognitive decline, low caregiver motivation might have been an important element for physical inactivity. A non-significant trend was also found for more severely impaired patients to not receive dietary therapy.

Chronic caregiving stress is associated with increased cerebrovascular risk. Earlier reports have provided evidence that caregiver burden is associated with carotid artery intima-media thickness and impaired endothelial function[27,28], particularly in the elderly, while chronically increasing serum levels of biomarkers of inflammation such as C-reactive protein and tumor necrosis factor α[29]. A recent Brazilian study[30] showed that caregivers have higher odds of negatively evaluating their physical health, disposition, mood, memory, and the capacity to perform leisure activities as compared with non-caregivers, reflecting poorly on their quality of life. Even though cerebrovascular risk of caregivers may influence the control of patients' cerebrovascular risk factors, one of the weaknesses of our study is that vascular health of caregivers was not assessed.

A total of 149 caregivers (68.7%) reported full awareness of the need to control cerebrovascular risk, but less than 6% of our patients received pharmacological treatment while following a diet and regularly practicing physical activities at the same time. It is possible that this is a result of low simultaneous engagement in all components of control of cerebrovascular risk rather than lack of education regarding such measures, particularly considering that more than 70% of our patients received pharmacological treatment for control of their cerebrovascular risk factors. Anti-hypertensive treatment[16,31], most importantly with angiotensin-converting enzyme inhibitors and diuretics[31], is particularly helpful in slowing cognitive decline for patients with dementia independently of blood pressure control.

To the best of our knowledge, this is the first original study to ever demonstrate the impact of caregiver awareness of cerebrovascular risk over the lifestyles of patients with dementia due to Alzheimer's disease. Regardless of the moderately large sample, its major limitations reside in the self-reported dietary and exercise patterns as sole measures of intensity, while its cross-sectional nature does not allow for causal inferences. Considering that spousal caregivers may have higher cardiovascular risk and all-cause mortality due to high levels of strain[17], further studies should also assess the impacts of cerebrovascular risk factors of patients over caregiver health. We conclude that public health policies should promote the knowledge that cerebrovascular risk is a major impact factor for the burden of dementia worldwide, and that control of cerebrovascular risk factors impacts both the incidence and the progression of dementia due to Alzheimer's disease.

Acknowledgements

This study was supported by *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Capes). The authors report no conflicts of interest.

Preliminary aspects of this paper were previously presented as an oral presentation on March 09th, 2012, at Parallel Session 22, at the following meeting: 27th International Conference of Alzheimer's Disease International, 7-10 March 2012, ExCel London, London, United Kingdom (http://www.medimond.com/proceedings/moreinfo/20120307_index.pdf).

Author contributions

Fabricio Ferreira de Oliveira designed the study, analyzed the data, wrote the first draft and approved the final version of the paper. Jose Roberto Wajman contributed in study design, revised the paper and approved the final version of the paper. Paulo Henrique Ferreira Bertolucci contributed in study design, revised the paper and approved the final version of the paper.

Conflicts of interest

None.

Supported by *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Capes).

Author disclosures

Fabricio F. Oliveira, MD, MSc, is a PhD student at the Federal University of São Paulo (Unifesp) in São Paulo, Brazil; he receives a scholarship for academic research from *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (Capes), and receives personal compensation for acting as a Healthcare Council Member for Gerson Lehrman Group.

