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REVIEW

Vascular risk factors and dementia – towards prevention strategies

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ABSTRACT

Several cohort studies have shown that vascular risk factors including hypertension, hypercholesterolaemia, diabetes mellitus, smoking, obesity and lack of physical exercise in midlife and to a lesser extent in late life, are associated with an increased risk of dementia.

The results from randomised controlled clinical trials on treatment of these risk factors are not conclusive for the effect on cognitive decline and dementia. Studies investigating the effect of a multi-component intervention aimed at vascular risk factors to prevent or slow down cognitive decline and dementia will hopefully give the answer as to whether such an intervention is efficacious. This requires large clinical trials in an elderly population with long follow-up and several competing risks, making it difficult from an organisational and methodological point of view. Major challenges for future studies are to select the optimal population, set the optimal treatment targets and select clinically relevant outcome parameters.

KEYWORDS

Dementia, cognitive decline, vascular risk factors, prevention, trial design

INTRODUCTION

Age is the strongest risk factor for dementia and with the increasing life expectancy the number of patients living with dementia worldwide is estimated to rise from 24 million currently to over 80 million by the year 2040.[1] The most common cause of dementia is Alzheimer's disease followed by vascular dementia and dementia with Lewy bodies.[2] These nosological entities in themselves are probably relatively rare and the majority of patients with dementia suffer from 'mixed dementia' characterised by multiple cerebral pathologies with prominent vascular involvement. This is especially the case in older dementia patients (over 80 years), which is the age group responsible for the increase in prevalence in the near future.[3,4] In several cohorts the occurrence of multiple cerebral pathologies has been confirmed.[5-8] Silent cerebral infarcts and white matter lesions increase the risk of future dementia and cerebrovascular lesions contribute to dementia severity in patients with Alzheimer's disease.[9-11] The attributable risk of vascular lesions for the occurrence of dementia in a model including age, Alzheimer changes, vascular lesions, Lewy bodies and atrophy is as high as 21%, which is higher than the attributable risk of cortical amyloid-beta plaques and neurofibrillary tangles together,[6] confirming the importance of the vascular component of dementia.

Currently no therapeutic options are available to target the neurodegenerative component of dementia, but the vascular component might offer opportunities for treatment and prevention strategies.[12,13] In this review the current knowledge of the relation between vascular risk factors and dementia, the effect of treatment aimed at vascular risk factors on incident dementia, and current ongoing randomised controlled trials (RCTs) evaluating the effect of treatment aimed at vascular risk factors are discussed. Finally, the design of future dementia prevention trials aiming at vascular risk modification to prevent dementia is discussed.

EPIDEMIOLOGICAL EVIDENCE

Results from several large prospective cohort studies have shown that vascular risk factors including hypertension, hypercholesterolaemia, diabetes mellitus (DM), obesity

and lack of physical exercise are all associated with an increased risk of dementia. Several systematic reviews on these associations have been published in recent years.[14-17] Most prospective cohort studies report on associations between midlife vascular risk factors and late life dementia and the associations are strongest for risk factors present in midlife. The associations in late life are less robust and some of these factors in late life, including hypertension and overweight, might even be associated with a decreased risk of dementia.[16,18,19]

Treatment aimed at several vascular risk factors has been associated with a decreased risk of incident dementia later in life from several of the same cohort studies. However, selection of study participants, lack of randomisation and confounding by indication are important sources of bias limiting the interpretation of treatment effects in observational studies.[20]

The relation between dementia and most relevant vascular risk factors is briefly discussed below.

