Effect of Caloric Restriction on Brain Health: Humans

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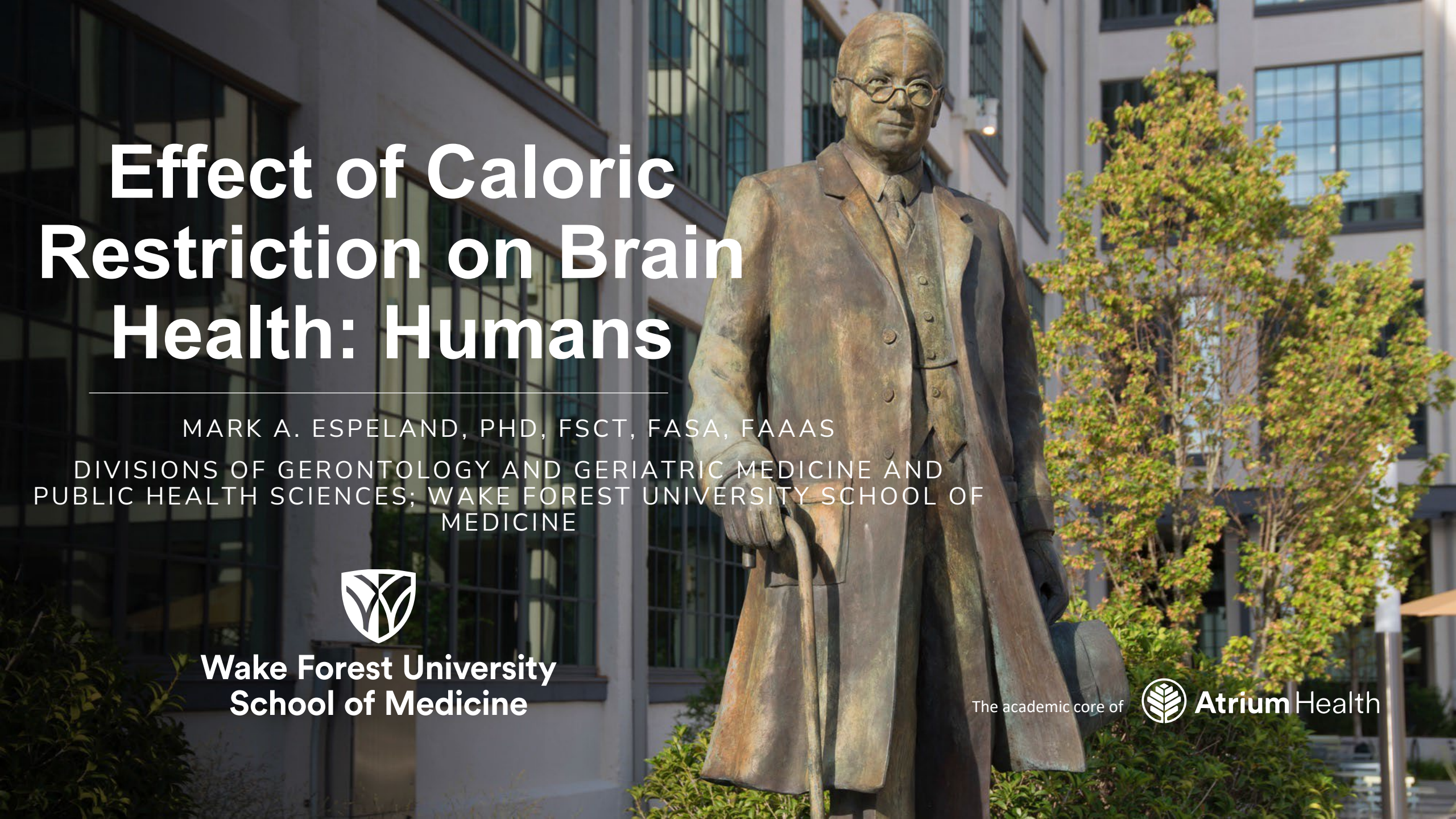


