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Gender Differences in Cognitive Function and Brain Structure in Overweight and Obese Adults with Type 2 Diabetes Mellitus: Emerging Findings from the Look AHEAD Trial

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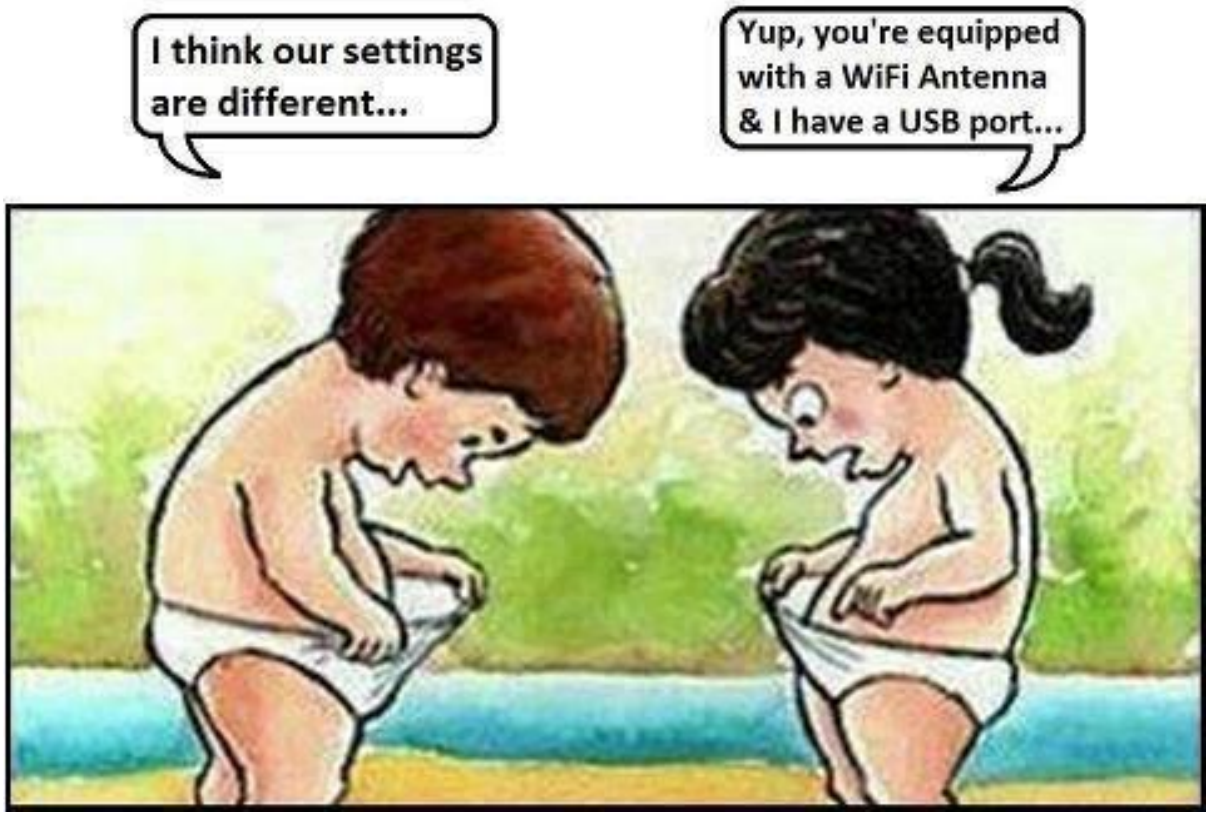
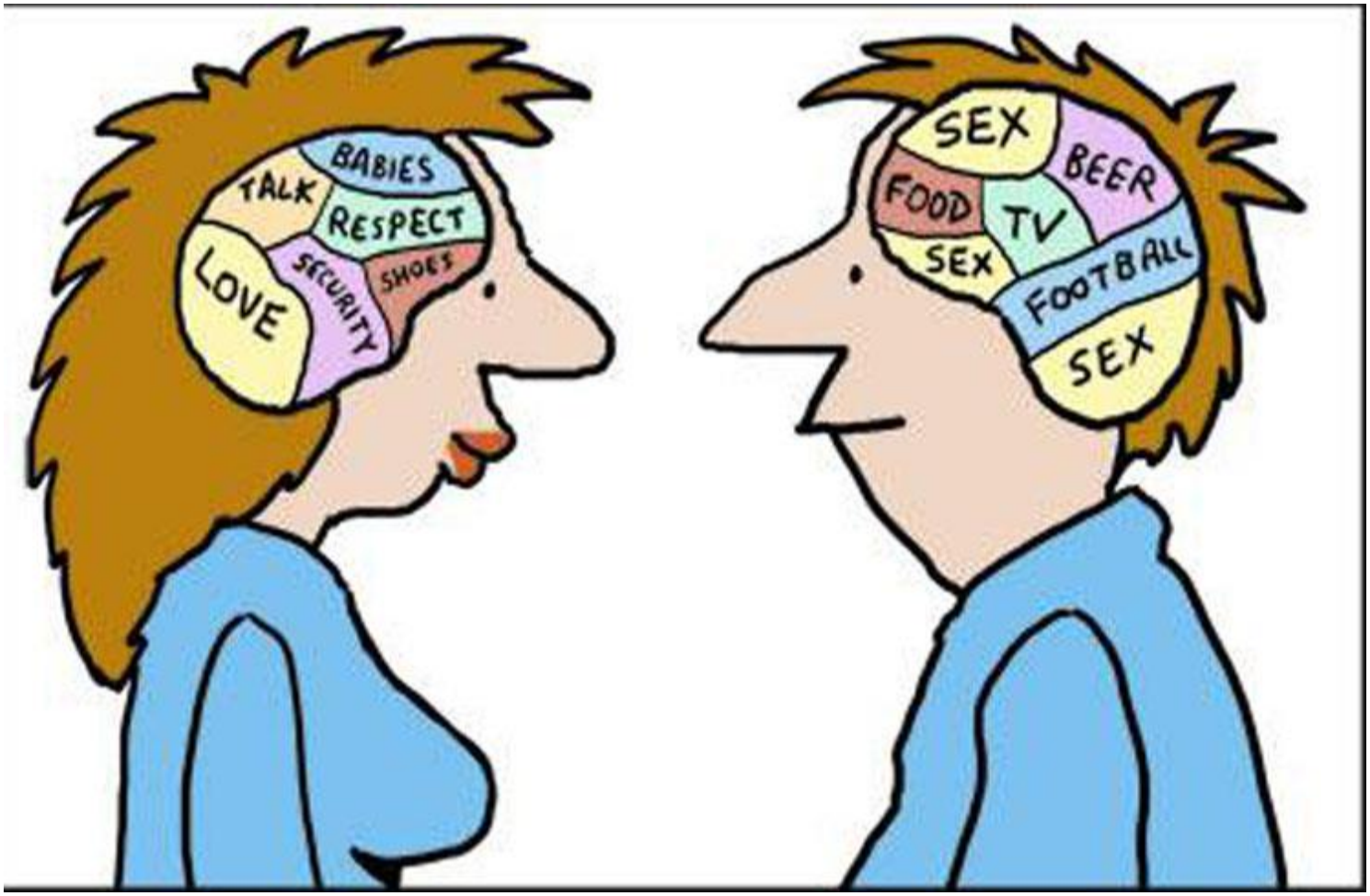
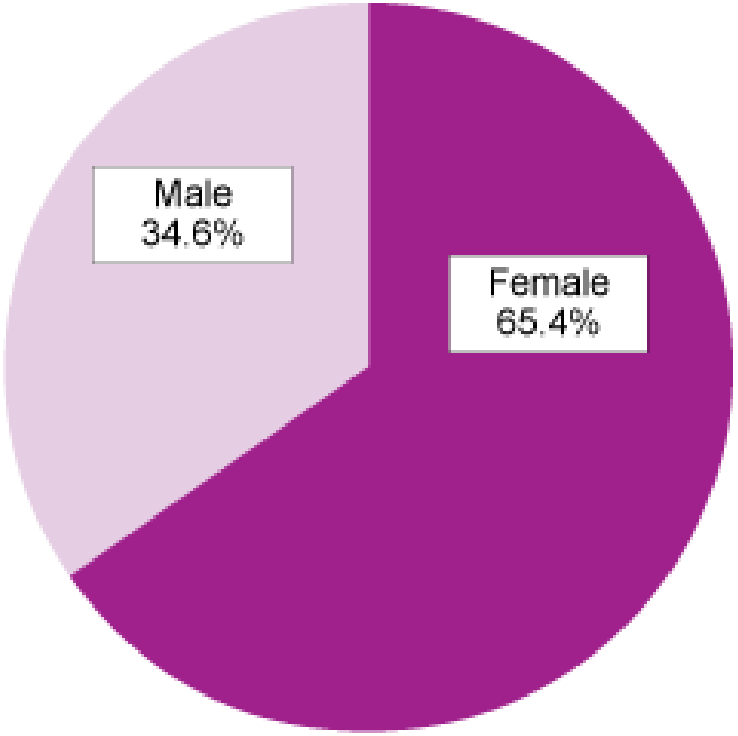
Look AHEAD
Action for Health in Diabetes


I think our settings are different...
Yup, you're equipped with a WiFi Antenna & I have a USB port...


