Harvesting Whole Foods | April 19, 2018

Supporting the Brain from Neurological Disorders to Nootropics

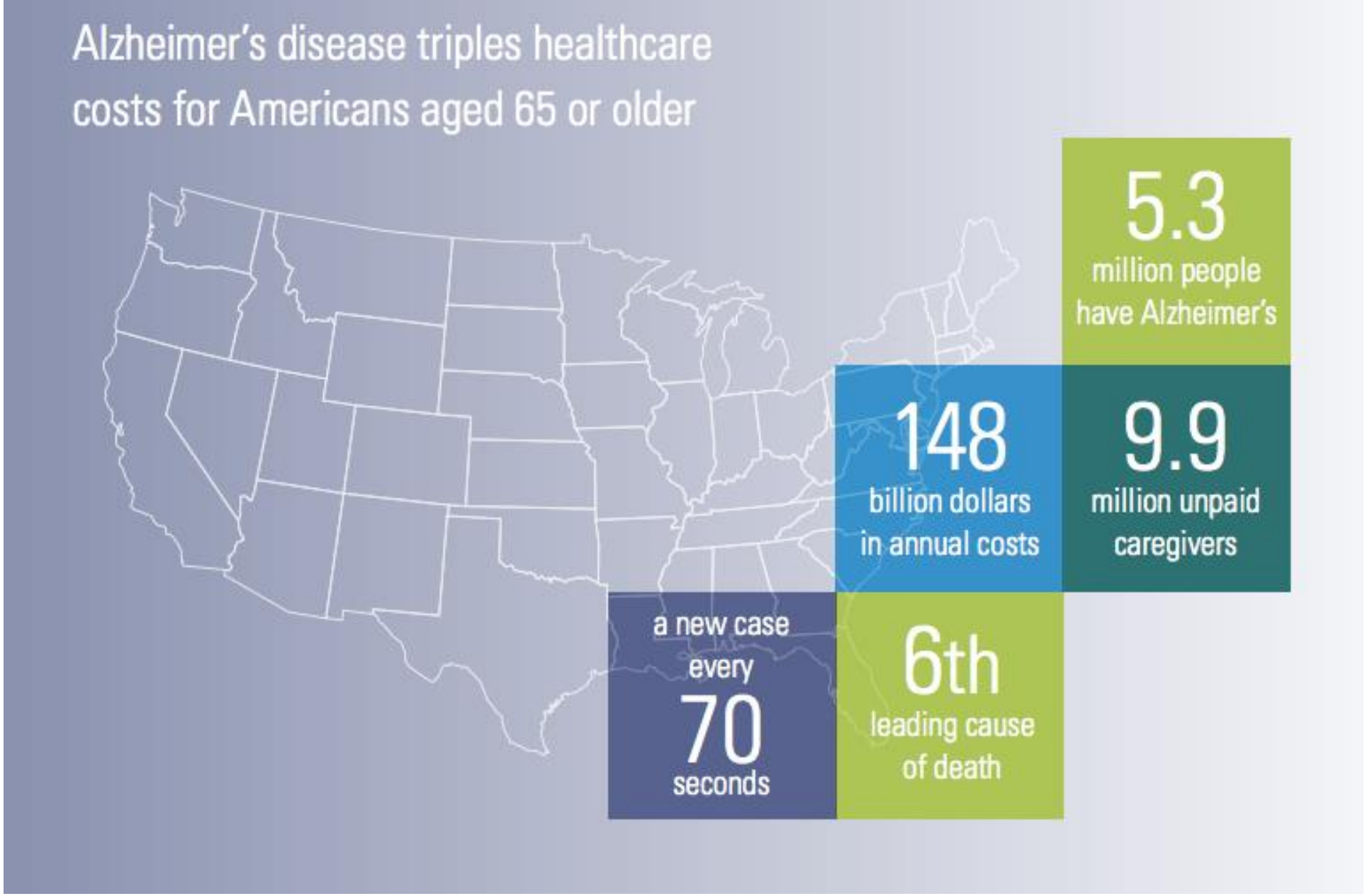
Cognitive Decline

Alzheimer's

disease and related disorders (ADRD) is used to define a group of diseases - mild cognitive impairment (MCI) or dementia.

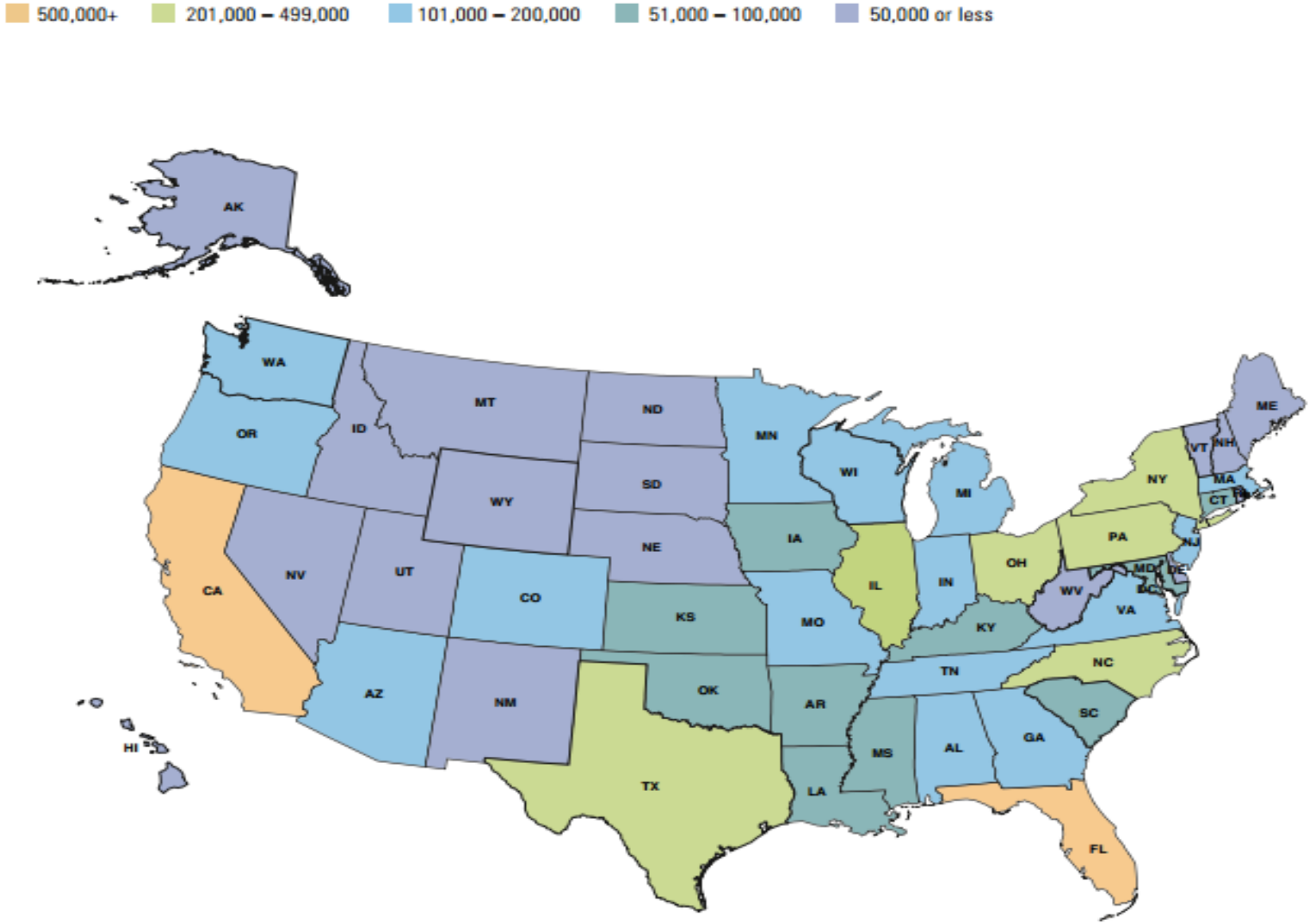
Dementia

is a progressive condition with two or more impairments in mental skills that interfere with a person's ability to function in their usual manner in their social, family, personal, or professional life.



www.alz.org-2010

Estimated Number of People with Alzheimer's by State, 2025



Created from data from Hebert et al. [19, A7]

Cognitive Decline

Alzheimer's disease (AD) begins an average of **30 years** before the first symptoms.

There is evidence that simple prevention strategies the risk of ADRD can be cut by up to **50%**.

Pathophysiology

Multifactorial

Genetic polymorphisms

Environmental mitochondrial toxins

Behavior factors

Elevated Risk	Risk Factor
3.5	One family member with Alzheimer's disease or other cause of dementia
7.5	More than one family member with Alzheimer's disease or other dementia
2.0	A single head injury with loss of consciousness for more than a few minutes
2.0	Several head injuries without loss of consciousness
4.4	Alcohol dependence or drug dependence in past or present
2.0	Major depression diagnosed by a physician in past or present
10	Stroke
2.5	Heart (coronary artery) disease or heart attack (myocardial infarction or MI)
2.1	High cholesterol (hyperlipidemia)
2.3	High blood pressure (hypertension)
2.0	High homocysteine levels
3.4	Diabetes
3.0	History of cancer or cancer treatment
1.5	Seizures in past or present
2.0	Obesity
2.0	Sleep apnea
2.0	Limited exercise (less than twice a week or less than 30 minutes per session)
2.0	Less than a high school education
2.0	Jobs that do not require periodically learning new information
2.0	Within the age range, 65 to 74 years old
7.0	Within the age range, 75 to 84 years old
38.0	Over 85 years old
2.3	Smoking cigarettes for 10 years or longer
2.5	Has one apolipoprotein E4 gene, (if known)
5.0	Has two apolipoprotein E4 genes, (if known)

Insulin Resistance and Future Cognitive Performance and Cognitive Decline in Elderly Patients with Cardiovascular Disease

Article type: Research Article

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Note: [1] This study was performed in partial fulfilment of the requirements for a Ph.D. degree for Miri Lutski, Sackler Faculty of Medicine, Tel Aviv University, Israel.

Abstract: Background: The role of insulin resistance (IR) in the pathogenesis of cognitive performance is not yet clear. Objective: To examine the associations between IR and cognitive performance and change in cognitive functions two decades later in individuals with cardiovascular disease with and without diabetes. Methods: A subset of 489 surviving patients (mean age at baseline 57.7±6.5 y) with coronary heart disease who previously participated in the secondary prevention Bezafibrate Infarction Prevention (BIP trial; 1990–1997), were included in the current neurocognitive study. Biochemical parameters including IR (using the homeostasis model of assessment; HOMA-IR) were measured at baseline. During 2004–2008, computerized cognitive assessment and atherosclerosis parameters were measured (T1; n=558; mean age 72.6±6.4 years). A second cognitive assessment was performed during 2011–2013 (T2; n=351; mean age 77.2±6.4 years). Cognitive function, overall and in specific domains, was assessed. We used linear regression models and linear mixed models to evaluate the differences in cognitive performance and decline, respectively. Results: Controlling for potential confounders, IR (top HOMA-IR quartile versus others) was associated with subsequent poorer cognitive performance overall (β=−4.45±Standard Error (SE) 1.54; p=0.004) and on tests of memory and executive function among non-diabetic patients (β=−7.16±2.38; p=0.003 and β=−3.33±1.84; p=0.073, respectively). Moreover, among non-diabetic patients, IR was related to a greater decline overall (β=−0.17±0.06; p=0.008), and in mem
observed associatio
Conclusion: IR is re
among patients with cardiovascular disease with and without diabetes.

Conclusion: IR is related to subsequent poorer cognitive performance and greater cognitive decline among patients with cardiovascular disease with and without diabetes.

Keywords: Cardiovascular disease, cognitive decline, cognitive impairments, insulin resistance

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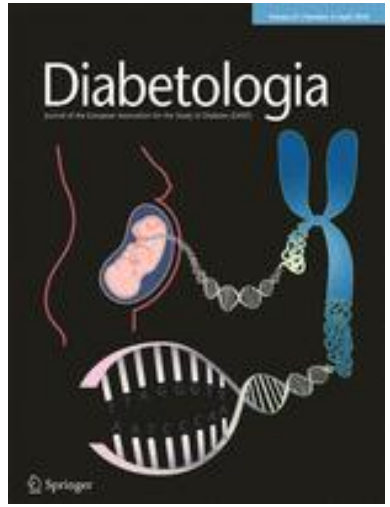

HbA_{1c}, diabetes and cognitive decline: the English Longitudinal Study of Ageing

Fanfan Zheng[1,2] · Li Yan[3] · Zhenchun Yang[3] · Baoliang Zhong[4] · Wuxiang Xie[3,5]

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Abstract

Aims/hypothesis The aim of the study was to evaluate longitudinal associations between HbA_{1c} levels, diabetes status and subsequent cognitive decline over a 10 year follow-up period.

Methods Data from wave 2 (2004–2005) to wave 7 (2014–2015) of the English Longitudinal Study of Ageing (ELSA) were analysed. Cognitive function was assessed at baseline (wave 2) and reassessed every 2 years at waves 3–7. Linear mixed models were used to evaluate longitudinal associations.

Results The study comprised 5189 participants (55.1% women, mean age 65.6 ± 9.4 years) with baseline HbA_{1c} levels ranging from 15.9 to 126.3 mmol/mol (3.6–13.7%). The mean follow-up duration was 8.1 ± 2.8 years and the mean number of cognitive assessments was 4.9 ± 1.5. A 1 mmol/mol increment in HbA_{1c} was significantly associated with an increased rate of decline in global cognitive *z* scores (−0.0009 SD/year, 95% CI −0.0014, −0.0003), memory *z* scores (−0.0005 SD/year, 95% CI −0.0009, −0.0001) and executive function *z* scores (−0.0008 SD/year, 95% CI −0.0013, −0.0004) after adjustment for baseline age, sex, total cholesterol, HDL-cholesterol, triacylglycerol, high-sensitivity C-reactive protein, BMI, education, marital status, depressive symptoms, current smoking, alcohol consumption, hypertension, CHD, stroke, chronic lung disease and cancer. Compared with participants with normoglycaemia, the multivariable-adjusted rate of global cognitive decline associated with prediabetes and diabetes was increased by −0.012 SD/year (95% CI −0.022, −0.002) and −0.031 SD/year (95% CI −0.046, −0.015), respectively (*p* for trend <0.001). Similarly, memory, executive function and orientation *z* scores showed an increased rate of cognitive decline with diabetes.

Conclusions/interpretation Significant longitudinal associations between HbA_{1c} levels, diabetes status and long-term cognitive decline were observed in this study. Future studies are required to determine the effects of maintaining optimal glucose control on the rate of cognitive decline in people with diabetes.

J Alzheimers Dis. 2015;43(3):957-66. doi: 10.3233/JAD-140621.

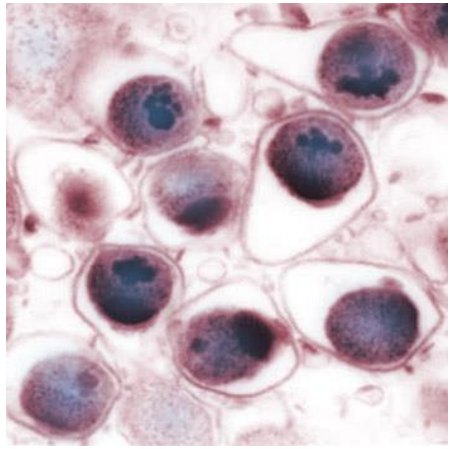
Bacterial infection and Alzheimer's disease: a meta-analysis.

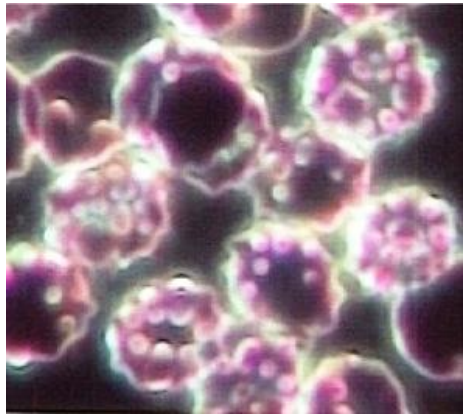
Maheshwari P[1], Eslick GD[1].

⊕ Author information

Abstract

The possibility of an infectious etiology for Alzheimer's disease (AD) has been repeatedly postulated over the past three decades. We provide the first meta-analysis to address the relationship between bacterial infection and AD. Studies examining the association between AD and spirochetal bacteria or Chlamydophila pneumoniae (Cpn) were identified through a systematic search of the databases MEDLINE, EMBASE, PubMed, and Google Scholar. Data combined from 25 relevant, primarily case-control studies demonstrated a statistically significant association between AD and detectable evidence of infection of either bacterial group. We found over a ten-fold increased occurrence of AD when there is detectable evidence of spirochetal infection (OR: 10.61; 95% CI: 3.38-33.29) and over a four-fold increased occurrence of AD in a conservative risk estimate (OR: 4.45; 95% CI: 2.33-8.52). We found over a five-fold increased occurrence of AD with Cpn infection (OR: 5.66; 95% CI: 1.83-17.51). This study shows a strongly positive association between bacterial infection and AD. Further detailed investigation of the role of bacterial infection is warranted.





J Alzheimers Dis. 2018;61(3):939-945. doi: 10.3233/JAD-161305.

Interaction between Cytomegalovirus and Herpes Simplex Virus Type 1 Associated with the Risk of Alzheimer's Disease Development.

Lövheim H[1,2], Olsson J[3], Weidung B[1,2], Johansson A[4,5], Eriksson S[1,5], Hallmans G[5], Elgh F[3].

⊕ Author information

Abstract

BACKGROUND: Several environmental factors, including infectious agents, have been suggested to cause Alzheimer's disease (AD). Cytomegalovirus (CMV) has been associated with AD in several recent studies.

OBJECTIVE: To investigate whether carriage of CMV, alone or in combination with Herpes simplex virus (HSV), increased the risk of developing AD.

METHODS: Plasma samples from 360 AD cases (75.3% women, mean age 61.2 years), taken an average of 9.6 years before AD diagnosis, and 360 age-, sex-, cohort-, and sampling date matched dementia-free controls were analyzed to detect anti-CMV (immunoglobulin [Ig] G and IgM), group-specific anti-HSV (IgG and IgM), and specific anti-HSV1 and HSV2 IgG antibodies by enzyme-linked immunosorbent assays. AD cases and dementia-free controls were compared using conditional logistic regression analyses.

RESULTS: The presence of anti-CMV IgG antibodies did not increase the risk of AD (odds ratio [OR], 0.857; p=0.497). Among AD cases, an association between CMV and HSV1 carriage was detected (OR 7.145, p<0.001); in a conditional logistic regression model, the interaction between CMV and HSV1 was associated with AD development (OR 5.662; p=0.007).

CONCLUSION: The present findings do not support a direct relationship between CMV infection and the development of AD; however, an interaction between CMV and HSV1 was found to be associated significantly with AD development. These findings suggest that CMV infection facilitates the development of HSV1-associated AD, possibly via its effects on the immune system.

J Alzheimers Dis. 2015;48(2):319-53. doi: 10.3233/JAD-142853.

Herpes Simplex Virus Type 1 and Other Pathogens are Key Causative Factors in Sporadic Alzheimer's Disease.

Harris SA[1], Harris EA[2].