Wake Forest University School of Medicine

The academic core of Atrium Health

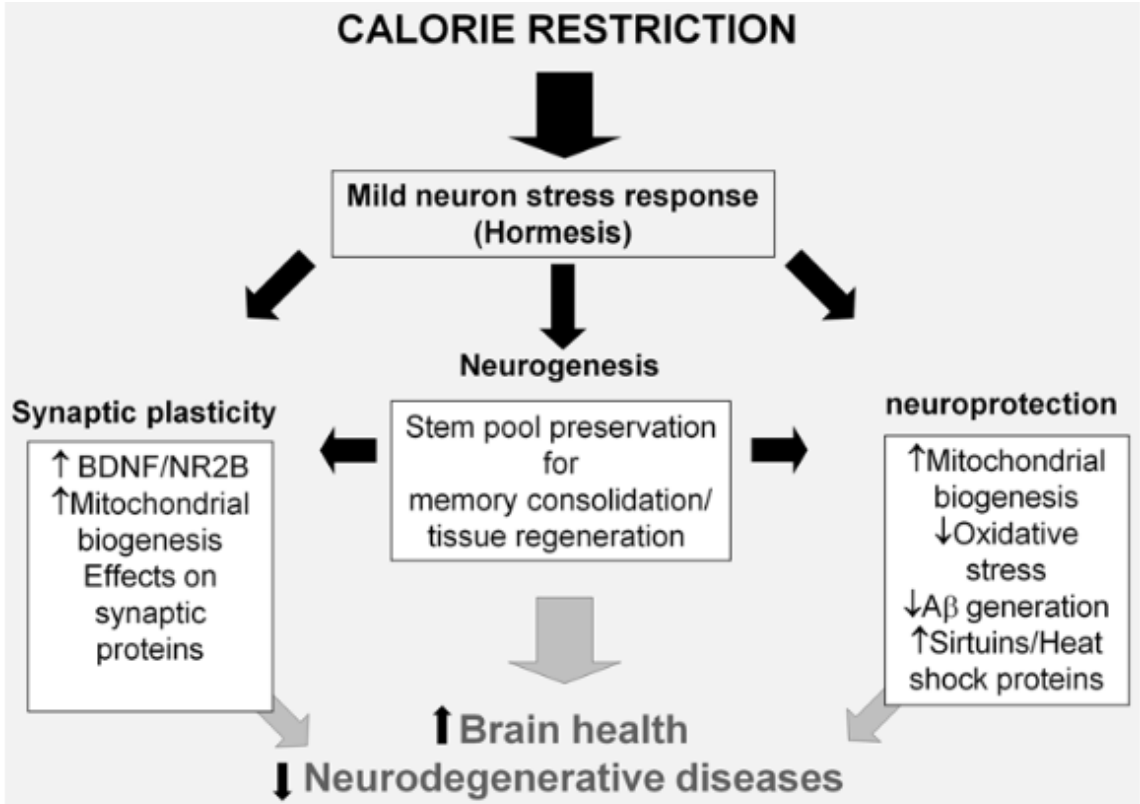
Disclosures

Industry

- Nestle
- Annovis Bio
- Acumen Pharmaceuticals

Other funding

- NIH
- Alzheimer’s Association
- Alzheimer’s Clinical Trial Consortium



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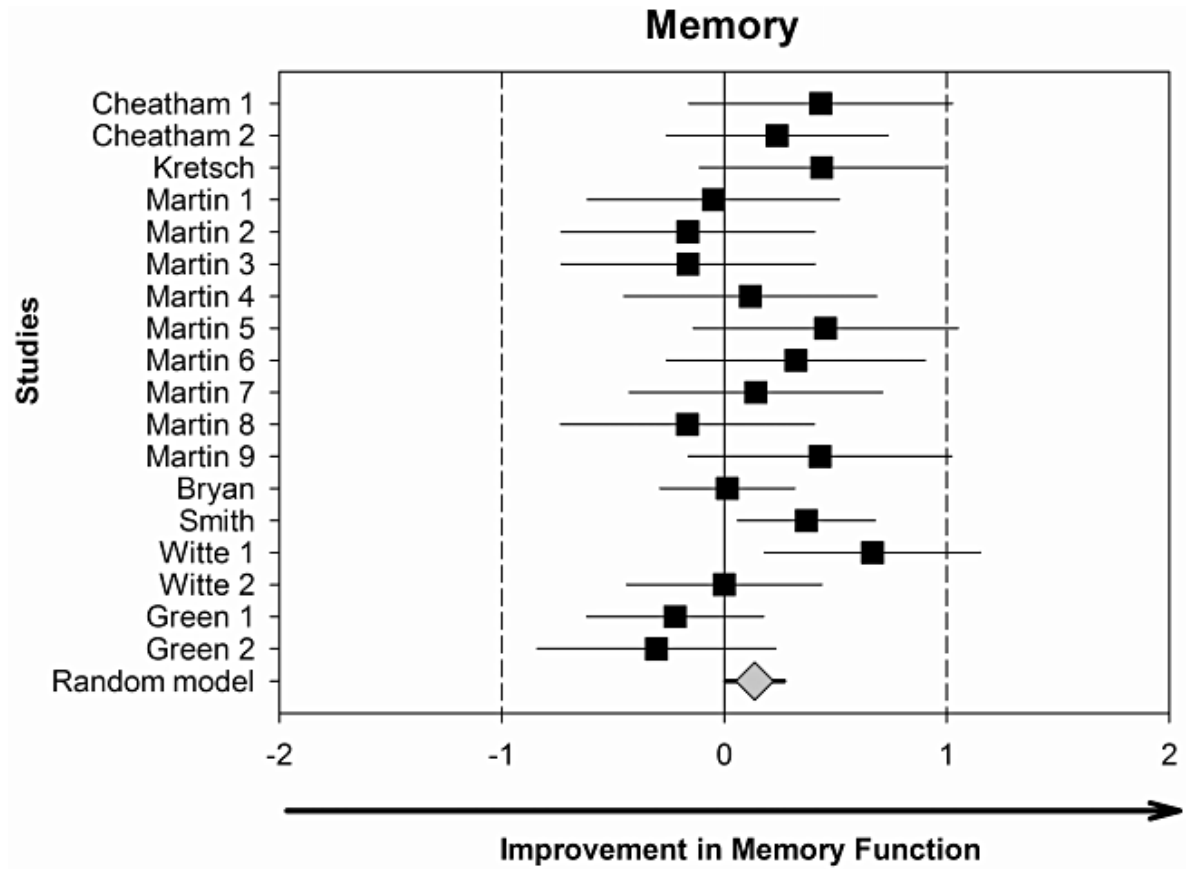
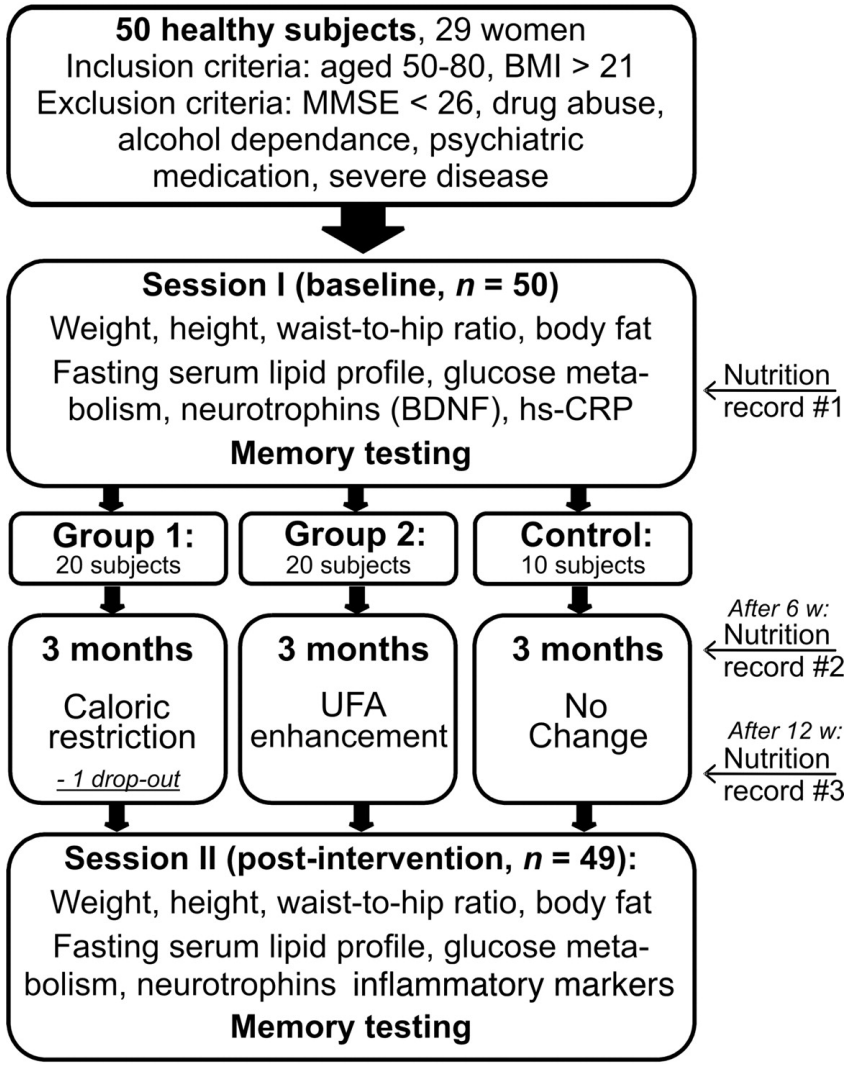
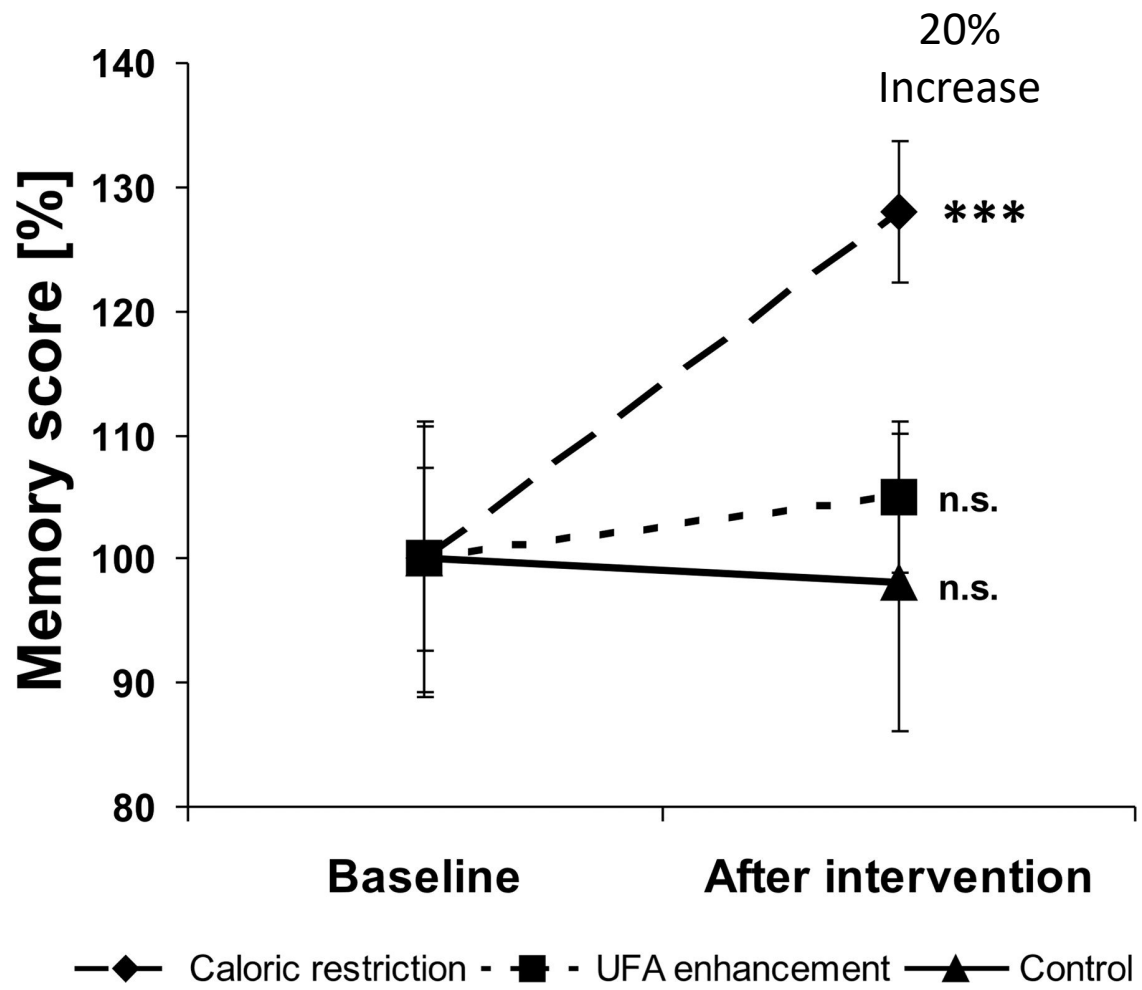


