

Evaluation of the Strength of Evidence for Supplementation Use for Healthy Cognitive Function

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A. The Cognitive Continuum

Peterson et al. (1996)

Normal Aging (Successful Aging),
Age-Associated Memory Impairment (AAMI)

Mild Cognitive Impairment (MCI)

Dementia/Alzheimer's

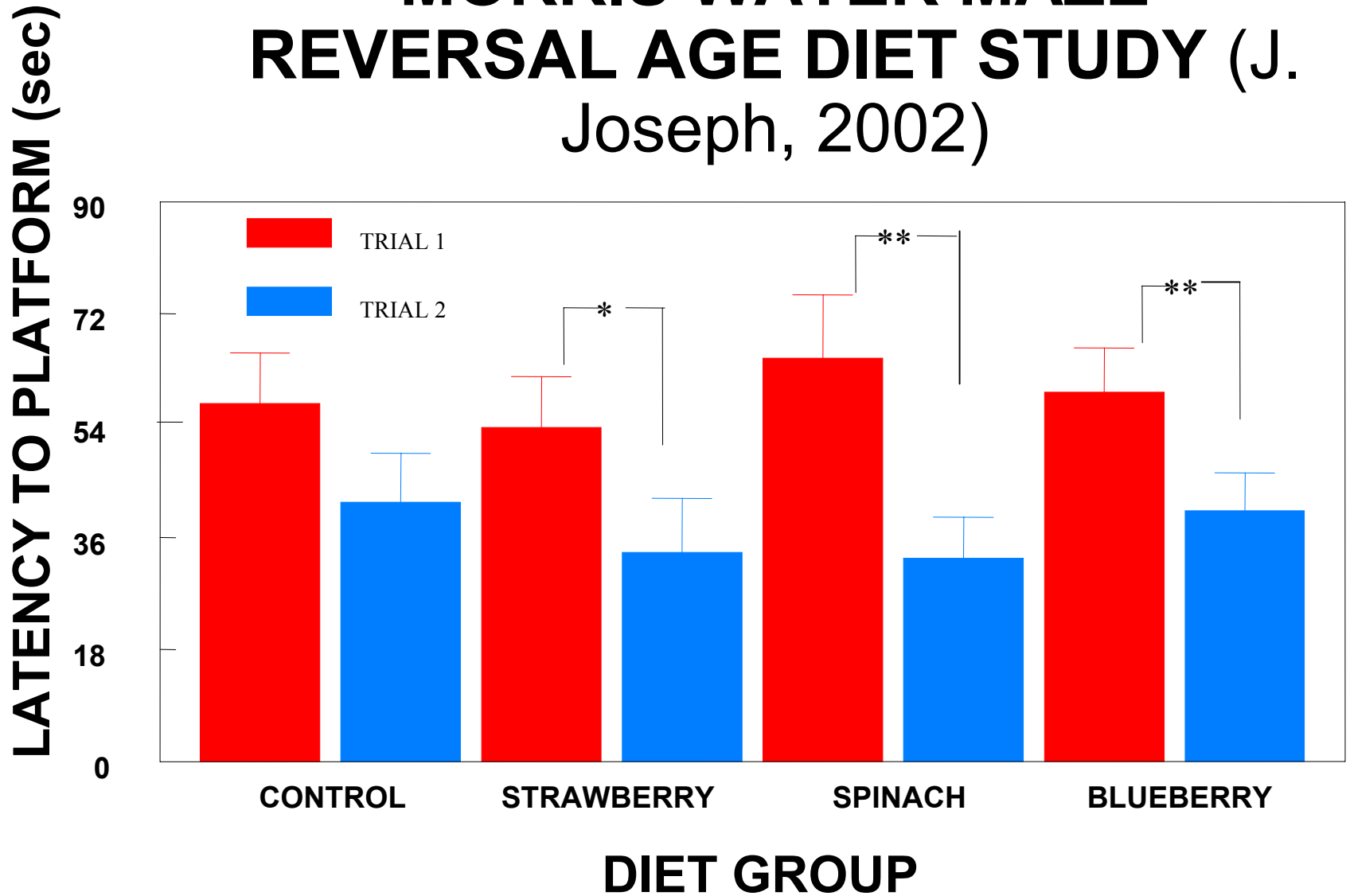
Dietary Supplements/variables

- Antioxidants
- Ginkgo
- Folate, B6, B12, homocysteine
- Cholesterol intake and statins
- Fatty acids
- (anti-inflammatory agents, estrogen)

Oxidative Damage and Brain Aging

- Aged animals and people accumulate oxidative damage to lipids, proteins and nucleic acids
- Antioxidant treatments in rodents can “reverse” the decline in learning and motor function, e.g., Vit. E, lipoic acid and ALCAR, PBN, blueberry extracts, etc.

MORRIS WATER MAZE REVERSAL AGE DIET STUDY (J. Joseph, 2002)



Observational Studies of the Effect of Antioxidant Intake on the Risk of Dementia and Alzheimer's Disease

Intake

Morris (2002)

vit E 3rd Q

vit E 4th Q

vit E 5th Q

vit C 3rd Q

vit C 4th Q

vit C 5th Q

Engelhart (2002)

vit E

vit C

Corrada (2002)