Author information

Abstract

This review focuses on research in epidemiology, neuropathology, molecular biology, and genetics regarding the hypothesis that pathogens interact with susceptibility genes and are causative in sporadic Alzheimer's disease (AD). Sporadic AD is a complex multifactorial neurodegenerative disease with evidence indicating coexisting multi-pathogen and inflammatory etiologies. There are significant associations between AD and various pathogens, including Herpes simplex virus type 1 (HSV-1), Cytomegalovirus, and other Herpesviridae, Chlamydophila pneumoniae, spirochetes, Helicobacter pylori, and various periodontal pathogens. These pathogens are able to evade destruction by the host immune system, leading to persistent infection. Bacterial and viral DNA and RNA and bacterial ligands increase the expression of pro-inflammatory molecules and activate the innate and adaptive immune systems. Evidence demonstrates that pathogens directly and indirectly induce AD pathology, including amyloid-β (Aβ) accumulation, phosphorylation of tau protein, neuronal injury, and apoptosis. Chronic brain infection with HSV-1, Chlamydophila pneumoniae, and spirochetes results in complex processes that interact to cause a vicious cycle of uncontrolled neuroinflammation and neurodegeneration. Infections such as Cytomegalovirus, Helicobacter pylori, and periodontal pathogens induce production of systemic pro-inflammatory cytokines that may cross the blood-brain barrier to promote neurodegeneration. Pathogen-induced inflammation and central nervous system accumulation of Aβ damages the blood-brain barrier, which contributes to the pathophysiology of AD. Apolipoprotein E4 (ApoE4) enhances brain infiltration by pathogens including HSV-1 and Chlamydophila pneumoniae. ApoE4 is also associated with an increased pro-inflammatory response by the immune system. Potential antimicrobial treatments for AD are discussed, including the rationale for antiviral and antibiotic clinical trials.

LETTER

doi:10.1038/nature14432

Structural and functional features of central nervous system lymphatic vessels

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One of the characteristics of the central nervous system is the lack of a classical lymphatic drainage system. Although it is now accepted that the central nervous system undergoes constant immune surveillance that takes place within the meningeal compartment[1–3], the mechanisms governing the entrance and exit of immune cells from the central nervous system remain poorly understood[4–6]. In searching for T-cell gateways into and out of the meninges, we discovered functional lymphatic vessels lining the dural sinuses. These structures express all of the molecular hallmarks of lymphatic endothelial cells, are able to carry both fluid and immune cells from the cerebrospinal fluid, and are connected to the deep cervical lymph nodes. The unique location of these vessels may have impeded their discovery to date, thereby contributing to the long-held concept of the absence of lymphatic vasculature in the central nervous system. The discovery of the central nervous system lymphatic system may call for a reassessment of basic assumptions in neuroimmunology and sheds new light on the aetiology of neuroinflammatory and neurodegenerative diseases associated with immune system dysfunction.

Seeking to identify routes responsible for the recirculation of surveying meningeal immune cells, we investigated the meningeal spaces and the immune cells that occupy those spaces. First, a whole-mount preparation of dissected mouse brain meninges was developed (Fig. 1a) and stained by immunohistochemistry for endothelial cells (Extended Data Fig. 1a), T cells (Fig. 1b) and major histocompatibility complex II (MHCII)-expressing cells (Extended Data Fig. 1b). Labelling of these cells revealed a restricted partitioning of immune cells throughout the meningeal compartments, with a high concentration of cells found in close proximity to the dural sinuses (Fig. 1b; Extended Data Fig. 1b–d).

The dural sinuses drain blood from both the internal and the external veins of the brain into the internal jugular veins. The exact localization of the T lymphocytes around the sinuses was examined to rule out the possibility of artefacts caused by incomplete intracardial perfusion. Coronal sections of the dura mater (Fig. 1c, d) were stained for CD3e (T cells) and for CD31 (endothelial cells). Indeed, the vast majority of the T lymphocytes near the sinuses were abluminal (Fig. 1e). To confirm this finding, mice were injected intravenously (i.v.) with DyLight 488 lectin or fluorescent anti-CD45 antibody before euthanasia and the abluminal localization was confirmed (Extended Data Fig. 1e, f) and quantified (Fig. 1f). Unexpectedly, a portion of T cells (and of MHCII-expressing cells) was aligned linearly in CD31-expressing structures along the sinuses (only few cells were evident in meningeal blood vessels of similar diameter), suggesting a unique function for these perisinusal vessels (Fig. 1g–i).

In addition to the cardiovascular system, the lymphatic vessels represent a distinct and prominent vascular system in the body[7,8]. Prompted by our observations, the perisinusal vessels were tested for markers associated with lymphatic endothelial cells (LEC). Whole-mount meninges from adult mice were immunostained for the LEC marker, Lyve-1. Two to three Lyve-1-expressing vessels were identified running parallel to the dural sinuses (Fig. 1j, k). Analysis of coronal sections labelled for Lyve-1 and the endothelial cell marker, CD31, revealed that Lyve-1 vessels are located adjacent to the sinus (Fig. 1l) and exhibit a distinct lumen (Fig. 1m). Intravenous injection of DyLight 488 lectin before euthanasia confirmed that these Lyve-1$^+$ vessels do not belong to the cardiovasculature (Extended Data Fig. 1g, Supplementary Video 1).

The lymphatic character of the perisinusal vessels was further interrogated by assessing the presence of several classical LEC markers. Expression of the main LEC transcription factor, Prox1, was indeed detectable in the Lyve-1$^+$ vessels using immunostaining in wild-type mice (Extended Data Fig. 2a) or in transgenic mice expressing tdTomato (tdT) under the Prox1 promoter (Prox1^{tdT}; Fig. 2a). Similar to peripheral lymphatic vessels, the Lyve-1 vessels were also found to express podoplanin (Fig. 2b, Extended Data Fig. 2b, c) and the vascular endothelial growth factor receptor 3 (VEGFR3) (Fig. 2c, Extended Data Fig. 2d). Injection of VEGFR3-specific recombinant VEGF-c into the cisterna magna resulted in an increase in the diameter of the meningeal lymphatic vessels, when examined 7 days after the injection (Fig. 2d, e, Extended Data Fig. 2e), suggesting a functional role of VEGFR3 on meningeal LECs. Finally, the presence of LECs in the meninges was confirmed by flow cytometry; a CD45$^-$CD31$^+$podoplanin$^+$ population of cells (LECs) was detected in the dura mater, and is similar to that found in the skin and diaphragm (Extended Data Fig. 3). We identified a potentially similar structure in human dura (Lyve-1$^+$podoplanin$^+$ CD68$^-$; Extended Data Fig. 4), but further studies will be necessary to fully assess and characterize the location and organization of meningeal lymphatic vessels in the human central nervous system.

Two types of afferent lymphatic vessels exist—initial and collecting. They differ anatomically (that is, the presence or absence of surrounding smooth muscle cells and lymphatic valves), in their expression pattern of adhesion molecules[7,9,10], and in their permissiveness to fluid and cell entry[9]. In contrast to the sinuses, the meningeal lymphatic vessels are devoid of smooth muscle cells (Fig. 2f, g). Furthermore, meningeal lymphatic vessels were also positive for the immune-cell chemoattractant protein, CCL21 (refs 11, 12; Extended Data Fig. 5a). Unlike the blood vessels that exhibit a continuous pattern of Claudin-5 and vascular endothelial (VE)-cadherin, the meningeal lymphatic vessels exhibit a punctate expression pattern of these molecules similarly to diaphragm lymphatic vessels[9] (Extended Data Fig. 5b–f). Also, expression of integrin-α9, which is characteristic of lymphatic valves[13], was not found on meningeal lymphatic vessels, but was readily detectable in

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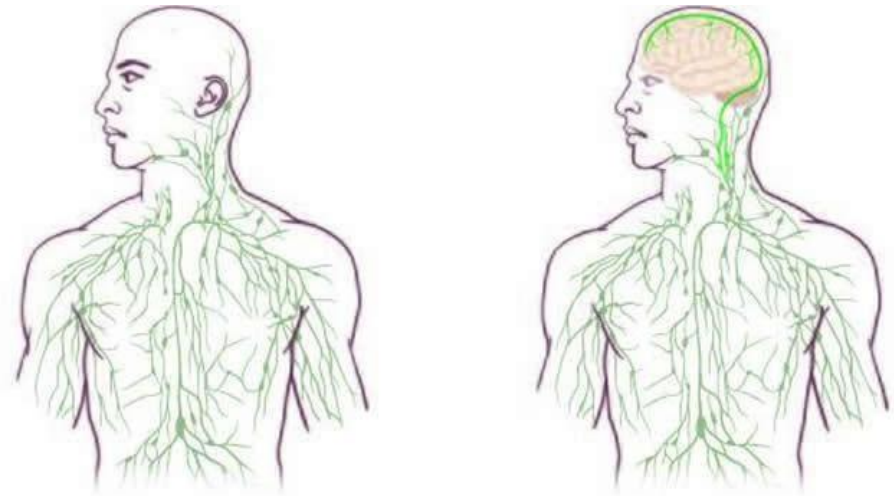


Pathophysiology

Image with no neuritic plaques

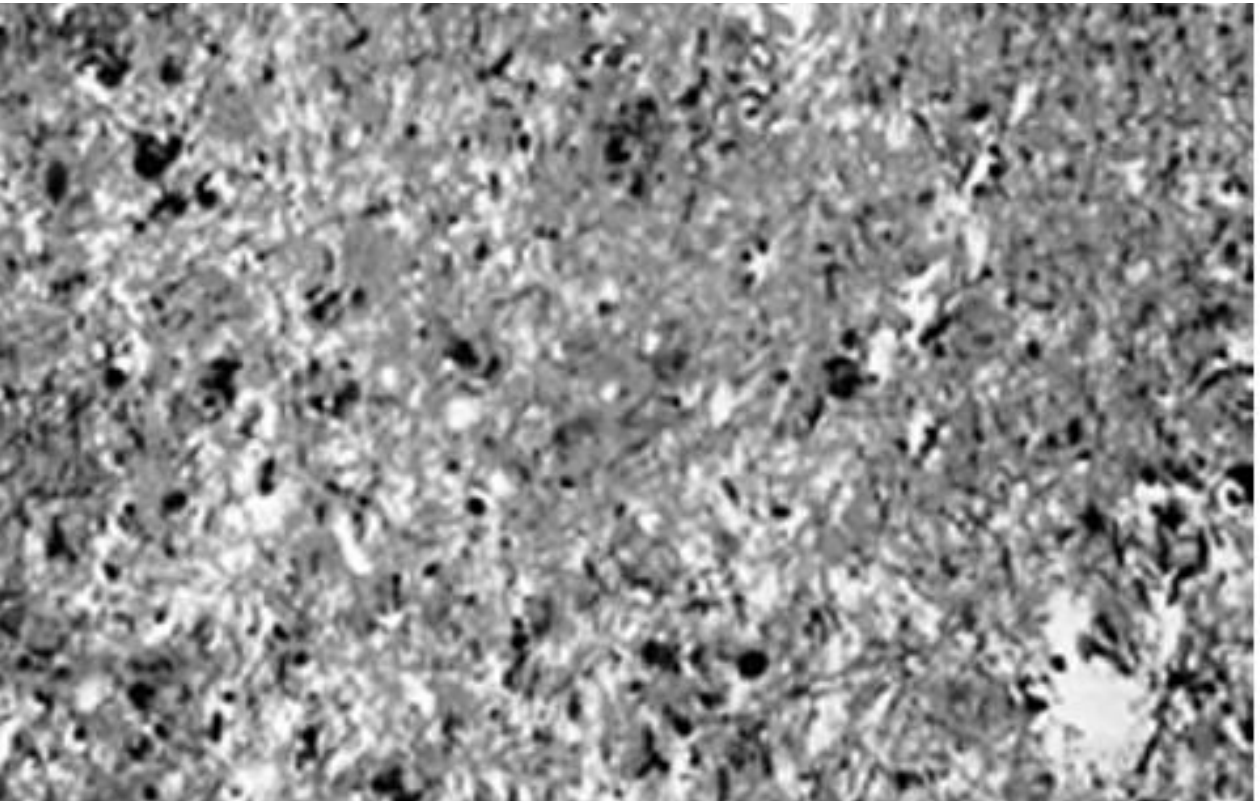
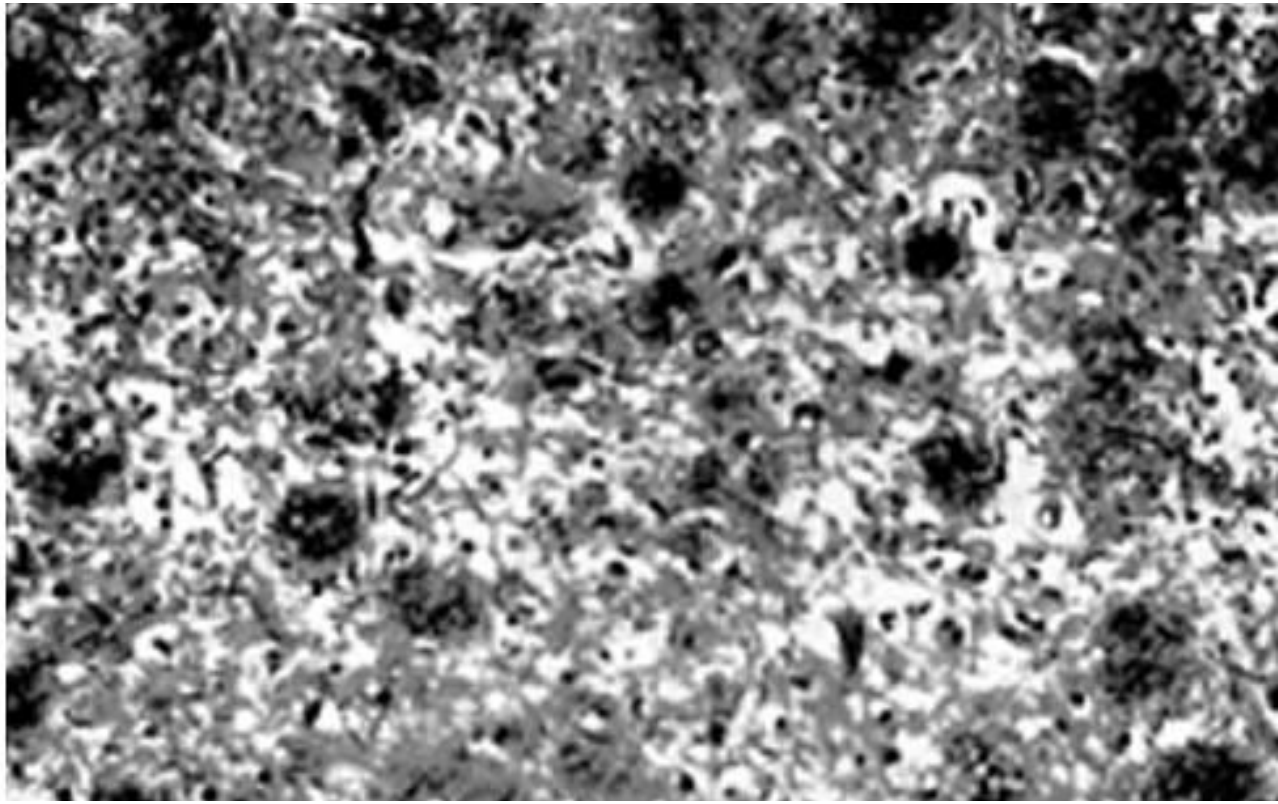
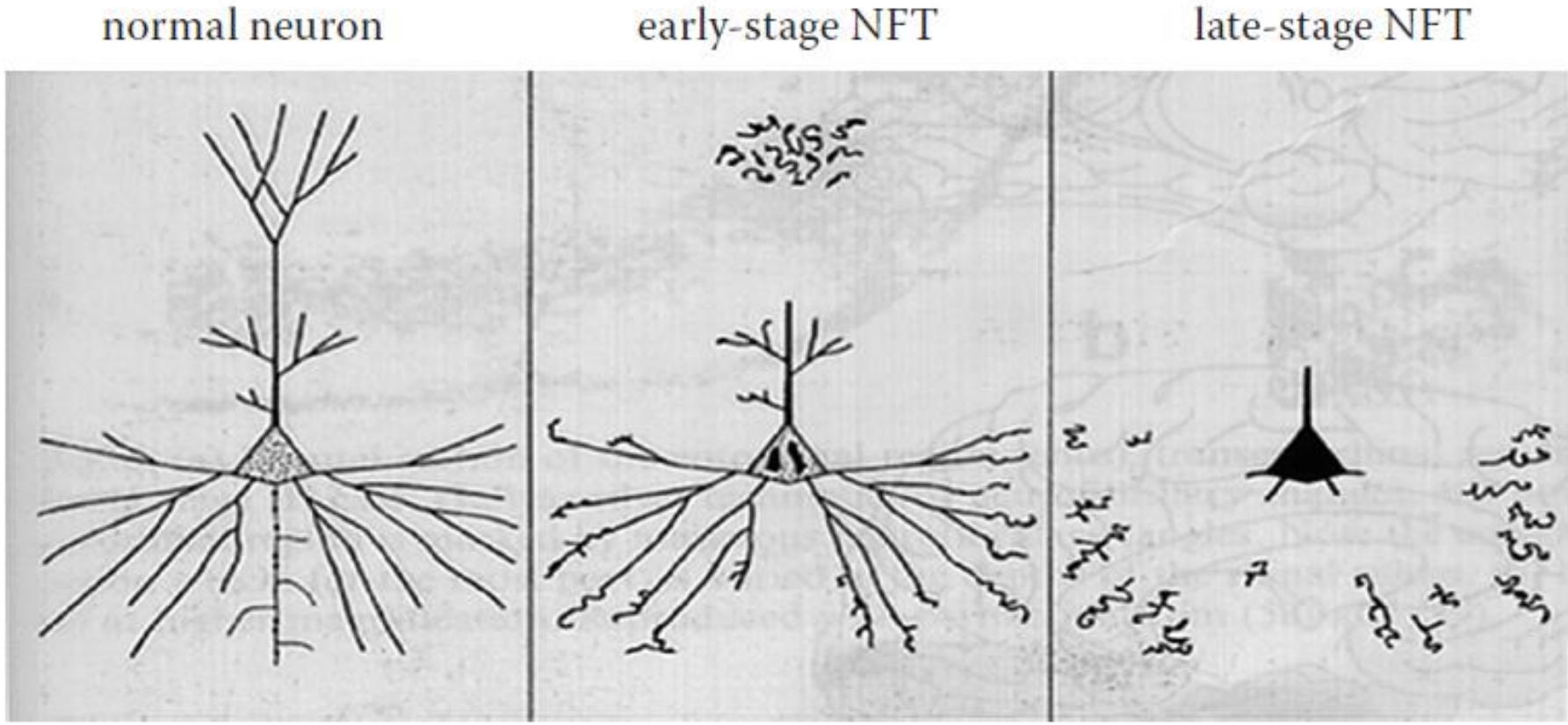
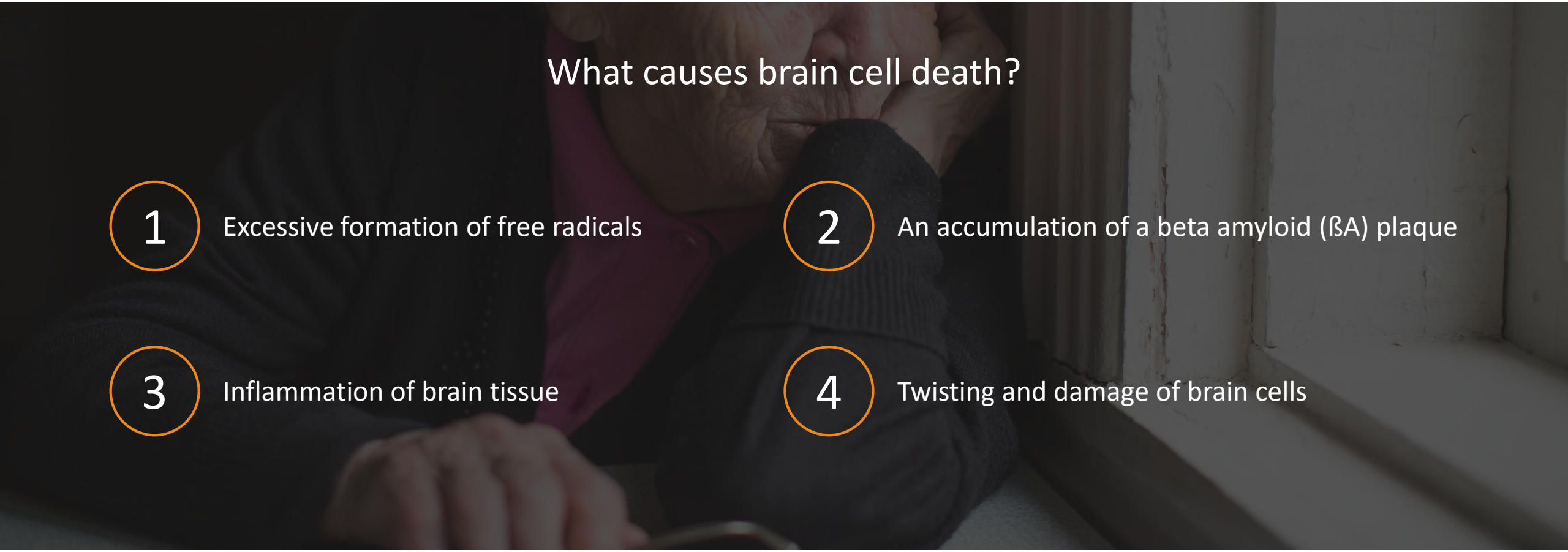


Image loaded with neuritic plaques




normal neuron
early-stage NFT
late-stage NFT
(note twisted dendrites)
a dead neuron

Pathophysiology



What causes brain cell death?

