Incidence and Prevalence of Alzheimer's Disease and Related Dementias (ADRD) among Men and Women

MICHELLE M. MIELKE, PHD
CHAIR, DEPARTMENT OF EPIDEMIOLOGY AND PREVENTION
PROFESSOR OF EPIDEMIOLOGY
PROFESSOR OF GERONTOLOGY AND GERIATRIC MEDICINE

Wake Forest University
School of Medicine

The academic core of Atrium Health

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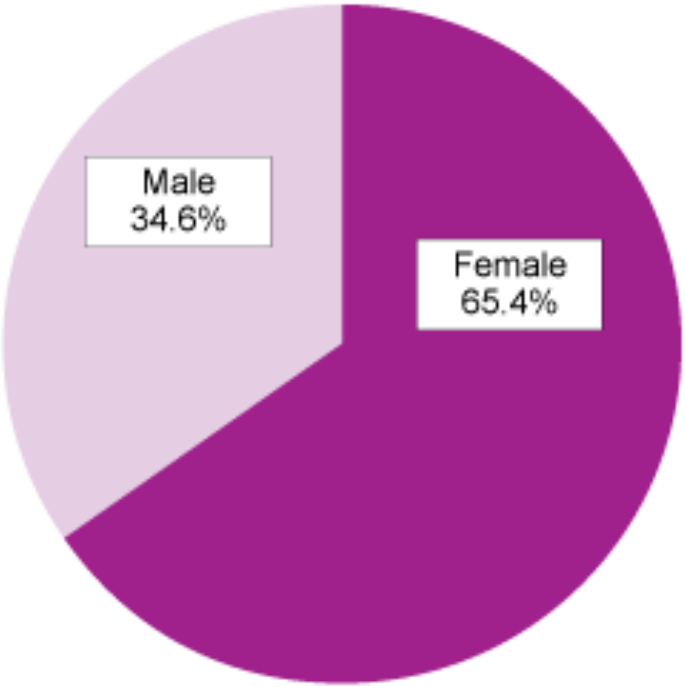
Outline

- Epidemiology of sex and gender differences in Alzheimer's disease and related dementias
- Sex and gender differences in risk factors
- Sex-specific risk factors

Are More Women Affected by AD
and
Are Women at Greater Risk?

More Women than Men have a Diagnosis of AD

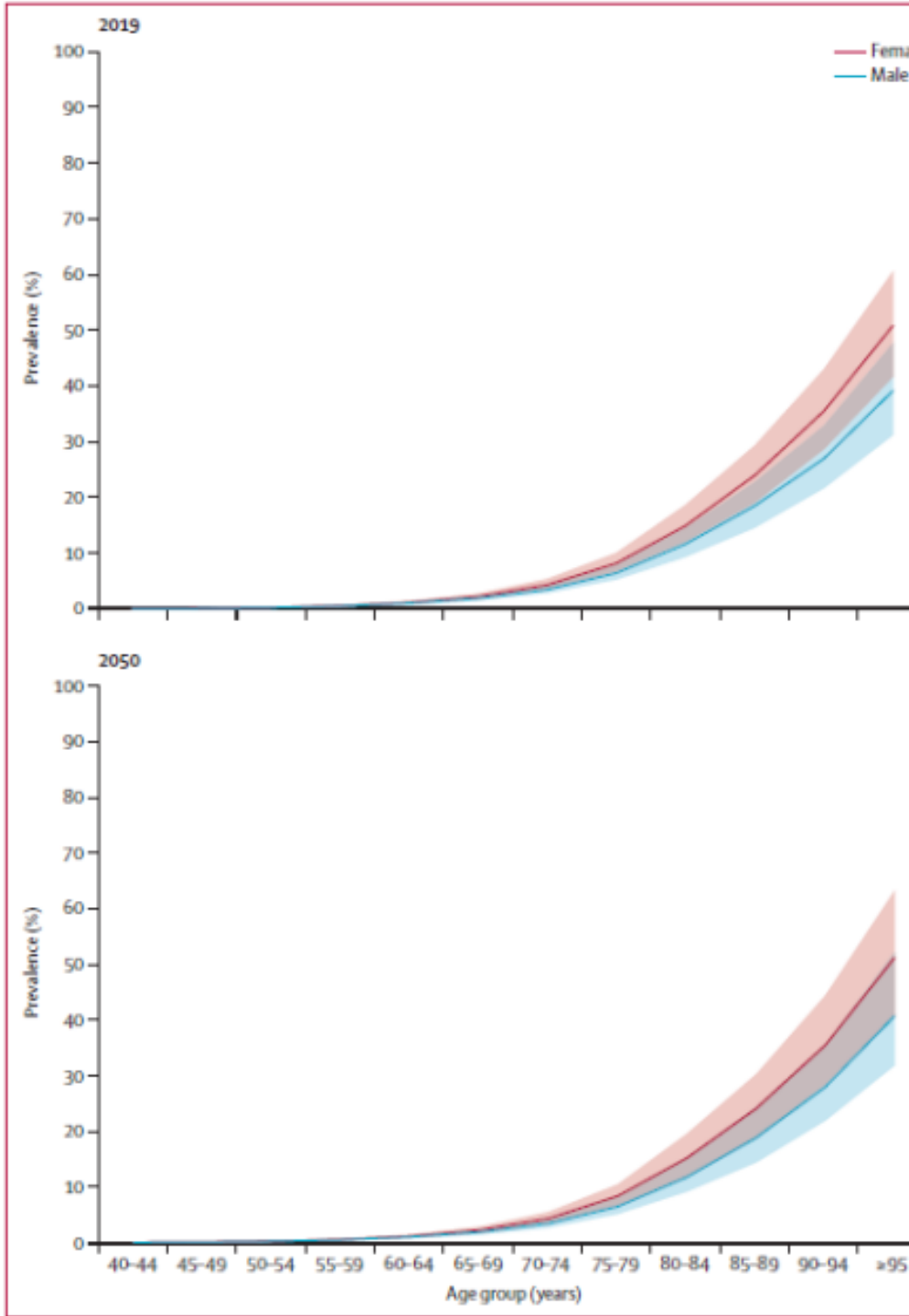
Adults Aged 65 and Older with Alzheimer's Disease,* By Sex, 2011



