Why are more women than men diagnosed with Alzheimer's?

Introduction: Several hypotheses have been posed but, to date, no empirical model has explained the difference in AD diagnosis between women and men. Advances in brain imaging are making it possible to empirically test a hypothesis that brain volume (BV) moderates associations between AD's pathologic mechanisms and presentation of clinical symptoms. BV is a sexually dimorphic and continuous characteristic, whereby men, being on average physically larger, tend to have larger BV than women.

Methods: A two-stage statistical model was developed using 2010 Census data and the National Alzheimer's Coordinating Center uniform data set. In stage one, relative risk estimates of AD diagnosis were calculated for BV, age, identified race, and sex/gender. Stage-two estimated an adjusted AD diagnosis risk in the 65+ population. This step used stage-one estimates, except that risk for self-report men and women was held equal.

Results/Discussion: We report the results of this analysis and briefly describe two lines of future study within this research agenda that aim to advance study of sex/gender in AD.

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PENN PROGRAM on PRECISION MEDICINE for the BRAIN

Background

65+	US Census	AD Patients
Women	56.9%	62.5%
Men	43.1%	37.5%

Relative risk ratio in women vs men = 62.5 / 37.5 = 1.67.

No data model to date explains the difference between men and women.

NARRATIVE: Introduction: The population risk of an Alzheimer's disease (AD) diagnosis in women compared to men is 1.67. Why are more women than men diagnosed with AD?

Several hypotheses have been posed but, to date, no empirical model has explained the difference in AD diagnosis between women and men. Advances in brain imaging are making it possible to empirically test a hypothesis that brain volume (BV) moderates associations between AD's pathologic mechanisms and presentation of clinical symptoms. BV is a sexually dimorphic characteristic, whereby men, being on average physically larger, tend to have larger BV than women.

Method

All National Alzheimer's Coordinating Center (NACC) uniform data set (UDS) participants with MRI volume data available

- MRI data from first MRI of record
- UDS clinic data from visit closest to MRI visit
- Sample size: 1088 unimpaired or AD primary pathology 65+ years old.
  - 646 Cognitively unimpaired
  - 453 Cognitively impaired

- The distribution of brain volume (BV) in cognitively unimpaired participants was segmented into percentiles.
- General linear model with binomial family and log link were used to estimate risk-adjusted risk ratios (RRs) of AD diagnosis

- Example:

BV 25th Percentile	AD Diagnosis: Yes	AD Diagnosis: No
Yes	A	B
No	C	D

$$RR = \frac{(A/(A+B))}{(C/(C+D))}$$

RR x prevalence = predicted proportion of disease in a population

Narrative: To test this hypothesis, a two-stage statistical model was developed using 2010 Census data and the NACC UDS. In stage one, relative risk estimates of AD diagnosis were calculated for BV, age, self-identified race, and sex/gender. Stage-two estimated an adjusted AD diagnosis risk in the 65+ population. This step used stage-one estimates, except that risk for self-report men and women was held equal.

The analyses adjust for age and race as these characteristics varied with brain volume.

Adjusting for probability of being man or woman at a given brain volume explains disparity in AD diagnosis.

Example: 25th Percentile

WOMEN: [(**0.57**+(0.188*__**0.36**__)(1.75*1.2*1.1) + (**0.57**+(1-0.188)*__**0.36**__)*(1*1.2*1.1)]

MEN: [(**0.43**+(0.188*__**0.07**__)(1.75*1.2*1.1) + (**0.43**+(1-0.188)*__**0.07**__)*(1*1.2*1.1)]