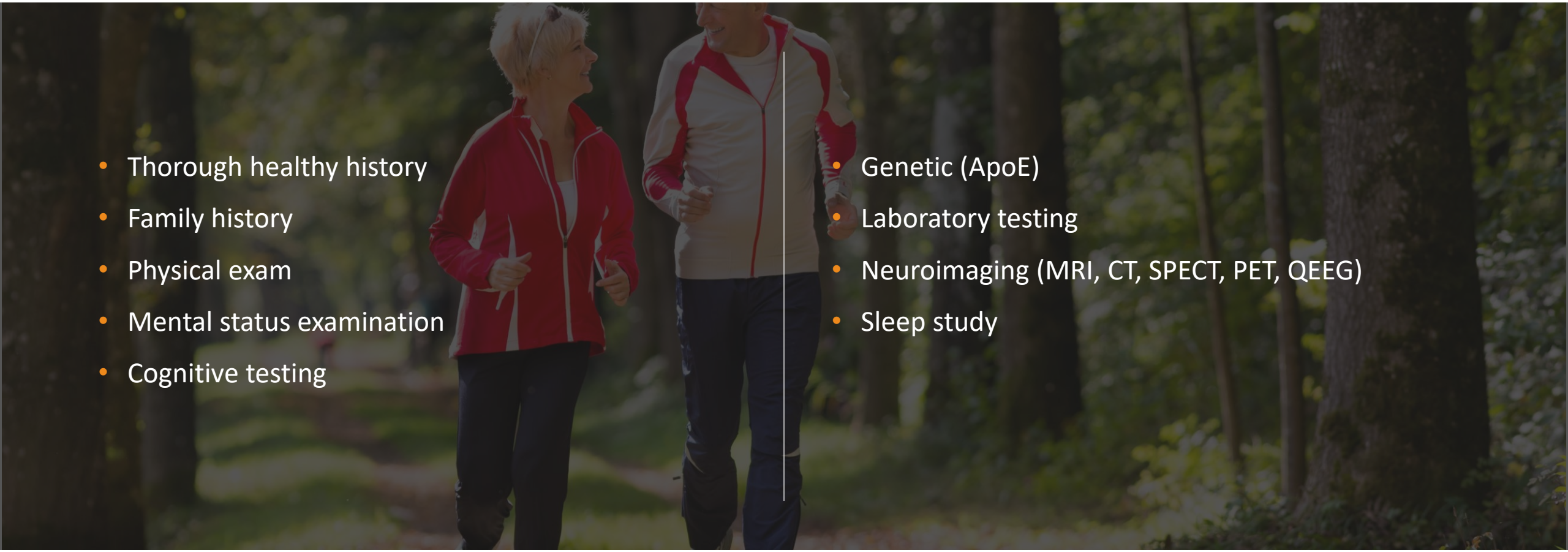
1. Excessive formation of free radicals
2. An accumulation of a beta amyloid (ßA) plaque
3. Inflammation of brain tissue
4. Twisting and damage of brain cells

Pathophysiology

Degenerative diseases usually occur after **40 years old** because cells are more susceptible to damage and death.

After **40 years old**, the body produces less energy due to slower metabolism → cells are less able to produce antioxidants.

Diagnosis

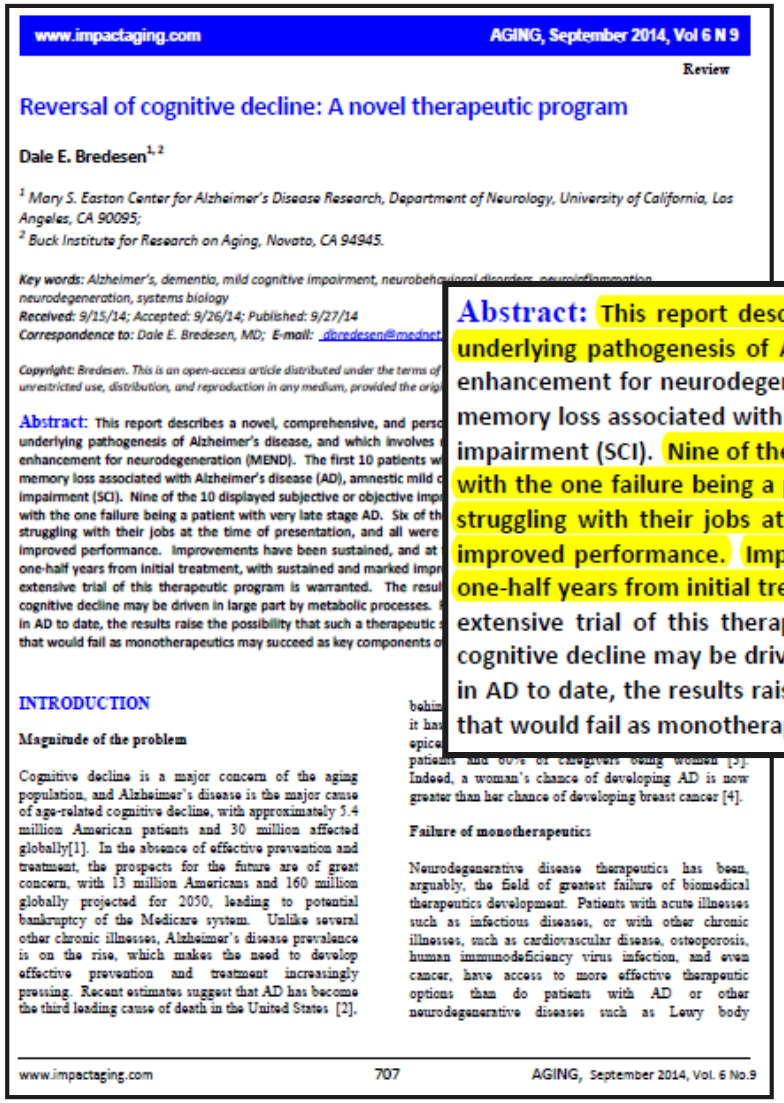


- Thorough healthy history
- Family history
- Physical exam
- Mental status examination
- Cognitive testing

- Genetic (ApoE)
- Laboratory testing
- Neuroimaging (MRI, CT, SPECT, PET, QEEG)
- Sleep study

Diagnosis

- 95% of individuals with ADRD are diagnosed years after the first symptoms appear.
- By this time they are moderately demented and dependent on others for care.
- Annual screening for diabetes, hypertension, heart disease, cancer, and other chronic diseases facilitates early detection and effective treatment.
- 95% of mild dementia and 75% of moderate dementia are not detected in a primary care setting. Neither are standardized screening and diagnostic criteria currently incorporated into the practices of 75% of primary care physicians.



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Review

Reversal of cognitive decline: A novel therapeutic program

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Key words: Alzheimer's, dementia, mild cognitive impairment, neurobehavioral disorder, neuroinflammation, neurodegeneration, systems biology
Received: 9/15/14; Accepted: 9/26/14; Published: 9/27/14
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Abstract: This report describes a novel, comprehensive, and perso underlying pathogenesis of Alzheimer's disease, and which involves enhancement for neurodegeneration (MEND). The first 10 patients w memory loss associated with Alzheimer's disease (AD), amnestic mild c impairment (SCI). Nine of the 10 displayed subjective or objective imp with the one failure being a patient with very late stage AD. Six of th struggling with their jobs at the time of presentation, and all were improved performance. Improvements have been sustained, and at one-half years from initial treatment, with sustained and marked impr extensive trial of this therapeutic program is warranted. The resul cognitive decline may be driven in large part by metabolic processes. in AD to date, the results raise the possibility that such a therapeutic that would fail as monotherapeutics may succeed as key components o

INTRODUCTION

Magnitude of the problem

Cognitive decline is a major concern of the aging population, and Alzheimer's disease is the major cause of age-related cognitive decline, with approximately 5.4 million American patients and 30 million affected globally[1]. In the absence of effective prevention and treatment, the prospects for the future are of great concern, with 13 million Americans and 160 million globally projected for 2050, leading to potential bankruptcy of the Medicare system. Unlike several other chronic illnesses, Alzheimer's disease prevalence is on the rise, which makes the need to develop effective prevention and treatment increasingly pressing. Recent estimates suggest that AD has become the third leading cause of death in the United States [2].

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patients and 60% of caregivers being women [3]. Indeed, a woman's chance of developing AD is now greater than her chance of developing breast cancer [4].

Failure of monotherapeutics

Neurodegenerative disease therapeutics has been, arguably, the field of greatest failure of biomedical therapeutics development. Patients with acute illnesses such as infectious diseases, or with other chronic illnesses, such as cardiovascular disease, osteoporosis, human immunodeficiency virus infection, and even cancer, have access to more effective therapeutic options than do patients with AD or other neurodegenerative diseases such as Lewy body

Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer's disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time the longest patient follow-up is two and one-half years from initial treatment, with sustained and marked improvement. These results suggest that a larger, more extensive trial of this therapeutic program is warranted. The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system.

Failure of monotherapeutics

Neurodegenerative disease therapeutics has been, arguably, the field of greatest failure of biomedical therapeutics development. Patients with acute illnesses

Goal	Approach	Rationale and References
Optimize diet: minimize simple CHO, minimize inflammation.	Patients given choice of several low glycemic, low inflammatory, low grain diets.	Minimize inflammation, minimize insulin resistance.
Enhance autophagy, ketogenesis	Fast 12 hr each night, including 3 hr prior to bedtime.	Reduce insulin levels, reduce Aβ.
Reduce stress	Personalized—yoga or meditation or music, etc.	Reduction of cortisol, CRF, stress axis.
Optimize sleep	8 hr sleep per night; melatonin 0.5mg po qhs; Trp 500mg po 3x/wk if awakening. Exclude sleep apnea.	[36]
Exercise	30-60' per day, 4-6 days/wk	[37, 38]
Brain stimulation	Posit or related	[39]
Homocysteine <7	Me-B12, MTHF, P5P; TMG if necessary	[40]
Serum B12 >500	Me-B12	[41]
CRP <1.0; A/G >1.5	Anti-inflammatory diet; curcumin; DHA/EPA; optimize hygiene	Critical role of inflammation in AD
Fasting insulin <7; HgbA1c <5.5	Diet as above	Type II diabetes-AD relationship
Hormone balance	Optimize fT3, fT4, E2, T, progesterone, pregnenolone, cortisol	[5, 42]
GI health	Repair if needed; prebiotics and probiotics	Avoid inflammation, autoimmunity
Reduction of A-beta	Curcumin, Ashwagandha	[43-45]
Cognitive enhancement	Bacopa monniera, MgT	[46, 47]
25OH-D3 = 50-100ng/ml	Vitamins D3, K2	[48]
Increase NGF	H. erinaceus or ALCAR	[49, 50]
Provide synaptic structural components	Citicoline, DHA	[51].
Optimize antioxidants	Mixed tocopherols and tocotrienols, Se, blueberries, NAC, ascorbate, α-lipoic acid	[52]
Optimize Zn:fCu ratio	Depends on values obtained	[53]
Ensure nocturnal oxygenation	Exclude or treat sleep apnea	[54]
Optimize mitochondrial function	CoQ or ubiquinol, α-lipoic acid, PQQ, NAC, ALCAR, Se, Zn, resveratrol, ascorbate, thiamine	[55]
Increase focus	Pantothenic acid	Acetylcholine synthesis requirement
Increase SirT1 function	Resveratrol	[32]
Exclude heavy metal toxicity	Evaluate Hg, Pb, Cd; chelate if indicated	CNS effects of heavy metals
MCT effects	Coconut oil or Axona	[56]

Table 2. Summary of patients treated with the therapeutic system described

Patient	History, evaluation	Diagnosis	Status
67F 3/3	2yr memory ⇓; FH+	aMCI	Normal x 2.5 yrs; working
69M 4/3	12yr memory ⇓; FDG-PET+, NPsych+	Early AD	"Clearly improved;" working
70M 4/3	4yr memory ⇓; NPsych+, failed MemTrax	AD	Improved; MemTrax passed
75M 3/3	1yr memory ⇓	SCI	Improved; working
75F C677T	1yr memory ⇓	aMCI/early AD	Improved
55F 3/3	4yr memory ⇓	aMCI/early AD	Normal; working
72M 3/3	7yr memory ⇓	aMCI	Improved; working
55M 4/3	2yr memory ⇓	SCI	Normal; working
63F 4/3	FH dementia, mild memory ⇓	SCI	Normal, negative amyloid PET; working
60F 4/3	4yr rapid decline; MoCA 6, amyloid PET+	Late AD	Decline

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Research Paper

Metabolic profiling distinguishes three subtypes of Alzheimer's disease

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Key words: *inflammation, neurodegeneration, cognition, insulin resistance, biomarkers, dementia, dyscalculia*
Received: *07/13/15; Accepted: 08/28/15; Published: 08/31/15*
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Abstract: The cause of Alzheimer's disease is incompletely defined, and no truly effective therapy exists. However, multiple studies have implicated metabolic abnormalities such as insulin resistance, hormonal deficiencies, and hyperhomocysteinemia. Optimizing metabolic parameters in a comprehensive way has yielded cognitive improvement, both in symptomatic and asymptomatic individuals. Therefore, expanding the standard laboratory evaluation in patients with dementia may be revealing. Here I report that metabolic profiling reveals three Alzheimer's disease subtypes. The first is inflammatory, in which markers such as hs-CRP and globulin:albumin ratio are increased. The second type is non-inflammatory, in which these markers are not increased, but other metabolic abnormalities are present. The third type is a very distinctive clinical entity that affects relatively young individuals, extends beyond the typical Alzheimer's disease initial distribution to affect the cortex widely, is characterized by early non-amnestic features such as dyscalculia and aphasia, is often misdiagnosed or labeled atypical Alzheimer's disease, typically affects ApoE4-negative individuals, and is associated with striking zinc deficiency. Given the involvement of zinc in multiple Alzheimer's-related metabolic processes, such as insulin resistance, chronic inflammation, ADAM10 proteolytic activity, and hormonal signaling, this syndrome of Alzheimer's-plus with low zinc (APLZ) warrants further metabolic, genetic, and epigenetic characterization.

However, accumulating data suggest important contributions from metabolic abnormalities such as insulin resistance, metabolic syndrome, chronic inflammation, hypovitaminosis D, hormonal deficiencies, and hyperhomocysteinemia, among others [2]. Despite this, most clinical evaluations of patients with cognitive decline do not include extensive metabolic or genomic evaluations. Furthermore, given that metabolic factors may play important roles in the neurodegenerative process, at least early in the pathogenetic process. Recent results from the evaluation of neural exosomes and nanosomes support the notion that metabolic abnormalities are present in patients with cognitive decline, often years prior to diagnosis of AD [4]. Therefore, it may be productive, both from the standpoint of identifying novel

Table 1. Patients with the third subtype of Alzheimer's disease described in the text, Alzheimer's-plus with low zinc.

Patient	Age at onset	Initial Symptoms	ApoE4?	Zinc	Other
1M	65	Visual agnosia	- (3/3)	56	MRI:general atrophy, mild FLAIR
2M	59	Dyscalculia, aphasia	- (2/3)	59	MRI:general atrophy, mild FLAIR; FDG PET: frontal, temporal, parietal abnl.
3F	50	Dyscalculia	- (3/3)	56	MRI:general atrophy, mild FLAIR; CSF +
4F	64	Dyscalculia, prosopagnosia, word finding	Declined	59	Cu:Zn=3:1
5M	55	Dyscalculia	- (3/3)	ND	MRI:general atrophy, CSF +
6F	57	Dyscalculia	+ (3/4)	70	MRI:general atrophy, mild FLAIR; amyloid PET +

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Research Paper

Inhalational Alzheimer's disease: an unrecognized—and treatable—epidemic

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Key words: *mycotoxins, neurodegeneration, cognition, chronic inflammatory response syndrome, biomarkers, dementia, biotoxins*
Received: *10/30/15; Accepted: 02/03/16; Published: 02/10/16*
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Abstract: **Alzheimer's disease is one of the most significant healthcare problems today, with a dire need for effective treatment. Identifying subtypes of Alzheimer's disease may aid in the development of therapeutics, and recently three different subtypes have been described: type 1 (inflammatory), type 2 (non-inflammatory or atrophic), and type 3 (cortical). Here I report that type 3 Alzheimer's disease is the result of exposure to specific toxins, and is most commonly inhalational (IAD), a phenotypic manifestation of chronic inflammatory response syndrome (CIRS), due to biotoxins such as mycotoxins. The appropriate recognition of IAD as a potentially important pathogenetic condition in patients with cognitive decline offers the opportunity for successful treatment of a large number of patients whose current prognoses, in the absence of accurate diagnosis, are grave.**

estimate ignores the many young Americans destined to develop AD during their lifetimes: given the lifetime risk of approximately 15% when including all ApoE genotypes, as many as 45 million of the 318 million Americans now living may develop AD during their lifetimes if no prevention is instituted [2].

