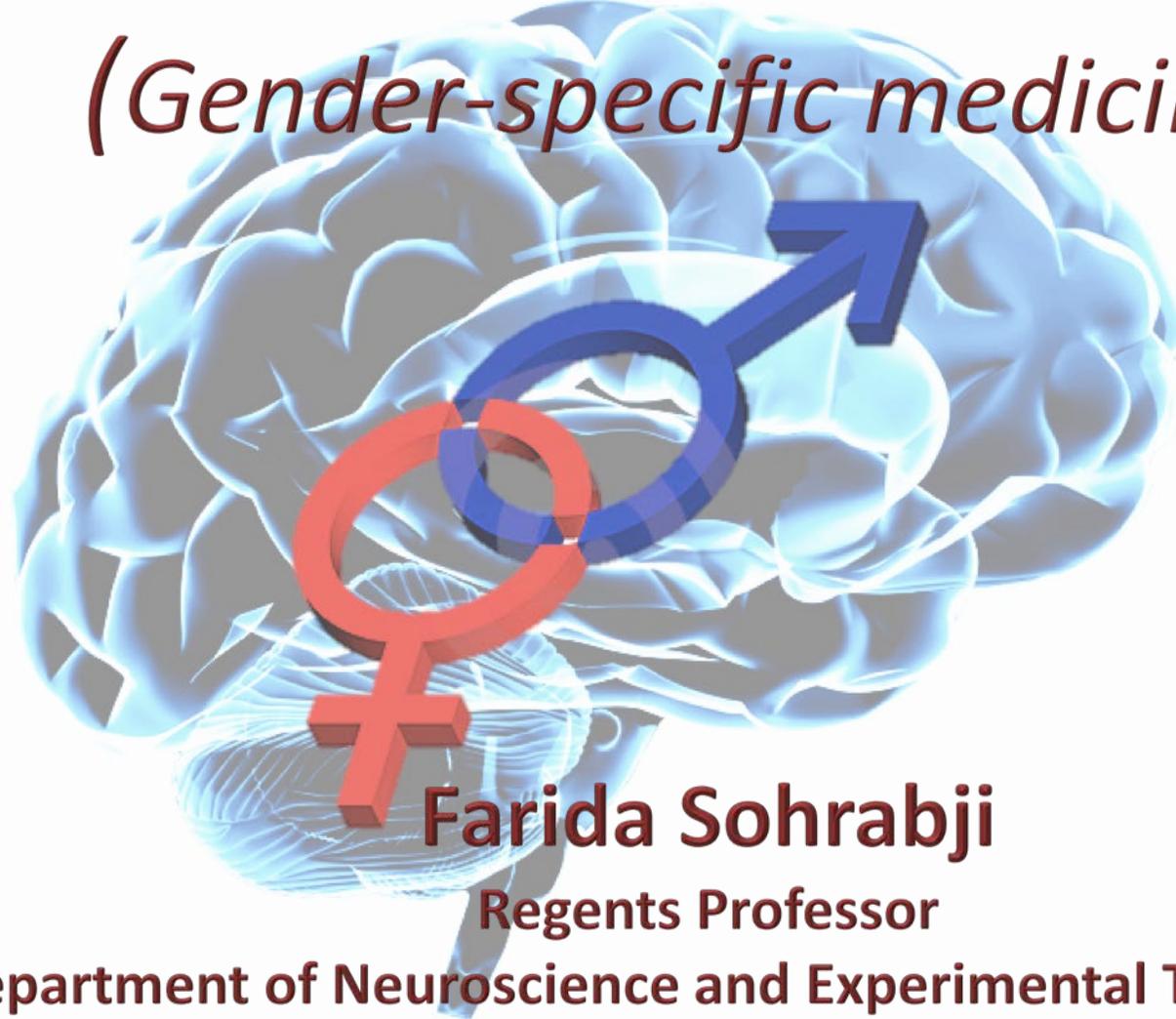


Sex differences in Brain Diseases

(Gender-specific medicine)



Farida Sohrabji

Regents Professor

Department of Neuroscience and Experimental Therapeutics

Texas A&M University College of Medicine

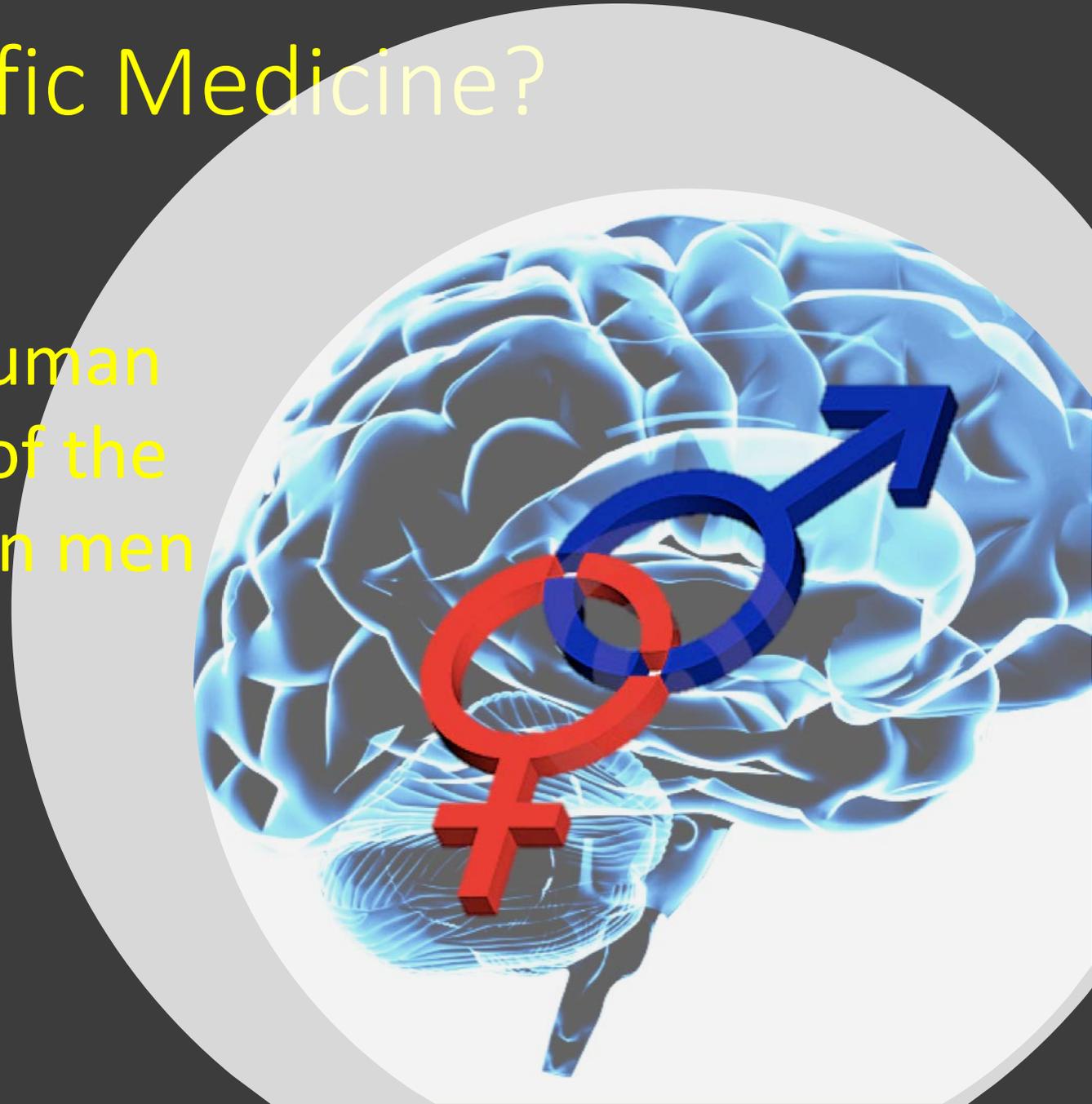
Overview of presentation

- Gender specific medicine
- Sex differences in neurological diseases: Stroke, Parkinson's Disease, Epilepsy
- Integrating sex differences in training efforts



What is Gender-Specific Medicine?

The science of how normal human function and the experience of the same diseases differs between men and women.



Why should we care about sex differences in *any* disease?

- To ensure better health care for both men and women
- To recognize that men and women may show different symptoms for the same disease
- To recognize that the same drugs and therapies may not equally effective in men and women





What are the consequences of *not* paying attention to sex differences?

Health disparities

Poor health outcomes

Misdiagnoses, inadequate treatment



- In the US, women are most likely to die from what disease?
- Who is more likely to die from breast cancer, men or women?
- Women are more likely to develop osteoporosis but are undertreated for this disease. True or false?
- Pregnancy increases the risk for several diseases, such as hypertension, stroke, type 2 diabetes but decreases the symptoms of one major disease. Which one?

Sex differences: from the obvious to the subtle

- Diseases *unique* to one sex
- Diseases occur *more frequently* in one sex compared to the other
- Diseases which *present differently* in one sex compared to the other
- Diseases *under-treated or under-recognized* in one sex compared to the other



Diseases *unique* to one sex



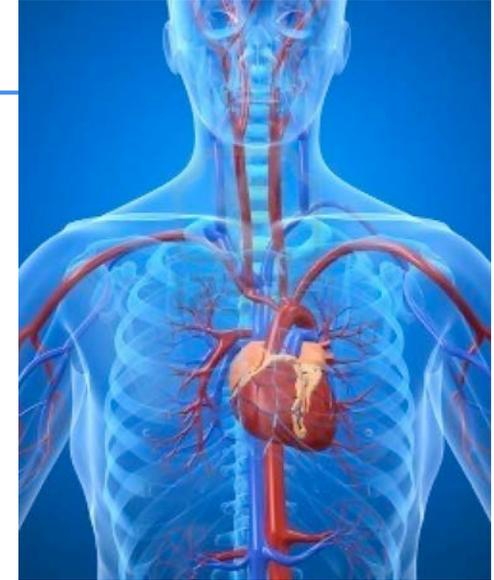
- Cancer or infections of the reproductive system
- Uterine cancer/Prostate Cancer
- Pregnancy-related disorders
- Menopause-associated disorders

Diseases under-treated or under-recognized in one sex compared to the other:

Cardiovascular (heart) disease

Advantage: male

- Women are also less likely to get heart disease in the 20-50 age range
- But it was assumed that their heart disease would be similar to men's disease, i.e. atherosclerotic disease.
- Later large-scale studies showed that women were 4.5X more likely to have a positive stress test with an angiogram that showed no blockages
- Findings of the WISE study suggest that many women have a form of Heart disease called coronary microvascular dysfunction (MVD) that isn't detected by standard diagnostic procedures and thus goes unrecognized and untreated.

