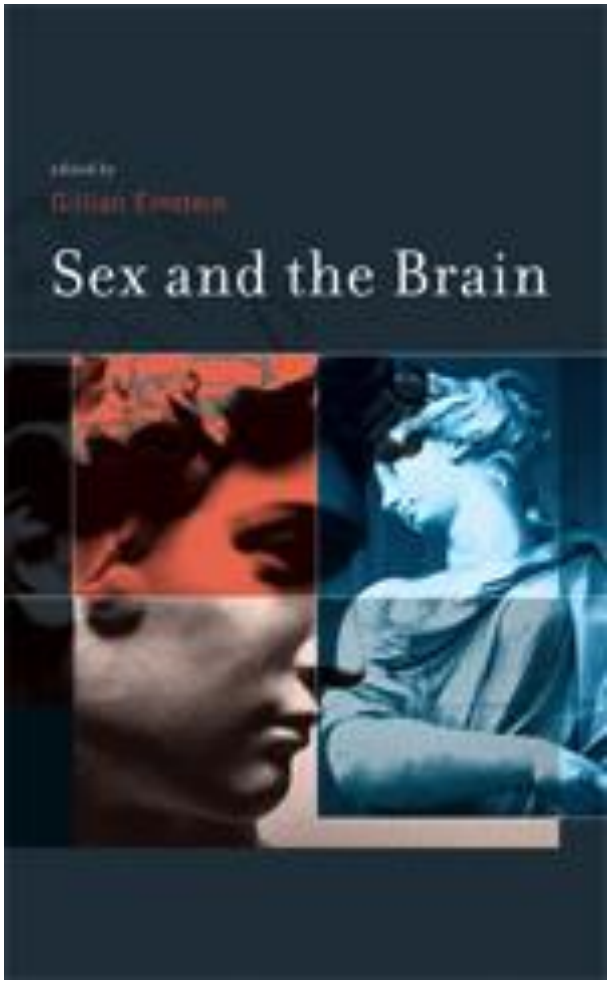

Why Do More Women than Men Have Alzheimer's Disease?

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CCNA CCNV
Canadian Consortium on Neurodegeneration in Aging
Consortium canadien en neurodégénérescence associée au vieillissement

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vii. Other: Employee of XXY Hospital Group: **NO**

I have no disclosures.

CFPC Conflict of Interest Template

Why do more women than men have AD?

Plan:

i. Sex and Gender

ii. Sex and Gender differences in AD

iii. 17-β estradiol and its effects on brain

iv. How does 17-b estradiol loss in younger women progress to an increased risk of AD?

v. Future Directions

Introduction:
Sex & Gender affect the brain

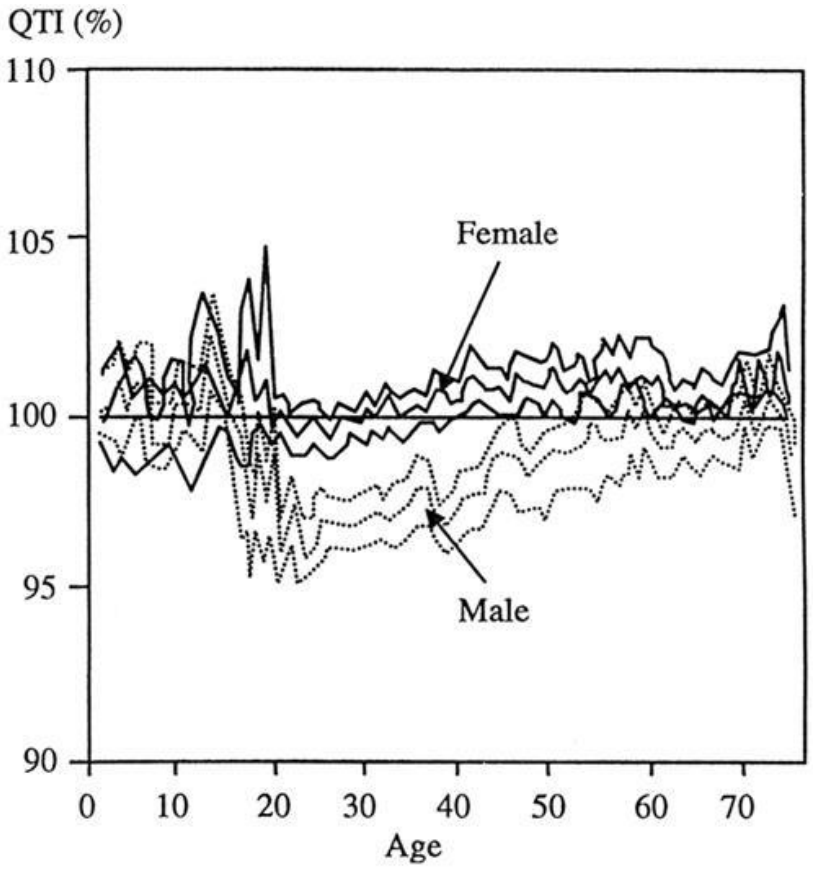
- Biological Factors = Sex
- Social Factors = Gender

Increases Scientific Rigour

Canadian Institutes of Health Research Institute of Gender & Health, established 2000

Biological Factors: Sex

Disease	Female/Male Ratio
Hashimoto thyroiditis	10
Primary biliary cirrhosis	9
Chronic active hepatitis	8
Graves' hyperthyroidism	7
Systemic lupus erythematosus[a]	6
Scleroderma	3
Rheumatoid arthritis	2.5
Idiopathic thrombocytopenic purpura[a]	2
Multiple sclerosis	2
Autoimmune hemolytic anemia	2
Pemphigus	1
Type 1 diabetes[a]	1
Pernicious anemia	1
Ankylosing spondylitis	0.3
Goodpasture nephritis / pneumonitis	0.2
[a]Age specific	



Immune System

Cardiovascular system

Villareal et al., 2001

Social Factors: Gender

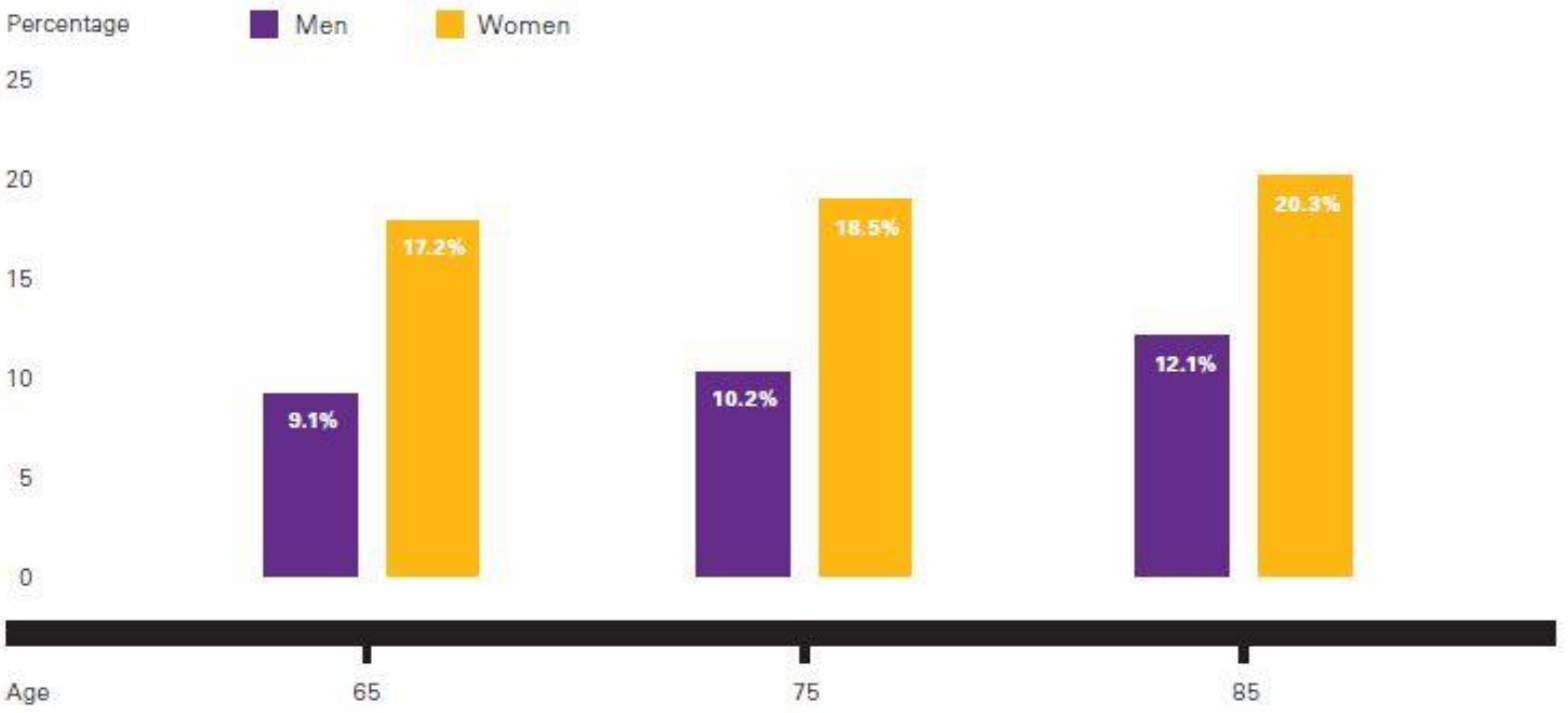
In Ontario, men are 22X more likely than women to be referred for knee & hip replacement
(Borkhoff et al, 2008)

Average caregiver is 49 year old woman who works outside the home
She provides 20 hours per week of unpaid care to her mother.
Female caregivers may spend as much as 50% more time providing care than male caregivers. (Family Caregiver Alliance) https://www.caregiver.org/women-and-caregiving-facts-and-figures

Sex and Gender Differences in AD

Estimated lifetime risk for AD at age 45 is approximately one in five (20%) for women and one in 10 (10%) for men

figure 2: Framingham Estimated Lifetime Risks for Alzheimer's by Age and Sex



Created from data from Seshadri et al. [71]

Sex and Gender Differences in AD

- Prevalence of AD is higher in women 2:1 (Hebert et al. 2013; Association As. Alzheimer's disease facts and figures, 2014)

- Female advantage in verbal memory maintained at prodromal stages of AD (Sundermann et al., 2016)

- Women have faster atrophy rates (Hua et al., 2010; Ardenkani et al., 2016; Holland et al., 2013, ADNI)

- 65–75 years with the APOE ε3/ε4 AD dementia risk 4X higher in women than that in men (Beydoun et al., 2012; Mortensen et al., 2001)

- Greater hippocampal atrophy and faster rate of cognitive decline in the presence of CSF Aβ42 and total tau (Koran et al., 2016)

- Aβ pet scans show women with higher Aβ decline faster than men; with APOEε4 decline is faster yet (Buckley et al., 2018)

Sex and Gender Differences in AD

"These results indicate that in addition to apolipoprotein E ε4 status, diagnostic and therapeutic strategies should take into account the effect of female sex on the Alzheimer disease process." (Dominic Holland et al., 2013, ADNI)

Sex and Gender Differences in AD

Risk Factors common in women and men with stronger effect in women

Sex

1. APOE ε4 allele confers higher risk of AD onset (Neu et al., 2017)
2. Depression at midlife can increase AD risk by 70%; women have 2X risk of depression increasing at menopause (Ownby et al., 2006)
3. Lower access to education increases risk and is more common in women (Nebel et al., 2018)
4. Disruption of slow wave sleep increases Aβ levels (Ju et al., 2017); Women have greater slow wave activity at all ages (Carrier et al., 2001; Mourtazaev et al., 1998); effects of disruption in women not known.
5. Apnea correlated with cognitive decline at an earlier age (Bixler et al., 2001); Greater in men but increases in women at menopause (Osorio et al., 2015).