Effective treatment of Alzheimer's disease has been lacking, but recently a novel programmatic approach involving metabolic enhancement (MEND) was described, with promising anecdotal results [3]. One of the strategies to optimize treatment development is to identify specific subtypes of Alzheimer's disease that may respond to different optimal programs. Metabolic

characterized by an atrophic profile, with reduced support from molecules such as estradiol, progesterone, testosterone, insulin, and vitamin D, often accompanied by increased homocysteine and insulin resistance. Type 3 is very dissimilar to the other two types, and may be mediated by a fundamentally different pathophysiological process (although, by definition, still β-amyloid positive and phospho-tau positive): the onset is typically younger (late 40s to early 60s); ApoE genotype is usually 3/3 instead of 4/4 or 3/4; the family history is typically negative (or positive only at much greater age); symptom onset usually follows a period of great stress, sleep loss, anesthesia, or menopause/andropause; presentation is not predominantly amnestic but is instead

AN Advances in Nutrition An International Review Journal

Vitamins Associated with Brain Aging, Mild Cognitive Impairment, and Alzheimer Disease: Biomarkers, Epidemiological and Experimental Evidence, Plausible Mechanisms, and Knowledge Gaps

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ABSTRACT

The key to preventing brain aging, mild cognitive impairment (MCI), and Alzheimer disease (AD) via vitamin intake is first to understand molecular mechanisms, then to deduce relevant biomarkers, and subsequently to test the level of evidence for the impact of vitamins in the relevant pathways and their modulation of dementia risk. This narrative review infers information on mechanisms from gene and metabolic defects associated with MCI and AD, and assesses the role of vitamins using recent results from animal and human studies. Current evidence suggests that all known vitamins and some "quasi-vitamins" are involved as cofactors or influence ≥1 of the 6 key sets of pathways or pathologies associated with MCI or AD, relating to *1*) 1-carbon metabolism, *2*) DNA damage and repair, *3*) mitochondrial function and glucose metabolism, *4*) lipid and phospholipid metabolism and myelination, *5*) neurotransmitter synthesis and synaptogenesis, and *6*) amyloidosis and Tau protein phosphorylation. The contemporary level of evidence for each of the vitamins varies considerably, but it is notable that B vitamins are involved as cofactors in all of the core pathways or pathologies and, together with vitamins C and E, are consistently associated with a protective role against dementia. Outcomes from recent studies indicate that the efficacy and safety of supplementation with vitamins to prevent MCI and the early stages of AD will most likely depend on *1*) which pathways are defective, *2*) which vitamins are deficient and could correct the relevant metabolic defects, and *3*) the modulating impact of nutrient-nutrient and nutrient-genotype interaction. More focus on a precision nutrition approach is required to realize the full potential of vitamin therapy in preventing dementia and to avoid causing harm. *Adv Nutr* 2017;8:958–70.

Keywords: vitamins, brain, aging, Alzheimer, biomarkers, epidemiology, interventions, mechanisms, knowledge gaps

Introduction

Aging of populations worldwide is increasing the numbers of people at high risk of degenerative diseases, including Alzheimer disease (AD), for which no cure exists (1–6). Mild cognitive impairment (MCI) is the prodromal stage of AD, and the risk for both increases with malnutrition (2–6). An understanding of which nutritional factors are associated with the risk of MCI and AD is essential in order to design appropriate preventive strategies based on dietary intervention. It is well recognized that prevention of AD requires intervention before or very early during the onset of MCI (5, 6). For this reason, biomarkers associated prospectively with eventual risk of MCI and AD are an important tool to determine the potential preventive effects of vitamins ingested either via nutrient-rich whole foods or as supplements. This review focuses on current knowledge regarding vitamins that have been associated with MCI and AD in animal models and in human epidemiological and interventional studies. It identifies important knowledge gaps and suggests new research directions, based on precision nutrition,

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Abbreviations used: AD, Alzheimer disease; APP, amyloid precursor protein; AUROC, area under the receiver operating characteristic curve; $A\beta_{42}$, amyloid beta 42; CK14, cytokeratin 14; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MTHFR, methylene tetrahydrofolate reductase; *MTR*, methionine synthase; PIB-PET, Pittsburgh compound B-positron emission tomography; PSEN, presenilin; REST, repressor element 1–silencing transcription factor; rRNA, ribosomal RNA; TET, 10–11 translocation; TOM, translocase of the mitochondrial outer membrane.

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Association with low dietary intake			Vitamins or "Quasi-vitamins"	Association with low blood conc.		
DNA Damage	Brain Pathology	AD Risk Low Cog		AD Risk Low Cog	Brain Pathology	DNA Damage
			Vitamin A			
			Thiamine			
			Riboflavin			
			Niacin			
			Choline			
			Pantothenic acid			
			Vitamin B-6			
			Biotin			
			Inositol			
			Folate			
			Vitamin B-12			
			Vitamin C			
			Vitamin D			
			Vitamin E			
			Vitamin K			

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Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease.

Clarke R[1], Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM.

Author information

Abstract

BACKGROUND: Recent studies suggest that vascular disease may contribute to the cause of Alzheimer disease (AD). Since elevated plasma total homocysteine (tHcy) level is a risk factor for vascular disease, it may also be relevant to AD.

OBJECTIVE: To examine the association of AD with blood levels of tHcy, and its biological determinants folate and vitamin B12.

DESIGN: Case-control study of 164 patients, aged 55 years or older, with a clinical diagnosis of dementia of Alzheimer type (DAT), including 76 patients with histologically confirmed AD and 108 control subjects.

SETTING: Referral population to a hospital clinic between July 1988 and April 1996.

MAIN OUTCOME MEASURES: Serum tHcy, folate, and vitamin B12 levels in patients and controls at entry; the odds ratio of DAT or confirmed AD with elevated tHcy or low vitamin levels; and the rate of disease progression in relation to tHcy levels at entry.

RESULTS: Serum tHcy levels were significantly higher and serum folate and vitamin B12 levels were lower in patients with DAT and patients with histologically confirmed AD than in controls. The odds ratio of confirmed AD associated with a tHcy level in the top third (> or = 14 micromol/L) compared with the bottom third (< or = 11 micromol/L) of the control distribution was 4.5 (95% confidence interval, 2.2-9.2), after adjustment for age, sex, social class, cigarette smoking, and apolipoprotein E epsilon4. The corresponding odds ratio for the lower third compared with the upper third of serum folate distribution was 3.3 (95% confidence interval, 1.8-6.3) and of vitamin B12 distribution was 4.3 (95% confidence interval, 2.1-8.8). The mean tHcy levels were unaltered by duration of symptoms before enrollment and were stable for several years afterward. In a 3-year follow-up of patients with DAT, radiological evidence of disease progression was greater among those with higher tHcy levels at entry.

CONCLUSIONS: Low blood levels of folate and vitamin B12, and elevated tHcy levels were associated with AD. The stability of tHcy levels over time and lack of relationship with duration of symptoms argue against these findings being a consequence of disease and warrant further studies to assess the clinical relevance of these associations for AD.

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Official Journal of the International Parkinson and Movement Disorder Society

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Vitamin B12 and homocysteine levels predict different outcomes in early Parkinson's disease.

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Author information

Abstract

BACKGROUND: In moderately advanced Parkinson's disease (PD), low serum vitamin B12 levels are common and are associated with neuropathy and cognitive impairment. However, little is known about B12 in early PD.

OBJECTIVE: To determine the prevalence of low vitamin B12 status in early PD and whether it is associated with clinical progression.

METHODS: We measured vitamin B12 and other B12 status determinants (methylmalonic acid, homocysteine, and holotranscobalamin) in 680 baseline and 456 follow-up serum samples collected from DATATOP participants with early, untreated PD. Borderline low B12 status was defined as serum B12 <184 pmol/L (250 pg/mL), and elevated homocysteine was defined as >15 µmol/L. Outcomes included the UPDRS, ambulatory capacity score (sum of UPDRS items 13-15, 29&30), and MMSE, calculated as annualized rates of change.

RESULTS: At baseline, 13% had borderline low B12 levels, 7% had elevated homocysteine, whereas 2% had both. Elevated homocysteine at baseline was associated with worse scores on the baseline MMSE. Analysis of study outcomes showed that compared with the other tertiles, participants in the low B12 tertile (<234 pmol/L; 317 pg/mL) developed greater morbidity as assessed by greater annualized worsening of the ambulatory capacity score. Elevated homocysteine was associated with greater annualized decline in MMSE (-1.96 vs. 0.06; P = 0001). Blood count indices were not associated with B12 or homocysteine status.

CONCLUSIONS: In this study of early PD, low B12 status was common. Low B12 at baseline predicted greater worsening of mobility whereas elevated homocysteine predicted greater cognitive decline. Given that low B12 and elevated homocysteine can improve with vitamin supplementation, future studies should test whether prevention or early correction of these nutritionally modifiable conditions slows development of disability.

Omega-3 Fatty Acid Status Enhances the Prevention of Cognitive Decline by B Vitamins in Mild Cognitive Impairment

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Accepted 26 October 2015

Abstract. A randomized tria
lower homocysteine slowed
omega-3 fatty acid status in
randomized to B vitamins (fo
dementia rating (CDR) scale
acids (omega-3 fatty acids) w
better in the B vitamin-treate
the placebo group were simil
treatment had global CDR s
concentrations of docosahexa
acid appeared less effective.
decline in MCI, but when on
trial of B vitamins combined
to AD.

Keywords: Alzheimer's disc

In conclusion, when plasma omega-3 fatty acid concentrations are low, B vitamin treatment does not slow cognitive decline in people with MCI. In contrast, when omega-3 fatty acid levels are in the upper range of normal, the slowing effects of B vitamins on both brain atrophy [27] and cognitive decline are enhanced. We

INTRODUCTION

Trials to delay or prevent cognitive decline and Alzheimer's disease with nutrients are increasingly relevant due to the lack of new drugs to treat older persons with cognitive impairment. It is likely that the earlier treatment or preventative measures are introduced, the better the resulting efficacy of intervention for those

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- 266 participants with MCI over 70 year of age were randomized to B vitamins (folic acid, vitamins B6 and B12) or placebo for 2 years
- Researchers performed baseline cognitive test performance, clinical dementia rating (CDR) scale, and plasma concentrations of homocysteine, DHA, and EPA fatty acids.
- Among all 3 outcome measures, higher concentrations of DHA alone significantly improved the cognitive effects of B vitamins, whereas EPA appeared to be less effective.
- This study demonstrated that B vitamins had no effect on cognitive decline in MCI when omega-3 levels are low. However, when omega-3 levels are in an upper normal range, B vitamins slow cognitive decline and brain atrophy.
- These findings suggest that a combination of fish oil supplements and B vitamins may help to improve cognition and reduce age-related memory decline.

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Examining the Relationship between Trace Lithium in Drinking Water and the Rising Rates of Age-Adjusted Alzheimer's Disease Mortality in Texas

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Handling Associate Editor: William Grant

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Abstract.
Background: Alzheimer's disease (AD) mortality rates have steadily increased over time. Lithium, the
treatment for bipolar disorder, can exert neuroprotective effects against AD.
Objective: We examined the relationship between trace levels of lithium in drinking water and cha
across several Texas counties.
Methods: 6,180 water samples from public wells since 2007 were obtained and averaged for 234 o
Changes in AD mortality rates were calculated by subtracting aggregated age-adjusted mortality ra
2000–2006 from those obtained between 2009–2015. Using aggregated rates maximized the number of
mortality data. Correlational analyses between average lithium concentrations and changes in AD mor
while also adjusting for gender, race, education, rural living, air pollution, physical inactivity, obesity,
Results: Age-adjusted AD mortality rate was significantly increased over time (+27%, $p<0.001$). Cha
were negatively correlated with trace lithium levels ($p=0.01$, $r=-0.20$), and statistical significance
controlling for most risk factors except for physical inactivity, obesity, and type 2 diabetes. Furtherm
obesity and type 2 diabetes positively correlated with changes in AD mortality ($p=0.01$ and 0.03,
negatively correlated with trace lithium in drinking water ($p=0.05$ and <0.0001, respectively).
Conclusion: Trace lithium in water is negatively linked with changes in AD mortality, as well as obesit
which are important risk factors for AD.

Keywords: Dementia, GSK3, neuroprotection, obesity, type 2 diabetes

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INTRODUCTION

Alzheimer's disease (AD), t
neurodegenerative disease, is a progressive neurological disorder characterized by the irreversible loss of neurons primarily in the cortex and hippocampus resulting in impaired memory, decision-making,

of tap water consumed, we estimate that Texas residents may be consuming 0.002 to 0.347 mg of lithium from tap water per day. Furthermore, given that counties above the median lithium concentration of 0.04 mg/L experienced significantly less increases in AD mortality over time, we estimate that individuals residing in these counties consume at least 0.03 mg of lithium per day from tap water. Indeed, the estimated median (0.03 mg) and maximum (0.347 mg) levels of lithium consumed from tap water are hundreds to thousands below the doses used to treat bipolar disorder (900–1200 mg/day), and therefore should be considered safe. Interestingly, a recent study found that treating AD patients with a similar microdose of 0.3 mg per day prevented cognitive loss with significant differences observed only three months after the start of treatment [26]. Thus, our results demon-

Original Investigation

Vitamin D Status and Rates of Cognitive Decline in a Multiethnic Cohort of Older Adults

Joshua W. Miller, PhD; Danielle J. Harvey, PhD; Laurel A. Beckett, PhD; Ralph Green, MD, PhD; Sarah Tomaszewski Farias, PhD; Bruce R. Reed, PhD; John M. Olichney, MD; Dan M. Mungas, PhD; Charles DeCarli, MD

IMPORTANCE Vitamin D (VitD) deficiency is associated with brain structural abnormalities, cognitive decline, and incident dementia.

OBJECTIVE To assess associations between VitD status and trajectories of change in subdomains of cognitive function in a cohort of ethnically diverse older adults.

DESIGN, SETTING, AND PARTICIPANTS Longitudinal multiethnic cohort study of 382 participants in an outpatient clinic enrolled between February 2002 and August 2010 with baseline assessment and yearly follow-up visits. Serum 25-hydroxyvitamin D (25-OHD) was measured, with VitD status defined as the following: deficient, less than 12 ng/mL (to convert to nanomoles per liter, multiply by 2.496); insufficient, 12 to less than 20 ng/mL; adequate, 20 to less than 50 ng/mL; or high, 50 ng/mL or higher. Subdomains of cognitive function were assessed using the Spanish and English Neuropsychological Assessment Scales. Associations were evaluated between 25-OHD levels (as continuous and categorical [deficient, insufficient, or adequate]) and trajectories of cognitive decline.

MAIN OUTCOMES AND MEASURES Serum 25-OHD levels, cognitive function, and associations

with adequate status after controlling for age, sex, education, ethnicity, body mass index, season of blood draw, vascular risk, and apolipoprotein E4 genotype. Vitamin D status was not significantly associated with decline in semantic memory or visuospatial ability. Exclusion of participants with dementia did not substantially affect the associations between VitD status and rates of cognitive decline.

CONCLUSIONS AND RELEVANCE Low VitD status was associated with accelerated decline in cognitive function domains in ethnically diverse older adults, including African American and Hispanic individuals who exhibited a high prevalence of VitD insufficiency or deficiency. It remains to be determined whether VitD supplementation slows cognitive decline.

CONCLUSIONS AND RELEVANCE Low VitD status was associated with accelerated decline in cognitive function domains in ethnically diverse older adults, including African American and Hispanic individuals who exhibited a high prevalence of VitD insufficiency or deficiency. It remains to be determined whether VitD supplementation slows cognitive decline.

Author Video Interview and JAMA Neurology Report Video at jamaneurology.com

Supplemental content at jamaneurology.com

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Effects of Lutein/Zeaxanthin Supplementation on the Cognitive Function of Community Dwelling Older Adults: A Randomized, Double-Masked, Placebo-Controlled Trial.

Hammond BR Jr[1], Miller LS[1,2], Bello MO[1], Lindbergh CA[1], Mewborn C[1], Renzi-Hammond LM[1].

Author information

Abstract

Background: High levels of xanthophyll carotenoids lutein (L) and zeaxanthin (Z) in the central nervous system have been previously correlated with improved cognitive function in community-dwelling older adults. In this study, we tested the effects of supplementing L and Z on older men and women with a range of baseline cognitive abilities. **Objective:** The purpose of this study was to determine whether or not supplementation with L+Z could improve cognitive function in community-dwelling, older adults. **Design:** Double-masked, randomized, placebo-controlled trial. A total of 62 older adults were randomized into groups receiving either 12 mg L+Z or a visually identical placebo. Data from 51 participants (M = 73.7 years) were available for analysis. Retinal L+Z levels (macular pigment optical density, MPOD) were measured psychophysically using heterochromatic flicker photometry as a biomarker of cortical L+Z levels. Cognitive function was measured using the CNS Vital Signs computerized test platform. **Results:** Participants receiving the active L+Z supplement had statistically significant increases in MPOD ($p < 0.03$) and improvements in complex attention ($p < 0.02$) and cognitive flexibility domains ($p < 0.04$), relative to participants taking the placebo. A trend was also seen for the executive function domain ($p = 0.073$). In male participants only, supplementation yielded improved composite memory ($p = 0.04$). **Conclusions:** Supplementation with L+Z improved cognitive function in community-dwelling, older men and women.

Alzheimer’s Nutrition Support

Lifestyle Recommendations:

- Reduce lifestyle stressors
- Do brain stimulating exercises
- Optimize sleep
- Stay socially active and engaged
- Stop smoking and avoid second-hand smoke as much as possible
- Exercise at least 30 minutes a day

JAMA Neurology | Original Investigation

Association Between Mentally Stimulating Activities in Late Life and the Outcome of Incident Mild Cognitive Impairment, With an Analysis of the *APOE* ε4 Genotype

Janina Krell-Roesch, PhD; Prashanthi Vemuri, PhD; Anna Pink, MD; Rosebud O. Roberts, MBChB, MS; Gorazd B. Stokin, MD, PhD; Michelle M. Mielke, PhD; Teresa J. H. Christianson, BS; David S. Knopman, MD; Ronald C. Petersen, MD, PhD; Walter K. Kremers, PhD; Yonas E. Geda, MD, MSc

IMPORTANCE Cross-sectional associations between engagement in mentally stimulating activities and decreased odds of having mild cognitive impairment (MCI) or Alzheimer disease have been reported. However, little is known about the longitudinal outcome of incident MCI as predicted by late-life (aged ≥70 years) mentally stimulating activities.

OBJECTIVES To test the hypothesis of an association between mentally stimulating activities in late life and the risk of incident MCI and to evaluate the influence of the apolipoprotein E (*APOE*) ε4 genotype.

DESIGN, SETTING, AND PARTICIPANTS This investigation was a prospective, population-based cohort study of participants in the Mayo Clinic Study of Aging in Olmsted County, Minnesota. Participants 70 years or older who were cognitively normal at baseline were followed up to the outcome of incident MCI. The study dates were April 2006 to June 2016.

MAIN OUTCOMES AND MEASURES At baseline, participants provided information about mentally stimulating activities within 1 year before enrollment into the study. Neurocognitive assessment was conducted at baseline, with evaluations at 15-month intervals. Cognitive diagnosis was made by an expert consensus panel based on published criteria. Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazards regression models after adjusting for sex, age, and educational level.