Siervo M, et al. Obes Rev. 2011;12(11):968-83.

30% Reduction





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The Journal of Nutrition 153 (2023) 733–740

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Nutrition and Disease

No Effect of Calorie Restriction or Dietary Patterns on Spatial Working Memory During a 2-Year Intervention: A Secondary Analysis of the CALERIE Trial

Rachel E. Silver [1,2,3], Susan B. Roberts [1,2], Arthur F. Kramer [4,5], Kenneth K.H. Chui [3], Sai Krupa Das [1,2,*]

N=218; 24 months; 21-50 yrs

The FASEB Journal

Nutrition | Free Access

CALERIE II: the effect of 25% calorie restriction over two years on cognitive function (629.7)

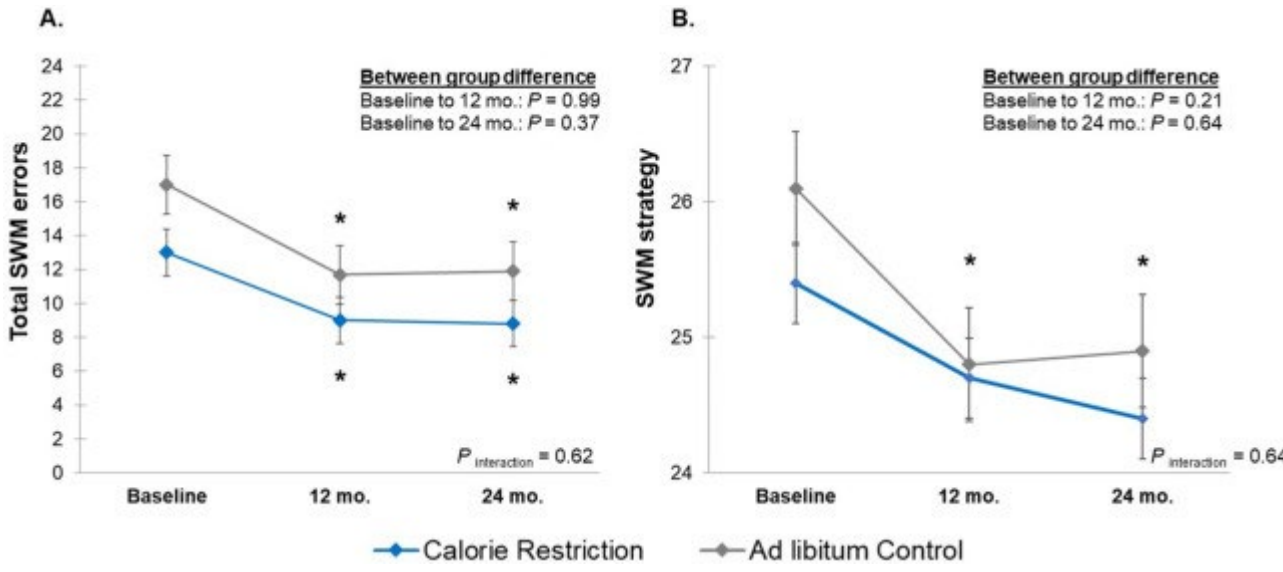
Tammy Scott, Sai Das, Corby Martin, Tiffany Stewart, Donald Williamson, Rick Stein, Manjushri Bhapkar, Carl Pieper, James Rochon, Susan Roberts