BABIES
TALK
RESPECT
LOVE
SECURITY
SHOES
SEX
BEER
FOOD
TV
SEX
FOOTBALL
SEX

Most Alzheimer's Patients Are Women

Adults Aged 65 and Older with Alzheimer's Disease,* By Sex, 2011



**Estimates are from the Chicago Health and Aging Project incidence rates converted to prevalence estimates and applied to 2011 U.S. Census Bureau estimates of the population aged 65 and older.*

Source: Alzheimer's Association. 2011 Alzheimer's Disease Facts and Figures. Retrieved from http://www.alz.org/alzheimers_disease_facts_and_figures.asp. Accessed 07/11/11.

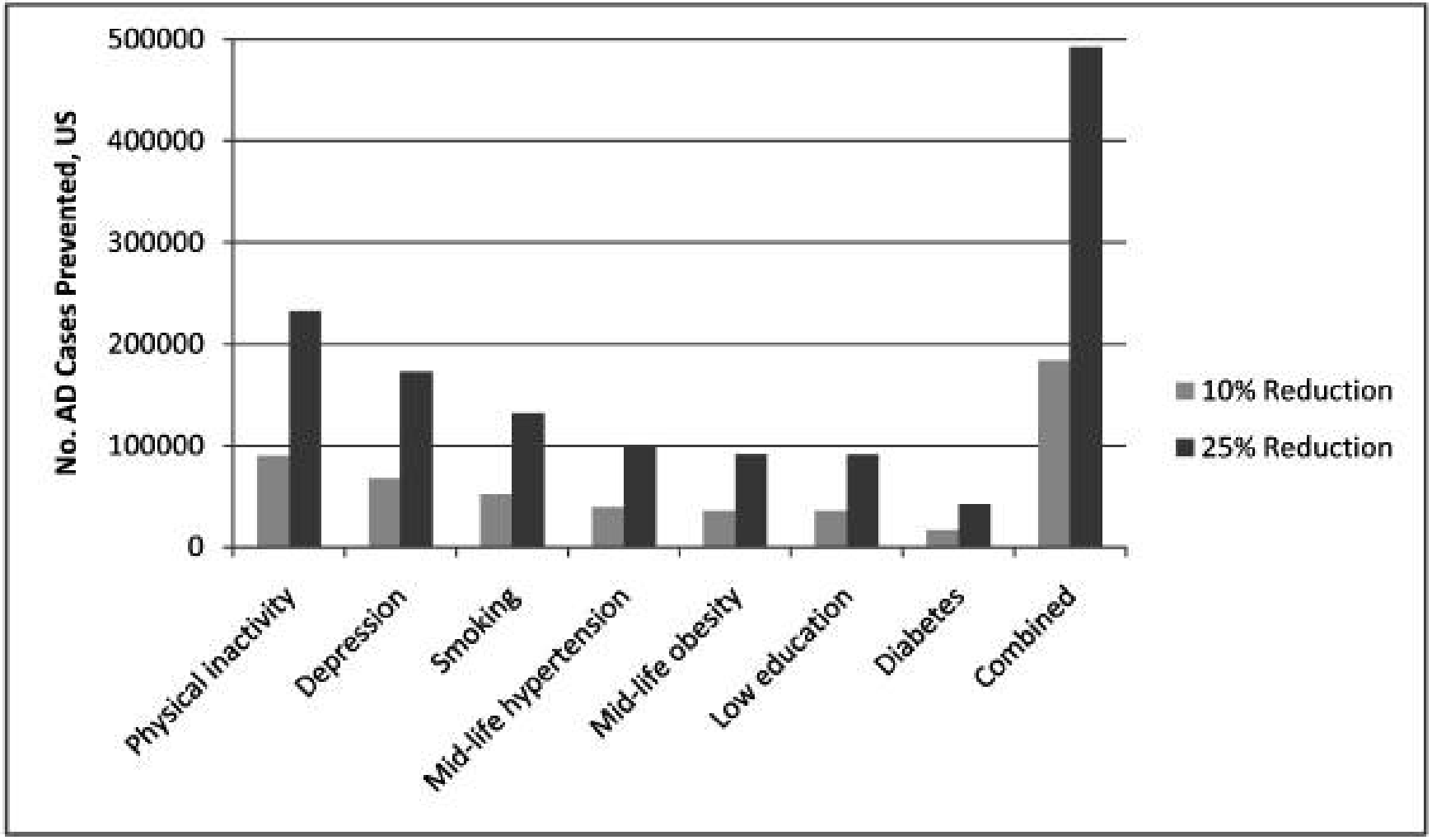
Potential Explanations for Differences in Risk Between Women and Men

- Lifestyle
- Social influences
- Exercise
- Lifespan
- Hormones

- Brain networks
- Sex chromosomes
- Vascular factors
- Brain structure
- Metabolism

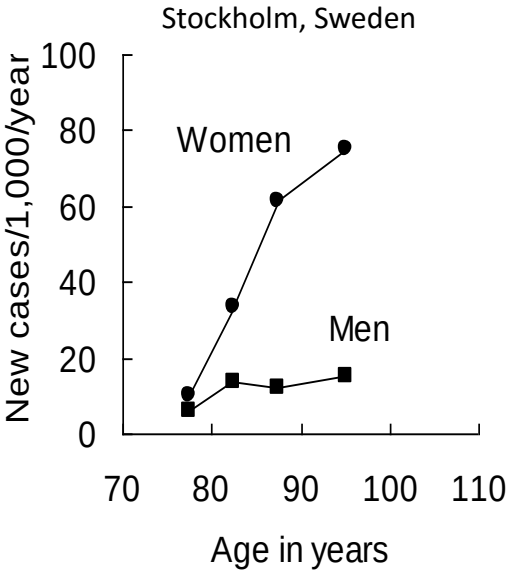
Mielke MM, et al. Clin Epidemiol 2014;6:37-48.
Snyder HM, et al. Alz Dementia 2016;12:1186-1199.

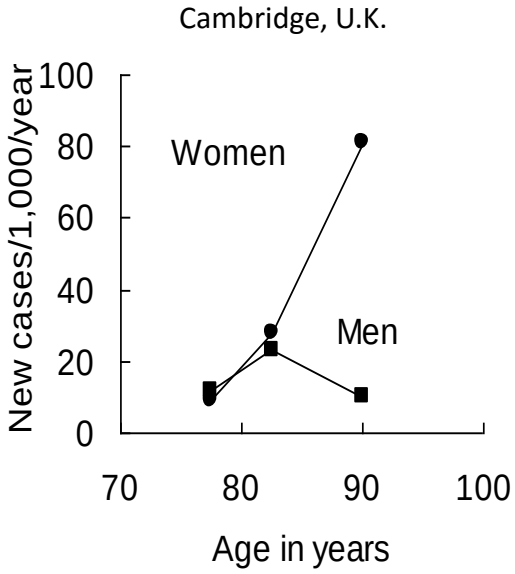
Modifiable Risk Factors for Alzheimer's Disease: US

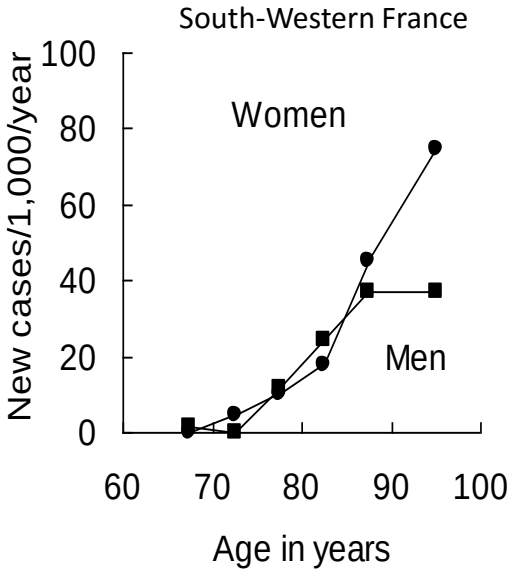


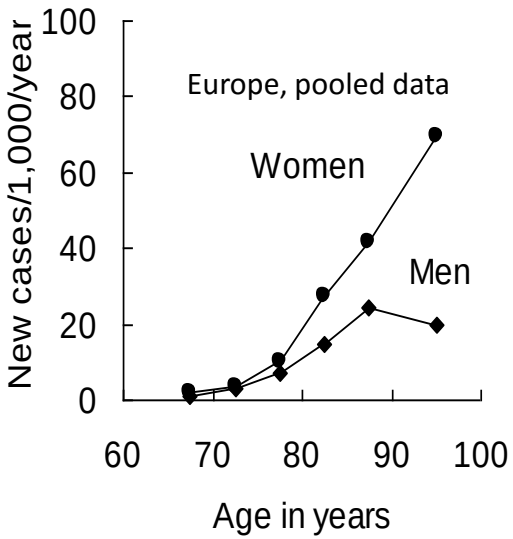
Barnes D, Yaffe K. Lancet Neurol 2011;10:819-828.