**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.*

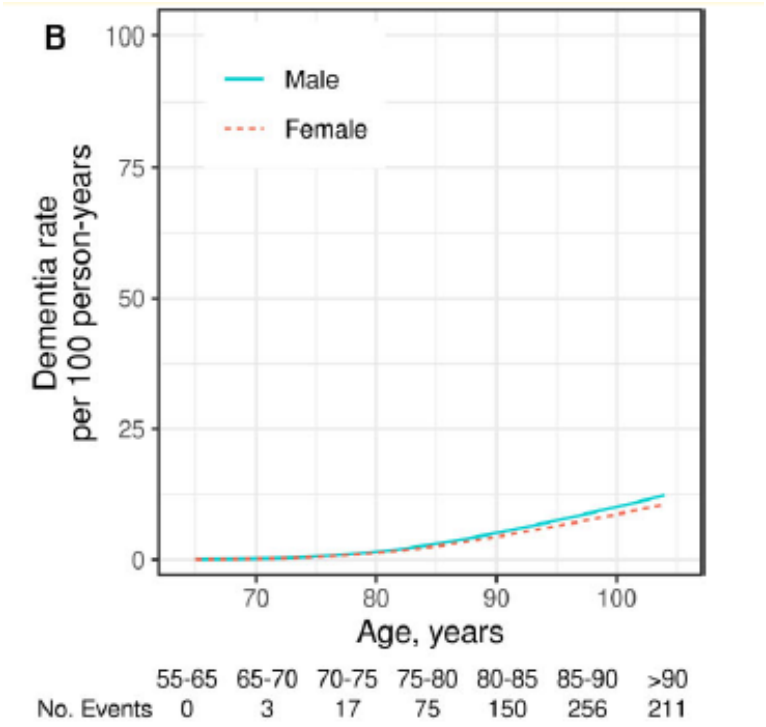
Source: Alzheimer's Association. 2011 Alzheimer's Disease Facts and Figures. Retrieved from http://www.alz.org/alzheimers_disease_facts_and_figures.asp. Accessed 07/11/11.

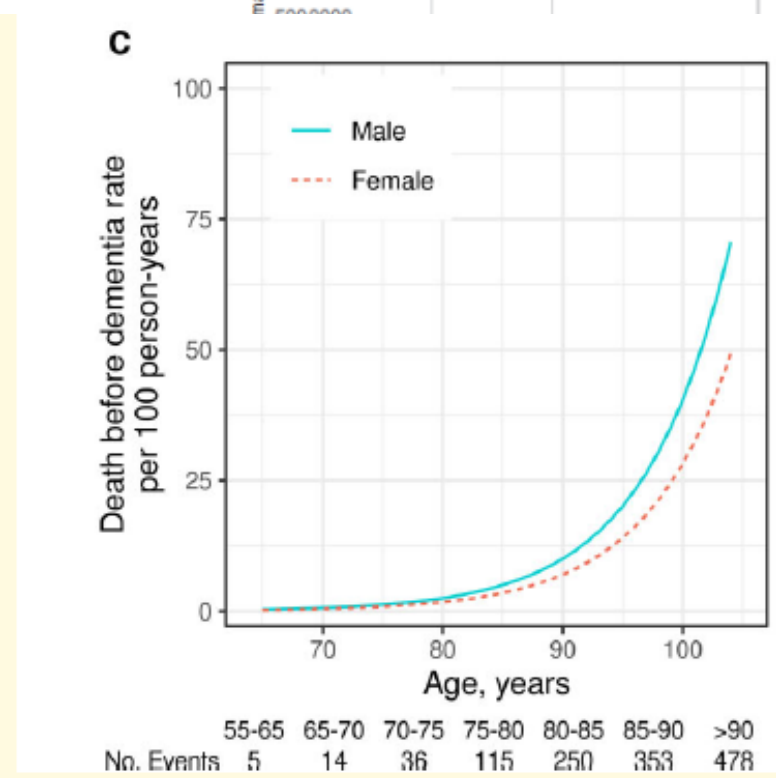
Global age-standardized prevalence of Alzheimer's disease and other dementias

