



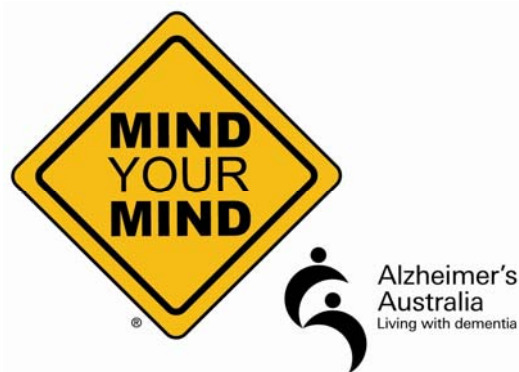
An Australian Government Initiative

DEMENTIA RISK REDUCTION RESEARCH

2006

Research relevant to Mind your Mind

**Compiled by Dr Maree Farrow, Research Fellow,
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Acknowledgements and Disclaimers

This paper was prepared as part of Alzheimer's Australia Vic's involvement in the Dementia Collaborative Research Centre Number 2: Prevention, Early Intervention and Risk Reduction.

The Dementia Collaborative Research Centres are an Australian Government funded initiative established to advance Australian research into dementia and the translation of research into clinical practice. The three Centres each focus on a different area of dementia research:

- Assessment and better care outcomes
- Prevention, early intervention and risk reduction
- Consumers, carers and social research

Visit the Dementia Collaborative Research Centres website at www.dementia.unsw.edu.au for further information about the people involved and the research activities.

For information and advice about dementia contact the National Dementia Helpline on 1800 100 500 or visit the Alzheimer's Australia website at www.alzheimers.org.au

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DEMENTIA RISK REDUCTION RESEARCH 2006

Journal articles relevant to Alzheimer's Australia's Mind your Mind® program

Compiled by Dr Maree Farrow, Research Fellow, Alzheimer's Australia Vic

This document includes summaries of research articles published in 2006 that describe or review research into risk factors, risk reduction or prevention of dementia. It is not intended to be a complete list of all research in the area, but instead concentrates on articles relevant to **Mind your Mind**, Alzheimer's Australia's dementia risk reduction community education program.

You can click on a title in the table of contents to go straight to that article. *Section One* includes review articles, papers that analyse the results of past research to address an issue, and *Section Two* includes papers describing individual research studies.

For each article, under the heading *Main Message*, the main points raised or main findings of the research are summarised. Under the heading *Note*, any issues to consider in interpreting the findings are noted. This is only included where relevant. Under the heading *Abstract*, is the abstract from the original article, i.e. the authors' summary of their paper.

The icons to the left of each article represent the **Mind your Mind** signposts that the research addresses. The seven signposts and their icons are:



Mind your Brain



Mind your Body



Mind your Diet



Mind your Health Checks



Mind your Social Life



Mind your Habits



Mind your Head

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SECTION ONE – REVIEWS



Hypertension and Alzheimer's disease

Date published: September 2006

Main Message

High blood pressure at midlife is associated with increased risk of later developing Alzheimer's disease (AD). However, blood pressure decreases before onset of and during the disease. This review looks at the various mechanisms that may explain the complex relationship between blood pressure and AD.

Abstract

Several studies report that blood pressure is increased in victims of Alzheimer's disease (AD) decades before the onset of the disease. Years before onset of Alzheimer's disease, blood pressure start to decrease and continues to decrease during the disease process. High blood pressure has also been related to pathological manifestations of Alzheimer's disease (senile plaques, neurofibrillary tangles, hippocampal atrophy). The exact mechanism behind these associations is not clear. Hypertension is also a risk factor for stroke, ischemic white matter lesions, silent infarcts, general atherosclerosis, myocardial infarction and cardiovascular diseases, and often clusters with other vascular risk factors, including diabetes mellitus, obesity and hypercholesterolemia. Also these risk factors have been related to Alzheimer's disease. Hypertension may thus cause cerebrovascular disease that may increase the possibility for individuals with AD encephalopathy to express a dementia syndrome. Hypertension may also lead to vessel wall changes in the brain, leading to hypoperfusion, ischemia and hypoxia which may initiate the pathological process of AD. Finally, subclinical AD may lead to increased blood pressure, and similar biological mechanisms may be involved in the pathogenesis of both disorders. Hypertension is a common disorder and often untreated. Several observational studies have reported that use of antihypertensives decreases risk of AD. Even though hypertension only results in a moderately increased risk of AD, or overall dementia, better treatment of hypertension may have an immense effect on the total number of demented individuals.

Reference

Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. *Neurological Research*, 2006, 28:605-611.



Cardiovascular risk factors also increase risk of Alzheimer's disease

Date published: August 2006

Main Message

Abnormal lipid, cholesterol and glucose metabolism are consistently indicated as central in the pathophysiology, and possibly the pathogenesis of Alzheimer's disease (AD). Evidence is accumulating that health conditions such as diabetes, obesity, and coronary artery disease are risk factors for AD, therefore appropriate changes to diets and lifestyles will likely reduce AD risk.

Abstract

High fat diets and sedentary lifestyles are becoming major concerns for Western countries. They have led to a growing incidence of obesity, dyslipidemia, high blood pressure, and a condition known as the insulin-resistance syndrome or metabolic syndrome. These health conditions are well known to develop along with, or be precursors to atherosclerosis, cardiovascular disease, and diabetes. Recent studies have found that most of these disorders can also be linked to an increased risk of Alzheimer's disease (AD). To complicate matters, possession of one or more apolipoprotein E epsilon4 (APOE epsilon4) alleles further increases the risk or severity of many of these conditions, including AD. ApoE has roles in cholesterol metabolism and Abeta clearance, both of which are thought to be significant in AD pathogenesis. The apparent inadequacies of ApoE epsilon4 in these roles may explain the increased risk of AD in subjects carrying one or more APOE epsilon4 alleles. This review describes some of the physiological and biochemical changes that the above conditions cause, and how they are related to the risk of AD. A diversity of topics is covered, including cholesterol metabolism, glucose regulation, diabetes, insulin, ApoE function, amyloid precursor protein metabolism, and in particular their relevance to AD. It can be seen that abnormal lipid, cholesterol and glucose metabolism are consistently indicated as central in the pathophysiology, and possibly the pathogenesis of AD. As diagnosis of mild cognitive impairment and early AD are becoming more reliable, and as evidence is accumulating that health conditions such as diabetes, obesity, and coronary artery disease are risk factors for AD, appropriate changes to diets and lifestyles will likely reduce AD risk, and also improve the prognosis for people already suffering from such conditions.

Reference

Martins IJ, et al. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. *Molecular Psychiatry*, 2006, 11:721-736.



Relationships between risk factors, pathology and cognition

Date published: August 2006

Main Message

Findings from 2 large studies suggest that the relationship between risk factors (including education and social networks), pathology (amyloid plaques and neurofibrillary tangles identified at post-mortem), and cognitive impairment (including Alzheimer's disease) is complex. Pathology can be present without clinical symptoms and vice-versa, and risk factors can mediate the relationship.

Note

The authors also highlighted the importance of incorporating postmortem indices into studies of aging and Alzheimer's disease in order to link risk factors to molecular changes in the brain.

Abstract

We present data from the Religious Orders Study and the Memory and Aging Project linking risk factors to pathology and cognitive function. Both studies involve more than 1000 older persons who agreed to annual clinical evaluation and brain donation at death. Published findings from the studies to date suggest that the relationship between risk factors, pathology, and cognitive impairment is complex. In some cases, known neuropathologic indices mediate the association of risk factors to cognition. In other cases, risk factors modify the relation of pathology to cognition. Finally, some risk factors seem to be related to clinical Alzheimer disease and cognitive decline, even decline in episodic memory, in the absence of any association with amyloid plaques, neurofibrillary tangles, or other pathologic indices that can be identified and quantified at this time. The findings to date illustrate the kinds of insights that can be gained into mechanisms of disease through the incorporation of pathologic indices into well-designed, epidemiologic studies of aging and Alzheimer disease.