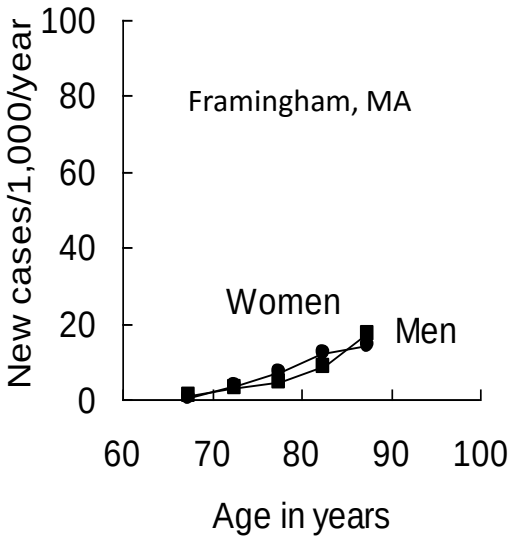
Incidence of Dementia By Age

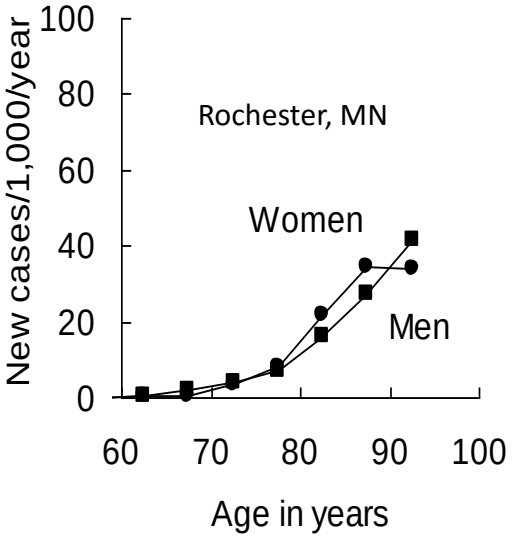






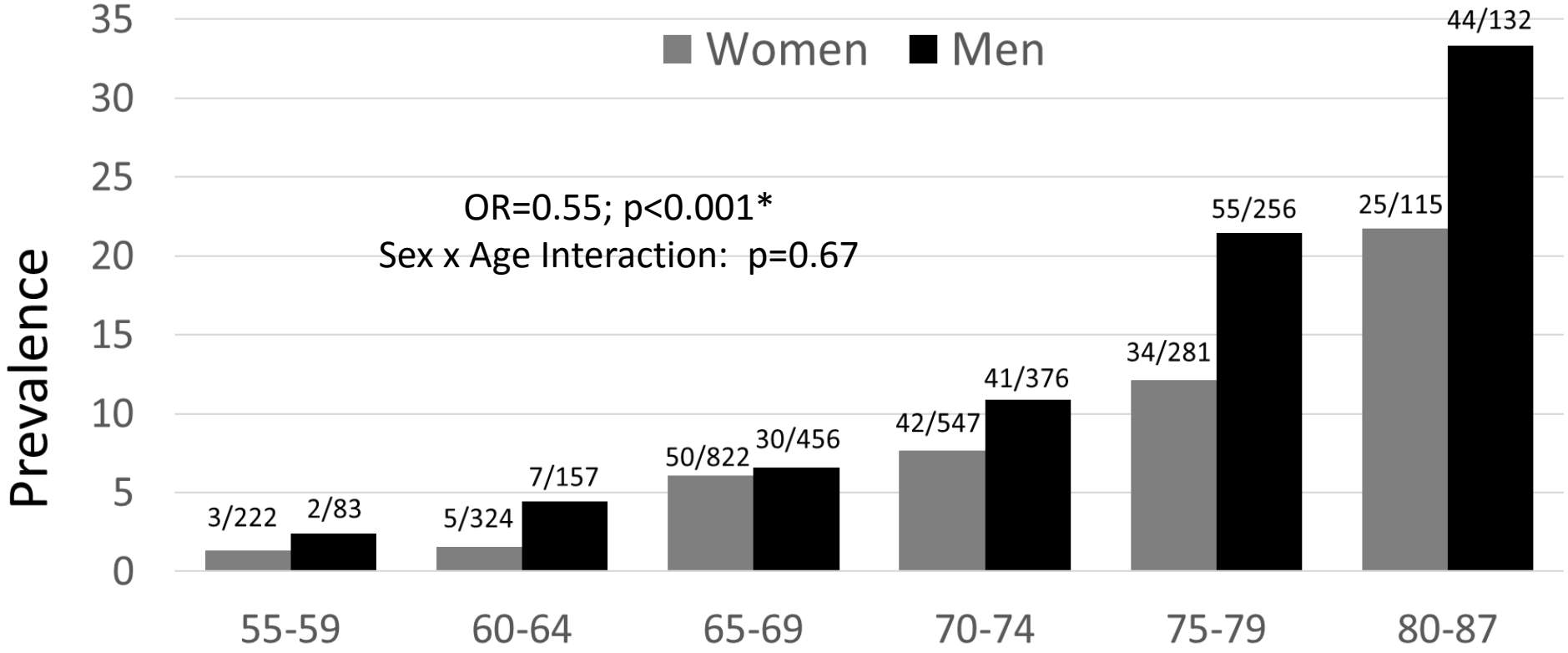






Courtesy of Walter Rocca and Michelle Mielke

Prevalence of Cognitive Impairment by Age and Sex



*Adjustment for age, education, race/ethnicity, and intervention

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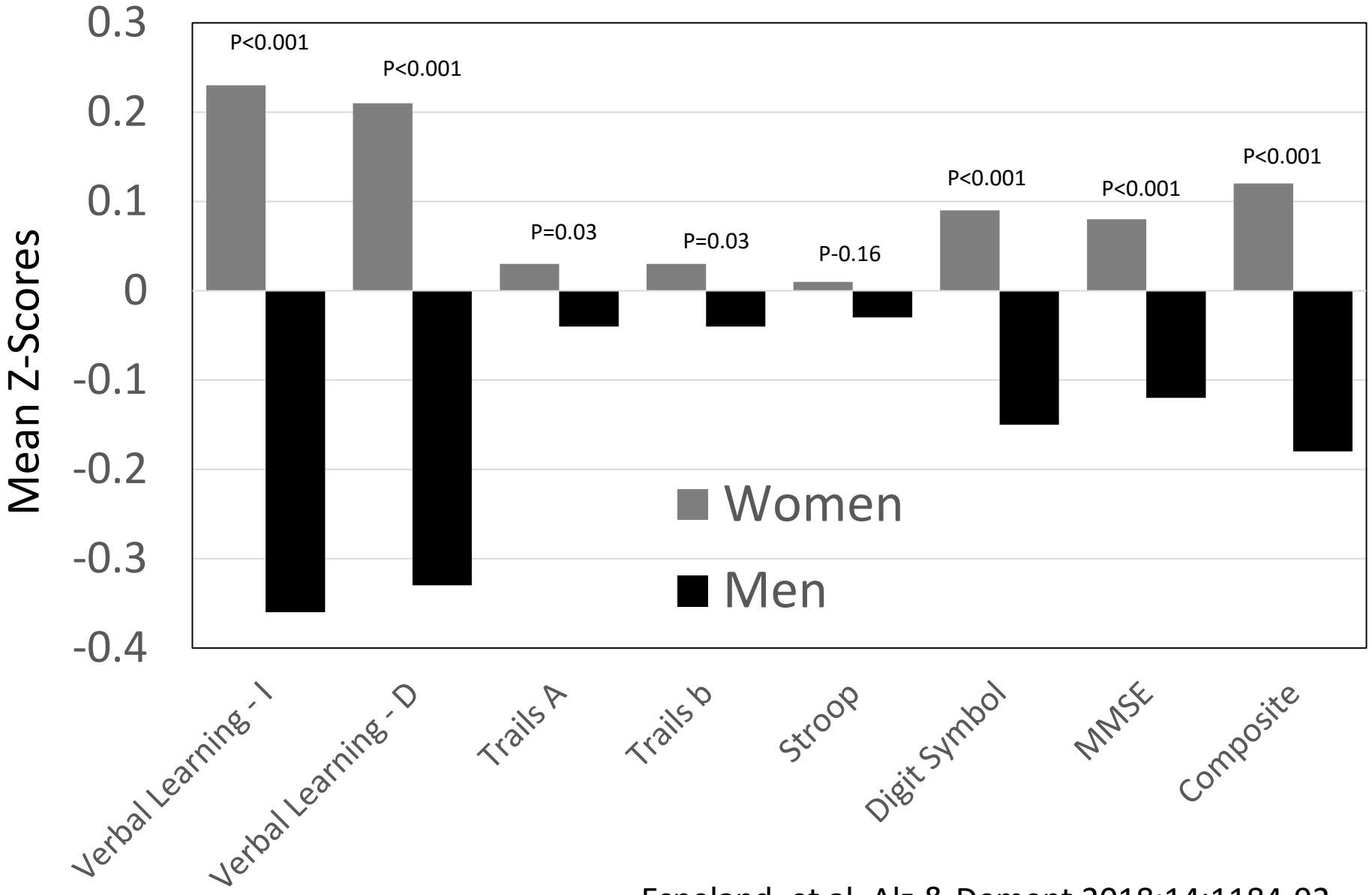
Espeland M, et al. Alz & Dement 2018;14:1184-92

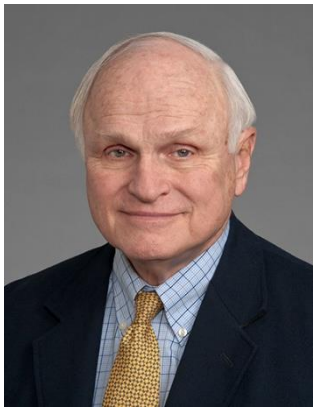
Mean Cognitive Function Scores by Gender



Espeland, et al. Alz & Dement 2018;14:1184-92.