Sex and Gender Differences in AD

Risk Factors common in women and men with stronger effect in women

Gender:

1. Education – women have lower access to education
2. Exercise – women exercise less than men
3. Marital status – men who have never married or are widowed have higher risk for AD
4. Traumatic Brain Injury – women exposed to TBI in intimate partner violence

Sex and Gender Differences in AD

Risk Factors common in women and men with stronger effect in women

Gender:

4. AD caregiving – women are 60% of the caregivers and higher for Hispanic and African American women – 2X greater caregiver burden than men -- Caregiving is associated with:
    - elevated levels of cortisol, impaired attention and executive function (Allen et al., 2017)
    - Spousal caregivers may be at higher risk of cognitive impairment than non-caregiver spouses in response to:
        - psychosocial (e.g., depression, social isolation, and sleep problems),
        - behavioral (e.g., exercise and diet), and
        - physiological (e.g., metabolic syndrome and inflammation) variables (Gallicchio et al., 2004)

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

1. Hypertensive Pregnancy Disorder (12%) associated with subjective cognitive complaints (Aukes et al, 2007; Postma et al., 2014)
    - HPD correlated with white matter hyperintensities (MRI) (Wagner et al., 2011; Wiegman et al., 2014; Mielke et al., 2016)
    - Imaged at mean age 61, WM hyperintensities still present, lasting decades post-pregnancy (Mielke et al., 2016)
2. OC Use?

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

3. Breast Cancer Chemotherapy
    - Subjective reports of ‘chemobrain’ or ‘chemofog’
    - Objective measures of cognitive decline show:
        - changes in default mode network (Kesler et al., 2013)
        - executive function (Kesler et al., 2011)
        - long lasting (Koppelmans et al., 2012; Habermann et al., 2013)
        - Chemo types show differences in extent of verbal memory decreases (immediate & delayed) & lower left precuneus connectivity in RS DFMN between chemo types (Kessler et al., 2016)
    - Leads to accelerated brain aging and late life dementia (Ahles et al., 2012; Koppelmans et al., 2013; Madelblatt et al., 2013)?
    - BUT: neither aromatase nor tamoxifen increase the risk of AD (Branigan et al., 2020)

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

4. Menopause
    - Spontaneous (>50 yrs)
    - Early (40-45 yrs)—absence of menses with no clinical reason
    - Premature (<40 yrs)
        - POI (1%) waxing and waning of ovarian function
    - Induced
        - Chemotherapy
        - Hysterectomy (can lead to ovarian dysfunction)
        - Oophorectomy (BSO)
        - Ovarian ablation via radiation (NAMS, 2014; Harlow et al., 2012)

Many Menopauses!

Distinct hormonal changes leading up to and after menses cessation; each has unique health and cognitive consequences (Edwards et al., 2019)

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

4. A. Spontaneous (natural) Menopause
   - Cross-sectional studies show verbal memory decrease in menopause but not in perimenopause (Jacobs et al., 2017) BUT other studies show decrease in verbal memory during the menopausal transition (Epperson et al., 2013)
   - Memory decrease linked to change in hippocampal function associated with loss of estradiol (Jacobs et al., 2016; Rentz, 2017)
   - Peri- & menopause FDG-PET imaging shows AD-like reductions in glucose metabolism; related to platelet mitochondrial activity; correlated with imm & delay memory scores (Mosconi et al., 2017)
   - Perimenopause decline in mitochondrial function; fuel source goes from glucose to lipids, potentially leading to loss of synaptic spines & ultimately neurodegeneration (Brinton et al., 2017)

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

4. B. Does Hormone Therapy Help?
   - Over 18 year follow-up, women with estrogen only therapy (ET) had a significantly lower risk of dying from AD or dementia than women randomized to placebo (WHI, Manson et al., 2017)
   - Over 18 year follow-up women randomized to estrogen plus progestin therapy (HT) did not show benefit
   - Initiating HT early in perimenopause or younger shows lower risk of AD than initiating HT later (Henderson, 2005; Shao et al., 2012; Whitmer et al., 2011)
   - Risk of death from AD was reduced by 15%–19% in Finnish women who used HT for at least 5 years.
   - Risk of death from vascular dementia was reduced from 37% to 39% independent of length of exposure or timing (Mikkola et al., 2017)

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

4. C. Induced menopause (prior to spontaneous menopause)
   - correlated with decreased verbal memory function if not replaced for 3 months post-oophorectomy (Sherwin, 1988)
   - E2 replacement improves verbal word recall after two months treatment post-oophorectomy (Phillips & Sherwin, 1992)
   - correlated with decreased verbal memory (Farrag et al., 2002)
   - age of oophorectomy is correlated with increased all causes of death and dementia risk (Rocca et al., 2007)

	Preoperatively	3 months postoperatively	6 months postoperatively
MMSE	23.54 ± 3.2	22.86 ± 3.0**	21.23 ± 2.9***
WMS			
Digit span	8.17 ± 1.7	7.86 ± 1.7	6.11 ± 1.9***
Mental control	2.19 ± 1.5	1.67 ± 1.3	1.21 ± 1.1***
Logical memory	9.19 ± 2.1	8.76 ± 1.7	7.99 ± 1.5**
Associate learning	10.94 ± 4.9	9.96 ± 4.4*	9.89 ± 4.6*
Visual reproduction	1.92 ± 1.3	1.63 ± 1.1	1.46 ± 1.2*
ERPs			
N100 latency	126.9 ± 26.9	128.2 ± 27.4	135.00 ± 29.5
P200 latency	227.96 ± 41.9	240.82 ± 34.3	236.91 ± 36.5
P300 latency	338.71 ± 37.9	360.09 ± 40.4*	367.82 ± 51.3**

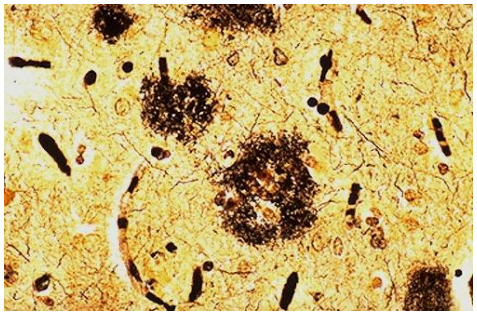
* $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$ (comparison with the preoperative data).

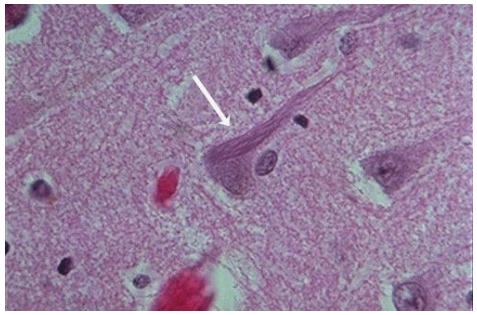
Sex and Gender Differences in AD

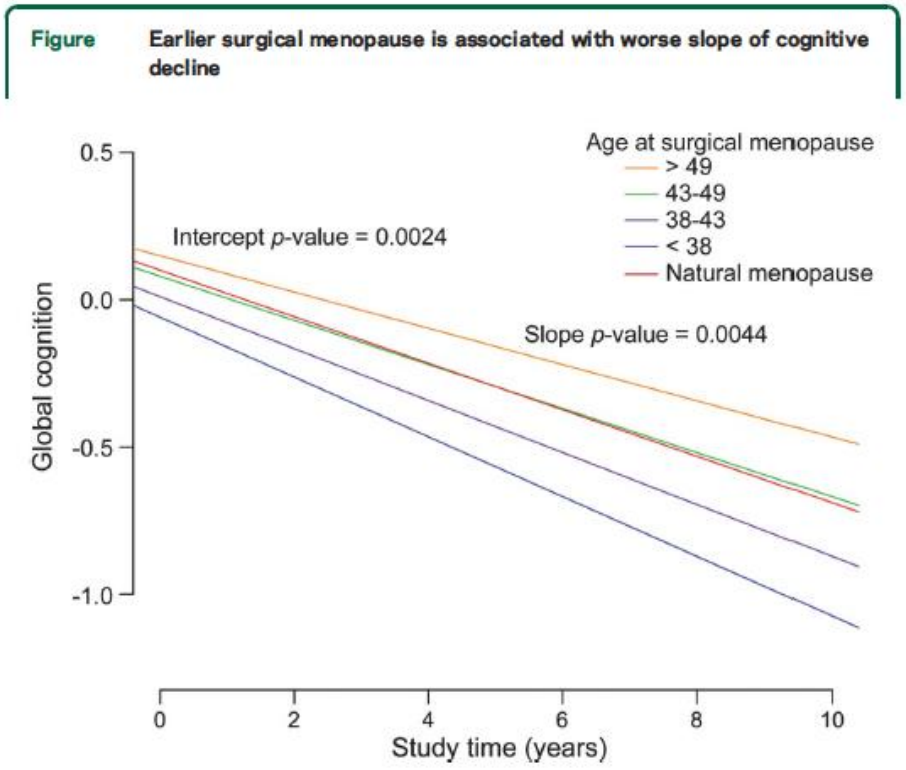
Risk Factors unique to women

Reproductive:

- Earlier induced (surgical) menopause leads to steeper slope of cognitive decline
- Increase in a global measure of the burden of AD pathology (Bove et al., 2014)





