Why and How to Address Gender & Sex in VA HSR&D Research

HSR&D Cyberseminar

July 17th, 2023

Elizabeth Goldsmith, MD, PhD, Jessica Friedman, PhD, MPH

and Elisheva Danan, MD, MPH

Learning Objectives

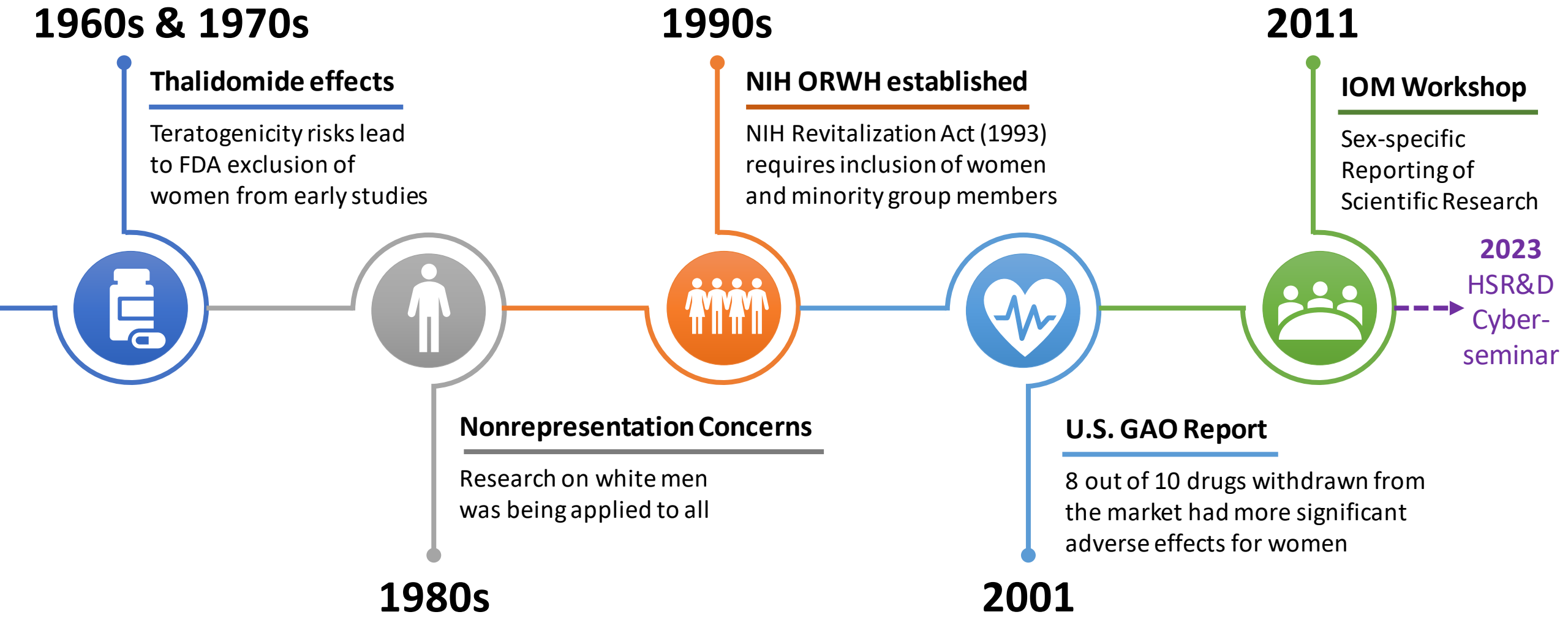
1. Define gender and sex in the context of health research
2. Illustrate strategies to overcome challenges in evaluating gender and sex in VA research
3. Demonstrate approaches to addressing gender and sex in primary and secondary data analysis and reporting
4. Appraise evaluation of sex and gender in grant proposals and manuscripts

What we are and are not talking about today:

- Discussing sex and gender in research broadly, as well as the unique challenges of research with women Veterans in VA
  - Legacy language: aware of the binary default in this field
  - Needs of “women veterans” can include needs of people who were assigned female sex at birth and/or people who identify as women
  - Gender minorities or gender-diverse: terms including people who are transgender and/or who identify with genders beyond “women” or “men”
  - More in-depth discussion/definitions of sex/gender to come

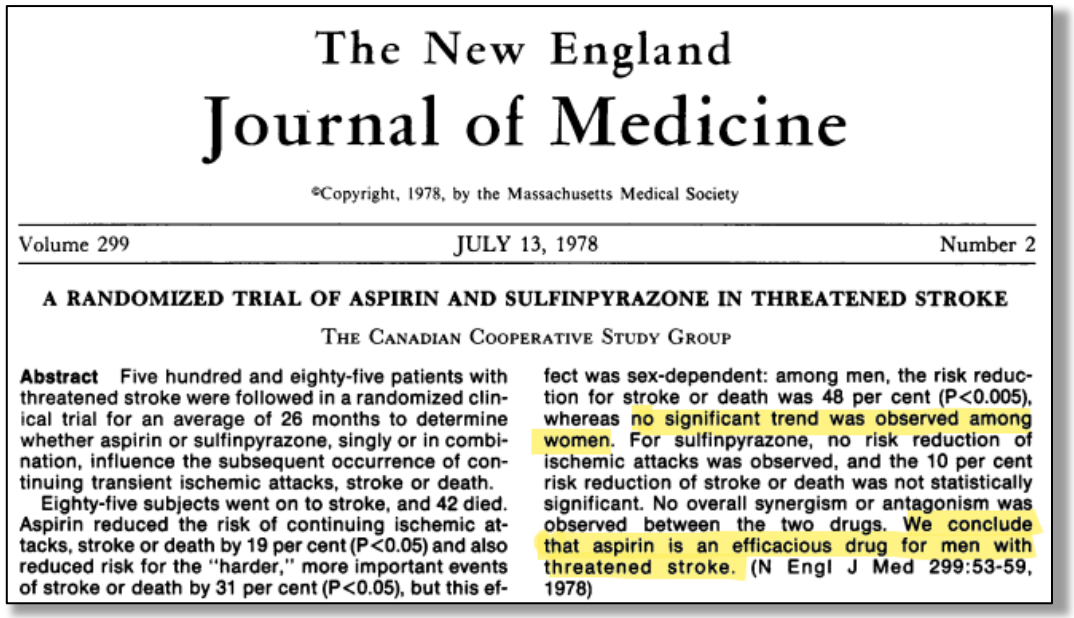
- Not addressing sexual orientation today

Brief history of sex & gender in health research



Spurious subgroup effect

Overgeneralization



The New England
Journal of Medicine

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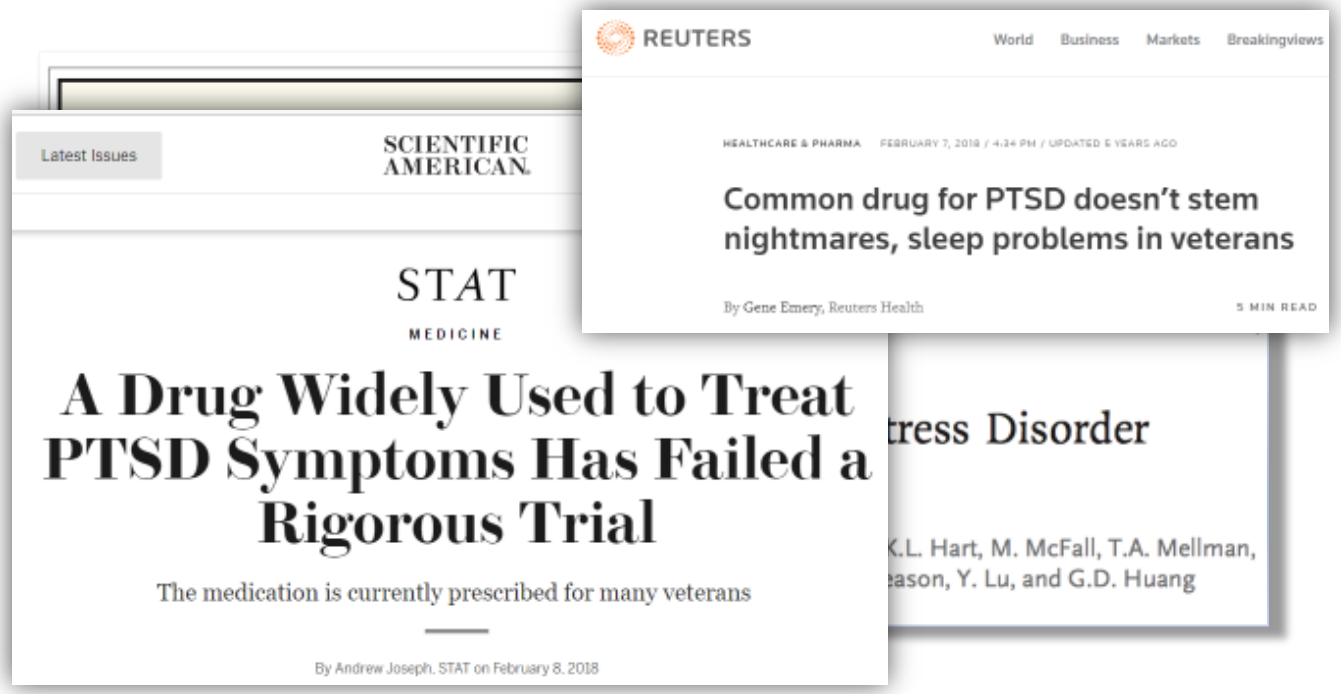
Volume 299 JULY 13, 1978 Number 2

A RANDOMIZED TRIAL OF ASPIRIN AND SULFINPYRAZONE IN THREATENED STROKE

THE CANADIAN COOPERATIVE STUDY GROUP

Abstract Five hundred and eighty-five patients with threatened stroke were followed in a randomized clinical trial for an average of 26 months to determine whether aspirin or sulfinpyrazone, singly or in combination, influence the subsequent occurrence of continuing transient ischemic attacks, stroke or death.