Owen Carmichael
LSU

Sevil Yasar
Johns Hopkins



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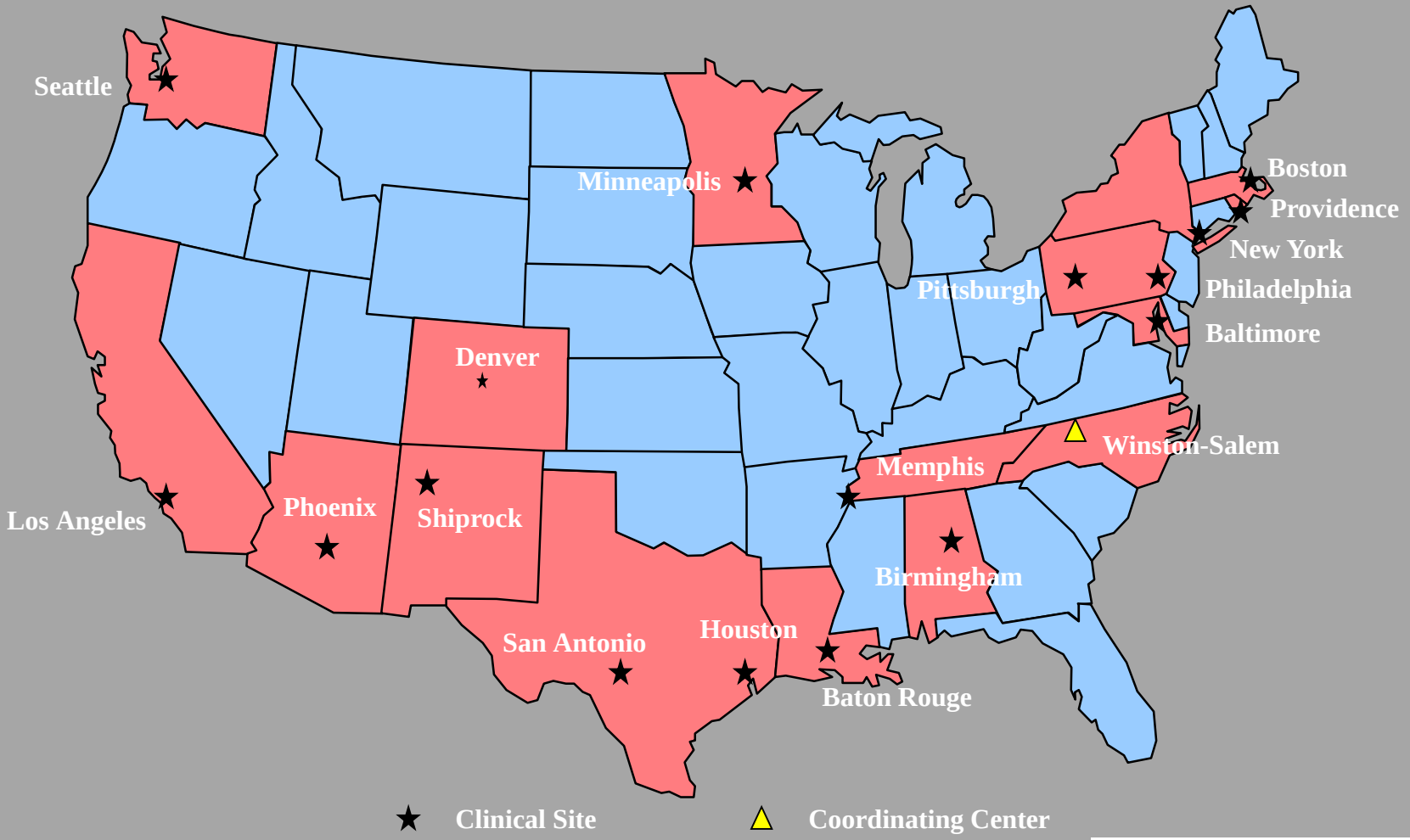
Clinical Sites



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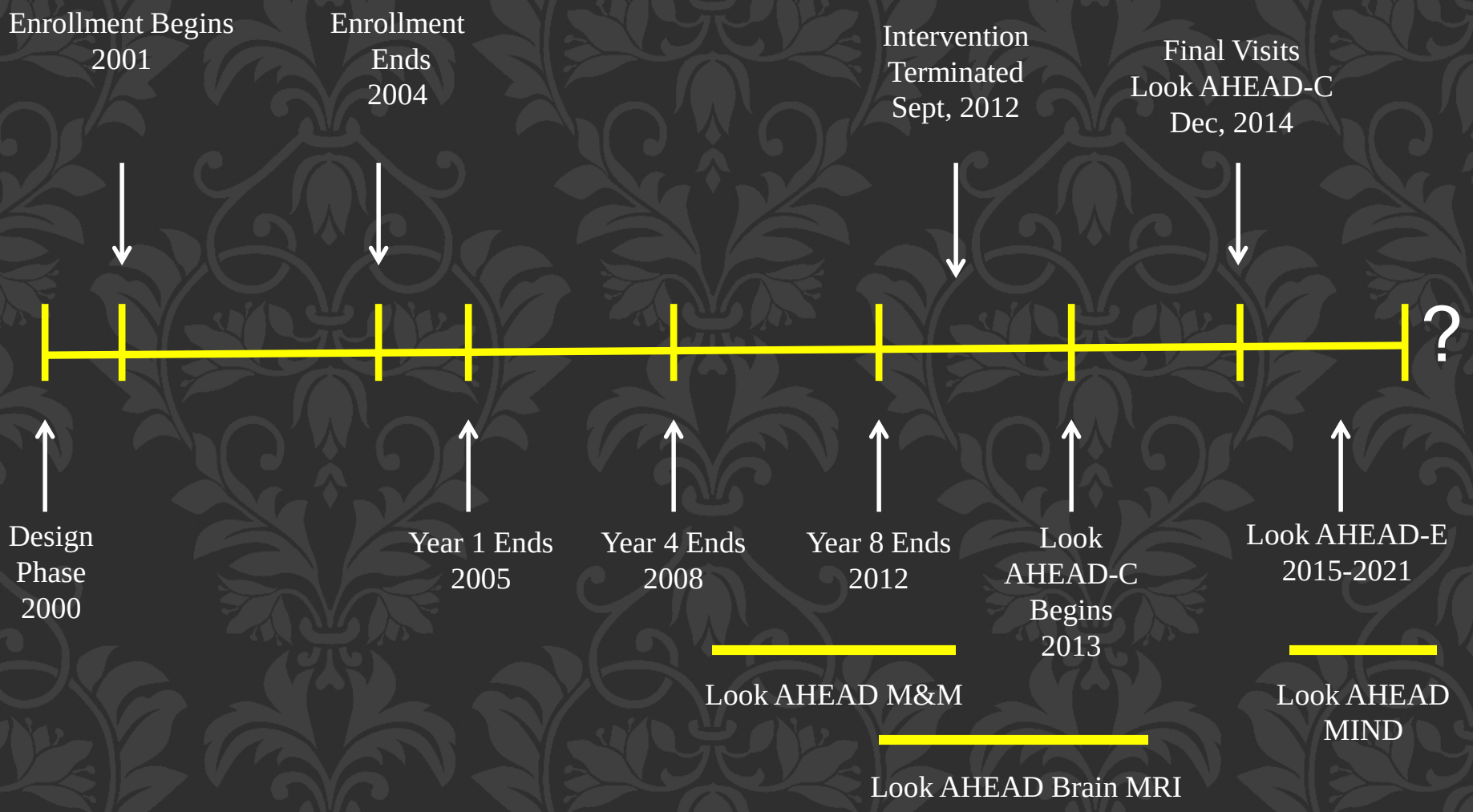
Look AHEAD Timeline