vit E 3rd Q

vit E 2nd Q

vit E 1st Q

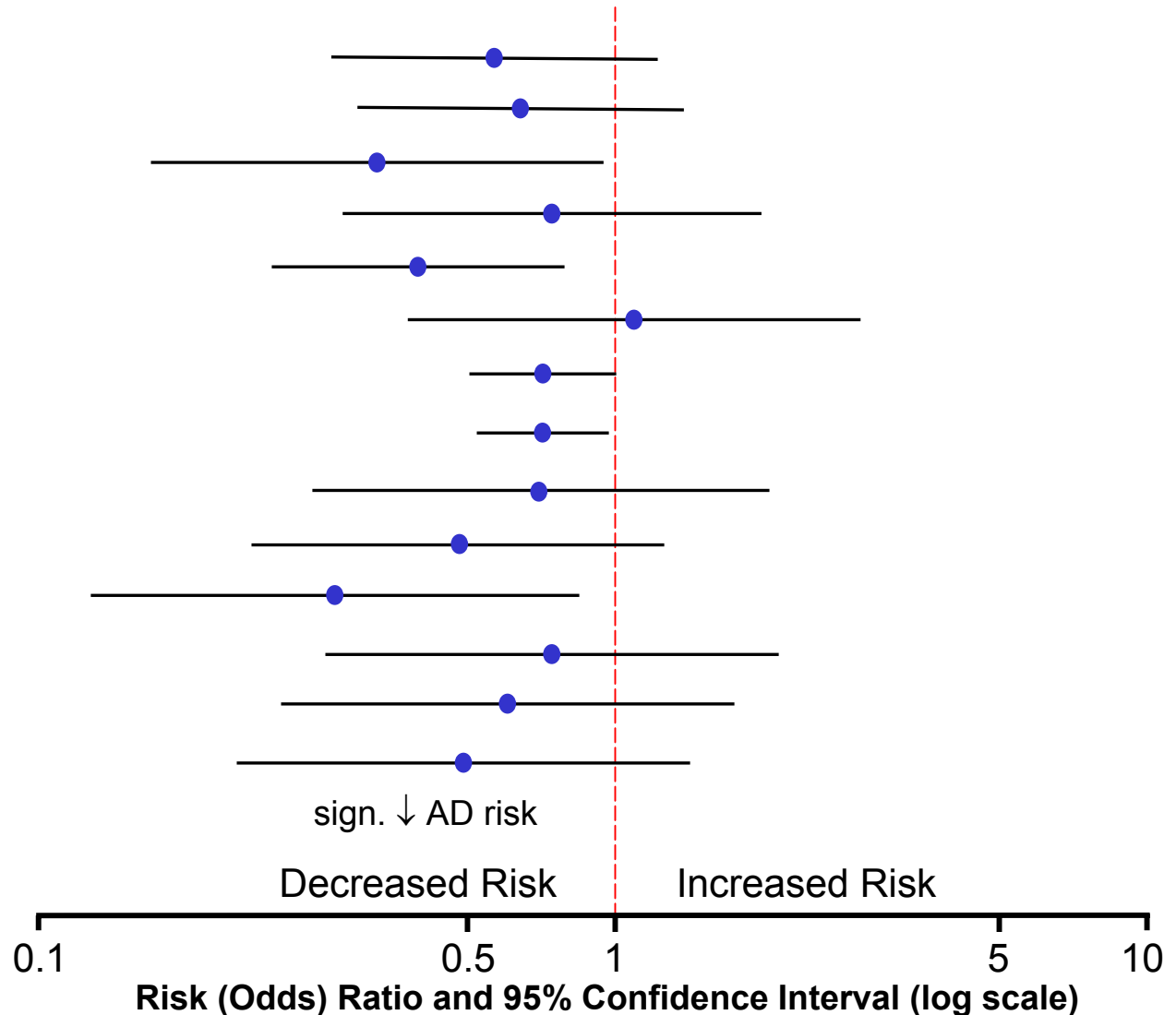
vit C 3rd Q

vit C 2nd Q

vit C 1st Q

Ortega

vit E



vit = Vitamin
 Q = quartile
 sign. = Significant

Observational Studies of the Effect of Antioxidant Supplement Use on the Risk of Dementia and Alzheimer's Disease

Supplement

Morris (1998)

vit E

sign. ↓ AD risk

vit C

non sign. ↓ AD risk

Masaki (2000)

vit E or C

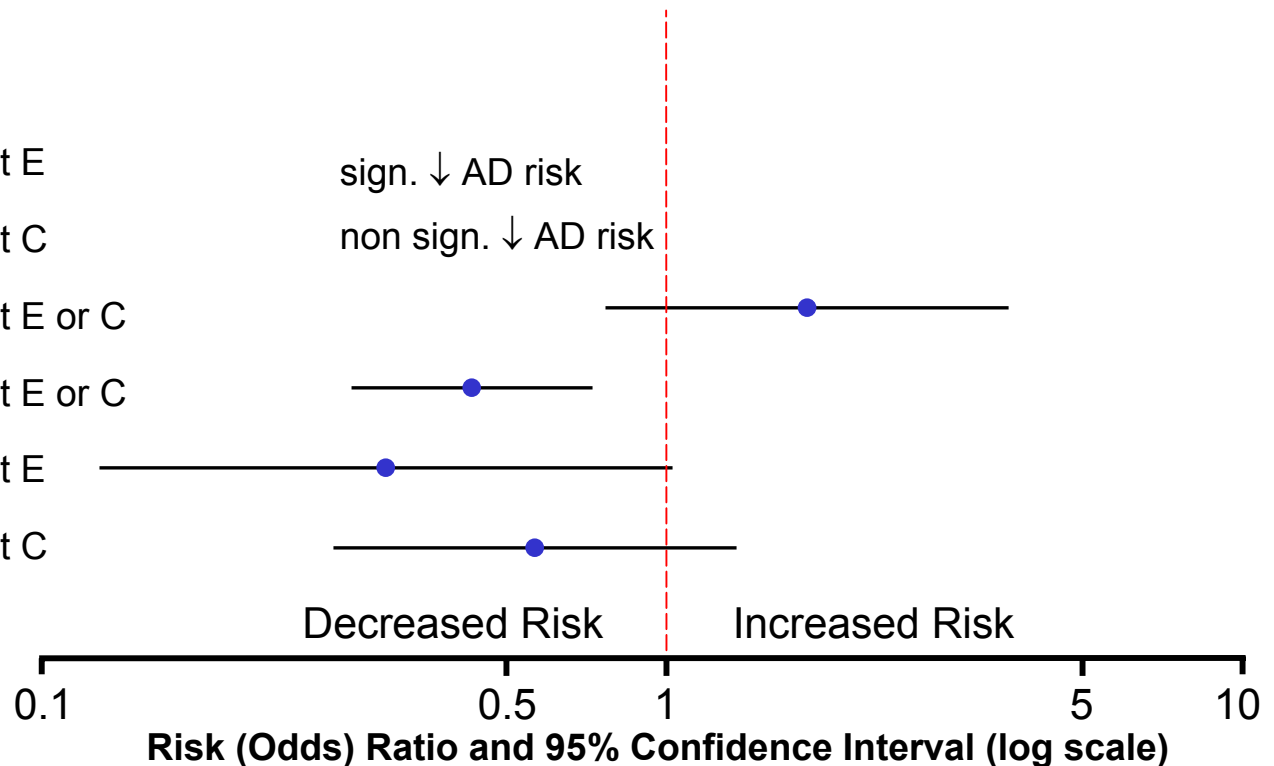
Grundman (2001)

vit E or C

Zandi (2002)