Eighty-five subjects went on to stroke, and 42 died. Aspirin reduced the risk of continuing ischemic attacks, stroke or death by 19 per cent (P<0.05) and also reduced risk for the "harder," more important events of stroke or death by 31 per cent (P<0.05), but this effect was sex-dependent: among men, the risk reduction for stroke or death was 48 per cent (P<0.005), whereas no significant trend was observed among women. For sulfinpyrazone, no risk reduction of ischemic attacks was observed, and the 10 per cent risk reduction of stroke or death was not statistically significant. No overall synergism or antagonism was observed between the two drugs. We conclude that aspirin is an efficacious drug for men with threatened stroke. (N Engl J Med 299:53-59, 1978)



REUTERS World Business Markets Breakingviews

HEALTHCARE & PHARMA FEBRUARY 7, 2018 / 4:34 PM / UPDATED 6 YEARS AGO

Common drug for PTSD doesn't stem nightmares, sleep problems in veterans

By Gene Emery, Reuters Health 5 MIN READ

Latest Issues SCIENTIFIC AMERICAN

STAT

MEDICINE

A Drug Widely Used to Treat PTSD Symptoms Has Failed a Rigorous Trial

The medication is currently prescribed for many veterans

By Andrew Joseph, STAT on February 8, 2018

tress Disorder

K.L. Hart, M. McFall, T.A. Mellman, eason, Y. Lu, and G.D. Huang

- Underpowered subgroup analysis (30% women)
- 1980: ASA FDA-approved for use in men only
- 1998: ASA FDA-approved for use in women for secondary stroke prevention

- VA CSP Study, n=304 (n=7 women, 2%)
- Variation by sex and/or gender:
  - PTSD causes, symptoms, and treatment needs
  - Prazosin dosing and side effects

Kauth et al, AJPH 2014; Kauth et al, Curr Sex Health Rep, 2017; Shipherd et al, Intl J Sexual Health, 2012; Gaffey et al, JWH 2021; Frayne et al, Women Veterans Sourcebook, 2018

Women and gender minorities in VA

- Changing populations in VA
- Differences in VA healthcare utilization & experiences

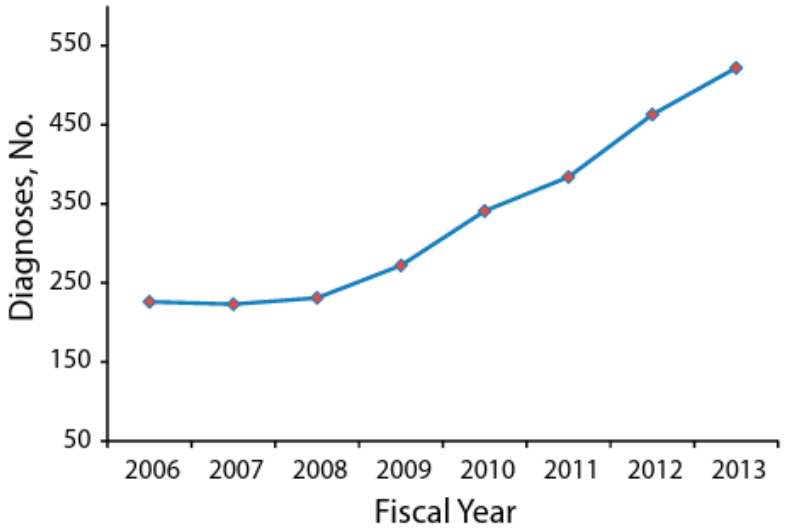
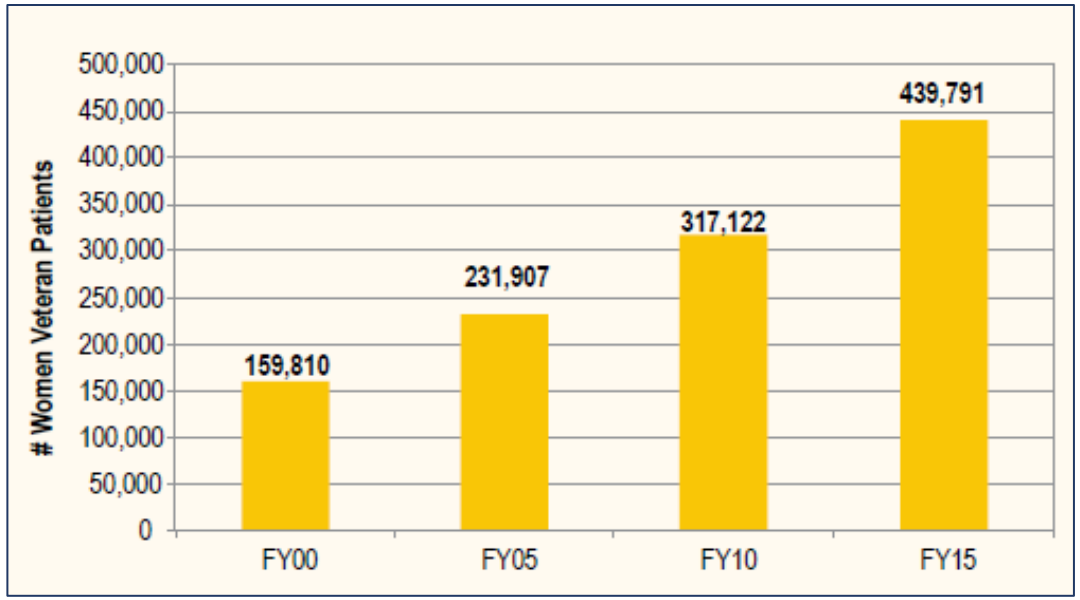


FIGURE 1—Number of new Veterans Health Administration transgender diagnoses by fiscal year: United States, 2006–2013.



- VA resources:
  - Women's Health Research Network
  - WERP (CSP Nodes)
  - LGBTQ+ Health Program

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Consider

Think about how sex and/or gender may be relevant for your research question

Collect

Define and measure gender and/or sex in primary data collection

Characterize

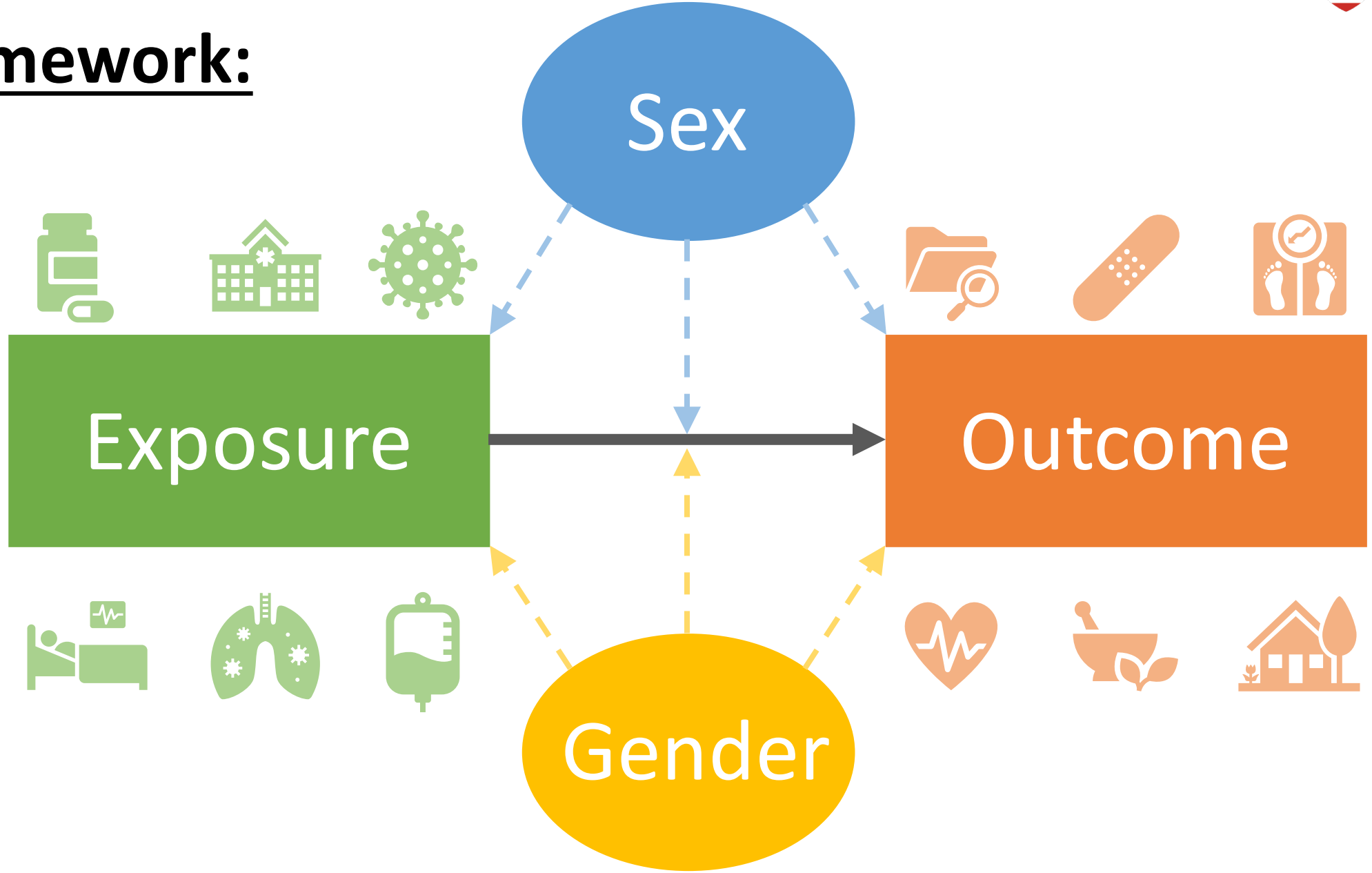
Analyze your data with attention to sex and/or gender