Baseline Characteristics of Participants

Baseline Characteristic	Intervention (N=2,570)	Control (N=2,575)
Women	59%	60%
Minority	37%	37%
Age [Range 45-76]	59 years	59 years
Insulin Users	15%	16%
History of Prior CVD Event	14%	14%
Body Mass Index	36 kg/m^2	36 kg/m^2

Intensive Lifestyle Intervention (ILI) Recommendations

Dietary Intake

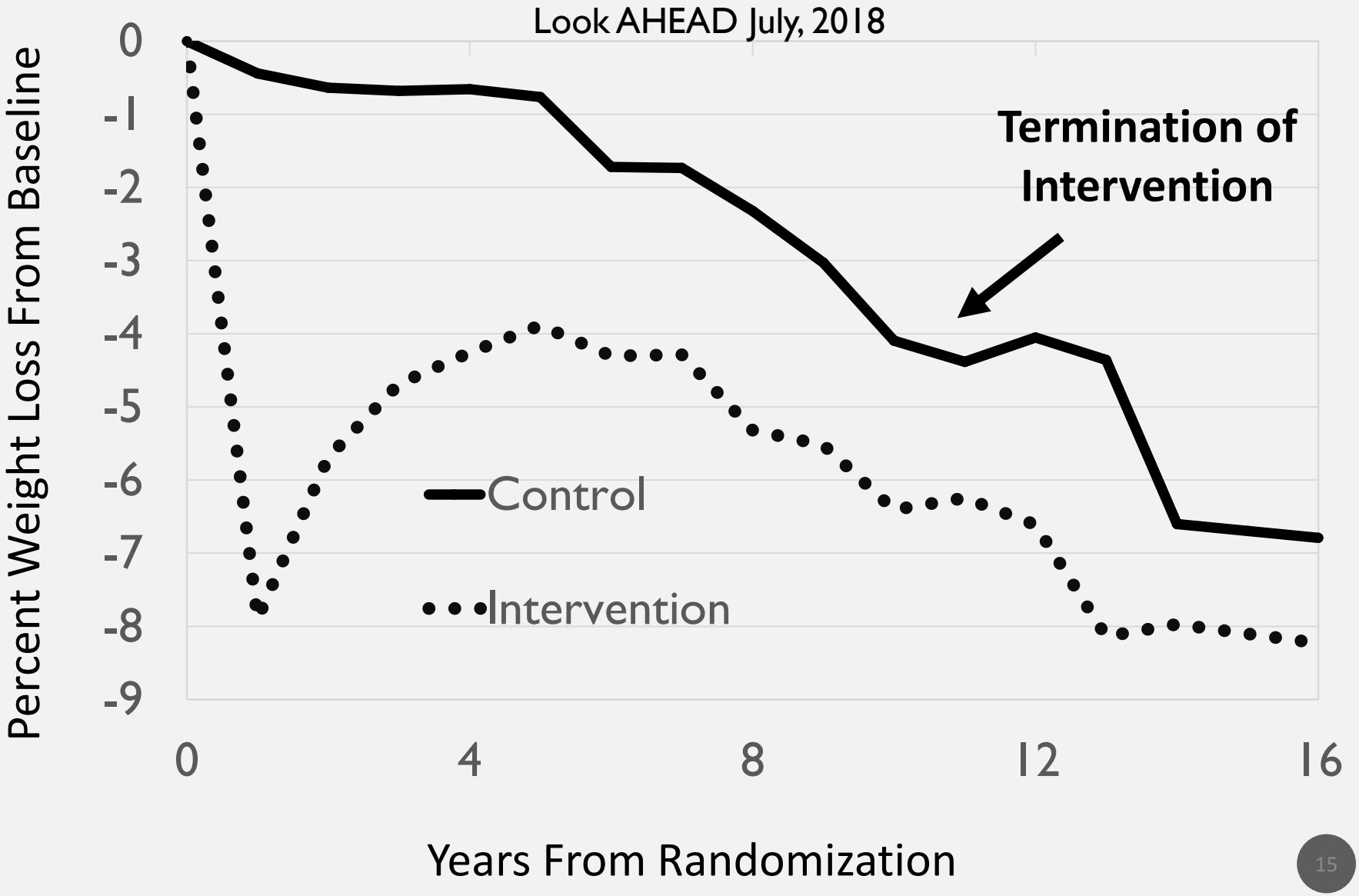
- 1200-1500 kcal/day < 250 lb
- 1500-1800 kcal/day ≥ 250 lb
- ≤ 30% calories from fat
- Meal replacements (2 meals and 1 snack/d in Months 1-4; reduced use thereafter)
- Menu plans provided

Physical Activity

- 175 min/week (achieved gradually)
- 10,000 steps

Look AHEAD Research Group. *Diabetes Care*, 2007;30:1374-83.

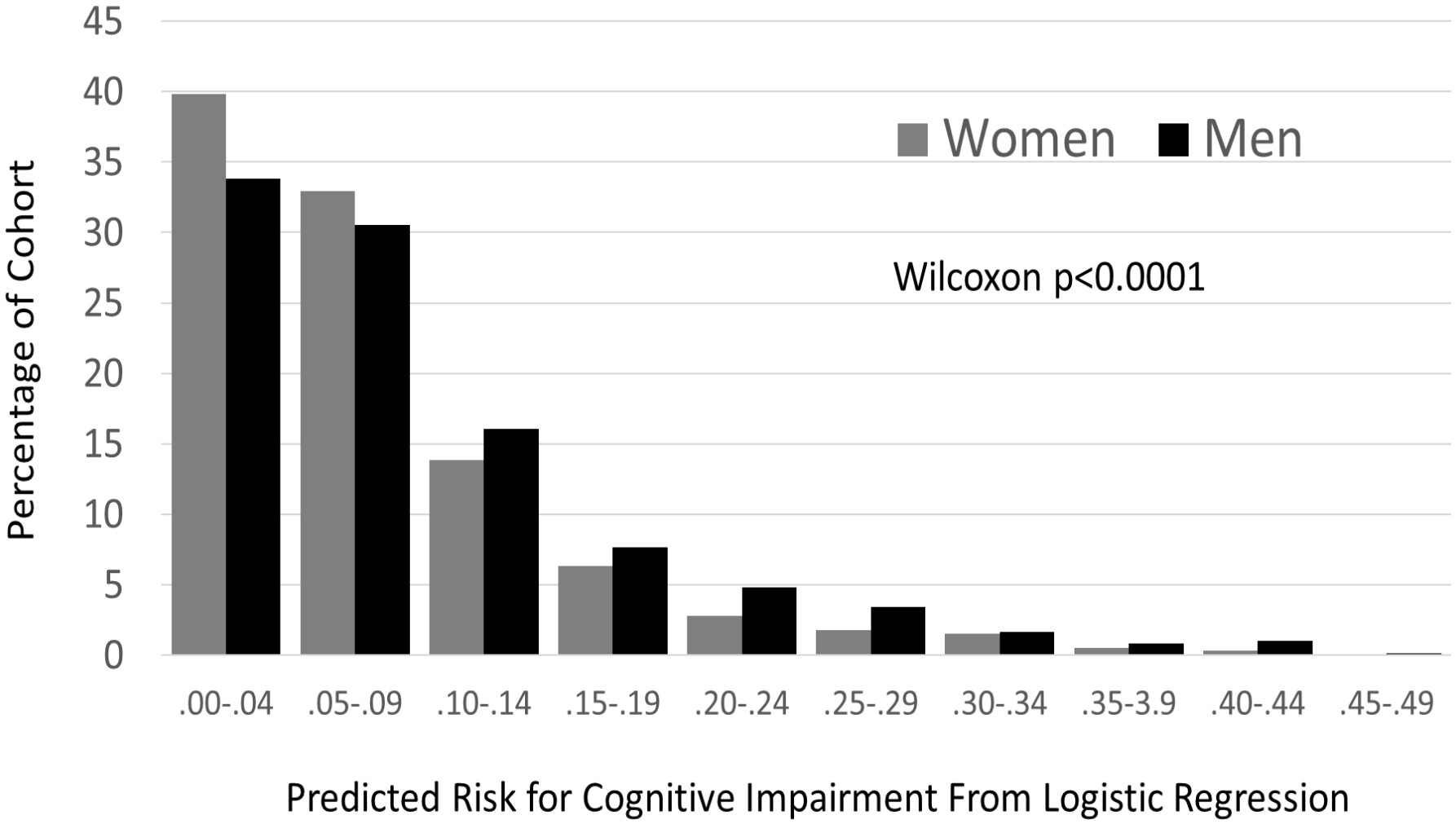
MEDIAN PERCENT WEIGHT LOSSES BY INTERVENTION ASSIGNMENT



How to Explain the Female Advantage in Cognitive Health in the Look AHEAD Cohort?

- Differences in
  - Risk factor burden
  - Risk factor relationships
  - Response to the intervention
  - Brain atrophy
  - Subclinical cerebral vascular disease
  - Cerebral blood flow
- Does the advantage extend to all women?