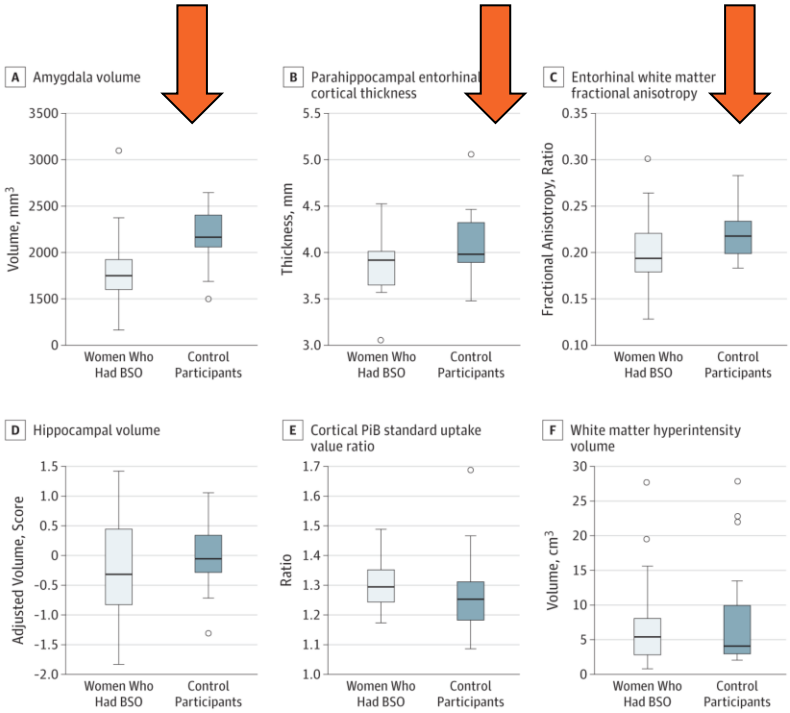


Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

- Imaging BSO at av. 46 by the age of 63 leads to:
  - Smaller amygdala
  - Thinner parahippocampal/ entorhinal cortex
  - Entorhinal white matter fractional anisotropy lower
- No difference in PIB score
- No difference in cognition
- No effect of HT (Zeydan et al., 2018)
- Sleep BSO compared SM (59-60):
  - Worse sleep duration
  - Worse sleep efficiency
  - More insomnia (Cho et al., 2018)

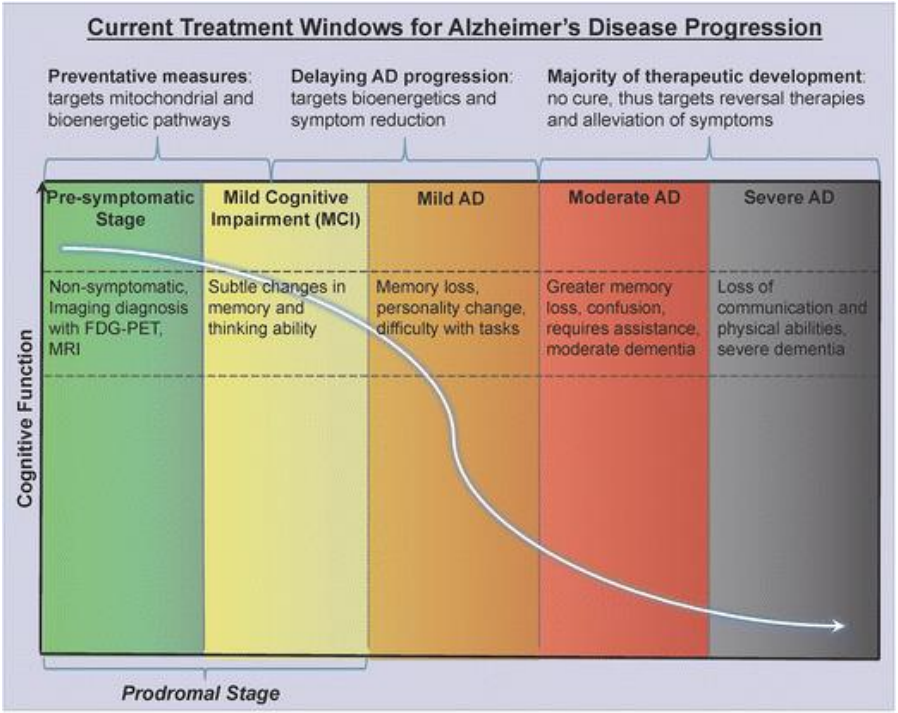


Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

For prevention, targeting earlier and earlier stages of AD, the perimenopause is a focus of research now (Caldwell et al., 2014)



Sex and Gender Differences in AD

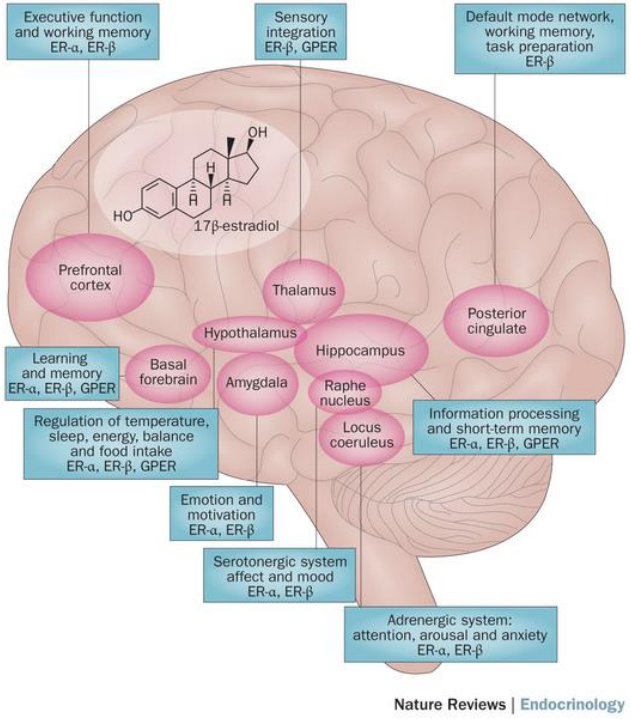
SUM so far

- Sex and Gender play a role in AD
- Some risk factors affect women & men but women more
- Reproductive risk factors affect women only; many life stages and treatments affect reproductive health
    - The perimenopause may be an important time of change & perhaps, intervention
    - There are many menopauses; risk & treatments may vary depending on the type
    - The reputation of HT is improving depending on timing & type
- We need to target earlier & earlier prodromal stages for successful prevention

Sex and Gender Differences in AD

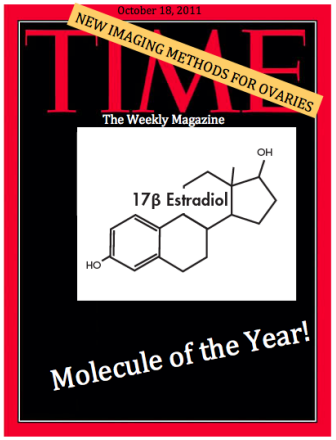
17-β estradiol Loss:

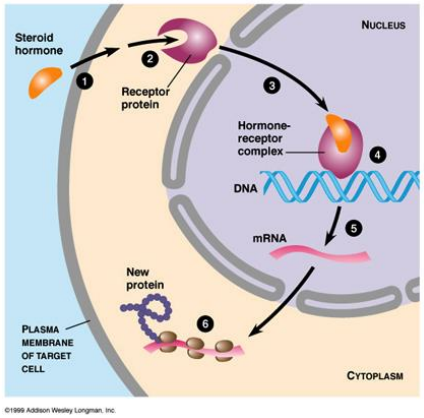
1. Associated with all the menopauses
2. 17-β estradiol receptors in key areas of the brain affected by AD
3. These regions potentially affected with 17-β estradiol loss due to different menopauses