vit E

vit C



vit = Vitamin
sign. = Significant

Cognitive Function and Serum Vitamin E Status*

Pfeiffer Mental Status Questionnaire

No Errors

Some Errors

Vitamin E

Men

19.7 ± 8.6 μmol/l

15.1 ± 5.6 μmol/l

Women

20.8 ± 8.4 μmol/l

14.9 ± 6.1 μmol/l

Vitamin E / Cholesterol

Men

3.5 ± 2.0 μmol/l

2.4 ± 20.8 μmol/l

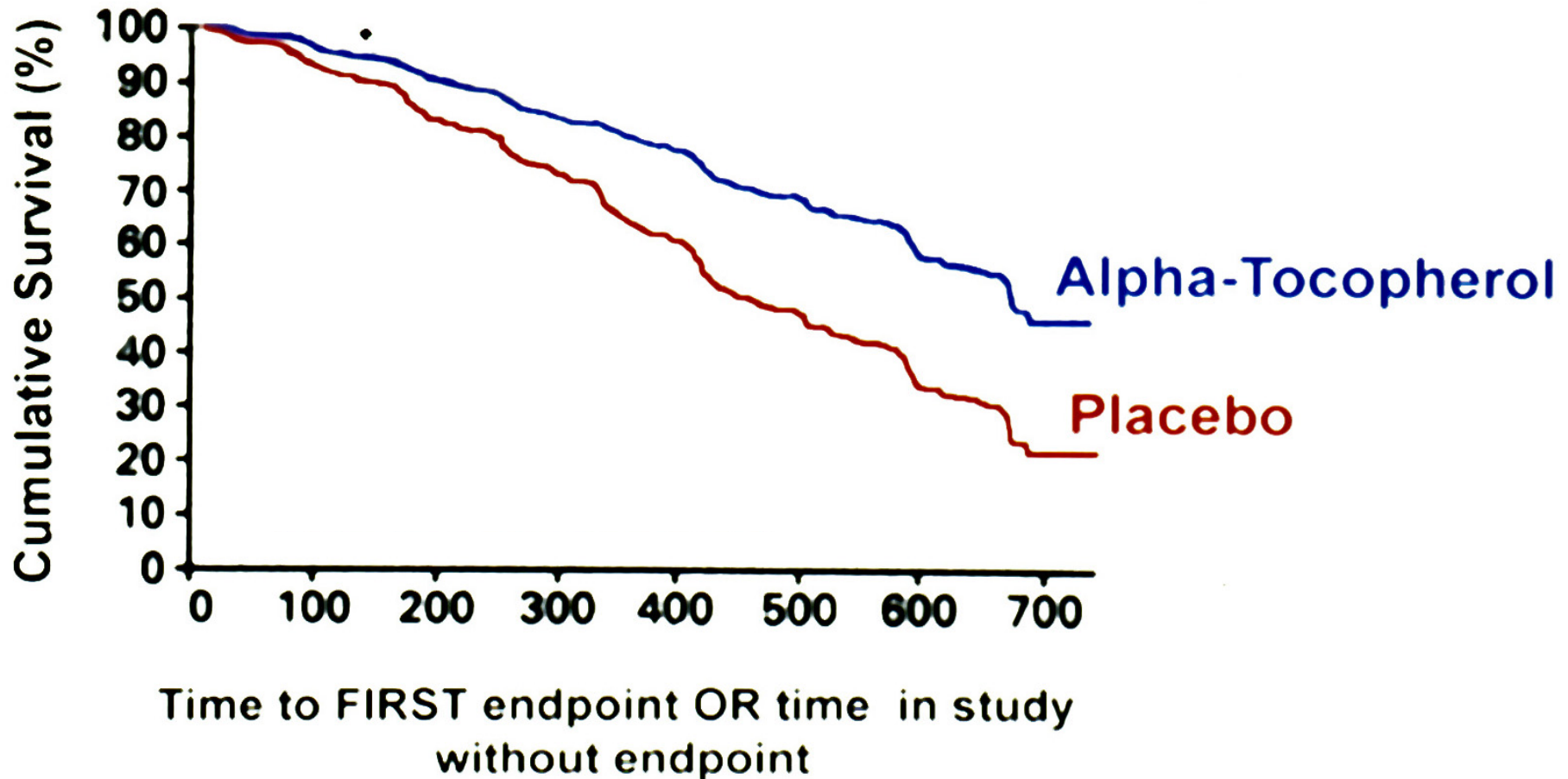
Women

2.9 ± 1.4 μmol/l

2.3 ± 1.3 μmol/l

Cox Survival Functions – ITT By Treatment Arm

Covariate: Baseline Mini Mental State Exam (Sano, 1997)



Challenges

- Studies to date are descriptive except for Vit. E in AD.
- Foods rich in antioxidants are also enriched in other dietary components that may be beneficial.
- Supplement doses, form unclear, eg., d.l vs. d vit E
- Peripheral markers may not reflect brain state, e.g., plasma Vit E/chol.
- Supplements may not be as effective as diet and it is likely combinations of antiox. are needed
- Life style is not taken into account
- Animal studies may help, particularly on higher mammals.

Canine (Dog) Aging and Cognition

Exhibit age-associated cognitive decline similar to humans, e.g., capable of complex learning tasks

Exhibit similar neuropathology to humans, e.g., β -amyloid, oxidative stress

Share many environmental conditions and the genome is similar to humans.

Protocol and Data Collection



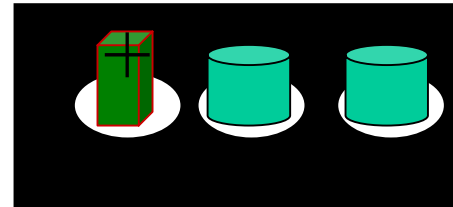
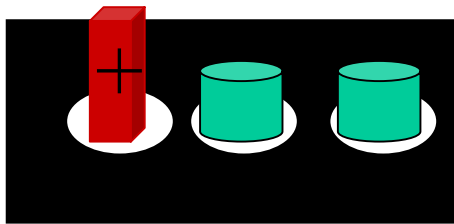
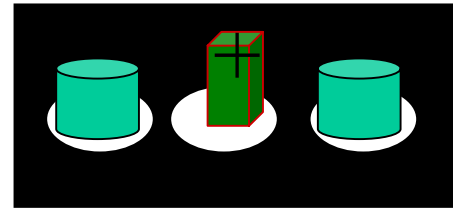
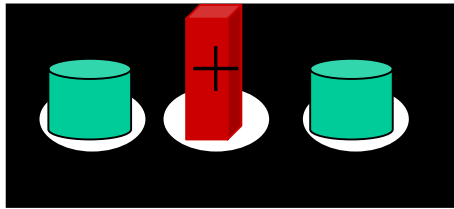
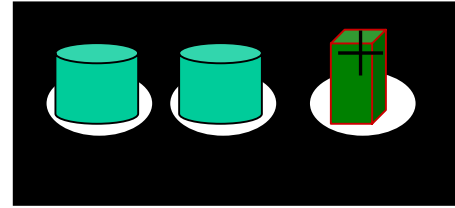
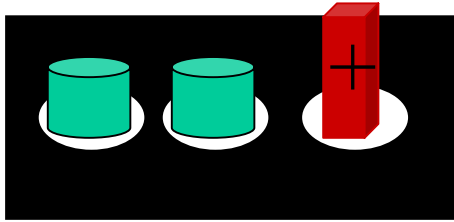
Dietary rationale

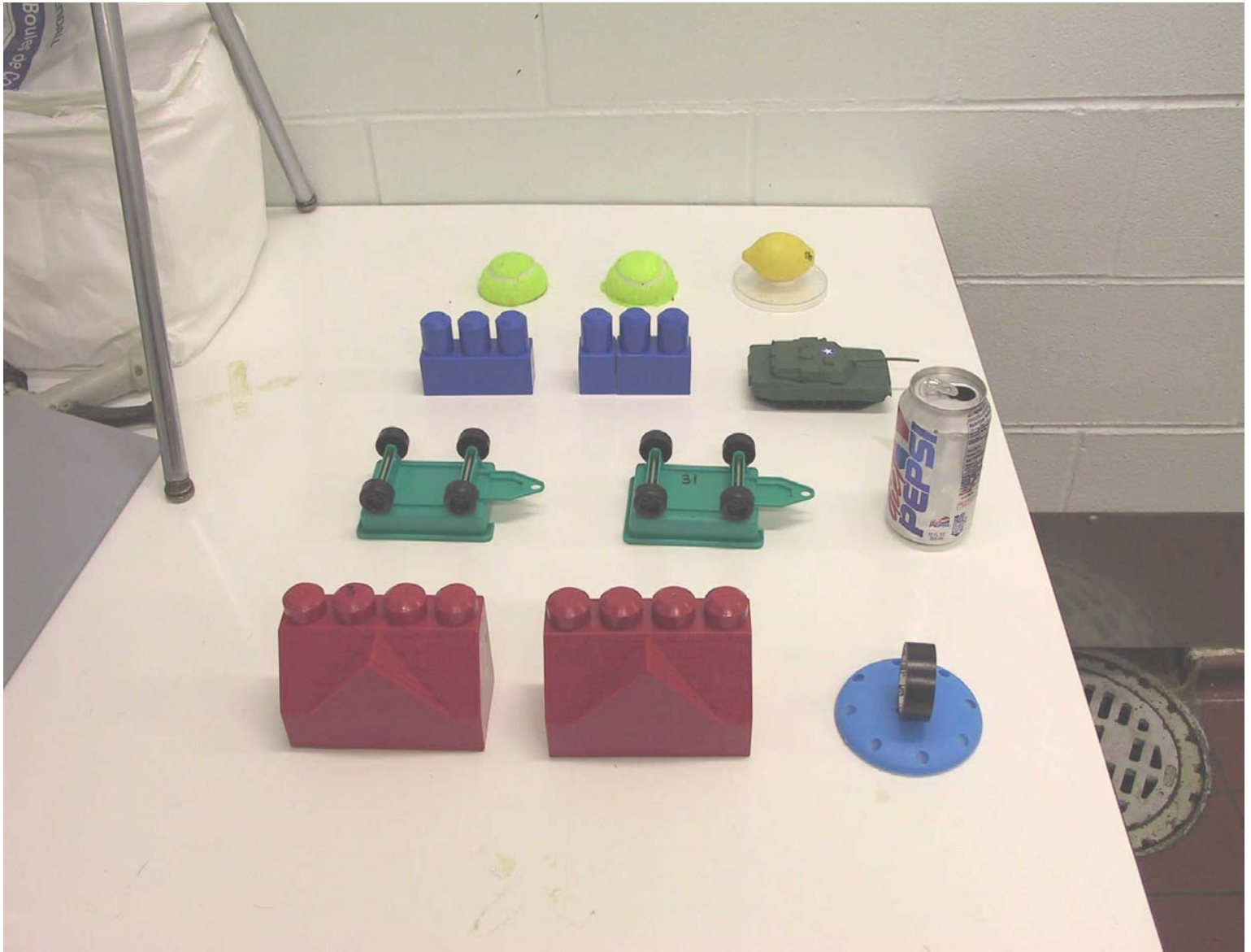
Intervention with antioxidants may slow or reverse changes associated with mental aging