First published: 01 April 2014 | https://doi.org/10.1096/fasebj.28.1_supplement.629.7 | Citations: 1

Special Article

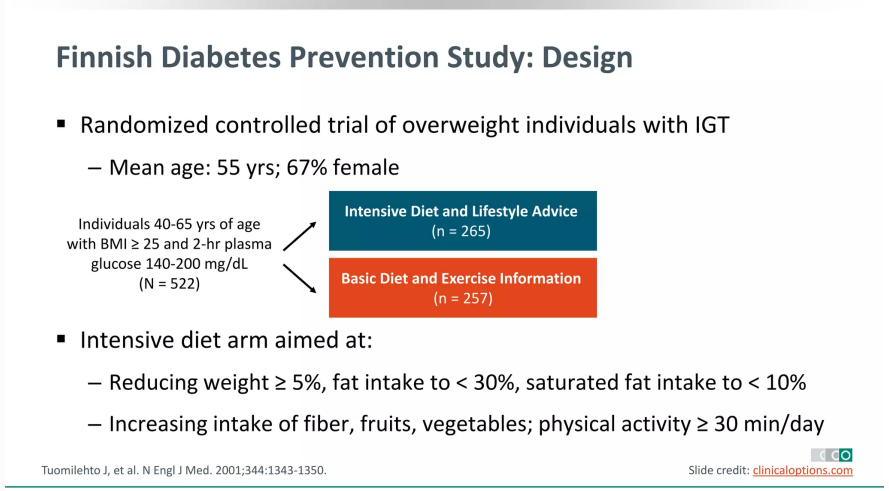
Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2

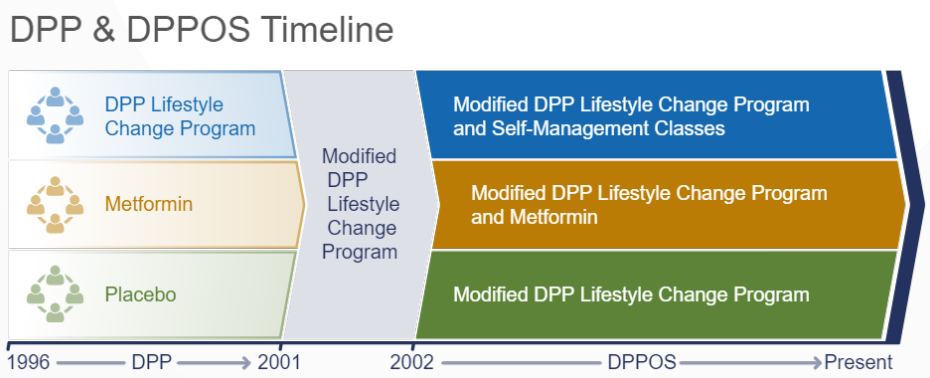
James L. Dorling, Stephan van Vliet, Kim M. Huffman, William E. Kraus, Manjushri Bhapkar, Carl F. Pieper, Tiffany Stewart, Sai Krupa Das, Susan B. Racette, Susan B. Roberts, Eric Ravussin, Leanne M. Redman, and Corby K. Martin for the CALERIE Study Group

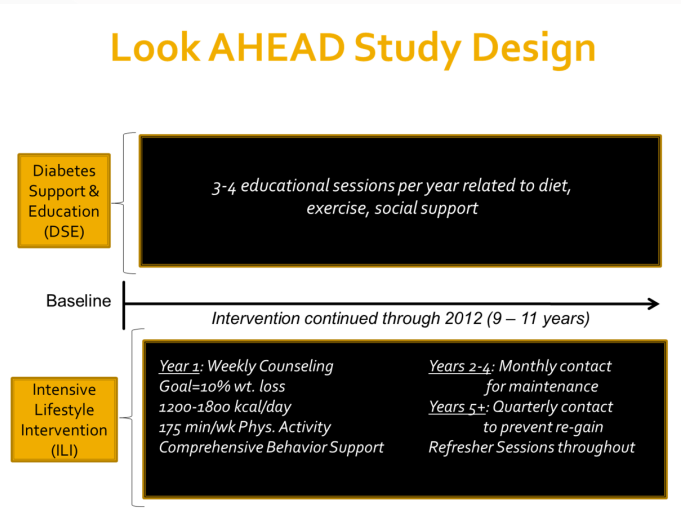


No Overall Evidence of General Long-Term Cognitive Benefits From RCTs of Behavioral Weight Loss Interventions

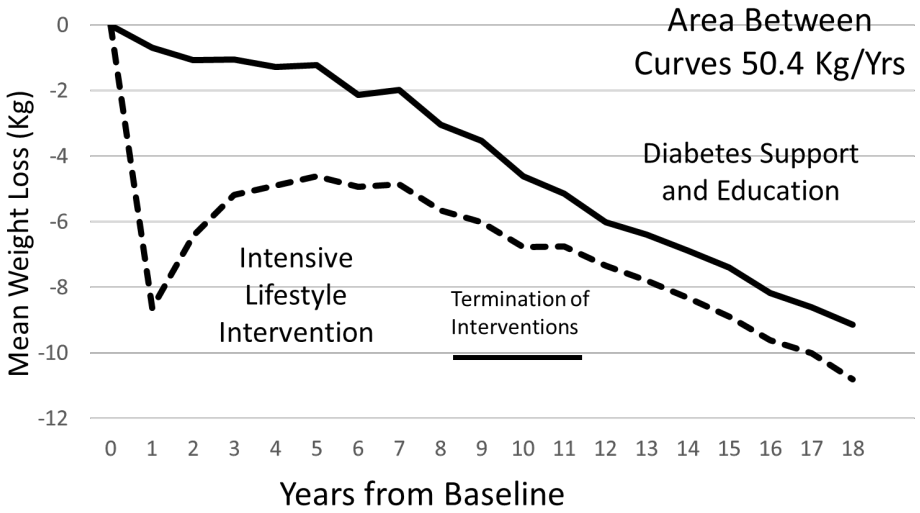
- Finnish Diabetes Prevention Study: 4-year intervention; Cognitive assessments at 9 years (Luchsinger, et al., 2015): N=364
- Diabetes Prevention Program Observational Study: 2- to 3-year intervention, Cognitive assessments at 8-10 years (Luchsinger, et al., 2017): N=2280
- Action for Health in Diabetes: 10-year intervention; Cognitive assessments throughout years 8-24 (Espeland, et al., 2014)







