Human Body Physiology

Kidneys – filter blood waste removal
 Lungs – filter out carbon dioxide
 GI tract – digest & filter out waste

What about our Nervous System?

SLEEP

Universal across the animal kingdom

Why do we need sleep?

The reasons remain one of the greatest mysteries in biology

Sleep – Why?

- Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009
- **Sleep drives metabolite clearance from the adult brain** Science 2013
- Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels Brain 2017
- Effect of sleep on overnight cerebrospinal fluid amyloid beta kinetics Ann. Neurology 2018
- The sleep-wake cycle regulates brain tau in mice and CSF tau in humans. Science 2019
- Sleep deprivation impairs molecular clearance from the human brain Brain 2021
- Neuronal dynamics direct cerebrospinal fluid perfusion and brain clearance Nature 2024

 CONCLUSION: Deep Sleep promotes clearance of metabolic waste from the brain

Deep Sleep = brain pulsating slowly and in sync to remove waste



Sleep – Slow Wave



Sleep – Slow Wave Sleep (SWS)

3rd stage of 90-minute sleep cycle
Lasts for 20-40 minutes
SWS same as Deep Sleep
Most restful stage of sleep
Brain & heart slow, BP drops
Increased Growth Hormone release

Slow Wave Sleep

 Research suggests that the brain <u>activates</u> <u>newly acquired memories</u> during SWS to cement memories into long-term memory.

 SWS may facilitate learning by helping to restore connections between brain cells

You need more SWS!

SWS augments clearance of clumping proteins of AD

In patients with AD, increased slow wave sleep = better cognition

Lower AD risk by increasing SWS?



 Framingham Cohort
 23-year study
 We naturally lose SWS as we age
 Loss of SWS over time increased AD risk

 Caveat: Loss SWS = AD OR AD = loss SWS??? More study needed

Key Points

Question Does the percentage of slow-wave sleep decline with aging, and are intra-individual declines associated with dementia risk?

How to increase SWS

Warm bath/shower 1-3 hrs before bed (10-30 min at 104)* Cool bedroom Fiber intake Moderate exercise Consistent sleep schedule White noise/Sleep mask/Ear plugs Reduce stress No caffeine after 3pm/Limit alcohol



- Framingham study Does losing SWS increase AD risk? YES <u>https://jamanetwork.com/journals/jamaneurology/fullarticle/2810957</u>
- Wash U Waste clearance from brain **Terrific paper!!** https://www.cell.com/neuron/fulltext/S0896-6273(24)00687-1#fig2
- Why deep sleep is important and ways to increase <u>https://www.calm.com/blog/how-to-get-more-deep-sleep</u>
- Nature / Northwestern U increase SWS by Core Body Temp https://www.nature.com/articles/s41598-024-53839-x
- U Texas Austin Timing of warm bath/shower before bed to improve SWS
 https://www.medicalnewstoday.com/articles/325818
- Hot water bathing in 1,000 older Japanese adults and Sleep improvement https://pmc.ncbi.nlm.nih.gov/articles/PMC8314650/





MIND & MOOD

Can a spoonful of daily olive oil ward off dementia death?

News briefs

August 1, 2024

By Heidi Godman, Executive Editor, Harvard Health Letter

Reviewed by Anthony L. Komaroff, MD, Editor in Chief, *Harvard Health Letter*; Editorial Advisory Board Member, Harvard Health Publishing



Olive Oil

 Harvard study 92,000 men and women
 28 years
 7 gms/day (1.5 tsp) = <u>28% lower</u> risk of dementia

Olive oil and Dementia Reduction

- Key Findings from the Study
- In an observational study that spanned nearly 30 years and included over 92,000 participants, researchers found that consuming at least 7 grams of olive oil per day (about half a tablespoon) was associated with a 28% lower risk of dementia-related death. This finding was consistent even after accounting for various factors such as diet quality, lifestyle choices, and genetic predispositions.
- One particularly compelling aspect of this study is that the benefits of olive oil consumption were observed regardless of the overall quality of participants' diets. Typically, individuals who use olive oil tend to have a higher diet quality overall, often following dietary patterns like the Mediterranean diet, which is rich in fruits, vegetables, whole grains, and healthy fats, such as olive oil. However, the study found that even among those with varying diet qualities, higher olive oil intake still provided significant protective benefits against dementia-related mortality.
- This suggests that olive oil alone has powerful health benefits that can contribute to reduced dementia risk, independent of other dietary factors.

