Healthy Brain Aging
& Dementia Prevention

UW NWGWEC – March 12, 2019

Emily Trittschuh, PhD
VA Puget Sound Health Care System
University of Washington School of Medicine

UNIVERSITY of WASHINGTON

VA | U.S. Department of Veterans Affairs
Veterans Health Administration
Geriatric Research, Education, and Clinical Centers

Disclosure

- Nothing to disclose
- The views and opinions in this presentation are those of the presenter and they do not necessarily reflect, and should not be taken as, official policy of the U.S. Department of Veterans Affairs or the University of Washington.

Objectives

- Dispel misconception that one can "prevent" dementia
- Review top modifiable risk factors
- Flip perspective from preventing disease to encouraging healthy brain aging
- Increase provider skills and confidence for how to respond to questions regarding dementia prevention and healthy brain aging
  - Review common myths and discuss approaches to address them
  - Pros and Cons of "early detection"

Can we prevent dementia?

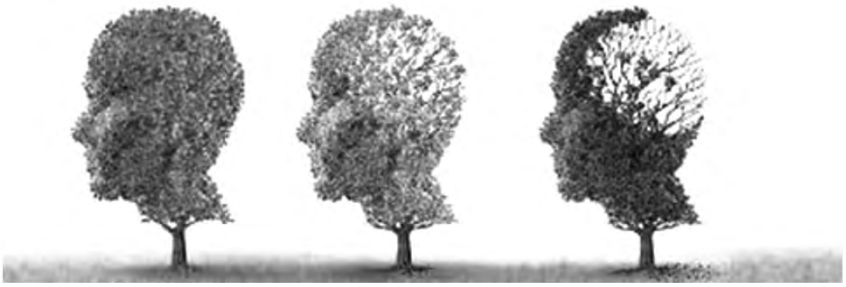
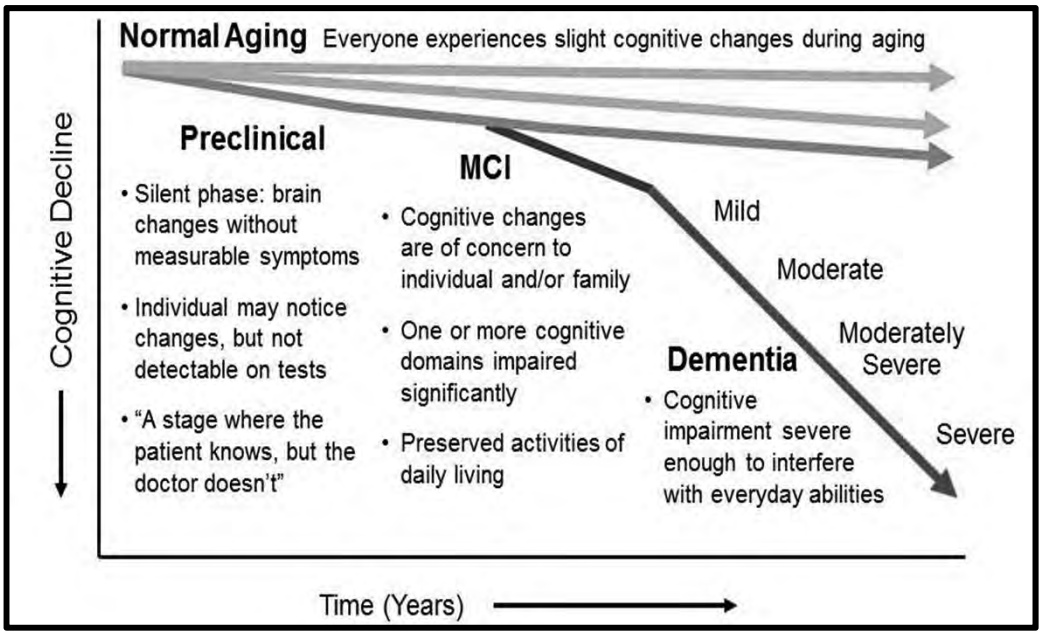


Image: PenCLAHRC - NIHR



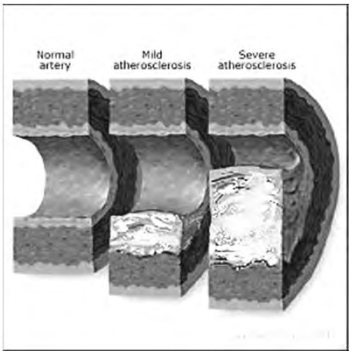
From S. McCurry who credits: http://health.mashangel.com

Approaches to Dementia Prevention

What are the top risk factors?