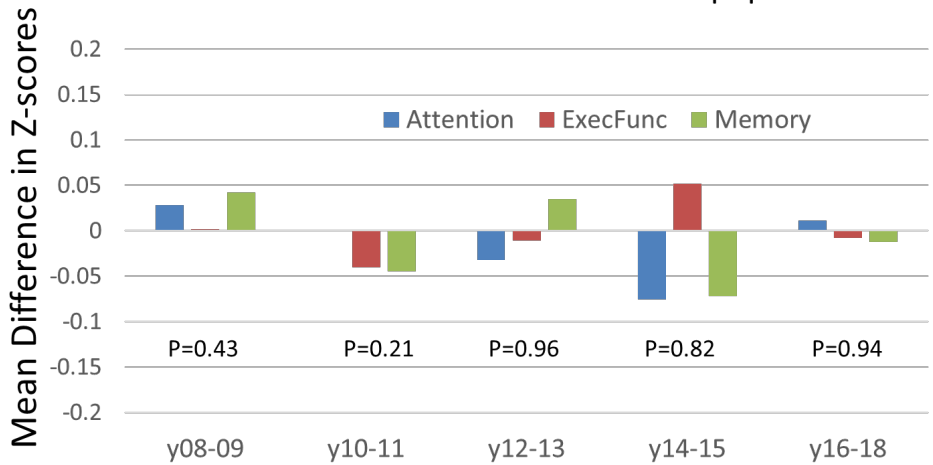
Mean Weight Change From Baseline



Mean Intervention Effect: ILI Minus DSE

No 95% Confidence Intervals Exclude 0

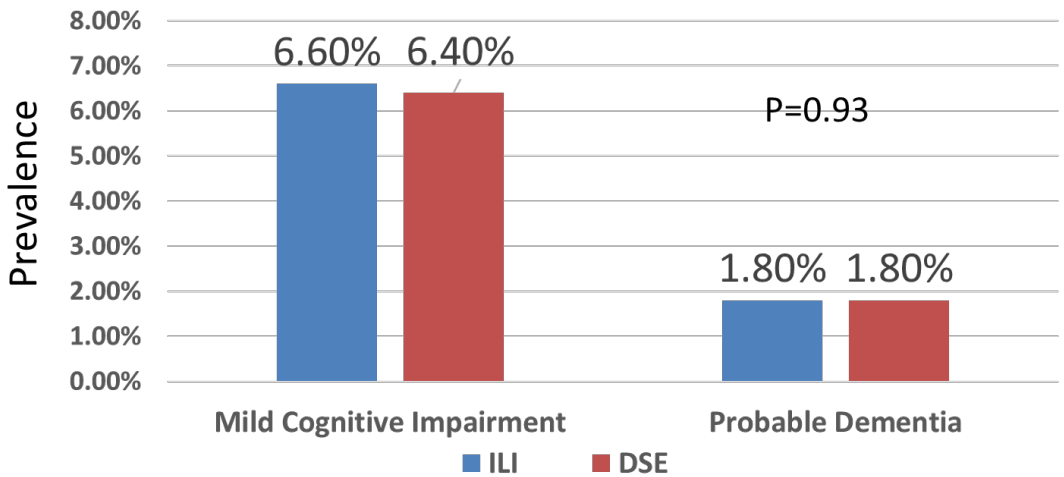
Overall Intervention Effects Across Follow-up: p=0.69



Years From Randomization

Unpublished Data

Prevalence of Cognitive Impairment in Look AHEAD by Intervention Assignment: Years 10-13



Espeland MA, et al. Neurology 2017

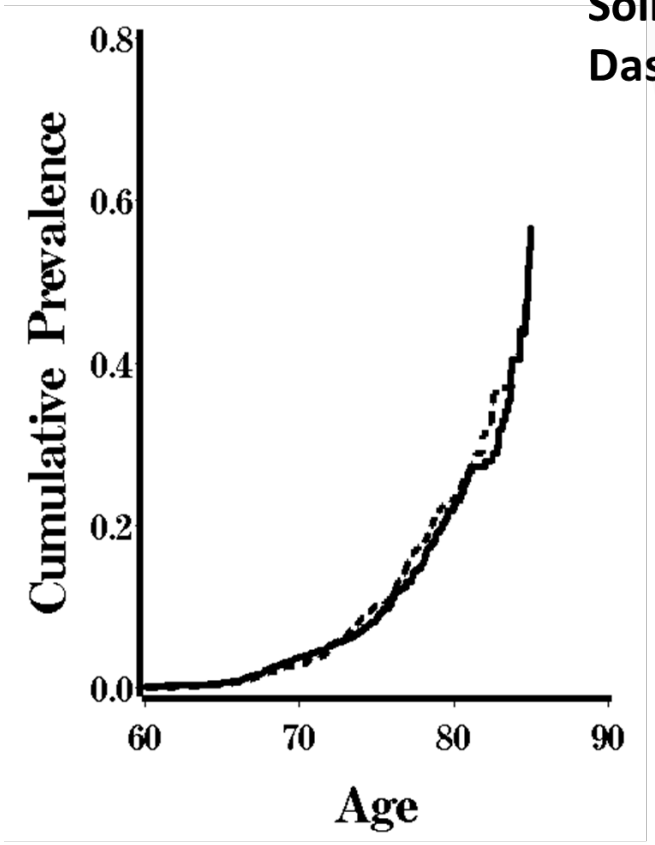
Look AHEAD Brain MRI Ancillary Study

Relative Intervention Effects		
Smaller Ischemic Lesion Volume	Smaller Ventricle Volume	Greater Cerebral Blood Flow
28%	9%	6%
P=0.02	P=0.04	P=0.04

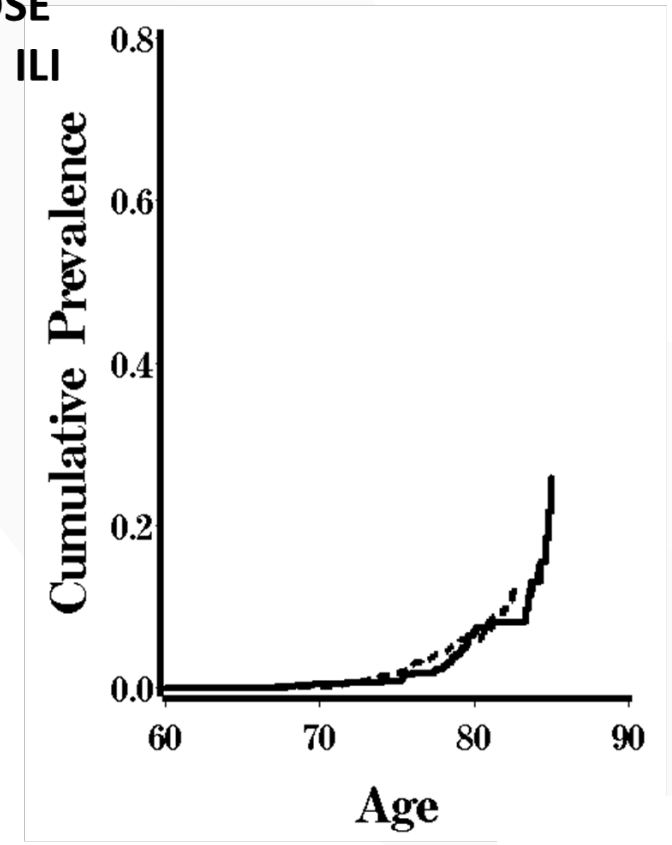
Espeland MA, et al. Diab Care 2016.
Espeland MA, et al. J Am Geriatr Soc 2018.