Reference

Bennett DA, et al. Postmortem indices linking risk factors to cognition: results from the religious order study and the memory and aging project. *Alzheimer Disease and Associated Disorders*, 2006, 20:S63-S68.



The role of cholesterol as a risk factor for dementia

Date published: August 2006



Main Message

The prevailing wisdom is that high cholesterol is a risk factor for dementia. However, the relationship between cholesterol and dementia may vary considerably depending on when cholesterol is measured over the life course or, alternatively, in relation to the underlying course of the disease. Several observational studies have suggested that statins, which are effective in lowering cholesterol, may reduce the risk of dementia, but the results of these reports are inconclusive.

Abstract

This review will focus on the current knowledge on circulating serum and plasma risk factors of cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD) linked to cholesterol homeostasis and lipoprotein disturbances, i.e. total cholesterol (TC), 24S-hydroxy-cholesterol, lipoprotein(a) (Lp(a)), or apolipoprotein E (APOE). These measures linked to lipoprotein metabolism appear to be altered in AD, VaD, or predementia syndrome relative to controls, but with contrasting results. At present, several studies have demonstrated the dependence of APOE serum levels upon the APOE genotype, nonetheless serum APOE levels seems not to be a credible risk factor or a biochemical marker for AD instead of APOE genotyping. In fact, there was no consistent association of serum or plasma apoE protein levels with the disease when controlled for APOE genotype. In addition, there are some evidence that higher Lp(a) levels could be linked with AD, although there are studies suggesting an increased presence of low molecular weight apo(a) in AD, VaD, and frontotemporal dementia, that are associated with elevated Lp(a) levels. In fact, the apo(a) gene is highly polymorphic in length due to variation in the numbers of a sequence encoding the apo(a) kringle 4 domain, and plasma levels of Lp(a) are inversely correlated with apo(a) size. Furthermore, although serum/plasma levels of TC and 24S-hydroxycholesterol are not credible diagnostic markers for AD and cognitive decline, the current evidence suggests that they may be modifiable risk/protective factors. The prevailing wisdom is that high TC is a risk factor for dementia. However, the relationship between TC and dementia may vary considerably depending on when cholesterol is measured over the life course or, alternatively, in relation to the underlying course of the disease. Several observational studies have suggested that statins, which are effective in lowering cholesterol, may reduce the risk of dementia, but the results of these reports are inconclusive. Thus, more studies with long-term follow-up and serial assessments of TC are needed to further clarify the causal relationship between cholesterol and dementia.

Reference

Panza F, et al. Lipid metabolism in cognitive decline and dementia. *Brain Research Reviews*, 2006, 51:275-292.



Brain reserve and risk of dementia (2)

Date published: August 2006

Main Message

Brain reserve is related to sustained and complex mental activity (education, occupation, mentally stimulating lifestyle). Integrated data across 18 studies (47,000 people) revealed higher brain reserve is associated with decreased cognitive decline, after controlling for covariates. This confirms the link between brain reserve and dementia.

Note

Companion paper below.

Abstract

BACKGROUND: A previous companion paper to this report (Valenzuela and Sachdev, *Psychological Medicine* 2006, 36, 441-454) suggests a link between behavioural brain reserve and incident dementia; however, the issues of covariate control and ascertainment bias were not directly addressed. Our aim was to quantitatively review an independent set of longitudinal studies of cognitive change in order to clarify these factors.

METHOD: Cohort studies of the effects of education, occupation, and mental activities on cognitive decline were of interest. Abstracts were identified in MEDLINE (1966-September 2004), CURRENT CONTENTS (to September 2004), PsychINFO (1984-September 2004), Cochrane Library Databases and reference lists from relevant articles. Eighteen studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Cognitive decline studies were integrated using a non-parametric method after converting outcome data onto a common effect size metric.

RESULTS: Higher behavioural brain reserve was related to decreased longitudinal cognitive decline after control for covariates in source studies ($\phi=1.70$, $p<0.001$). This effect was robust to correction for both multiple predictors and multiple outcome measures and was the result of integrating data derived from more than 47000 individuals.

CONCLUSIONS: This study affirms that the link between behavioural brain reserve and incident dementia is most likely due to fundamentally different cognitive trajectories rather than confound factors.

Reference

Valenzuela MJ, Sachdev P. Brain reserve and cognitive decline: a non-parametric systematic review. *Psychological Medicine*, 2006, 36:1065-1073.



Brain reserve and risk of dementia (1)

Date published: April 2006

Main Message

Brain reserve is related to sustained and complex mental activity (education, occupation, mentally stimulating lifestyle). Integrated data across 22 studies (29,000 people) revealed higher brain reserve reduced dementia risk by 46%.

Note

Companion paper above.

Abstract

BACKGROUND: Behavioural brain reserve is a property of the central nervous system related to sustained and complex mental activity which can lead to differential expression of brain injury. Behavioural brain reserve has been assessed using autobiographical data such as education levels, occupational complexity and mentally stimulating lifestyle pursuits. So far there have been several epidemiological reports but no systematic review to put conflicting results into context. Our aim was to quantitatively review evidence for the effect of brain reserve on incident dementia.

METHOD: Cohort studies of the effects of education, occupation, premorbid IQ and mental activities on dementia risk were of interest. Abstracts were identified in MEDLINE (1966-September 2004), CURRENT CONTENTS (to September, 2004), PsychINFO (1984-September 2004), Cochrane Library Databases and reference lists from relevant articles. Twenty-two studies met inclusion criteria. Key information was extracted by both reviewers onto a standard template with a high level of agreement. Studies were combined through a quantitative random-effects meta-analysis.

RESULTS: Higher brain reserve was associated with a lowered risk for incident dementia (summary odds ratio, 0.54; 95% confidence interval, 0.49-0.59). This effect was found over a median of 7.1 years follow-up and resulted from integrating data across more than 29000 individuals. Notably, increased complex mental activity in late life was associated with lower dementia rates independent of other predictors; a dose-response relationship was also evident between extent of complex mental activities in late life and dementia risk.

CONCLUSIONS: This study demonstrates robust evidence that complex patterns of mental activity in the early, mid- and late-life stages is associated with a significant reduction in dementia incidence. Randomized control trials based on brain-reserve principles are now required.

Reference

Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. *Psychological Medicine*, 2006, 36:441-454.



Can blood pressure lowering prevent dementia?

Date published: April 2006

Main Message

Across 3 large studies, there was no convincing evidence that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease.

Note

The authors also concluded that from cross-sectional, longitudinal, and observational studies along with the RCTs, there is moderately strong evidence to support the view that hypertension in midlife, especially if not treated effectively, negatively affects cognition and contributes to the development of dementia and AD in later life. There is less evidence from these studies that the same negative effect on cognition is present for hypertension in later life.

Abstract

BACKGROUND: Hypertension and cognitive impairment are prevalent in older people. It is known that hypertension is a direct risk factor for vascular dementia and recent studies have suggested hypertension also impacts upon prevalence of Alzheimer's disease. The question is therefore whether treatment of hypertension lowers the rate of cognitive decline.

OBJECTIVES: To assess the effects of blood pressure lowering treatments for the prevention of dementia and cognitive decline in patients with hypertension but no history of cerebrovascular disease.

SEARCH STRATEGY: The trials were identified through a search of CDCIG's Specialised Register, CENTRAL, MEDLINE, EMBASE, PsycINFO and CINAHL on 27 April 2005.

SELECTION CRITERIA: Randomized, double-blind, placebo controlled trials in which pharmacological or non-pharmacological interventions to lower blood pressure were given for at least six months.