Communicate

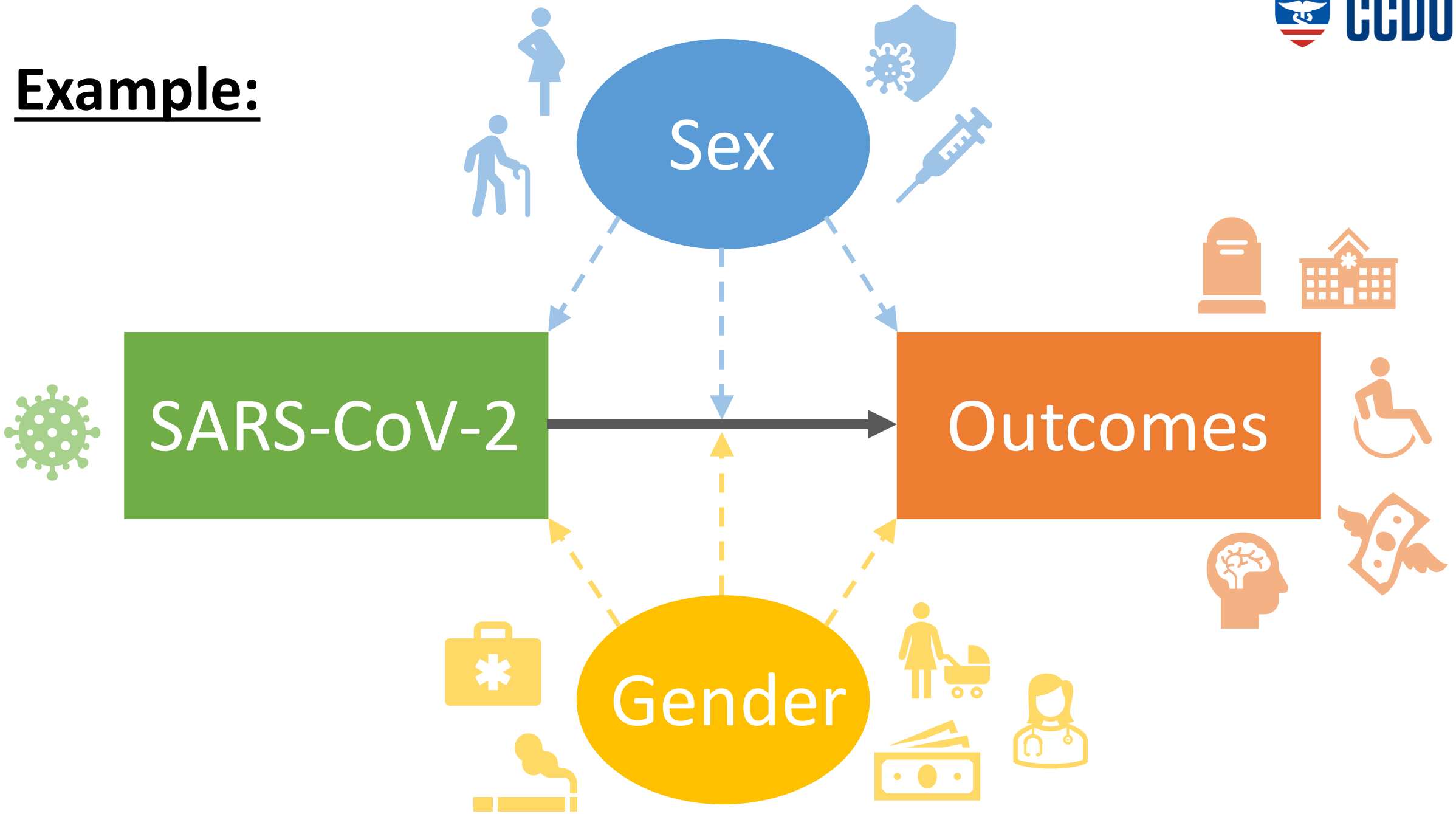
Report and publish sex and/or gender specific results; address limitations

Adapted from 4 C's, NIH ORWH at https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable.

Framework:



Example:

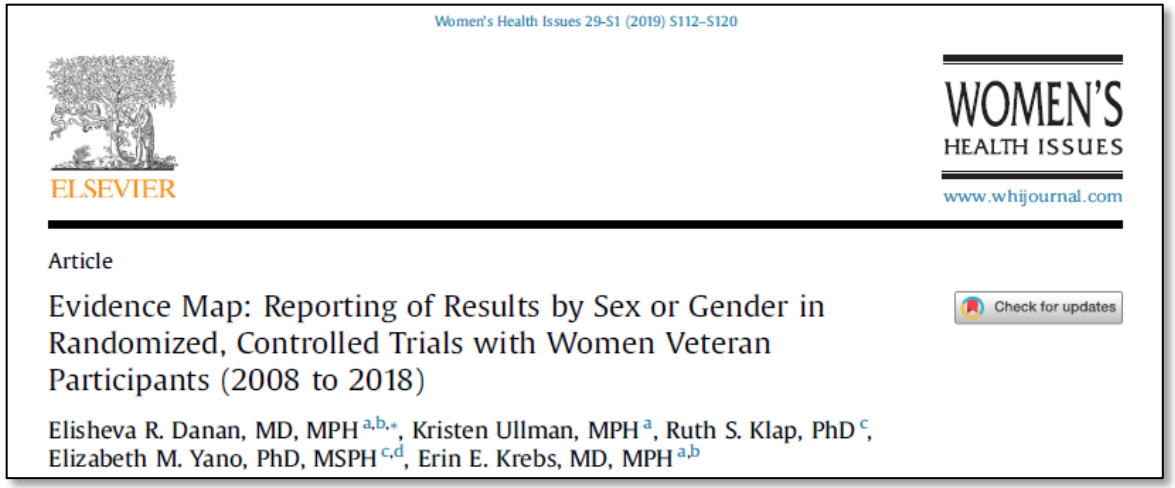


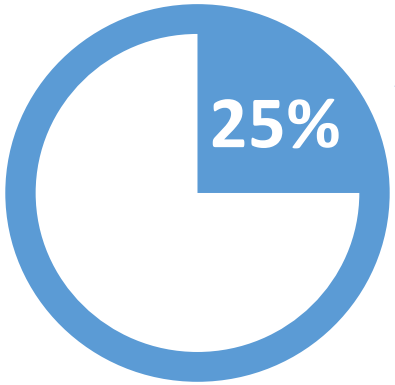
Most studies don't consider sex or gender

Systematic review of 4,420 COVID-19 studies on ClinicalTrials.gov:

- 5% planned sex-matched or representative samples
- 4% planned sex/gender as an analytical variable.

18% of the first 45 published COVID-19 trials reported results by sex or gender





Reported results by sex or gender

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Report and publish sex and/or gender specific results; address limitations

Adapted from 4 C's, NIH ORWH at https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable.

Conduct

Recruit and Retain women and/or gender minorities in VA trials

Consider

Think about how sex and/or gender may be relevant for your research question

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Analyze your data with attention to sex and/or gender

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Report and publish sex and/or gender specific results; address limitations

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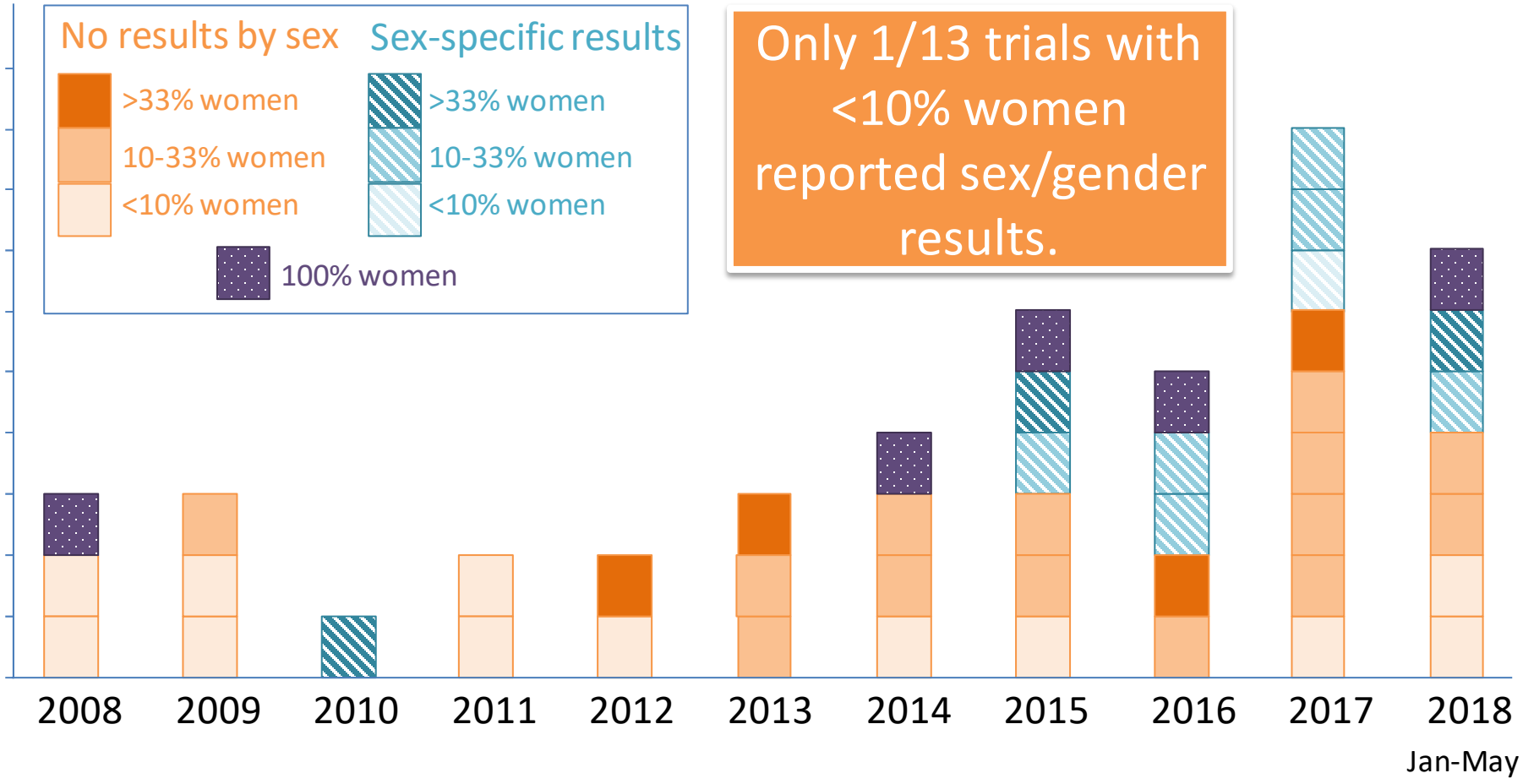
VA Evidence Map:

Proportion of women Veterans in RCTs *and* results reporting by sex or gender



Research with women in VA

- **Recruitment**
  - Exceed population-level representation
  - Multiple VA sites (PBRN or CSP)
  - Build WH/LGBTQ+ Health Programs partnerships
  - Tailored materials (Veteran engagement)
  - Study team configuration and training
- **Retention**
  - Earn and maintain trust
  - Burden of participation
  - Build in flexibility

WERP
Women's Enhanced Recruitment Process

https://vhacdwdwhweb100.vha.med.va.gov/phenotype/index.php/WERP_Toolkit

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Identity

- Sex: assigned at birth
- Gender: self-identified

Measure gender and/or sex in primary data collection

Birth Sex

What sex were you assigned at birth?

