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Dietary Supplements, Caffeine, and Cognitive Aging

Steven T. DeKosky, MD
Visiting Professor, Department of Radiology
University of Pittsburgh School of Medicine

Professor of Neurology and Psychiatry and Behavioral Sciences
University of Virginia School of Medicine
Disclosures

- **Consultant/Advisory Boards:**
  - AstraZeneca, Lilly, Merck, Rivermend

- **Clinical Trials:**
  - Baxter, Elan, Janssen, Novartis, Pfizer
Overview

- Definitions
- Issues of purity, doses, mixtures, toxicity
- Commercial pressures
- Use of supplements by the elderly
- Exemplar studies in cognition
- Caffeine and coffee data
- Observations/Conclusions
Definitions

- Vitamins, minerals, botanicals, enzymes, amino acids, lipids
- Oral administration
- Labeled as being a “dietary supplement”
  - Has the familiar
- Safety data are only required for ingredients marketed after 1994*
- Supplements sold prior to 1994 “presumed safe based on history”
- FDA monitors AEs, label contents, safety

* Dietary Supplement Health and Education Act of 1994
What are typical supplements taken for cognition by the elderly?

- Omega 3 and Omega 6 (essential FAs)
- Green tea and other teas (antioxidants)
- Antioxidants
- Ginkgo biloba
- Vitamins, minerals
Dietary Supplements

- 3 types of claims can be made for supplements
  - Nutrient content: has a nutrient in it
  - Health claim: relationship to risk reduction
  - Structure-function:
    "supports good {brain*} health"

- BUT the last requires the statement:
  "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease."

*Or prostate, lung, gastrointestinal, joint…*
Commercial Aspects

- Immense international market
- >$10 Billion revenue annually
- Many studies funded by industry
- Most cognitive studies negative
- Positive aspects publicized
- Examples: Vitamin E, Vitamin D, Ginkgo, omega (fish) oils, plant extracts from various sources (Okinawa diet)
Methodological Issues

- What is the time frame for results? acute, subacute, chronic (longitudinal)?
- Midlife vs. late life administration
- Retrospective vs. prospective study
- Adequacy of data re intake/compliance
- Memory for supplement intake, e.g., in mid-life
Frequency of Supplement Use by Normal Elderly

- In GEM Study, at entry 74% of normal subjects were using at least one Rx drug and one dietary supplement
- 32.5% used 3 or more Rx drugs and 3 or more supplements
- N > 3000 Ss, from 4 different locations in US; no regional differences
BLAS: baseline & ~2 year follow-up

- Data from 7 day food diaries
- “Putative beneficial effects of caffeine intake and nutrient adequacy on domains of global cognition, verbal memory, and attention”
- Caffeine intake was associated with better baseline global cognition among participants with a baseline > age 70 years

Beydoun et al. J Nutrition 2014
Honolulu Asia Aging Study: Coffee Intake in Midlife

- Coffee and caffeine intake in *midlife* not associated with
  - cognitive impairment
  - dementia
  - neuropathologic lesions at autopsy

- Higher caffeine intake associated with a lower odds of having any of the lesion types at autopsy.

Women’s Antioxidant Cardiovascular Study (France)

- n = 2400; antioxidants, vitamin B supplements
- Caffeine intake assessed at baseline (1995-96) then assessments every 2 years
- Slower cognitive decline found over 5 years
- In caffeinated coffee drinkers but not in other caffeinated products
- Positive interaction with vitamin B suppl.
  Vercambre et al., J Alz Dis, 2013
### Caffeine Effects on Cognitive Decline in Aging

![Graph showing relative risk estimates for caffeine consumption categories.](image)

**Caffeine**
- (14) (F) 22-62 vs <22
- (14) (F) >62 vs <22
- (14) (F) ≥ 75 vs <75
- (14) (M) 22-62 vs <22
- (14) (M) >62 vs <22
- (14) (M) ≥ 75 vs <75
- (13) (F) 1-2 vs 0
- (13) (F) 2-3 vs 0
- (13) (F) >3 vs 0
- (13) (M) 1-2 vs 0
- (13) (M) 2-3 vs 0
- (13) (M) >3 vs 0

**Coffee**
- (8) (M,o) occasionally vs rarely
- (8) (M,o) ≥ 250 mL/day vs rarely
- (8) (F,o) occasionally vs rarely
- (8) (F,o) ≥ 250 mL/day vs rarely
- (8) (F,t) Low
- (8) (F,t) Med
- (8) (F,t) High
- (8) (M,t) Low
- (8) (M,t) Med
- (8) (M,t) High

**Tea**
- (8) (F) occasionally vs rarely
- (8) (F) ≥ 250 mL/day vs rarely
- (8) (M) occasionally vs rarely
- (8) (M) ≥ 250 mL/day vs rarely

Arab et al. 2013
Summary of Caffeine Effects

- Possible protective role (preserving cognition) especially in older women
- Wide variety of methodologies in the studies
- No dose-response relationship found
- Suggests some other factor may influence
- Polyphenols in coffee?
- Toxicity largely GI upset, sleep disruption
- Statistical significance not clearly clinically significant
Observations

- Retrospective studies do not show significant effects on altering trajectories of cognitive decline.
- Longer term DBPC trials are not common in field.
- Industry sponsored trials are numerous but associated frequently with small N, short duration.
- Structure-function assertions have appealing logic.
- Marketing of supplements is significant.
- Trials are not simple, & are frequently expensive.
Ginkgo in Evaluation of Memory (GEM) Study

- DBPC randomized trial of 120mg Ginkgo biloba (EGb761) twice daily
- Age =/> 75
- Ss assessed to have normal cognition or mild impairment
- Incidence rate estimate provided by NIH in the RFA
- Study powered to show a 30% decline in incident dementia/AD
- Primary outcome: effect on dementia incidence
- Secondary outcome: effect on decline in cognition in aging
- Funded by NCCAM, NIA, NHLBI, NINDS
  - Drug and placebo provided by Schwabe Pharmaceuticals
Incidence rate of dementia did not rise to 3% per year until year 4.
Study had to be renewed to reach the necessary N for statistical significance.
No effect of Ginkgo on incidence of dementia
DeKosky et al., JAMA, 2008

No effect of Ginkgo on decline in cognition in normal aging
Snitz et al., JAMA 2009
Summary

- Coffee consumption, but perhaps not other sources of caffeine, are associated with preservation of cognition in elderly women
- Ginkgo biloba initiated at age 75 does not mitigate age-associated cognitive decline
- Multiple other studies show variable results, although methodological issues render them less reliable
Final Thoughts

- Non-invasive biomarkers are now available to determine preclinical disease in elderly
  - MRI
  - Molecular Pathology PET Scans (amyloid, tau)
  - Identify mid-life or elderly with no evidence of two of the major cognitive diseases of late life
  - Genetics (e.g., APOE) and peripheral blood markers of risk can aid in defining low disease risk group

- This screened population represents a valuable group for studies of (relatively) enriched cognitive aging subjects
Change in Amyloid Imaging (PiB) in a Cognitively Normal Control over 2 Years