"Food Swap"

- How to Maximize the Benefits
- The key to reaping the benefits of olive oil, according to this study, is to replace other dietary fats such as margarine, mayonnaise and butter with olive oil. Here are some ways to increase your olive oil intake:
- Replace bottled salad dressings with simple dressings you make at home by mixing olive oil and vinegar or lemon juice.
- Replace mayo with olive oil in recipes like tuna salad or potato salad.
- Dip bread in olive oil instead of using butter or margarine as a spread.
- Use olive oil as your main cooking fat for sautéing, baking or frying.
- Replace butter on vegetables with a drizzle of flavorful olive oil.
- By making these delicious food swaps, you may not only support your brain health but also benefit from the numerous other health advantages associated with olive oil.

Olive oil – Did you know?

- Olives are fruits that grow on trees
- Extra Virgin Olive Oil (EVOO) is the first cold pressing, unrefined and using no heat to extract oil
- The <u>USDA</u> recommends regular olive oil as a safe oil for deep frying with a smoke point of 410° F, compared to the highest smoke point of soybean or peanut oil at 450° F.
- Olive oils can be used as a substitute for vegetable oils in baking and give a distinctive flavor. Regular olive oil matches flavor closer to neutral oils, such as canola or a vegetable oil blend

Whole grain bread Brown rice Oats Barley Corn Rye Quinoa (also high in protein)

6 or more servings per day High fiber Reduces LDL "bad" cholesterol Lower blood pressure Weight loss Lower inflammation Stabilize insulin levels/blood sugar Promote healthy digestion Reduces risk of heart disease

High in fiber

- 25gm women
- 35gm men

 Studies = reduced chronic disease and better weight loss

Lower Blood Pressure

 12-week study = whole grains lowered blood pressure corresponding to 15% reduction in CV disease and stroke

Is there an easier way?

MIND Diet!!

MIND Diet

Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND):

- Can slow memory loss
- Reduced Alzheimer's dementia risk
- Reduce chance of brain shrinkage by 70%
- greater brain volume.
- less Alzheimer's disease (AD) pathology.



lower likelihood of hippocampal disease.

Why might MIND Diet work? Fatty Acids (Omega 3 and 6)

Polyphenols (plant micronutrients)
 Act as antioxidants

Polyphenols

Plant micronutrients:

• 8,000 types (resveratrol, quercitin, capsaicinoids)

• Powerful Antioxidants (blood vessel health, promote circulation, reduce chronic inflammation; control blood sugars; lower cancer risk; raise immunity)

Studies >650mg/day

Polyphenol Foods

- **1. Berries** (blue 535mg serving; elderberries 900mg)
- 2. Herbs and spices (Cloves 542mg; peppermint, star anise, oregano, sage, rosemary, thyme)
- 3. Cocoa powder (515mg/tbsp, milk only 35mg UGH!)
- 4. Nuts (chestnuts 350mg/ounce; pecans, almonds)
- **5.** Flaxseeds (229mg/tbsp)
- 6. Vegetables (3 cups per day artichoke s, onion, spinach)

FLAVANOIDS

BACKGROUND: Fruits are an important source of flavonoids, and greater intake of dietary flavonoids in older adults has been shown to be associated with decreased risk of dementia. It is unclear whether this relationship is similar or different between younger adults and older adults. OBJECTIVES: We examined for associations between midlife and late-life intake of flavonoid-rich fruits and incident dementia. We hypothesized that greater total cumulative intake of flavonoid-rich fruits in midlife and late-life adults would be associated with reduced risk of all-cause dementia. DESIGN: Longitudinal, cohort study design. SETTING: Framingham Heart Study, which is a longitudinal, multi-generational community-based cohort based in Framingham, Massachusetts, USA. PARTICIPANTS: Participants from the Framingham Heart Study Offspring cohort were included (n = 2,790) who attended the fifth core exam between 1991 to 1995, and were dementia-free and at least 45 years of age at that time, as well as had valid food frequency questionnaires from the fifth to ninth core exams. MEASUREMENTS: Consumption of fruits with high flavonoid content or are important contributors to overall flavonoid intake was collected via food frequency questionnaire. Flavonoid-rich fruits from the food frequency questionnaire included raisins or grapes, prunes, bananas, fresh apples or pears, apple juice or cider, oranges, orange juice, grapefruit, grapefruit juice, strawberries, blueberries, and peaches, apricots, or plums. Dementia ascertainment was based on a multidisciplinary consensus committee, and included all-cause dementia and Alzheimer's disease dementia diagnoses based on research criteria. Cox models were used to examine associations between cumulative fruit intake and incident dementia, stratified by midlife (45-59 years; n = 1,642) and late-life (60-82 years; n = 1,148). RESULTS: Greater cumulative total fruit intake in midlife, but not late-life, was significantly associated with a 44% decreased risk of all-cause dementia (HR = 0.56; 95% CI = 0.32 - 0.98; p = 0.044). Decreased risk of all-cause dementia was also associated with higher intake of apples or pears in midlife and late-life, as well as higher intake of raisins or grapes in midlife only, and higher intake of oranges, grapefruit, blueberries, and peaches, apricots, or plums in late-life only. CONCLUSIONS: Among participants from the Framingham Heart Study, greater overall consumption of flavonoid-rich fruits in midlife was associated with reduced risk of dementia, though intake of specific fruits in midlife and late-life may have a protective role against developing dementia. These findings may help to inform future recommendations on when dietary interventions may be most beneficial to healthy brain aging across the life course.