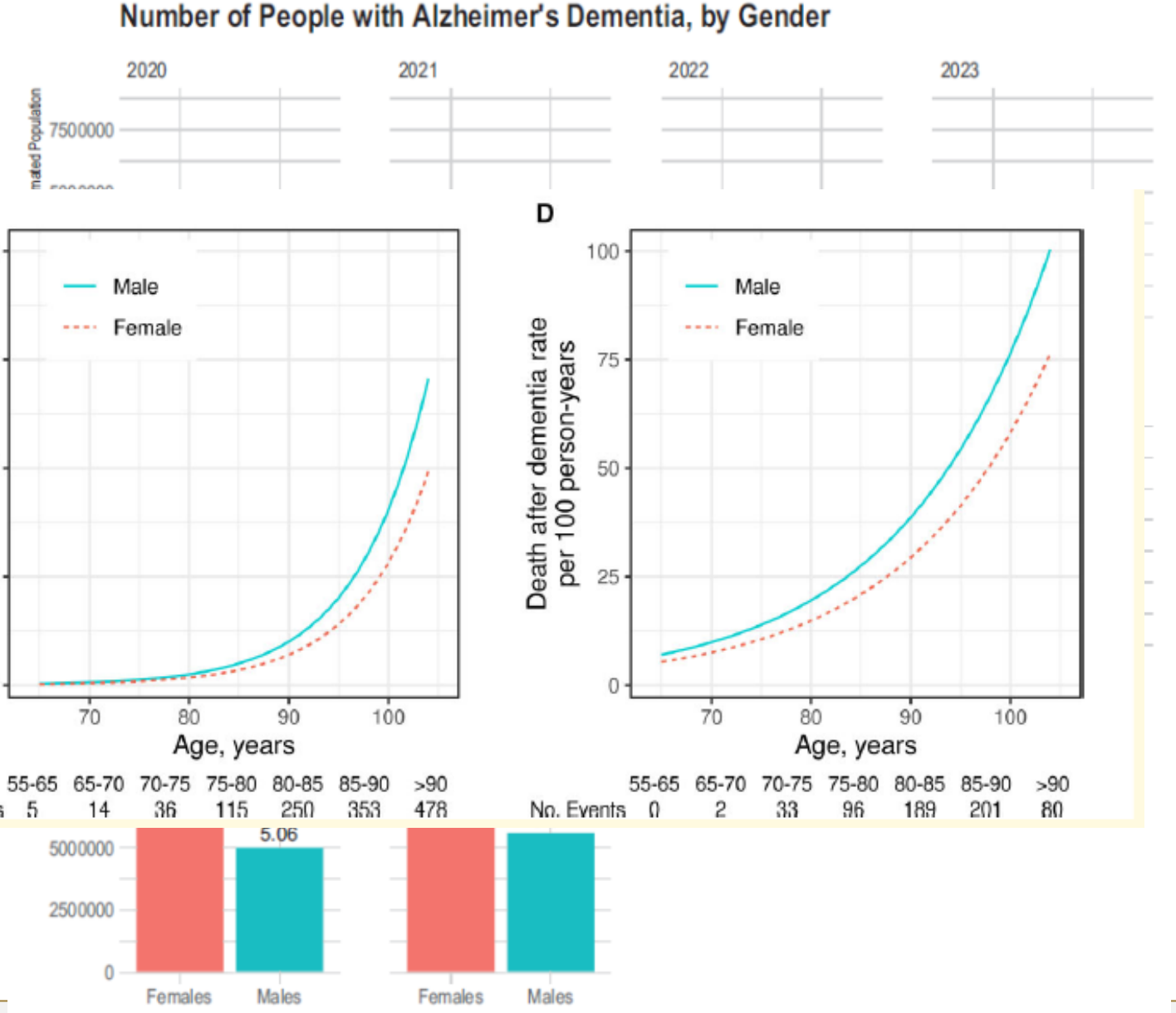


GBD 2019 Dementia Collaborators, Lancet, Neurology

US prevalence estimates

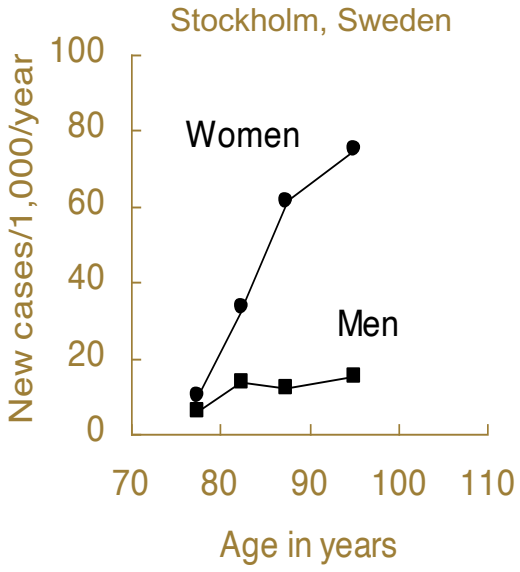


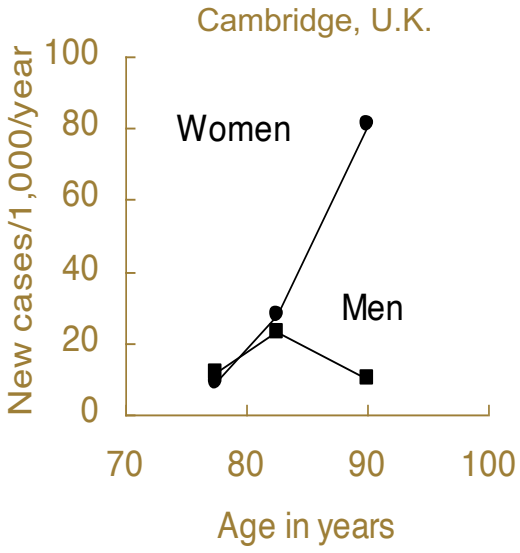


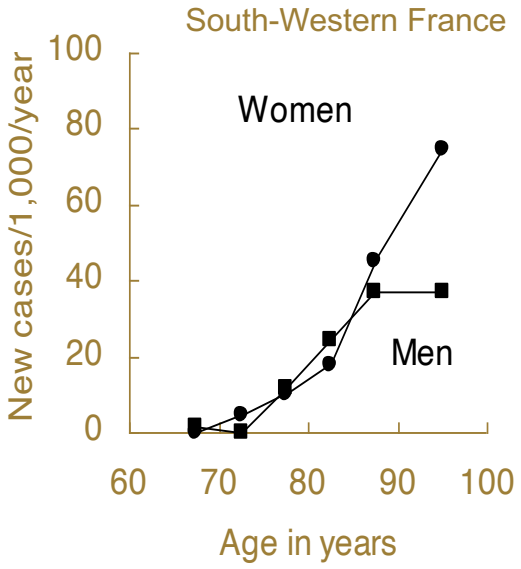


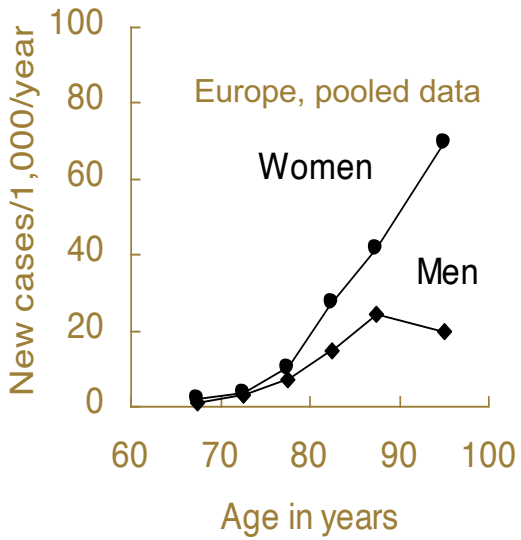