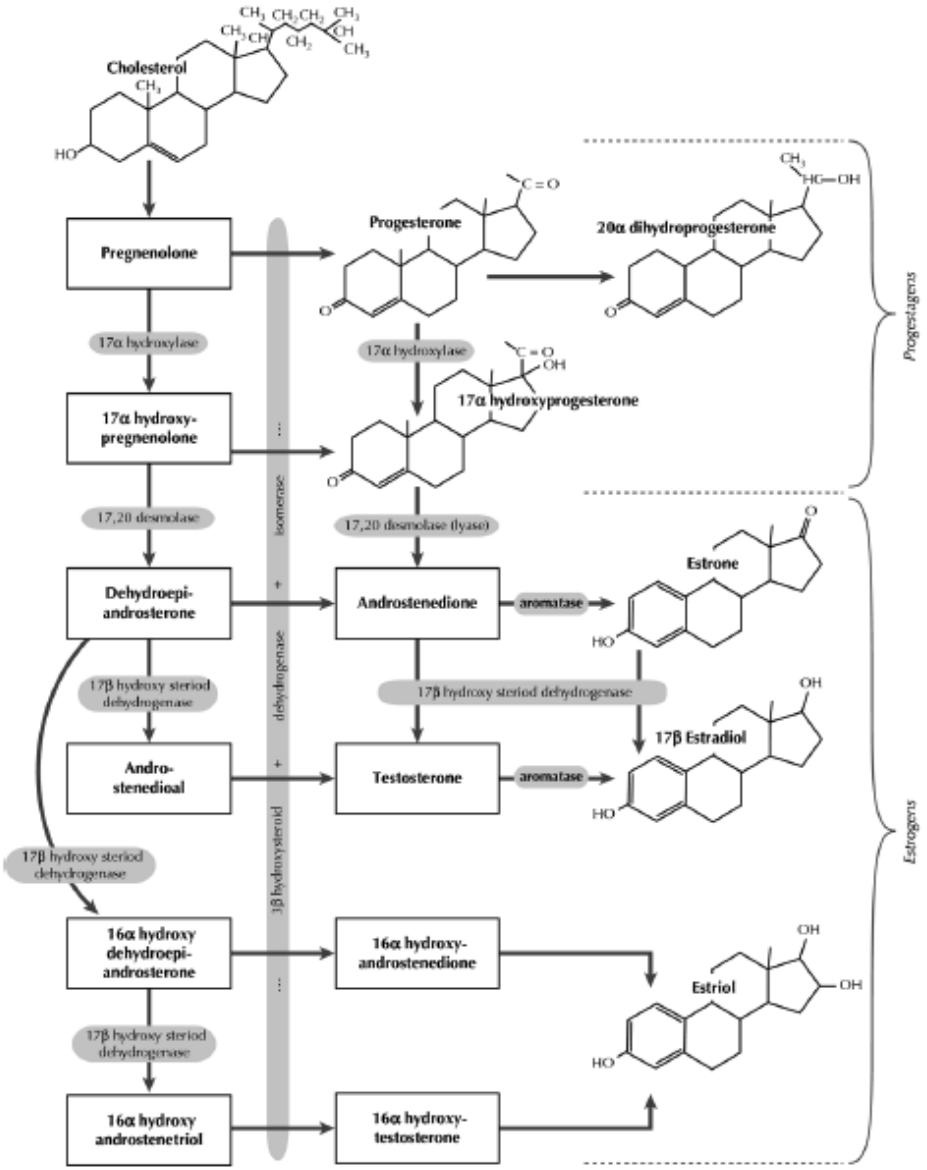


Sex and Gender Differences in AD

17-β estradiol

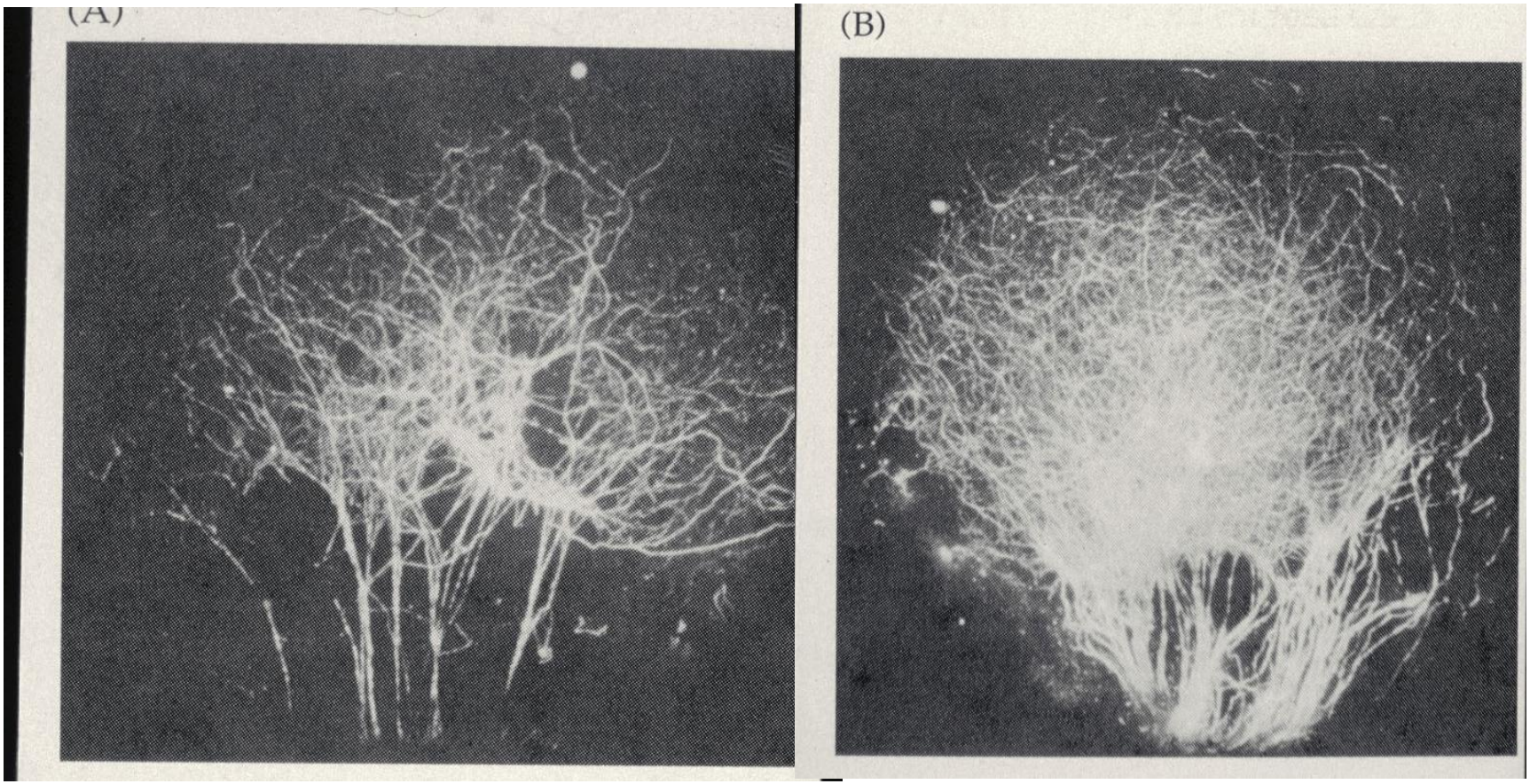






Sex and Gender Differences in AD

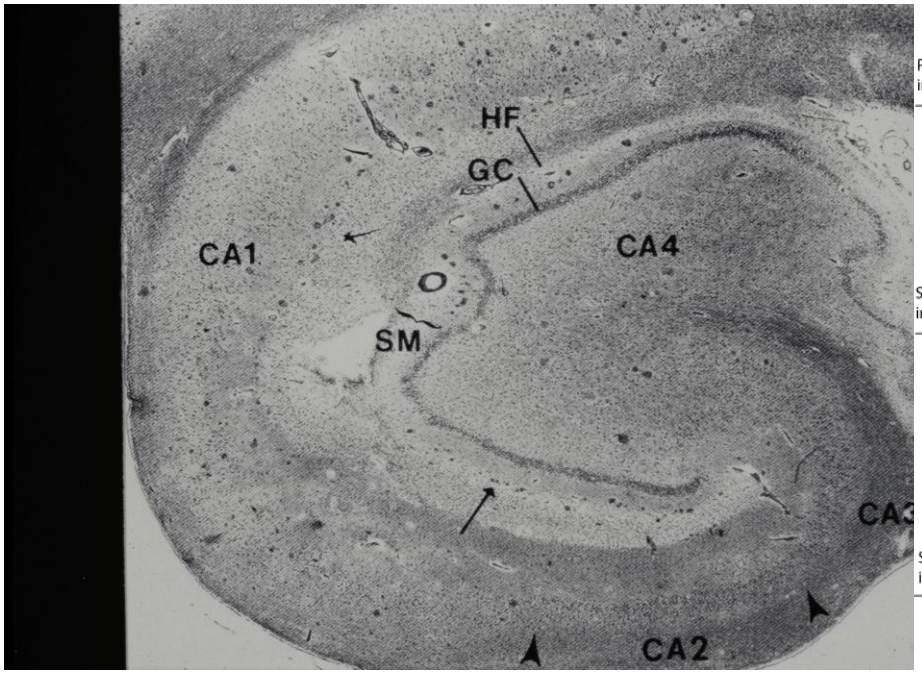
17-β estradiol Loss

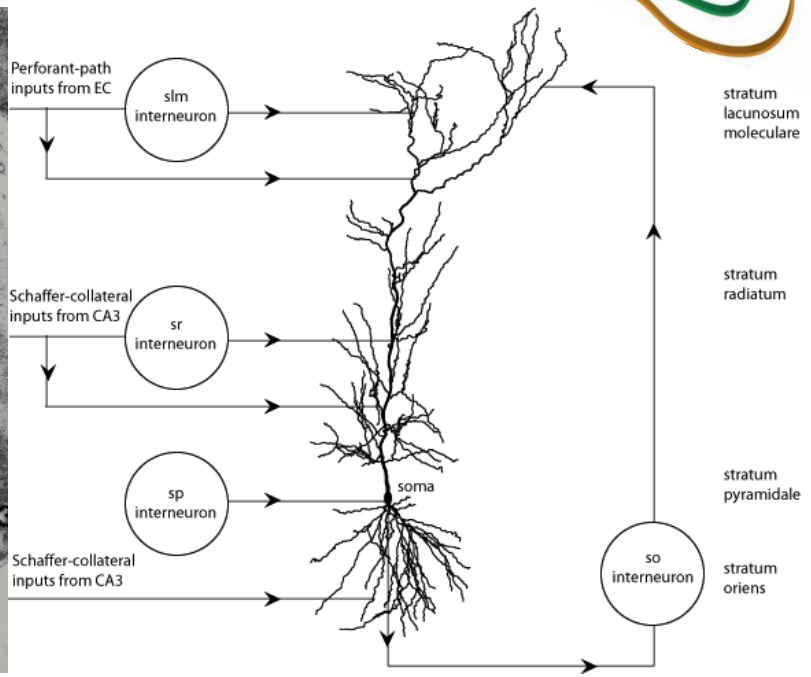


(Toran-Allerand, 1976)

Sex and Gender Differences in AD

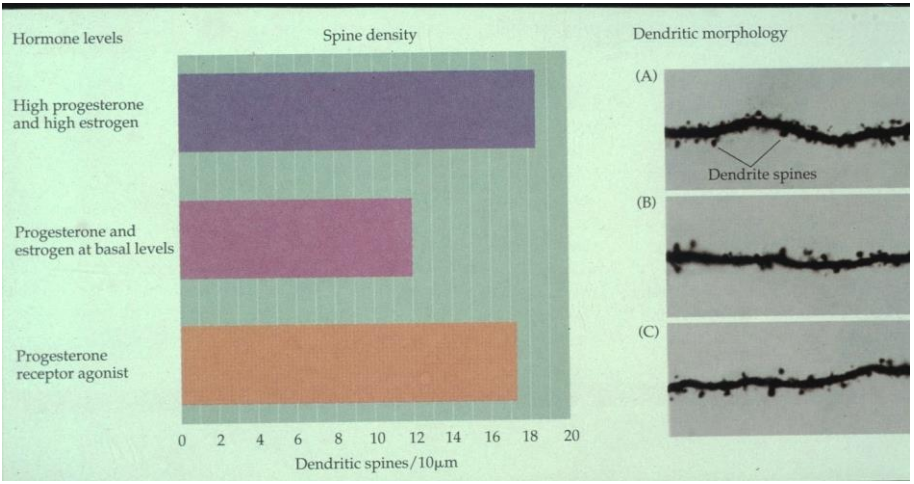
17-β estradiol Loss





Sex and Gender Differences in AD

17-β estradiol Loss : CA1



(Woolley & McEwen, 1992)

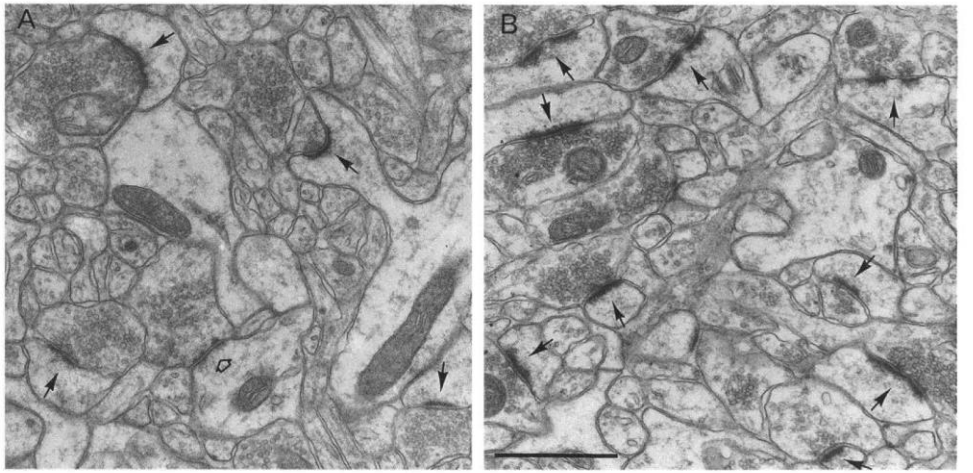
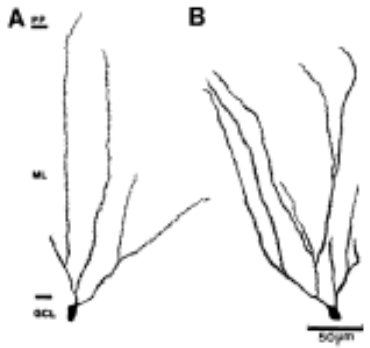