DATA COLLECTION AND ANALYSIS: Two independent reviewers assessed trial quality and extracted data. The following outcomes were assessed: incidence of dementia, cognitive change from baseline, blood pressure level, incidence and severity of side effects and quality of life.

MAIN RESULTS: Three trials including 12,091 hypertensive subjects were identified. Average age was 72.8 years. Participants were recruited from industrialised countries. Mean blood pressure at entry across the studies was 170/84 mmHg. All trials instituted a stepped care approach to hypertension treatment, starting with a calcium-channel blocker, a diuretic or an angiotensin receptor blocker. The combined result of the three trials reporting incidence of dementia indicated no significant difference between treatment and placebo (Odds Ratio (OR) = 0.89, 95% CI 0.69, 1.16). Blood pressure reduction resulted in a 11% relative risk reduction of dementia in patients with no prior cerebrovascular disease but this effect was not statistically significant ($p = 0.38$) and there was considerable heterogeneity between the trials. The combined results from the two trials reporting change in Mini Mental State Examination (MMSE) did not indicate a benefit from treatment (Weighted Mean Difference (WMD) = 0.10, 95% CI -0.03, 0.23). Both systolic and diastolic blood pressure levels were reduced significantly in the two trials assessing this outcome (WMD = -7.53, 95% CI -8.28, -6.77 for systolic blood pressure, WMD = -3.87, 95% CI -4.25, -3.50 for diastolic blood pressure). Two trials reported adverse effects requiring discontinuation of treatment and the combined results indicated a significant benefit from placebo (OR = 1.18, 95% CI 1.06, 1.30). When analysed separately, however, more patients on placebo in SCOPE were likely to discontinue treatment due to side effects; the converse was true in SHEP 1991. Quality of life data could not be analysed in the three studies. There was difficulty with the control group in this review as many of the control subjects received antihypertensive treatment because their blood pressures

exceeded pre-set values. In most cases the study became a comparison between the study drug against a usual antihypertensive regimen.

AUTHORS' CONCLUSIONS: There was no convincing evidence from the trials identified that blood pressure lowering prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease. There were significant problems identified with analysing the data, however, due to the number of patients lost to follow-up and the number of placebo patients given active treatment. This introduced bias. More robust results may be obtained by analysing one year data to reduce differential drop-out or by conducting a meta-analysis using individual patient data.

Reference

McGuinness B, et al. The effects of blood pressure lowering on development of cognitive impairment and dementia in patients without apparent prior cerebrovascular disease. *Cochrane Database of Systematic Reviews*, 2006, Issue 2. Art. No.: CD004034. DOI: 10.1002/14651858.CD004034.pub2.



Vascular risk factors and their relation to dementia

Date published: March 2006

Main Message

Studies over the past 10 years have implicated several vascular risk factors for Alzheimer's disease, including hypertension, atherosclerosis, atrial fibrillation, diabetes, high body mass index and stroke. Longitudinal studies are needed to clarify the relationship between these factors and dementia over the lifespan and to determine how these factors are interrelated.



Abstract

Multiple studies have implicated vascular-related conditions as risk factors for dementia. Clarification of these factors in dementia is important because most are modifiable, and may serve as the basis for preventive strategies. Several hematologic factors are associated with vascular diseases, but their relation to dementia is unclear. This review examines biological and epidemiological evidence concerning the role of these hematologic factors in dementia, and dementia subtypes. Reviewed factors include homocysteine, cholesterol, fatty acids, antioxidants, and C-reactive protein. The vast majority of studies reviewed are cross-sectional. Longitudinal studies with serial hematologic measures are needed to clarify the relationship between these factors and dementia over the lifespan. A necessary step is to examine multiple hematologic factors simultaneously, rather than in isolation, to determine how these factors are interrelated.

Reference

Mielke MM, Zandi PP. Hematologic risk factors of vascular disease and their relation to dementia. *Dementia and Geriatric Cognitive Disorders*, 2006, 21:335-352.



What is the evidence that physical activity reduces dementia risk?

Date published: March 2006

Main Message

Physical activity is associated with better cognitive function and less cognitive decline in later life. There is only scant evidence suggesting that physical activity may reduce the risk of dementia and Alzheimer's disease. Data to support the systematic introduction of physical activity programmes to reduce the risk of dementia in later life are not as yet available from randomized clinical trials.



Abstract

PURPOSE OF REVIEW: With the rapid ageing of the world's population, investigating protective factors that may prevent or delay age-related disorders has become a new public health priority. Dementia is a common age-related disorder, affecting up to one in every two people reaching 80 years of age or above. Amongst the various potential 'protective factors' currently under investigation, physical activity seems to hold promise for the primary and the secondary prevention of dementia. This paper critically reviews the evidence in support of the association between exercise and cognitive decline/dementia, as reported by cohort studies or clinical trials.

RECENT FINDINGS: The results of cohort studies show that physical activity is associated with better cognitive function and less cognitive decline in later life although there is only scant evidence suggesting that physical activity may in fact reduce the risk of dementia and Alzheimer's disease. In addition, data to support the systematic introduction of physical activity programmes to reduce the risk of dementia in later life are not as yet available from randomized clinical trials.

SUMMARY: The results of observational studies are largely consistent with the hypothesis that physical activity reduces the risk of cognitive decline and dementia in later life. These findings are, however, not as yet adequately supported by data from randomized clinical trials.

Reference

Lautenschlager NT, Almeida OP. Physical activity and cognition in old age. *Current Opinion in Psychiatry*, 2006, 19:190-193.



Health professionals should educate patients about preventative lifestyle approaches

Date published: February 2006

Main Message

Observational studies suggest that preventive approaches, such as healthy lifestyle, ongoing education, regular physical activity, and blood pressure and cholesterol control, play a role in prevention of Alzheimer's disease. These approaches can and should be used for every patient because they carry no significant risk.

Abstract

OBJECTIVE: To review the evidence regarding prevention of Alzheimer disease (AD) in order to highlight the role of family medicine.

QUALITY OF EVIDENCE: Most of the evidence relating to prevention of AD is derived from observational (cross-sectional, case-control, or longitudinal) studies. Evidence from randomized controlled trials (RCTs) is available only for blood pressure control and for hormone replacement therapy for menopausal women.

MAIN MESSAGE: Many preventive approaches to AD have been identified, but no RCTs support their efficacy. Evidence from RCTs supports the effectiveness of blood pressure control in reducing incidence of AD, but demonstrates that postmenopausal women's use of estrogen is ineffective in reducing it. Observational studies suggest that some preventive approaches, such as healthy lifestyle, ongoing education, regular physical activity, and cholesterol control, play a role in prevention of AD. These approaches can and should be used for every patient because they carry no significant risk. Currently, no effective pharmacologic interventions have been researched enough to support their use in prevention of AD.

CONCLUSION: Health professionals should educate patients, especially patients at higher risk of AD, about preventive strategies and potentially modifiable risk factors.

Reference

Scalco MZ, van Reekum R. Prevention of Alzheimer disease: Encouraging evidence. *Canadian Family Physician*, 2006, 52:200-207.



Risk factors affecting the cognitive and emotional health of older people

Date published: January 2006

Main Message

A large number of lifestyle and health behaviours alter the risk for maintenance of cognitive and emotional health in late life. Risk factors previously associated with increased risk of cardiovascular disease are consistently associated with cognitive decline, as are educational experience, depression and anxiety, and genetic factors.

Note

This review focussed on risk factors for cognitive decline in late life, not dementia per se.

Abstract

BACKGROUND: The Cognitive and Emotional Health Project (CEHP) seeks to identify the demographic, social, and biological determinants of cognitive and emotional health in the older adult. As part of the CEHP, a critical evaluation study committee was formed to assess the state of epidemiological research on demographic, social, and biological determinants of cognitive and emotional health.