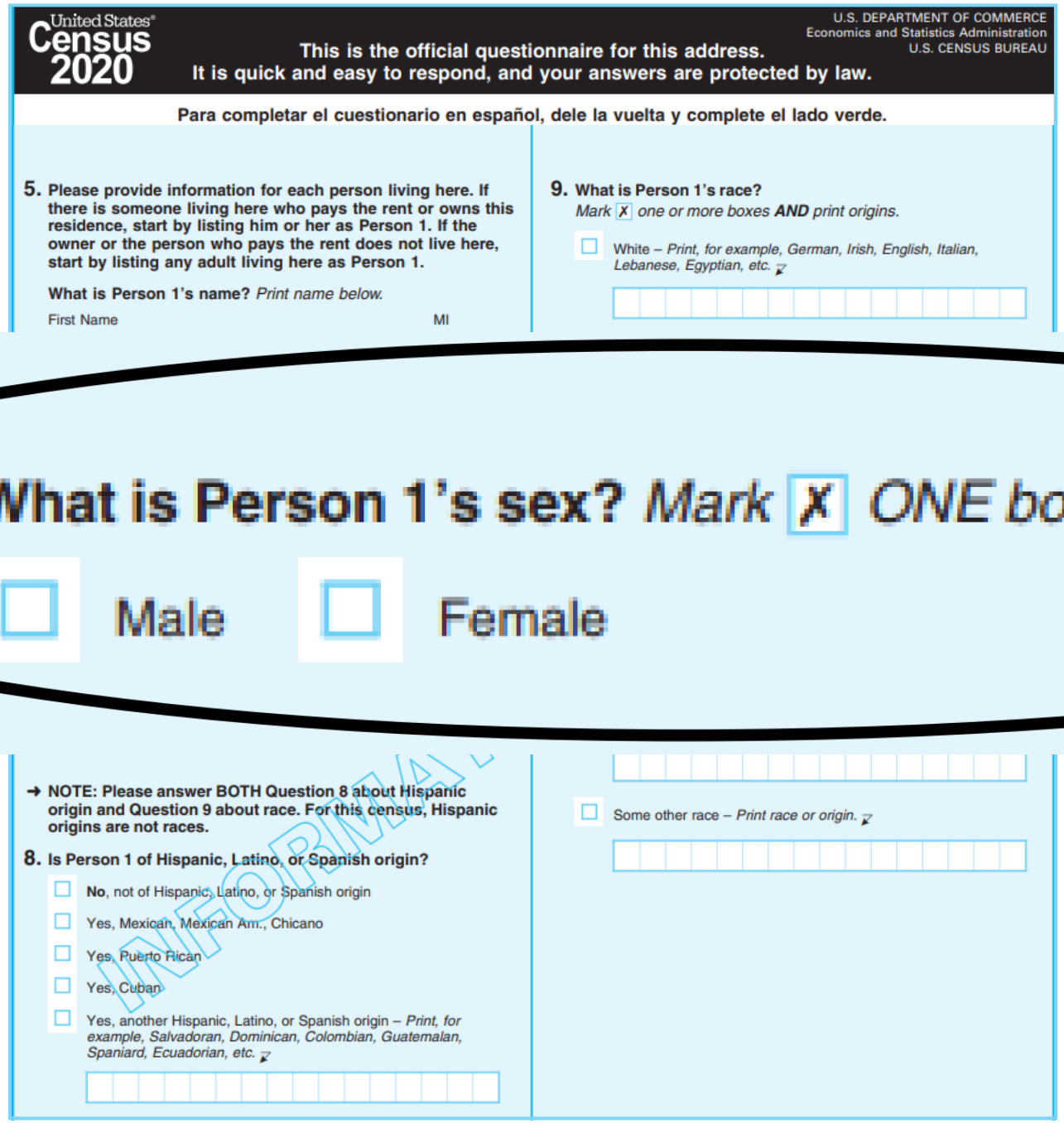
- ○ Female
- ○ Male
- ○ Intersex
- ○ A sex not listed here (please specify)
- ○ Prefer not to state

Current Gender Identity

What is your current gender identity? (Please select all that apply)

- ○ Woman
- ○ Man
- ○ Non-binary
- ○ A gender identity not listed here (please specify)
- ○ Prefer not to state

Tate et al 2013, Reisner et al 2014; Gendered Innovations, Stanford University


United States Census 2020

This is the official questionnaire for this address.
It is quick and easy to respond, and your answers are protected by law.

U.S. DEPARTMENT OF COMMERCE
Economics and Statistics Administration
U.S. CENSUS BUREAU

Para completar el cuestionario en español, dele la vuelta y complete el lado verde.

5. Please provide information for each person living here. If there is someone living here who pays the rent or owns this residence, start by listing him or her as Person 1. If the owner or the person who pays the rent does not live here, start by listing any adult living here as Person 1.

What is Person 1's name? *Print name below.*

First Name MI

9. What is Person 1's race?
Mark X one or more boxes ***AND*** *print origins.*

White – *Print, for example, German, Irish, English, Italian, Lebanese, Egyptian, etc.*

6. What is Person 1's sex? *Mark X ONE box.*

Male Female

→ NOTE: Please answer BOTH Question 8 about Hispanic origin and Question 9 about race. For this census, Hispanic origins are not races.

8. Is Person 1 of Hispanic, Latino, or Spanish origin?

No, not of Hispanic, Latino, or Spanish origin

Yes, Mexican, Mexican Am., Chicano

Yes, Puerto Rican

Yes, Cuban

Yes, another Hispanic, Latino, or Spanish origin – *Print, for example, Salvadoran, Dominican, Colombian, Guatemalan, Spaniard, Ecuadorian, etc.*

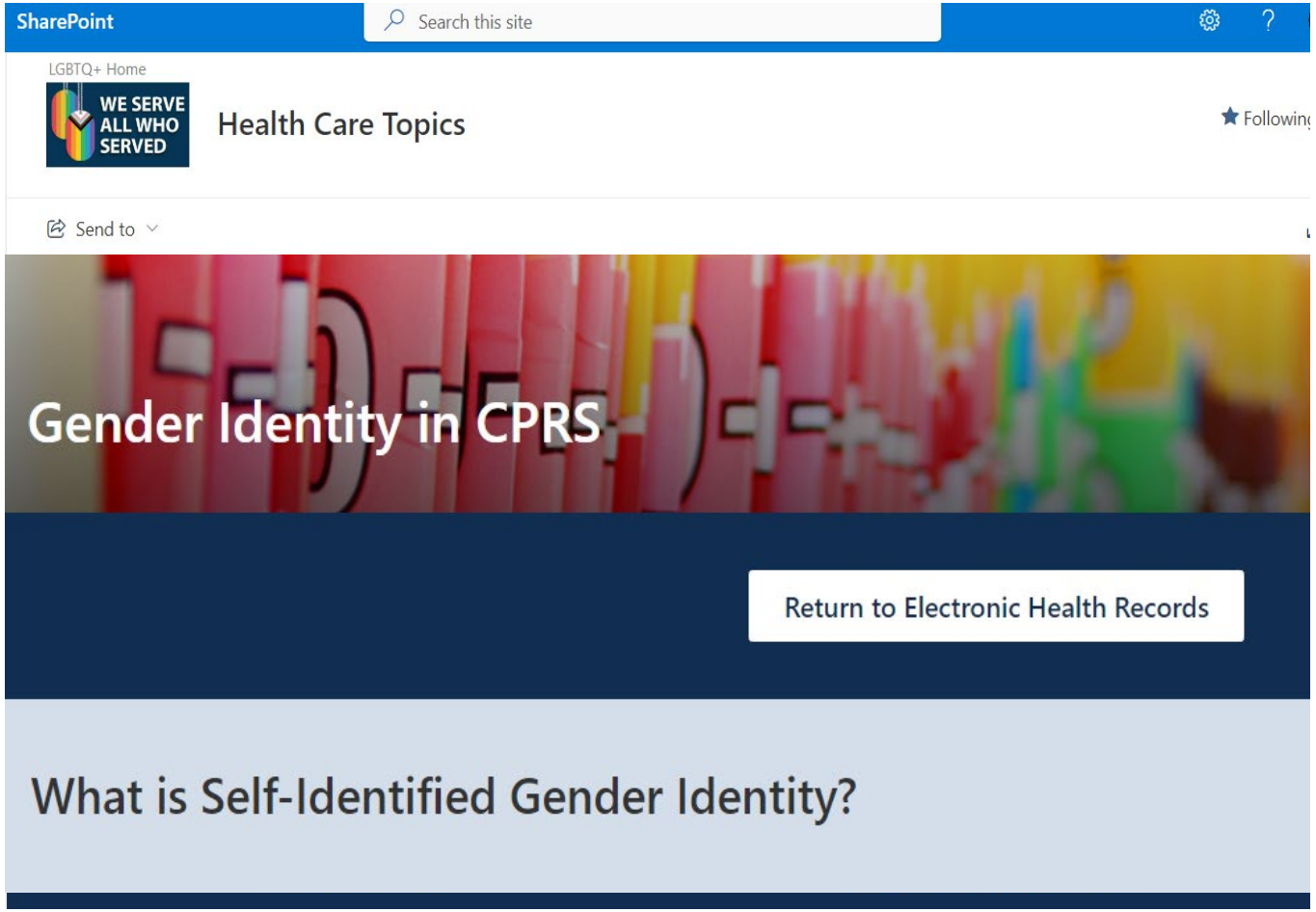
Some other race – *Print race or origin.*

https://www.census.gov/programs-surveys/decennial-census/technical-documentation/questionnaires.2020_Census.html