Prevalence of Cognitive Impairment and Dementia in Look AHEAD After Termination of Intervention

Solid Line: DSE
Dashed Line: ILI

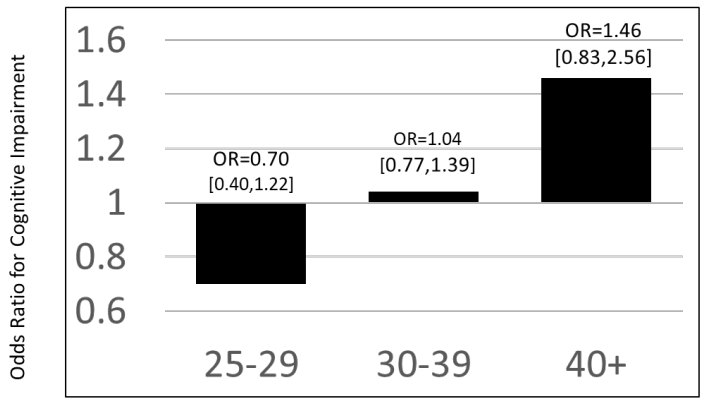


Mild Cognitive Impairment or Dementia



Dementia

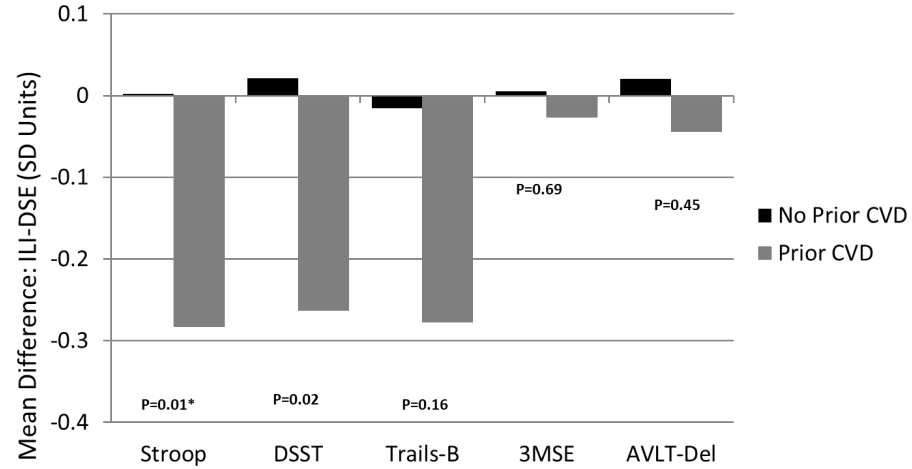
Cognitive Impairment (MCI or Dementia) Relative Intervention Effect: ILI vs DSE



BMI x Intervention Interaction p=0.03

Espeland MA, et al. Neurology 2017.

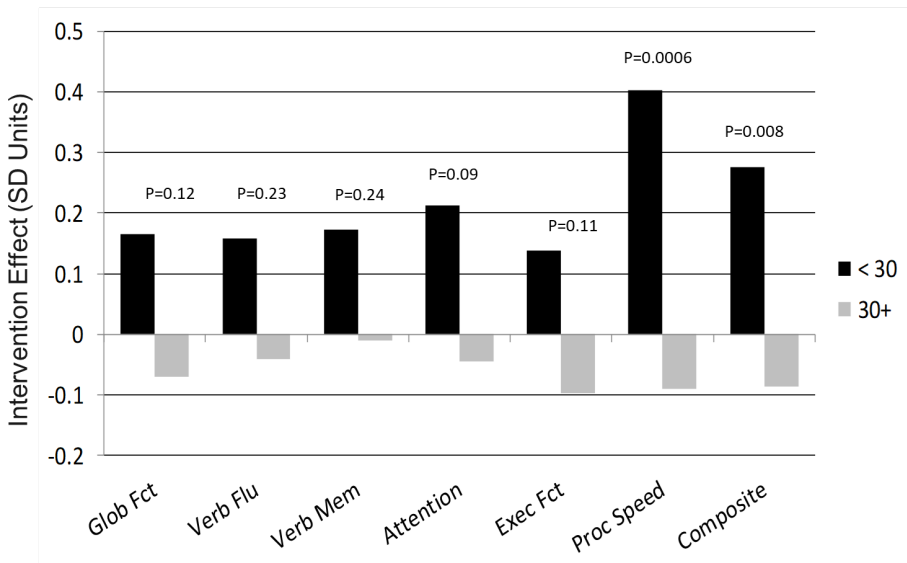
Mean Intervention Effects on Cognitive Function Tests** by CVD History at Baseline



*Interaction Test: Covariate adjustment for baseline age, SF-36 mental score, clinic, education, and race/ethnicity
**Negative mean differences indicate poorer performances among the ILI compared to DSE participants

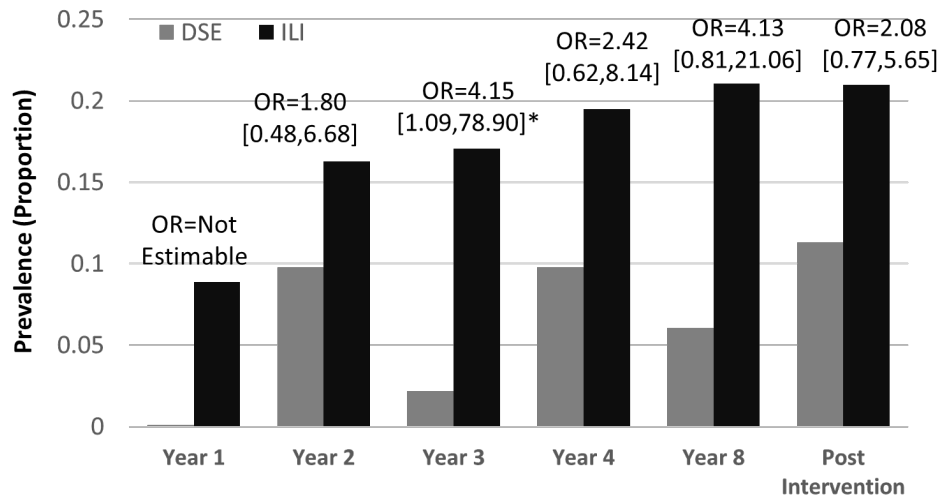
Espeland MA, et al. J Geront Med Sci 2014.