METHODS: Criteria for inclusion in the survey were large cohort studies, longitudinal in design, participants predominantly 65 years or older, with measurements of both cognition and emotion, and information on a wide variety of demographic, psychosocial, and biological factors. North American and European studies, which met these criteria, were selected for the review. Outcome measures included cognition, cognitive decline, and cognitive function. For emotion, symptoms included depression and anxiety, positive and negative affect, subjective well being, mastery, and resilience.

RESULTS: Ninety-six papers were identified that addressed cognitive and emotional outcomes. A large variety of risk factors were consistently identified with cognitive outcomes, particularly those previously associated with increased risk of cardiovascular disease. There was considerable overlap between risk factors for cognitive and emotional outcomes.

CONCLUSION: This review identifies a large number of lifestyle and health behaviours that alter the risk for maintenance of cognitive and emotional health. Large longitudinal cohort studies are a unique source to explore factors associated with cognitive and emotional health. Secondary analyses of these studies should be encouraged as should the development of standardized questionnaires to measure cognitive and emotional health. Future research in this field should study cognitive and emotional health simultaneously.

Reference

Hendrie HC, et al. The NIH cognitive and emotional health project: Report of the critical evaluation study committee. *Alzheimer's and Dementia*, 2006, 2:12-32.



Omega-3 fatty acids and risk of dementia

Date published: January 2006

Main Message

The available data are insufficient to draw strong conclusions about the effects of omega–3 fatty acids on cognitive function in normal aging or on the incidence or treatment of dementia. However, limited evidence suggests a possible association between omega–3 fatty acids and reduced risk of dementia.

Abstract

We systematically reviewed the published literature on the effects of omega–3 fatty acids on measures of cognitive function in normal aging, incidence and treatment of dementia. Computerized databases were searched for published literature to identify potentially relevant studies with the intent to conduct a meta-analysis. We screened 5,865 titles, reviewed 497 studies of which 49 underwent a detailed review, and found 5 studies that pertained to our objectives. We included controlled clinical trials and observational studies, including prospective cohort, case-control, and case series designs; we excluded case reports. We had no language restrictions. We abstracted data on the effects of omega–3 fatty acids and on study design, relevant outcomes, study population, source, type, amount, and duration of omega–3 fatty acid consumption, and parameters of methodological quality. A single cohort study has assessed the effects of omega–3 fatty acids on cognitive function with normal aging and found no association for fish or total omega–3 consumption. In four studies that assessed the effects of omega–3 fatty acids on incidence and treatment of dementia, a trend in favour of omega–3 fatty acids (fish and total omega–3 consumption) toward reducing risk of dementia and improving cognitive function was reported. The available data are insufficient to draw strong conclusions about the effects of omega–3 fatty acids on cognitive function in normal aging or on the incidence or treatment of dementia. However, limited evidence suggests a possible association between omega–3 fatty acids and reduced risk of dementia.

Reference

Issa AM, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. *Dementia and Geriatric Cognitive Disorders*, 2006, 21:88-96.





Omega-3 fatty acids and prevention of dementia

Date published: January 2006



Main Message

Available clinical studies comparing the occurrence of Alzheimer's disease (AD) between elderly persons with different levels of dietary omega-3 intake, suggest that risk of AD is significantly reduced among those with higher levels of fish and omega-3 consumption. However, because these studies are not randomized trials, they provide insufficient evidence to recommend dietary and supplemental omega-3 for the explicit purpose of dementia prevention. This review yielded no clinical trials that could confirm or refute the utility of omega-3 in preventing cognitive impairment or dementia.

Note

Results of two clinical trials are expected in 2008.

Abstract

BACKGROUND: Accruing evidence from observational and epidemiological studies suggests an inverse relationship between dietary intake of omega 3 polyunsaturated fatty acid (PUFA) and risk of dementia. Postulated mechanisms that might qualify omega 3 PUFA as an interventional target for the primary prevention of dementia include its anti-atherogenic, anti-inflammatory, anti-oxidant, anti-amyloid and neuroprotective properties.

OBJECTIVES: To review the evidence that omega 3 PUFA supplementation prevents cognitive impairment and dementia in cognitively intact elderly persons.

SEARCH STRATEGY: The Cochrane Dementia and Cognitive Improvement Group's (CDCIG) Specialized register, MEDLINE, EMBASE, CINAHL, PsycINFO, AMED AND CENTRAL and several ongoing trials databases were searched on 5 and 6 October 2005. The CDCIG Register is updated regularly and contains records from all major medical databases and many ongoing trials databases.

SELECTION CRITERIA: In order to be selected, trials needed to be randomized, placebo-controlled, doubled blinded, of minimum study duration of 6 months, involved persons aged 60 years and above without pre-existing dementia at study onset, and employed cognitive endpoints.

DATA COLLECTION AND ANALYSIS: Reviewers, working independently, were to select, quality assess and extract relevant data where appropriate and possible. In comparing intervention with placebo, the pooled odds ratios or weighted mean differences and standardized mean difference were to be estimated.

MAIN RESULTS: There were no randomized trials found in the search that met the selection criteria. Results of two clinical trials are expected in 2008.

AUTHORS' CONCLUSIONS: There is a growing body of evidence from biological, observational and epidemiological studies that suggests a protective effect of omega 3 PUFA against dementia. However, until data from randomized trials become available for analysis, there is no good evidence to support the use of dietary or supplemental omega 3 PUFA for the prevention of cognitive impairment or dementia.

Reference

Lim WS, et al. Omega 3 fatty acid for the prevention of dementia (Review). *Cochrane Database of Systematic Reviews*, 2006, Issue 1. Art. No.: CD005379. DOI: 10.1002/14651858.CD005379.pub2.

SECTION TWO – STUDIES



Mediterranean diet reduces risk of Alzheimer's disease

Date published: December 2006

Main Message

Higher adherence to the Mediterranean diet was associated with lower risk for Alzheimer's disease. This association does not seem to be mediated by vascular comorbidity.



Abstract

OBJECTIVES: To examine the association between the Mediterranean diet (MeDi) and Alzheimer disease (AD) in a different AD population and to investigate possible mediation by vascular pathways.

DESIGN, SETTING, PATIENTS, AND MAIN OUTCOME MEASURES: A case-control study nested within a community-based cohort in New York, NY. Adherence to the MeDi (0- to 9-point scale with higher scores indicating higher adherence) was the main predictor of AD status (194 patients with AD vs 1790 nondemented subjects) in logistic regression models that were adjusted for cohort, age, sex, ethnicity, education, apolipoprotein E genotype, caloric intake, smoking, medical comorbidity index, and body mass index (calculated as weight in kilograms divided by height in meters squared). We investigated whether there was attenuation of the association between MeDi and AD when vascular variables (stroke, diabetes mellitus, hypertension, heart disease, lipid levels) were simultaneously introduced in the models (which would constitute evidence of mediation).

RESULTS: Higher adherence to the MeDi was associated with lower risk for AD (odds ratio, 0.76; 95% confidence interval, 0.67-0.87; $P < .001$). Compared with subjects in the lowest MeDi tertile, subjects in the middle MeDi tertile had an odds ratio of 0.47 (95% confidence interval, 0.29-0.76) and those at the highest tertile an odds ratio of 0.32 (95% confidence interval, 0.17-0.59) for AD (P for trend $< .001$). Introduction of the vascular variables in the model did not change the magnitude of the association.

CONCLUSIONS: We note once more that higher adherence to the MeDi is associated with a reduced risk for AD. The association does not seem to be mediated by vascular comorbidity. This could be the result of either other biological mechanisms (oxidative or inflammatory) being implicated or measurement error of the vascular variables.