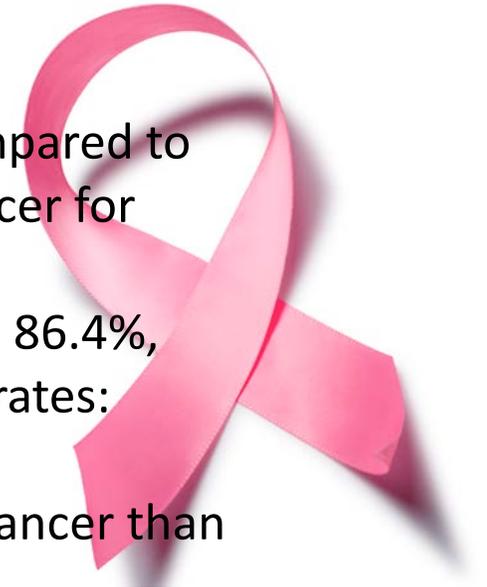


Diseases under-treated or under-recognized in one sex compared to the other

Breast Cancer:

Advantage: female

- Male breast cancer is rare: 2,100 case/yr compared to the 226,870 new cases of invasive breast cancer for women in 2012
- Five-year survival rate for women overall was 86.4%, compared to 77.6% for men, overall survival rates: 45.8% males vs 60.4% females
- More men were diagnosed with later-stage cancer than women
- Men diagnosed with hormone-receptor-positive breast cancer were less likely to be treated with hormonal therapy than women (57.9% vs 70.2%)



Diseases under-treated or under-recognized in one sex compared to the other

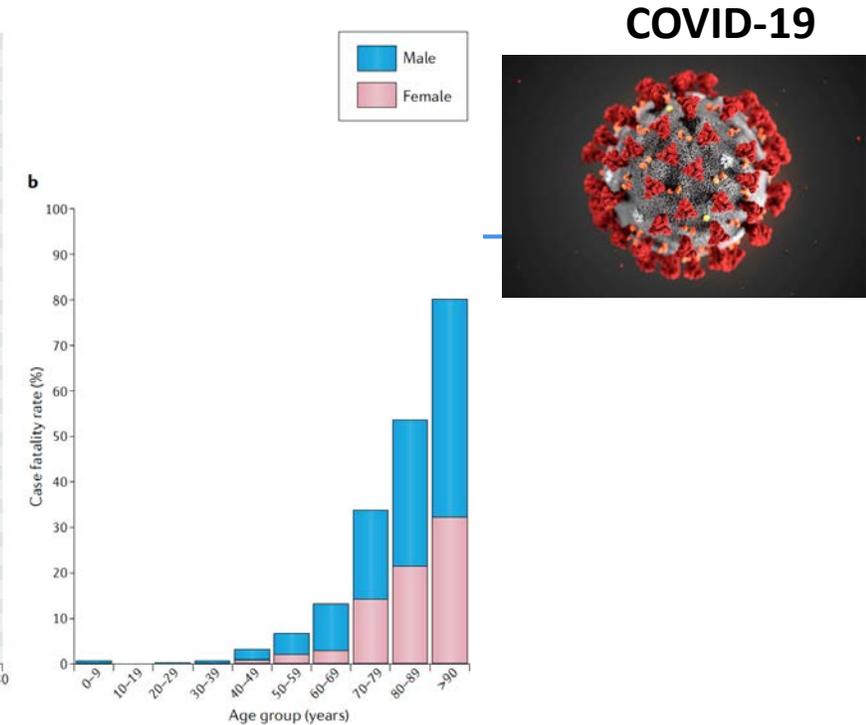
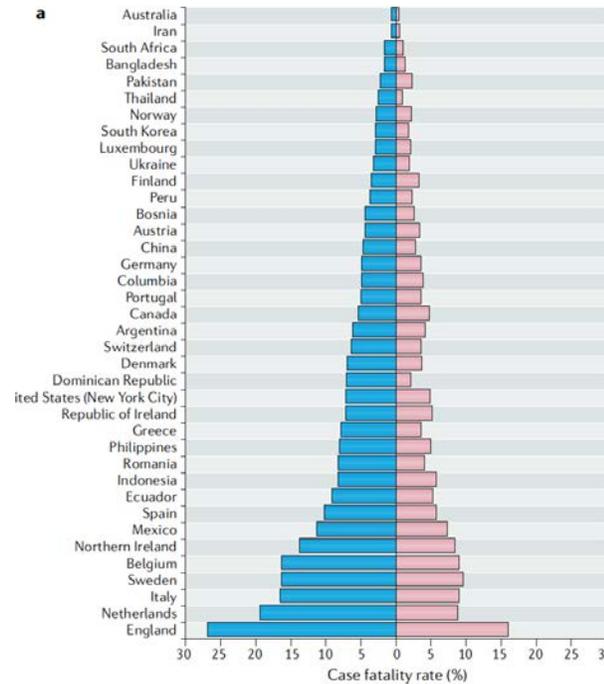
Advantage: female

- Osteoporosis is often considered to be a disease of older women. However, the lifetime fracture risk for men age over the age of 50 is up to 30% and approximately 30–40% of all osteoporosis-related fractures occur in men
- Men have a higher mortality rate after sustaining a hip fracture compared with women (31% and 17% respectively).
- Men tended to receive less bisphosphonate prescriptions compared with women after hip fractures.
- Anti-fracture efficacy data are lacking for most pharmacological agents: most treatments are licensed for use in men on the basis of BMD end points and extrapolation of fracture data in women.

Osteoporosis:



Diseases with greater fatality in one sex compared to the other



Scully et al. 2020 *Nat Rev Immunol* 10.1038/s41577-020-0348-8

- Cases vary depending on exposure (behavior and occupation and even access to testing)
- Overall it does not appear that there is much difference between the sexes in cases.
- A consistent sex difference is noted in hospitalization, admission to the ICU, and death, which is roughly two-fold higher for men than women

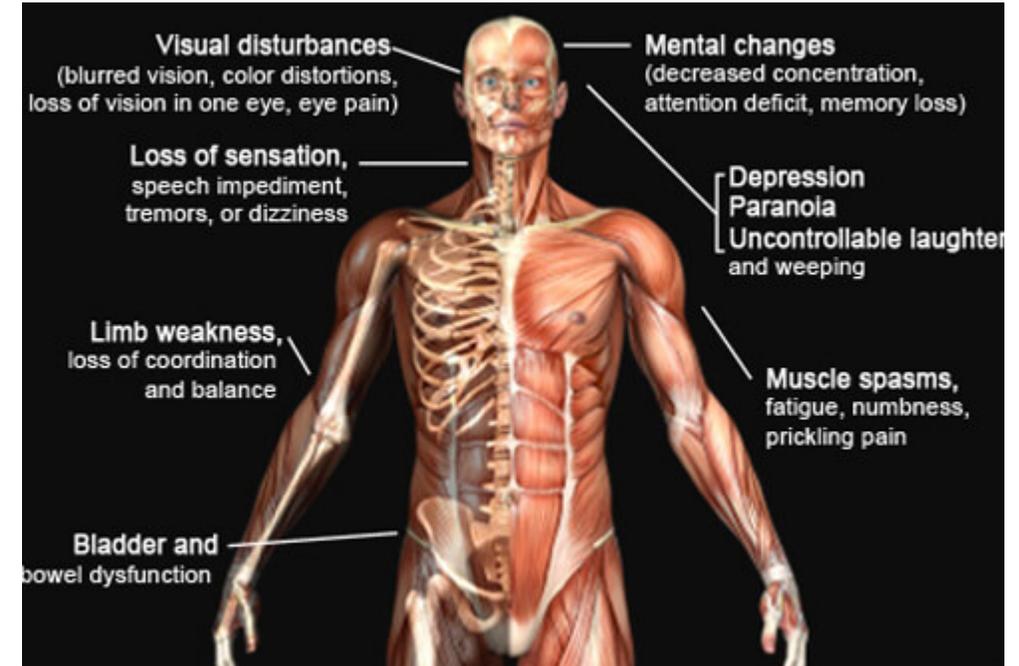
Sex differences in neurological diseases



Neurological diseases that occur more frequently in one sex compared to the other



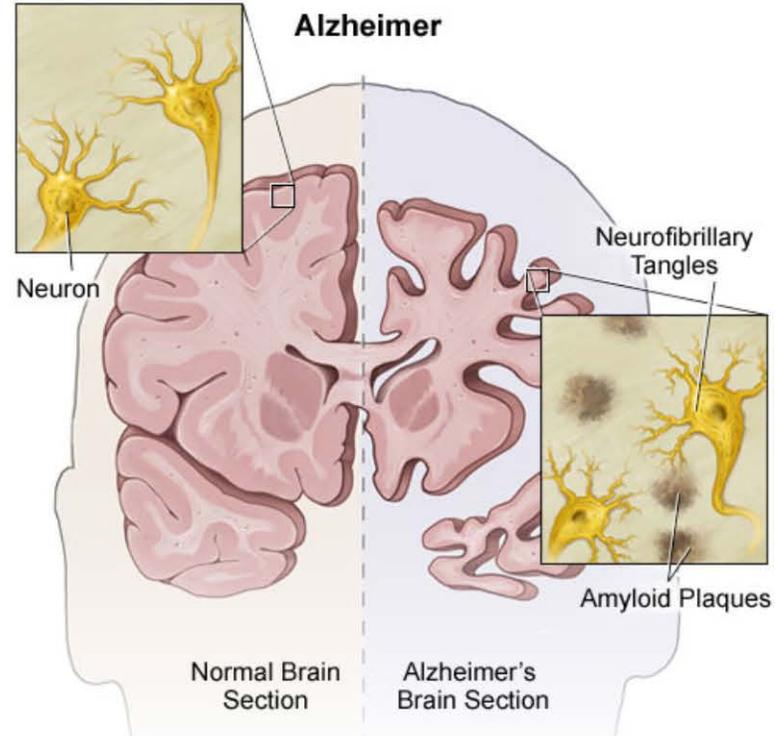
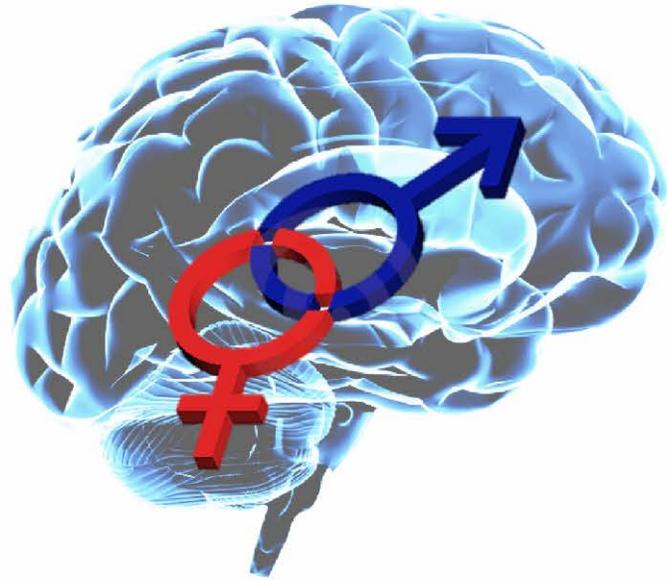
Multiple Sclerosis



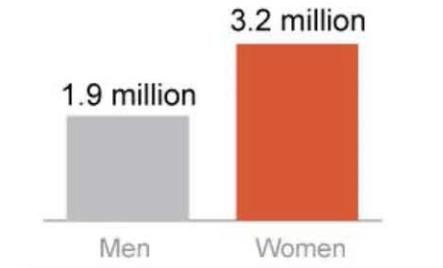
- **Multiple sclerosis:**
- females > males, 3:1
- occurs in young individuals

Diseases that occur more frequently in one sex compared to the other

Alzheimer's Disease



Number of people ages 65 and older in the U.S. with Alzheimer's:



1 in 6

In her 60s, a woman's estimated lifetime risk for developing Alzheimer's is 1 in 6. For breast cancer it is 1 in 11.