Self-identified gender identity (SIGI) in VA data

Welcome to the LGBTQ+ Health Program

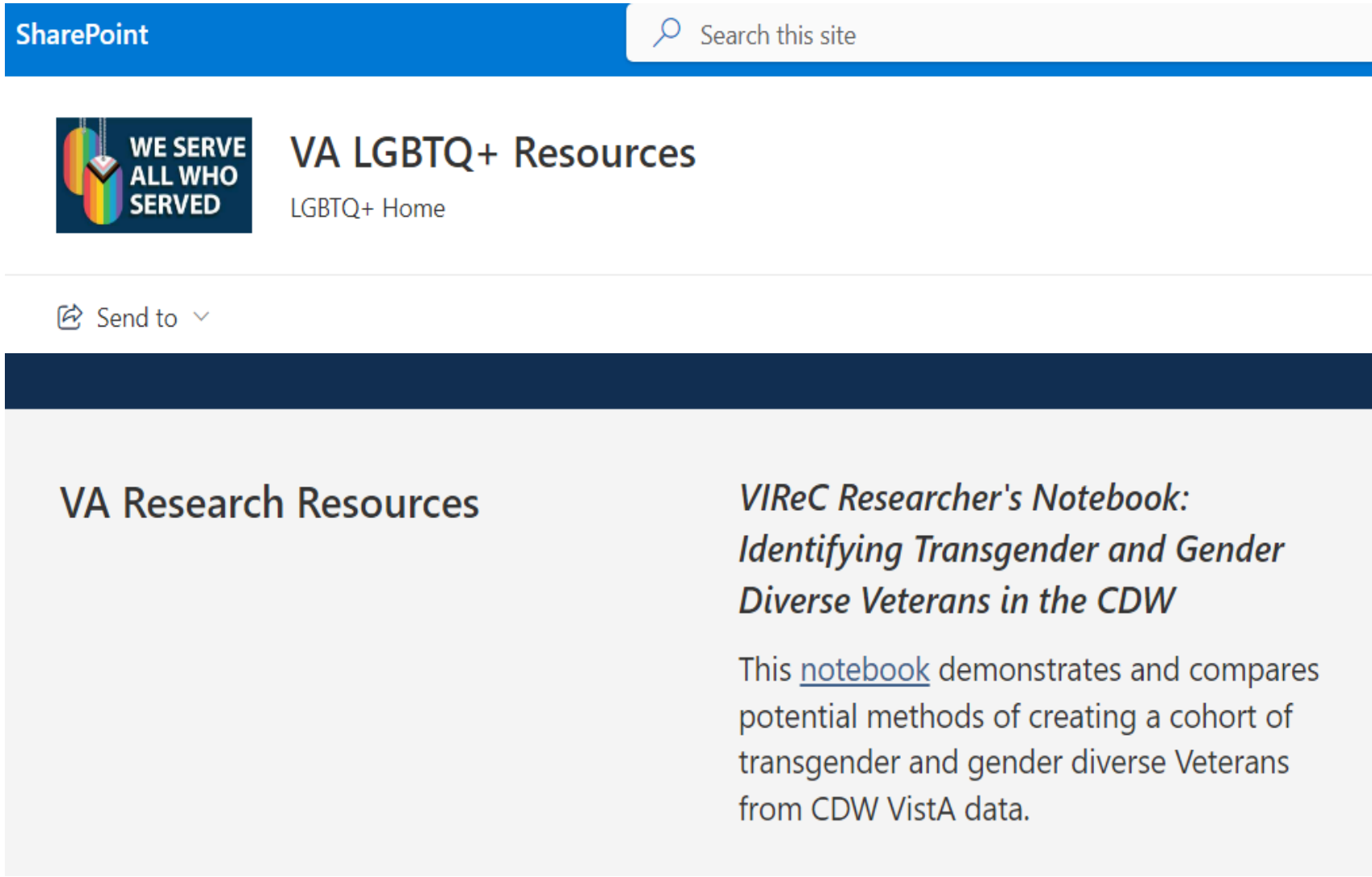
- Gold standard: Veteran opt-in self-entry on VA.gov
  - >137,000 entries Jun ‘22 - Jun ‘23
- Separate from legacy administrative variables
- Info on VA National LGBTQ+ Sharepoint (link in resources)



VA research in transgender / gender-diverse health

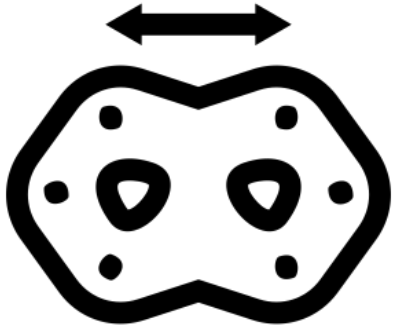
LGBTQ+ Research tools/resources have expanded…

- Data landing page with specs and SQL codes
- Searchable index of LGBTQ+ Veteran research since 2013
- Research listserv
- Quarterly workgroup meetings…



Sex	Gender
A set of biological attributes	A set of experiences and behaviors influenced by social & cultural environment

Sex

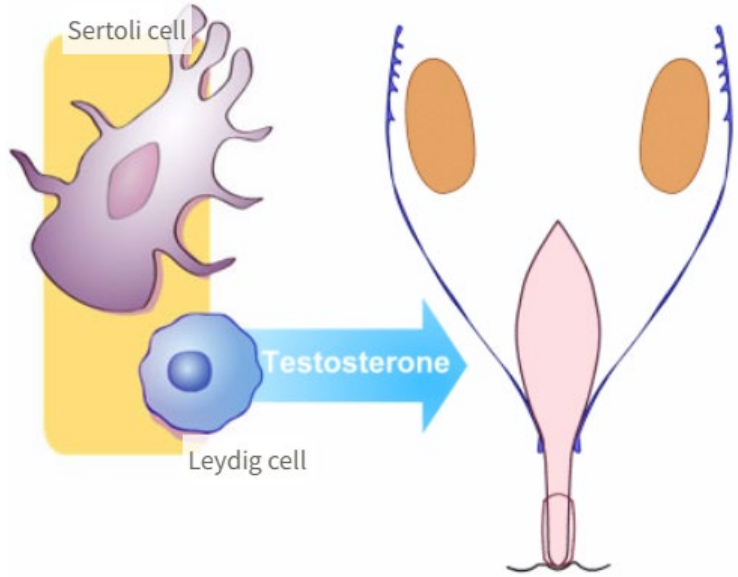


A set of biological attributes

- Chromosomes
- Hormones
- Anatomy
  - Internal
  - External

Binary excludes some people

- Intersex



How sex development works (utoronto.ca)

Sex

A set of biological attributes

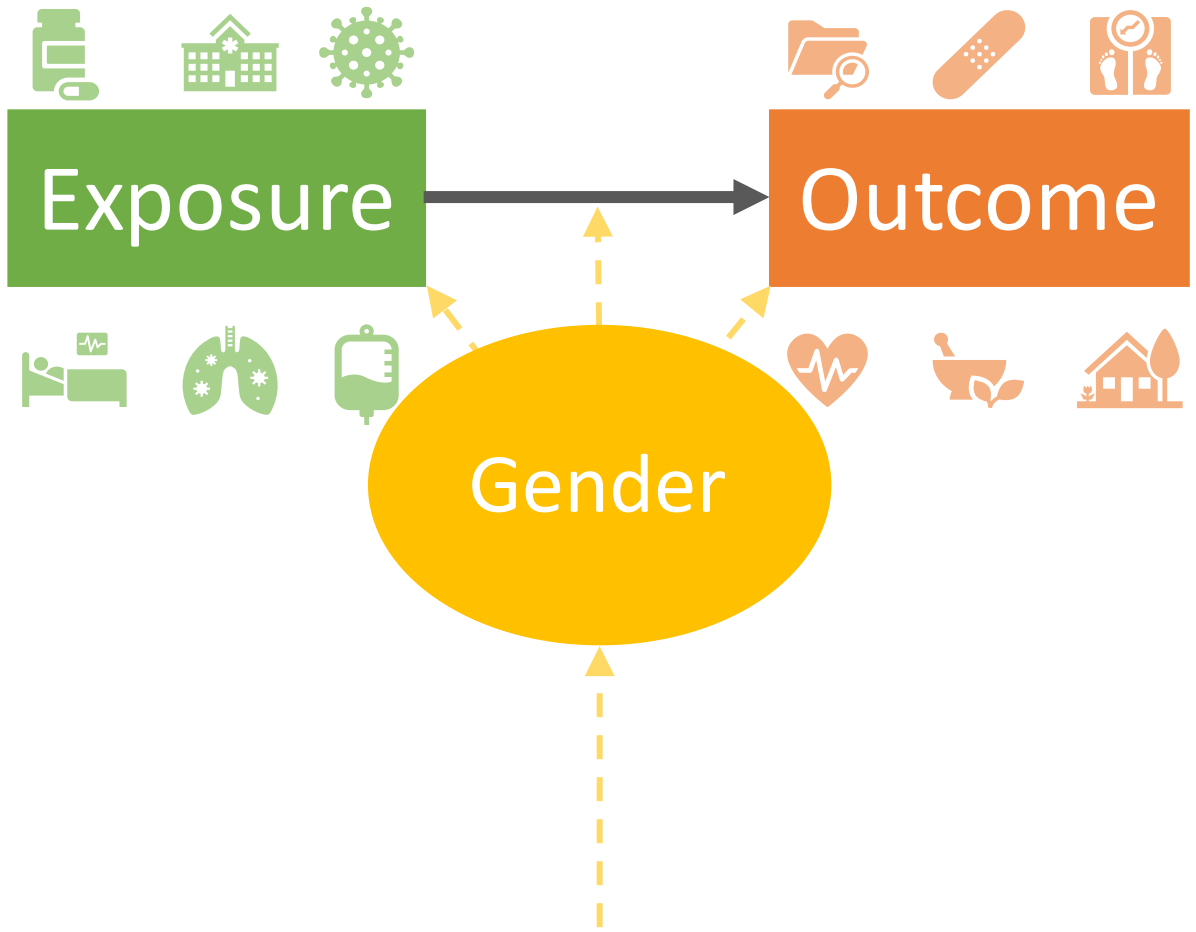
- Chromosomes
- Hormones
- Anatomy
  - Internal
  - External

Binary oversimplifies for all, and **excludes** some

Which sex attributes matter?
Depends on the question.