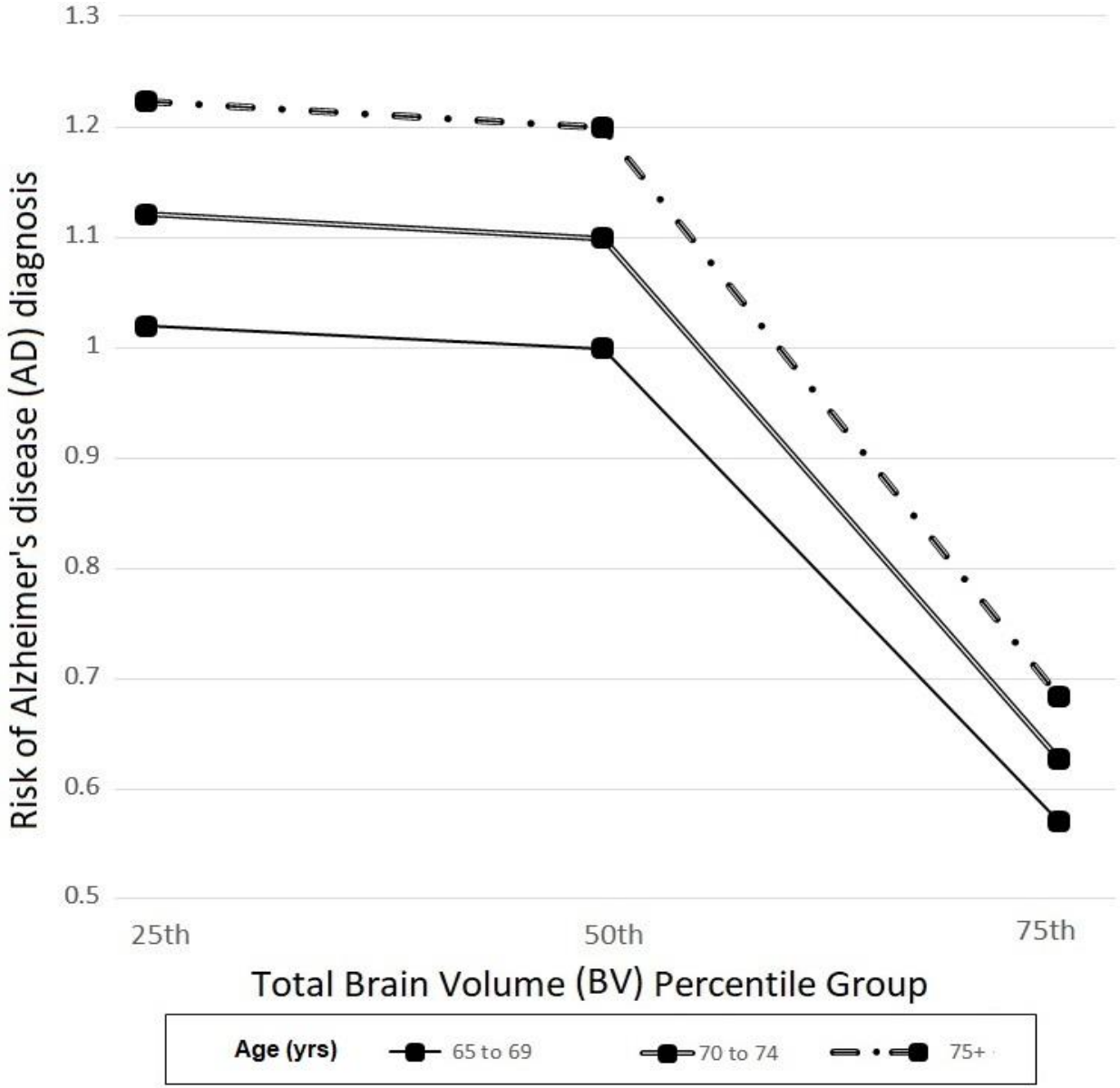
Sex, Race & Age Risk-Adjusted Relative Risk (RR)

	25th %tle	50th %tle	75th %tle	Overall
Women	1.12	0.93	0.57	0.99
Men	0.56	0.75	0.48	0.68
RR Ratio	2.01	1.67	1.05	**1.67**

Narrative: So what happens to the proportions of men and women diagnosed with AD when you assume the risks posed to the two groups are the same? Here are the equations for the lower 25th percentile. One for men. One for women. Please note that almost all the numbers between the two equations are the same with a couple exceptions that I've underlined and bolded. Those numbers adjust for two things, which I've color coded. First, the probability of being a man or woman in the 65+ general public (purple). Second, the probability of being a man or women in the 25th percentile of the brain volume distribution (green).

Narrative: The race and age adjusted relative risk of AD diagnosis in the mid-range of the BV distribution (50th%tle) was 0.93 for women and 0.75 for men. The overall population risk ratio of AD diagnosis risk matched the observed lifetime population risk of 1.67.

Brain volume (BV) and age adjusted risk of Alzheimer's disease (AD) diagnosis



Narrative: Let's look here at a visual summary. This figure shows risk estimates of Alzheimer's diagnosis. We show just one set of lines because a line is the same for a man or woman. Each line represents risk of diagnosis. As you read from left to right, the risk changes with increasing amounts of brain volume. I show three of these lines, one for each age group. And you can see, as expected, older age is associated with a relatively higher risk of diagnosis.

Keenly, what's observable here is that we can think about this as a higher risk of diagnosis in lower brain volumes OR we can see that above the 50th percentile of brain volume there's a significant protective factor.

Conclusion: Size Matters

- Women are diagnosed with AD more than men because brain size matters
  - Binary sex has no effect on risk of diagnosis in analysis adjusted for total brain volume

- **Two Next Steps:** Conduct a series of studies using existing data from AD prevention trials and population aging cohorts in order to:
  - Further evaluate the study hypothesis: a) summarize extant literature in a peer-reviewed publication, and b) replicate the findings in cross-sectional and longitudinal samples. This work will inform an application for an administrative supplement to the PI's new investigator grant (K23).
  - Characterize contributions of gender, biologic sex, and their interactions to variance in BV and test associations between total and regional BV and specific clinical symptom presentations. The results will generate pilot data to compete successfully for an R01.

- **Narrative:** The study results support the study hypothesis. If substantiated in further investigations, this information would be a notable advance in the field of AD, offering an important insight into the disease mechanism that could help inform development of a disease-modifying intervention.

Thank you.

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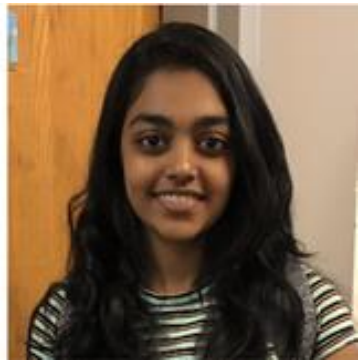

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