- Can't change **age**
- Can't change **genetics**
- Focus on modifiable risk factors

Vascular Disease



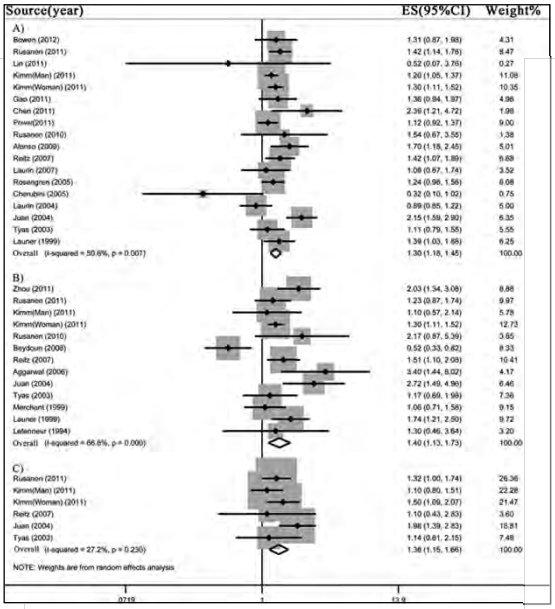
Hypertension/Atherosclerosis

- Longitudinal studies have suggested that high blood pressure in midlife is associated with a higher incidence of both AD and VaD in later life.
- Some studies suggest that hypotension; especially low diastolic blood pressure in late-life is also associated with an increased risk of AD.
- Long-standing hypertension may lead to severe atherosclerosis and impaired cerebrovascular autoregulation.
- Decline in BP in later life may contribute to diminished cerebral perfusion which may in turn lead to increased beta-amyloid

Kennelly, Lawlor, & Kenny, *Ageing Research Reviews*, 2009

Smoking

- Prospective cohort studies (n=37 high quality)
- Versus never smokers, current smokers had an increased risk of all-cause dementia (risk ratio (RR) 1.30, 95% (CI) 1.18–1.45), AD (RR 1.40, 95% CI 1.13–1.73) and VaD (RR 1.38, 95% CI 1.15–1.66). For all-cause dementia, the risk increased by 34% for every 20 cigarettes per day (RR 1.34, 95% CI 1.25–1.43). Former smokers did not show an increased risk of all-cause dementia (RR 1.01, 95% CI 0.96–1.06), AD (RR 1.04, 95% CI 0.96–1.13) and VaD (RR 0.97, 95% CI 0.83–1.13). Subgroup analyses indicated that (1) the significantly increased risk of AD from current smoking was seen only in apolipoprotein E ε4 noncarriers; (2) current smokers aged 65 to 75 years at baseline showed increased risk of all-cause dementia and AD compared to those aged over 75 or under 65 years; and (3) sex, race, study location and diagnostic criteria difference in risk of dementia was not found.
- **Smokers had an increased risk of dementia, and smoking cessation decreases the risk to that of never smokers.**
- **Current smoking increased risk of AD in the Apoe e4-**
- **Survival bias and competing risk reduce the risk of dementia from smoking at extreme age.**



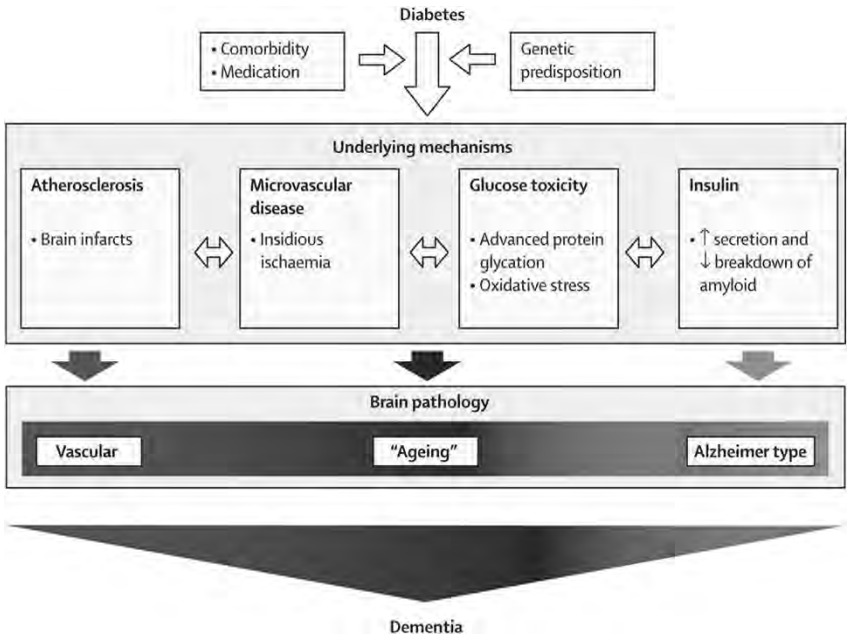
Zhong, et al, *PLOS*, 2015

Diabetes

- Diabetes Type 1 and 2 are associated with cognitive weaknesses
  - Processing speed and flexibility (DM I & II)
  - Learning and Memory (DM II)
- Faster rate of decline in older adults with DM II
- Fairly consistent finding that Diabetes is related to higher risk of "any dementia" – with specific findings for Alzheimer's (50-100%) and Vascular dementia (100-150%) types
- Mechanisms are not entirely clear, but reasonable hypotheses exist . . .