Distribution of Risk Factor Burdens Between Women and Men

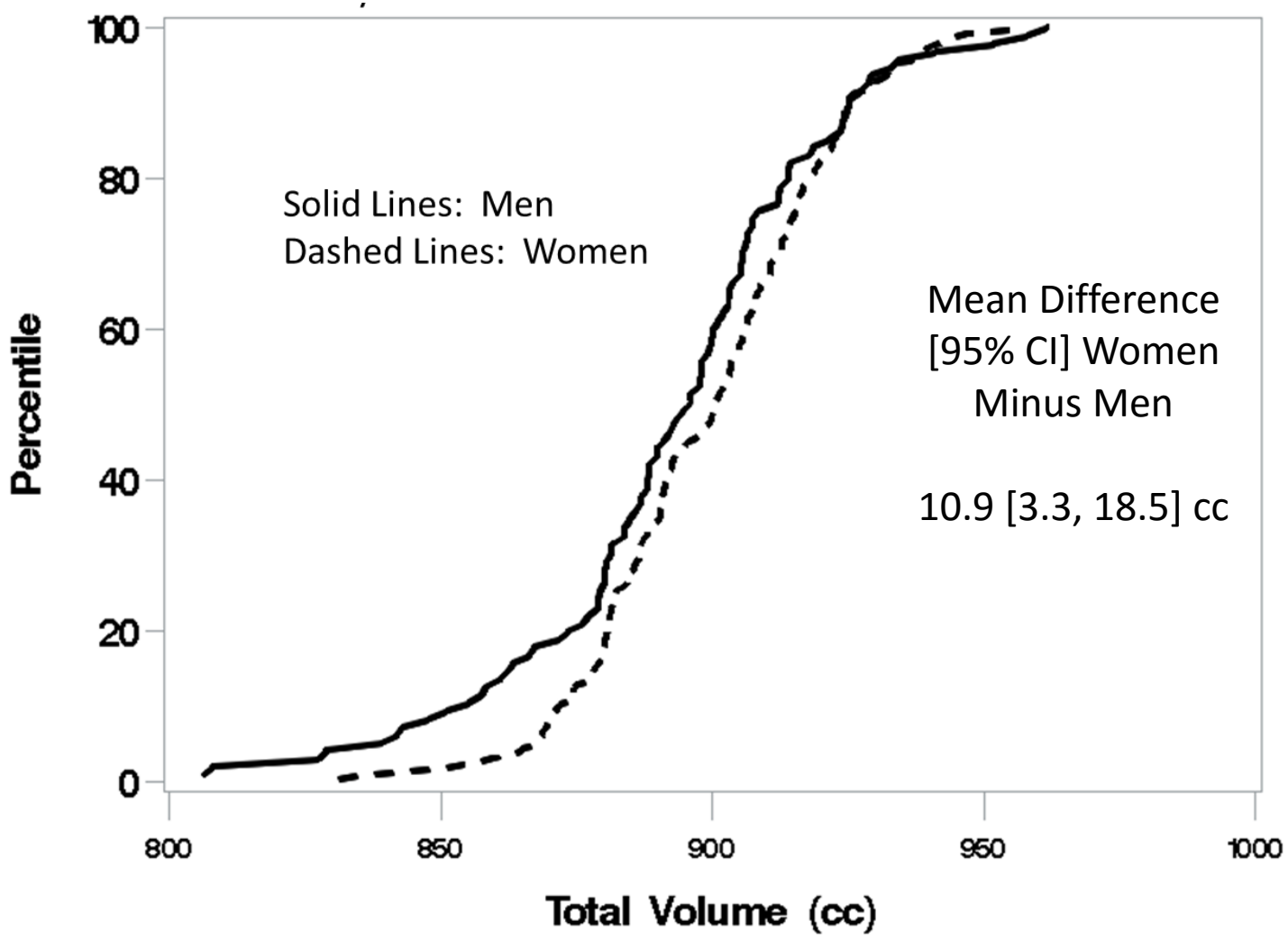


Included: age, CVD, education, depressed mood, intervention assignment*BMI interaction, APOE

Gender Differences Not Explained by Risk Factors or Intervention Effects

Adjustment	Odds Ratio [95% Confidence Interval]
Age, Education, Race/Ethnicity, Intervention	0.55 [0.43,0.71]
Risk Factor Score	0.60 [0.47,0.76]
Intervention Control Intensive Lifestyle	 0.50 [0.35,0.70] 0.61 [0.43,0.86]
Changes in HbA1c, Glucose, Weight, Medications	No Change

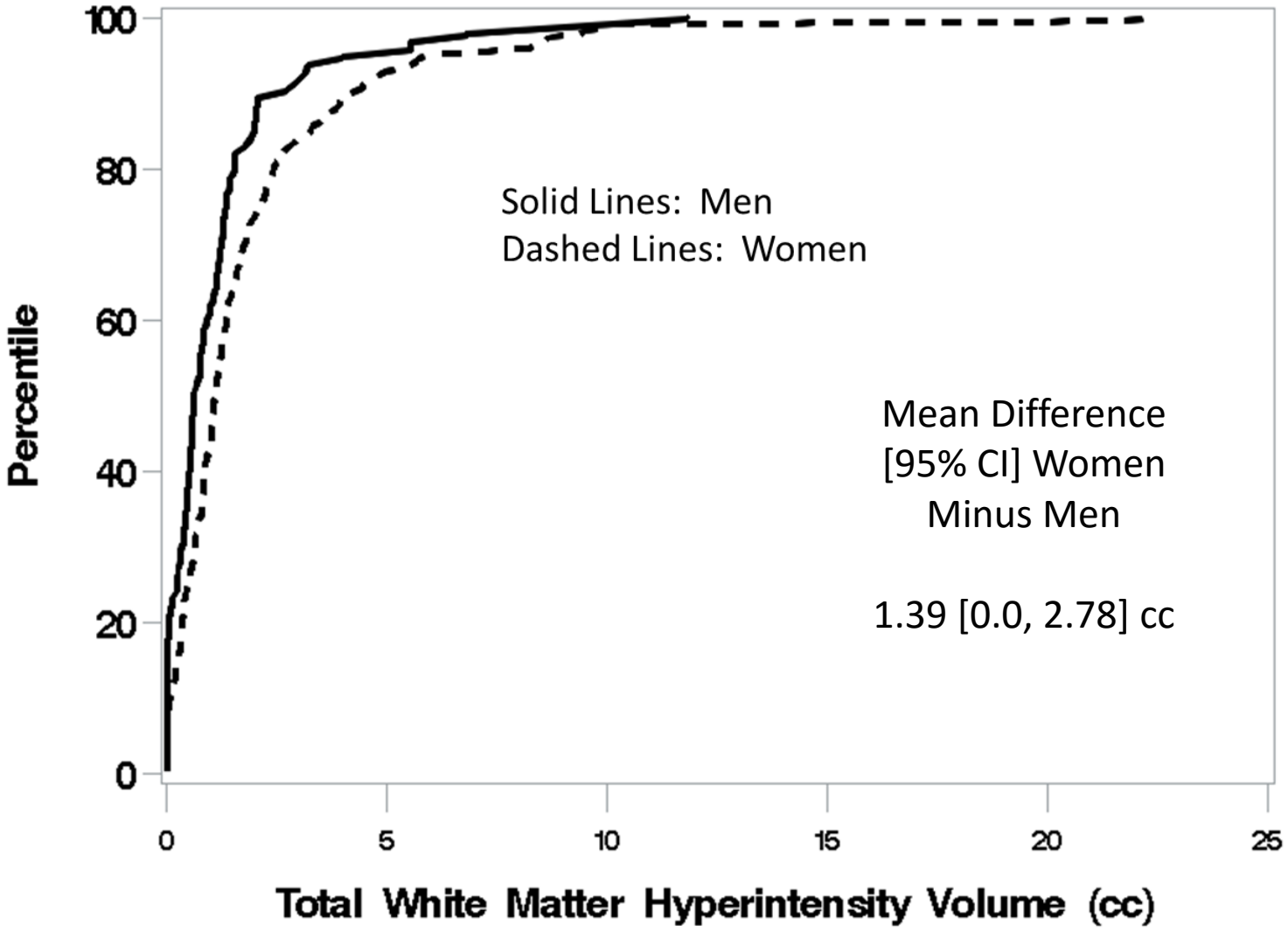
Cumulative Distribution of Adjusted* Summed Brain Volumes By Gender: Women Have Less Evidence of Atrophy



*Adjustment for intracranial volume, age, randomization assignment, and study site.

Espeland M, et al. JGMS 2019 (in press).