- Hemophilia: X chromosome-linked
- Prostate or breast cancer: anatomy and hormones
- Electrocardiogram (ECG) intervals: …heart size?

Almost always a proxy, sometimes a poor one



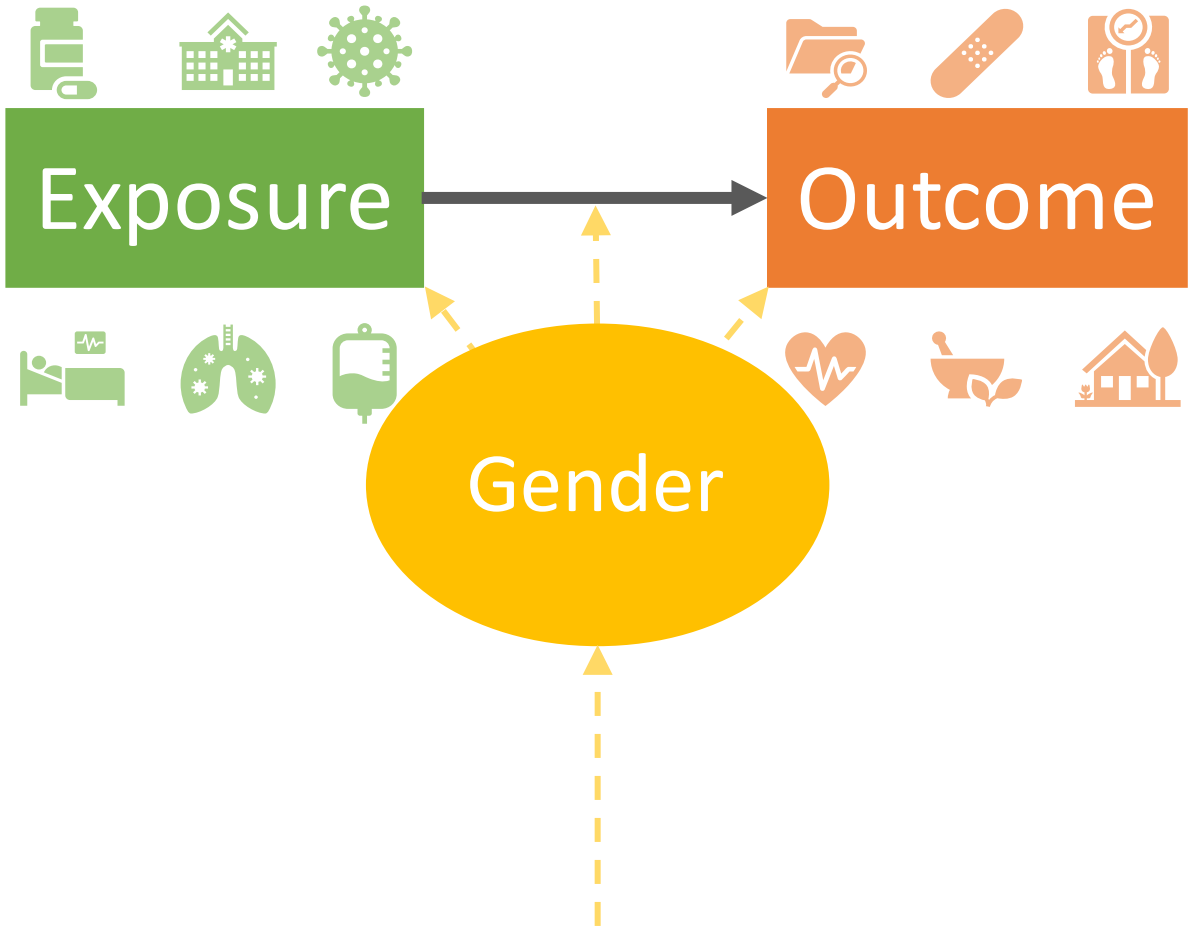
Which *components* of gender?

Experiences and behaviors influenced by social and cultural environment

Binary excludes some people…

- Gender-diverse, including
  - Transgender
  - Non-binary

…and oversimplifies for all



Which *components* of gender?

Experiences and behaviors influenced by social and cultural environment

- **Identity** and **expression**
- **Relations**
- **Norms/roles**
- **Institutionalized gender**

Gender identity	How someone self-identifies, often associates with social and cultural constructs of masculinity/femininity *Distinct from **gender expression**, though related
Gender relations	How someone interacts with / is treated by others, based on gender identity, expression, or how perceived
Gender norms / roles	Social and cultural attitudes and expectations about which behaviors, preferences, expressions, etc. are appropriate for women and men
Institutionalized gender	The way power, resources, and opportunities are distributed in society based on gender

Gender identity measures	Personal Attributes Questionnaire (PAQ)
Gender relations measures	Ambivalent Sexism Inventory
Gender norms measures	Conformity to Masculine Norms Inventory (CMNI) Conformity to Feminine Norms Inventory (CFNI)
Institutionalized gender measures	Gender Inequality Index

Gender Differences in the Relationship Between Shiftwork and Work Injury

Peter M. Smith, PhD, Jihan Ibrahim-Dost, Tessa Keegel, PhD, and Ewan MacFarlane, PhD

Work injury among shift workers

Higher among women (OR 2.4, 95% CI 2.0-3.0)

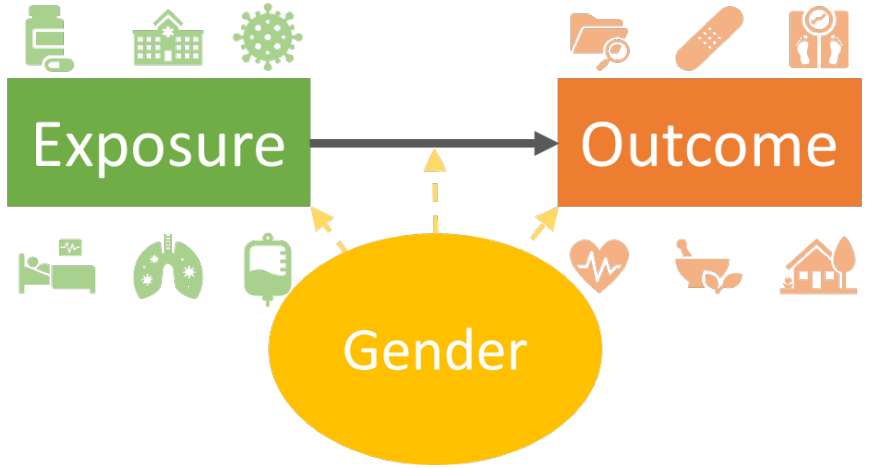
than among men (OR 1.6, 95% CI 1.3-1.9)

→Should shift work injury prevention programs focus on women?

What *components* of gender may be

(1) relevant

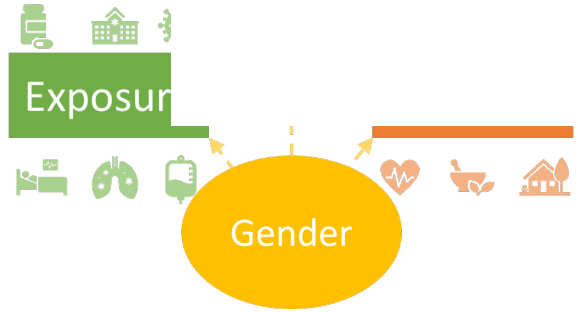
(2) available (in some form) in the data?



Smith et al 2013

CIHR-IGH

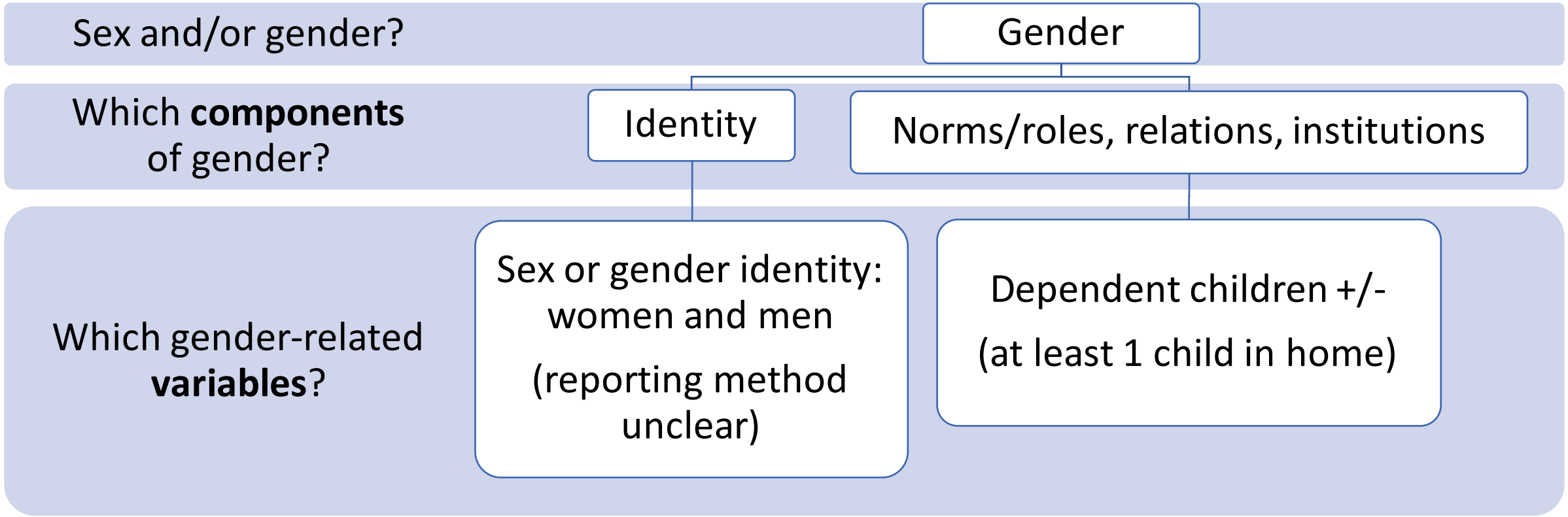
Which *components* of gender?