Biessels, et al., *Lancet Neurology*, 2006

Diabetes



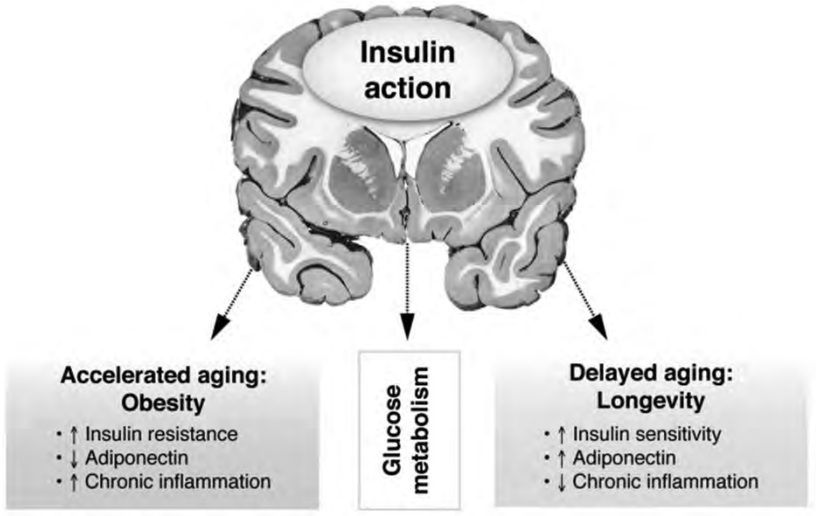
Biessels, et al., *Lancet Neurology*, 2006

Insulin and Glucose Metabolism

Putative relationship between central insulin action and glucose metabolism in models of accelerated or delayed aging.

Obesity as a model for accelerated aging is associated with peripheral insulin resistance, decreased adiponectin levels, and enhanced chronic inflammation.

The opposite is observed in healthy longevity.



Akintola and van Heemst, Frontiers in Endocrinology, 2015

Mental Health Conditions

Image: www.socialworker.com

Depression

- Early-onset depression before age 65 years and recurrent depression, may constitute long-term risk factors for development of dementia
- Late-onset depressive symptoms may be a feature of prodromal phase of dementia
- Recent studies suggest that long-term treatment with antidepressants may decrease the risk
  - Kessing, Curr Opin Psychiatry, 2012

Post-traumatic stress disorder

- Double the risk in Veteran groups studied
  - Yaffe, et al, 2010; Quereshi, et al, 2010

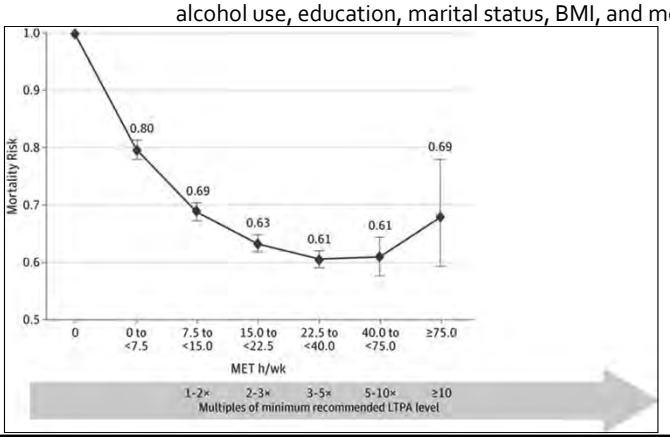
Anxiety

- Not associated with the risk of dementia or cognitive decline: the Rotterdam Study.
  - de Bruijn, et al, Am J Geriatr Psychiatry, 2014

Brain Health **Promotion**

Physical Activity

- 2008 Physical Activity Guidelines recommended 75 vigorous or 150 moderate intensity minutes/weekly (7.5 METS weekly)
- Dose response? Pooled analysis of 6 prospective, pop-based studies
- N > 660,000; Median age = 62 (range 21-98); > 116,000 deaths over 11 years
  - Cox Proportional Hazards Regression for overall mortality; Similar for cardiovascular and cancer-related deaths; Model adjusted for gender, smoking, alcohol use, education, marital status, BMI, and medical comorbidities



Arem, et al, *JAMA Int Med*, 2015

Physical Activity in Older Adults

Does physical activity prevent cognitive decline and dementia?