Reference

Scarmeas N, et al. Mediterranean diet, Alzheimer disease, and vascular mediation. *Archives of Neurology*, 2006, 63:1709-1717.



Long term effects of cognitive training

Date published: December 2006

Main Message

Ten sessions of training in tasks of memory, reasoning and speed of processing produced improved performance on those tasks that was still evident after 5 years (although small effects for memory and reasoning).

Note

An earlier paper on the same study, reporting 2 year follow up (Ball et al 2002, JAMA 288:2271-2281), showed only 26% of memory trained participants demonstrated reliable improvement. Also, there was no improvement seen in related activities of daily living, only on the specific task for which training was received.

Abstract

CONTEXT: Cognitive training has been shown to improve cognitive abilities in older adults but the effects of cognitive training on everyday function have not been demonstrated.

OBJECTIVE: To determine the effects of cognitive training on daily function and durability of training on cognitive abilities.

DESIGN, SETTING, AND PARTICIPANTS: Five-year follow-up of a randomized controlled single-blind trial with 4 treatment groups. A volunteer sample of 2832 persons (mean age, 73.6 years; 26% black), living independently in 6 US cities, was recruited from senior housing, community centers, and hospitals and clinics. The study was conducted between April 1998 and December 2004. Five-year follow-up was completed in 67% of the sample.

INTERVENTIONS: Ten-session training for memory (verbal episodic memory), reasoning (inductive reasoning), or speed of processing (visual search and identification); 4-session booster training at 11 and 35 months after training in a random sample of those who completed training.

MAIN OUTCOME MEASURES: Self-reported and performance-based measures of daily function and cognitive abilities.

RESULTS: The reasoning group reported significantly less difficulty in the instrumental activities of daily living (IADL) than the control group (effect size, 0.29; 99% confidence interval [CI], 0.03-0.55). Neither speed of processing training (effect size, 0.26; 99% CI, -0.002 to 0.51) nor memory training (effect size, 0.20; 99% CI, -0.06 to 0.46) had a significant effect on IADL. The booster training for the speed of processing group, but not for the other 2 groups, showed a significant effect on the performance-based functional measure of everyday speed of processing (effect size, 0.30; 99% CI, 0.08-0.52). No booster effects were seen for any of the groups for everyday problem-solving or self-reported difficulty in IADL. Each intervention maintained effects on its specific targeted cognitive ability through 5 years (memory: effect size, 0.23 [99% CI, 0.11-0.35]; reasoning: effect size, 0.26 [99% CI, 0.17-0.35]; speed of processing: effect size, 0.76 [99% CI, 0.62-0.90]). Booster training produced additional improvement with the reasoning intervention for reasoning performance (effect size, 0.28; 99% CI, 0.12-0.43) and the speed of processing intervention for speed of processing performance (effect size, 0.85; 99% CI, 0.61-1.09).

CONCLUSIONS: Reasoning training resulted in less functional decline in self-reported IADL. Compared with the control group, cognitive training resulted in improved cognitive abilities specific to the abilities trained that continued 5 years after the initiation of the intervention.

Reference

Willis SL, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *Journal of the American Medical Association*, 2006, 296:2805-2814.



DHA fatty acid reduces risk of dementia

Date published: November 2006

Main Message

Subjects in the upper quartile of baseline plasma DHA levels (who had a mean fish intake of 3.0 servings per week), compared with subjects in the lower 3 quartiles, had a 47% reduced risk of developing all-cause dementia and a 39% reduced risk of developing Alzheimer's disease.

Abstract

BACKGROUND: Docosahexaenoic acid (DHA) is an abundant fatty acid in the brain. In the diet, DHA is found mostly in fatty fish. The content of DHA has been shown to be decreased in the brain and plasma of patients with dementia.

OBJECTIVE: To determine whether plasma phosphatidylcholine (PC) DHA content is associated with the risk of developing dementia.

DESIGN, SETTING, AND PARTICIPANTS: A prospective follow-up study in 899 men and women who were free of dementia at baseline, had a median age of 76.0 years, and were followed up for a mean of 9.1 years for the development of all-cause dementia and Alzheimer disease.

MAIN OUTCOME MEASURES: Plasma PC fatty acid levels were measured at baseline. Cox proportional regression analysis was used to assess relative risks of all-cause dementia and Alzheimer disease according to baseline plasma levels.

RESULTS: Ninety-nine new cases of dementia (including 71 of Alzheimer disease) occurred during the follow-up. After adjustment for age, sex, apolipoprotein E epsilon4 allele, plasma homocysteine concentration, and education level, subjects in the upper quartile of baseline plasma PC DHA levels, compared with subjects in the lower 3 quartiles, had a relative risk of 0.53 of developing all-cause dementia (95% confidence interval, 0.29-0.97; $P=.04$) and 0.61 of developing Alzheimer disease (95% confidence interval, 0.31-1.18; $P=.14$). Subjects in the upper quartile of plasma PC DHA levels had a mean DHA intake of 0.18 g/d and a mean fish intake of 3.0 servings per week ($P<.001$) in a subset of 488 participants. We found no other significant associations.

CONCLUSION: The top quartile of plasma PC DHA level was associated with a significant 47% reduction in the risk of developing all-cause dementia in the Framingham Heart Study.

Reference

Schaefer EJ, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham heart study. *Archives of Neurology*, 2006, 63:1545-1550.



Distress proneness increases risk of dementia

Date published: September 2006

Main Message

Older persons with a high level of distress proneness were 2.7 times more likely to develop Alzheimer's disease (AD) than those not prone to distress. Distress proneness was also associated with more rapid cognitive decline, but was unrelated to diverse measures of AD pathology.

Abstract

Clinical and pathological data from the Rush Memory and Aging Project were used to test the hypothesis that distress proneness is associated with increased risk of Alzheimer's disease (AD). More than 600 older persons without dementia completed a 6-item measure of neuroticism, a stable indicator of proneness to psychological distress. At annual intervals thereafter, they underwent uniform evaluations that included clinical classification of AD and administration of 18 cognitive tests. Those who died underwent brain autopsy from which composite measures of AD pathology were derived. During a mean of about 3 years of follow-up, 55 people were clinically diagnosed with AD. In analyses that controlled for age, sex, and education, persons with a high level of distress proneness (score = 24, 90th percentile) were 2.7 times more likely to develop AD than those not prone to distress (score = 6, 10th percentile). Adjustment for depressive symptomatology or frequency of cognitive, social, and physical activity did not substantially change this effect. Distress proneness was also associated with more rapid cognitive decline. Among 45 participants who died and underwent brain autopsy, distress proneness was unrelated to diverse measures of AD pathology and was inversely related to cognition after controlling for AD pathology. The results support the hypothesis that distress proneness is associated with increased risk of dementia and suggest that neurobiologic mechanisms other than AD pathology may underlie the association.

Reference

Wilson RS, et al. Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology*, 2006, 27:143-153.



Metabolic syndrome increases risk of Alzheimer's disease

Date published: September 2006

Main Message

In adults aged 69-78, the incidence of Alzheimer's disease (AD) was more than doubled in subjects with metabolic syndrome, compared to those without. The association was especially strong for women.

Note

The incidence of AD in those with metabolic syndrome was 7%, so most people with the syndrome did not have AD.

Abstract

OBJECTIVE: To assess the association of metabolic syndrome (MetS) with Alzheimer disease (AD).