Sex and/or gender?

Gender

Shift work ← gender → injury

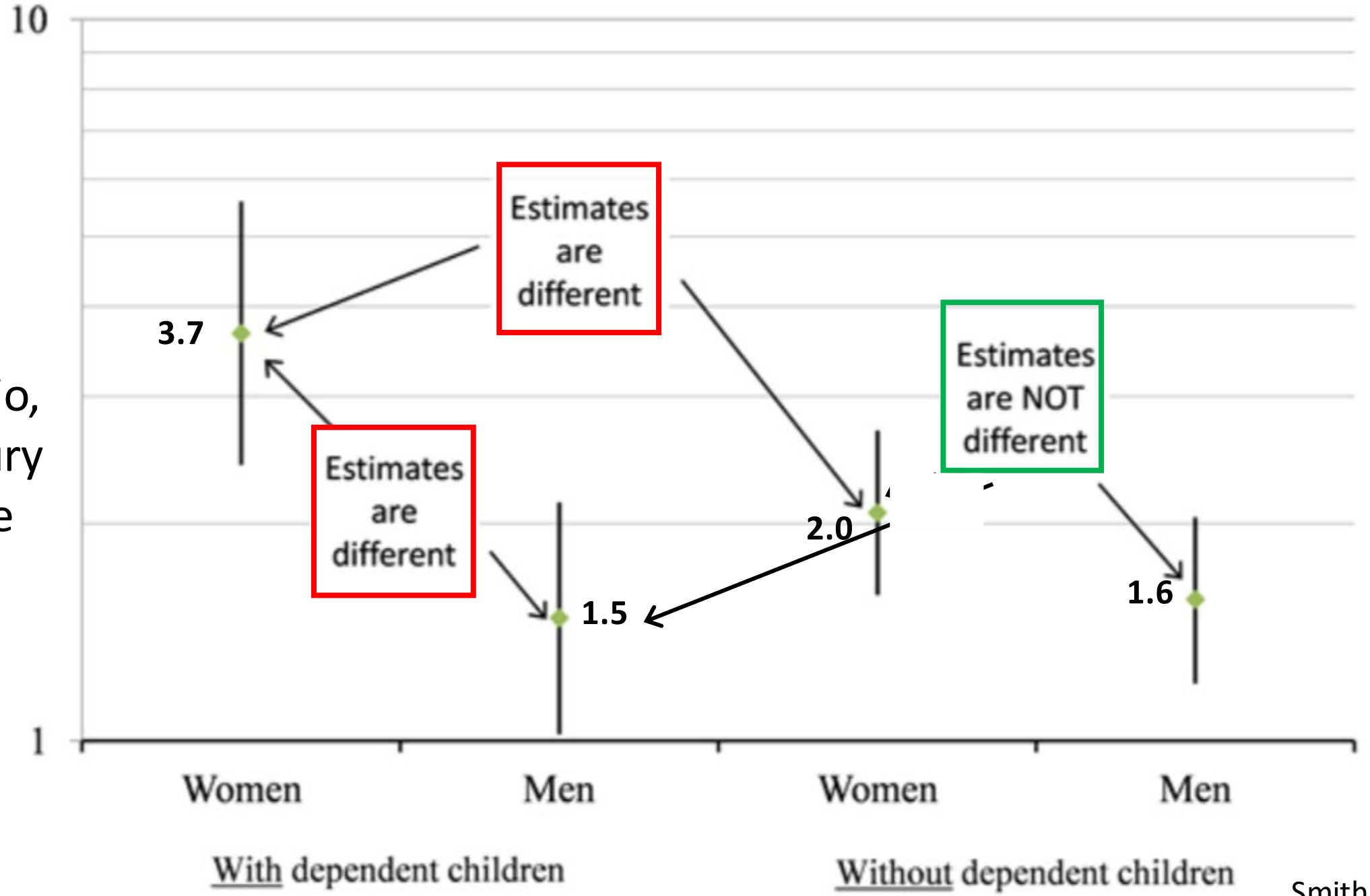


Examine work injury rates

Among women and among men

by presence vs. absence of dependent children

Odds ratio, work injury vs. none



Smith et al 2013

CIHR-IGH

Sex	Gender
A set of biological attributes	A set of experiences and behaviors influenced by social and cultural environment

- Chromosomes
- Hormones
- Anatomy
  - Internal
  - External
	- Identity
	- Norms
	- Roles
	- Relations

Binary oversimplifies for all, and excludes some	
- Intersex	- Gender-diverse

Consider

Collect

Characterize

Communicate

What do we need to know about sex and/or gender to evaluate our questions?

Simplifying assumptions may be necessary.

- Which assumptions best serve our questions?
- How can we be transparent about assumptions?

Conduct

Recruit and Retain women and/or gender diverse Veterans in VA trials

Consider

Think about how sex and/or gender may be relevant for your research question

Collect

Define and measure gender and/or sex in primary data collection

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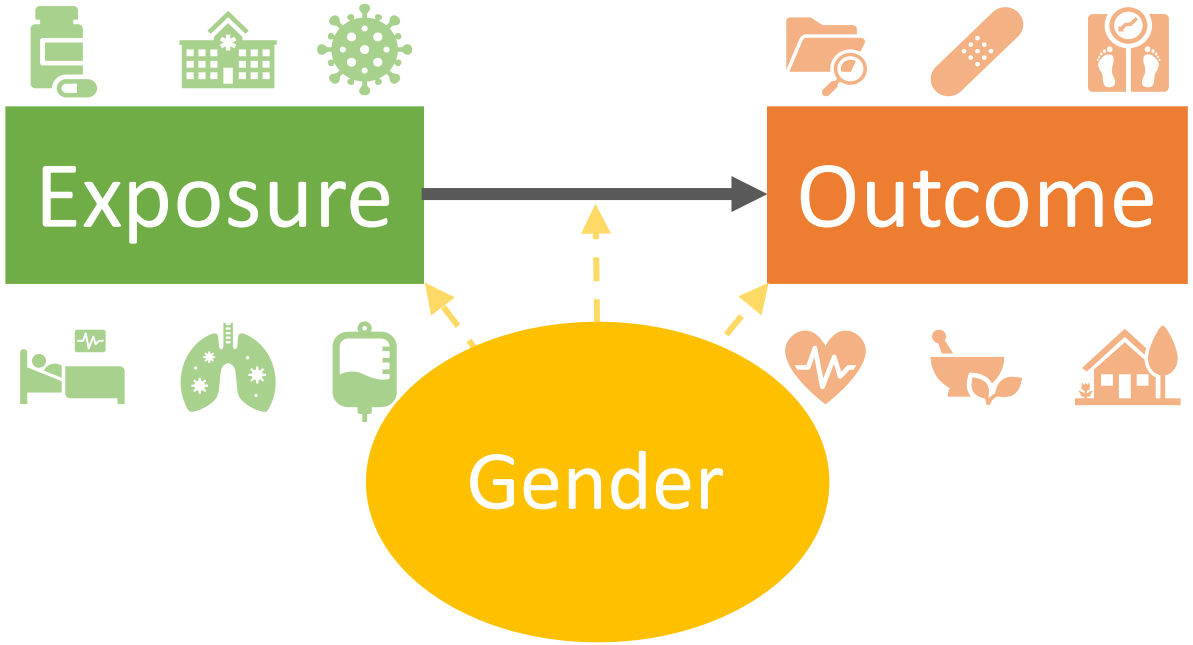
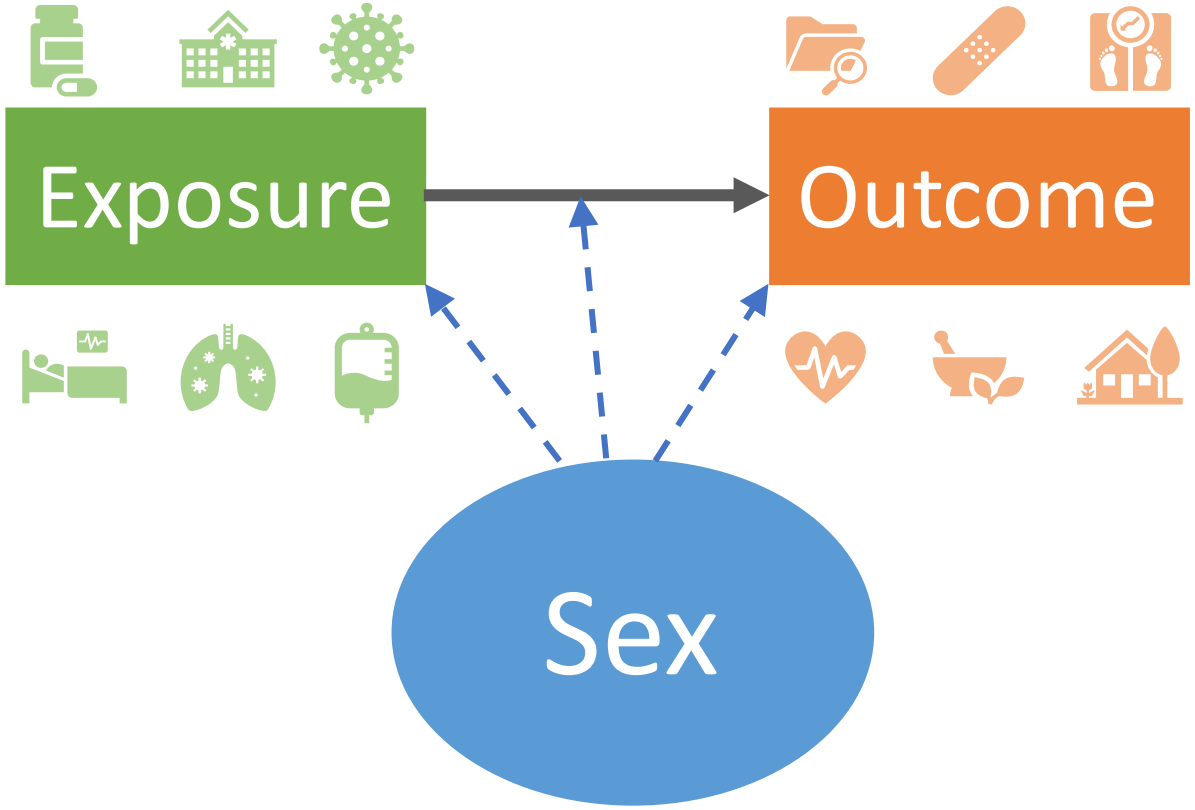