Forty-seven cohorts, derived from two previous systematic reviews and an updated database search, were used in the meta-analyses. Participants were aged ≥40 years, in good health and/or randomly selected from the community.

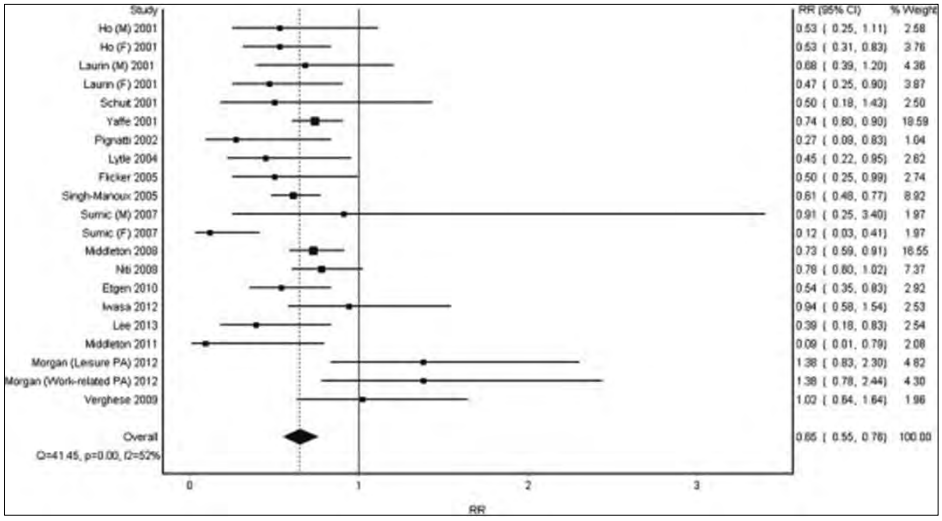
RESULTS: Twenty-one cohorts on physical activity and cognitive decline and twenty-six cohorts on physical activity and dementia were included. Participants with higher levels of physical activity, when compared to those with lower levels, are at reduced risk of cognitive decline, RR 0.65, 95% CI 0.55-0.76, and dementia, RR 0.86, 95% CI 0.76-0.97.

Sensitivity analyses revealed a more conservative estimate of the impact of physical activity on cognitive decline and dementia for high quality studies, studies reporting effect sizes as ORs, greater number of adjustments (≥10), and longer follow-up time (≥10 years). When one heavily weighted study was excluded, physical activity was associated with an 18% reduction in the risk of dementia (RR 0.82; 0.73-0.91).

CONCLUSIONS: Longitudinal observational studies show an association between higher levels of physical activity and a reduced risk of cognitive decline and dementia. A case can be made for a causal interpretation. Future research should use objective measures of physical activity, adjust for the full range of confounders and have adequate follow-up length. Ideally, randomised controlled trials will be conducted.

Blondell, Hammersley-Mather, & Veerman, *BMC Pub Health*, 2014

Physical Activity in Older Adults



Blondell, Hammersley-Mather, & Veerman, *BMC Pub Health*, 2014

Alas . . .

- RCTs of aerobic exercise programs for NC people 55+ which measured effects on both fitness and cognition. Comparison to wait list or other non-aerobic activity
  - 12 trials including 754 participants met inclusion criteria.
  - Eight of the 12 trials reported that the aerobic exercise interventions resulted in increased fitness of the trained group.
- However, when results were combined across trials, no significant benefits of aerobic exercise or increased fitness on any aspect of cognition.
- Many included trials had problems with their methods or reporting which reduced confidence in the findings.
- No evidence that aerobic exercise or increased fitness improves cognitive function in older people.
- However, it remains possible that it may be helpful for particular subgroups of people, or that more intense exercise programs could be beneficial.

Young, et al, *Cochrane Rev*, 2015

Social Interaction

Numerous studies have found associations between healthy brain aging and social interaction

- Rush Memory and Aging Project (MAP): a longitudinal, epidemiological clinical–pathological study (for this study, n=89 older adults without known dementia at baseline and with brain autopsy data).
- Baseline questions about social network size and uniform structured clinical assessments including the following: medical history, neurological examination, and neuropsychological performance.
- Covariates included cognitively stimulating activities, physical activities, social activities, and seven common chronic diseases.
- The results indicate that even when participants demonstrated severe levels of global disease pathology, cognitive performance remained higher for participants with larger network sizes even after controlling for covariates.