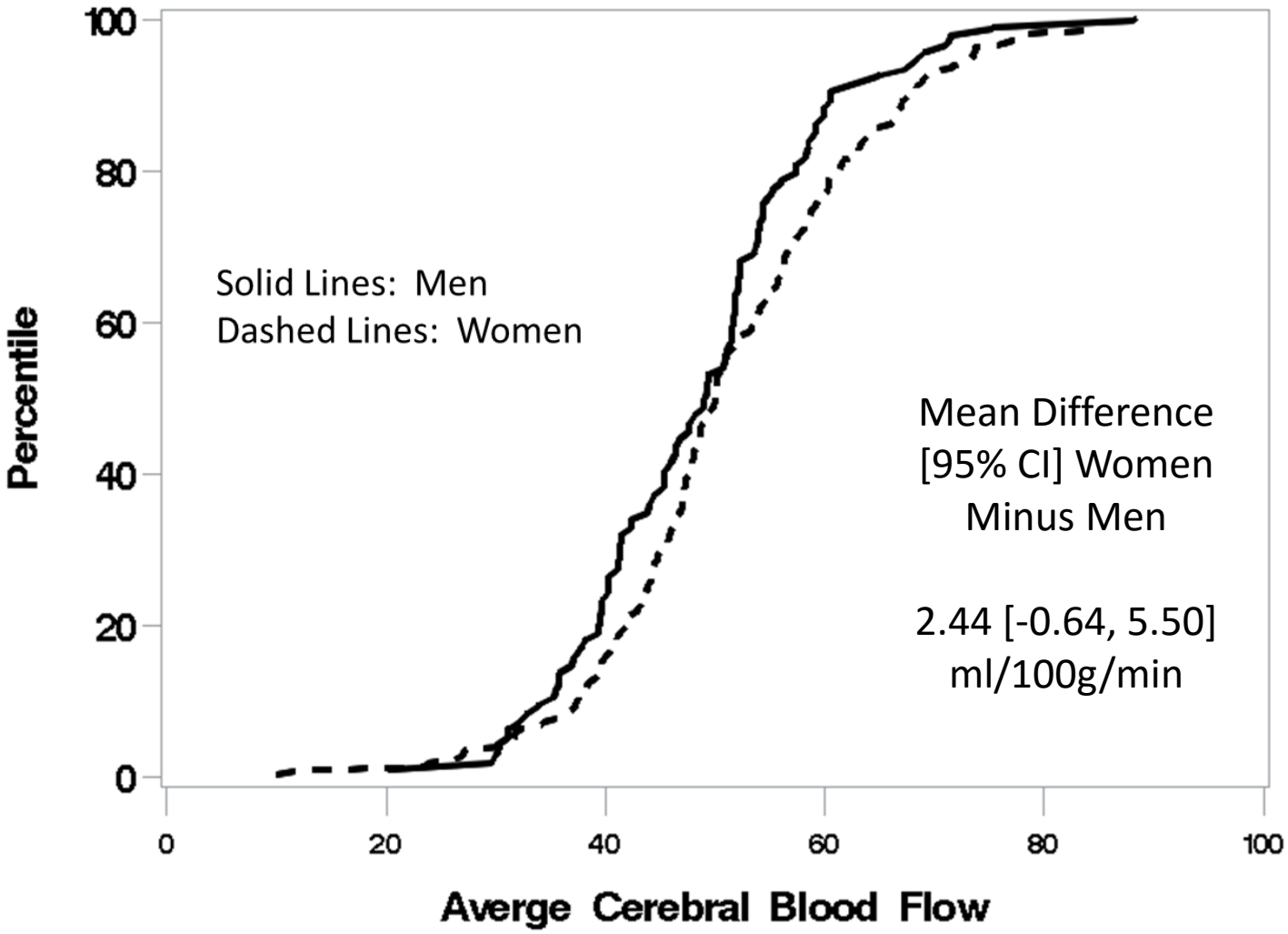
Cumulative Distribution of Adjusted* Summed White Matter Hyperintensity Volumes By Gender: Women Have More Subclinical Cerebrovascular Disease



*Adjustment for age, randomization assignment, and study site.

Espeland M, et al. JGMS 2019 (in press).

Cumulative Distribution of Adjusted* Mean Cerebral Blood Flow By Gender: Women Have Slightly Greater Cerebral Blood Flow



*Adjustment for age, randomization assignment, study site, and systolic and diastolic blood pressure.

Espeland M, et al. JGMS 2019 (in press).

Gender Differences in Cognitive Function Were Unrelated to Differences in MRI Outcomes

Mechanism Underlying Benefits May Be Independent of Subclinical Cerebrovascular Disease and Atrophy


GO
FIGURE

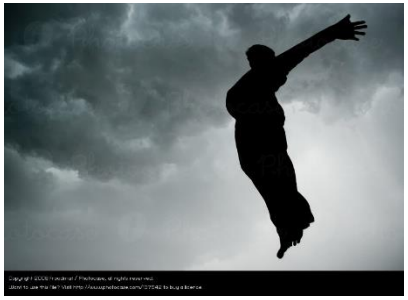
Clues?

- Women's relative advantage is limited to those not carrying the APO-e4 genotype
- Women's relative advantage was stronger among those who had prior exposure to postmenopausal hormone therapy than those who did not
  - However, random assignment to hormone therapy to older women with diabetes increases their risk for cognitive impairment by 83%*, which appears to be driven by brain atrophy**

*Espeland, et al. Diabetes Care 2015;38:2316-24.
**Espeland, et al. Neurology 2015;85:1131-8.

Speculation on Women's Cognitive Benefits

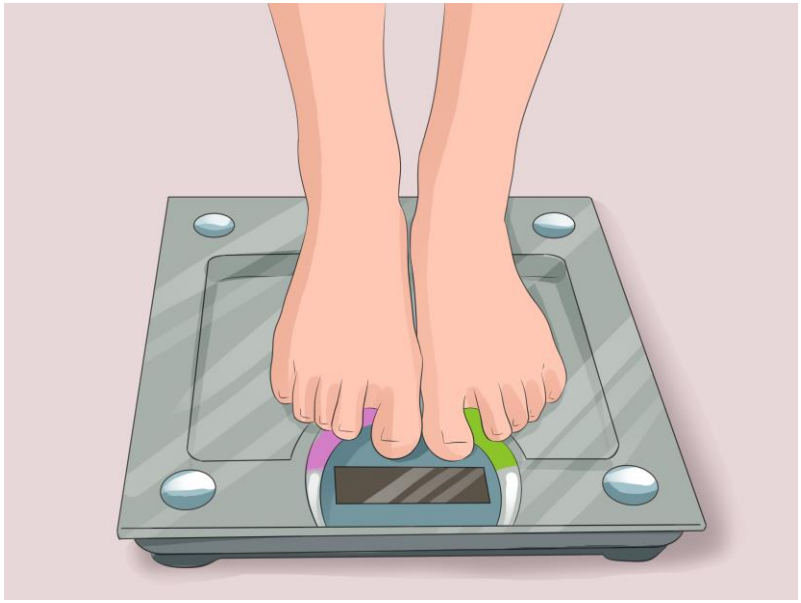
- It may be related to endogenous estrogens and energy metabolism in the brain
  - Postmenopausal women transition to less reliance on glucose metabolism as they age
  - Back-up ketone-based energy sources are increasingly important
  - Glucose sources may not generally be reliable in diabetes
  - Perhaps increased levels of endogenous estrogens related to adipose tissue (and perhaps hormone therapy during the menopausal transition) enhance use of glucose-based energy sources
  - APOE-ε4 women and older women are more dependent on ketone-based energy sources, which may be down-regulated by estrogen, and thus may not be as protected by adiposity