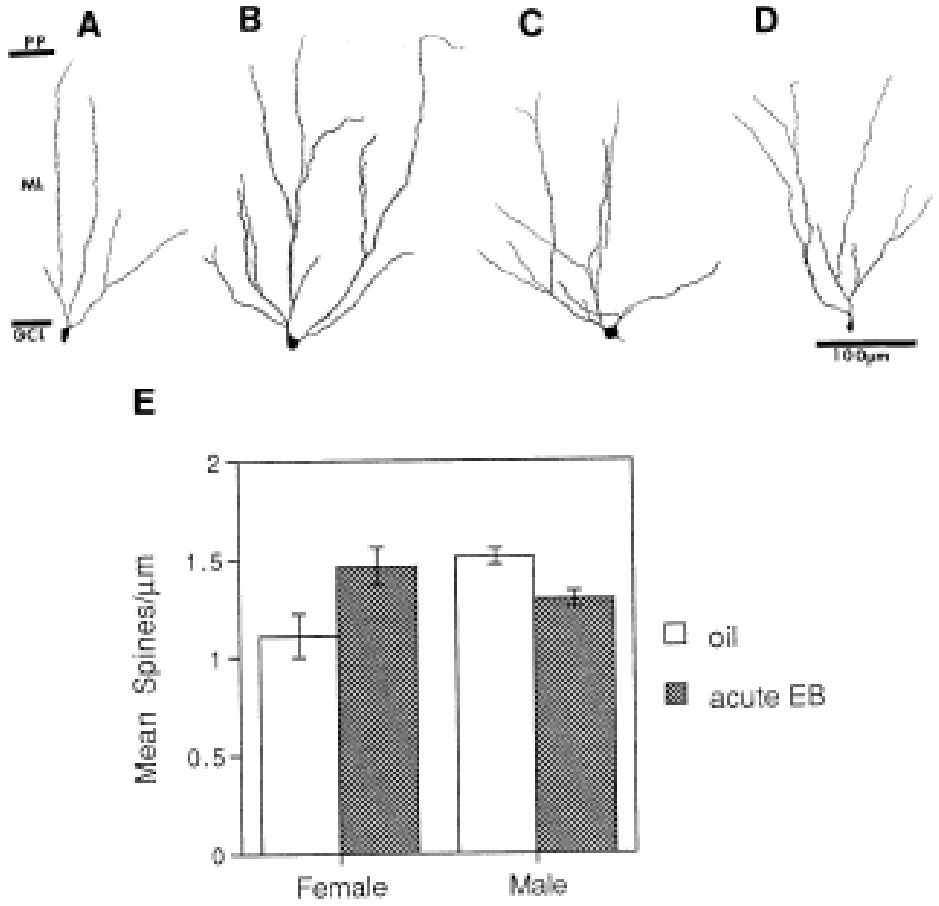
Figure 2. Electron micrographs of the stratum radiatum in the hippocampal CA1 region of an ovariectomized adult female rat that received oil (*A*) or estradiol (*B*). Synapses on dendritic spines are marked by *solid arrows*, whereas the *open arrow* in *A* marks a synapse on a dendritic shaft. Scale bar, 1 μm.

Sex and Gender Differences in AD

17-β estradiol Loss : Dentate GC

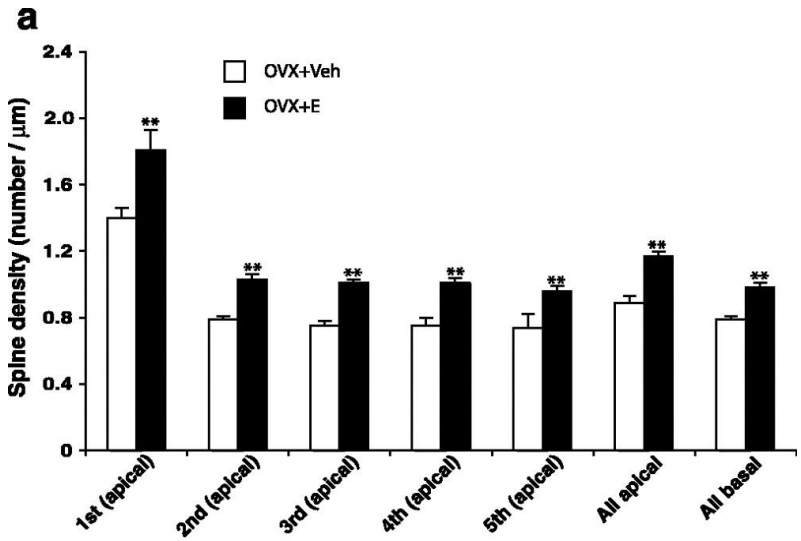


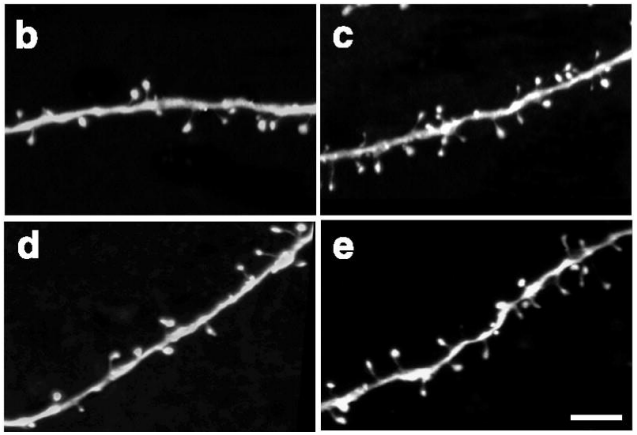
(Miranda et al, 1999)



Sex and Gender Differences in AD

17-β estradiol Loss : PFC



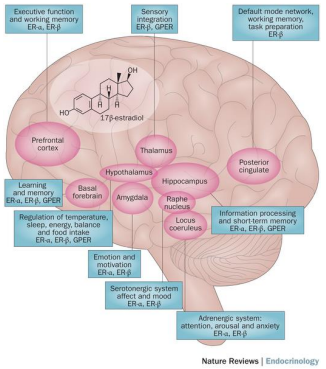


(Hao et al, 2004)

Sex and Gender Differences in AD

SUM so far

- 17-β estradiol is synthesized from cholesterol
- It requires aromatase for synthesis
- It acts as a growth factor



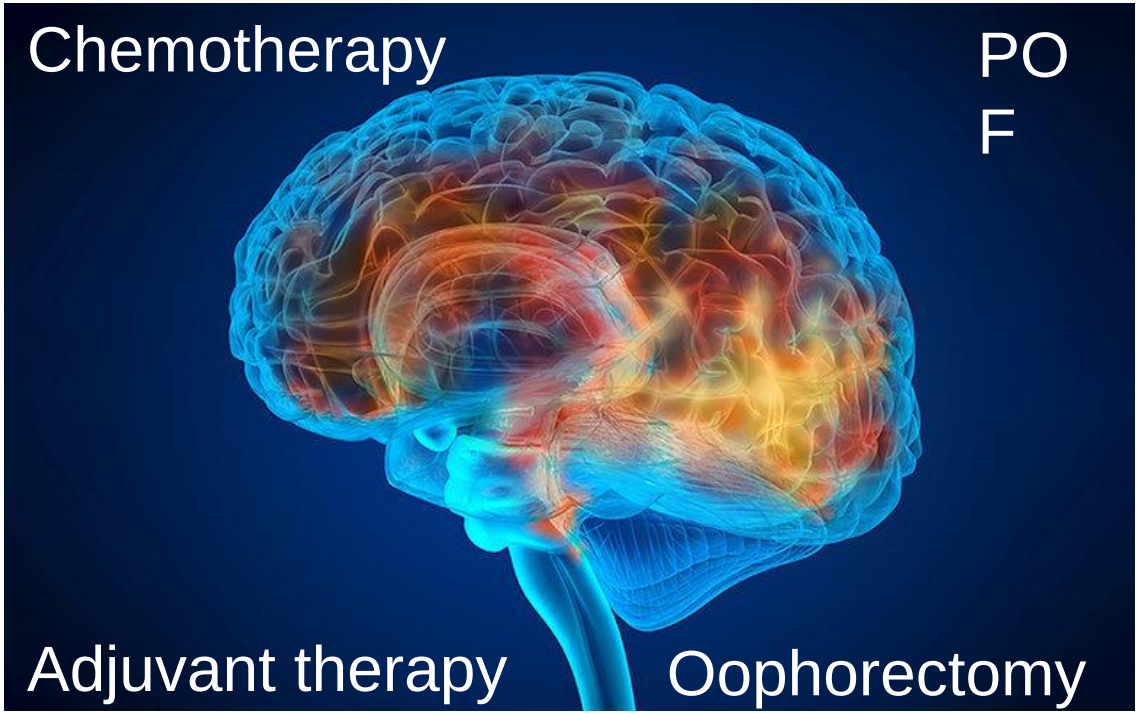
- ERs are located in key brain regions affected by AD
- ER are members of the steroid-thyroid superfamily
- Loss and replacement of 17-β estradiol leads to spine loss and proliferation in regions affected by AD

Sex and Gender Differences in AD

Risk Factors unique to women

Reproductive:

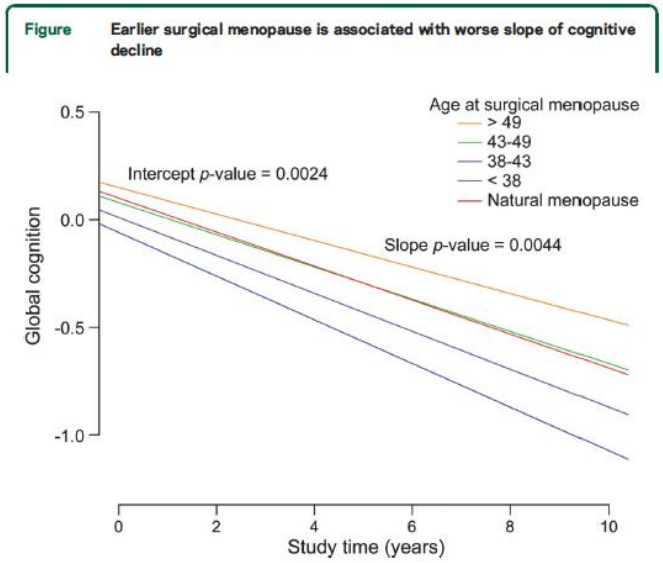
Consider all E2-reducing risks prior to SM