Bennett, et al, 2006

Mood / Emotional Wellness

- Treating Mental Health Issues can reduce the associated dementia risk
- Take steps to decrease stress and increase laughter
- Low neuroticism and high extraversion associated with reduced dementia incidence; however, those with low neuroticism who were inactive and socially isolated were at increased risk for dementia[1]
- High scores on psychological wellbeing and high lifetime motivational abilities were associated with preserved cognitive function in older age[2]

1. Wang, et al, 2009, 2. Forstmeier and Maercker, 2008

Nutrition

Mediterranean Diet

- High intake of vegetables, fruits, nuts, legumes, and unrefined grains
- High intake of olive oil, but low intake of saturated fats
- Moderately high intake of fish
- Low intake of dairy, meat, and poultry
- Moderate intake of wine with meals

- Observational studies: In addition to reduced mortality, reduced chronic disease, including cardiovascular disease[1] – increased healthy aging[2]
- Cochrane Review: n=11 trials (52k+) demonstrated limited evidence[3]
- Review of studies with strict reduction in fat intake (cohort and RCTs): limited evidence for reduction in cardiovascular events, breast CA, and type 2 diabetes[4]

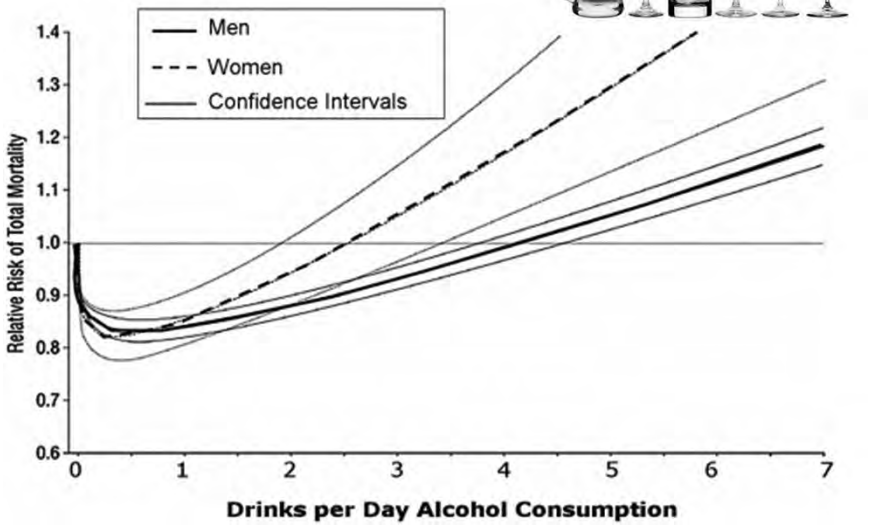
1. Trichopoulou, et al, *N Engl J Med*, 2003, 2. Samieri, et al, *Ann Intern Med*, 2013, 3. Rees, et al, *Cochrane Reviews*, 2013, 4. Bloomfield, et al, *Ann Int Med*, 2016

Alcohol

- Alcohol can be a Primary or Secondary cause of dementia
- Long-term, excessive drinking of alcohol is known to cause damage to the brain – resulting in neurological damage and impaired cognitive function
  - Alcohol-related dementia
  - Wernicke-Korsakoff syndrome
- Drinking more than recommended amounts increases risk of developing common types of dementia (AD and VaD)
- Increases risk of stroke and heart disease
- 2-10% of older adults abuse alcohol or are alcohol dependent[1]
- Increases the risk of many other potential geriatric syndromes: falls, head injury, delirium

Farcnik & Persyko, *Can AD Review*, 2005; Rigler, *AmFamPhys*, 2000

Alcohol



See Castelnuovo, et al, 2006 for meta-analysis

Alcohol & Aging

- Lower alcohol tolerance due to decreased metabolism and blood flow, decreased lean body mass and decreased water
- Women especially have slower metabolism
- At-risk drinking found in ~15% of adults 65+
- Potential interaction of alcohol and medications
- **Recommended Drinking Limits for Older Adults**
  - *No more than 1 standard drink per day or 7 per week*
  - *No more than 2-3 drinks on any drinking day*
  - *Stricter limits for older women*

Special Populations: Older Adults on www.niaaa.nih.gov

Responding to our patients

Keeping up with the latest news flash or fad

Healthy Brain Aging? OR The Latest Fad?

- Ginkgo biloba
- Omega-3 fatty acids
- Coconut oil
- Alcohol (light to moderate)
- Red wine (resveratrol)
- Statins
- Diet manipulations
- Brain games
- Vitamin E & selenium
- What else have you heard?