RESULTS The final cohort consisted of 1929 cognitively normal persons (median age at baseline, 77 years [interquartile range, 74-82 years]; 50.4% [n = 973] female) who were followed up to the outcome of incident MCI. During a median follow-up period of 4.0 years, it was observed that playing games (HR, 0.78; 95% CI, 0.65-0.95) and engaging in craft activities (HR, 0.72; 95% CI, 0.57-0.90), computer use (HR, 0.70; 95% CI, 0.57-0.85), and social activities (HR, 0.77; 95% CI, 0.63-0.94) were associated with a decreased risk of incident MCI. In a stratified analysis by *APOE* ε4 carrier status, the data point toward the lowest risk of incident MCI for *APOE* ε4 noncarriers who engage in mentally stimulating activities (eg, computer use: HR, 0.73; 95% CI, 0.58-0.92) and toward the highest risk of incident MCI for APOE ε4 carriers who do not engage in mentally stimulating activities (eg, no computer use: HR, 1.74; 95% CI, 1.33-2.27).

CONCLUSIONS AND RELEVANCE Cognitively normal elderly individuals who engage in specific mentally stimulating activities even in late life have a decreased risk of incident MCI. The associations may vary by *APOE* ε4 carrier status.

Author Video Interview and JAMA Report Video

Supplemental content

Jan. 30, 2017

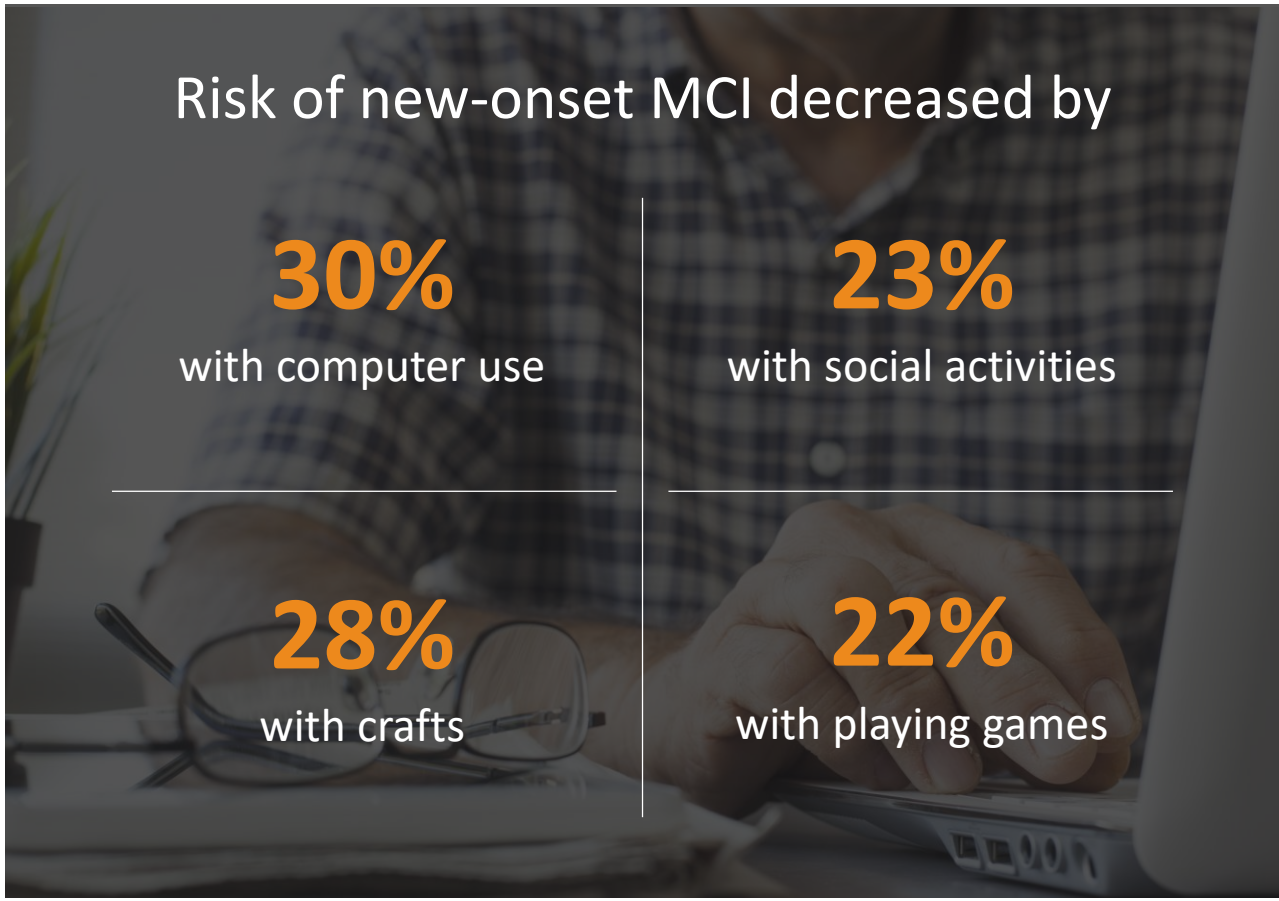
JAMA Neurology January 2017

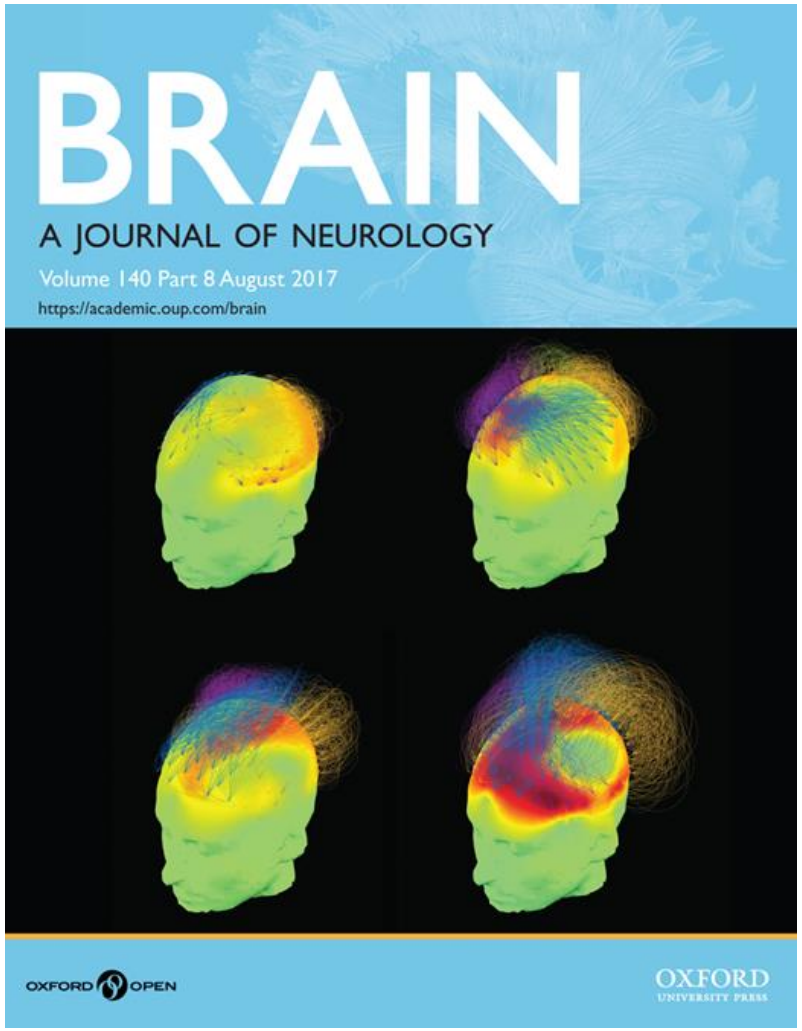
Healthy individuals age 70 or older who were active on a computer, played games, and involved in crafts and social activities had a ↓ risk of developing MCI

1,929 participants over ~ 4 years

Benefits of being cognitively engaged were also seen in those with the apolipoprotein E (APOE) gene

Researchers found that only computer use and social activities were associated with a reduced risk of MCI in APOE carriers





Brain. 2017 Aug 1;140(8):2104-2111. doi: 10.1093/brain/awx148.

Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels.

Ju YS[1,2], Ooms SJ[3,4,5], Sutphen C[1,2], Macauley SL[1,2], Zangrilli MA[1], Jerome G[1,2], Fagan AM[1,2,6], Mignot E[7], Zempel JM[1], Claassen JAHR[3,4,5], Holtzman DM[1,2,6].

Author information

Abstract

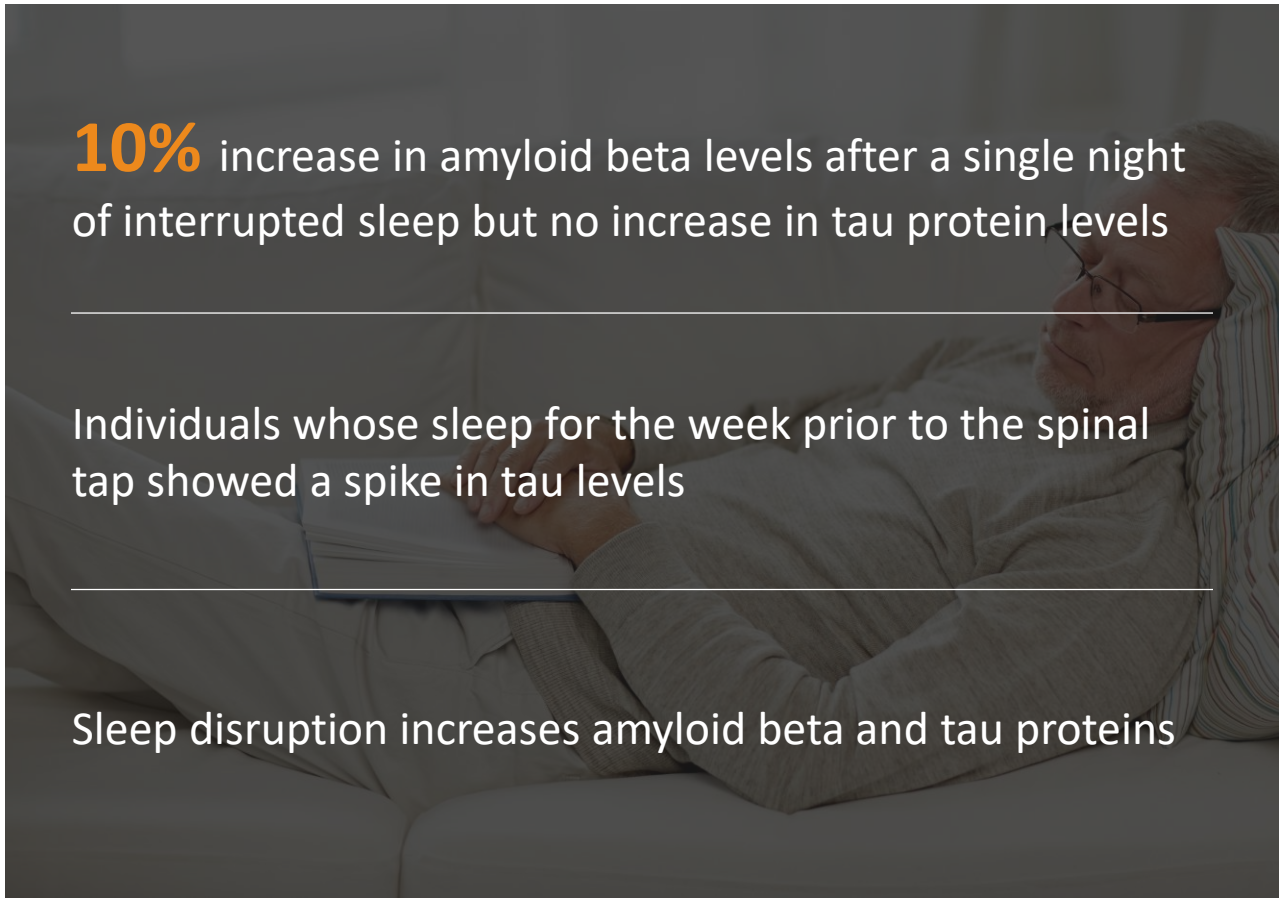
See Mander et al. (doi:10.1093/awx174) for a scientific commentary on this article.Sleep deprivation increases amyloid-β, suggesting that chronically disrupted sleep may promote amyloid plaques and other downstream Alzheimer's disease pathologies including tauopathy or inflammation. To date, studies have not examined which aspect of sleep modulates amyloid-β or other Alzheimer's disease biomarkers. Seventeen healthy adults (age 35-65 years) without sleep disorders underwent 5-14 days of actigraphy, followed by slow wave activity disruption during polysomnogram, and cerebrospinal fluid collection the following morning for measurement of amyloid-β, tau, total protein, YKL-40, and hypocretin. Data were compared to an identical protocol, with a sham condition during polysomnogram. Specific disruption of slow wave activity correlated with an increase in amyloid-β40 ($r = 0.610$, $P = 0.009$). This effect was specific for slow wave activity, and not for sleep duration or efficiency. This effect was also specific to amyloid-β, and not total protein, tau, YKL-40, or hypocretin. Additionally, worse home sleep quality, as measured by sleep efficiency by actigraphy in the six nights preceding lumbar punctures, was associated with higher tau ($r = 0.543$, $P = 0.045$). Slow wave activity disruption increases amyloid-β levels acutely, and poorer sleep quality over several days increases tau. These effects are specific to neuronally-derived proteins, which suggests they are likely driven by changes in neuronal activity during disrupted sleep.

Brain August 2017

17 adults ages **35** to **65**

with no sleep issues or cognitive impairment wore a sleep monitor for up to two weeks

Each person had a spinal tap to measure the levels of amyloid beta and tau in the CSF fluid



10% increase in amyloid beta levels after a single night of interrupted sleep but no increase in tau protein levels

Individuals whose sleep for the week prior to the spinal tap showed a spike in tau levels

Sleep disruption increases amyloid beta and tau proteins

Alzheimer’s Nutrition Support

Dietary Recommendations:

- Optimize gut health
- Limit or avoid stimulants and potentially neurotoxic compounds
- Support blood sugar balance
- Consume foods that are rich in healthy, anti-inflammatory fats and antioxidants

Am J Geriatr Psychiatry. 2016 Sep;24(9):729-37. doi: 10.1016/j.jagp.2016.05.007. Epub 2016 May 13.

Modifiable Risk Factors and Brain Positron Emission Tomography Measures of Amyloid and Tau in Nondemented Adults with Memory Complaints.

Merrill DA[1], Siddarth P[2], Raji CA[3], Emerson ND[2], Rueda F[2], Ercoli LM[2], Miller KJ[2], Lavretsky H[2], Harris LM[4], Burggren AC[4], Bookheimer SY[4], Barrio JR[5], Small GW[2].

Author information

Abstract

OBJECTIVE: Exercise and diet impact body composition, but their age-related brain effects are unclear at the molecular imaging level. To address these issues, the authors determined whether body mass index (BMI), physical activity, and diet relate to brain positron emission tomography (PET) of amyloid plaques and tau tangles using 2-(1-(6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile (FDDNP).

METHODS: Volunteers (N = 44; mean age: 62.6 ± 10.7 years) with subjective memory impairment (N = 24) or mild cognitive impairment (MCI; N = 20) were recruited by soliciting for memory complaints. Levels of physical activity and extent of following a Mediterranean-type diet were self-reported. FDDNP-PET scans assessed plaque/tangle binding in Alzheimer disease-associated regions (frontal, parietal, medial and lateral temporal, posterior cingulate). Mixed models controlling for known covariates examined BMI, physical activity, and diet in relation to FDDNP-PET.

RESULTS: MCI subjects with above normal BMI (>25) had higher FDDNP-PET binding compared with those with normal BMI (1.11(0.03) versus 1.08(0.03), ES = 1.04, t(35) = 3.3, p = 0.002). Greater physical activity was associated with lower FDDNP-PET binding in MCI subjects (1.07(0.03) versus 1.11(0.03), ES = 1.13, t(35) = -3.1, p = 0.004) but not in subjects with subjective memory impairment (1.07(0.03) versus 1.07(0.03), ES = 0.02, t(35) = -0.1, p = 0.9). Healthier diet related to lower FDDNP-PET binding, regardless of cognitive status (1.07(0.03) versus 1.09(0.02), ES = 0.72, t(35) = -2.1, p = 0.04).

CONCLUSION: These preliminary findings are consistent with a relationship between risk modifiersand brain plaque/tangle deposition in nondemented individuals and supports maintenance of normal body weight, regular physical activity, and healthy diet to protect the brain during aging. (clinicaltrials.gov; NCT00355498).

American Journal of Geriatric Psychiatry Sept 2016

ULCA Researchers demonstrated that a healthy diet & regular exercise reduce amyloid plaque accumulation

44 adults ranging from 40 to 85 years of age with MCI had PET scans to measure the level of plaque and tangles in the brain

A Mediterranean diet and a healthy BMI were all associated with lower levels of plaques and tangles on brain scans

These factors have also been shown to reduce shrinking of the brain and lower rates of atrophy in individuals with Alzheimer's

nutrients

Nutrients. 2017 Aug 23;9(9). pii: E919. doi: 10.3390/nu9090919.

Avocado Consumption Increases Macular Pigment Density in Older Adults: A Randomized, Controlled Trial.

Scott TM[1], Rasmussen HM[2], Chen O[3], Johnson EJ[4].

Author information

Abstract

Lutein is selectively incorporated into the macula and brain. Lutein levels in the macula (macular pigment; MP) and the brain are related to better cognition. MP density (MPD) is a biomarker of brain lutein. Avocados are a bioavailable source of lutein. This study tests the effects of the intake of avocado on cognition. This was a six-month, randomized, controlled trial. Healthy subjects consumed one avocado (n = 20, 0.5 mg/day lutein, AV) vs. one potato or one cup of chickpeas (n = 20, 0 mg/day lutein, C). Serum lutein, MPD, and cognition were assessed at zero, three, and six months. Primary analyses were conducted according to intent-to-treat principles, with repeated-measures analysis. At six months, AV increased serum lutein levels by 25% from baseline (p = 0.001). C increased by 15% (p = 0.030). At six months, there was an increase in MPD from baseline in AV (p = 0.001) and no increase in C. For both groups, there was an improvement in memory and spatial working memory (p = 0.001; p = 0.032, respectively). For AV only there was improved sustained attention (p = 0.033), and the MPD increase was related to improved working memory and efficiency in approaching a problem (p = 0.036). Dietary recommendations including avocados may be an effective strategy for cognitive health.