- **Vitamin E slowed progression of Alzheimer's in people** (Sano 1997)
- **Carnitine and lipoic acid improved mitochondrial health and impairments in old rats** (Hagen 1999; McC
- **Blueberry extract reversed aged rat learning disabilities** (Joseph 1999)
- **High intake of fruits/veg. decrease dementia risk by 19%** (Engelhart 2000)



Oddity Task

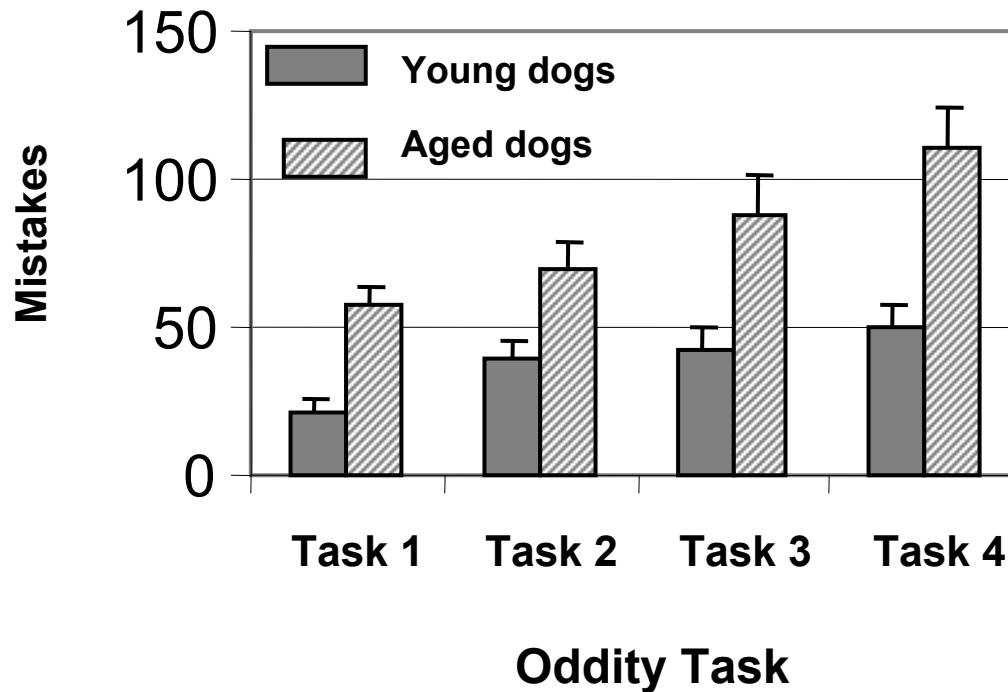




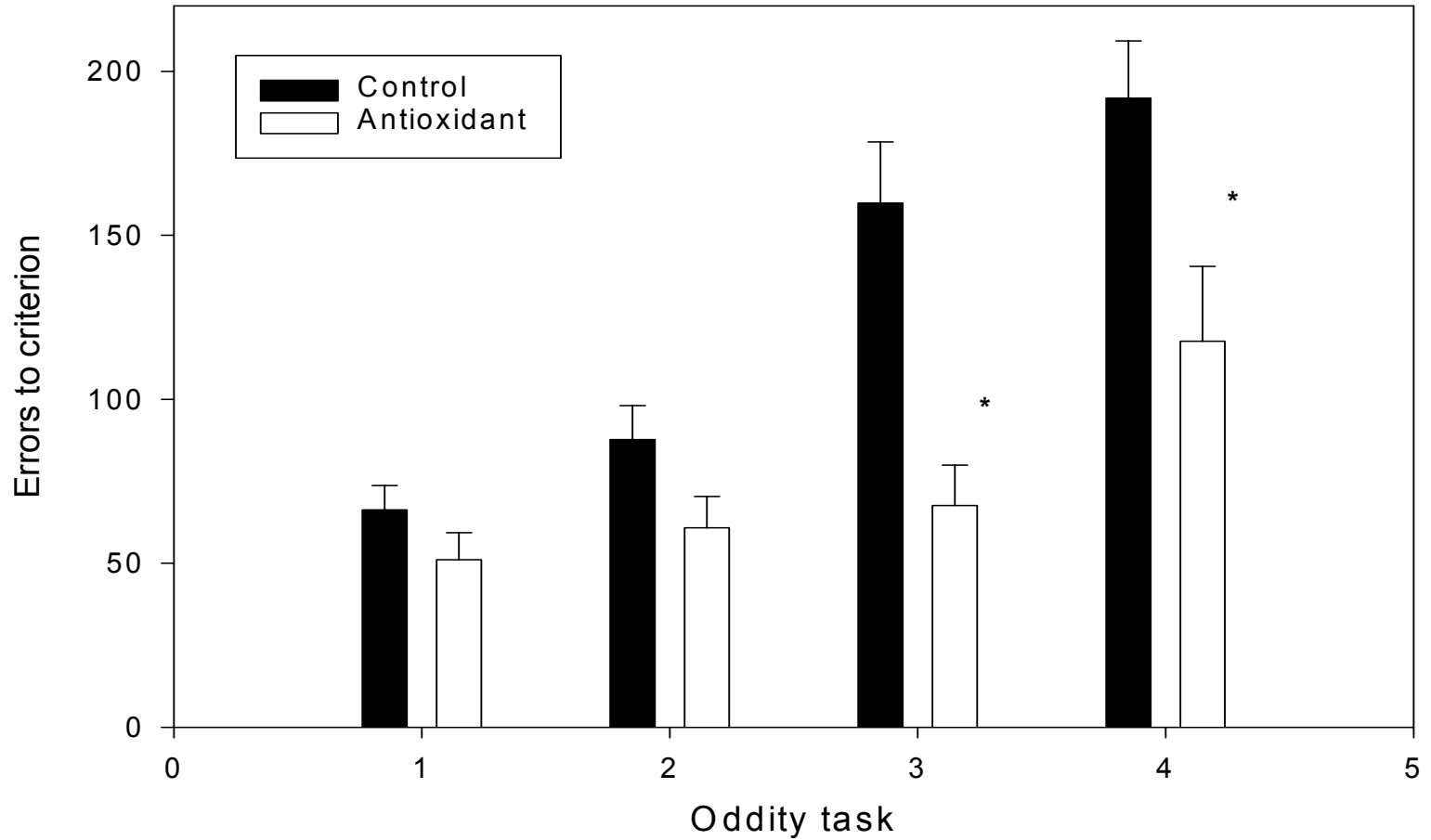
6 months

Dog Aging and Cognition Project

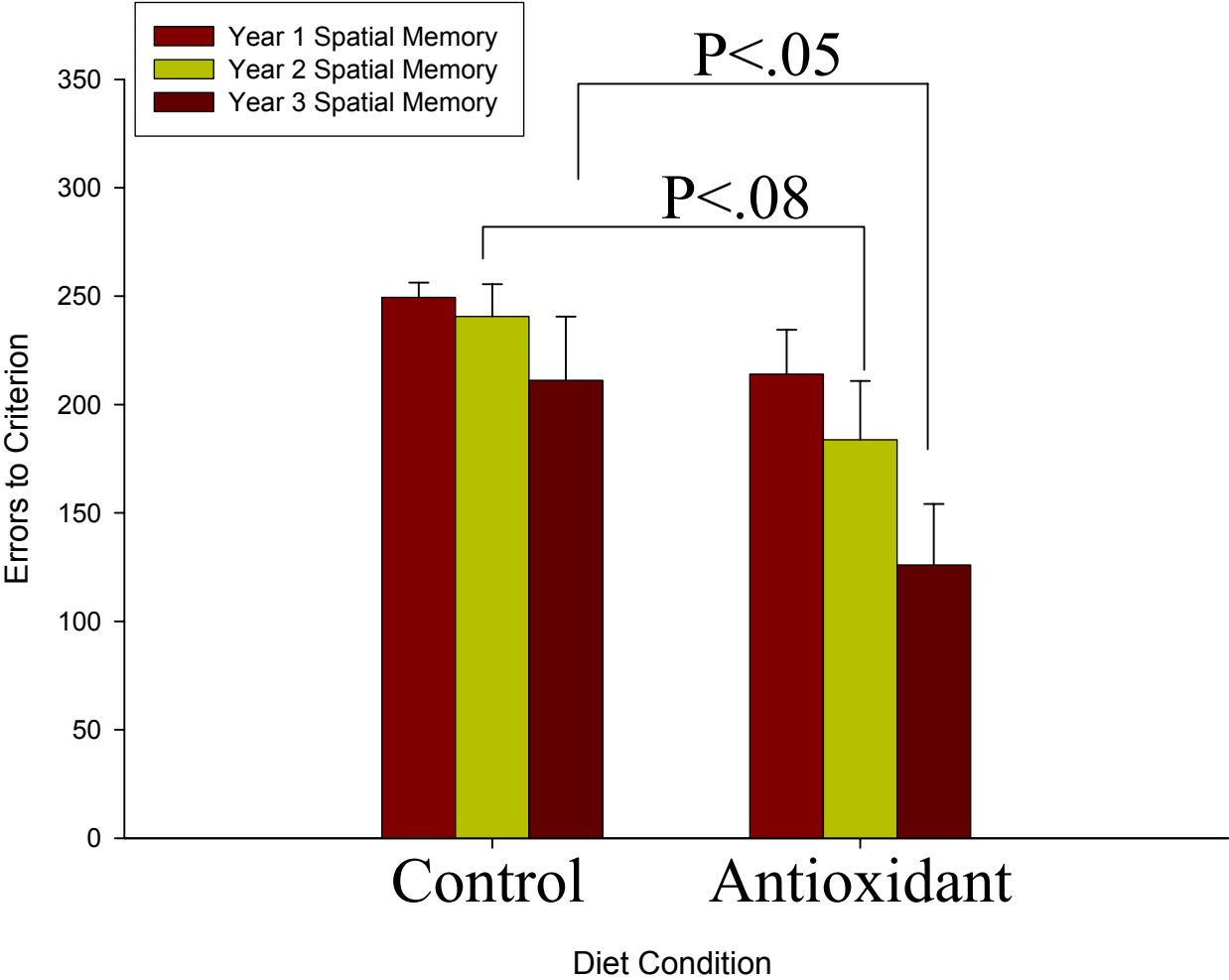
Oddity testing in young and aged dogs

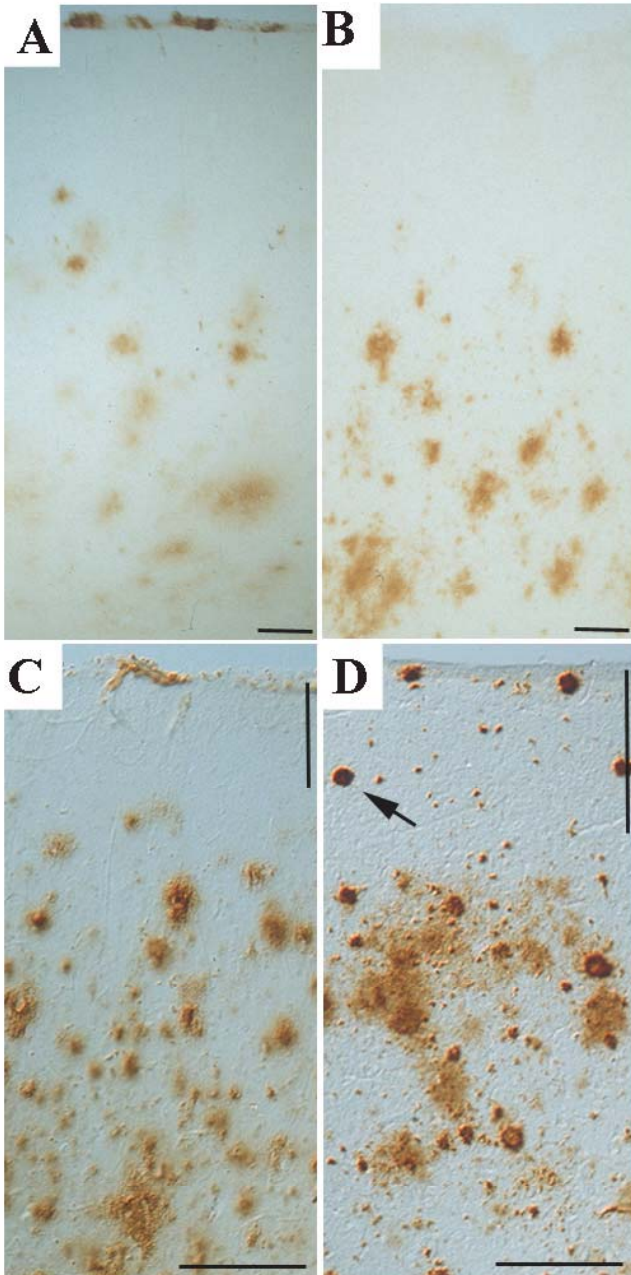