METHODS: The authors derived subjects from a population-based study of 980 randomly selected elderly subjects. After exclusion of all non-Alzheimer dementia cases, the final study population included 959 subjects (337 men and 622 women) aged 69 to 78 years. The presence of MetS was defined according to the National Cholesterol Education Program (Adult Treatment Panel III) criteria, and the diagnosis of AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

RESULTS: Of the study subjects, 418 (43.6%) had MetS. Probable or possible AD was diagnosed in 45 subjects (4.7%). AD was more frequently detected in subjects with MetS than in subjects without MetS (7.2 vs 2.8%; $p < 0.001$). The prevalence of AD was higher in women with MetS vs women without the syndrome (8.3 vs 1.9%; $p < 0.001$), but in men with MetS, the prevalence of AD was not increased (3.8 vs 3.9%; $p = 0.994$). In univariate logistic regression analysis, MetS was significantly associated with AD (odds ratio [OR] 2.71; 95% CI 1.44 to 5.10). In multivariate logistic regression analysis including also apolipoprotein E4 phenotype, education, age, and total cholesterol, MetS was significantly associated with AD (OR 2.46; 95% CI 1.27 to 4.78). If only nondiabetic subjects were included in the multivariate analysis, MetS was still significantly associated with AD (OR 3.26; 95% CI 1.45 to 7.27).

CONCLUSION: Metabolic syndrome is associated with Alzheimer disease in elderly subjects.

Reference

Vanhanen M, et al. Association of metabolic syndrome with Alzheimer disease: a population based study. *Neurology*, 2006, 67:843-847.



Life long cognitive engagement delays dementia onset

Date published: August 2006

Main Message

Education significantly affects dementia onset. Differences in education are reflected in differences in leisure activities and occupation, suggesting that differences in cognitive engagement begin early and persist over the life course. Such findings point to the importance of taking a life-course perspective in interventions to delay or to prevent dementia.

Abstract

Research findings suggest that dementia risk is lower in individuals with more extensive education, greater engagement in mentally stimulating leisure activities during adulthood, and higher occupational complexity. Other recent findings support the importance of early-life risk factors, such as socioeconomic conditions, early-life development, and exposure to infection, in explaining individual differences in dementia risk. Life-style variables have been conceptualized as delaying factors, postponing onset of dementia and thereby reducing total population burden of dementia. Using a sample of Swedish twins from the HARMONY study, we found that education significantly affects dementia onset, that is, occurrence and timing of dementia symptoms. In the HARMONY data, we also showed that differences in education are reflected in differences in leisure activities and occupation, suggesting that differences in cognitive engagement begin early and persist over the life course. Such findings point to the importance of taking a life-course perspective to designing interventions to delay or to prevent dementia.

Reference

Gatz M, et al. Lifestyle risk and delaying factors. *Alzheimer Disease and Associated Disorders*, 2006, 20:S84-S88.





Saturated fats increase, but unsaturated fats reduce, risk of dementia

Date published: June 2006

Main Message

Moderate intake of unsaturated fats at midlife is protective, whereas moderate intake of saturated fats may increase the risk of dementia and Alzheimer's disease, especially among ApoE epsilon4 carriers.

Abstract

BACKGROUND: Lifestyle and vascular factors have been linked to dementia and Alzheimer's disease (AD), but the role of dietary fats in the development of dementia is less clear.

METHODS: Participants were derived from random, population-based samples initially studied in midlife (1972, 1977, 1982, or 1987). Fat intake from spreads and milk products was assessed using a structured questionnaire and an interview. After an average follow-up of 21 years, a total of 1,449 (73%) individuals aged 65-80 years participated in the re-examination in 1998. Altogether 117 persons had dementia.

RESULTS: Moderate intake of polyunsaturated fats at midlife decreased the risk of dementia even after adjustment for demographic variables, other subtypes of fats, vascular risk factors and disorders, and apolipoprotein E (ApoE) genotype (OR 0.40, CI 0.17-0.94 for the 2nd quartile vs. 1st quartile), whereas saturated fat intake was associated with an increased risk (OR 2.45, CI 1.10-5.47 for the 2nd quartile). The associations were seen only among the ApoE epsilon4 carriers.

CONCLUSIONS: Moderate intake of unsaturated fats at midlife is protective, whereas a moderate intake of saturated fats may increase the risk of dementia and AD, especially among ApoE epsilon4 carriers. Thus, dietary interventions may potentially modify the risk of dementia, particularly among genetically susceptible individuals.

Reference

Laitinen MH, et al. Fat intake at midlife and risk of dementia and Alzheimer's disease: a population-based study. *Dementia and Geriatric Cognitive Disorders*, 2006, 22:99-107.



Antihypertensive drugs reduce risk of dementia

Date published: May 2006

Main Message

In adults aged 65 and over, use of antihypertensive medications was associated with a 36% lower incidence of Alzheimer's disease 3 years later. Comparing different drugs, the greatest risk reduction, 74%, was associated with potassium sparing diuretics.

Abstract

BACKGROUND: Recent reports suggest that antihypertensive (AH) medications may reduce the risk of dementing illnesses.

OBJECTIVES: To examine the relationship of AH medication use with incidence of Alzheimer disease (AD) among the elderly population (aged 65 years and older) of Cache County, Utah, and to examine whether the relationship varies with different classes of AH medications.

METHODS: After an initial (wave 1) multistage assessment (1995 through 1997) to identify prevalent cases of dementia, we used similar methods 3 years later (wave 2) to identify 104 incident cases of AD among the 3308 survivors. At the baseline assessment, we obtained a detailed drug inventory from the study participants. We carried out discrete time survival analyses to examine the association between the use of AH medications (including angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blockers, and diuretics) at baseline with subsequent risk of AD.

RESULTS: Use of any AH medication at baseline was associated with lower incidence of AD (adjusted hazard ratio, 0.64; 95% confidence interval, 0.41-0.98). Examination of medication subclasses showed that use of diuretics (adjusted hazard ratio, 0.57; 95% confidence interval, 0.33-0.94), and specifically potassium-sparing diuretics (adjusted hazard ratio, 0.26; 95% confidence interval, 0.08-0.64), was associated with the greatest reduction in risk of AD. Corresponding analysis with a fully examined subsample controlling for blood pressure measurements did not substantially change our findings.

CONCLUSIONS: These data suggest that AH medications, and specifically potassium-sparing diuretics, are associated with reduced incidence of AD. Because the latter association is a new finding, it requires confirmation in further study.

Reference

Khachaturian AS, et al. Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. *Archives of Neurology*, 2006, 63:686-692.



Long term treatment with antihypertensive drugs reduces risk of dementia

Date published: May 2006



Main Message

In men who were hypertensive from midlife, longer treatment with antihypertensive drugs was associated with reduced risk of dementia and Alzheimer's disease. Those treated for > 12 years had 60% reduced risk compared to those never treated, and a similar risk to those without hypertension.

Abstract

BACKGROUND AND PURPOSE: The efficacy of treating older persons for hypertension remains controversial. Although clinical trials suggest no short-term harm, or some benefits, there are little data on the effect on cognitive function of long-term antihypertensive treatment. We evaluated the risk of dementia and cognitive decline associated with duration of antihypertensive treatment.

METHODS: Data are from the Honolulu Asia Aging Study on Japanese American men followed since 1965. The subjects included in this analysis were hypertensive from midlife and dementia-free in 1991 (mean age 76.7 years). In 1991, 1994 and 1997, global cognitive function was assessed with the Cognitive Abilities Screening Instrument (CASI) and dementia by a standardized examination using international criteria. The sample was grouped by treatment duration (never-treated hypertensives (NTH), <5 years, 5 to 12 years, >12 years). Normotensive subjects up to 1991 were included in the analysis as a control group.

RESULTS: For each additional year of treatment there was a reduction in the risk of incident dementia (hazard ratio [HR]=0.94, 95% CI, 0.89 to 0.99). The risk for dementia in subjects with >12 years of treatment was lower compared to NTH (HR for dementia=0.40; 95% CI, 0.22 to 0.75 and for Alzheimer disease HR=0.35; 95% CI, 0.16 to 0.78) and was similar to the normotensives. Nondemented subjects with 5 to 12 years of treatment had lower yearly CASI decline compared to NTH.