Ginkgo biloba

Only two RCT, double-blind trials

RESULTS:

- Meta-analysis of the two trials involving 5,889 participants indicated no significant difference in dementia rate between Ginkgo biloba and the placebo (347/2,951 vs. 330/2,938, odds ratio = 1.05, 95% CI 0.89-1.23) and there was no considerable heterogeneity between the trials. The two studies revealed no statistically significant differences in the rate of serious adverse effect between Ginko biloba and the placebo.

CONCLUSION:

- There is no convincing evidence from this review that demonstrated Ginkgo biloba in late-life can prevent the development of dementia. Using it for this indication is not suggested at present.

Charemboon and Jaisin, J MedAssocThai, 2015

Omega 3 fatty acid

- Why? Diets high in omega-3 long-chain polyunsaturated fatty acids (PUFA) may protect people from cognitive decline and dementia.
- Direct evidence on the effect of omega-3 PUFA on incident dementia is lacking.
- Trials showed no benefit of omega-3 PUFA supplementation on cognitive function in cognitively healthy older people.
- Omega-3 PUFA supplementation is generally well tolerated with the most commonly reported side-effect being mild gastrointestinal problems.
- Longer-term studies may identify greater change in cognitive function in study participants which may enhance the ability to detect the possible effects of omega-3 PUFA supplementation in preventing cognitive decline in older people.

Sydenham, Dangour, and Lim, *Cochrane Review*, 2012

Why choose this? When you can choose these?

Coconut Oil

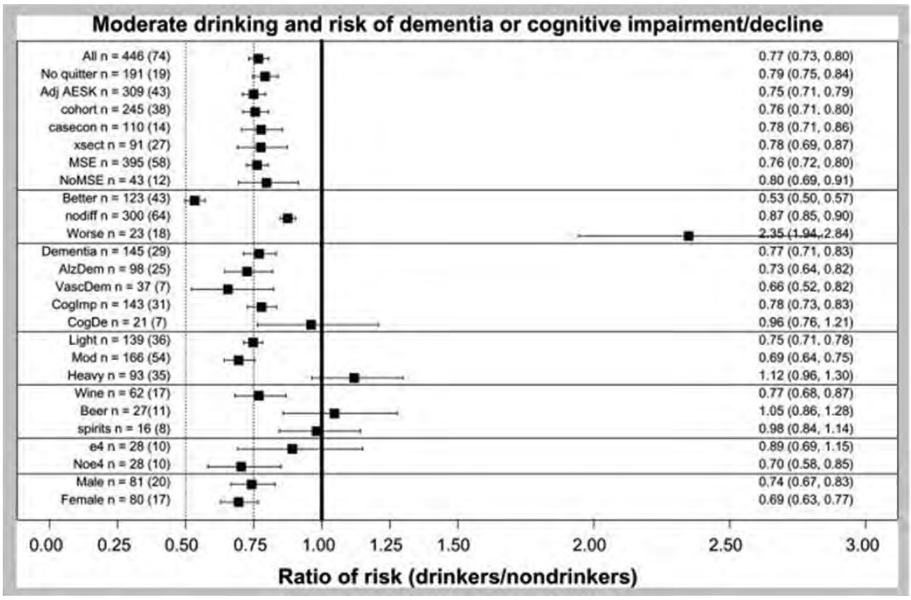
What is it? An edible oil extracted from coconuts. It has a high saturated fat content which means it's slow to oxidize (go rancid)

- The claims: can improve thinking in dementia; can reverse dementia; can prevent dementia

What the pros say:

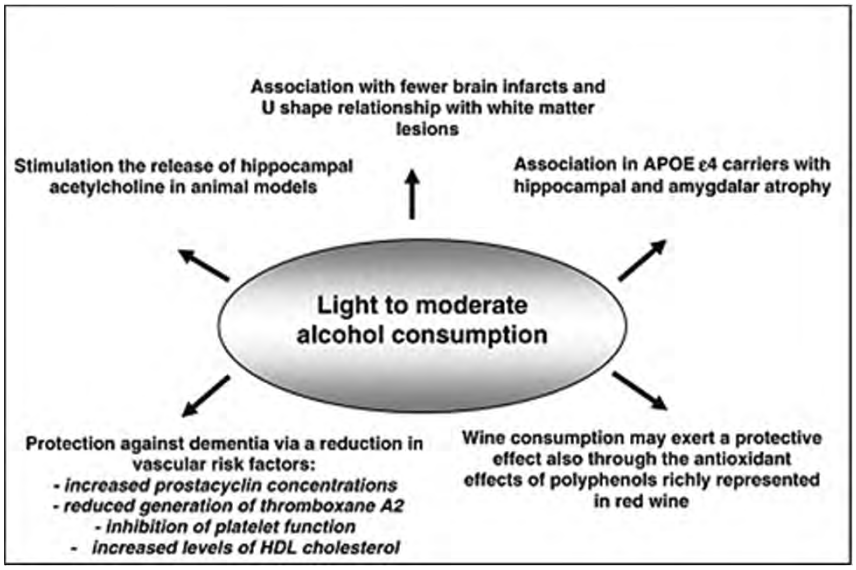
- Coconut oil consumption should be limited or avoided
- World Health Organization, United States FDA, International College of Nutrition, the US Dept of Health and Human Services, American Dietetic Association, American Heart Association