Effect of diet on oddity discrimination in aged beagles



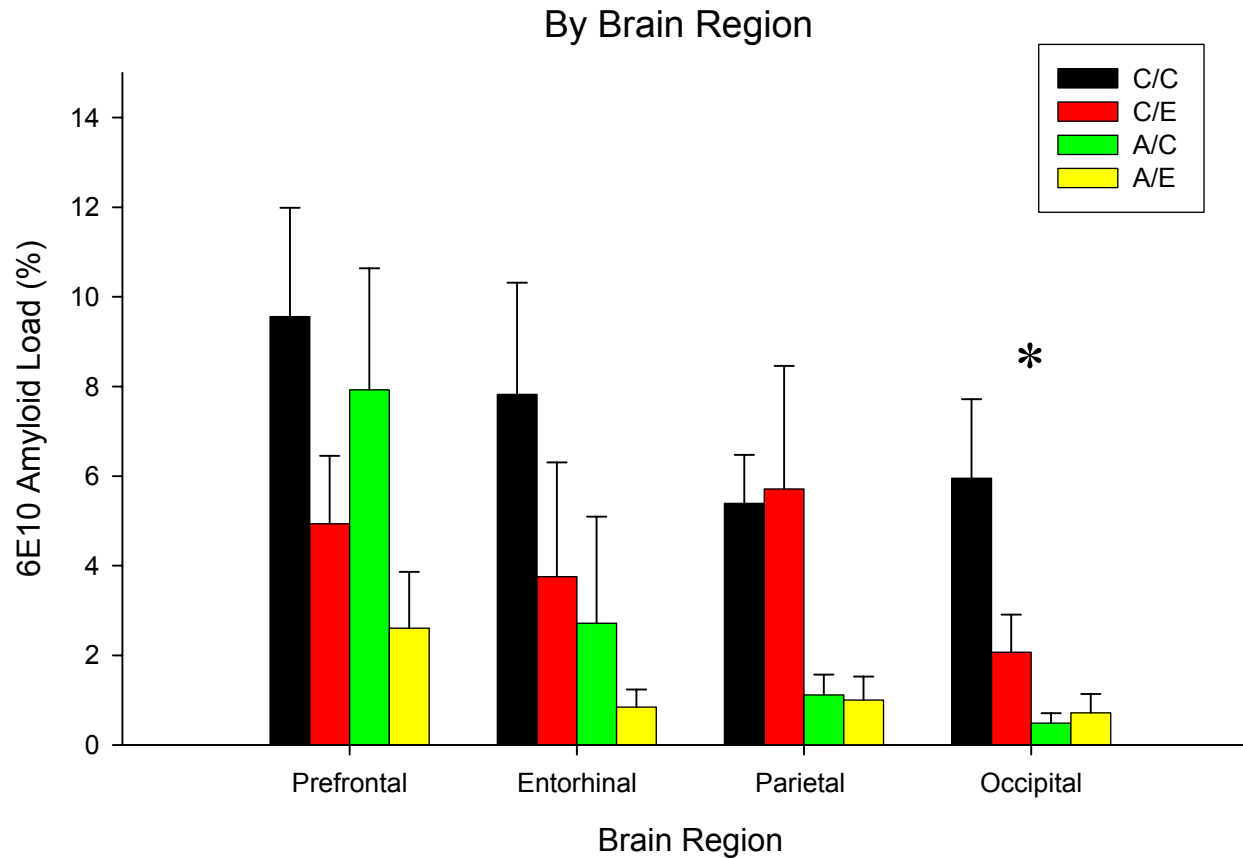
Spatial Memory and Antioxidant Diet





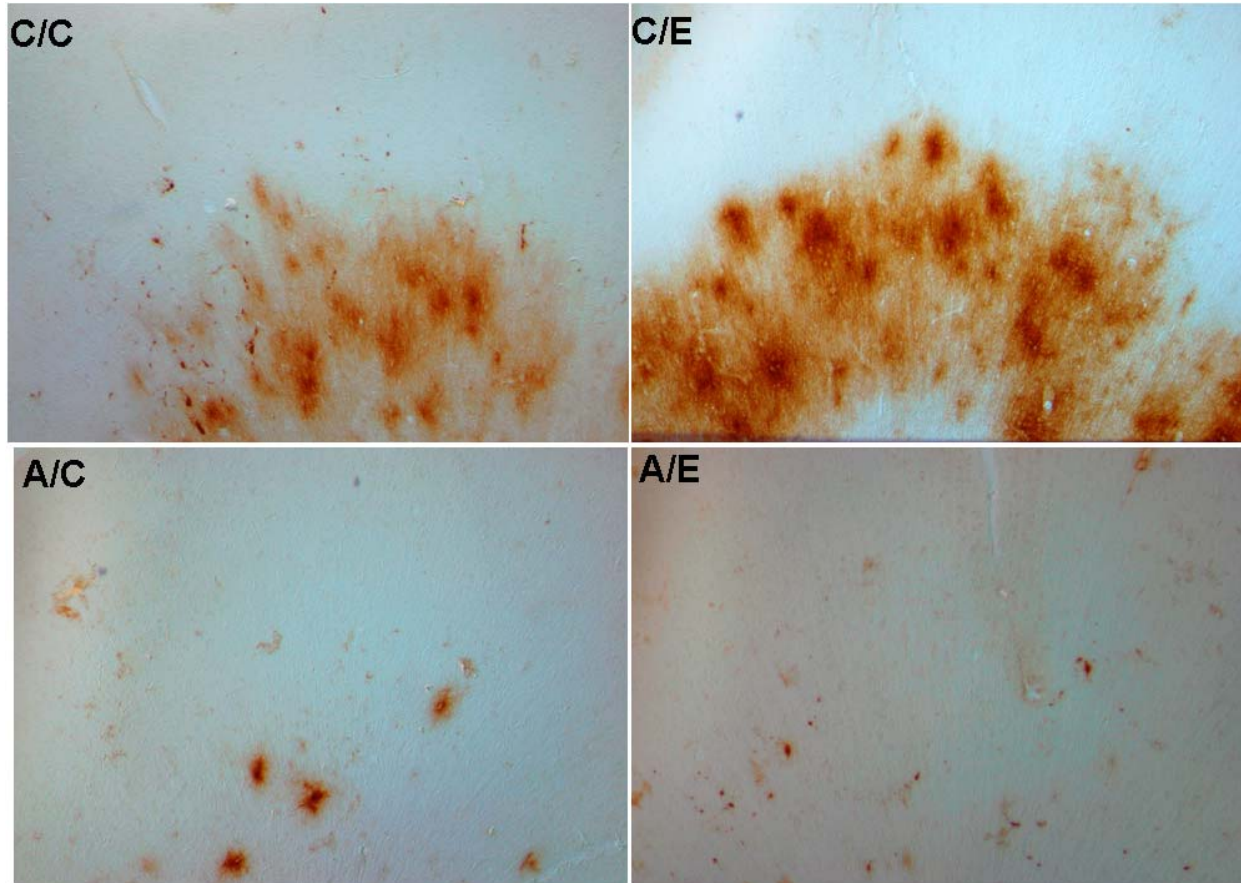
Plaque Accumulation in
Unimpaired and Impaired
Dogs: Comparison with
Normal Elderly and
Alzheimer's disease
Human Brain

Effect of Treatment on Total Amyloid Load (6E10)



*Includes archival data

Beta-amyloid in Canines after A/E treatments

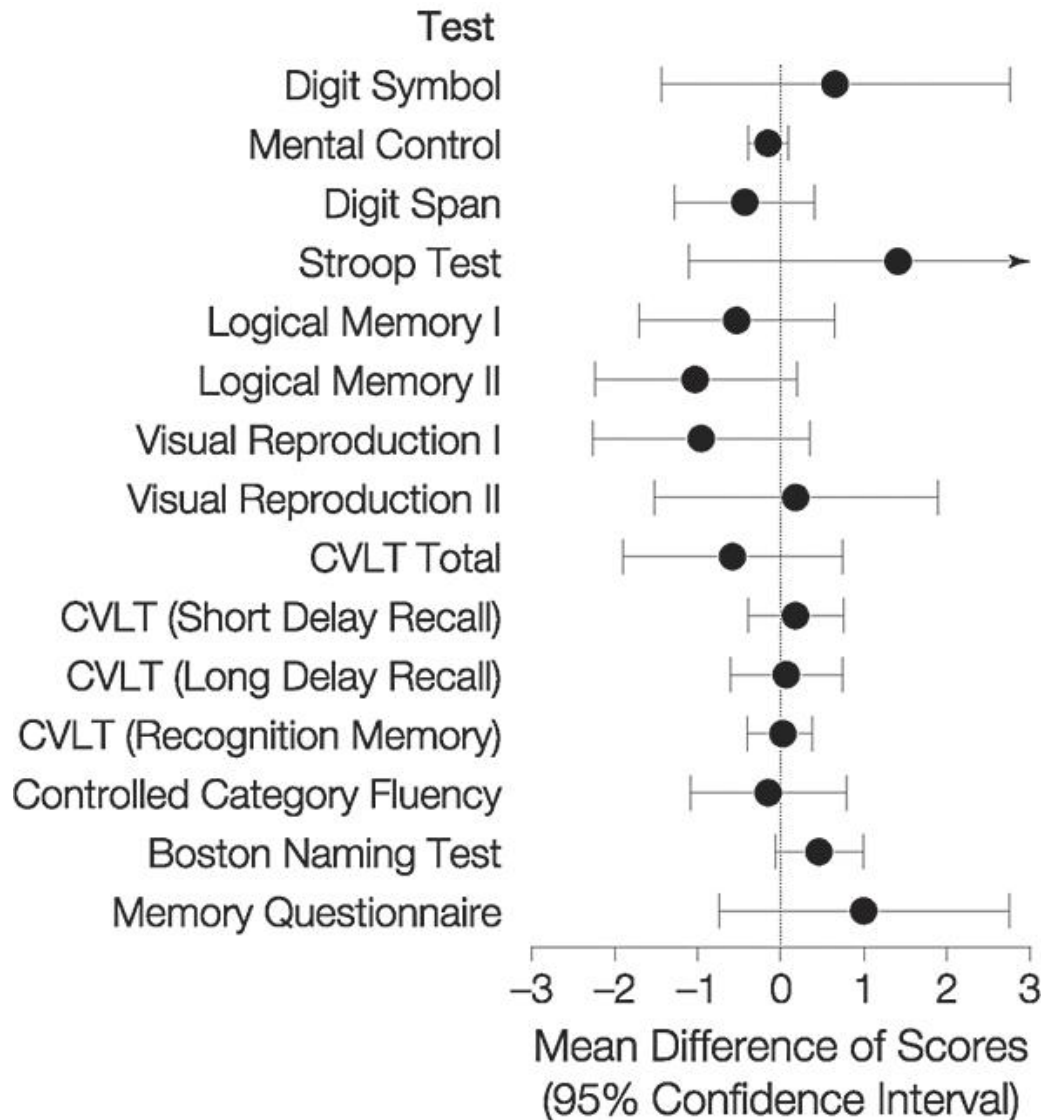


Ginkgo

- Widely prescribed and used
- Over 50 report showing effects on one or more measures of cognitive function
- No effect on healthy non-demented subjects (n=230, 6months) (*Solomon, JAMA, 2002*)
- Dementia patients (n=202) treated with ginkgo show 0.1 decline on ADAS-Cog vs. 1.48 in placebo. No subjective differences reported by family or physicians (*LeBars, JAMA, 1997*)

Ginkgo for Memory Enhancement

A Randomized Controlled Trial



Homocysteine; folate, B6,12
and the decline in cognitive
function

High homocysteine increases risk for neuronal damage

- Increases neuronal DNA damage
- Sensitizes neurons to oxidative damage and degeneration
- Folate, B6, B12 protect in animal models, eg., AD mouse.