2/3

Almost two-thirds of Americans with Alzheimer's are women.

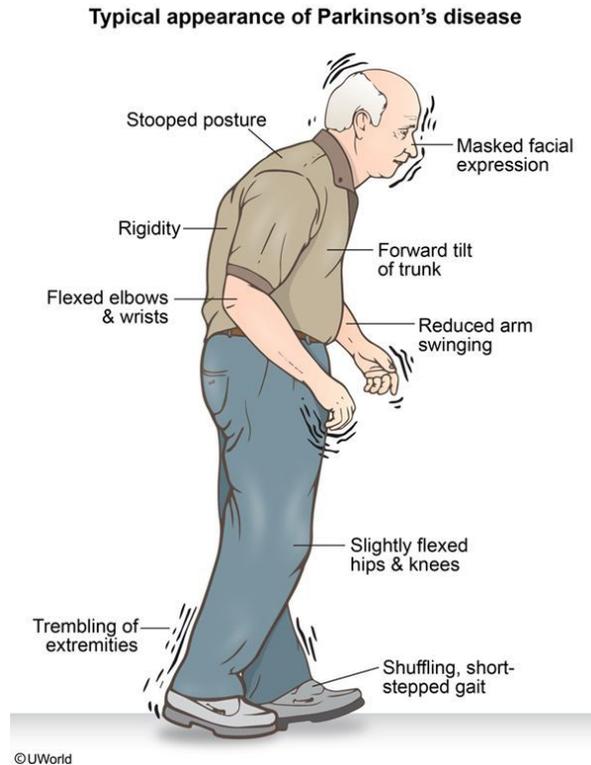


Alzheimer's Disease:

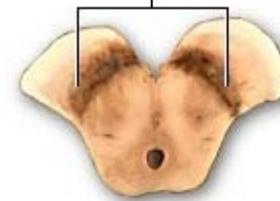
- Greater prevalence in females than males

Brain Diseases that occur more frequently in one sex compared to the other:

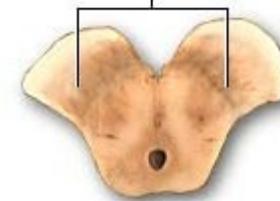
Parkinson's Disease



Substantia nigra



Diminished substantia nigra as seen in Parkinson's disease



- **Parkinson's disease:**

- males > women 3:2

- risk increases in women who have had ovaries and uterus surgically removed.

Parkinson's Disease: Evidence for Hormone effects

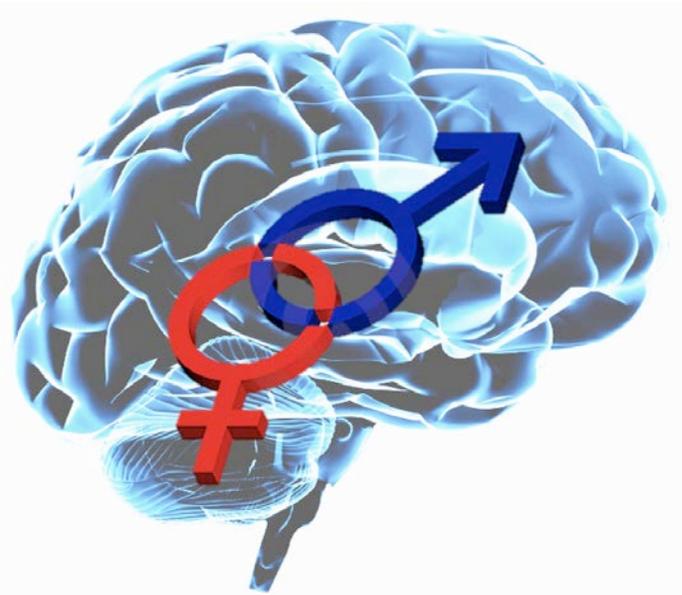


Table 3 Cohort analyses for women who underwent either unilateral or bilateral oophorectomy and for referent women in Olmsted County, MN

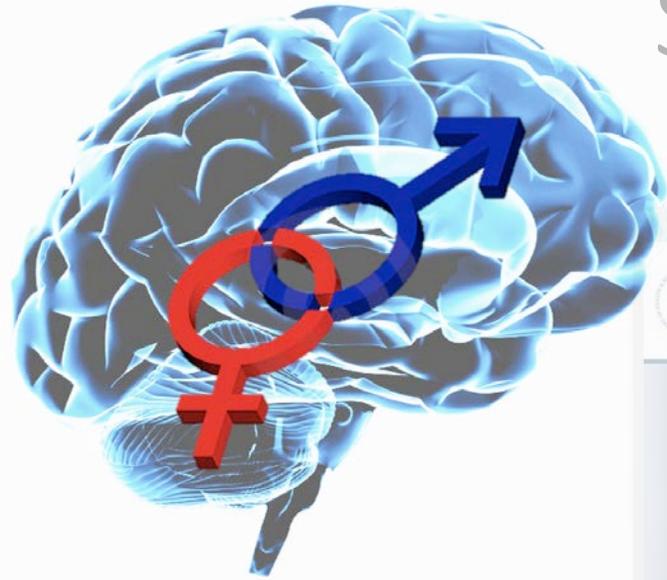
Cohort or stratum	Women at risk	Person-years of follow-up	Women with parkinsonism	Unadjusted hazard ratio (95% CI) ^a	p	Adjusted hazard ratio (95% CI) ^a	p
Referent women	2,368	58,834	28	1.00 (ref.)	—	1.00 (ref.)	—
Any oophorectomy	2,327	62,290	51	1.68 (1.06-2.67)	0.03	1.75 (1.04-2.95) ^a	0.04
Age at surgery, y ^b							
T1 (<38)							
T2 (38-45)							
T3 (>45)							
T1 + T2 (≤45)							
Indication for surgery							
Benign conditions							
No specified indication ^c							

Table 5 Cohort analyses for women who underwent bilateral oophorectomy and for referent women in Olmsted County, MN

Cohort or stratum	Women at risk	Person-years of follow-up	Women with parkinsonism	Unadjusted hazard ratio (95% CI) ^a	p	Adjusted hazard ratio (95% CI) ^a	p
Referent women	2,368	58,834	28	1.00 (ref.)	—	1.00 (ref.)	—
Bilateral oophorectomy	1,075	26,858	28	1.78 (1.06-3.01)	0.03	1.80 (1.00-3.26)	0.05
Age at surgery, y ^b							
T1 (<43)	355	9,365	6	2.17 (0.89-5.25)	0.09	1.87 (0.64-5.46)	0.25
T2 (43-48)	326	8,172	10	2.11 (1.02-4.34)	0.04	2.09 (0.89-4.90)	0.09
T3 (>48)	394	9,321	12	1.46 (0.74-2.88)	0.27	1.64 (0.79-3.39)	0.19
T1 + T2 (≤48)	681	17,537	16	2.13 (1.15-3.94)	0.02	2.00 (0.97-4.15)	0.06
Age at estrogen deficiency, y ^b							
T1 (<46)	347	9,118	6	1.69 (0.70-4.09)	0.24	1.78 (0.67-4.71)	0.25
T2 (46-51)	337	8,258	9	1.80 (0.85-3.82)	0.12	1.78 (0.76-4.18)	0.19
T3 (>51)	391	9,482	13	1.81 (0.94-3.51)	0.08	1.83 (0.87-3.87)	0.11
T1 + T2 (≤51)	684	17,376	15	1.76 (0.94-3.29)	0.08	1.78 (0.88-3.60)	0.11
Indication for surgery							
Benign conditions	544	14,097	16	2.16 (1.17-3.99)	0.01	2.20 (1.09-4.45)	0.03
Prophylactic ^c	531	12,760	12	1.45 (0.73-2.84)	0.29	1.48 (0.70-3.14)	0.30

Increased risk of parkinsonism in women who underwent oophorectomy before menopause.
 Rocca, W; MD, MPH; Bower, J; Maraganore, D; Ahlskog, J; PhD, MD; Grossardt, B; de Andrade, M; Melton, L; III MD, MPH
 Neurology. 70(3):200-209, January 15, 2008.
 DOI: 10.1212/01.wnl.0000280573.30975.6a

Sex differences – Parkinson's Disease



Help | Glossary | References

Neurological Disease

Epidemiology: Presentation in Women



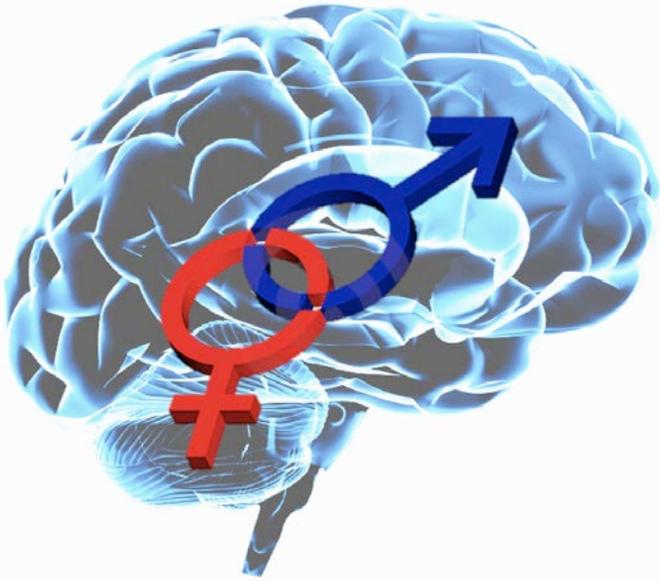
Studies⁶⁸ have identified these sex differences for women:

- More likely to present with tremor
- Shorter time to and higher likelihood of developing motor fluctuations (though women are less likely to receive deep brain stimulation surgery for this condition)
- More likely to have dyskinesia (abnormal, uncontrollable, involuntary movements)⁶⁶
- Self-reporting or displaying more depression, fatigue, nervousness, constipation, pain, and restless legs, and reporting higher disability
- Slower progression to cognitive impairment⁶⁹

Continue ▶

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PREV



Sex differences--Epilepsy



NIH

FDA

Neurological Disease

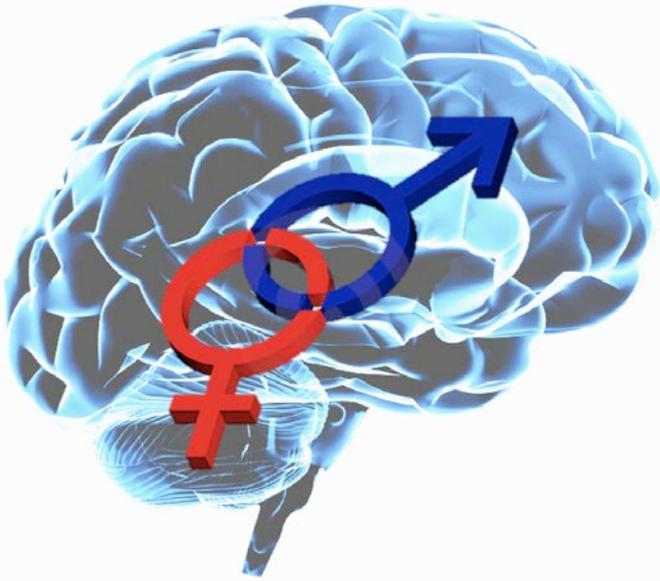
Sex Differences in Specific Epilepsy Syndromes



There are sex and age differences in specific epilepsy syndromes. Some affect women more than men, for example, or younger people more than older people. Others show different trends.

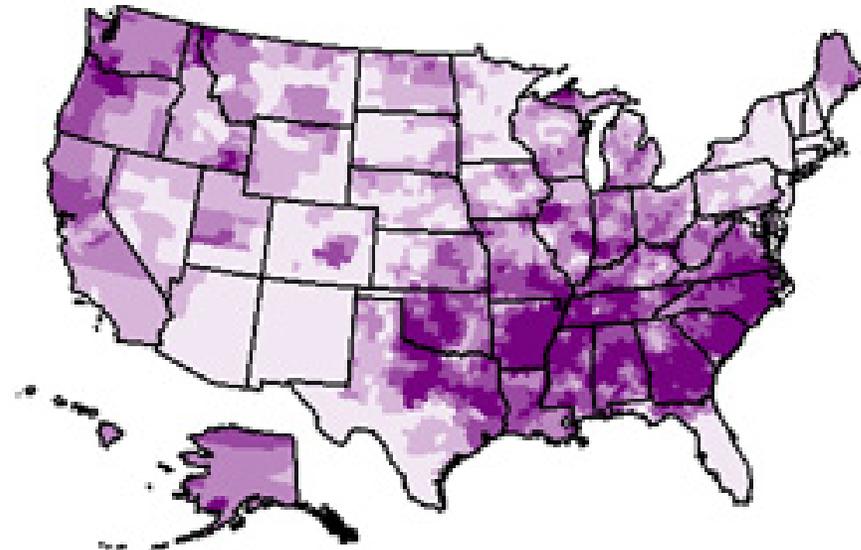
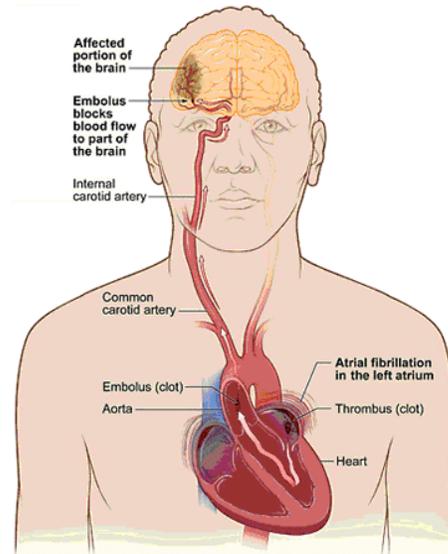
- Genetic /idiopathic generalized epilepsies (IGEs): F>M^{106,107}
- Focal/localization-related epilepsy:
 - Symptomatic: M>F^{97,106-109}
 - Cryptogenic: F>M (not found in other studies)^{106,107}
 - Mesial temporal lobe epilepsy:
 - Hippocampal sclerosis: F=M¹¹⁰
 - Isolated auras: F>M^{111,112}
 - Secondary generalization: M>F¹¹¹
 - Focal cortical dysplasia: M>F¹¹³
 - Periventricular nodular heterotopia: M>F¹¹⁴
- Photosensitive epilepsy: F>M¹¹⁵

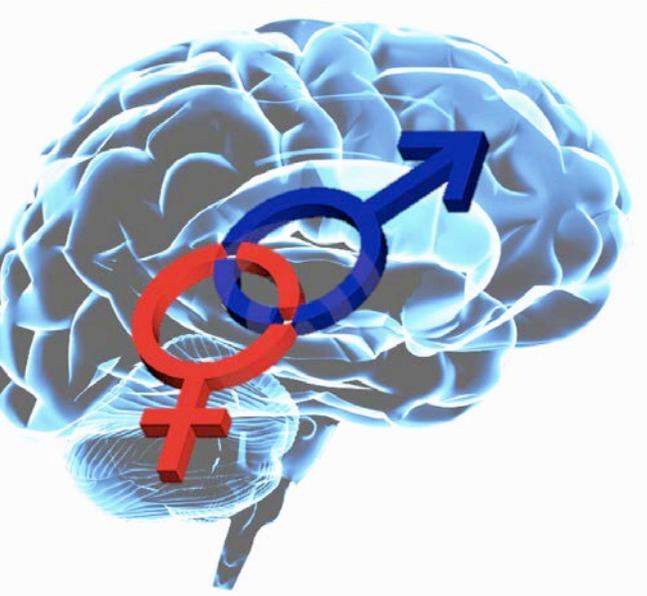
Continue ▶



Sex Differences in Stroke

- Stroke is the 5th leading cause of death and the leading cause of long term disability
- Yearly cost of \$74 billion for stroke care
- 795,000 people will experience a new or recurrent stroke





Stroke: Sex differences

- Incidence
- Risk Factors
- Outcomes
- Symptoms
- Therapies



Gender, age, and stroke

- Incidence
- Risk Factors
- Outcomes
- Symptoms
- Therapies

Help | Glossary | References

Neurological Disease
Epidemiology: Sex Differences

NIH FDA

What does the epidemiology of ischemic stroke teach us about sex differences in neurological disorders?
Explore these differences here. *Select each circle.*

In 2015, 58.3% of U.S. stroke deaths were in women. The rate of stroke in women increases from 2.4% (ages 40-59) to 6.1% (ages 60-79). The stroke rate increases again for women over the age of 80 (14.9%), surpassing the rate in men (13.8%).⁹

Continue

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Gender, age, and stroke



NIH

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Neurological Disease

Epidemiology: Sex Differences



What does the epidemiology of ischemic stroke teach us about sex differences in neurological disorders?
Explore these differences here. *Select each circle.*

- Incidence
- Risk Factors
- Outcomes
- Symptoms
- Therapies

Women have a higher lifetime risk of stroke than men because they live longer. Stroke is the third-leading cause of death in women in the U.S. Approximately 55,000 more women than men have a stroke in the U.S. every year.¹⁷

Continue ▶

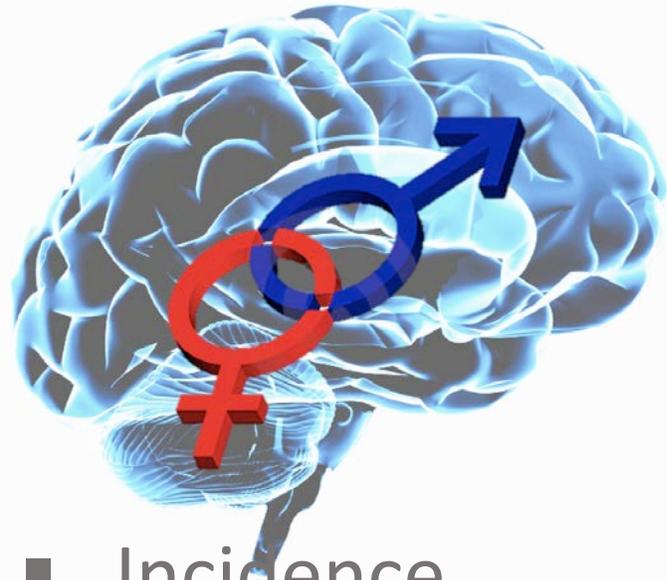
Stroke risk factors



- Incidence
- **Risk Factors**
- Outcomes
- Symptoms
- Therapies

- Pregnancy
- Cigarette smoking, especially women on birth control medication
- Diabetes: after age 45 women are 2x more likely to develop diabetes
- Hormone therapy after menopause.
- Atrial Fibrillation: Women with A-Fib are more likely to suffer stroke

Gender, age, and stroke



- Incidence
- **Risk Factors**
- Outcomes
- Symptoms
- Therapies

Help | Glossary | References

Neurological Disease
Age, Sex, Gender, and Race

NIH FDA



The interactions of sex and age in stroke complicate efforts to interpret research results and to develop precision treatments for all population groups. Gender, race, and societal differences make the picture even more complex. For example:

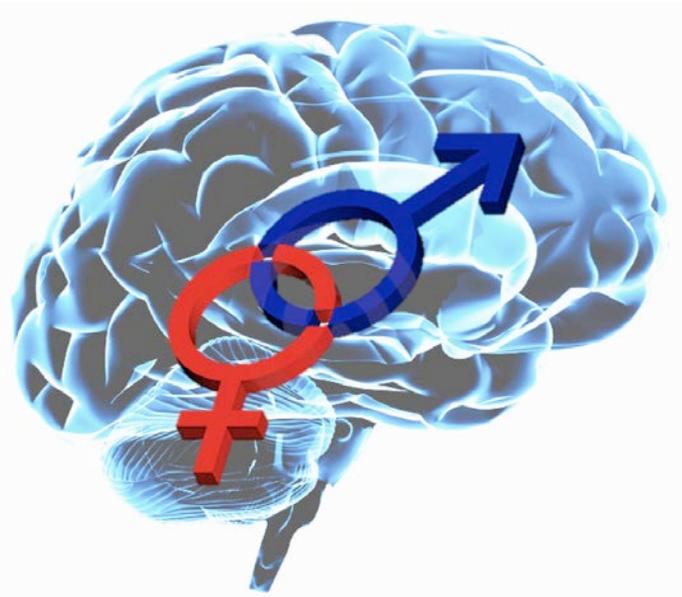
- In many countries, more women than men live alone.²²
- Living alone raises the risk of delayed access to care—and with stroke, the speed of access to care is critical to the outcome.²³
- Cultural and geographical factors influence sex differences in stroke awareness, willingness to undertake preventive measures, and risk factors.^{4,24}

Continue ▶

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PREV

Stroke Symptoms

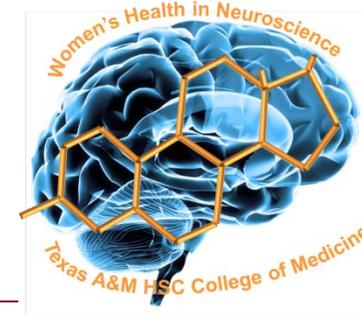


- The majority of males and females show “traditional” stroke symptoms (facial droop, aphasia/slurred speech)
 - Women are more likely to report “weakness”
 - Women are also more likely to report a somatic cluster of symptoms: feeling nauseous, migraines, neck pain, face pain
-
- Recognizing symptoms and acting fast can save lives and limit disabilities. “Time is brain”



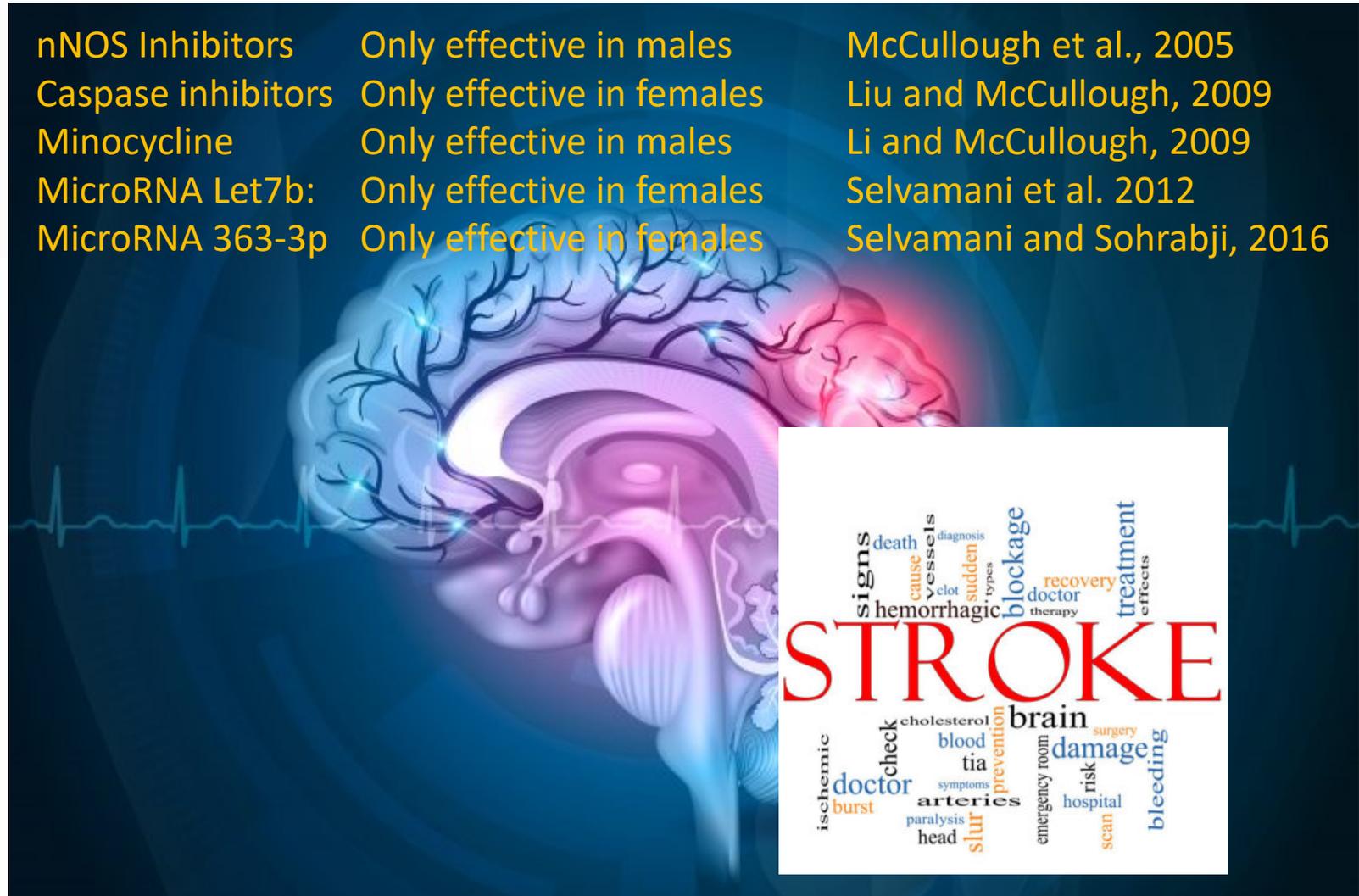


Preclinical Studies: Stroke therapies



nNOS Inhibitors	Only effective in males	McCullough et al., 2005
Caspase inhibitors	Only effective in females	Liu and McCullough, 2009
Minocycline	Only effective in males	Li and McCullough, 2009
MicroRNA Let7b:	Only effective in females	Selvamani et al. 2012
MicroRNA 363-3p	Only effective in females	Selvamani and Sohrabji, 2016