Rajan KB et al. 2021 Alzheimer's & Dementia; Jack CR et al. 2022 Brain Comm

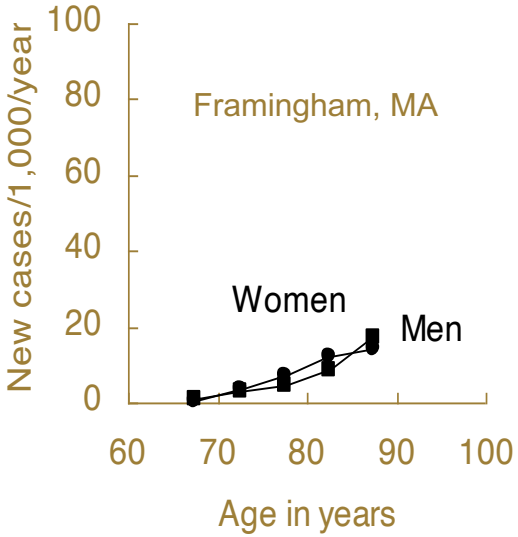
Are women at greater risk?

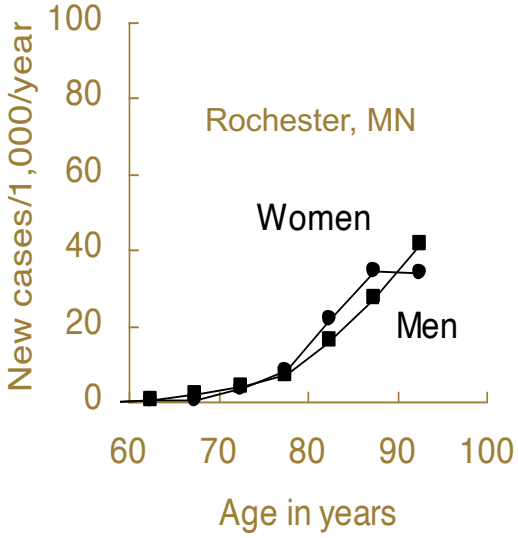












Edlund S et al, Arch Neurology, 2002

Other incidence studies

Women at greater risk at older ages (>85 or 90 years)

