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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I think our settings are different...

Yup, you're equipped with a WiFi Antenna & I have a USB port...
Most Alzheimer’s Patients Are Women

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

- Male: 34.6%
- Female: 65.4%

*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.

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

Modifiable Risk Factors for Alzheimer’s Disease: US

Incidence of Dementia By Age

Stockholm, Sweden

Cambridge, U.K.

South-Western France

Europe, pooled data

Framingham, MA

Rochester, MN

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

New cases/1,000/year

Age in years

Men

Women

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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Look AHEAD Timeline

- Design Phase 2000
- Enrollment Begins 2001
- Enrollment Ends 2004
- Year 1 Ends 2005
- Year 4 Ends 2008
- Year 8 Ends 2012
- Intervention Terminated Sept, 2012
- Final Visits Look AHEAD-C Dec, 2014
- Look AHEAD M&M
- Look AHEAD Brain MRI
- Look AHEAD-C Begins 2013
- Look AHEAD-E 2015-2021
- Look AHEAD MIND
- ?

- Look AHEAD - C Begins 2013
- Look AHEAD - E 2015-2021
- Look AHEAD MIND

- ?
## Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Intervention (N=2,570)</th>
<th>Control (N=2,575)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>59%</td>
<td>60%</td>
</tr>
<tr>
<td>Minority</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Age [Range 45-76]</td>
<td>59 years</td>
<td>59 years</td>
</tr>
<tr>
<td>Insulin Users</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>History of Prior CVD Event</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>36 kg/m²</td>
<td>36 kg/m²</td>
</tr>
</tbody>
</table>
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/day in Months 1-4; reduced use thereafter)
- Menu plans provided

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

MEDIAN PERCENT WEIGHT LOSSES BY INTERVENTION ASSIGNMENT

Look AHEAD July, 2018

Termination of Intervention

Percent Weight Loss From Baseline

Years From Randomization
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

Wilcoxon p<0.0001

Predicted Risk for Cognitive Impairment From Logistic Regression

Included: age, CVD, education, depressed mood, intervention assignment*BMI interaction, APOE
Gender Differences Not Explained by Risk Factors or Intervention Effects

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Odds Ratio [95% Confidence Interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Education, Race/Ethnicity, Intervention</td>
<td>0.55 [0.43,0.71]</td>
</tr>
<tr>
<td>Risk Factor Score</td>
<td>0.60 [0.47,0.76]</td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.50 [0.35,0.70]</td>
</tr>
<tr>
<td>Intensive Lifestyle</td>
<td>0.61 [0.43,0.86]</td>
</tr>
<tr>
<td>Changes in HbA1c, Glucose, Weight, Medications</td>
<td>No Change</td>
</tr>
</tbody>
</table>
Cumulative Distribution of Adjusted* Summed Brain Volumes By Gender: Women Have Less Evidence of Atrophy

Mean Difference [95% CI] Women Minus Men

10.9 [3.3, 18.5] cc

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

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

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

Mean Difference [95% CI] Women Minus Men

2.44 [-0.64, 5.50] ml/100g/min

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

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

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

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
What About Weight Loss?
Cognitive Impairment by Intervention Assignment
Odds Ratios From Logistic Regression With Adjustment for Age, Education, and Race/Ethnicity

Females

<table>
<thead>
<tr>
<th>Baseline Body Mass Index</th>
<th>Odds Ratio for Cognitive Impairment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>1.52</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>1.22</td>
<td></td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th>Baseline Body Mass Index</th>
<th>Odds Ratio for Cognitive Impairment</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-29</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td>1.47</td>
<td></td>
</tr>
</tbody>
</table>

Unpublished Data
Adjusted Mean Composite z-scores by Arm and Menopausal Status

Interaction p value= 0.0295

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

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Women N=2323</th>
<th>Men N=1479</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>0.12 (0.02)</td>
<td>-0.18 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate</td>
<td>0.23 (0.02)</td>
<td>-0.36 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed</td>
<td>0.21 (0.02)</td>
<td>-0.33 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trail-making Test, seconds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>0.03 (0.02)</td>
<td>-0.04 (0.02)</td>
<td>0.032</td>
</tr>
<tr>
<td>Part B</td>
<td>0.03 (0.02)</td>
<td>-0.04 (0.02)</td>
<td>0.031</td>
</tr>
<tr>
<td>Modified Stroop Color and Word Test</td>
<td>0.01 (0.02)</td>
<td>-0.03 (0.03)</td>
<td>0.155</td>
</tr>
<tr>
<td>Digit Symbol Coding</td>
<td>0.09 (0.02)</td>
<td>-0.15 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Modified MiniMental State Exam</td>
<td>0.08 (0.02)</td>
<td>-0.12 (0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes Support and Education</td>
<td>Baseline Mean (SD)</td>
<td>Change From Baseline Mean (SD)</td>
<td></td>
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<tr>
<td>--------------------------------</td>
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<tr>
<td></td>
<td></td>
<td>Year 1-4 Mean</td>
<td>Year 5-8 Mean</td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>95.45 (17.45)</td>
<td>-1.10 (6.61)</td>
<td>-2.26 (9.47)</td>
</tr>
<tr>
<td>Men</td>
<td>108.89 (17.97)</td>
<td>-0.74 (5.29)</td>
<td>-1.11 (8.24)</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.001</td>
<td>p=0.210</td>
<td>p=0.007</td>
</tr>
<tr>
<td>Waist girth, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>111.0 (13.7)</td>
<td>-1.03 (6.58)</td>
<td>-0.490 (8.09)</td>
</tr>
<tr>
<td>Men</td>
<td>117.8 (13.0)</td>
<td>-0.59 (6.93)</td>
<td>0.942 (8.64)</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.001</td>
<td>p=0.163</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Physical activity, kcal¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>675.1 (890.2)</td>
<td>68.2 (888.9)</td>
<td>-48.8 (1003.6)</td>
</tr>
<tr>
<td>Men</td>
<td>1166.2 (1290.3)</td>
<td>180.1 (1366.8)</td>
<td>-121.0 (1549.8)</td>
</tr>
<tr>
<td>p-value</td>
<td>p&lt;0.001</td>
<td>p=0.147</td>
<td>p=0.410</td>
</tr>
</tbody>
</table>

| 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, kcal¹       |                   |               |               |               |
| 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        |