PsyPost

Home > Exclusive > Mental Health > Dementia > Alzheimer's Disease

Study links certain fatty acids in blood to decreased Alzheimer's risk

by Eric W. Dolan - January 6, 2024 in Alzheimer's Disease







Volume 79, Issue 1 January 2024

< Previous Next >

JOURNAL ARTICLE

Associations Between Blood Nutritional Biomarkers and Cerebral Amyloid-β: Insights From the COGFRAIL Cohort Study Getaccess > Natasha A Grande de França, PhD ☎, Gustavo Díaz, MSc, Laetitia Lengelé, PhD, Gaëlle Soriano, PhD, Sylvie Caspar-Bauguil, PhD, Laure Saint-Aubert, PhD, Pierre Payoux, MD, PhD, Laure Rouch, PhD, Bruno Vellas, MD, PhD, Philipe de Souto Barreto, PhD ... Show more

The Journals of Gerontology: Series A, Volume 79, Issue 1, January 2024, glad248, https://doi.org/10.1093/gerona/glad248
Published: 25 October 2023 Article history ▼

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Abstract

Understanding the relationship between blood nutrients and neurodegeneration could contribute to devising strategies for preventing Alzheimer's disease. We investigated the associations between fatty acids, vitamins D, B6, B12, folate, homocysteine, and the cerebral load of amyloid β (A β). This cross-sectional study included 177 older adults (70–96 years, 65% female) with objective cognitive impairment, prefrail, or frail. Cerebral A β load was determined using positron emission tomography Standardized Untake





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Fatty Acids?

177 Patients Amyloid PET Positive

 Measured Various Nutrients: Vitamins, Amino Acids, Fatty Acids (Omega 3, Omega 6)

Statistically significant finding of Omega 3 EPA (metabolite) = less Amyloid!!



CraigCurtisMD.com



Are you a member of a club?

If you are a member of a club and would like Dr. Curtis to speak please don't hesitate to talk to him!!



Dean Ornish MD supplement

Memory Supplements



MIND & MOOD

Don't buy into brain health supplements

August 8, 2023



Forget about those over-the-counter products that promise better memory.

A recent survey found that about 25% of adults over age 50 take a <u>supplement</u> to improve their brain health with the promise of enhanced memory and sharper attention and focus.

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The Washington Post Democracy Dies in Darkness

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Snow

BRAIN MATTERS

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Why Viagra has been linked with better brain health

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February 22, 2024 at 8:20 a.m. EST





(George Wylesol for The Washington Post)



Alzheimer's blood test performs as well as FDA-approved spinal fluid tests

Could make early Alzheimer's diagnosis, treatment accessible to more people

by Tamara Schneider • February 21, 2024





Missed diagnosis: The hidden crisis of mild cognitive impairment in America

Two new USC Dornsife studies suggest that of the 8 million Americans who have MCI, more than 90% don't know it — an especially worrisome finding since early diagnosis is key to delaying onset of dementia and Alzheimer's disease.

By **Katharine Gammon** December 12, 2023

After moving back to Oceanside, Calif., Jean Bland looked forward to reconnecting with the familiar streets of her youth. But not long after settling in, her husband Mike noticed that Jean, with whom he'd shared 41 years of marriage, would occasionally find herself lost in the very places she once knew so well. Initially concerned, he dismissed it as a common sign of aging.