- Rotterdam study – increased risk after 90 (Ruitenberg et al., 2001)
- Cache County study - increased risk after 85 (Miech et al., 2002)

No differences:

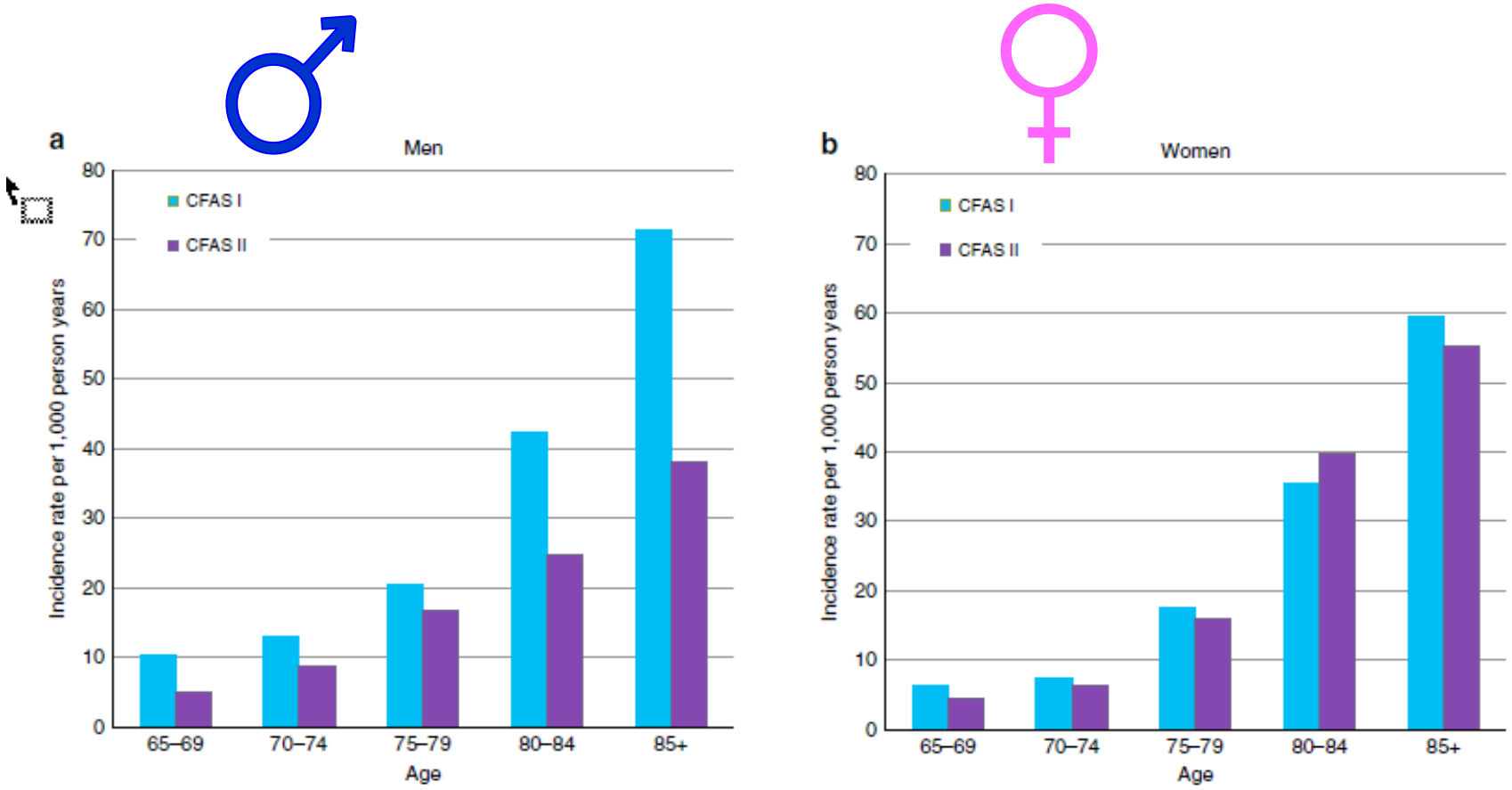
- Cardiovascular Health Cognition Study, Religious Order Study, EPESE project, Canadian Study of Health and Aging, BLSA, 90+ study
- Fiest et al (2016) – systematic review and meta-analysis of 22 studies
  - Trend for women, but not statistically significant