Hypertension

On the subject of vascular risk factors and dementia most studies have focused on hypertension and the risk of dementia. Several cohort studies with long follow-up have consistently associated hypertension in middle-aged subjects with an increased risk of dementia and cognitive decline later in life.[21-24] This association is less clear for hypertension in late life and the relation appears to be age-dependent.[25,26] In fact, some longitudinal studies have shown that *low* blood pressure in later life (above 75 years of age) is associated with an increased risk of future dementia.[27-29] In addition, several cross-sectional studies in late life have shown an association between high blood pressure and better cognitive functioning and between low blood pressure and prevalent dementia.[30,31] Medical treatment of hypertension has been associated with a decreased incidence of dementia in several longitudinal studies, but results are difficult to interpret due to the mentioned sources of bias inherent to such analyses of associations.[32-34]

Cholesterol

Hypercholesterolaemia in midlife has consistently been associated with an increased risk of future dementia.[35,36] Hypercholesterolaemia in late life, however, has been associated with a decreased risk of dementia in some longitudinal studies.[19,37] No association between statin use and incident dementia has been observed in several large prospective cohort studies. [38-41]

Diabetes mellitus

Reports about the association between DM and incident dementia are fairly consistent.[17] DM is the only vascular risk factor which is associated with an increased dementia risk independent of age. This was shown in several longitudinal cohort studies on both midlife DM[36,42] and late life DM[43-46] and the risk of incident dementia. In addition, the occurrence of severe hypoglycaemia in patients with type 2 DM has been associated with an increased risk of future dementia; this risk increases with the number of hypoglycaemic episodes.[47]

Obesity and physical exercise

Midlife obesity has been associated with an increased risk of future dementia in several cohort studies with a very long follow-up.[48,49] As with hypertension, this relationship seems to be modified by age, as in late life a higher BMI is associated with a decreased risk of dementia, whereas a low BMI is associated with an increased risk of dementia.[18,50] Physical activity both in midlife and in late life has repeatedly been reported to be associated with a decreased risk of dementia.[51-53]

The presence of several risk factors in one subject probably has an additive effect and the constellation of vascular risk factors defined as the 'metabolic syndrome' has been associated to an increased dementia risk as well.[54,55]

Interpretation and comparison of the results from different prospective cohort studies is difficult for several reasons. In the first place the operationalisation of risk factors differs across the studies. There is no uniform definition of hypertension, hypercholesterolaemia, obesity or lack of physical exercise and different values or algorithms have been used in different studies. In addition, different outcome parameters have been used. Some studies used Alzheimer's disease as an outcome, some studies vascular dementia and some studies dementia in general. Considering the increasing awareness that the strict division between Alzheimer's disease and vascular dementia is no longer tenable and the probably high percentage of cases suffering from mixed dementia in most of the studies mentioned, all incident dementia outcomes are included in this review.

TREATMENT AND PREVENTION OF DEMENTIA

Currently available medical treatment

The currently available medical treatment of dementia is only symptomatic and limited to the use of acetylcholinesterase inhibitors (AChEI) in mild to moderate Alzheimer's disease and memantine, an NMDA receptor antagonist, in moderate to severe dementia. Gradually the indication for these drugs is being broadened to include vascular dementia and dementia with Lewy bodies (DLB). Most benefit from AChEI can probably be expected in DLB patients, especially when certain symptoms including hallucinations and attention deficit are prominent.[56] In spite of major efforts, including randomised controlled trials, to develop drugs that interfere with amyloid

metabolism, the neurodegenerative component of the disease is currently not amenable to treatment and no disease-modifying drugs are as yet available.[57,58]

Interventions aimed at vascular risk factors

While the neurodegenerative component of dementia is not yet amenable to treatment, the vascular component might offer a potential target for treatment or even prevention, as was already recognised almost 20 years ago.[12,13,59]

Most available evidence from randomised controlled clinical trials comes from cardiovascular studies using stroke, coronary heart disease or mortality as primary outcome measures, and assessing cognitive function or incident dementia as a secondary endpoint. This was recently systematically reviewed, and will be briefly discussed here.[20]