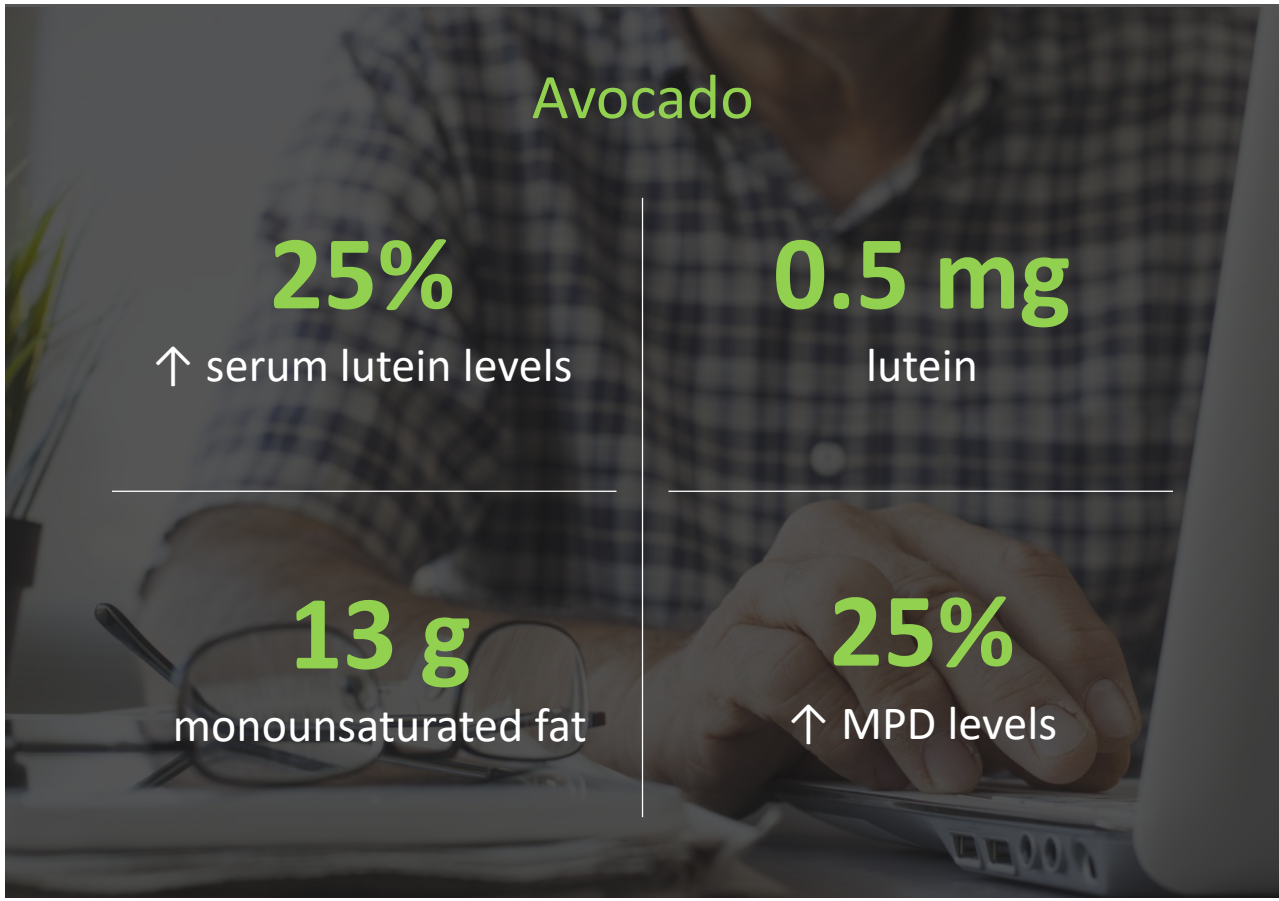
Nutrients August 2017

6 month, randomized, controlled trial including 40 individuals

Consumed 1 avocado per day or 1 potato or 1 cup of chickpeas

Serum lutein, macular pigment density (MPD), and cognition were assessed at baseline, three, and six months

At 6 months there an ↑ in MPD and working memory



Food vs. Supplementation

- 12 mg/day lutein supplementation for 4 months in older adults significantly increased MPD by 0.041 OD (Total lutein 1440 mg)

Wang, L.; Bordi, P.L.; Fleming, J.A.; Hill, A.M.; Kris-Etherton, P.M. Effect of a moderate fat diet with and without avocados on lipoprotein particle number, size and subclasses in overweight and obese adults: A randomized, controlled trial. J. Am. Heart Assoc. **2015**, 4.

- In this present study, 0.5 mg/day lutein contained in avocado for 6 months significantly increased MP density by 0.101 OD (Total lutein 90 mg)
- Daily avocado consumption increased MPD by more than double that of the supplement

Dietary Intakes of Berries and Flavonoids in Relation to Cognitive Decline

Elizabeth E. Devore, ScD,[1] Jae Hee Kang, ScD,[1] Monique M. B. Breteler, MD, PhD,[2] and Francine Grodstein, ScD[1]

Objective: Berries are high in flavonoids, especially anthocyanidins, and improve cognition in experimental studies. We prospectively evaluated whether greater long-term intakes of berries and flavonoids are associated with slower rates of cognitive decline in older women.

Methods: Beginning in 1980, a semiquantitative food frequency questionnaire was administered every 4 years to Nurses' Health Study participants. In 1995–2001, we began measuring cognitive function in 16,010 participants, aged ≥70 years; follow-up assessments were conducted twice, at 2-year intervals. To ascertain long-term diet, we averaged dietary variables from 1980 through the initial cognitive interview. Using multivariate-adjusted, mixed linear regression, we estimated mean differences in slopes of cognitive decline by long-term berry and flavonoid intakes.

Results: Greater intakes of blueberries and strawberries were associated with slower rates of cognitive decline (eg, for a global score averaging all 6 cognitive tests, for blueberries: *p*-trend = 0.014 and mean difference = 0.04, 95% confidence interval [CI] = 0.01–0.07, comparing extreme categories of intake; for strawberries: *p*-trend = 0.022 and mean difference = 0.03, 95% CI = 0.00–0.06, comparing extreme categories of intake), after adjusting for multiple potential confounders. These effect estimates were equivalent to those we found for approximately 1.5 to 2.5 years of age in our cohort, indicating that berry intake appears to delay cognitive aging by up to 2.5 years. Additionally, in further supporting evidence, greater intakes of anthocyanidins and total flavonoids were associated with slower rates of cognitive decline (*p*-trends = 0.015 and 0.053, respectively, for the global score).

Interpretation: Higher intake of flavonoids, particularly from berries, appears to reduce rates of cognitive decline in older adults.

term cognitive performance with flavonoid-rich fruit juices, including blueberry juice.[8,9] Supporting these findings, berries are particularly high in a subclass of flavonoids called anthocyanidins, which can cross the blood–brain barrier and localize in areas of learning and memory (eg, hippocampus).[10] Moreover, flavonoids more generally have powerful antioxidant and anti-inflammatory properties, and both oxidative stress and inflammation are thought to be important contributors to cognitive impairment; thus, increased flavonoid con-

explored dietary flavonoids in relation to cognitive decline in older adults. Because easily utilized databases of diverse flavonoids recently became available, we evaluated the associations of long-term dietary intake of berries and flavonoids, including anthocyanidins, with cognitive decline in a large, prospective cohort of older women in the Nurses' Health Study. Our a priori hypothesis was that greater intake of berries and flavonoids would be associated with slower rates of cognitive decline.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.23594

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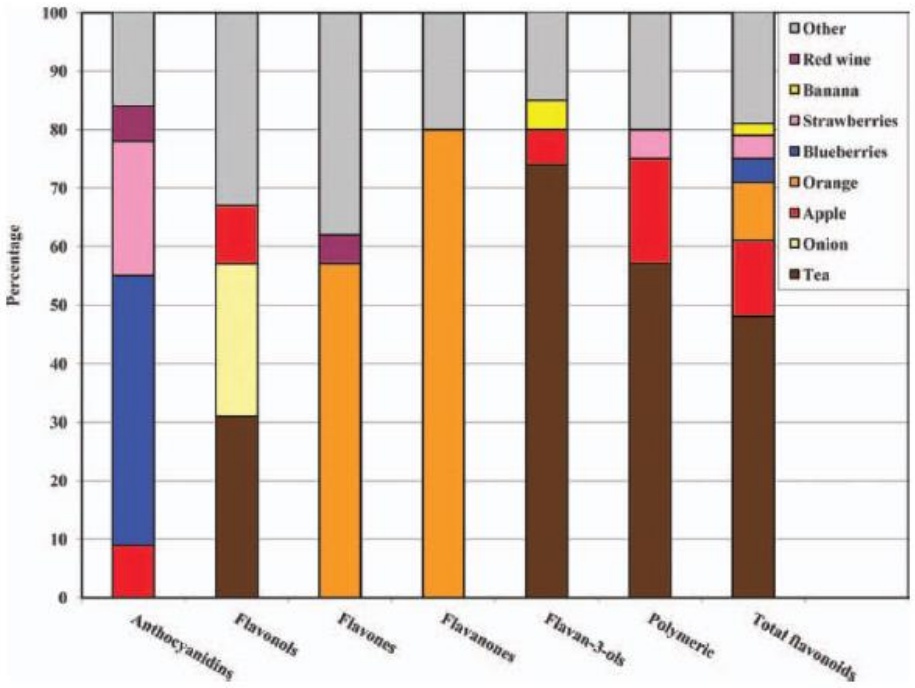
From the [1]Channing Laboratory, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA; and [2]German Center for Neurodegenerative Diseases, Bonn, Germany.

Additional supporting information can be found in the online version of this article.



epidemiologic evidence that greater intakes of blueberries and strawberries (top food contributors to anthocyanidin intake) were highly associated with slower rates of cognitive decline, consistent with a large body of experimental

Very small trials have indicated that berry supplementation can enhance cognitive function over 12 weeks in older adults with early cognitive impairments.[8,9] In a

Appl Physiol Nutr Metab. 2017 Jul;42(7):773-779. doi: 10.1139/apnm-2016-0550. Epub 2017 Mar 1.

Enhanced task-related brain activation and resting perfusion in healthy older adults after chronic blueberry supplementation.

Bowtell JL[1], Aboo-Bakkar Z[1], Conway ME[2], Adlam AR[3], Fulford J[4].

⊕ Author information

Abstract

Blueberries are rich in flavonoids, which possess antioxidant and anti-inflammatory properties. High flavonoid intakes attenuate age-related cognitive decline, but data from human intervention studies are sparse. We investigated whether 12 weeks of blueberry concentrate supplementation improved brain perfusion, task-related activation, and cognitive function in healthy older adults. Participants were randomised to consume either 30 mL blueberry concentrate providing 387 mg anthocyanidins (5 female, 7 male; age 67.5 ± 3.0 y; body mass index, 25.9 ± 3.3 $kg \cdot m^{-2}$) or isoenergetic placebo (8 female, 6 male; age 69.0 ± 3.3 y; body mass index, 27.1 ± 4.0 $kg \cdot m^{-2}$). Pre- and postsupplementation, participants undertook a battery of cognitive function tests and a numerical Stroop test within a 1.5T magnetic resonance imaging scanner while functional magnetic resonance images were continuously acquired. Quantitative resting brain perfusion was determined using an arterial spin labelling technique, and blood biomarkers of inflammation and oxidative stress were measured. Significant increases in brain activity were observed in response to blueberry supplementation relative to the placebo group within Brodmann areas 4/6/10/21/40/44/45, precuneus, anterior cingulate, and insula/thalamus ($p < 0.001$) as well as significant improvements in grey matter perfusion in the parietal (5.0 ± 1.8 vs -2.9 ± 2.4%, $p = 0.013$) and occipital (8.0 ± 2.6 vs -0.7 ± 3.2%, $p = 0.031$) lobes. There was also evidence suggesting improvement in working memory (2-back test) after blueberry versus placebo supplementation ($p = 0.05$). Supplementation with an anthocyanin-rich blueberry concentrate improved brain perfusion and activation in brain areas associated with cognitive function in healthy older adults.

British Journal of Nutrition

Review Article

The role of dietary coconut for the prevention and treatment of Alzheimer's disease: potential mechanisms of action

W. M. A. D. B. Fernando[1,2], Ian J. Martins[1,2], K. G. Goozee[1,2,3,4], Charles S. Brennan[5], V. Jayasena[6] and R. N. Martins[1,2,3,4]*

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(Submitted 22 September 2014 – Final revision received 23 March 2015 – Accepted 2 April 2015 – First published online 22 May 2015)

Abstract

Coconut, *Cocos nucifera* L., is a tree that is cultivated to provide a large number of products, although it is mainly grown for its nutritional and medicinal values. Coconut oil, derived from the coconut fruit, has been recognised historically as containing high levels of saturated fat; however, closer scrutiny suggests that coconut should be regarded more favourably. Unlike most other dietary fats that are high in long-chain fatty acids, coconut oil comprises medium-chain fatty acids (MCFA). MCFA are unique in that they are easily absorbed and metabolised by the liver, and can be converted to ketones. Ketone bodies are an important alternative energy source in the brain, and may be beneficial to people developing or already with memory impairment, as in Alzheimer's disease (AD). Coconut is classified as a highly nutritious 'functional food'. It is rich in dietary fibre, vitamins and minerals; however, notably, evidence is mounting to support the concept that coconut may be beneficial in the treatment of obesity, dyslipidaemia, elevated LDL, insulin resistance and hypertension – these are the risk factors for CVD and type 2 diabetes, and also for AD. In addition, phenolic compounds and hormones (cytokinins) found in coconut may assist in preventing the aggregation of amyloid-β peptide, potentially inhibiting a key step in the pathogenesis of AD. The purpose of the present review was to explore the literature related to coconut, outlining the known mechanistic physiology, and to discuss the potential role of coconut supplementation as a therapeutic option in the prevention and management of AD.

Key words: **Coconut: Saturated fat: Amyloid: Alzheimer's: Diabetes**

In line with the global predictions for the prevalence of Alzheimer's disease (AD), Australia declared AD as the ninth National health priority in 2012. Alzheimer's is a complex disease that progresses over many years, such as diabetes, heart disease and other chronic conditions. The gradual accumulation of the pathology of cerebral extracellular AD known as amyloid, which is mostly composed of aggregated amyloid-β (Aβ) peptides[(1)], as well as the accumulation of intracellular neurofibrillary tangles, appears to start up to 17–20 years before a clinically observable disease[(2)]. A number of factors may increase or decrease an individual's chances of developing the disease. These risk factors include age, genetics, environment, lifestyle and metabolic diseases.

Coconut oil:

- 62-70% MCT
- Supports ketosis
- Reduces insulin resistance
- Improves lipid metabolism
- ↑ % Polyphenolic compounds

J Alzheimers Dis. 2018;61(3):867-883. doi: 10.3233/JAD-170874.

Nutrition: Review on the Possible Treatment for Alzheimer's Disease.

Botchway BOA[1,2], Moore MK[2], Akinleye FO[2], Iyer IC[2], Fang M[1].

Author information

Abstract

Since its discovery some hundred years ago, Alzheimer's disease (AD), a neurodegenerative disease and an eminent cause of most dementia, continues to pose problems for affected families and society, especially in developed countries. With the approved medications by the Food and Drugs Administration in the United States, effectual treatment of AD apropos to the complete eradication of the disease continues to be elusive due to complexities relating to the pathophysiology of the disease. Nutrition has and continues to play a salient role in the survival of living organisms with no exception for human beings. Herein, we report the connection between nutrition and AD with particular attention to vitamins, curcumin, and the Mediterranean diet.

Journal of Alzheimer's Disease January 2018

- Alzheimer's disease population had significantly lower plasma levels of folate, vitamin B12, C and E.
- Low levels of vitamin A are a risk factor for Alzheimer's disease.
- Numerous genes involved in Alzheimer's are maintained in the immune system by vitamin A.
- Curcumin and vitamin D work together to enhance the brain's immune system to protect against amyloid-induced toxicity.
- Fish oil → absorbs oxidative stress and increase cell membrane fluidity
- Mediterranean diet has been associated with lower incidences of stroke, diabetes, and cardiovascular disease all of which are risk factors for Alzheimer's disease.

International Journal of Preventive Medicine

Review Article Open Access

Possible Role of Common Spices as a Preventive and Therapeutic Agent for Alzheimer's Disease

Omid Mirmosayyeb[1,2], Amirpouya Tanhaei[1], Hamid R. Sohrabi[3], Ralph N. Martins[3], Mana Tanhaei[4], Mohammad Amin Najafi[1], Ali Safaei[1], Rokhsareh Meamar[5,6]

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ABSTRACT

For centuries, spices have been consumed as food additives or medicinal agents. However, there is increasing evidence indicating the plant-based foods in regular diet may lower the risk of neurodegenerative diseases including Alzheimer disease. Spices, as one of the most commonly used plant-based food additives may provide more than just flavors, but as agents that may prevent or even halt neurodegenerative processes associated with aging. In this article, we review the role and application of five commonly used dietary spices including saffron turmeric, pepper family, zingiber, and cinnamon. Besides suppressing inflammatory pathways, these spices may act as antioxidant and inhibit acetyl cholinesterase and amyloid β aggregation. We summarized how spice-derived nutraceuticals mediate such different effects and what their molecular targets might be. Finally, some directions for future research are briefly discussed.

Keywords: Alzheimer's disease, dementia, spice

INTRODUCTION

Alzheimer disease (AD), the most common type of dementia, is a progressive and irreversible neurodegenerative disease that affects more 27 million people worldwide.[1] The neuropathological hallmarks of AD comprise neuritic plaques, neurofibrillary tangles, and neuronal loss.[2] Over the past two decades, a significant number of research projects have been conducted to farther our knowledge of the underlying mechanisms of AD and to investigate novel intervention and preventive approaches. However, current therapeutic approaches to manage AD have temporary symptom relief effects and do not inhibit or converse the underlying disease mechanisms.[3,4] Therefore, treatment of AD still remains a great challenge and the development of novel strategies is an active field of research. For centuries, spices have been used in various forms including flavoring agents, colorants, and preservatives. The importance of plant-based foods in regular diet to decrease the risk of chronic diseases is increasingly examined and spices are now considered to add more than flavors;[5] that is, they are agents that may delay, prevent or even treat age-related diseases such as AD. Some of the most widely investigated spices are presented in Tables 1 and 2.