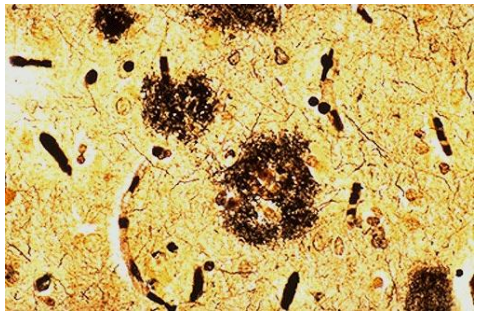


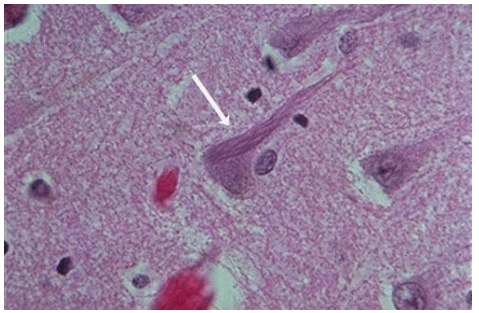
modified from Bright Focus Foundation

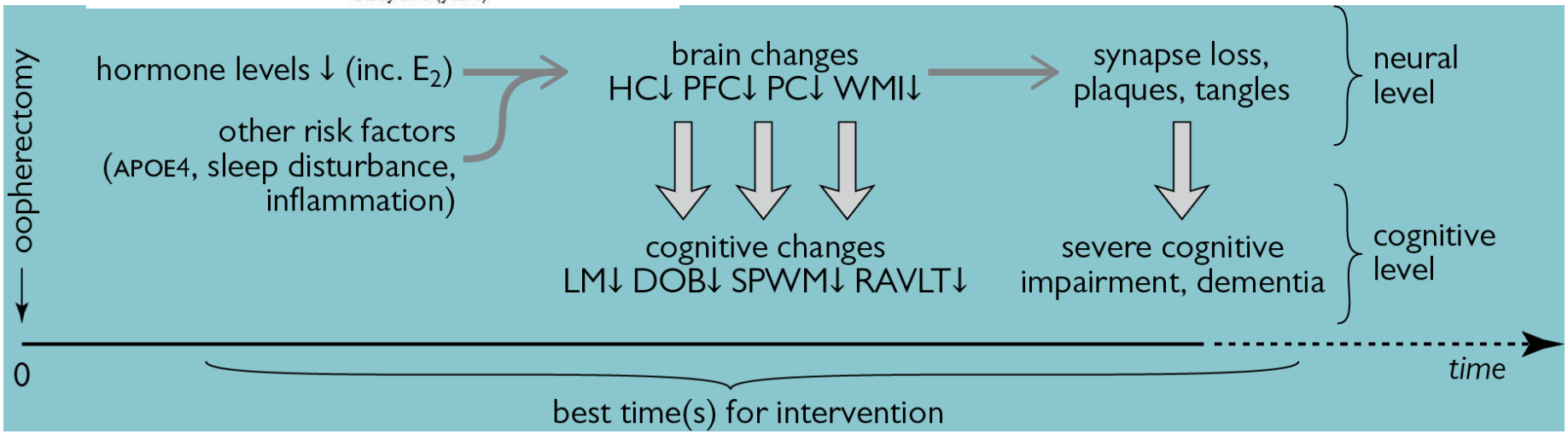
Why do more women than men have AD?

What happens in young women with 17-β estradiol loss?







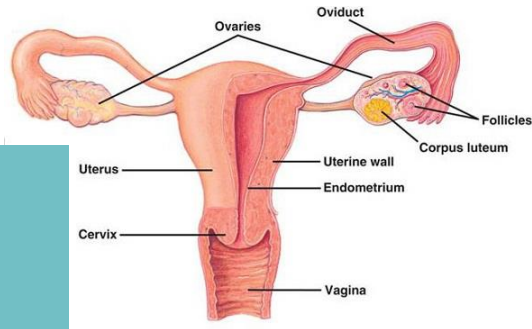


Why do more women than men have AD?

What happens in young women with 17-β estradiol loss?

BRCA1/2 Recommended Prophylaxis: Bilateral Salpingo-oophorectomy (BSO)

- Recommended before age 40
- 80% reduction in risk of dying from ovarian cancer
- 56% reduction in risk of dying from breast cancer
- 77% reduction in risk of dying from any cause (NCI)
- Prophylaxis, women are healthy at testing

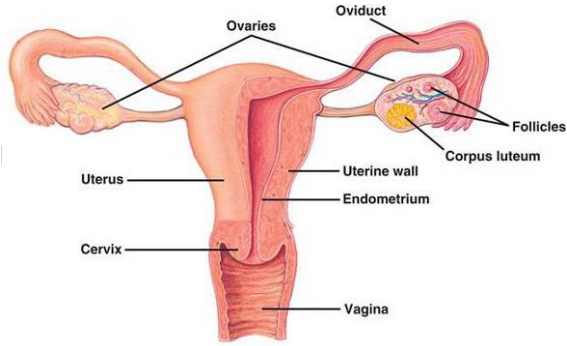


Oophorectomies
• In US—600,000 oophorectomies performed annually
• 50% are BSO

Why do more women than men have AD?

What happens in young women with 17-β estradiol loss?

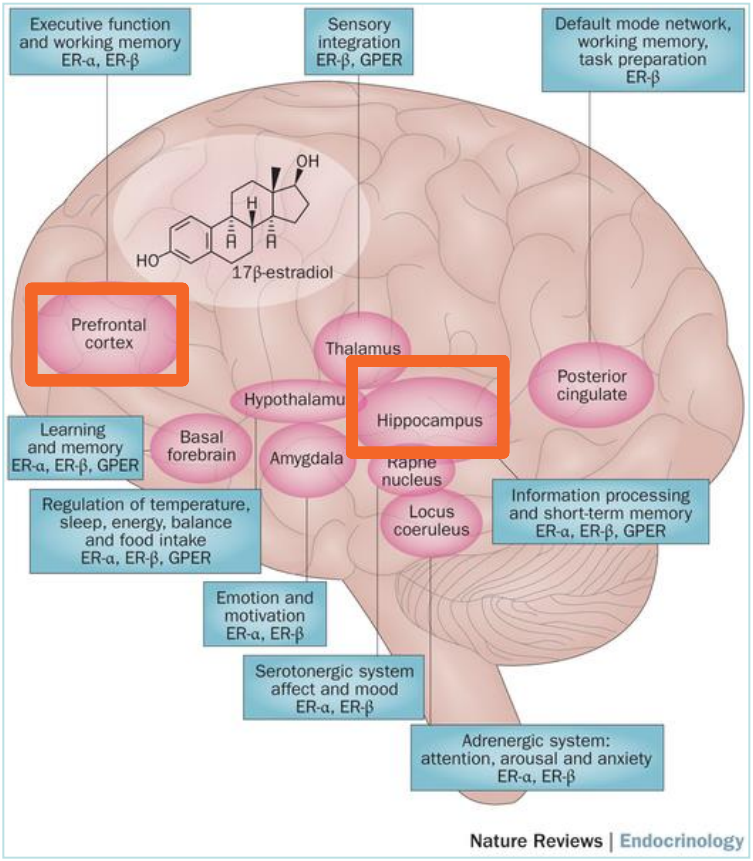
- Tested 1 – 10 years post-oophorectomy
- Each women tested once a year for 3 years
- Provides information from 1 – 13 years post oophorectomy
- Neuropsychological measures
- Imaging
- Sleep
- Measure E2, P4, APOE genotype



Toronto, Linköping, Sweden & Montreal

Why do more women than men have AD?

What happens to young women with 17-β estradiol loss?



- Neuropsych
- Frontal cortical thickness
- Hippocampal volume
- Sleep
- Effects of 17-β estradiol replacement

Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

Gervais et al., 2020

Nicole Gervais

April Au

Elizabeth Baker-Sullivan

Demographics – T

Participant characteristics by group (Mean ± SD)

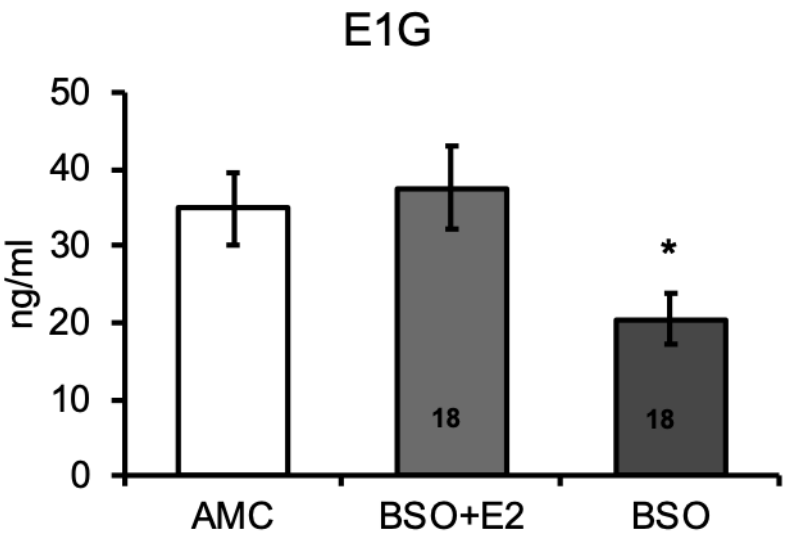
	AMC	BSO+E2	BSO
Age (years)	42.25 ± 5.27	44.38 ± 4.84	46.89 ± 7.94
Education (years)	18.95 ± 3.05	16.43 ± 2.43	17.00 ± 3.20
BMI	24.77 ± 4.42	27.35 ± 6.49	25.95 ± 3.82
Age at BSO (years)	--	38.88 ± 3.14	42.56 ± 6.62
Time since BSO (years)	--	5.56 ± 3.76	4.28 ± 2.96
History of chemo/radiotherapy (percent of group)	--	5%	21%
CES-D	9.24 ± 7.91	10.26 ± 8.35	10.28 ± 8.54
NAART	113.25 ± 7.96	112.09 ± 7.48	110.90 ± 6.16

Note. AMC = age-matched control; BMI = body mass index; BSO = bilateral salpingo-oophorectomy; CES-D = Center for Epidemiological Studies – Depression Scale; E2 = Estradiol-based; NAART = North American Adult Reading Test;