The strongest evidence for an effect on incident dementia is available for treatment of hypertension. Nevertheless, results from RCTs with different primary endpoints and different populations at baseline are inconsistent on the effect of antihypertensive treatment on cognitive decline or dementia.[60-65] So far only the Syst-Eur study has reported on a convincing effect of blood pressure (BP)-lowering therapy in hypertensive subjects over 60 years of age.[61] Treatment resulted in a 55% absolute risk reduction of incident dementia in the treatment arm of the study with an average follow-up of 3.9 years. A recent study in subjects over 80 years of age had to be terminated prematurely because of a favourable effect on several cardiovascular endpoints, and the follow-up of 2.2 years was too short to find an effect on cognition.[63] A meta-analysis including four RCTs investigating BP-lowering therapy revealed a hazard ratio of 0.87 (95% CI 0.76 to 1.00) for incident dementia.[63] Only two RCTs evaluated the effect of cholesterol-lowering therapy with a statin on cognition.[66,67] No effect on cognition was reported, and a Cochrane review confirmed that currently there is no evidence for an effect of statin treatment on cognitive decline.[68]

In spite of the repeatedly reported association between obesity and cognitive decline and incident dementia, no RCTs on this subject using cognitive decline or incident dementia have been performed.

One RCT evaluating the effect of intensive glucose control versus standard glucose control evaluated cognitive decline and incident dementia in diabetic subjects with a history of micro- or macro-vascular disease or at least one other cardiovascular risk factor. Although a significant effect on glycated haemoglobin level was achieved, this did not result in an effect on cognitive decline or incident dementia during a median follow-up of five years.[69]

The effects of multi-component interventions aimed at vascular risk factors are largely unknown in elderly populations. One small RCT among 400 patients at high cardiovascular risk assessed the effect of optimising pharmacological and non-pharmacological treatment of vascular risk factors on cognitive decline, but no effect was observed in this study, which may have been underpowered.[70] One RCT evaluating the effect of an intervention aimed at vascular risk factors compared a multi-component intervention to regular care in early Alzheimer's patients with cerebrovascular lesions on MRI.[71] After two years of follow-up no effect on cognitive decline was found, but the progression of white matter lesions was slightly less in the intervention arm.[72] This study is not a dementia primary prevention study, but a secondary prevention study, considering the diagnosis of early dementia. Caution is warranted when interpreting the results of these RCTs, and results cannot easily be translated to the whole population of elderly subjects.

DESIGN OF DEMENTIA PREVENTION TRIALS

The optimal design for an RCT to investigate the effect of interventions aimed at vascular risk factors is dependent on many variables, and the best design is subject of debate.

Population under study

The first major question is which population should be studied. As mentioned above, most epidemiological data confirm the relationship between midlife risk factors and late-life dementia, but the associations with risk factors in late life are less robust. The incidence of dementia in midlife is too low to find an effect of an intervention, unless a very long follow-up (i.e. ten years or longer) or large sample size (i.e. 10,000 subjects or more) is achieved. The realisation of such a study would be very complicated from a methodological point of view. The incidence of dementia in the population under study needs to be sufficiently high to find an effect of the intervention within a reasonable duration of follow-up. If the population under study is too old, the incidence of dementia might be high, but attrition due to death of other causes will seriously influence the results and these competing risks complicate the interpretation of such a study.

Therefore it seems reasonable to search for a practicable compromise between the downsides of an intervention in subjects who are either too young or too old, and aim for a population somewhere between 65 and 75 years of age at baseline.

Selecting subjects at increased risk of dementia could result in higher incidence during follow-up and limit the number of subjects needed in an intervention trial. Subjects could be selected based on previously developed dementia risk scores which take vascular risk factors into account.[73,74] By using such an 'enrichment strategy' the participation of large groups of subjects at very low risk of the primary

outcome, whose chance of benefiting from the intervention is very low, can be avoided. Whether or not subjects with a low dementia risk score or vascular risk score actually benefit from such an intervention is, however, unknown. Subgroup analyses of currently ongoing trials might offer an opportunity to evaluate this in the near future.

Another enrichment strategy commonly proposed is enrolling subjects who already have slight cognitive deficits, but who do not fulfil criteria for dementia yet, so-called mild cognitive impairment (MCI). Since MCI is considered a pre-dementia stage, and on average about 10% of the patients progress to dementia every year, such a study should not be considered as primary prevention, but rather as secondary prevention of dementia. As such this strategy could be valuable in addressing the same general research question: can modification of vascular risk factors prevent cognitive decline or dementia?