High Homocysteine and Low Folate and Vitamin B12 as a Risk Factor for Cognitive Decline (AD)

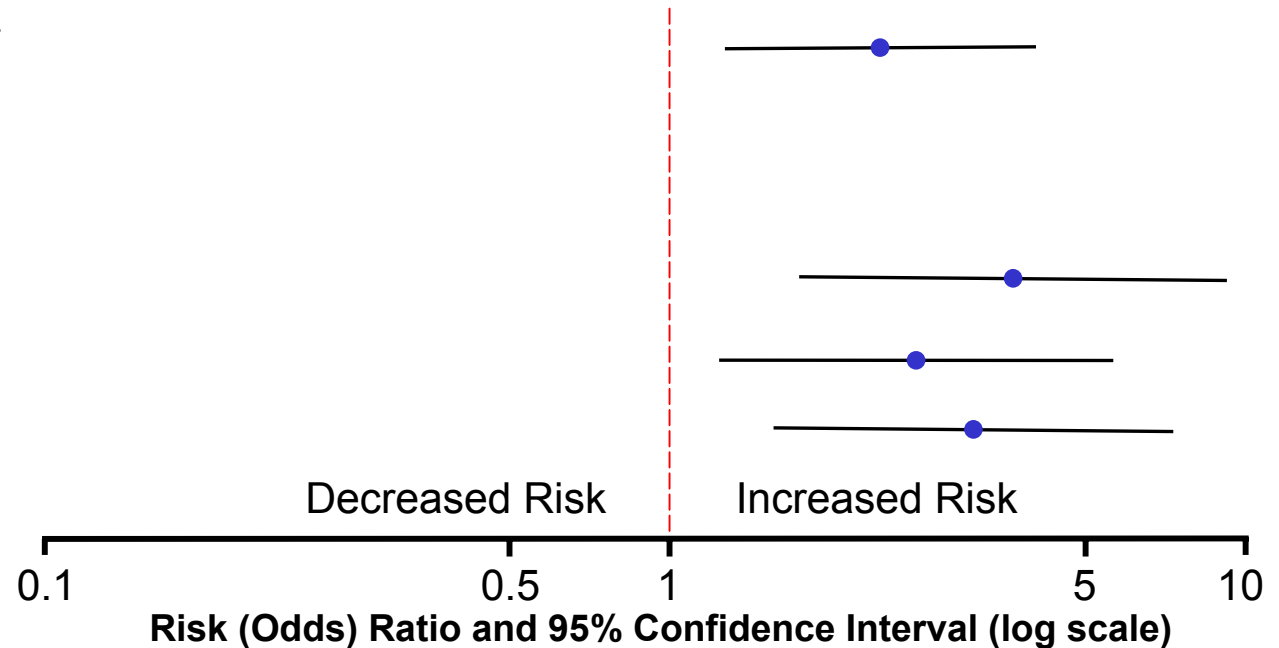
Seshadri (2002)*

Clarke (1998)**

Homocysteine

Folate

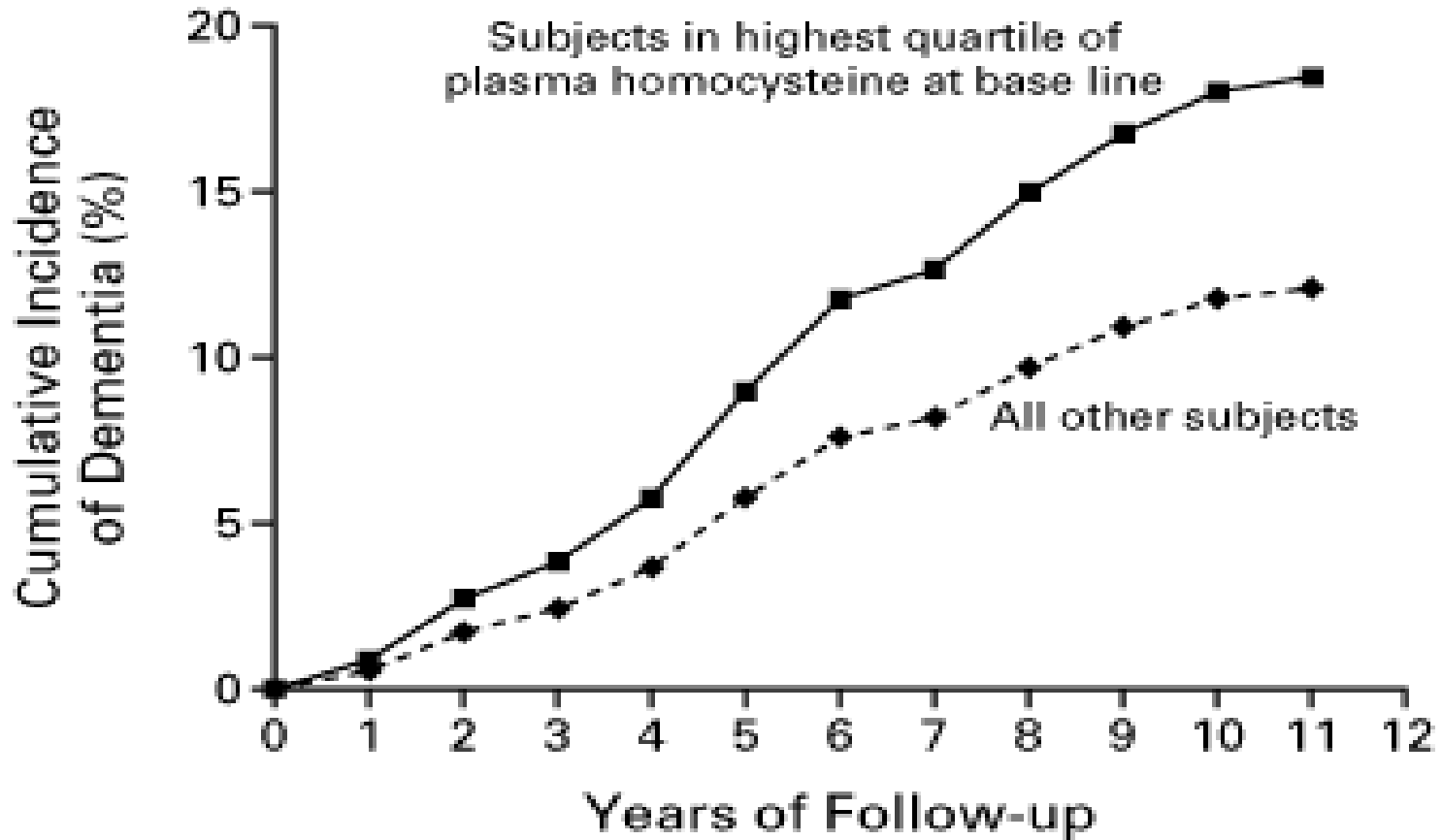
B12



*An increase in plasma homocysteine levels of 5 $\mu\text{mol/l}$ increases risk by 40%

**Radiologic evidence of AD also greater in those with high homocysteine at entry

Incidence of Dementia among subjects with HC in highest quartile (Seshadri, NJM,2002)



Fatty acids and dementia

- Animal studies indicate that select fatty acid improve learning and memory in rats
- Human studies are unclear as to whether or not high total fat, sat. and trans fat and low mono and polyunsat and unsat. fatty acids protect
- Cholesterol - probably

Fatty Acids and Dementia, The Rotterdam Study (2002)

- Total fat 0.93 (95% CI 0.79-1.05)
- Sat. fat 0.91 (95% CI 0.91-1.10)
- n-3 polyunsat 1.07 (95% CI 0.94- 1.07)