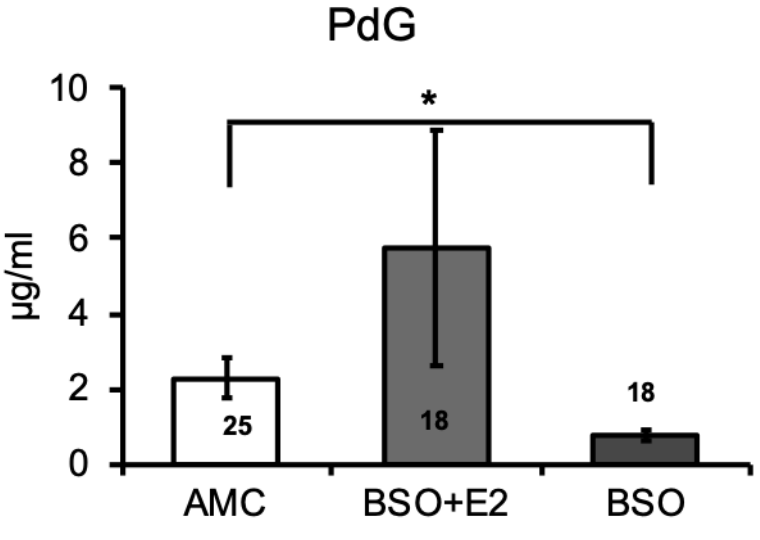
Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

BSO reduces 17-β estradiol & progesterone metabolites



H = 6.46, p = .04; BSO < BSO+E2/AMC
p < .05, d = 0.76-.91

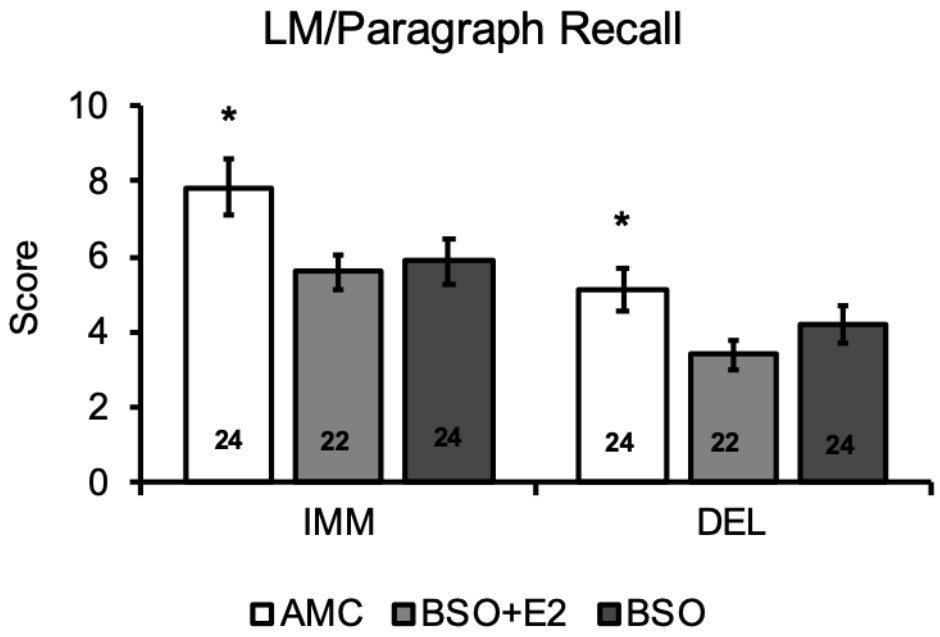


H = 6.15, p = .046; BSO vs AMC:
p = .015, d = 0.79

Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

BSO reduces verbal memory recall; E2-based therapy does not seem to protect verbal memory

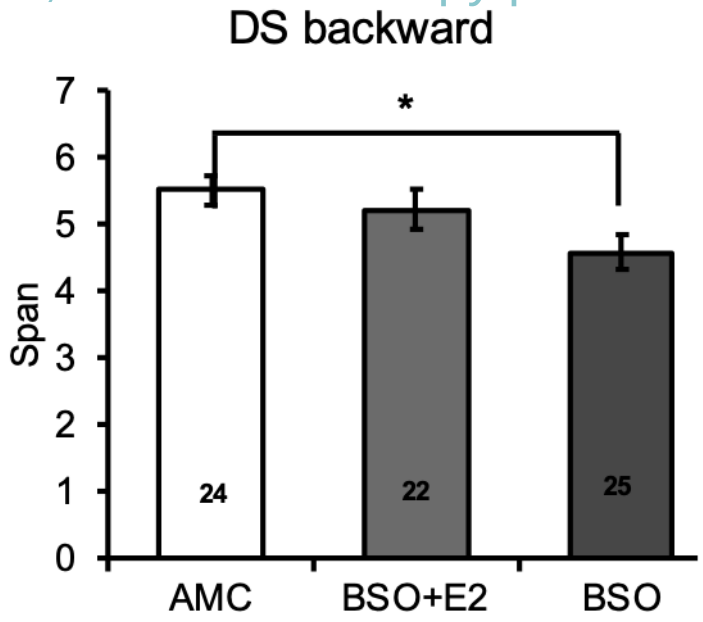


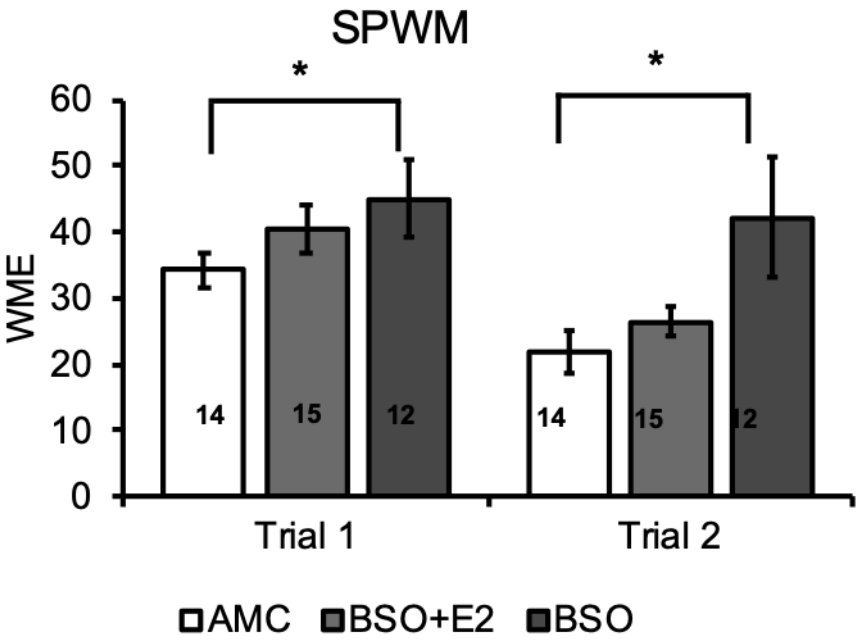
$F(2,65) = 3.52$, $p = .035$ $\eta^2 = .10$; AMC vs BSO/BSO+E2: $p < .05$, $d = 0.21$-$.38$

Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

BSO reduces working memory, effects are large when BSO compared only with AMC; E2-based therapy protects WM





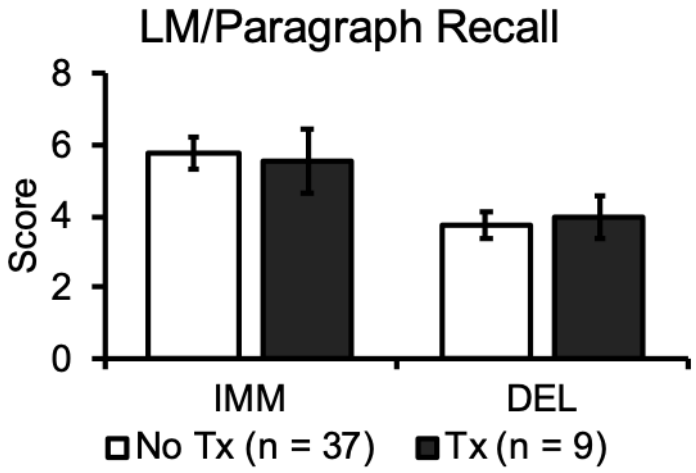
$F(2,67) = 2.99$, $p = .057$ $\eta^2 = .08$
AMC vs BSO: $p = .018$, $d = 0.77$

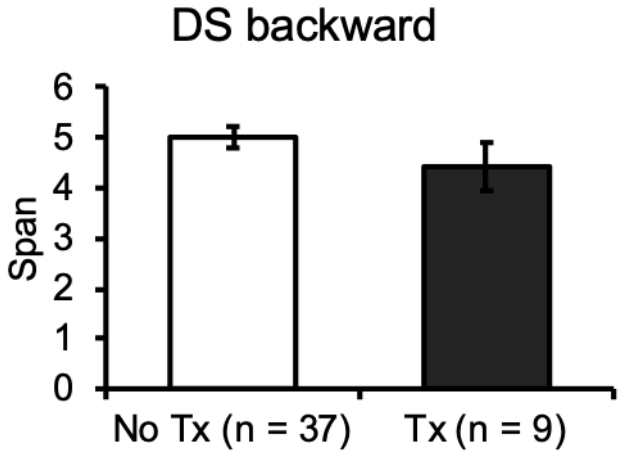
$F(2,37) = 3.56$, $p = .039$ $\eta^2 = .16$
AMC vs BSO: $p = .012$, $d = 1.05$

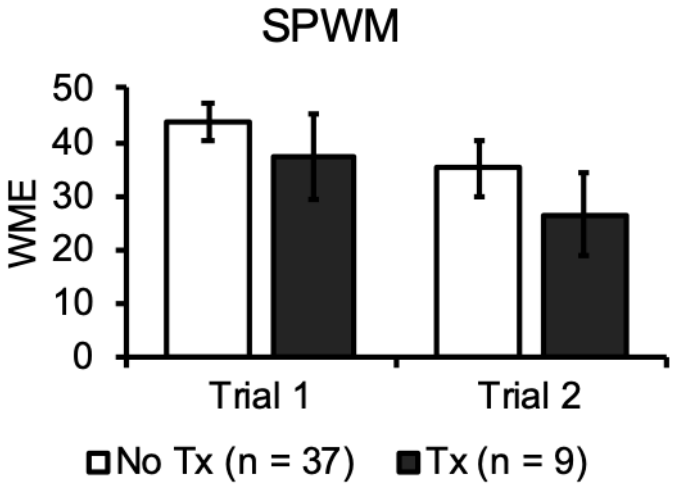
Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

No effect of chemotherapy







Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

- Do changes continue over time; Do women taking E2 do better?
- How do genes affect performance?

Rebekah Reuben

Laura Gravelsins

- Does hippocampal volume change? Do women taking E2 have larger volumes?
- Does sleep affect memory? Do women taking E2 have better sleep?
- Are there increases in inflammatory markers? Do these mediate the changes in brain and memory?

Nicole Gervais

Why do more women than men have AD?

What happens to young women with 17-b estradiol loss?

- Does frontal cortex volume decrease; Do women taking E2 maintain PFC volume?