CONCLUSIONS: Results suggest that in hypertensive men, the duration of the antihypertensive treatment is associated with a reduced risk for dementia and cognitive decline.

Reference

Peila R, et al. Reducing the risk of dementia: efficacy of long-term treatment of hypertension. *Stroke*, 2006, 37:1165-1170.



Larger social networks protect cognitive function in the presence of Alzheimer's disease pathology

Date published: May 2006



Main Message

Social network size modified the relationship between Alzheimer's disease pathology and cognitive function, especially memory. Even at more severe levels of disease pathology, cognitive function remained higher for participants with larger social network sizes.

Abstract

BACKGROUND: Few data are available about how social networks reduce the risk of cognitive impairment in old age. We aimed to measure this effect using data from a large, longitudinal, epidemiological clinicopathological study.

METHODS: 89 elderly people without known dementia participating in the Rush Memory and Aging Project underwent annual clinical evaluation. Brain autopsy was done at the time of death. Social network data were obtained by structured interview. Cognitive function tests were Z scored and averaged to yield a global and specific measure of cognitive function. Alzheimer's disease pathology was quantified as a global measure based on modified Bielschowsky silver stain. Amyloid load and the density of paired helical filament tau tangles were also quantified with antibody-specific immunostains. We used linear regression to examine the relation of disease pathology scores and social networks to level of cognitive function.

FINDINGS: Cognitive function was inversely related to all measures of disease pathology, indicating lower function at more severe levels of pathology. Social network size modified the association between pathology and cognitive function (parameter estimate 0.097, SE 0.039, $p=0.016$, $R(2)=0.295$). Even at more severe levels of global disease pathology, cognitive function remained higher for participants with larger network sizes. A similar modifying association was observed with tangles (parameter estimate 0.011, SE 0.003, $p=0.001$, $R(2)=0.454$). These modifying effects were most pronounced for semantic memory and working memory. Amyloid load did not modify the relation between pathology and network size. The results were unchanged after controlling for cognitive, physical, and social activities, depressive symptoms, or number of chronic diseases.

INTERPRETATION: These findings suggest that social networks modify the relation of some measures of Alzheimer's disease pathology to level of cognitive function.

Reference

Bennett DA, et al. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *The Lancet Neurology*, 2006, 5:406-412.



Vascular factors increase risk of Alzheimer's disease and vascular dementia

Date published: May 2006



Main Message

In adults aged 65 and over, there was no association between self-reported history of hypertension and high cholesterol and Alzheimer's disease (AD). Hypertension increased risk of vascular dementia (VaD), obesity increased risk of AD only in females, diabetes increased risk of VaD only in females. The results suggest that vascular factors may increase risks for AD and VaD differentially by sex.

Note

Presence of cardiovascular risk factors was determined by self report, not measured objectively.

Abstract

Vascular risk factors for Alzheimer disease (AD) and vascular dementia (VaD) have been evaluated; however, few studies have compared risks by dementia subtypes and sex. We evaluated relationships between cardiovascular risk factors (hypertension, high cholesterol, diabetes mellitus, and obesity), events (stroke, coronary artery bypass graft surgery, and myocardial infarction), and subsequent risk of AD and VaD by sex in a community-based cohort of 3264 Cache County residents aged 65 or older. Cardiovascular history was ascertained by self-report or proxy-report in detailed interviews. AD and VaD were diagnosed using standard criteria. Estimates from discrete-time survival models showed no association between self-reported history of hypertension and high cholesterol and AD after adjustments. Hypertension increased the risk of VaD [adjusted hazard ratio (aHR) 2.42, 95% confidence interval (CI) 0.95-7.44]. Obesity increased the risk of AD in females (aHR 2.23, 95% CI 1.09-4.30) but not males. Diabetes increased the risk of VaD in females after adjustments (aHR 3.33, 95% CI 1.03-9.78) but not males. The risk of VaD after stroke was increased in females (aHR 16.90, 95% CI 5.58-49.03) and males (aHR 10.95, 95% CI 2.48-44.78). The results indicate that vascular factors increase risks for AD and VaD differentially by sex. Future studies should focus on specific causal pathways for each of these factors with regard to sex to determine if sex differences in the prevalence of vascular factors have an influence on sex differences in dementia risk.

Reference

Hayden KM, et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Disease and Associated Disorders*, 2006, 20:93-100.



Low social engagement increases risk of dementia

Date published: March 2006

Main Message

Low levels of social engagement in late life and decreasing social engagement from midlife to late life were associated with increased risk of dementia.

Note

Does reduced social activity in late life increase risk of dementia, or does early dementia/cognitive impairment lead to reduced social activity?

Abstract

The authors examined whether low levels of social engagement in midlife and late life were associated with the risk of incident dementia in 2,513 Japanese-American men who have been followed since 1965 as part of the Honolulu Heart Program and the Honolulu-Asia Aging Study. In 1991, assessment of dementia began; incident dementia cases (n = 222) were diagnosed in 1994 and 1997. Social engagement was assessed in midlife (1968) and late life (1991). The relation between social engagement and dementia risk was examined using Cox proportional hazards models. No level of midlife social engagement was associated with the risk of dementia. In late life, compared with participants in the highest quartile of late-life social engagement, those in the lowest quartile had a significantly increased risk of dementia (hazard ratio = 2.34, 95% confidence interval: 1.18, 4.65). However, compared with those who were in the highest quartile of social engagement at both midlife and late life, only decreased social engagement from midlife to late life was associated with an increased risk of dementia (hazard ratio = 1.87, 95% confidence interval: 1.12, 3.13). Although low social engagement in late life is associated with risk of dementia, levels of late-life social engagement may already have been modified by the dementing process and may be associated with prodromal dementia.

Reference

Saczynski JS, et al. The effect of social engagement on incident dementia: the Honolulu-Asia aging study. *American Journal of Epidemiology*, 2006, 163:433-440.



Gene status affects link between high cholesterol and Alzheimer's disease risk

Date published: January 2006

Main Message

Increasing levels of cholesterol and LDL were associated with increased risk of Alzheimer's disease (AD) in individuals without the APOE-epsilon4 allele, but not in those with APOE-epsilon4. APOE status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies.



Abstract

OBJECTIVE: To examine the relationship between cholesterol and other lipids, APOE genotype, and risk of Alzheimer disease (AD) in a population-based study of elderly Yoruba living in Ibadan, Nigeria.

METHODS: Blood samples and clinical data were collected from Yoruba study participants aged 70 years and older (N = 1,075) as part of the Indianapolis-Ibadan Dementia Project, a longitudinal epidemiologic study of AD. Cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels were measured in fasting blood samples. DNA was extracted and APOE was genotyped. Diagnoses of AD were made by consensus using National Institute of Neurologic Disorders/Stroke-Alzheimer's Disease and Related Disorders Association criteria.

RESULTS: Logistic regression models showed interaction after adjusting for age and gender between APOE-epsilon4 genotype and biomarkers in the risk of AD cholesterol*genotype ($p = 0.022$), LDL*genotype ($p = 0.018$), and triglyceride*genotype ($p = 0.036$). Increasing levels of cholesterol and LDL were associated with increased risk of AD in individuals without the APOE-epsilon4 allele, but not in those with APOE-epsilon4. There was no significant association between levels of triglycerides and AD risk in those without APOE-epsilon4.

CONCLUSIONS: There was a significant interaction between cholesterol, APOE-epsilon4, and the risk of Alzheimer disease (AD) in the Yoruba, a population that has lower cholesterol levels and lower incidence rates of AD compared to African Americans. APOE status needs to be considered when assessing the relationship between lipid levels and AD risk in population studies.

Reference

Hall K, et al. Cholesterol, APOE genotype, and Alzheimer disease: an epidemiological study of Nigerian Yoruba. *Neurology*, 2006, 66:223-227.