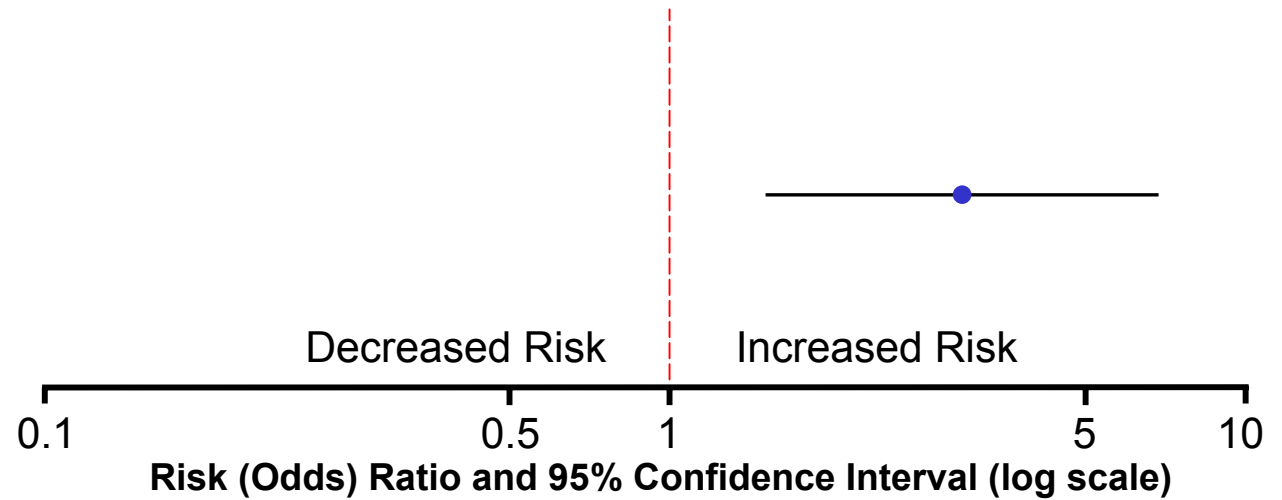
When corrected for age, education, total energy intake and Vit. E

Clinical trial suggests improvement possible

- Supplementation with essential fatty acids in AD patients (n=100) was reported to improve quality of life and short term memory (Yehuda, 1996)

High Serum Cholesterol is a Risk Factor for Alzheimer's Disease

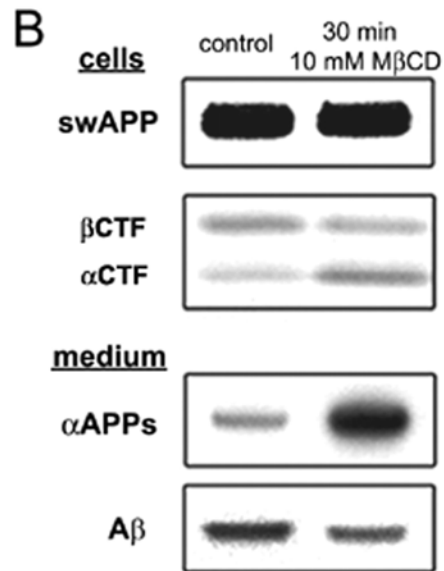
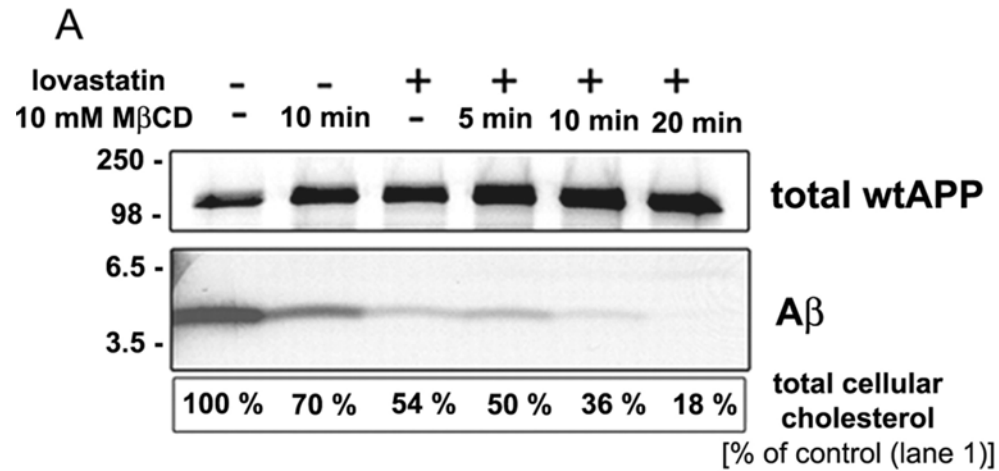
Notkola (1998)



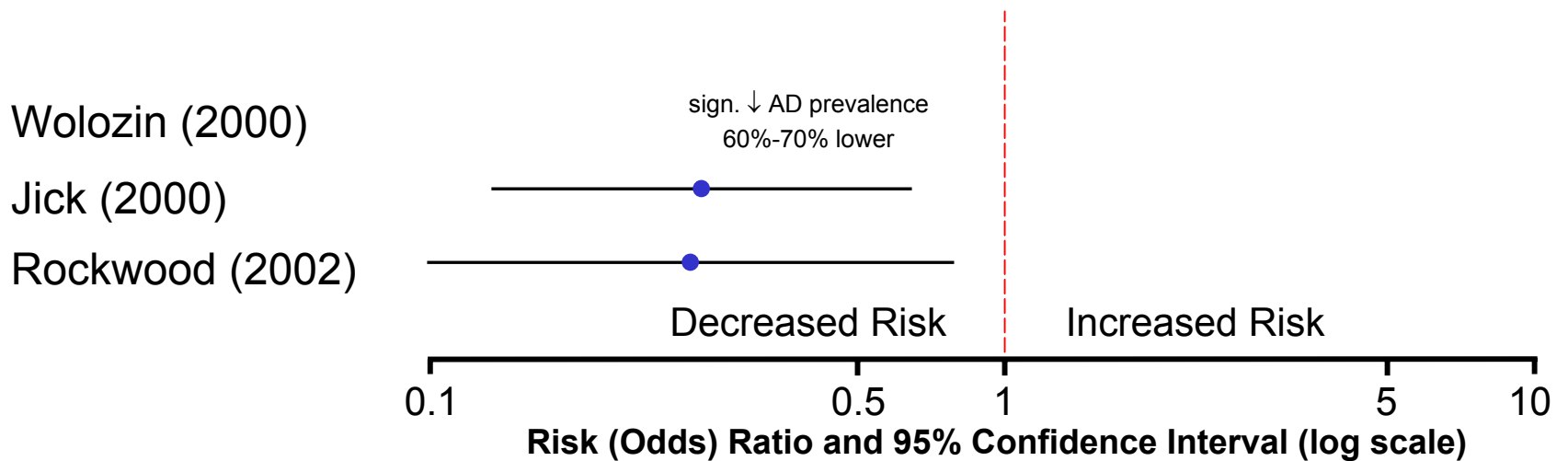
Cholesterol lowering drugs

- Statins delay onset of dementia, e.g., levostatin
- Reduce B-amyloid in rodent models

Cholesterol Depletion Inhibits Beta Amyloid Cleavage



Observational Studies of the Effect of Statin Use on the Risk of Dementia and Alzheimer's Disease



sign. = Significant

Conclusions

- Select antioxidants; folate/B6,12; cholesterol lowering strategies may provide benefit
- Animal data are strong for all 3
- Human studies to date are descriptive though trials are ongoing
- Ginkgo data are unclear but a primary prevention trial for AD is ongoing
- Cognitive measures need to be challenging, graded for endpoints other than dementia
- Environmental enrichment and lifestyle interact with diet and are not taken into account

Methodology

- Larger populations?
- Better mechanistic-based cognitive tests
- Informatics approaches to facilitate data collection and more data points
- Biomarkers as pre-endpoints

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