Jean, 79, a former nurse known for her meticulous nature and attention to detail, always came prepared to her doctor's appointments, armed with a litany of questions and notes. So, when she walked into the exam room two years ago without any list and displayed signs of forgetfulness, it

raised eventrows. Her physician sensing something wasn't right recommended a series of tests

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Spying on α-Synuclein Inclusions: PET Tracers Inch Closer to Success

Series - Alzheimer's Association International Conference (AAIC) - 2023: Part 5 of 10: S ~

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ARTICLE COMMENTS REFERENCES FURTHER READING

04 Aug 2023

PET tracers that illuminate α -synuclein in the brain have been hard to come by, but scientists may be getting closer. According to a study published August 3 in Cell, an 18F- tracer developed at Emory University, Atlanta, binds to α-synuclein aggregates in human Parkinson's disease brain samples, in mouse models of synucleinopathy, and in nonhuman primates. Crucially, it does so while shunning Aβ plaques or tau tangles, which commonly co-occur with Lewy bodies. Led by Keqiang Ye, now at the Chinese Academy of Sciences in Shenzhen, the study used cryo-electron microscopy to unveil the structural details of the tracer's specific liaison with α -synuclein. 18F-F0502B joins a growing field of candidate tracers, including three presented at the Alzheimer's Association International Conference, held July 16-20 in Amsterdam. One, made by AC Immune, binds to a-synuclein aggregates when they are highly concentrated in the brain, including in people with multiple system atrophy and in a genetic form of PD. The company's other up-andcoming tracer candidate holds promise in latching onto the smaller inclusions that predominant in the PD brain. Another, made by Merck, bound synuclein in mouse models of PD.

- New PET tracer binds α-synuclein aggregates in mice and nonhuman primates.
- · Cryo-EM shows it nestles in groove along the fibrils.
- · AC Immune and Merck report new candidates at AAIC.

"We are on the cusp of having a selective αsynuclein PET tracer that performs well in Parkinson's disease," said Jamie Eberling of the Michael J. Fox Foundation, which contributes funding for several ongoing efforts to develop the tracers, including AC Immune and Merck's.

A PET ligand for α -synuclein would help

immensely with diagnosis and prognosis of synucleinopathies, and with recruitment and monitoring in clinical trials. Yet, suitable tracers have eluded the field for years, due to their subpar affinity for α-synuclein within the brain, as well as off-target binding to other types of aggregates, including A β plaques and neurofibrillary tangles. Making matters worse, α -synuclein deposits in the brain can be dwarfed by other protein inclusions. In a landmark for the field last year, AC Immune's 18F-ACI-12589 detected α -synuclein aggregates in people with multiple system atrophy, but failed to label inclusions in people with other synucleinopathies, including PD (Mar 2022 conference news).

In their hunt, co-first authors Jie Xiang, Youqi Tao, and Yiyuan Xia and colleagues took hints from compounds known to bind and block α-synuclein oligomerization, including molecules with catechol groups, such as dopamine and its derivatives. After screening an initial batch of 23 commercially available compounds for binding to preformed, recombinant a-synuclein fibrils, the

PRIMARY PAPERS

Xiang J, Tao Y, Xia Y, Luo S, Zhao Q, Li B, Zhang X, Sun Y, Xia W, Zhang M, Kang SS, Ahn EH, Liu X, Xie F, Guan Y, Yang JJ, Bu L, Wu S, Wang X, Cao X, Liu C, Zhang Z, Li D, Ye K. Development of an a-synuclein positron emission tomography tracer for imaging synucleinopathies. Cell. 2023 Aug 3;186(16):3350-3367.e19. Epub 2023 Jul 7 PubMed.

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alzforum.org/news/research-news/meet-two-new-biomarker-candidates-lewy-body-diseases



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Meet the Two New Biomarker Candidates for Lewy Body Diseases

ARTICLE COMMENTS

REFERENCES FURTHER READING

21 Sep 2023

With several fluid biomarkers for Alzheimer's in hand, the search is on for counterparts in Parkinson's disease and dementia with Lewy bodies (DLB). Four new papers introduce two candidates: DOPA decarboxylase (DDC), the enzyme that converts levodopa into dopamine, and mitochondrial DNA damage.

- People with Lewy body disease (LBD) make ample DOPA decarboxylase (DDC).
- High DDC in CSF or blood distinguishes LBD from controls with up to 91 percent accuracy.
- DDC pegs preclinical LBD, foretells imminent symptom onset.
- Another marker, mitochondrial DNA damage, detected Parkinson's with 85 percent accuracy.

In the September 13 Nature Communications, researchers led by Charlotte Teunissen at Amsterdam University Medical Centers, The Netherlands, reported that high cerebrospinal fluid levels of DDC distinguished people with DLB from controls. Per Svenningsson, Karolinska Institutet, Stockholm, Sweden, found the same in PD, as reported in the September 4 Translational Neurodegeneration. So, too, did Oskar Hansson, Lund University, Sweden, in both DLB and PD. In the September 18 Nature Aging, his group also reported that DDC was up in blood from people with those diseases and that

CSF DDC predicted progression within three years in people with preclinical DLB or PD.