Risk factors under study

It is important to realise that even a very modest effect of treatment aimed at a specific risk factor can have a major impact at population level if the risk factor is highly prevalent, the so called prevention paradox. Effects of antihypertensive therapy may serve as an example. Hypertension is highly prevalent among elderly non-demented subjects, as was shown in several population-based cohorts and the baseline data of one of the ongoing intervention trials.[75] If this risk factor can be modified in a large proportion of the subjects, the effect on the overall incidence of dementia can be substantial, even if individual effects are negligible. In this context it is important to know the population attributable risk (PAR) of each risk factor to determine the potential effect of an intervention aimed at the prevention of dementia. If the PAR is high, i.e. a large proportion of incident dementia cases can be attributed to the presence of hypertension, it is more likely that this intervention will be effective at population level. In the case of hypertension, the PAR has been estimated to be as high as 27%, making it a very suitable treatment target for the prevention of dementia.[76]

When assessing the effect of a primary prevention intervention, the intended intervention should be affordable, acceptable to the patient, easy to implement on a large scale, have few serious adverse events and should not impose too heavy a burden on the health care system as a whole. Large groups of subjects would be exposed to the intervention. With the predicted increase of life expectancy and the resulting increase of older subjects in Western societies this issue will become even more relevant.

Outcome measures

The optimal outcome measure for dementia prevention trials is subject of debate. In dementia research it is common to use deterioration on either a neuropsychological test battery or an extensive screening instrument as primary outcome measure. Small differences between groups can be detected this way, but clinical relevance of such differences is often unclear. Incident dementia in our opinion is a more clinically relevant outcome measure which is easy to interpret and with clear clinical relevance.

In addition to cognitive endpoints, other clinically relevant outcomes to be used are mortality, institutionalisation and disability or handicap. It is expected that interventions targeting vascular risk factors will sort an effect on vascular endpoints including stroke, myocardial infarction and peripheral vascular disease as well. Therefore outcome measures evaluating the effect on both cognitive decline and cardiovascular disease would be preferable. The Amsterdam Linear Disability Scale (ALDS) is a handicap scale which possesses these clinimetric properties; it assesses both basic and instrumental activities of daily living and is generic (i.e. not disease specific) and linear, as opposed to most handicap or disability scales which are disease-specific and ordinal.[77] Due to its test characteristics, both cognitive decline and handicap as a result of cardiovascular disease (e.g. stroke or myocardial infarction), will translate into deterioration on the ALDS.

ONGOING DEMENTIA PREVENTION INITIATIVES

Currently three RCTs investigating the effect of a multi-component intervention including treatment aimed at vascular risk factors are ongoing. All three studies aim at preventing cognitive decline or incident dementia, but the interventions and the selection of subjects are different.

The 'Prevention of Dementia by Intensive Vascular Care' trial (preDIVA) is a cluster-randomised trial among 3534 elderly non-demented subjects aged 70 to 78 years to evaluate the effect of a multi-component vascular intervention with a follow-up of six years.[75] In the intervention group subjects visit a practice nurse every four months, who assesses the presence of vascular risk factors including blood pressure, cholesterol level, diabetes mellitus, smoking, body mass index (BMI) and level of physical exercise.

Vascular risk factors are treated according to a standardised protocol in line with existing guidelines for cardiovascular risk management. Primary outcomes are incident dementia and disability as measured with the ALDS.[77] Secondary outcomes are all-cause mortality, cardiovascular disease (including stroke, myocardial infarction and peripheral vascular disease), death, cognitive decline and depression. The control group receives usual care.

The 'Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability' (FINGER) is a

randomised controlled trial among 1200 subjects aged 60 to 75 years with a high dementia risk score and with mild memory impairment evaluating the effect of a multi-domain intervention to delay cognitive impairment with a two-year follow-up with a planned extension.[78] In addition to management of vascular risk factors, the intervention comprises nutritional guidance, advice on physical activity and cognitive training. Primary outcomes are cognitive impairment, dementia and disability; secondary outcomes include depression, vascular disorders and quality of life. The control group attends regular health advice groups.

