Disentangling the Effects of Sex vs. Gender across Neurodegenerative Diseases

Developed in WGH 207: Advanced Topics of Women, Gender, and Health
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Appropriate Harvard T.H. Chan School of Public Health Course:
This teaching example is designed to be used in EPI 284: Epidemiology of Neurologic Diseases. This course focuses on the most common neurologic diseases such as ALS, Parkinson's Disease, and Alzheimer's Disease (AD) as well as other related dementias (ADRD). Students learn about how epidemiology contributes to the understanding of multiple neurologic diseases including neurodegenerative (ND) conditions. There are no prerequisite requirements for enrollment.

Brief Background:
Neuroepidemiology research, including the study of ND diseases such as ADRD, often cites differences between men and women in disease incidence and risk factors. In much of the existing literature, these differences are termed *sex differences* and can be attributed to both biological factors (e.g., hormone level differences) related to sex-based biology and behavioral risk factors (e.g., differences in head injury rates) relevant to gender identity. Looking at this research through a gender critical lens, however, it is clear that *sex differences* and *gender differences* are aggregated into an undifferentiated *sex* category for analysis. Due to this false aggregation, the complex interactions between sex-based biology and gender identity are erased, and structural causes of ND disease development are being overlooked for more proximal causes. For examples of epidemiologic concepts on this topic, see **Appendix A**. To help address these limitations and to promote the conduct of equity-focused research there is a need to disentangle the risk factors associated with gender identity, gender expression, sex assigned at birth, and other dimensions of gender, and to study sociocultural factors that are leading to gender inequities in ADRD.[1]

Learning Objectives for Students:
1. Differentiate between sex- and gender-based risk factors of ADRD and identify at which level these risk factors operate (i.e., individual, interpersonal, institutional, systemic).
2. Examine and explain differences in ADRD incidence, risk/protective factors, and clinical presentations across sex assigned at birth, gender identity, and gender expression.
3. Examine and explain the intersection of epidemiological (e.g., incidence, risk/protective factors) and gender identity, sex assigned at birth and gender expression concepts, and possible means to differentiate them in data collection for clinical research.

Teaching Methods:

1. **Begin the class with an overview of gender and health,** including definitions of related concepts; an explanation of the levels at which gendered factors can operate; and a figure illustrating the multidimensionality of gender and the intersection between gendered and sexed factors. See **Appendix B** for an abridged list of definitions to be assigned for student review before class.
2. **Set ground rules around language and content before delving into discussion**: See a suggested example statement in **Appendix C**.
3. **Facilitate small group discussion of the vignettes**: Break students up into groups of 2 to 3 and allow for 10 minutes of discussion. Display Vignette #1 (**Appendix D**) on the screen and provide the following prompts for discussion:
    a. What are some of the pathways in *which structural sexism and cisgenderism* impact Jean's presentation to the clinic?
    b. What are some ways in which *gender expression* impacts the final diagnosis of AD? Was there any connection between gender expression and sex assigned at birth?
    c. What are some ways in which *gender identity* impacts the final diagnosis of AD? How does it impact the risk of developing AD?
    d. How would you expect the issues that arose from this vignette to impact *clinical* research on ADRD?
        i. *Example responses: incorrect staging of disease promotes the systematic exclusion of marginalized people from clinical trials; exclusion from trials leads to lack of generalizability of the findings; clinical diagnostic criteria should be assessed for reliability and validity (who and what defines challenges with personal hygiene and how does this definition impact staging and diagnosis)*
    e. How would you expect the issues that arose from this vignette to impact *epidemiologic* research on ADRD?
        i. *Example response: in studies that use EHRs, reduced healthcare contact due to structural sexism and cisgenderism may create selection bias; dominant views on concepts like "hygiene difficulties" may create measurement error and misclassification bias for certain populations which is amplified in large epidemiologic studies and compromises study validity.*
4. **Facilitate large group discussion**: Bring back all groups for a classroom discussion. Ask students to share any initial thoughts they had on the vignette (5 to 10 minutes). After reflections have been shared, facilitate student discussion aimed at connecting this vignette with larger themes in neuroepidemiology (e.g., incidence and prevalence of ND). Listed are some potential prompts for discussion:
    a. While the vignette was an example of an interpersonal interaction, the impact of sex and gender operate on multiple levels. List an example of a *structural factor* that impacted Jean's ability to receive a timely, accurate, and unbiased AD diagnosis.

b. Assume that Jean is not alone in these experiences, and that many nonbinary people who were assigned female at birth were staged incorrectly. The CDR scale has been empirically validated, but likely not for specific populations such as trans and gender non-conforming people. In the study design phase, are there ways to improve the generalizability of clinical ADRD assessment?
c. The vignette lists several individual-level risk factors for ADRD that may be more prevalent among minoritized populations such as trans and gender non-conforming people. If we adjusted for these listed risk factors, would you expect the rate of ADRD to be higher, lower, or the same among gender minorities? To what extent are the individual-level risk factors influenced by sexism and cisgenderism?
d. How can we better design studies to reduce the systematic exclusion of gender minorities?
e. Studies have found - albeit inconclusively - an association between head injuries and AD. Studies show that men are 40% more likely to experience a traumatic brain injury than women.[2] These studies posit this as a *sex-based risk factor* for disease and did not measure gender identity. Would you expect this primarily to be a sex-based risk factor, a gender identity-based risk, a gender expression-based risk factor, or a combination of several dimensions of gender and sex?