Scientists led by Laurie Sanders, Duke University School of Medicine, Durham, North Carolina, measured mitochondrial DNA damage in blood cells. In the August 30 Science Translational Medicine, they reported that blood cells of people with PD and non-symptomatic carriers of a PDcausing mutation had more mitochondrial DNA damage than controls.

"A blood-based biomarker is critically needed for synucleinopathies as current modalities involve either procedures, e.g., lumbar puncture for CSF or skin biopsy, or expensive brain imaging," wrote

PRIMARY PAPERS

Pereira JB, Kumar A, Hall S, Palmqvist S, Stomrud E, Bali D, Parchi P, Mattsson-Carlgren N, Janelidze S, Hansson O. **DOPA decarboxylase is an emerging biomarker for Parkinsonian disorders including preclinical Lewy body disease**. Nat Aging. 2023 Sep 18; PubMed.

Paslawski W, Khosousi S, Hertz E, Markaki I, Boxer A, Svenningsson P. **Large-scale proximity extension assay reveals CSF midkine and DOPA decarboxylase as supportive diagnostic biomarkers for Parkinson's disease**. *Transl Neurodegener*. 2023 Sep 4;12(1):42. PubMed.

Del Campo M, Vermunt L, Peeters CF, Sieben A, Hok-A-Hin YS, Lleó A, Alcolea D, van Nee M, Engelborghs S, van Alphen JL, Arezoumandan S, Chen-Plotkin A, Irwin DJ, van der Flier WM, Lemstra AW, Teunissen CE. **CSF proteome profiling reveals biomarkers to discriminate dementia** with Lewy hodies from Alzheimer´s



CV risk and diet



Back to Basics: AD risk

1 in 20 age 65-74
1 in 8 age 75-84
1/3 of those 85 or older

ApoE 4 gene

Who has it?
What does it do?
What are treatment implications?

ApoE 4/4 risk of AD approx. 50% ApoE 4/4 AD onset approx. 71 yo

1992 - Amyloid Cascade Hypothesis

Dr. John Hardy

- Mayo Clinic chair Neuroscience Dept
- NIH chief of Laboratory of Neurogenetics
- St Mary's London

 Based on his and others (Tanzi (Harvard), Roses & Stritmatter (Duke) earlier discovery in 1980's of Amyloid gene mutation leading to early onset Alzheimer's Dementia Modifiable and Non-modifiable Risk Factors (Cornell University Alz Prevention)

Non-Modifiable

- Age
- Genetics
- Gender
- Family History
- Past Medical Problems

Modifiable

- Diet
- Physical Exercise
- Brain Exercise
- Slow Wave Sleep
- Stress Reduction
- BP/Cholesterol

Weil Cornell

- "Research has shown that 40% of Alzheimer's cases may be preventable based on modifiable risk factors," Dr. Niotis says. Based on current scientific evidence, she suggests:
- Exercising at least three hours per week
- Eating a Mediterranean-style diet rich in green leafy vegetables, berries, and fatty fish like wild salmon, mackerel, and albacore tuna
- Reducing "bad" carbohydrates or "empty calories" like bread, pasta, rice, sweets
- Minimizing alcohol intake
- Getting adequate amounts of sleep
- Engaging in stress reduction techniques
- Protecting your head from injury
- Having your hearing checked and seeking appropriate management for hearing loss
- Staying socially engaged
- Learning new things, like language, dance, or a musical instrument
- Seeing your primary care doctor on a regular basis

Hearing Loss and Dementia

2011 Johns Hopkins study

- Mild hearing loss = 2x risk
- Moderate = 3x risk
- Severe = 5x risk
- The exact connection between hearing loss and dementia remains a mystery
- Theories: Its possible that hearing loss deprives brain areas of stimulation leading to increased risk of dementia
 <u>OR</u> could be the reverse where dementia somehow affects the ability to hear



TAU progression = memory decline



TAU progression = memory decline

Stages I-II Transentorhinal Clinically Silent



NFT stages I + II



Stages III-IV Limbic Incipient AD









NFT stage VI



Tau progression PET scan





WILEY

Jan 2016

Harvard Medical School

Keith Johnson, MD Resia Sperling, MD

Intensity (SUVR)



AMYLOID and TAU cascade



A. Braak stages (post mortem)





Limbic (III/IV)



Neocortical (V/VI)

B. Tau tracer uptake (PET)

Transentorhinal (I/II)



Stage_{I/II} > Stage₀



Stage_{III/IV} > Stage_{I/II}



Stage_{V/VI} > Stage_{III/IV}



Thank you!



Craig Curtis, MD

K2 Summit Research The Villages, FL