Light to Moderate Alcohol



Neafsey & Collins, 2011

Light to Moderate Alcohol



Panza, et al, 2012

Resveratrol

- What about resveratrol supplements?
- Synthesized in many plants, peanuts, blueberries, pine nuts, and yes, grapes
- Animal studies have suggested it can increase longevity, but human studies have been inconclusive

Semba, et al, *JAMA Intern Med*, 2014

Statins: good or evil?

OBJECTIVES: To evaluate the efficacy and safety of statins for the prevention of dementia in people at risk of dementia due to their age and to determine whether the efficacy and safety of statins for this purpose depends on cholesterol level, apolipoprotein E (ApoE) genotype or cognitive level.

MAIN RESULTS: 26,340 participants aged 40-82 years of whom 11,610 were aged 70+. All participants had a history of, or risk factors for, vascular disease. The studies used different statins (simvastatin and pravastatin). Mean follow-up was 3.2 years in 1 study and 5 years in the other. Only one study reported on the incidence of dementia (20,536 participants, 31 cases in each group; odds ratio (OR) 1.00, 95% CI 0.61 to 1.65, moderate quality evidence, downgraded due to imprecision). No differences between statin & placebo groups on 5 different cognitive tests (high quality evidence). Rates of treatment discontinuation due to non-fatal adverse events were less than 5% in both studies and there was no difference between statin and placebo groups in the risk of withdrawal due to adverse events (26,340 participants, 2 studies, OR 0.94, 95% CI 0.83 to 1.05).

CONCLUSIONS: Good evidence that statins given in late life to people at risk of vascular disease do not prevent cognitive decline or dementia. Biologically, it seems feasible that statins could prevent dementia due to their role in cholesterol reduction and initial evidence from observational studies was very promising. However, indication bias may have been a factor in these studies and the evidence from subsequent RCTs has been negative. There were limitations in the included studies involving the cognitive assessments used and the inclusion of participants at moderate to high vascular risk only.

McGuinness, et al, *Cochrane Review*, 2016

Diet Manipulations

Low-Carb Diets and Insulin Resistance

- Diets that restrict carbohydrates can have incredibly powerful benefits against metabolic syndrome and type 2 diabetes, and this is partly mediated by reduced insulin resistance
- However, when carb intake is very low, such as on a ketogenic diet, the body may induce an insulin resistant state in order to spare blood sugar for the brain

Recent study

- N=363, overweight and obese subjects – given the choice of low-carb, ketogenic vs low-calorie (24 weeks)
- In the LCKD group, initial dose of some antidiabetic medications was decreased to half and some discontinued at the beginning
- Both diets had beneficial effects on all parameters
  - Body weight, body mass index, changes in waist circumference, blood glucose level, changes in hemoglobin and glycosylated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides
  - LCKD changes were of greater statistical significance

Hussain, et al, Nutrition, 2012

Diet Manipulations - Continued

Caloric restriction

- A CR Diet provides all essential nutrients and vitamins, BUT has significantly lower calories (30-70%)
- Evidence suggests this affects 1) insulin/insulin-like growth factor signaling, and 2) target of rapamycin (TOR) signaling[1]
- In various animal models, this can extend the maximal lifespan and/or delay morbidity[2]
- Only observational data in humans
- RCTs? Ethical?

1. Kenyon, Nature, 2010; 2. Zhao, et al, PLOS, 2014

Brain Games

- The benefit of cognitive training seems to be domain specific.
- Several trials found that while cognitive training can improve memory, reasoning, and mental processing speed in older adults, cognitive training did not generalize across domains and did not affect everyday functioning.
- Older adults with memory impairment may be less able to make gains from memory training than those without impairment.