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DOI: 10.4103/2009-7902.199640

Table 1: List of spices with potential against cognitive decline

Spice	Scientific name	Molecuar formula
Saffron	*C. sativus*	$C_{20}H_{24}O_4$
Turmeric	*C. longa*	$C_{21}H_{20}O_6$
Cinnamon	*C. zeylanicum*	C_9H_9O
Zingiber	*Z. officinale*	$-C_{15}H_{24}$
Ginseng	*A. sinensis*	$C_{15}H_{24}N_2O$
Sage	*S. officinalis*	-
Garlic	*A. sativum*	$C_6H_{10}OS_2$
Black pepper	*P. nigrum*	-
Bell pepper	*C. annuum*	-

Feb. 7, 2017

Table 2: Clinical studies evaluating effects of common spices on Alzheimer's disease

First author	Spice	Year	Title	Location	Number of patients	Main finding
Akhondzadeh	Crocus	2010	A 22-week, multicenter, randomized, double-blind controlled trial of *C. sativus* in the treatment of mild-to-moderate AD	Iran	44	Saffron was found to be effective similar to donepezil in the treatment of mild-to-moderate AD after 22 weeks
			Saffron in the treatment of patients with mild to moderate AD: A 16-week, randomized and placebo-controlled trial	Iran	46	After 16 weeks, saffron produced a significantly better outcome on cognitive function than placebo in the treatment of patients with mild to moderate AD
Farokhnia	Crocus	2014	Comparing the efficacy and safety of *C. sativus* L. with memantine in patients with moderate to severe AD: A double-blind randomized clinical trial	Iran	68	In addition to its favorable safety profile, 1-year administration of saffron extract capsules showed to be comparable with memantine in reducing cognitive decline in patients with moderate to severe AD
Baum	Curcumin	2008	6-month randomized, placebo-controlled, double-blind, pilot clinical trial of curcumin in patients with AD	USA	34	Curcumin did not seem to cause side effects in AD patients (rather, there was a tendency toward fewer adverse events on 4 g). Thus, longer and larger trials to test the efficacy of curcumin for treating AD may be safely commenced
Ringman	Curcumin	2008	Biochemical markers in persons with preclinical FAD	USA	21	Our finding of elevated F2-isoprostane levels in the CSF of preclinical FAD MCs suggests that oxidative stress occurs downstream to mismetabolism of amyloid precursor protein
Ringman	Curcumin	2012	Oral curcumin for AD: Tolerability and efficacy in a 24-week randomized, double blind, placebo-controlled study	USA	36	Curcumin was generally well-tolerated although three subjects on curcumin withdrew due to gastrointestinal symptoms

AD=Alzheimer's disease, CSF=Cerebrospinal fluid, FAD=Familial Alzheimer's disease, MCs=Mutation carriers, *C. sativus=Crocus sativus*

Goal	Approach	Rationale and References
Optimize diet: minimize simple CHO, minimize inflammation.	Patients given choice of several low glycemic, low inflammatory, low grain diets.	Minimize inflammation, minimize insulin resistance.
Enhance autophagy, ketogenesis	Fast 12 hr each night, including 3 hr prior to bedtime.	Reduce insulin levels, reduce Aβ.
Reduce stress	Personalized—yoga or meditation or music, etc.	Reduction of cortisol, CRF, stress axis.
Optimize sleep	8 hr sleep per night; melatonin 0.5mg po qhs; Trp 500mg po 3x/wk if awakening. Exclude sleep apnea.	[36]
Exercise	30-60' per day, 4-6 days/wk	[37, 38]
Brain stimulation	Posit or related	[39]
Homocysteine <7	Me-B12, MTHF, P5P; TMG if necessary	[40]
Serum B12 >500	Me-B12	[41]
CRP <1.0; A/G >1.5	Anti-inflammatory diet; curcumin; DHA/EPA; optimize hygiene	Critical role of inflammation in AD
Fasting insulin <7; HgbA1c <5.5	Diet as above	Type II diabetes-AD relationship
Hormone balance	Optimize fT3, fT4, E2, T, progesterone, pregnenolone, cortisol	[5, 42]
GI health	Repair if needed; prebiotics and probiotics	Avoid inflammation, autoimmunity
Reduction of A-beta	Curcumin, Ashwagandha	[43-45]
Cognitive enhancement	Bacopa monniera, MgT	[46, 47]
25OH-D3 = 50-100ng/ml	Vitamins D3, K2	[48]
Increase NGF	H. erinaceus or ALCAR	[49, 50]
Provide synaptic structural components	Citicoline, DHA	[51].
Optimize antioxidants	Mixed tocopherols and tocotrienols, Se, blueberries, NAC, ascorbate, α-lipoic acid	[52]
Optimize Zn:fCu ratio	Depends on values obtained	[53]
Ensure nocturnal oxygenation	Exclude or treat sleep apnea	[54]
Optimize mitochondrial function	CoQ or ubiquinol, α-lipoic acid, PQQ, NAC, ALCAR, Se, Zn, resveratrol, ascorbate, thiamine	[55]
Increase focus	Pantothenic acid	Acetylcholine synthesis requirement
Increase SirT1 function	Resveratrol	[32]
Exclude heavy metal toxicity	Evaluate Hg, Pb, Cd; chelate if indicated	CNS effects of heavy metals
MCT effects	Coconut oil or Axona	[56]

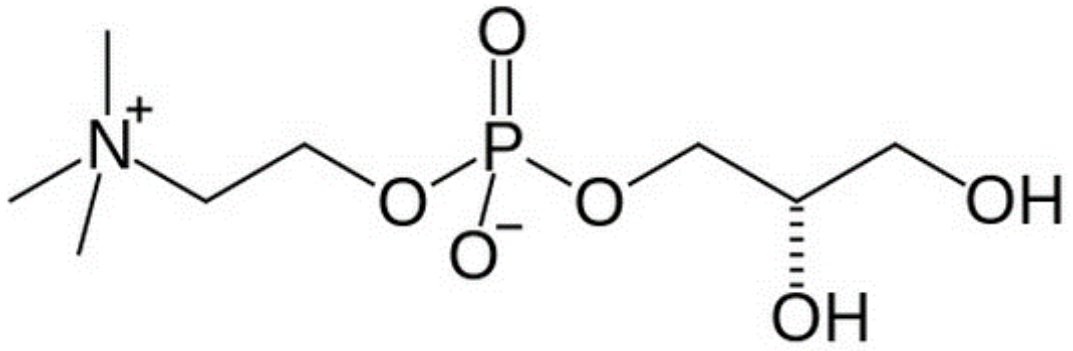
Alzheimer's Nutrition Support

Nutrients	Between Meals	Breakfast	Between Meals	Lunch	Between Meals	Dinner	Before Bed
Acetyl-l-carnitine	-	750-1500 mg	-	750- 1500 mg	-	-	-
GPC	-	300-600 mg	-	300-600 mg	-		
CDP-cholne	-	125-250 mg	-	125-250 mg	-		-
Magnesium L-Threonate	-	48-96 mg	-	48-96 mg	-	48-96 mg	
Curcumin	-	400 mg-800 mg	-	-	-	400 mg- 800 mg	-
Phosphatidylserine	125-250 mg		-	-	125-250 mg		-
Fish Oil	-	1-3 grams	-		-	1-3 grams	-

Acetyl-L-Carnitine

- Participates in cellular energy production by assisting fatty acid transport and metabolism
- Reverses age-related decline in mitochondrial function and it stabilizes membrane cell fluidity
- Improves memory and general mental function especially in the elderly
- Slows mental deterioration in ADRD
- Elevates levels of nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF)

GPC

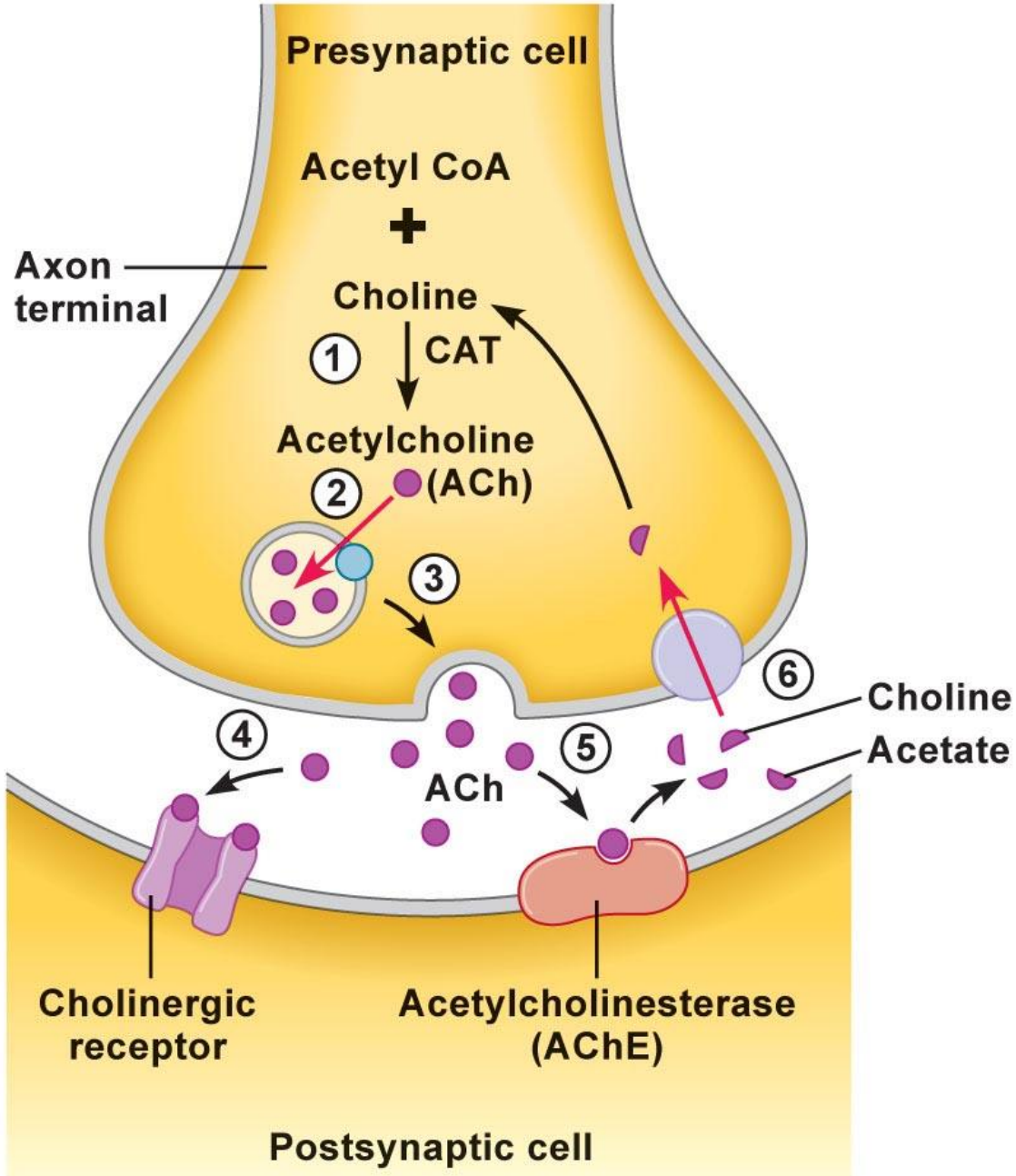


Improvements in attention, mental focus and cognition whether linked to Alzheimer's or poor brain circulation

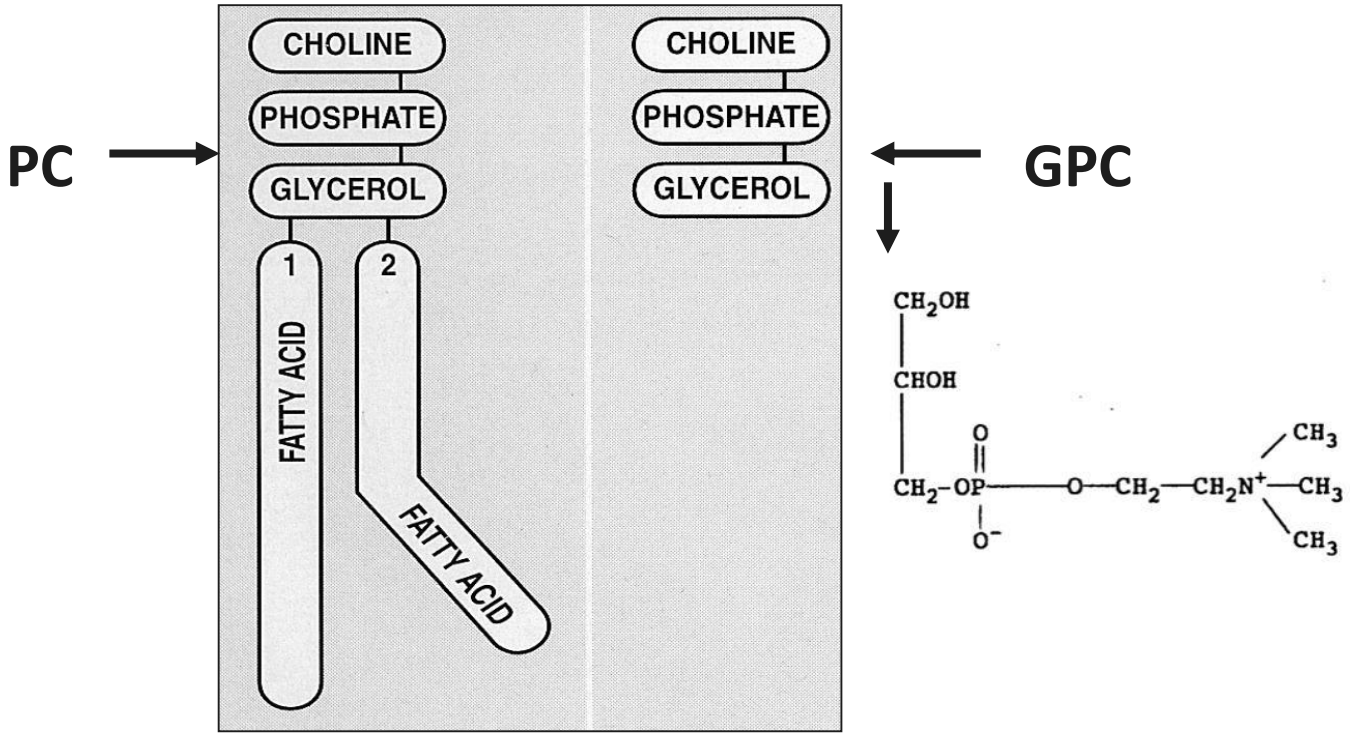
May compensate for AcCh decline due to aging

Better cognition and social behavior for patients with Alzheimer's and vascular/ age-related dementia

Less brain volume shrinkage in Alzheimer's



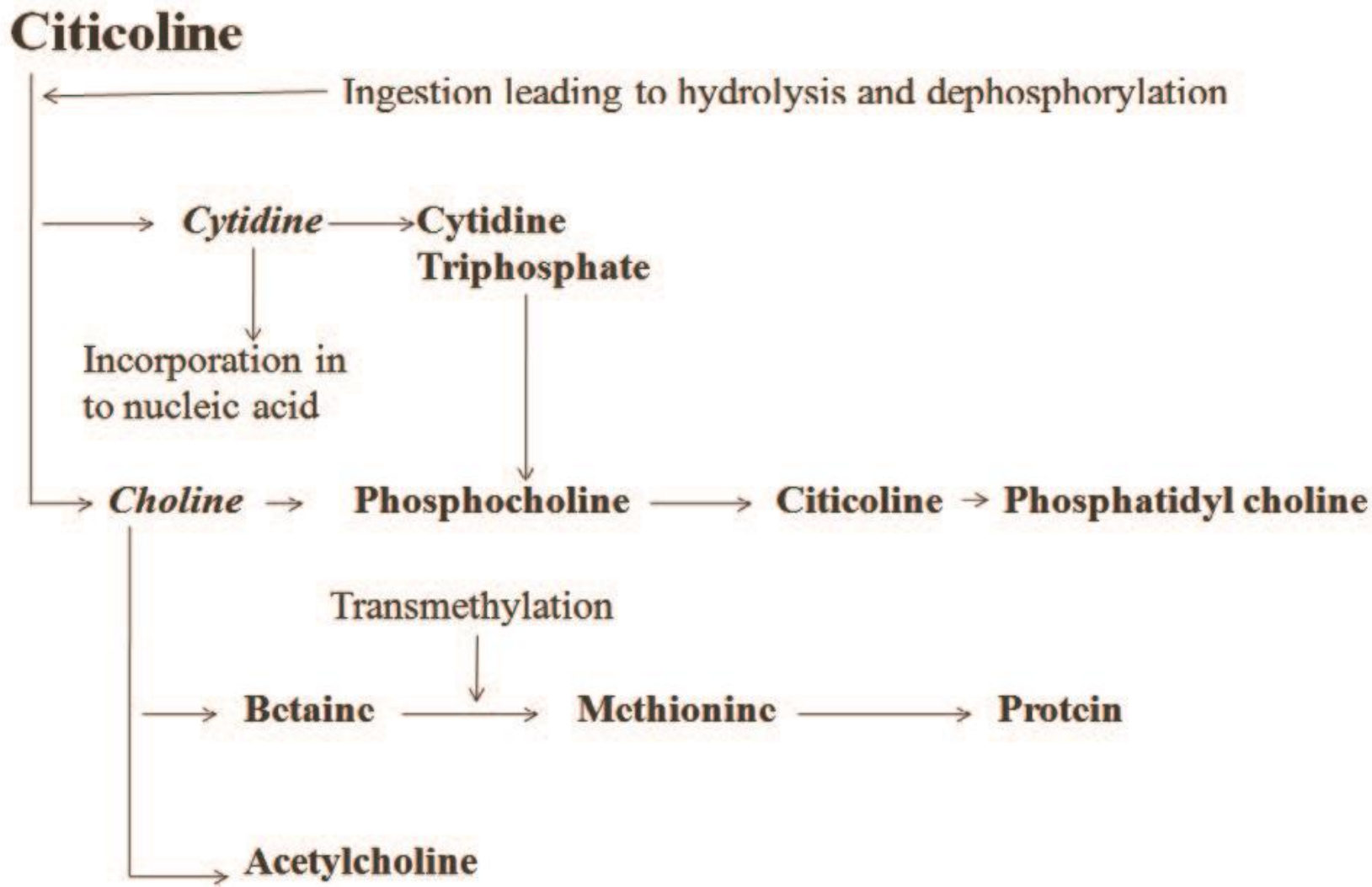
GPC



Left: Molecular organization of PC (phosphatidylcholine). Right: Molecular organization of GPC. Note the GPC molecule lacks the two fatty acid "tails" of PC.