- Incidence
- Risk Factors
- Outcomes
- Symptoms
- Therapies

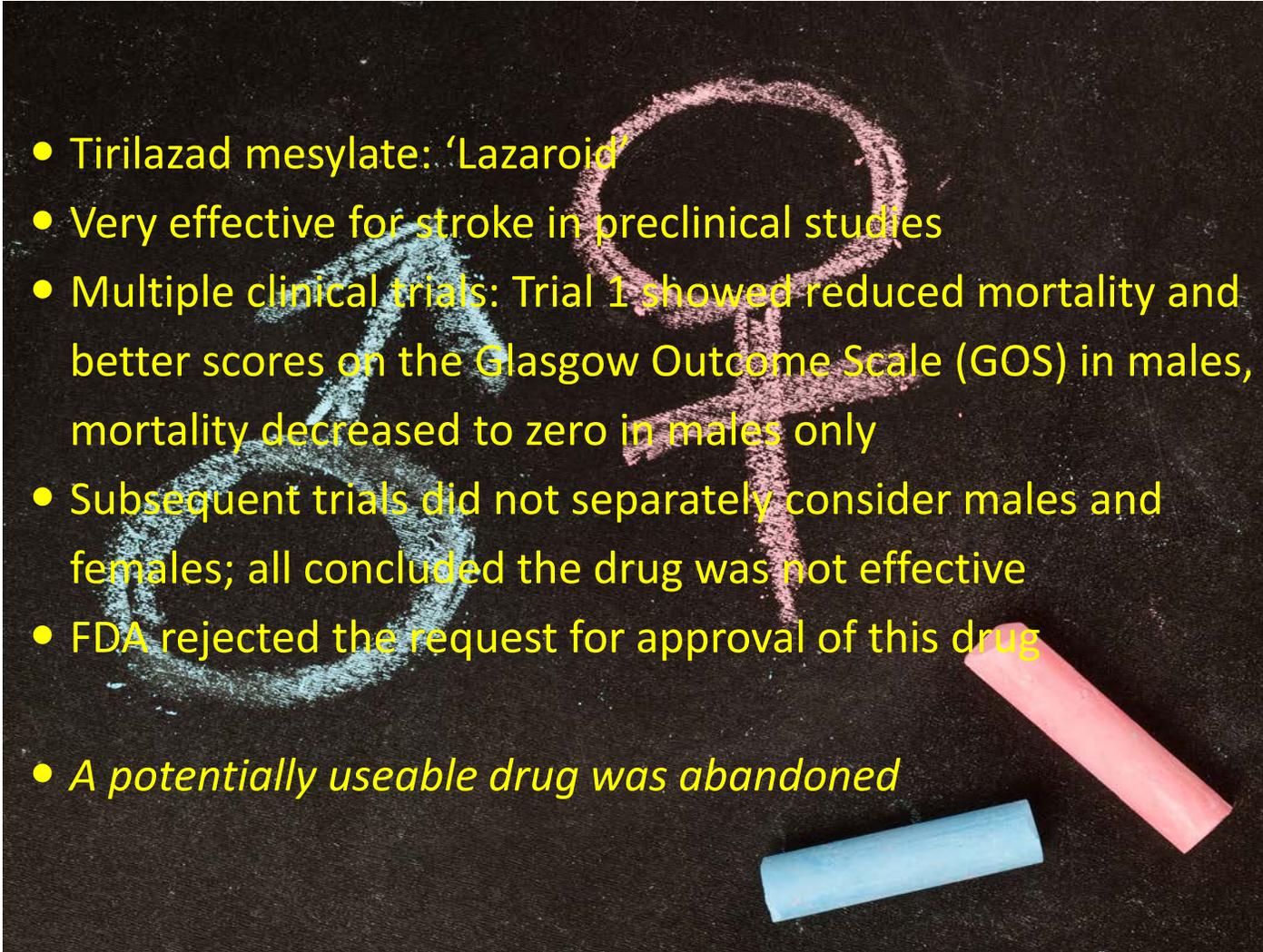




Sex-specific therapies: Case study

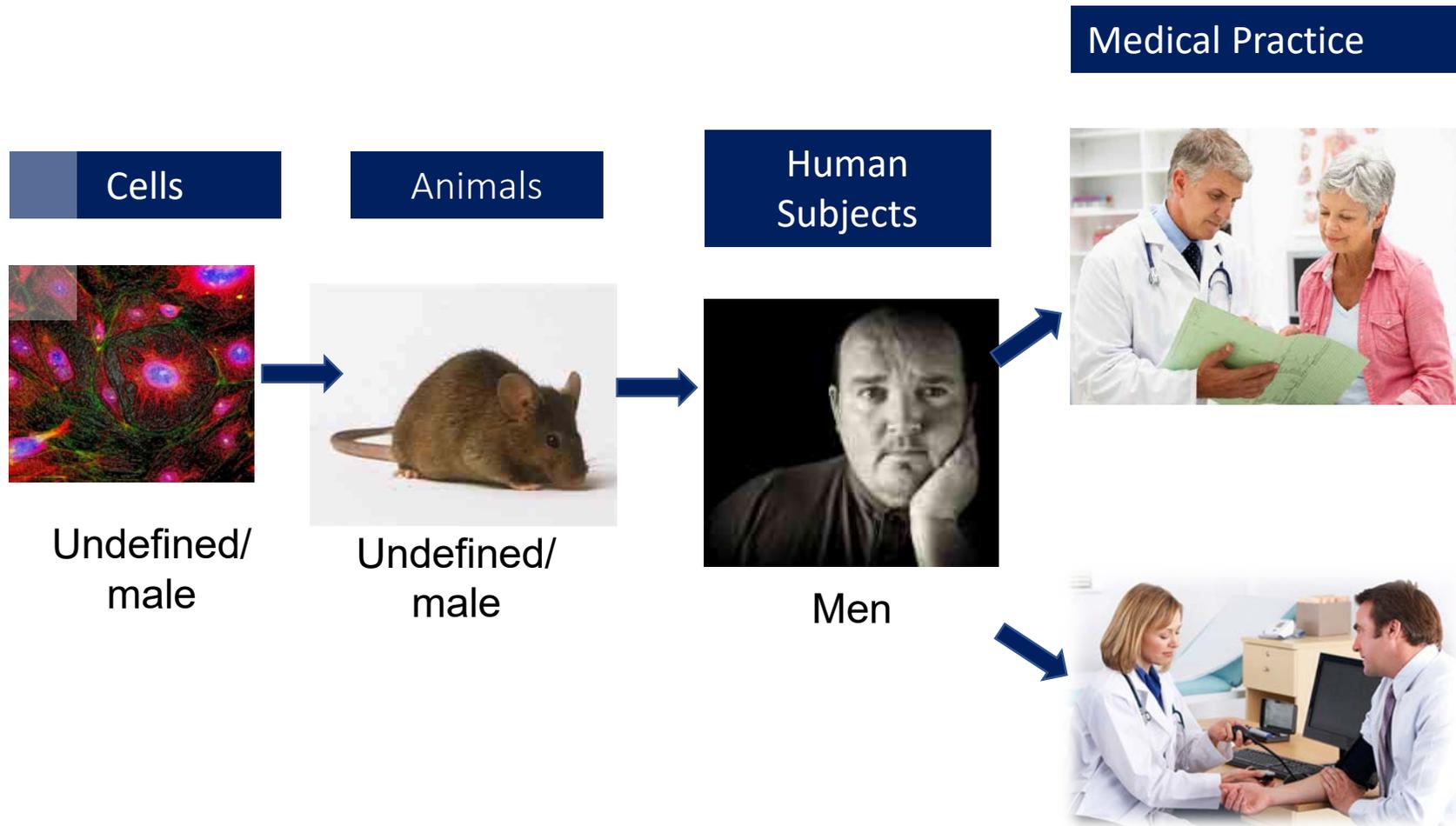


Cahill and Hall, *Journal of Neuroscience Research*, 2016

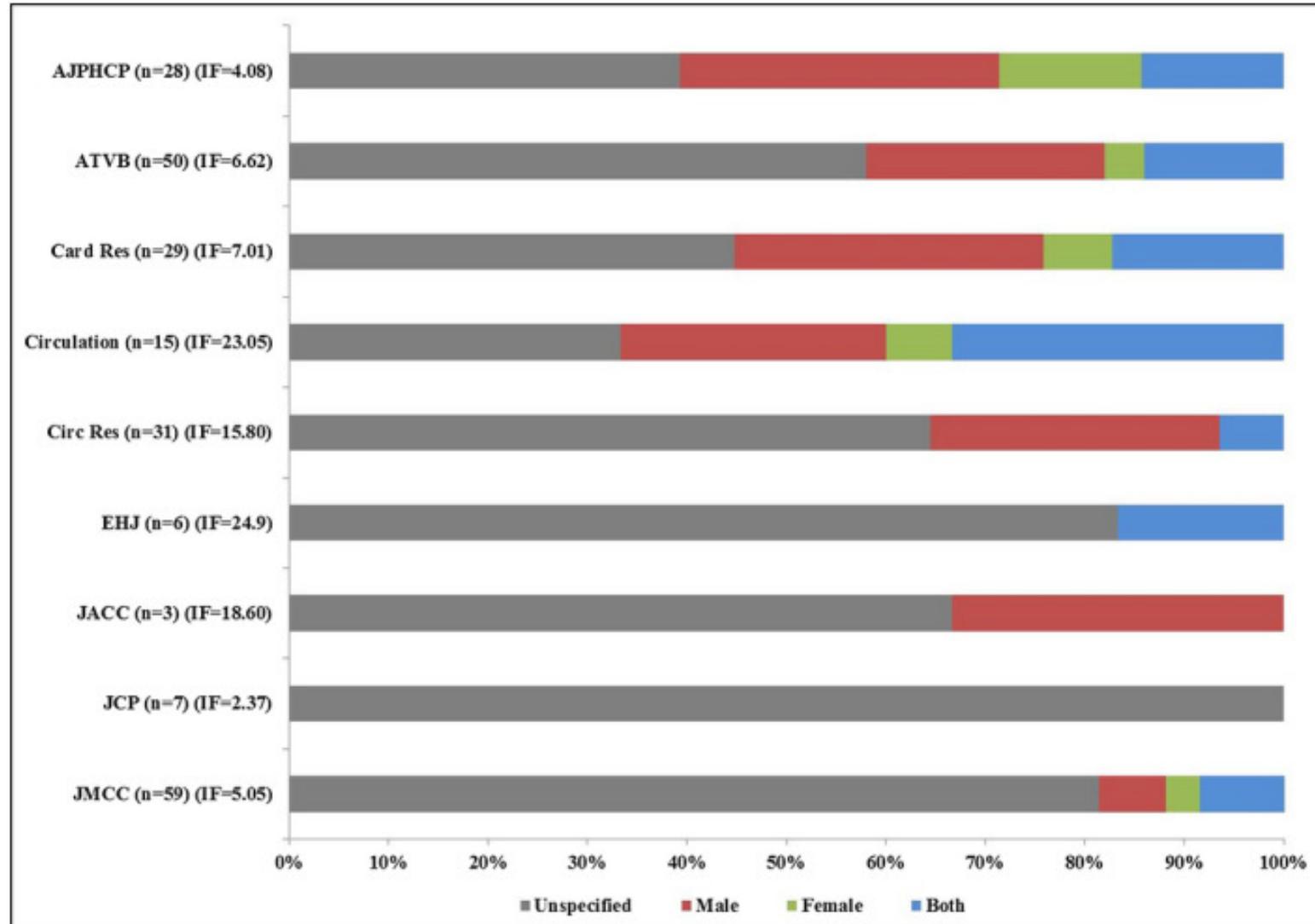
- 
- Tirilazad mesylate: 'Lazaroid'
 - Very effective for stroke in preclinical studies
 - Multiple clinical trials: Trial 1 showed reduced mortality and better scores on the Glasgow Outcome Scale (GOS) in males, mortality decreased to zero in males only
 - Subsequent trials did not separately consider males and females; all concluded the drug was not effective
 - FDA rejected the request for approval of this drug
 - *A potentially useable drug was abandoned*



Emphasizing sex differences in research efforts

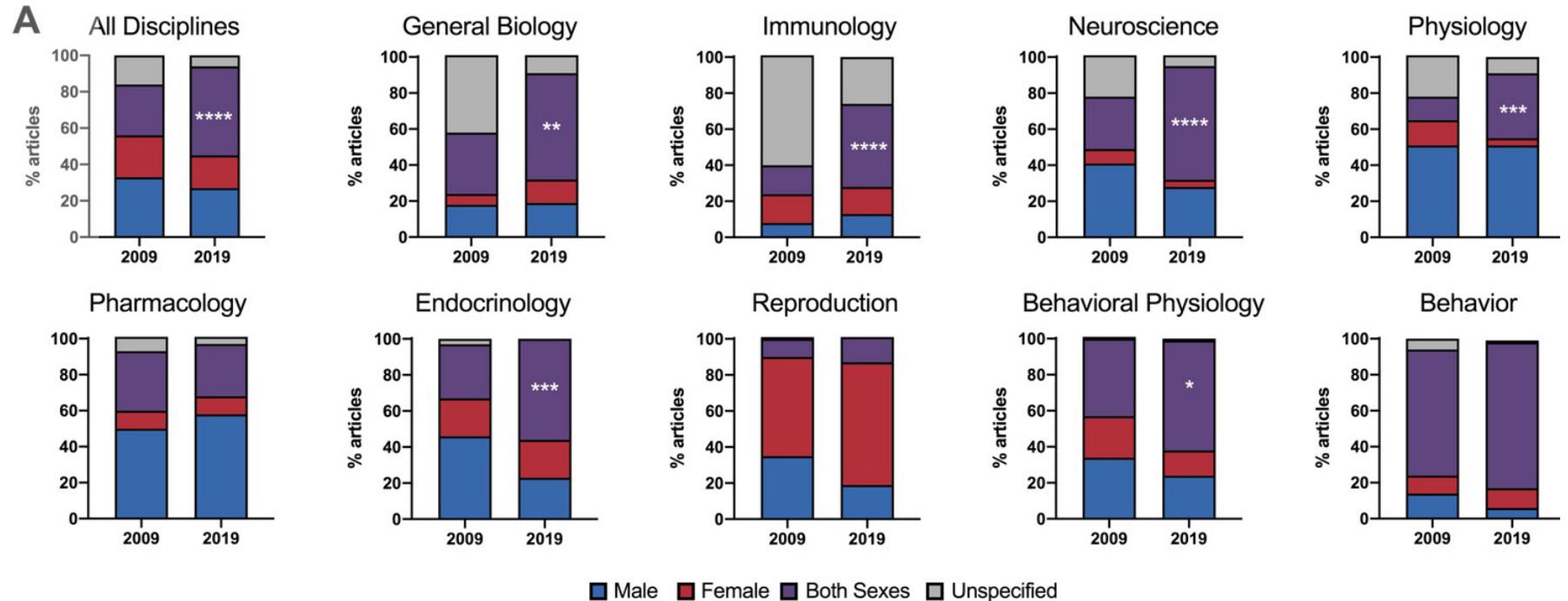


Reporting Sex of Cells used in Studies of Cardiovascular Function – 2020



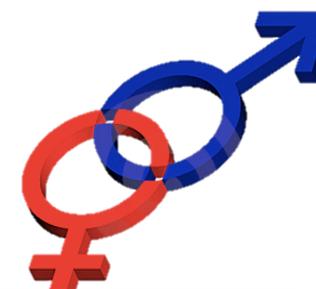
Vallabhajosyula et al. Reporting of sex as a variable in cardiovascular studies using cultured cells: A systematic review. *FASEB J.* 2020;34(7):8778-8786. doi:10.1096/fj.202000122R