European meta-analysis

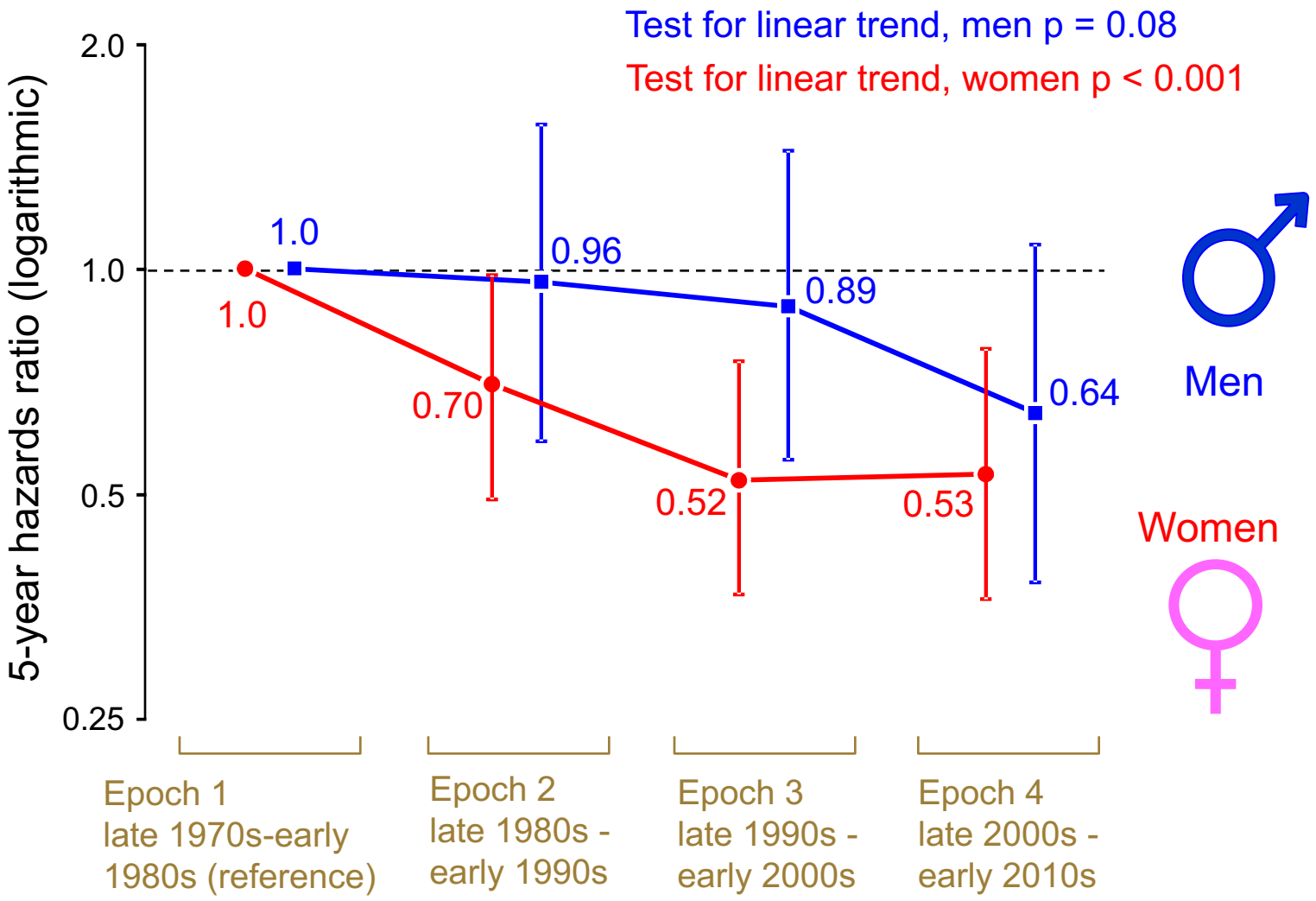
- Niu et al (2017) – 11 European studies
  - Men: 7.02/1000 person-years
  - Women: 13.25/1000 person-years

Time trends for dementia in the United Kingdom 1989-2011

Cognitive Function and Aging Studies I and II



Incidence of dementia in Framingham, MA



Satizabal et al., 2016

Potential Explanations for Disparities

- Mixed dementia pathologies
- Differential diagnosis by sex (Liesinger AM et al. 2018; Sundermann E et al., 2019)
- Social, cultural, historical events (Time & Place)
  - World War II and Cold-War
  - Would European countries see a similar sex difference in future generations?
  - What about other countries/regions?
    - Avon & Hachinski 2022 Alz Dem – Men 1.8-fold great increase 1990-2019 BUT dependent on country
  - Sociocultural factors – impact of gender

Gender Norms (1) - Education

- Historically, women have had less access to education compared to men; differs by country/region

- Bloomberg et al. (2021) – English Longitudinal Study of Ageing and Whitehall Study
    - N>15,000 participants born between 1930 and 1955; 19 years of follow-up
    - Women performed better in memory
    - Memory decline faster in men vs. women after considering education
    - Women in latest birth cohort and highest education group had better memory and fluency scores

- Results suggest role of education and secular changes in education level in determining cognitive performance in women

Bloomberg et al. 2021, Lancet Public Health

Gender Norms (2) – Work/Family

- Mayeda et al. (2020) – Health and Retirement Study
  - Objective: assess whether life course patterns of employment, marriage, and childrearing between 16-50 years influence memory decline after age 55

Figure 1 Estimated memory trajectories (95% confidence intervals) by work-family profile among women born between 1935 and 1956 in the Health and Retirement Study