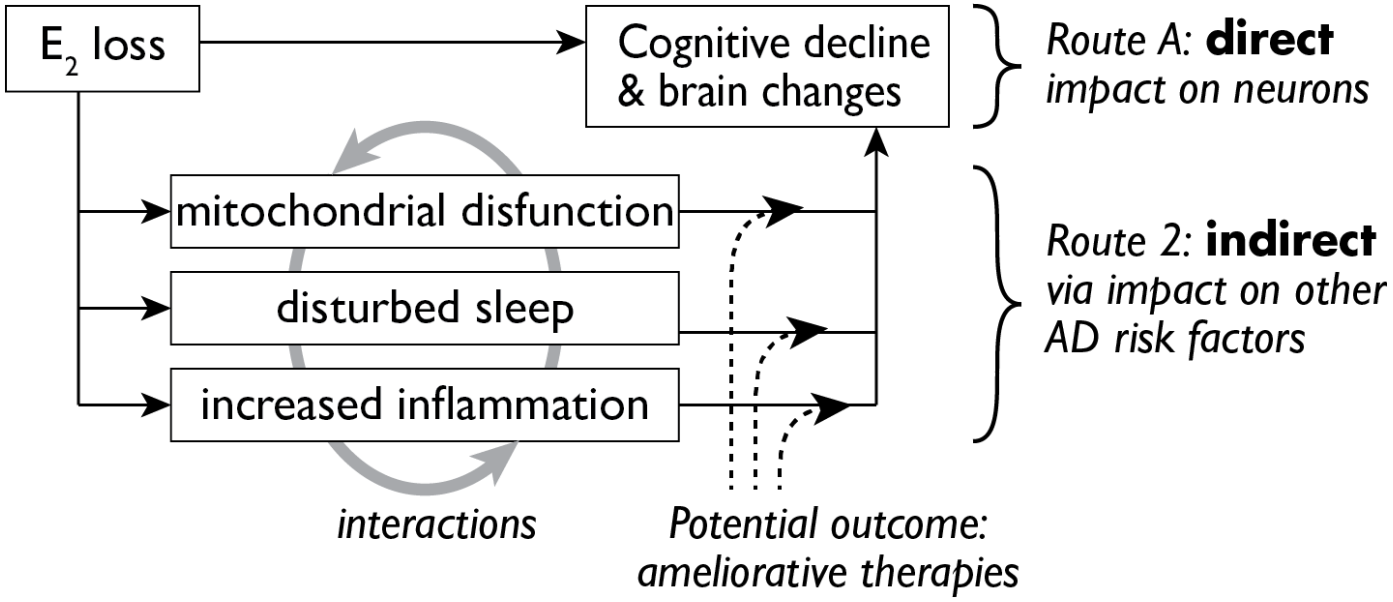
Anne Almey

- Does associative memory change? How do these women compare with naturally menopausal women?

Alana Brown

Why do more women than men have AD?

Considering the route of 17-β estradiol loss' effects suggests pathways for prevention



Why do more women than men have AD?

Putting it all together

- Sex & Gender play a role in the risk factors for AD—ameliorate as many gendered risk factors as possible
- Gendered/reproductive health treatments may increase risk—consider risk/benefits of each treatment
- Some menopauses take more of a toll than others—consider simple ameliorations to 17-b estradiol loss
  - Start therapies early, prior to or during early menopause
  - E2 may be indicated
  - Improve bioenergetics with anti-oxidents
  - Reduce inflammation
  - Take sleep seriously
  - Keep your ovaries if you possibly can!

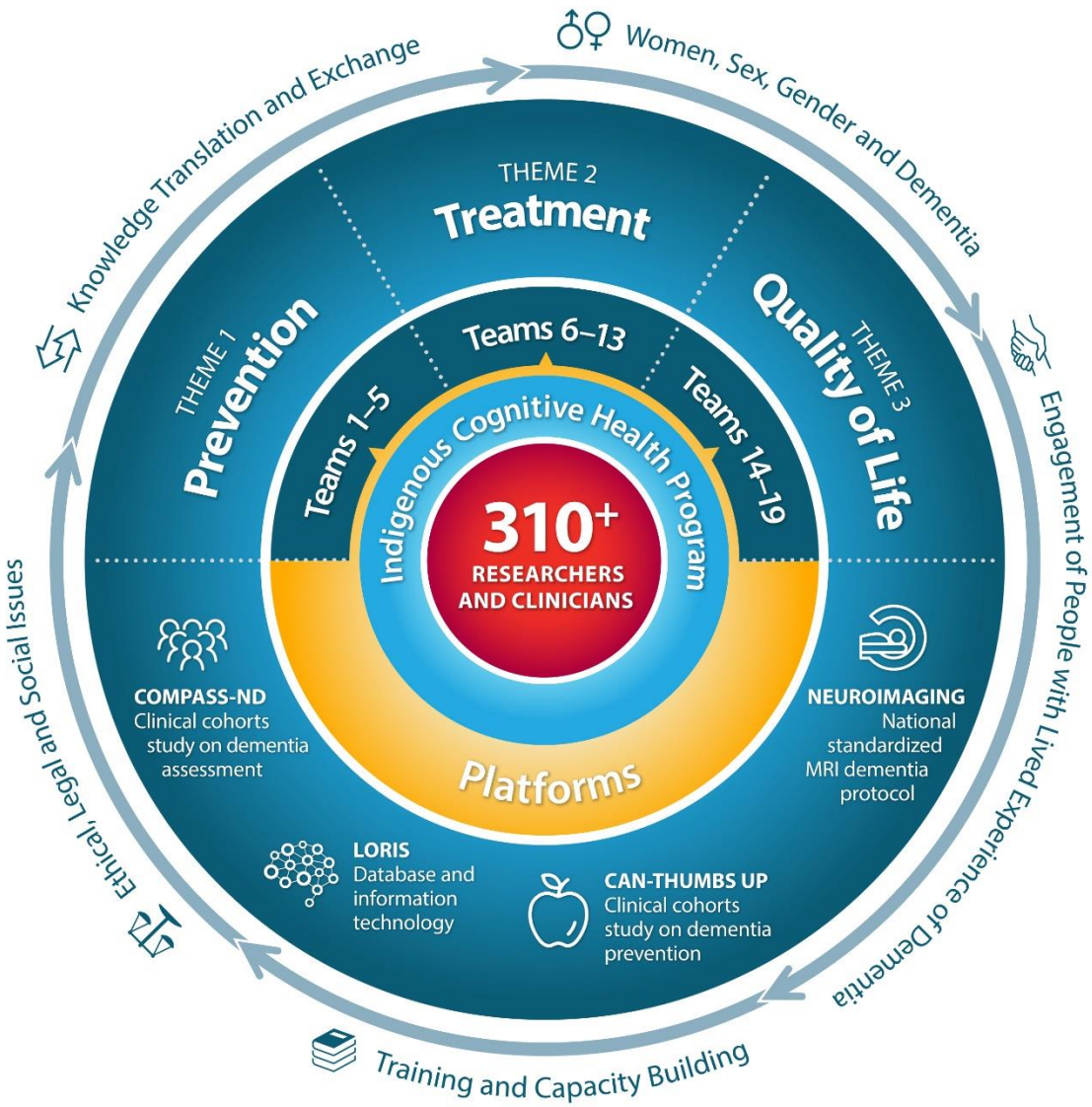
Why do more women than men have AD?

Future Directions

More that we need to understand

- How do different cancer therapies affect young women's brain health?
- Do the same factors affect cognitive reserve in women as in men?
- What do Subjective Cognitive Decline and Mild Cognitive Decline look like in women?
- What factors provide resilience and resistance to women to prevent or stave off AD?
- Would drug development succeed if we tested new compounds on female as well as male mice?

CCNA Phase II at a glance



CCNA
Canadian Consortium on Neurodegeneration in Aging

CCNV
Consortium canadien en neurodégénérescence associée au vieillissement

310+ RESEARCHERS AND CLINICIANS

Over 310 Canadian scientists in 19 research teams are collaborating on preventing, treating, and curing age-related neurodegenerative diseases (NDD), and on improving the quality of life of people with lived experience of dementia.

INDIGENOUS COGNITIVE HEALTH PROGRAM

Members of CCNA's Team 18 are working on Indigenous cognitive health, on supporting capacity building across CCNA, and are supporting CCNA researchers in exploring questions related to Indigenous health and healthcare.

3 RESEARCH THEMES AND 19 TEAMS

Theme 1:
Teams aim to identify and prevent the causes of NDD.

Theme 2:
Teams aim to improve early detection and treatment of NDD.

Theme 3:
Teams aim to improve the quality of healthcare and quality of life of those living with NDD.

4 NATIONAL PLATFORMS

The platforms enable teams to test their research hypotheses and foster collaborations by collecting, processing, and pooling big data.

5 CROSS-CUTTING PROGRAMS

Cross-cutting programs support the work of CCNA's 19 teams and accelerate idea uptake.

PARTNER ORGANIZATIONS

CCNA is a Government of Canada initiative, also supported by several national, provincial and non-profit organizations.

Women, Sex, Gender, & Dementia Cross-cutting Program

- **Illuminate the Sex & Gender Lens for Aging & Dementia Research**
  - Develop Network of CCNA S&G Champions Community of Practice
  - Sponsor International Meeting on: Why do more women than men have AD?
  - Establish a WSGD Advisory Committee by engaging CCNA as well as outside S&G experts as Advisory to the WSGD
  - Distribute base funds to all teams for S&G Research + Run competition for 3 teams to receive monies to add S&G project to their team
- **Build Capacity in Sex & Gender Aging & Dementia Research**
  - Partner with TCB to provide training for CCNA graduate students and postdocs
  - Provide workshops at Science Day on S&G in research: Methods & Measures
  - Support 5 trainees a year to present their work in Sex and Gender at international conferences (competitive process)

Sex and Gender Differences in AD

Further Reading

- Nebela et al., (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's & Dementia 14*: 1171-1183.
- Galeaa et al., (2017). Why estrogens matter for behavior and brain health. *Neuroscience and Biobehavioral Reviews 76*: 363–379.
- Edwards et al., (2018) The many menopauses: Implications for research and clinical practice. *Menopause 26*: 45-65.
- Cavedoa et al. (2018). Sex differences in functional and molecular neuroimaging biomarkers of Alzheimer's disease in cognitively normal older adults with subjective memory complaints. *Alzheimer's & Dementia 14*: 1204-1215.
- Mosconi et al., (2017). Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. *PLOS ONE* | https://doi.org/10.1371/journal.pone.0185926
- Ferretti et al., (2018). Sex differences in Alzheimer disease - the gateway to precision medicine. *Nat Rev Neurol*. 14(8):457-469. doi: 10.1038/s41582-018-0032-9

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- Cheryl Grady
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- Suzanne Witt
- Elisabet Classen

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Wendy Meschino, MD
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Preben Kolhede

Funders

The Posluns Family Foundation

Why do more women than men have AD?

Thank you

We are still recruiting AMC!

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