Reporting of Sex of Animals in Basic Science Studies



Woitowich NC et al. A 10-year follow-up study of sex inclusion in the biological sciences. *Elife*. 2020;9:e56344

NIH Policy: Human Trials



Policy & Compliance

[NIH Grants Policy Statement](#)

[Notices of Policy Changes](#)

[Compliance & Oversight](#)

[Select Policy Topics](#) +

Inclusion of Women and Minorities as Participants in Research Involving Human Subjects - Policy Implementation Page

General Information

The NIH is mandated by law ([Public Health Service Act sec. 492B, 42 U.S.C. sec. 289a-2](#)) to ensure the inclusion of women and minority groups in clinical research. The goal is to ensure that individuals are included in clinical research in a manner that is appropriate to the scientific question under study.

Inclusion Guidance Links

The NIH has transitioned inclusion data monitoring from the Population Tracking system in eRA to the **Inclusion Management System (IMS)** (October 2014).

The following pages are links for inclusion related policies, FAQs, and the IMS Deployment page.

1. [Policy and Procedures](#)
2. [Training, FAQs and Other Resources](#)

Related Resources

News Flash

[NOT-OD-15-078: Updated Inclusion Enrollment Format Now Required for Successful Submission of RPPR](#)

Inclusion Resources

[How to Video: IMS for Principal Investigators \(PIs\)](#)

[Inclusion FAQs](#)

[NIH Definition of Clinical Research](#)

[Decision Tree: What is Subject to Inclusion](#)

NIH Policy: Animal Research



Consideration of Sex as a Biological Variable in NIH-funded Research

Notice Number: NOT-OD-15-102

Key Dates

Release Date: June 9, 2015

Related Announcements

[NOT-OD-16-034](#)
[NOT-OD-16-031](#)
[NOT-OD-16-012](#)
[NOT-OD-16-011](#)
[NOT-OD-15-103](#)

Issued by

National Institutes of Health (NIH)

Purpose

The National Institutes of Health (NIH) is committed to improving the health outcomes of men and women through the nature and behavior of living systems. Sex and gender play a role in how health and disease processes differ and informs the development and testing of preventive and therapeutic interventions in both sexes. This notice focuses on sex as a biological variable in vertebrate animal and human studies. Clarification of these expectations is reflected in the application instructions and review questions; once approved by the Office of Management and Budget (OMB), the notice will be effective on 10/1/2016, due date and thereafter. Please refer to [NOT-OD-15-103](#) for further consideration of NIH expectations about sex as a biological variable.

Background

Women now account for roughly half of all participants in NIH-supported clinical research, which is subject to NIH policies. Often than not, basic and preclinical biomedical research has focused on male animals and cells.³ An over-reliance on male influences on health processes and outcomes.

Accounting for sex as a biological variable begins with the development of research questions and study design.

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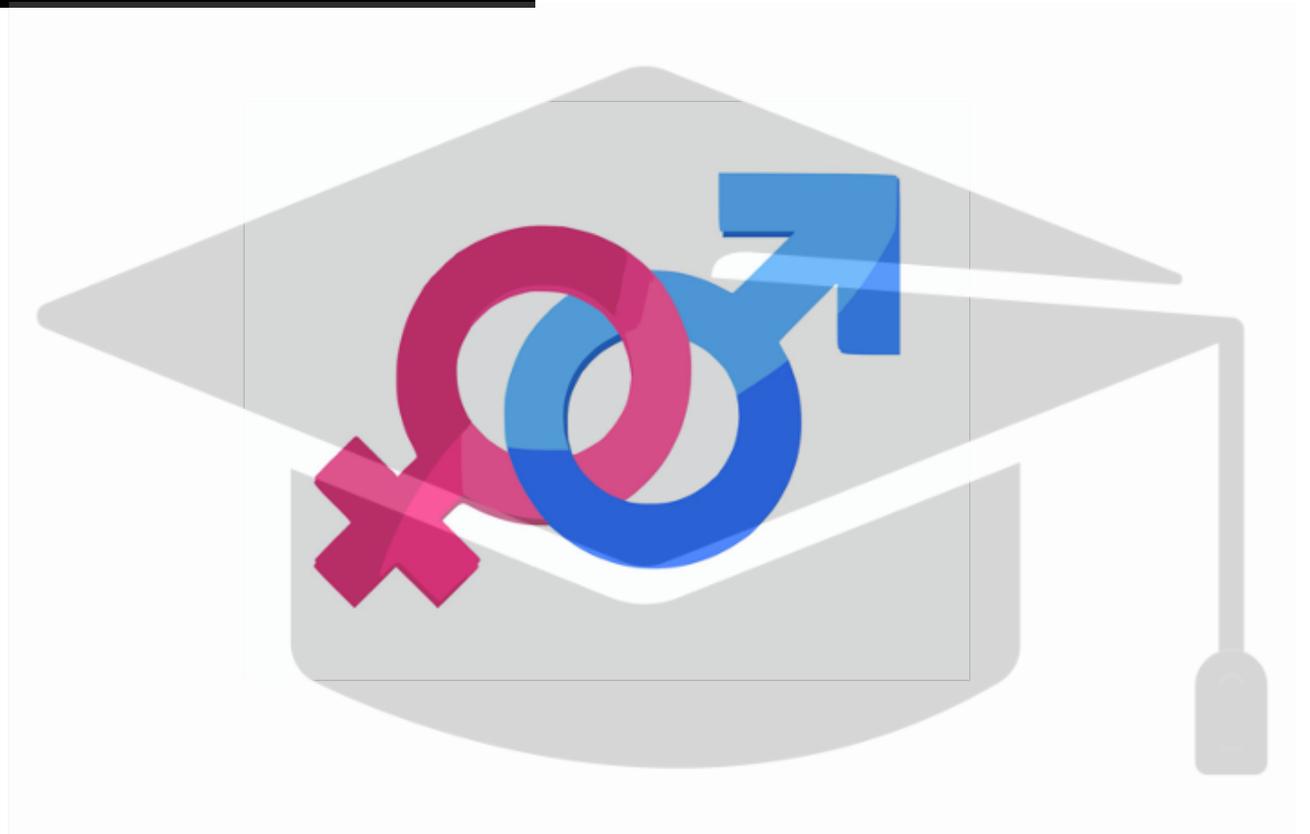
Considering sex as a biological variable in preclinical research

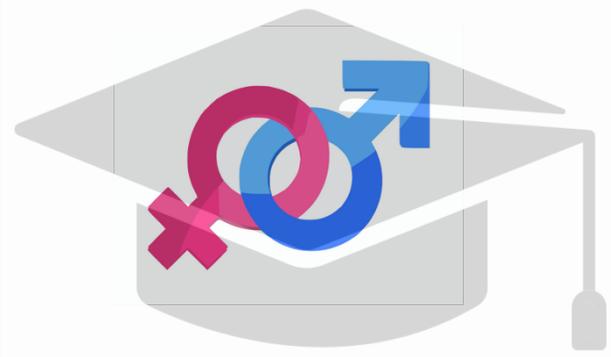
Leah R. Miller,^{*,1} Cheryl Marks,[†] Jill B. Becker,[‡] Patricia D. Hum,[§] Wei-Jung Chen,[¶] Teresa Woodruff,^{||} Margaret M. McCarthy,[¶] Farida Sohrabji,[¶] Londa Schiebinger,^{**} Cora Lee Wetherington,^{††} Susan Makris,^{‡‡} Arthur P. Arnold,^{§§,¶¶} Gillian Einstein,^{||,¶¶,***} Virginia M. Miller,^{†††,‡‡‡} Kathryn Sandberg,^{§§§,¶¶¶} Susan Maier,^{*} Terri L. Cornelison,^{*} and Janine A. Clayton^{*}

^{*}Office of Research on Women's Health and [†]Division of Cancer Biology, National Cancer Institute, and ^{††}National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland, USA; [‡]Molecular and Behavioral Neuroscience Institute and [§]School of Nursing, University of Michigan, Ann Arbor, Michigan, USA; [¶]Department of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, Bryan, Texas, USA; ^{||}Women's Health Research Institute, Northwestern University, Chicago, Illinois, USA; ^{¶¶}Department of Pharmacology, University of Maryland, Baltimore, Maryland, USA; ^{**}History of Science, Stanford University, Stanford, California, USA; ^{††}Office of Research and Development, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA; ^{‡‡}Department of Integrative Biology and Physiology and ^{§§}Laboratory of Neuroendocrinology of the Brain Research Institute, University of California, Los Angeles, Los Angeles, California, USA; ^{¶¶}Department of Psychology and ^{‡‡‡}The Dallia Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; ^{§§§}Women's College Research Institute, Toronto, Ontario, Canada; ^{¶¶¶}Department of Surgery and Physiology and ^{†††}Department of Biomedical Engineering, Mayo Clinic, Rochester, Minnesota, USA; and ^{§§§}Department of Medicine and ^{†††}Center for the Study of Sex Differences in Health, Aging and Disease, Georgetown University Medical Center, Washington, D.C., USA

ABSTRACT: In June 2015, the National Institutes of Health (NIH) released a *Guide* notice (NOT-OD-15-102) that highlighted the expectation of the NIH that the possible role of sex as a biologic variable be factored into research design, analyses, and reporting of vertebrate animal and human studies. Anticipating these guidelines, the NIH Office of Research on Women's Health, in October 2014, convened key stakeholders to discuss methods and techniques for integrating sex as a biologic variable in preclinical research. The workshop focused on practical methods, experimental design, and approaches to statistical analyses in the use of both male and female animals, cells, and tissues in preclinical research. Workshop participants also considered gender as a modifier of biology. This article builds on the workshop and is meant as a guide to preclinical investigators as they consider methods and techniques for inclusion of both sexes in preclinical research and is not intended to prescribe exhaustive/specific approaches for compliance with the new NIH policy.—Miller, L. R., Marks, C., Becker, J. B., Hum, P. D., Chen, W.-J., Woodruff, T., McCarthy, M. M., Sohrabji, F., Schiebinger, L., Wetherington, C. L.,

Integrating sex differences in training efforts





How can we emphasize sex differences in our training efforts?