1. Acevedo, et al, *J Geriatr Psychiatry Neurol* 2007; 2. Ball, et al, *JAMA* 2002; 3. Unverzagt , et al, *JINS*, 2007

Antioxidant supplements

Take home message:

SUPPLEMENTS WITHOUT EVIDENCE OF DEFICIENCY, OR ON TOP OF A HEALTHY DIET, ARE NOT RECOMMENDED

- Selenium and Vitamin E Cancer Prevention Trial (SELECT) enrolled 7540 elderly men who were exposed to the supplements for an average of 5.4 years
- Randomized to E, selenium, both, or placebo
- Trial closed in 2009 due to futility analysis
- The Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADViSE) study is ancillary - a subset of 3786 men agreed to be observed for up to 6 additional years.
- Dementia incidence (4.4%) did not differ among the 4 study arms.
- Neither supplement can be recommended as a preventive agent

Kryscio, et al, *JAMA Neurology*, 2014

What else have you heard?

Tips for talking to your patients

#1 Be Composed

- Try to avoid a strong positive or negative response
- Keep up with the literature
- Pay attention to the popular press
- Show, don't tell, when providing education
- The "inverted U" or "J-shaped curve" when discussing doses
- Provide guidance on where to find reputable information
- Big claims and asking for big money? Get suspicious
- HOPE – don't squash it

Early Detection: Pros and Cons

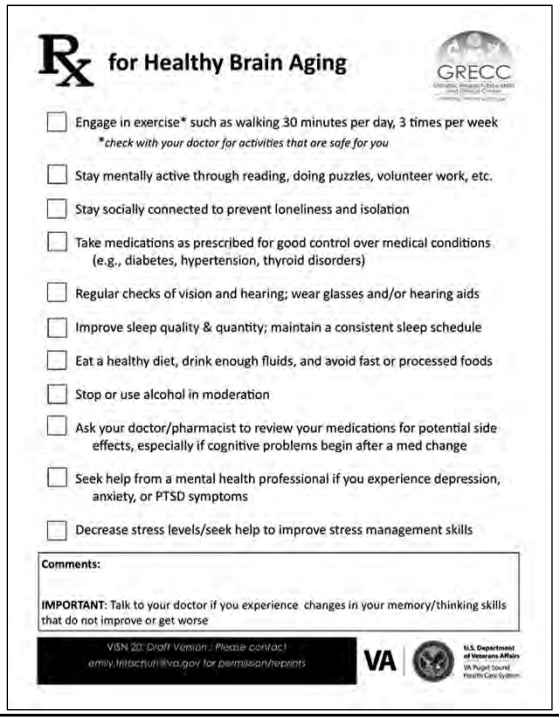
UK National Screening Committee

- The condition is important and common — Yes.
- Its natural history is well understood — No. It is a syndrome not a disease. The syndrome has very many underlying associated pathologies. Those pathologies do not always lead to manifest clinical syndromes.
- There should be an effective treatment which, if given early enough, changes the natural history — No. There is no such evidence as yet.
- There must be a relatively simple, cost-effective, reliable, and valid test — No. Not tested in relevant populations with sufficient follow-up and establishment of harms/benefits.

- BUT, there is a difference between screening all and evaluating those with red flags . . .

Fox, et al, *British J. of Gen Prac*, 2013

Rx for Healthy Brain Aging



Rx for Healthy Brain Aging

GRECC

- ☐ Engage in exercise* such as walking 30 minutes per day, 3 times per week
  **check with your doctor for activities that are safe for you*
- ☐ Stay mentally active through reading, doing puzzles, volunteer work, etc.
- ☐ Stay socially connected to prevent loneliness and isolation
- ☐ Take medications as prescribed for good control over medical conditions (e.g., diabetes, hypertension, thyroid disorders)
- ☐ Regular checks of vision and hearing; wear glasses and/or hearing aids
- ☐ Improve sleep quality & quantity; maintain a consistent sleep schedule
- ☐ Eat a healthy diet, drink enough fluids, and avoid fast or processed foods
- ☐ Stop or use alcohol in moderation
- ☐ Ask your doctor/pharmacist to review your medications for potential side effects, especially if cognitive problems begin after a med change
- ☐ Seek help from a mental health professional if you experience depression, anxiety, or PTSD symptoms
- ☐ Decrease stress levels/seek help to improve stress management skills

Comments:

IMPORTANT: Talk to your doctor if you experience changes in your memory/thinking skills that do not improve or get worse

VISN 20: Draft Version : Please contact emily.trittschuh@va.gov for permission/reprints

VA

U.S. Department of Veterans Affairs
VA Puget Sound Health Care System

Summary Points

- No such thing as "Dementia Prevention"
- Promotion of Healthy Brain Aging is our top goal
- Top modifiable risk factors include diabetes, vascular disease, excessive alcohol use, smoking
- Keep up to date on how to promote brain health
- Help our patients seek out reliable information and make positive behavioral changes

Dementia Prevention = **Healthy (Brain) Aging**

Thank you!

https://www.nia.nih.gov/health/publication/brain-health-resource

etritt@uw.edu

emily.trittschuh@va.gov