References

1) Mielke MM, Aggarwal NT, Vila-Castelar C, et al. Consideration of sex and gender in Alzheimer's disease and related disorders from a global perspective. *Alzheimers Dement*. 2022;18(12):2707-2724. doi:10.1002/alz.12662
2) Gupte R, Brooks W, Vukas R, Pierce J, Harris J. Sex differences in traumatic brain injury: What we know and what we should know. *J Neurotrauma*. 2019;36(22):3063-3091. doi: 10.1089/neu.2018.6171.
3) Rose G, Barker DJ. Epidemiology for the uninitiated: Measurement error and bias. *Br Med J*. 1978;2(6149):1417-8. doi: 10.1136/bmj.2.6149.1417. PMID: 719432; PMCID: PMC1608609.
4) Bours MJL. A nontechnical explanation of the counterfactual definition of confounding. *J Clin Epidemiol*. 2020;121:91-100. doi: 10.1016/j.jclinepi.2020.01.021.

Appendix A: Epidemiologic Concepts

	Definition	Application to Gender and Neuro Epi
Measurement Error	Errors in measurement of the exposure or outcome	Binary collection of data on gender inaccurately captures gender for those who are nonbinary, genderqueer, etc. This error may lead to inaccurate ascertainment of gender-based risk factors of neurodegenerative disease development
Selection Bias	When the study subjects are not representative of the target population about which conclusions are to be drawn[3]	Electronic health record-based studies tend to underrepresent populations who have less contact with the medical system. If, due to medical distrust and economic disenfranchisement, trans and gender diverse populations have less contact with medical systems on average, the study population will underrepresent this group and would not be representative of the entire US population.
Confounding	When all or part of the association between exposure and outcome can be accounted for by a third variable that affects the outcome and is not affected by the exposure[4]	If we find that coffee consumption is associated with Parkinson's Disease, and know that gender influences coffee consumption and PD development, then we can say that gender may explain some of all of the association between coffee consumption and Parkinson's development

Appendix B: Relevant Definitions

A more comprehensive list of definitions can be found at *https://pflag.org/glossary/*

Assigned sex (sex assigned at birth): The sex assigned to an infant at birth based on the child's visible sex organs, including genitalia and other physical characteristics

Butch: A person who is masculine of center in dress, attitude, and/or presentation. It is often, but not exclusively, used in a lesbian context

Cisgender: A term used to refer to an individual whose gender identity aligns with the sex assigned to them at birth

Cissexism: Prejudice, stereotyping, or discrimination on the basis of sex, specifically towards transgender and gender-expansive people

Gender: Broadly, gender is a set of socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate

Gender identity: A person's deeply held core sense of self in relation to gender

Gender expression: The manner in which a person communicates about gender to others through external means such as clothing, appearance, or mannerisms

Nonbinary: Refers to people who do not subscribe to the gender binary. They might exist between or beyond the man-woman binary. Some use the term exclusively, while others may use it interchangeably with terms like genderqueer, genderfluid, gender non-conforming, gender diverse, or gender expansive

Trans (transgender): A term describing a person's gender identity that does not necessarily match their assigned sex at birth

Appendix C: Rules around Language and Content

"Here are some ground rules for both small and large group discussion that you are expected to follow. Conversations will remain respectful; the presence of differences between a person's gender identity and their sex assigned at birth, as well as the validity of trans and gender diverse experiences, are not up for debate. This conversation will focus on the methodological implications of these already validated concepts. Do not expect a classmate or member of the teaching staff to speak on behalf of their entire gender or identity group. If someone in your group makes a comment that compromises the learning environment for you or a peer, feel free to correct them in the moment and/or bring this to your teaching team after class. Treat all information discussed with your classmates as confidential; if a peer shares about their experiences as a trans or gender diverse person, do not assume this is information they want shared outside of class."

Appendix D: Example Vignette

Jean is a 65-year-old, white, nonbinary butch lesbian assigned female at birth presenting in clinic with subjective cognitive decline and no prior diagnosis of Alzheimer's Disease or other dementia. Jean is brought in by their partner after noticing that Jean has had difficulty coordinating their monthly dinner party and has forgotten how to pay their electric bill despite completing this task for the last 30 years. Jean, aided by their partner, reported a history of depression, cigarette smoking, and moderate alcohol use. Upon examination, Jean's physician notes reduced memory and attention compared to their most recent preventative care visit 5 years ago. Jean has been unable to attend yearly preventative visits due to lapses in insurance coverage and difficulty taking time off of work. Additionally, the physician notes Jean's unshaven legs and the presence of facial hair as evidence of difficulties with personal hygiene and bathing-related activities of daily living (ADLs). After the initial examination, before any follow-up imaging is conducted, Jean is told they have Alzheimer's Disease. Using the CDR criteria for Alzheimer's dementia (provided below), the physician told Jean they were at a moderate dementia stage. At this stage, Jean is no longer eligible for clinical trial participation but gives consent for researchers to pull their electronic health records for research purposes.

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Score only as decline from previous usual level due to cognitive loss, not impairment due to other factors.

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414. doi:10.1212/wnl.43.11.2412-a