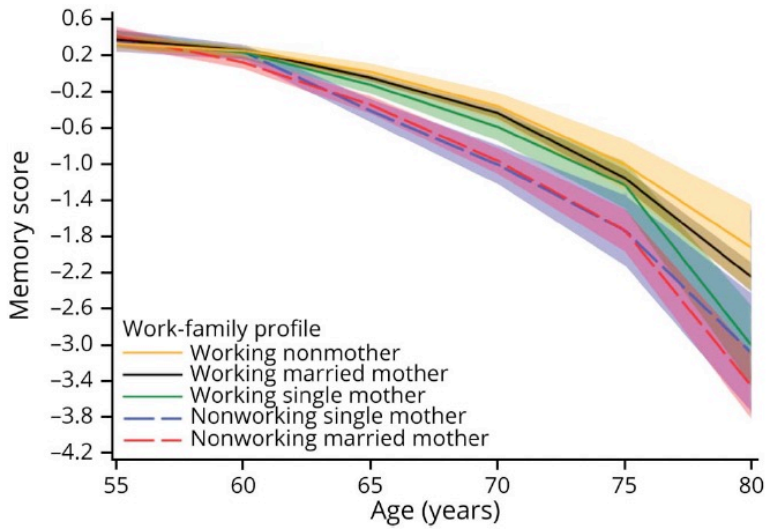
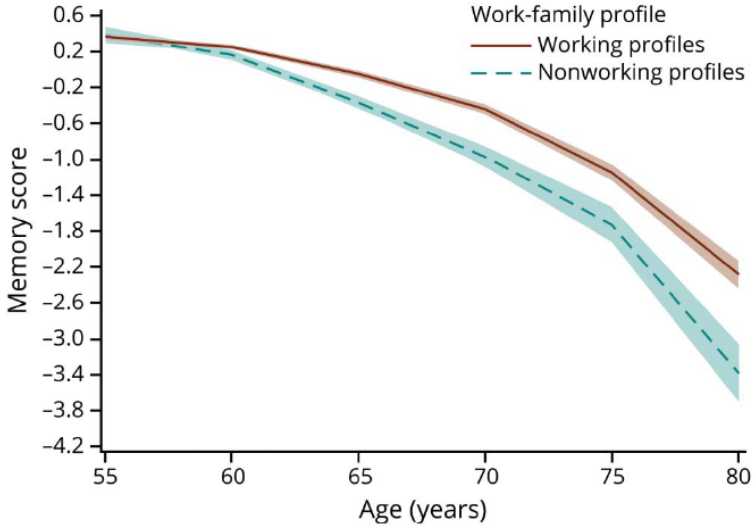


Figure 2 Estimated memory trajectories (95% confidence intervals) by working vs nonworking profiles among women born between 1935 and 1956 in the Health and Retirement Study



Mayeda ER et al. 2020, Neurology

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PERSPECTIVE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective

Michelle M. Mielke[1,2] | Neelum T. Aggarwal[3,4] | Clara Vila-Castelar[5] | Puja Agarwal[4,6] | Eider M. Arenaza-Urquijo[7,8,9] | Benjamin Brett[10] | Anna Brugulat-Serrat[7,8,9,11] | Lyndsey E. DuBose[12] | Willem S. Eikelboom[13] | Jason Flatt[14] | Nancy S. Foldi[15,16] | Sanne Franzen[13] | Paola Gilsanz[17] | Wei Li[18] | Alison J. McManus[19] | Debora Melo van Lent[20,21,22] | Sadaf Arefi Milani[23] | C. Elizabeth Shaaban[24] | Shana D. Stites[25] | Erin Sundermann[26] | Vidyani Suryadevara[27] | Jean-Francoise Trani[28] | Arlener D. Turner[29] | Jet M. J. Vonk[30,31] | Yakeel T. Quiroz[5,32] | Ganesh M. Babulal[33,34,35] | for the Diversity and Disparity Professional Interest Area Sex and Gender Special Interest Group

Little research in LMICs – fastest growing incidence of age-related disease

<u>Sex and gender-related impact:</u>
Child marriage
Intimate partner violence
Female genital mutilation
War/trauma
Political and governmental systems
*Healthcare access

Despite equivocal findings and uncertainty that risk of AD and other dementias differ by sex,
do we continue to explore sex and gender differences in AD?

Absolutely!!!

Risk Factors

Examples of Sex Differences in Risk Factors for MCI in the Mayo Clinic Study on Aging, aged 70+

- **Both**
  - Education<12 years
  - Memory concerns
  - Stroke
  - Atrial fibrillation
- **Women**
  - Current smoker
  - Midlife hypertension
  - Midlife high cholesterol
- **Men**
  - BMI≥30
  - Never married/widowed

Pankratz S et al., Neurology 2015

Sex-specific factors for females

- Pregnancy
  - Gestational diabetes, hypertensive pregnancy disorders (HPD)
- Menopause
  - Ovarian insufficiency or Bilateral oophorectomy prior to the age of 40 years
  - Transition
- Hormone use
  - Contraceptives (varying doses and medications)
  - Menopausal Hormone Therapy
  - Breast Cancer Treatments/Preventive medications