- NIH-supported efforts:
- ORWH BIRCWH & SCORE programs, ORWH E-Learning program



Building Interdisciplinary
Research Careers in
Women's Health



Specialized Centers of
Research Excellence
on Sex Differences

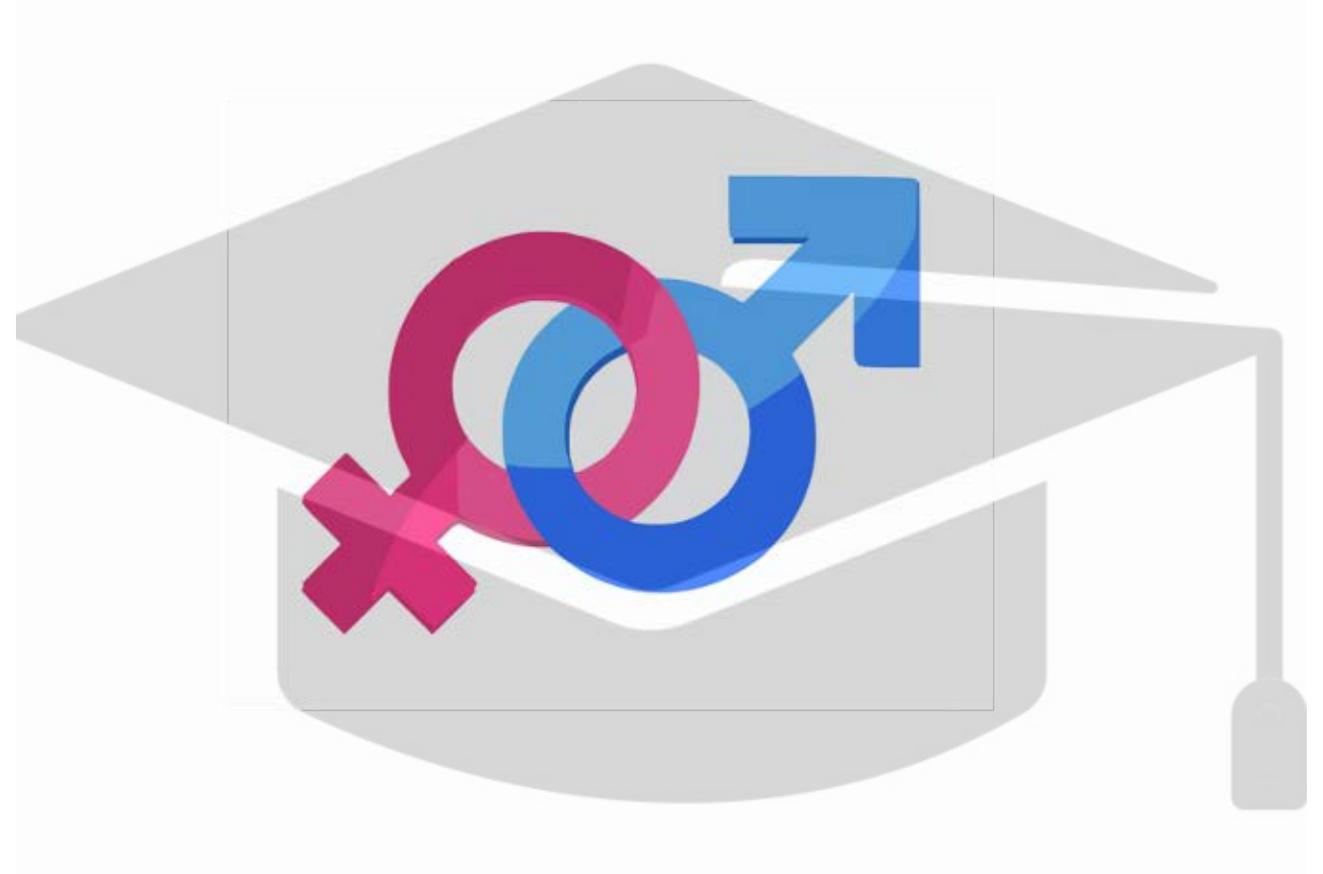


ORWH
E-Learning
Program



How can we emphasize sex differences in our training efforts?

- Local efforts : in your classroom
 - It starts with the individual faculty
 - Some disciplines lend themselves more easily to these discussions (Cardiovascular medicine, Neuroscience)
 - An example of a local research and training effort: WHIN



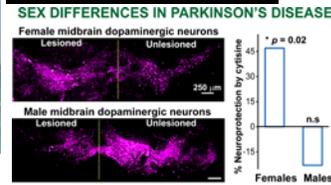


TEXAS A&M
HEALTH
SCIENCE
CENTER

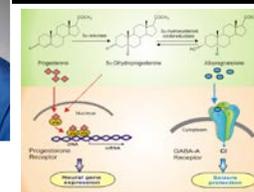
Women's Health in Neuroscience



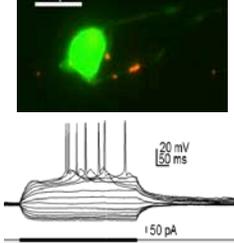
Dr. Rahul Srinivasan
Neurodegeneration, Parkinson's disease, astrocytes and neuroprotection



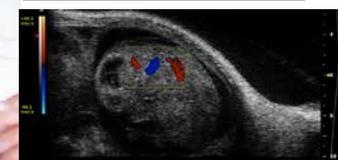
Dr. Samba Reddy
Role of neurosteroids in the pathophysiology and treatment of catamenial epilepsy in women



Dr. William Griffith
Neuropharmacology of aging u



Dr. Rajesh Miranda
Effects of maternal alcohol use on stem cell differentiation



WHIN Clinical Advisory Group



Dr. Nancy Dickey



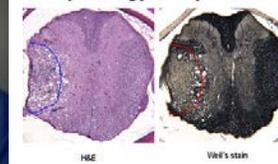
Dr. Jonathon Friedman



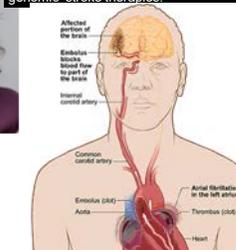
Dr. William Rayburn

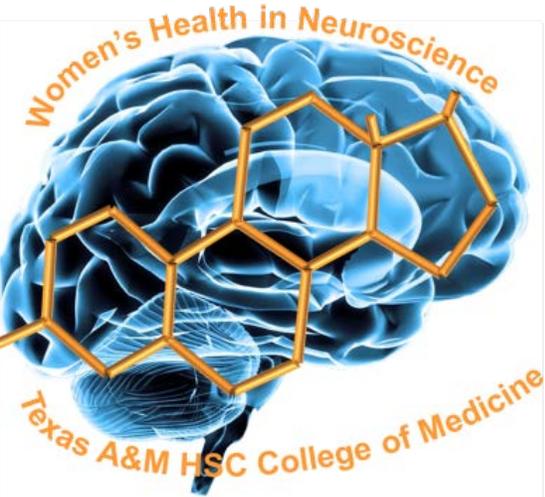


Dr. C. Jane Welsh
Multiple Sclerosis
Histopathology -demyelination



Dr. Farida Sohrabji
Pathophysiology of stroke and neuroinflammation in females/protein and genomic stroke therapies.





WHIN Scholars:

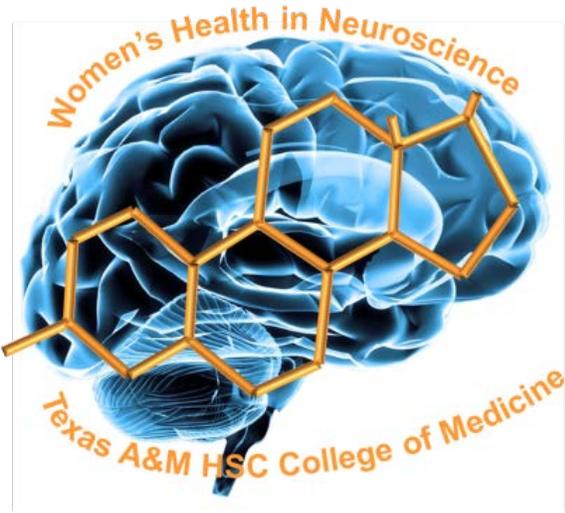
Min Jung Park: currently Assistant Professor, Chungnam University

Previously: Associate research scientist, Texas A&M University (2017-2018)

Projects: Developing Dietary/Epigenetic Interventions to Cure Neurological and Metabolic Diseases

- “While I was developing my own grant in inner ear research, I included sex as a biological variable. The inclusion of both sexes helped me to obtain my first independent 5-yr research support and to have opportunity to investigate the exciting unknown field of research. “



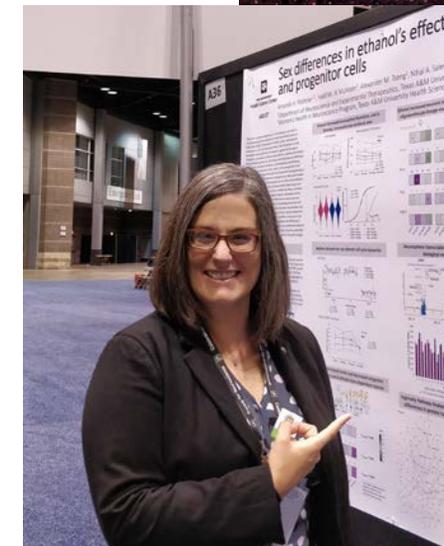


WHIN scholars:

Amanda Mahnke, PhD: Currently Associate Research Scientist, TAMU

Research interest: Neural development/Teratology/Effect of drugs on neural progenitor cells

"Being a Women's Health in Neuroscience Scholar has not only opened the door into a world of scientifically interesting biology questions but allows me to perform better translational research, designing diagnostics that will be able to diagnose prenatal drug exposure in both sexes."





**ORGANIZATION FOR THE
STUDY OF SEX DIFFERENCES**

Founded by the Society for Women's Health Research



President-Elect
Liisa Galea, Ph.D.
University of British Columbia



President
Rhonda Voskuhl, MD
University of California, Los Angeles



Immediate Past President
Sabra L. Klein, Ph.D.
Johns Hopkins University

Thank you

Questions?