Mean Intervention Effects (Intervention Minus Control): By Baseline BMI



Espeland MA, et al. J Geront Med Sci 2014.

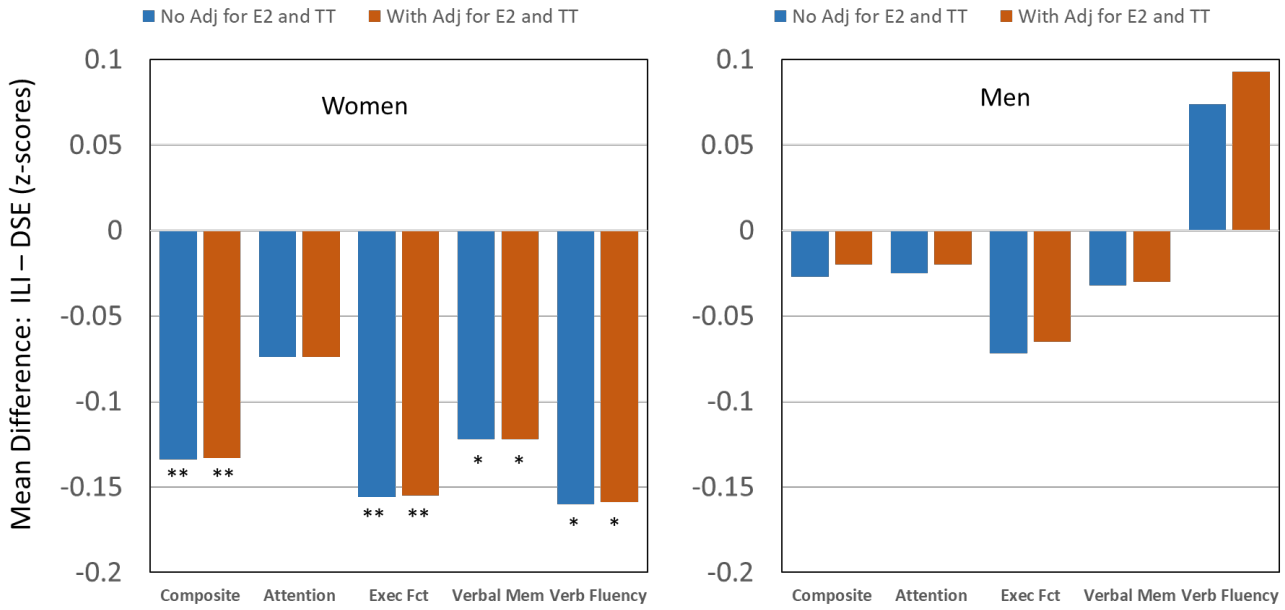
Prevalence of self-reported difficulties in problem-solving over time for participants with baseline difficulties & history of CVD



*95% Confidence Interval Excludes 1

Espeland MA, et al. J Geront Med Sci 2018.

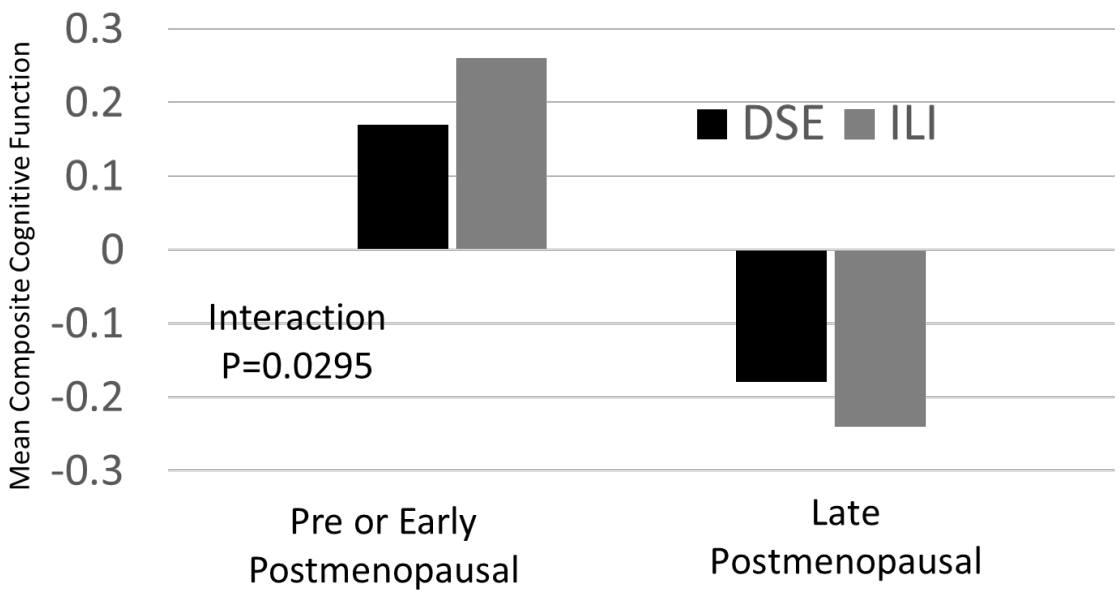
Long-term Differences in Cognitive Function Between Intervention Groups for Women and Men



* p<0.10; ** P<0.05

Mean Composite (z-score) Cognitive Function by Intervention Assignment and Menopausal Status

Covariate adjustment for Sociodemographic and Cardiometabolic Risk Factors



Espeland, et al., J Diab Compl 2022;36:108268.
Yassine, et al. Neurobiology Aging 2020;92:61-72.

Major Gaps in the Field

The long-term effects of CR on cognitive function on cognition have not been assessed in older individuals with normal glucose metabolism.

Why is there a disconnect between the expected benefits seen for other health outcomes and the lack of cognitive benefits seen in major clinical trials?

How are the subgroup differences seen in the Look AHEAD trial explained and how do these inform personalized intervention approaches? Is there a “window of opportunity” for CR to be effective in preventing cognitive decline?