Menopausal transition

- Menopause as a risk factor for ADRD?
  - Many changes over the transition – cardiovascular, fat redistributions
  - Brain changes may be temporary (e.g., Mosconi et al. 2021)
- All women go through menopause BUT all do not develop AD
- What aspects of the menopause transition can help identify women at greater risk of poorer brain health?
  - More severe hot flashes
  - More severe mood changes
  - Reproductive span
  - ***Age***

Table 2. Associations of Bilateral Oophorectomy With MCI at the Time of Cognitive Evaluation

Bilateral oophorectomy strata	MCI (n = 283) No. (%)	Unimpaired (n = 2449) No. (%)	Unadjusted[a] OR (95% CI)	Unadjusted[a] *P* value	Adjusted[b] aOR (95% CI)	Adjusted[b] *P* value
Overall						
Without bilateral oophorectomy	202 (71.4)	1905 (77.8)	1.0 (referent)	–	1.0 (referent)	–
With bilateral oophorectomy	81 (28.6)	544 (22.2)	1.26 (0.95-1.66)	0.11	1.26 (0.94-1.68)	0.13
Age at bilateral oophorectomy before menopause, y						
<46[c]	30 (10.6)	131 (5.4)	2.11 (1.37-3.25)	<0.001	2.21 (1.41-3.45)	<0.001
46-49	10 (3.5)	88 (3.6)	1.01 (0.51-2.00)	0.97	0.79 (0.37-1.68)	0.54
≥50	14 (5.0)	103 (4.2)	1.20 (0.67-2.16)	0.54	1.25 (0.69-2.26)	0.47
Indication for bilateral oophorectomy[f]						
Cancer	2 (0.7)	15 (0.6)	0.96 (0.21-4.34)	0.96	1.01 (0.22-4.64)	0.99
Benign ovarian condition	17 (6.1)	60 (2.5)	2.44 (1.38-4.31)	0.002	2.43 (1.36-4.33)	0.003
No ovarian condition	16 (5.8)	131 (5.4)	1.22 (0.70-2.11)	0.48	1.07 (0.58-1.96)	0.83

Rocca WA...Mielke MM, JAMA Network Open 2021

Discussion

- More women than men have AD; incidence is equivocal
  - Even with the same prevalence of a disease, risk factors can differ by sex
- There are too few studies that examine sex and gender differences; typically adjust instead
  - Need uniform reporting
  - More diverse cohorts (e.g., bilateral oophorectomy/hypertensive pregnancies)
- Intersection between sex/gender and diversity/disparities

Thank You!

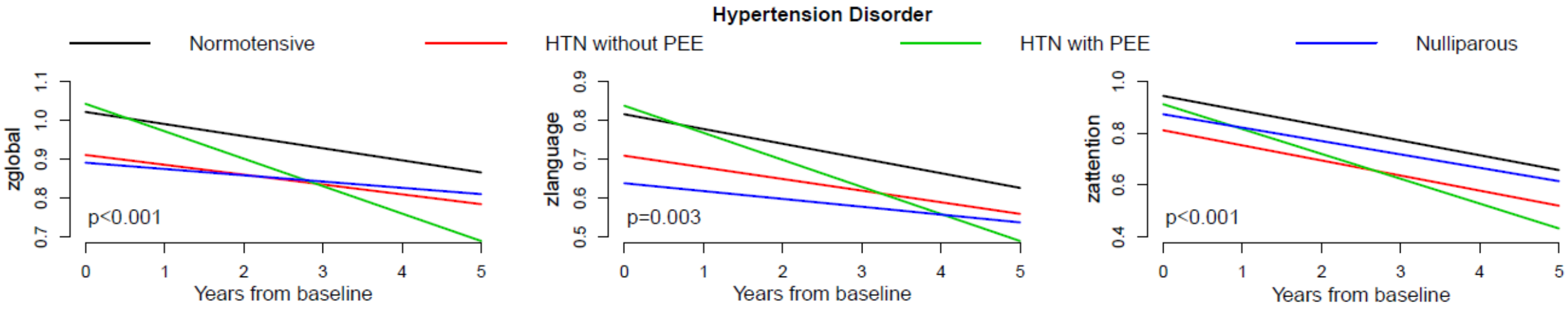
Mielke.Michelle@wakehealth.edu

Pregnancy and Risk of Dementia

- Historical and recent literature
  - Number of pregnancies and risk of dementia
- What is the mechanism?
  - Hormones, stress, inflammation, vascular, etc.
- Pregnancy is a ‘stress test’
- Hypertensive pregnancy disorders associated with worse cognitive performance and lower brain volume at a mean of 60 years (Mielke MM et al., 2016)
- Pre-eclampsia associated with lower grey area volumes and MCI (Fields et al., 2016; Raman et al., 2017)
- *Relationship with Alzheimer’s or vascular pathology and general brain aging?*

HPD associated with cognitive decline

Among 2,261 women in Mayo Clinic Study of Aging (median of 74 years at baseline):



Neuroimaging results:

- Associated with increasing white matter hyperintensities and worsening white matter integrity
- No association with amyloid or tau PET

Mielke MM et al. Neurology 2023