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References

1. Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, et al. Vascular risk factors, incidence of MCI, and rates of progression of dementia. Neurology. 2004;63:1882-91.
2. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. Neurology. 2005;65:545-51.
3. Sousa MFB, Santos RL, Arcoverde C, Dourado M, Laks J. Awareness of disease in Alzheimer's disease: preliminary results of a longitudinal study. Rev Psiq Clín. 2011;38:57-60.
4. Oliveira FF, Bertolucci PHF, Chen ES, Smith MAC. Caregiver awareness of diagnosis and treatment of cerebrovascular risk factors in patients with dementia due to Alzheimer's disease at an university hospital in São Paulo, Brazil. In: Acosta D, Ketteringham A, Ballard C, editors. Proceedings of the 27th International Conference of Alzheimer's Disease International (Bologna): Medimond; 2012, p. 71-74. Available from: <http://www.medimond.com/proceedings/moreinfo/20120307_index.pdf>.
5. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993;43:2412-4.
6. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack Jr CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement. 2011;7:263-9.
7. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure – The JNC 7 Report. JAMA. 2003;289:2560-72.
8. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2006;29(S1):S43-8.
9. National Cholesterol Education Program. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106:3143-421.
10. De Oliveira FF, Bertolucci PHF, Chen ES, Smith MAC. Pharmacological modulation of cognitive and behavioral symptoms in patients with dementia due to Alzheimer's disease. J Neurol Sci. 2014;336:103-8.
11. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011;377:1019-31.
12. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol. 2011;10:819-28.
13. Kalaria RN, Maestre GE, Arizaga R, Friedland RP, Galasko D, Hall K, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol. 2008;7:812-26.
14. Das SK, Pal S, Ghosal MK. Dementia: Indian scenario. Neurol India. 2012;60:618-24.
15. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. Arch Neurol. 2009;66:1210-5.
16. Gorelick PB, Scuteri A, Black SE, DeCarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia – a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:2672-713.
17. Collins LG, Swartz K. Caregiver care. Am Fam Physician. 2011;83:1309-17.
18. Lee EB. Obesity, leptin, and Alzheimer's disease. Ann N Y Acad Sci. 2011;1243:15-29.
19. Pivi GAK, Silva RV, Juliano Y, Novo NF, Okamoto IH, Brant CQ, et al. A prospective study of nutrition education and oral nutritional supplementation in patients with Alzheimer's disease. Nutr J. 2011;10:98.
20. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil. 2004;85:1694-704.
21. Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, et al. Cardiovascular fitness, cortical plasticity, and aging. Proc Natl Acad Sci U S A. 2004;101:3316-21.
22. Jang Y, Mortimer JA, Haley WE, Graves ARB. The role of social engagement in life satisfaction: its significance among older individuals with disease and disability. J Appl Gerontol. 2004;23:266-78.
23. Geda YE, Roberts RO, Knopman DS, Christianson TJH, Pankratz S, Ivnik RJ, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. Arch Neurol. 2010;67:80-6.
24. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med. 2006;144:73-81.
25. Vemuri P, Lesnick TG, Przybelski SA, Knopman DS, Roberts RO, Lowe VJ, et al. Effect of lifestyle activities on Alzheimer disease biomarkers and cognition. Ann Neurol. 2012;72:730-8.
26. Azad NA, Bugami MA, Loy-English I. Gender differences in dementia risk factors. Gend Med. 2007;4:120-9.
27. Roepke SK, Allison M, von Känel R, Mausbach BT, Chattillion EA, Harmell AL, et al. Relationship between chronic stress and carotid intima-media thickness (IMT) in elderly Alzheimer's disease caregivers. Stress. 2012;15:121-9.
28. Mausbach BT, Roepke SK, Ziegler MG, Milic M, von Känel R, Dimsdale JE, et al. Association between chronic caregiving stress and impaired endothelial function in the elderly. J Am Coll Cardiol. 2010;55:2599-606.
29. von Känel R, Mills PJ, Mausbach BT, Dimsdale JE, Patterson TL, Ziegler MG, et al. Effect of Alzheimer caregiving on circulating levels of c-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. Gerontology. 2012;58:354-65.
30. Inouye K, Pedrazzani ES, Pavarini SCI. Implications of Alzheimer's disease for the caregiver's quality of life: a comparative study. Cad Saude Publica. 2010;26:891-9.
31. Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. Am J Geriatr Pharmacother. 2009;7:250-61.