Regular exercise reduces risk of dementia

Date published: January 2006



Main Message

In adults over 65 years, those who exercised 3 or more times per week had reduced risk of dementia (by 38%), compared to those who exercised less. The results suggest that regular exercise is associated with a delay in onset of dementia and Alzheimer's disease, further supporting its value for older persons.

Abstract

BACKGROUND: Alzheimer disease and other dementing disorders are major sources of morbidity and mortality in aging societies. Proven strategies to delay onset or reduce risk for dementing disorders would be greatly beneficial.

OBJECTIVE: To determine whether regular exercise is associated with a reduced risk for dementia and Alzheimer disease.

DESIGN: Prospective cohort study.

SETTING: Group Health Cooperative, Seattle, Washington.

PARTICIPANTS: 1740 persons older than age 65 years without cognitive impairment who scored above the 25th percentile on the Cognitive Ability Screening Instrument (CASI) in the Adult Changes in Thought study and who were followed biennially to identify incident dementia.

MEASUREMENTS: Baseline measurements, including exercise frequency, cognitive function, physical function, depression, health conditions, lifestyle characteristics, and other potential risk factors for dementia (for example, apolipoprotein E ϵ 4); biennial assessment for dementia.

RESULTS: During a mean follow-up of 6.2 years (SD, 2.0), 158 participants developed dementia (107 developed Alzheimer disease). The incidence rate of dementia was 13.0 per 1000 person-years for participants who exercised 3 or more times per week compared with 19.7 per 1000 person-years for those who exercised fewer than 3 times per week. The age- and sex-adjusted hazard ratio of dementia was 0.62 (95% CI, 0.44 to 0.86; $P < 0.004$). The interaction between exercise and performance-based physical function was statistically significant ($P < 0.013$). The risk reduction associated with exercise was greater in those with lower performance levels. Similar results were observed in analyses restricted to participants with incident Alzheimer disease.

LIMITATIONS: Exercise was measured by self-reported frequency. The study population had a relatively high proportion of regular exercisers at baseline.

CONCLUSION: These results suggest that regular exercise is associated with a delay in onset of dementia and Alzheimer disease, further supporting its value for elderly persons.

Reference

Larson EB, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Annals of Internal Medicine*, 2006, 144:73-81.



Mental, physical and social activities equally contribute to decrease dementia risk

Date published: January 2006

Main Message

In adults over 75 years, higher mental/physical/social activity reduced dementia risk by 29%, 39% and 32% respectively. Higher activity in 2 or all 3 components reduced dementia risk by 47%, suggesting a variety of activities combining components is most beneficial.



Abstract

BACKGROUND: There is accumulating evidence in the literature that leisure engagement has a beneficial effect on dementia. Most studies have grouped activities according to whether they were predominantly mental, physical or social. Since many activities contain more than one component, we aimed to verify the effect of all three major components on the dementia risk, as well as their combined effect.

METHODS: A mental, social and physical component score was estimated for each activity by the researchers and a sample of elderly persons. The correlation between the ratings of the authors and the means of the elderly subjects' ratings was 0.86. The study population consisted of 776 nondemented subjects, aged 75 years and above, living in Stockholm, Sweden, who were still nondemented after 3 years and were followed for 3 more years to detect incident dementia cases.

RESULTS: Multi-adjusted relative risks (RRs) of dementia for subjects with higher mental, physical and social component score sums were 0.71 (95% CI: 0.49-1.03), 0.61 (95% CI: 0.42-0.87) and 0.68 (95% CI: 0.47-0.99), respectively. The most beneficial effect was present for subjects with high scores in all or in two of the components (RR of dementia = 0.53; 95% CI: 0.36-0.78).

CONCLUSIONS: These findings suggest that a broad spectrum of activities containing more than one of the components seems to be more beneficial than to be engaged in only one type of activity.

Reference

Karp A, et al. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. *Dementia and Geriatric Cognitive Disorders*, 2006, 21:65-73.



Traumatic brain injury and alcohol abuse increase risk of younger onset dementia

Date published: January 2006

Main Message

Those with young onset dementia (onset < 65 years) had significantly more dementia attributed to traumatic brain injury and alcohol abuse compared to those with late onset. The findings highlight the importance of preventable causes of dementia in the young.



Abstract

BACKGROUND: Research on the epidemiology of dementia has focused on the elderly. Few investigations have studied differences in etiologic frequencies between early-onset dementia (EOD), with onset at an age of less than 65 years old, and the more common late-onset disorder.

OBJECTIVES: To determine relative frequencies and characteristics of EOD versus late-onset dementia (LOD; age of onset > or =65 years) diagnosed in a large memory disorders program over a 4-year period.

METHODS: We reviewed medical records, including an extensive neurobehavioral and neurological evaluation, of all patients seen at a large Veteran's Affairs Medical Center Memory Disorders clinic between 2001 and 2004 and assessed demographic variables, final diagnoses, presence of dementia, and differential diagnosis of dementing illnesses.

RESULTS: Among 1,683 patients presenting for evaluation of an acquired decline in memory or cognition, 948 (56%) met established clinical criteria for a dementing illness. About 30% (n = 278) of these had an age of onset of <65 years, compared to 670 with LOD. Patients were predominantly male (98%). Compared to the late-onset group, the EOD patients were less severely impaired on presentation, but they did not differ in gender distribution or educational background. The EOD group had significantly more dementia attributed to traumatic brain injury, alcohol, human immunodeficiency virus (HIV), and frontotemporal lobar degeneration compared to the LOD patients. In contrast, the LOD group had significantly more Alzheimer's disease compared to the EOD group.

CONCLUSIONS: This study, conducted at a Veterans Affairs Hospital, is the largest series to date on EOD, and found a previously unexpectedly large number of patients below the age of 65 with cognitive deficits and impaired functioning consequent to head trauma, alcohol abuse, and HIV. These findings highlight the differential distribution and importance of preventable causes of dementia in the young.

Reference

McMurtray A, et al. Early-onset dementia: frequency and causes compared to late-onset dementia. *Dementia and Geriatric Cognitive Disorders*, 2006, 21:59-64.



Lifestyle factors and risk of dementia

Date published: January 2006

Main Message

In 2805 people aged 60 and older followed for 16 years, any intake of alcohol was associated with a 34% lower risk of dementia, daily gardening was associated with 36% lower risk, and daily walking with 38% lower risk in men only. Poorer respiratory function was associated with 84% higher risk and depression with 50% higher risk.

Abstract

OBJECTIVE: To identify risk factors for dementia in an elderly Australian cohort.

DESIGN AND SETTING: A longitudinal cohort study conducted in Dubbo, NSW.

PARTICIPANTS: 2805 men and women aged 60 years and older living in the community and initially free of cognitive impairment, first assessed in 1988 and followed for 16 years.

MAIN OUTCOME MEASURE: Admission to hospital or nursing home with any kind of dementia.

RESULTS: There were 115 cases of dementia in 1233 men (9.3/100) and 170 cases in 1572 women (10.8/100). In a proportional hazards model for dementia, any intake of alcohol predicted a 34% lower risk, and daily gardening a 36% lower risk. Daily walking predicted a 38% lower risk of dementia in men, but there was no significant prediction in women. The lowest tertile of peak expiratory flow predicted an 84% higher risk of dementia, the upper tertile of depression score predicted a 50% higher risk.

CONCLUSION: While excess alcohol intake is to be avoided, it appears safe and reasonable to recommend the continuation of moderate alcohol intake in those already imbibing, as well as the maintenance of physical activity, especially daily gardening, in the hope of reducing the incidence of dementia in future years.

Reference

Simons LA, et al. Lifestyle factors and risk of dementia: Dubbo study of the elderly. *The Medical Journal of Australia*, 2006, 184:68-70.