Flying Leap Into the Dark

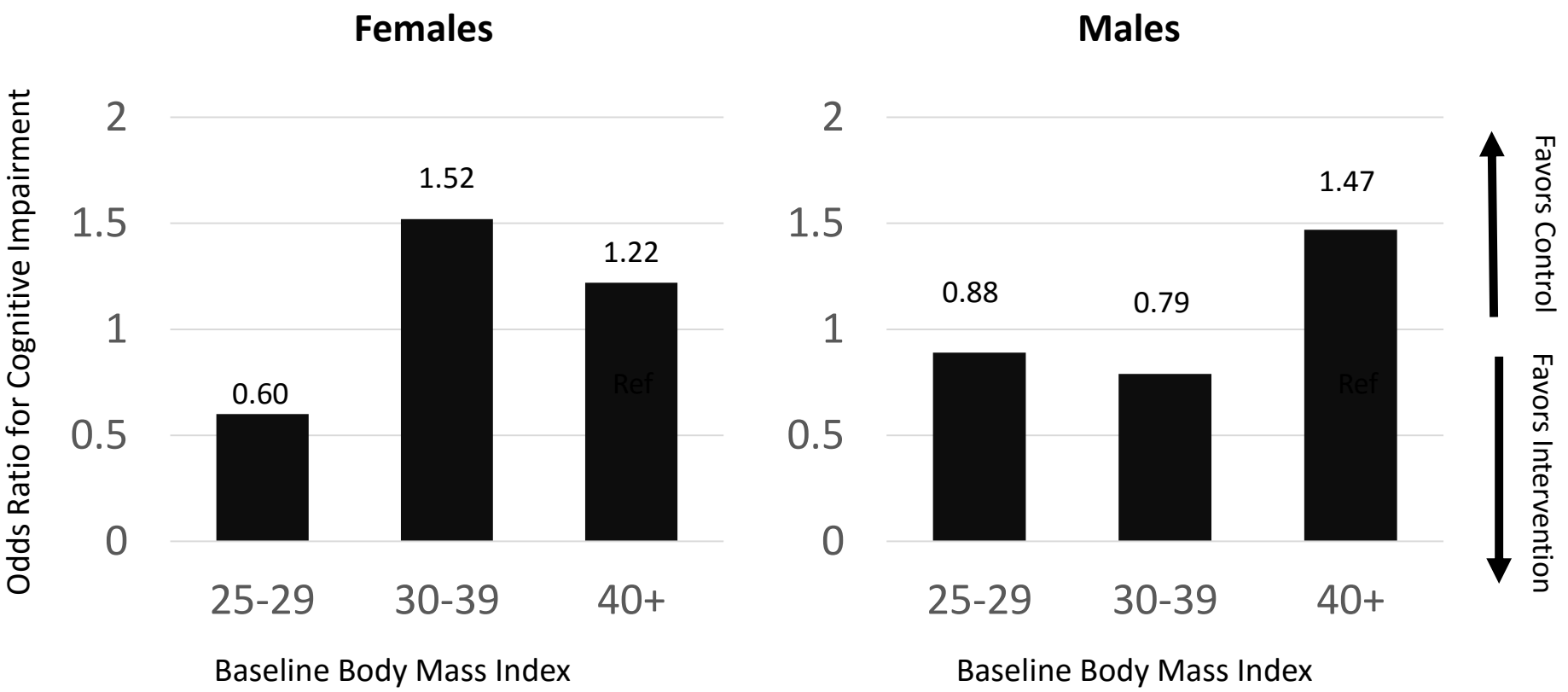
Liedtke S, et al. Obesity, 2012;20:1088-95.
Zhao L, et al. Neurobiol Aging 2016;42:69-69.
Riedel BC, et al. J Steroid Biochem Molecular Biol 2016;160:134-47.

What About Weight Loss?



Cognitive Impairment by Intervention Assignment

Odds Ratios From Logistic Regression With Adjustment for Age, Education, and Race/Ethnicity



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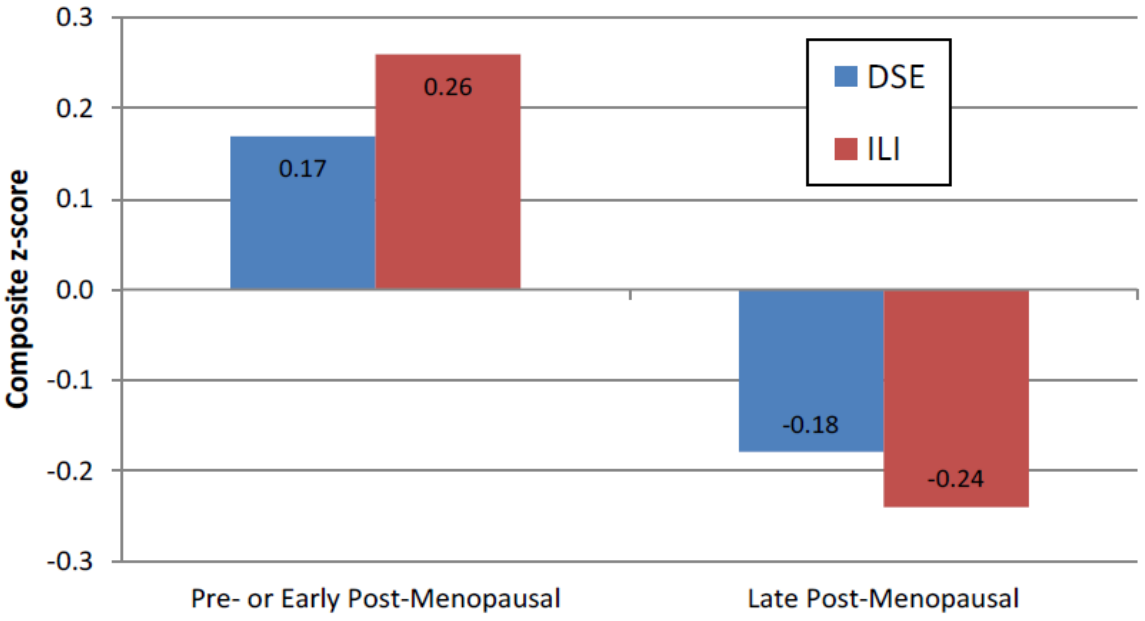
Unpublished Data

Adjusted Mean Composite z-scores by Arm and Menopausal Status



Interaction p value= 0.0295

Yassine H, et al. Under Review, 2019

Conclusion/Discussion

- *Look AHEAD findings on gender-related differences in brain health are intriguing:*
  - *Women have*
    - *Better overall cognitive function*
    - *Lower prevalence of cognitive impairment*
    - *Greater cerebral blood flow*
    - *Larger brain volumes and less evidence of atrophy*
  - *Men have*
    - *Less subclinical cerebrovascular disease*
- *Potential clues*
  - *Women's cognitive benefits appear to be*
    - *Unrelated to risk factors or differences in risk factor relationships*
    - *Unrelated to responses to the lifestyle intervention*
    - *Unrelated to brain structure or cerebral blood flow*
    - *For cognitive impairment: limited to women with prior exposure to hormone therapy and without APO-ε4*
    - *For cognition: Any intervention benefits are limited to women who are <5 years from menopause*

Conclusion/Discussion

- *The Look AHEAD Intensive Lifestyle Intervention appears to*
  - *Benefit both women and men who are initially not obese*
  - *Harm both women and men who are initially very heavy*
- *Ancillary studies to shed light on this are underway*
  - *Look AHEAD MIND*
    - *Cognitive testing; Sex hormones; Angiogenesis markers; Inflammation markers*
- *Look AHEAD is a remarkable platform for developing and conducting gender-related research*

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QUESTIONS ?

Cognitive function test scores (transformed into z-scores), with covariate adjustment for age, education, race/ethnicity, and intervention assignment.

Cognitive Measure	Women N=2323	Men N=1479	p-value
Composite	0.12 (0.02)	-0.18 (0.02)	<0.001
Rey Auditory Verbal Learning			
Immediate	0.23 (0.02)	-0.36 (0.02)	<0.001
Delayed	0.21 (0.02)	-0.33 (0.02)	<0.001
Trail-making Test, seconds			
Part A	0.03 (0.02)	-0.04 (0.02)	0.032
Part B	0.03 (0.02)	-0.04 (0.02)	0.031
Modified Stroop Color and Word Test	0.01 (0.02)	-0.03 (0.03)	0.155
Digit Symbol Coding	0.09 (0.02)	-0.15 (0.02)	<0.001
Modified MiniMental State Exam	0.08 (0.02)	-0.12 (0.02)	<0.001

Markers of Weight Loss and Intervention Adherence				
Diabetes Support and Education	Baseline Mean (SD)	Change From Baseline Mean (SD)		
		Year 1-4 Mean	Year 5-8 Mean	Year 9-12 Mean
Weight, kg				
Women	95.45 (17.45)	-1.10 (6.61)	-2.26 (9.47)	-4.76 (10.50)
Men	108.89 (17.97)	-0.74 (5.29)	-1.11 (8.24)	-3.08 (10.36)
p-value	p<0.001	p=0.210	p=0.007	p<0.001
Waist girth, cm				
Women	111.0 (13.7)	-1.03 (6.58)	-0.490 (8.09)	-0.765 (9.21)
Men	117.8 (13.0)	-0.59 (6.93)	0.942 (8.64)	0.822 (9.86)
p-value	p<0.001	p=0.163	p<0.001	p<0.001
Physical activity, kcal[1]				
Women	675.1 (890.2)	68.2 (888.9)	-48.8 (1003.6)	-205.6 (1115.1)
Men	1166.2 (1290.3)	180.1 (1366.8)	-121.0 (1549.8)	-274.1 (1584.7)
p-value	p<0.001	p=0.147	p=0.410	p=0.462
Intensive Lifestyle Intervention				
Weight, kg				
Women	94.43 (17.74)	-5.58 (6.69)	-4.54 (8.55)	-6.29 (9.97)
Men	108.40 (18.98)	-7.50 (7.51)	-4.89 (8.21)	-5.95 (9.52)
p-value	p<0.001	p<0.001	p=0.377	p=0.466
Waist girth, cm				
Women	109.9 (13.2)	-4.55 (7.42)	-2.00 (8.28)	-1.78 (9.51)
Men	117,8 (13.8)	-6.20 (7.67)	-1.84 (8.19)	-1.25 (8.89)
p-value	p<0.001	p<0.001	p=0.668	p=0.229
Physical activity, kcal[1]				
Women	715.7 (914.3)	544.7 (1163.1)	125.8 (1788.9)	-156.9 (1118.5)
Men	1033.7 (1147.4)	774.8 (1433.2)	235.0 (1826.1)	-30.9 (1589.1)
p-value	p<0.001	p=0.010	p=0.383	p=0.180