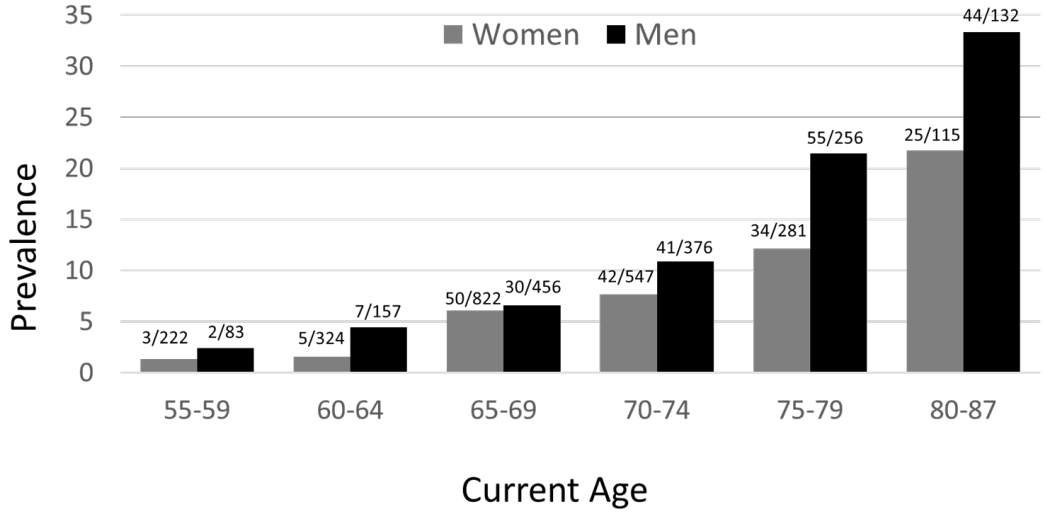
Should CR be combined with other approaches to prevent cognitive decline as a multidomain intervention strategy?

Questions

Better Glycemic Control Is Associated with Better Cognitive Function Among Individuals with Overweight

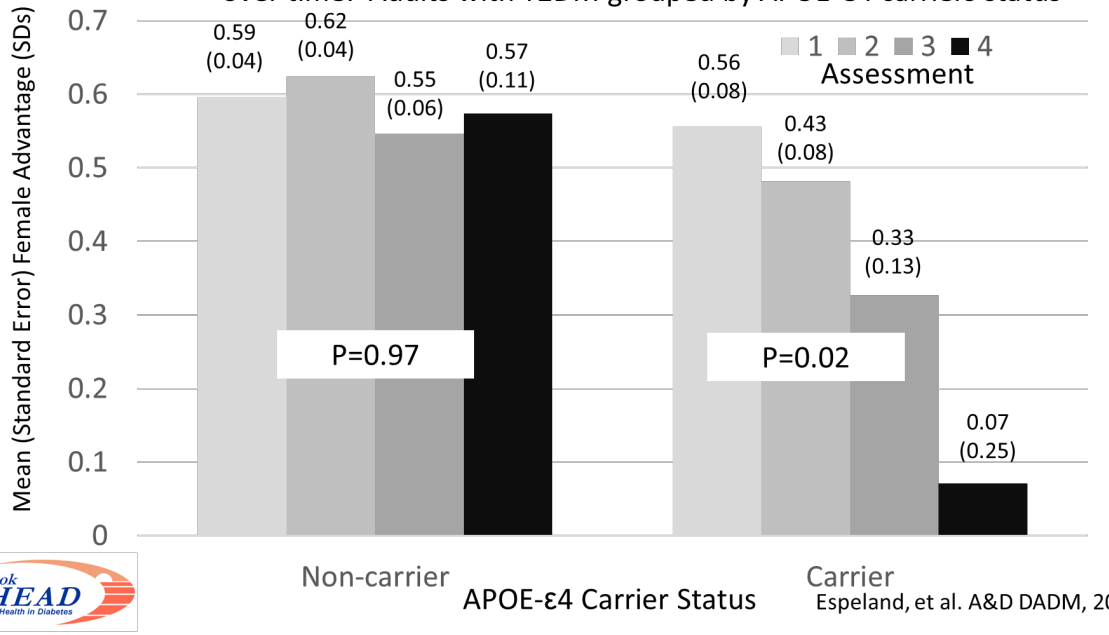
Carmichael OT, et al. J Clin Endocrinol Metabol 2020.

Prevalence of Cognitive Impairment by Age and Sex

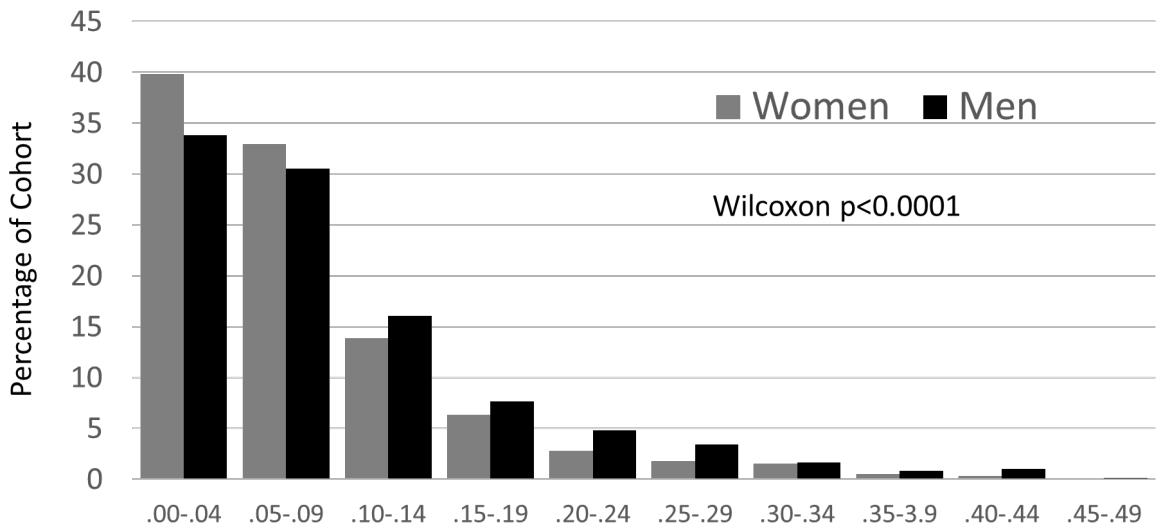


No interaction between age and sex (p=0.669)

Cognitive advantage that women have over men for composite cognitive function over time: Adults with T2DM grouped by *APOE*-e4 carriers status



Espeland, et al. A&D DADM, 2021.



Predicted Risk for Cognitive Impairment From Logistic Regression

Covariate-Adjusted MRI Outcomes Across 5 ROIs

MRI Outcome	Women	Men	Difference Women minus Men	
	Mean (SE)	Mean (SE)	Mean (SE)	95% CI
Total volume (cc)	900.8 (1.8)	890.0 (3.0)	10.9 (3.9)	[3.3,18.5]*
Total white matter hyperintensity volume (cc)	3.97 (0.39)	2.58 (0.59)	1.39 (0.71)	[0.0,2.78]*
Cerebral blood flow (mL/100g/min)	51.11 (0.85)	48.65 (1.30)	2.44 (1.57)	[-0.64,5.50]

*95% CI excludes 0

Espeland, et al. Alz & Dement 2018;14:1184-92.
Espeland, et al. J Gerontol A Biol Sci Med Sci 2020;75:771-8.