The Multidomain Alzheimer Prevention Trial (MAPT) is a randomised controlled clinical trial among 1200 'frail' elderly subjects over 70 years of age randomised to receive omega 3 capsules, a multi-domain intervention, both, or placebo with a three year follow-up.[79] The multi-domain intervention comprises cognitive training, physical training, nutritional counselling and preventive consultation including vascular risk factors assessment. The primary outcome is change in cognitive function as measured by a short memory test.

Considering the different populations under study and the different types of interventions, it is expected that the results from these three trials will result in valuable knowledge about effective intervention strategies and the type of population that will benefit most from it.

DISCUSSION

The mechanisms through which the vascular risk factors contribute to an increased dementia risk have not been fully elucidated yet. The multi-factorial aetiology of dementia in old age and the interplay between vascular changes and neurodegenerative changes in the brain prevents conclusions about the exact mechanistic processes underlying the clinical syndrome of cognitive decline. In addition to the contribution of (clinically silent) stroke to cognitive decline, blood-brain barrier (BBB) changes have been implicated to play an important role in the pathophysiology of the relationship between vascular risk factors and dementia and the interaction with neurodegenerative changes.[80,81]

In spite of the overwhelming evidence of associations between vascular risk factors and dementia and the reported associations between treatment of some vascular risk factors and dementia risk from prospective cohort studies, RCTs that confirm the exact effects of such interventions are lacking. Since treatment aimed at vascular risk factors to prevent coronary heart disease, stroke and peripheral vascular disease is undisputed, certainly as secondary prevention, this leads to the inevitable question whether new RCTs investigating the effect of intensive vascular care are ethical. In the first place it is not known whether such interventions can contribute to dementia prevention and therefore the research question is relevant. In the second place it is unknown whether there might be potential negative effects of such interventions in old age, such as potential side effects of a relatively low blood pressure and low cholesterol, illustrating the necessity of such studies. Both low BMI and decreasing blood pressure have been implicated as symptoms of early Alzheimer's disease, and the reported associations might therefore not represent a causal relationship, but a consequence of the disease. Finally, all subjects in the control arms of the ongoing intervention studies receive at least care as usual according to current guidelines, so no therapy with proven efficacy is withheld from any participant. This is a prerequisite for any future trial to be designed as well. In this way, future studies may either confirm or falsify the general claim that more intensive vascular care reduces the incidence of dementia.

The results of the observational studies and the limited evidence from RCTs on the effect of antihypertensive medication are encouraging. Due to the high incidence of dementia in the elderly population and the high prevalence of hypertension, a small treatment effect can result in a large effect at the population level. The treatment targets (e.g. BP level, cholesterol level) of vascular care in elderly populations are still to be determined, and might be different for primary and secondary prevention groups.

Results from RCTs as described above will hopefully answer the question whether a multi-component intervention aimed at vascular risk factors can lead to the prevention of dementia, and which factor of such an intervention has most effect.

REFERENCES

1. Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, et al. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005;366:2112-7.
2. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, et al. Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology. 2000;54:S10-5.
3. Langa KM, Foster NL, Larson EB. Mixed dementia: emerging concepts and therapeutic implications. JAMA. 2004;292:2901-8.
4. Zekry D, Hauw JJ, Gold G. Mixed dementia: epidemiology, diagnosis, and treatment. J Am Geriatr Soc. 2002;50:1431-8.
5. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. (MRC CFAS): Lancet. 2001;357:169-75.
6. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. PLoS Med. 2009;6:e1000180.

7. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C. Age, neuropathology, and dementia. N Engl J Med. 2009;360:2302-9.

8. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Neurology. 2007;69:2197-204.

9. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Cerebral white matter lesions and the risk of dementia. Arch Neurol. 2004;61:1531-4.

10. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA. 1997;277:813-7.

11. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ, Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348:1215-22.

12. Alagiakrishnan K, McCracken P, Feldman H. Treating vascular risk factors and maintaining vascular health: is this the way towards successful cognitive ageing and preventing cognitive decline? Postgrad Med J. 2006;82:101-5.

13. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology. 2009;72:368-74.

14. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. Psychol Med. 2009;39:3-11.

15. Anstey KJ, Lipnicki DM, Low LF. Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis. Am J Geriatr Psychiatry. 2008;16:343-54.

16. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487-99.

17. Kloppenborg RP, van den Berg E, Kappelle LJ, Biessels GJ. Diabetes and other vascular risk factors for dementia: which factor matters most? A systematic review. Eur J Pharmacol. 2008;585:97-108.

18. Luchsinger JA, Patel B, Tang MX, Schupf N, Mayeux R. Measures of adiposity and dementia risk in elderly persons. Arch Neurol. 2007;64:392-8.

19. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, et al. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005;64:1689-95.

20. Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E, et al. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia – a systematic review. Vasc Health Risk Manag. 2010;8:775-85.

21. Launer LJ, Ross GW, Petrovitch H, Masaki K, Foley D, White LR, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging. 2000;21:49-55.

22. Ruitenberg A, Skoog I, Ott A, Aevarsson O, Witteman JC, Lernfelt B, vet al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. Dement Geriatr Cogn Disord. 2001;12:33-9.

23. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ. 2001;322:1447-51.

24. Skoog I, Lernfelt B, Landahl S, Palmertz B, Andreasson LA, Nilsson L, et al. 15-year longitudinal study of blood pressure and dementia. Lancet. 1996;347:1141-5.

25. Kennelly SP, Lawlor BA, Kenny RA. Blood pressure and the risk for dementia: a double edged sword. Ageing Res Rev. 2009;8:61-70.

26. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol. 2005;4:487-99.

27. Morris MC, Scherr PA, Hebert LE, Glynn RJ, Bennett DA, Evans DA. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol. 2001;58:1640-6.

28. Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L. Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Arch Neurol. 2003;60:223-8.

29. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. Neurology. 2003;61:1667-72.

30. Guo Z, Viitanen M, Fratiglioni L, Winblad B. Low blood pressure and dementia in elderly people: the Kungsholmen project. BMJ. 1996;312:805-8.

31. Morris MC, Scherr PA, Hebert LE, Bennett DA, Wilson RS, Glynn RJ, et al. The cross-sectional association between blood pressure and Alzheimer's disease in a biracial community population of older persons. J Gerontol A Biol Sci Med Sci. 2000;55:M130-6.

32. Haag MD, Hofman A, Koudstaal PJ, Breteler MM, Stricker BH. Duration of antihypertensive drug use and risk of dementia: A prospective cohort study. Neurology. 2009;72:1727-34.

33. Khachaturian AS, Zandi PP, Lyketsos CG, Hayden KM, Skoog I, Norton Mcet al. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. Arch Neurol. 2006;63:686-92.

34. Peila R, White LR, Masaki K, Petrovitch H, Launer LJ. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. Stroke. 2006;37:1165-70.

35. Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Intern Med. 2002;137:149-55.

36. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64:277-81.

37. Reitz C, Tang MX, Luchsinger J, Mayeux R. Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol. 2004;61:705-14.

38. Li G, Higdon R, Kukull WA, Peskind E, Van Valen MK, Tsuang D, et al. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. Neurology. 2004;63:1624-8.

39. Rea TD, Breitner JC, Psaty BM, Fitzpatrick AL, Lopez OL, Newman AB, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol. 2005;62:1047-51.

40. Zandi PP, Sparks DL, Khachaturian AS, Tschanz J, Norton M, Steinberg M, et al. Do statins reduce risk of incident dementia and Alzheimer disease? The Cache County Study. Arch Gen Psychiatry. 2005;62:217-24.

41. Shobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. Lancet Neurol. 2005;4:841-52.

42. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology. 1999;53:1937-42.

43. 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.

44. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. Arch Neurol. 2004;61:661-6.

45. Luchsinger JA, Tang MX, Stern Y, Shea S, Mayeux R. Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. Am J Epidemiol. 2001;154:635-41.

46. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes. 2002;51:1256-62.

47. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301:1565-72.

48. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med. 2003;163:1524-8.

49. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ. 2005;330:1360.

50. Hughes TF, Borenstein AR, Schofield E, Wu Y, Larson EB. Association between late-life body mass index and dementia: The Kame Project. Neurology. 2009;72:1741-6.

51. Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. J Gerontol A Biol Sci Med Sci. 2008;63:62-6.

52. Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol. 2001;58:498-504.

53. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, et al. Physical activity, diet, and risk of Alzheimer disease. JAMA 2009;302:627-37.

54. Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hanninen T, Soininen H, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology. 2006;67:843-7.

55. Yaffe K. Metabolic syndrome and cognitive disorders: is the sum greater than its parts? Alzheimer Dis Assoc Disord. 2007;21:167-71.

56. Lemstra AW, Eikelenboom P, van Gool WA. The cholinergic deficiency syndrome and its therapeutic implications. Gerontology 2003;49:55-60.

57. Gilman S, Koller M, Black RS, Jenkins L, Griffith SG, Fox NC, et al. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology. 2005;64:1553-62.

58. Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, et al. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA. 2009;302:2557-64.

59. Hachinski V. Preventable senility: a call for action against the vascular dementias. Lancet. 1992;340:645-8.

60. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991;265:3255-64.

61. Forette F, Seux ML, Staessen JA, Thijs L, Babarskiene MR, Babeanu S, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. Arch Intern Med. 2002;162:2046-52.

62. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens. 2003;21:875-86.

63. Peters R, Beckett N, Forette F, Tuomilehto J, Clarke R, Ritchie C, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol. 2008;7:683-9.

64. Prince MJ, Bird AS, Blizard RA, Mann AH. Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults. BMJ. 1996;312:801-5.

65. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163:1069-75.

66. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002;360:7-22.

67. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002;360:1623-30.

68. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009;CD003160.

69. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560-72.

70. Strandberg TE, Pitkala KH, Berglind S, Nieminen MS, Tilvis RS. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: a randomized, controlled trial. Am Heart J. 2006;152:585-92.

71. Richard E, Kuiper R, Dijkgraaf MG, van Gool WA. Vascular care in patients with Alzheimer's disease with cerebrovascular lesions-a randomized clinical trial. J Am Geriatr Soc. 2009;57:797-805.

72. Richard E, Gouw AA, Scheltens P, van Gool WA. Vascular care in patients with Alzheimer disease with cerebrovascular lesions slows progression of white matter lesions on MRI: the evaluation of vascular care in Alzheimer's disease (EVA) study. Stroke. 2010;41:554-6.

73. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. Neurology. 2009;73:173-9.

74. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol. 2006;5:735-41.

75. Richard E, van den Heuvel E, Moll van Charante EP, Achthoven L, Vermeulen M, Bindels PJ, et al. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. Alzheimer Dis Assoc Disord. 2009;23:198-204.

76. Launer LJ, Hughes T, Yu B, Masaki K, Petrovitch H, Ross GW, et al. Lowering midlife levels of systolic blood pressure as a public health strategy to reduce late-life dementia: perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. Hypertension. 2010;55:1352-9.

77. Holman R, Lindeboom R, Vermeulen M, de Haan RJ. The AMC Linear Disability Score project in a population requiring residential care: psychometric properties. Health Qual Life Outc. 2004;2:42.

78. Ahtiluoto S, Rauramaa R, Soininen H, et al. Scandinavian multi-domain interventions to delay cognitive impairment. Abstract. Alzheimer's Association International Conference on Alzheimer's disease. Juli 2009, Vienna, Austria.

79. Gillette-Guyonnet S, Andrieu S, Dantoine T, Dartigues JF, Touchon J, Vellas B. Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." The Multidomain Alzheimer Preventive Trial (MAPT): a new approach to the prevention of Alzheimer's disease. Alzheimers Dement. 2009;5:114-21.

80. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol. 2004;3:184-90.

81. Duron E, Hanon O. Vascular risk factors, cognitive decline, and dementia. Vasc Health Risk Manag. 2008;4:363-81.