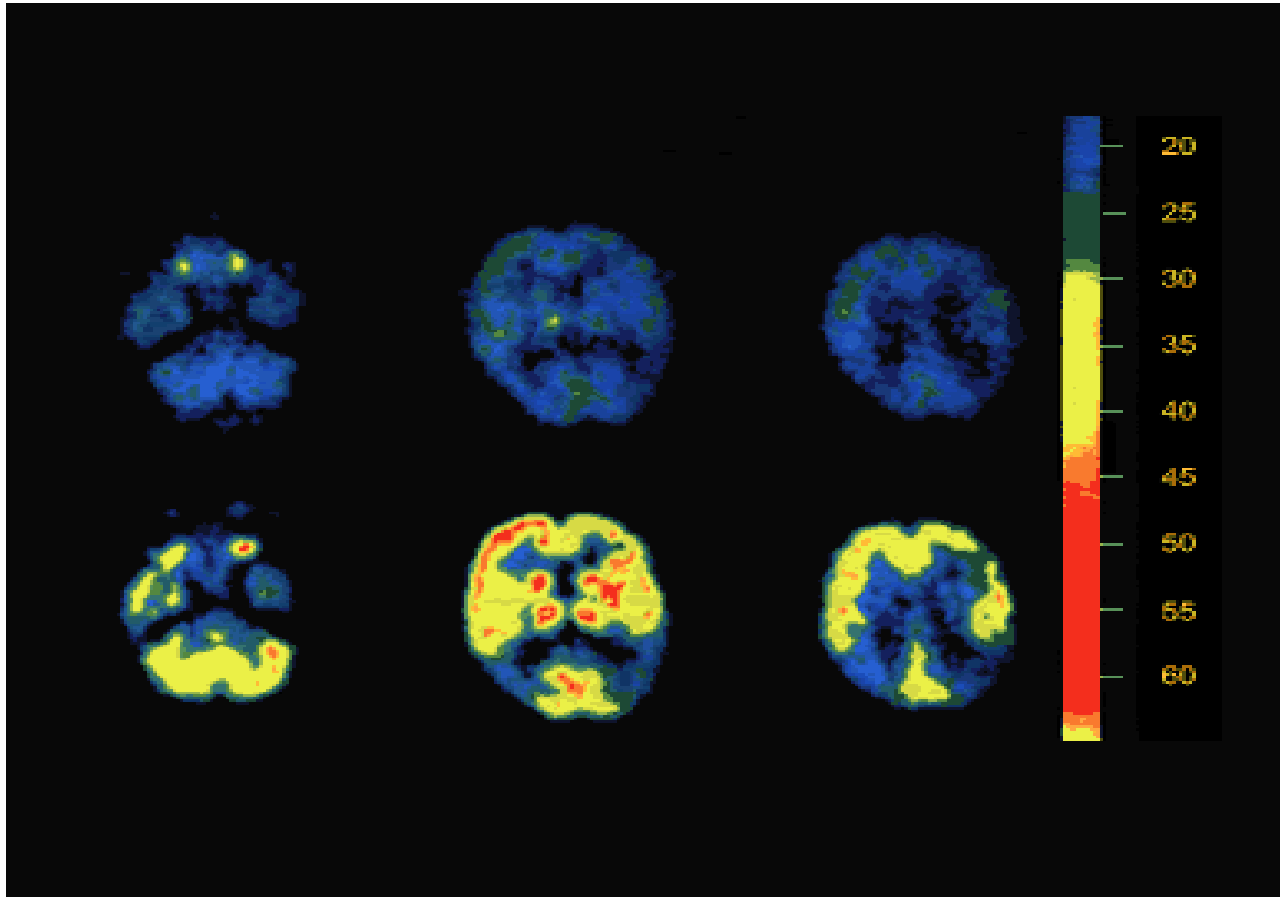
CDP-choline

- Supplies precursors for the synthesis of phospholipids (choline and cytidine)
- This mechanism of action is unique of CDP-choline compared to GPC
- Supports brain and cognitive health and performance
- Protects neural structures from free radical damage
- Supports brain DNA synthesis and repair


Citicoline
Ingestion leading to hydrolysis and dephosphorylation
Cytidine
Cytidine Triphosphate
Incorporation in to nucleic acid
Choline
Phosphocholine
Citicoline
Phosphatidyl choline
Transmethylation
Betaine
Methionine
Protein
Acetylcholine

Phosphatidylserine

- An essential nutrient for optimal brain function
- Improves memory and focus and may help reverse or slow age-related memory decline and dementia
- Improved brain energy consumption



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Regulation of structural and functional synapse density by L-threonate through modulation of intraneuronal magnesium concentration

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ABSTRACT

Oral administration of the combination of L-threonate (threonate) and magnesium (Mg^{2+}) in the form of L-Threonic acid Magnesium salt (L-TAMS) can enhance learning and memory in young rats and prevent memory decline in aging rats and in Alzheimer's disease model mice. Recent results from a human clinical trial demonstrate the efficacy of L-TAMS in restoring global cognitive abilities of older adults. Previously, we reported that neuronal intracellular Mg^{2+} serves as a critical signaling molecule for controlling synapse density, a key factor that determines cognitive ability. The elevation of brain Mg^{2+} by oral administration of L-TAMS in intact animals plays a significant role in mediating the therapeutic effects of L-TAMS. The current study sought to elucidate the unique role of threonate. We aimed to understand if threonate acts directly to elevate intraneuronal Mg^{2+}, and why Mg^{2+} given without threonate is ineffective for enhancing learning and memory ability. We discovered that threonate is naturally present in cerebrospinal fluid (CSF) and oral treatment with L-TAMS elevated CSF threonate. In cultured hippocampal neurons, threonate treatment directly induced an increase in intracellular Mg^{2+} concentration. Functionally, elevating threonate upregulated expression of NR2B-containing NMDAR, boosted mitochondrial membrane potential ($\Delta\Psi_m$), and increased functional synapse density in neuronal cultures. These effects are unique to threonate, as other common Mg^{2+} anions failed to have the same results. Mechanistically, threonate's effects were specifically mediated through glucose transporters (GLUTs). We also evaluated the effects of threonate in human neural stem cell-derived neurons, and found it was equally effective at upregulating synapse density. The current study provides an explanation for why threonate is an essential component of L-TAMS and supports the use of L-TAMS to promote cognitive abilities in human.

1. Introduction

L-Threonate, (2R,3S)-2,3,4-Trihydroxybutanoate, is a naturally occurring sugar acid present in the body, with the structure $C_4H_7O_5$. It has been found in the periphery in plasma and the aqueous humor of the eye (Deutsch et al., 1999; Harding et al., 1999). How threonate is eliminated from the body is not fully understood; however, so far we know that approximately 10% is excreted in urine (Lawson et al., 1976; Thompson et al., 1975; Wang et al., 2011).

Recent studies show that threonate might have a physiological function. In the periphery, threonate has been linked to bone health. Threonate can prevent bone degradation by inhibiting osteoclast resorption from bone (He et al., 2005). Threonate also supports bone formation in two ways. One, it promotes calcium bioavailability, allowing for rapid absorption of calcium into the body (Wang et al., 2013). Two, threonate increases bone mineralization by inhibiting DHT-inducible dickkoppf-1 (DKK-1) expression. DKK-1 is an osteoblast inhibitory factor whose overexpression can negatively impact bone formation and density (Kwack et al., 2008, 2010; Monroe et al., 2012).

Our previous work showed that threonate also has effects in the central nervous system (CNS). Oral treatment with the combination of threonate and magnesium (Mg^{2+}) in the form of L-threonic acid Magnesium salt (L-TAMS) increases synapse density and memory ability in both aged rats and late stage Alzheimer's disease (AD) model mice (Li et al., 2014; Slutsky et al., 2010). A recent study shows that L-TAMS is also effective at improving cognitive deficits in humans (Liu et al., 2015).

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0028-3908/

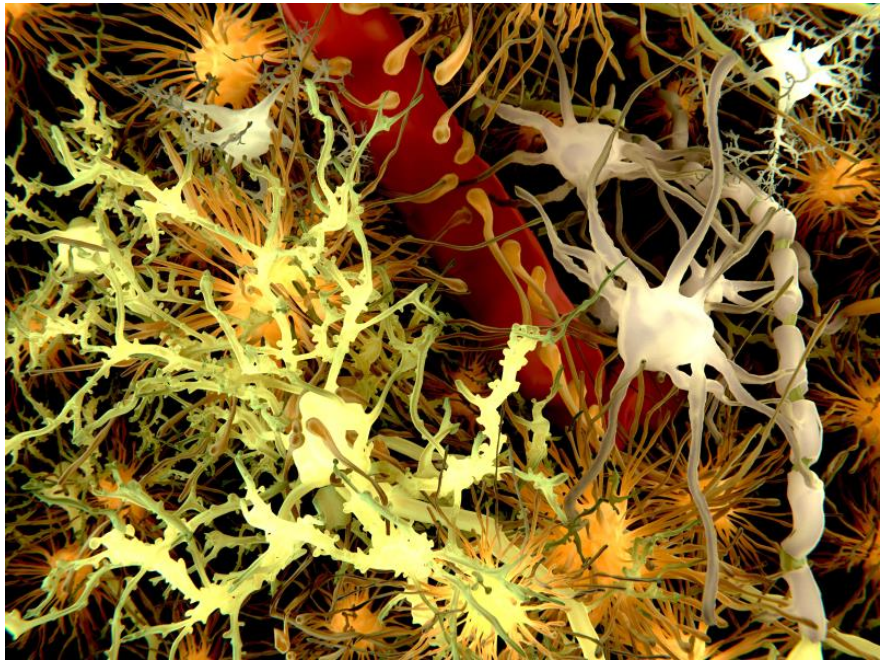
The greatest increase *in vitro* of intracellular [Mg^{2+}] and functional synapse density occurred with the concurrent increase of threonate and extracellular [Mg^{2+}] (Figs. 2B and 5A, B). *In vivo*, threonate and Mg^{2+} oral treatment (L-TAMS) increased brain threonate by approximately 50% (Fig. 1C) and CSF Mg^{2+} by approximately 15%, leading to an increase of synapse density by as much as 67% (Slutsky et al., 2010). The current study provides more mechanistic insight into the therapeutic potential of L-TAMS for cognitive impairment. A recent double-blinded placebo-controlled clinical study showed promise for L-TAMS in treating cognitive impairment in humans (Liu et al., 2015).

May 6, 2016

Brain Health

Nootropics (Wikipedia)

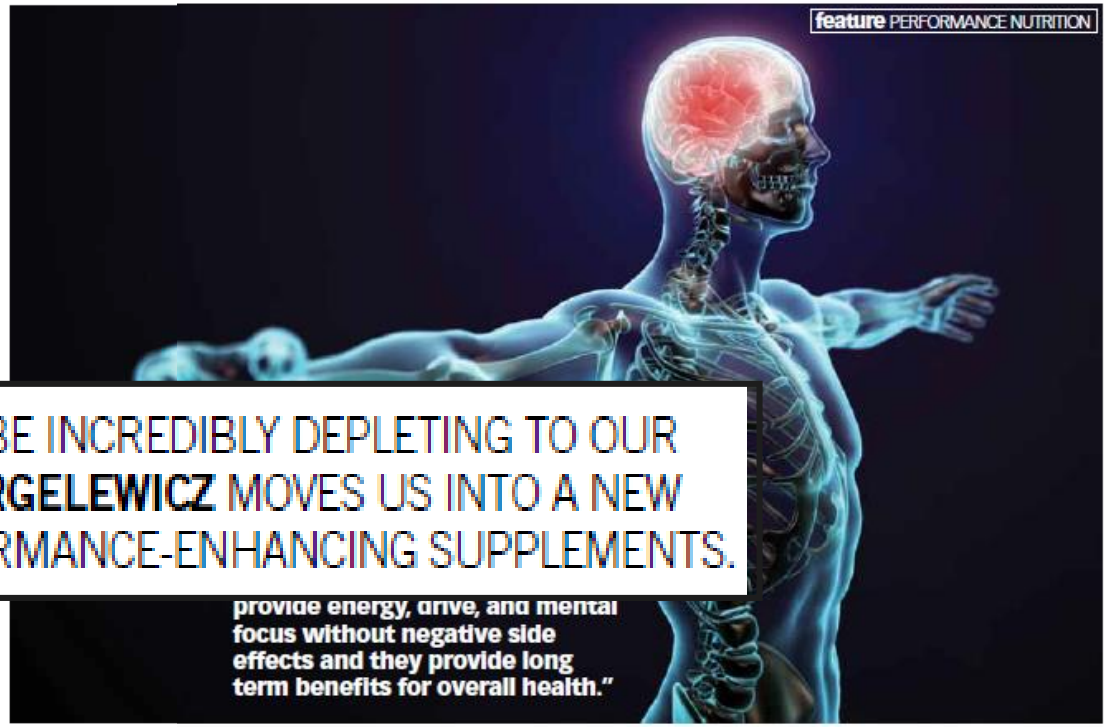
“Smart drugs”, memory enhancers, neuro enhancers, cognitive enhancers, and intelligence enhancers, are drugs, supplements, nutraceuticals that improve one or more aspects of mental function, such as working memory, motivation, and attention.



CDP-Choline

It supports focus and attention and specifically reduce errors while on task

Novel supplements for central nervous system support and athletic performance



PRE-WORKOUT SUPPLEMENTS CAN BE INCREDIBLY DEPLETING TO OUR BODIES. HOWEVER, **DR MICHAEL JURGELEWICZ** MOVES US INTO A NEW REALM OF NOURISHING AND PERFORMANCE-ENHANCING SUPPLEMENTS.

workout product that stimulates the sympathetic nervous system and usually has high doses of caffeine. There is nothing wrong with a little caffeine, but numerous pre-workout supplements on the market contain as much caffeine as five cups of coffee. Pre-workout supplements have never been more popular. They provide increased energy and endurance for one's workout; however, there are several issues to consider when choosing the nutrients for this purpose. These products can put a heavy burden on the adrenal glands, increasing the stress response, which can ultimately lead to fatigue. They can also cause other negative side effects, such as sleep disturbances, irritability, anxiousness, and they can negatively impact the appetite.

In addition, many of these products also contain food dyes and artificial sweeteners, with most powders being sweetened with sucralose. While food manufacturing companies and global health authorities have deemed sucralose safe for consumption, most health care providers know that this is not the case.

According to a recent study in the *Journal of Toxicology and*

I know the importance of nutrients for supporting focus, energy, and endurance. The challenge is finding good, health-promoting products that do not have excessive amounts of caffeine, while also being free of artificial sweeteners and food dyes. Are there other nutrients one can use that will serve this purpose, but also have long term benefits on overall health without these negative side effects?

Nootropics have become increasing popular for improving memory and preventing age-related memory decline. These are nutrients that improve mental function, working memory, and motivation. Medically, nootropics are commonly used to help stroke victims (2), relieve depression (3), and to slow the progression of Alzheimer's disease (4). Recently, with their ability to enhance memory, focus, and attention, these supplements have found a niche amongst students and business executives. There has been a lot of research demonstrating the benefits of nootropics on brain health, but what about athletic performance?

I started weight training 19 years ago and have been a competitive powerlifter for the past six years.

training

des the

these cognitive processes should be optimal if an athlete wants to perform at their best. Therefore, nootropics can be used to increase performance significantly in the gym as a pre-workout supplement and also to support brain health. Nootropics stimulate the brain and not the adrenal glands. As a result, these brain nutrients provide energy, drive, and mental focus without negative side effects and they provide long term benefits for overall health.

These are some nootropics that I have personally found to be effective and safe to take prior to training:

Glycerophosphocholine (GPC)

GPC is a naturally occurring choline intermediary that is formed when the body breaks down cell membranes for choline. It is used for age-related brain conditions and brain recovery from stoke or trauma. GPC is a highly bio-available form of choline that crosses the blood brain barrier and raises choline levels (5). Acetylcholine is a cognitive neurotransmitter, as well as a neuromodulator of muscular functions, which also improves muscle control and balance. Not only does it help with learning and memory processes, but also with muscle movement, coordination and balance. Higher levels of acetylcholine will also lead to increased focus, which is essential during training.

Learning, memory, focus, and reaction time are all interconnected. Raising neurotransmitter levels can enhance the brain's ability to communicate more efficiently. Nootropics may increase working memory and as a result, improve reaction times.

In addition, many of the positive adaptations resulting from resistance exercise training, such as increased muscle mass and strength and decreased fat mass, are thought to be mediated partially by exercise-induced increases in growth hormone (6). GPC has also been demonstrated to increase growth hormone levels. In one study, a single 1000mg dose of GPC induced an acute increase of plasma choline levels. Plasma growth hormone levels were increased by about 290 per cent 60 minutes after the oral administration of GPC. In comparison, a single session of moderate intensity aerobic exercise has been shown to increase growth hormone secretion by 210 per cent after exercise (7).

In another study, a single 600mg dose of GPC taken 90 minutes prior to resistance exercise significantly increased post-exercise serum growth hormone. In addition, peak bench press force was increased by 14 per cent (6). Typical therapeutic dosing is 600mg to 1200mg, taken once to twice daily. I have personally found that 1200mg of GPC taken 45 min prior to training has worked best for me.

Acetyl l-carnitine

Acetyl l-carnitine is one of the most researched brain nutrients. It has been shown to quickly enhance mental focus and energy. It has a similar structure to acetylcholine, and can therefore stimulate acetylcholine receptors in the brain. The acetyl group allows it to cross the blood brain barrier, which cannot be said about l-carnitine. Acetyl l-carnitine will support the brain as effectively as everything else that l-carnitine can do.

Carnitine is abundant in animal muscle tissue, including red meats. Its main function is to transport fatty acids across the mitochondrial membrane for fatty acid oxidation. Skeletal and cardiac tissues rely heavily on fatty acid oxidation and have high concentrations of carnitine (8). The supplementation of carnitine has been studied in many scientific areas, including metabolism, cardiovascular disease, and sports enhancement (9).

L-carnitine has been shown to improve exercise performance by enhancing the delivery of fat fuel to the muscles. It has also been shown to increase the anaerobic threshold, delaying the event where the muscles feel a 'burn' from lactic acid (10).

Most people associate acetyl l-carnitine with the prevention of age-related memory decline and the slowing of Alzheimer's disease. However, it is also very effective for increasing mental focus and energy when taken pre-workout. Acetyl l-carnitine increases dopamine levels, which has the effect of enhancing focus and motivation. Most individuals dose acetyl l-carnitine between 500mg and 3000mg per day, depending on the application. This is one of those nutrients where you really feel an increase in focus and energy within about 15 to 20 minutes of taking it, which is best achieved by taking 1500mg 30 minutes prior to training. This also happens to be the dosage at which the reversal of many of the signs of brain ageing occurs (11). In addition, there are no recognised side effects, only long term benefits to overall brain health.

There was also a study published in

Brain Health Nutrition Support

Lifestyle Recommendations:

- Reduce lifestyle stressors
- Do brain stimulating exercises
- Optimize sleep
- Stay socially active and engaged
- Stop smoking and avoid second-hand smoke as much as possible
- Exercise at least 30 minutes a day

Brain Health Nutrition Support

Dietary Recommendations:

- Optimize gut health
- Eat a gluten-free, anti-inflammatory diet
- Add healthy omega-3 fats
- Add healthy spices and herbs
- Eat organic foods whenever possible

Brain Health Nutrition Support

Nutrients	Between Meals	Breakfast	Between Meals	Lunch	Between Meals	Dinner	Before Bed
Acetyl-l-carnitine	-	250-750 mg	-	250-750 mg	-	-	-
GPC	-	150-300 mg	-	150-300 mg	-		
CDP-cholne	-	125-250 mg	-	125-250 mg	-		-
Magnesium L-Threonate	-	48 mg	-	48 mg	-	48 mg	
Curcumin	-	200-400 mg	-	-	-	200-400 mg	-
Fish Oil	-	0.5-2 grams	-		-	0.5-2 grams	-

Acetyl-L-Carnitine

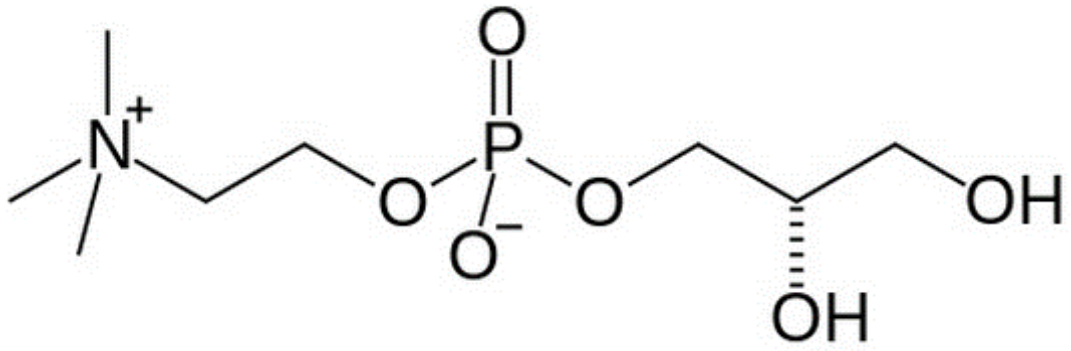
One of the most researched brain nutrients

The acetyl group allows it to cross the blood brain barrier

Quickly improves mental focus and energy

Increases dopamine which enhances focus and motivation

GPC



Improved memory, mental focus, and reaction time in the elderly and young.

Boosts growth hormone production in young and elderly.

Increases muscle strength.

Thank You