Decide sex, gender, or both?

What is Subgroup Analysis?

- Reanalysis of study data to identify important differences in treatment effects across different groups

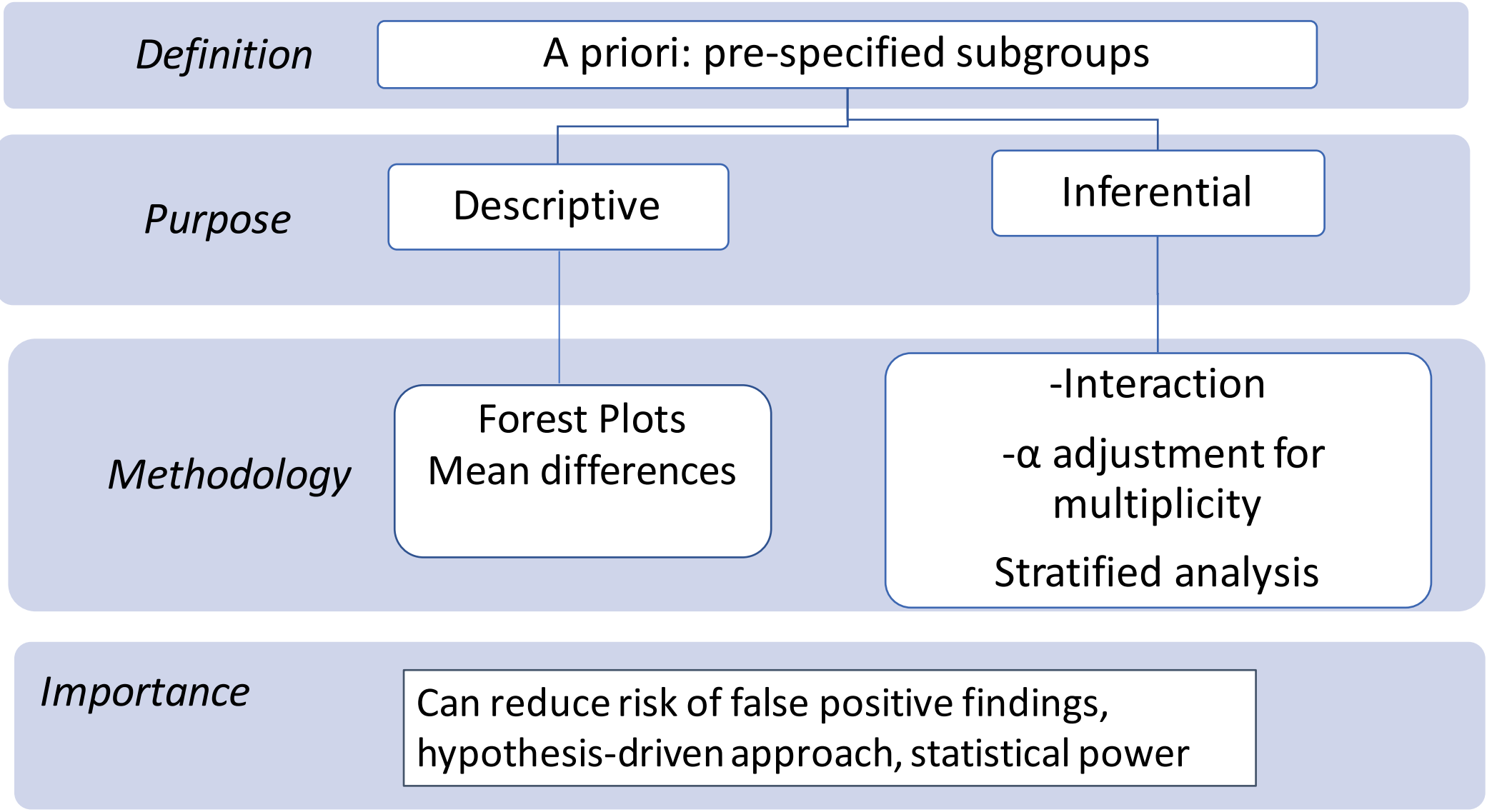
- The primary analysis of study data often presents the average treatment effect across all participants
  - *What* if you believe there may be important differences in the treatment effect across subgroups (heterogeneity of treatment effects) that warrant further investigation?

  - *Why* - knowing differences in treatment effects across groups of patients has implications for policies, clinical practice, and health communication strategies.
- There needs to be a logical reason to investigate potential differences.

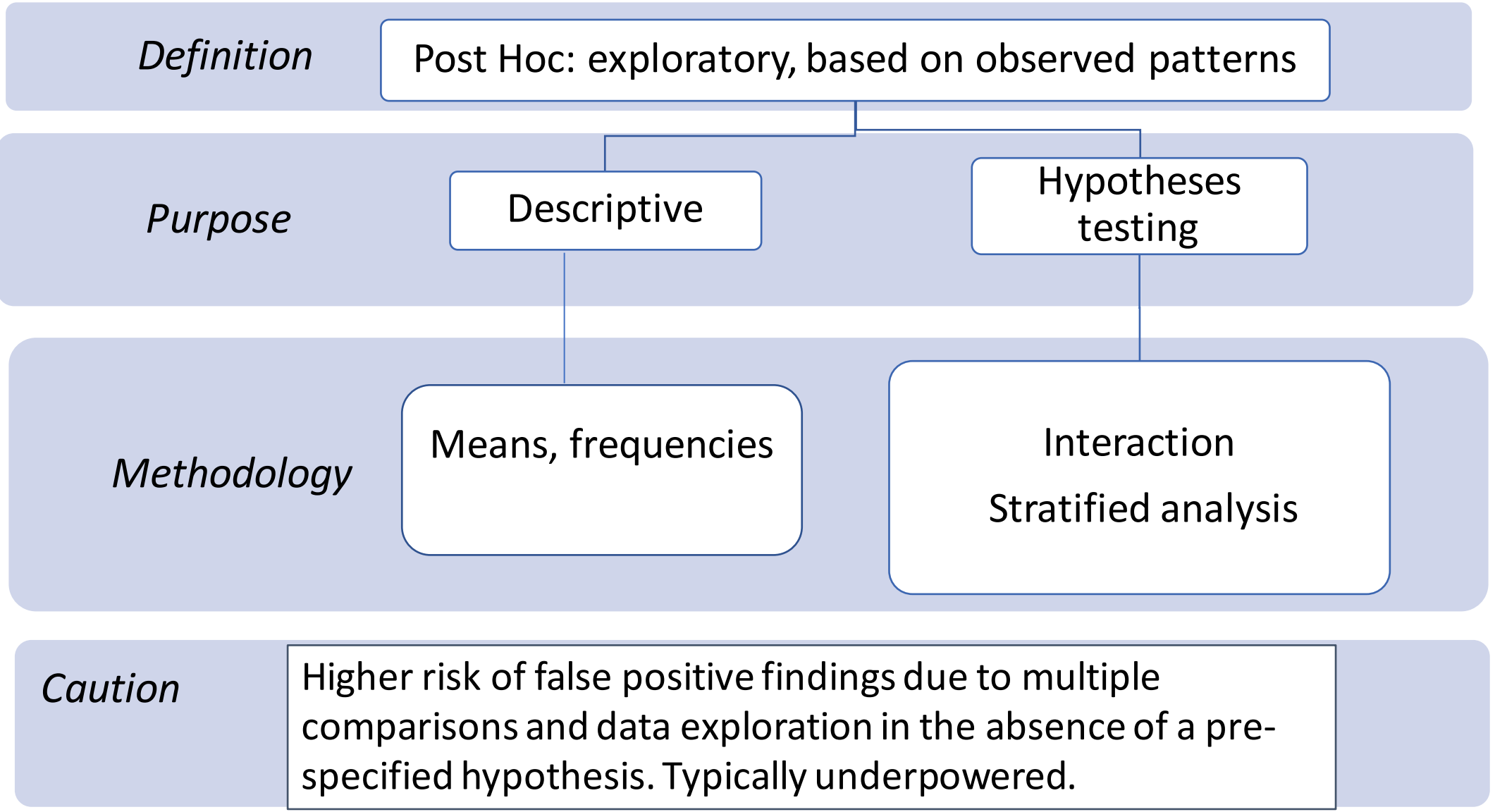
What is guiding your subgroup analysis?

Type of sub-group analysis	Post hoc	A priori

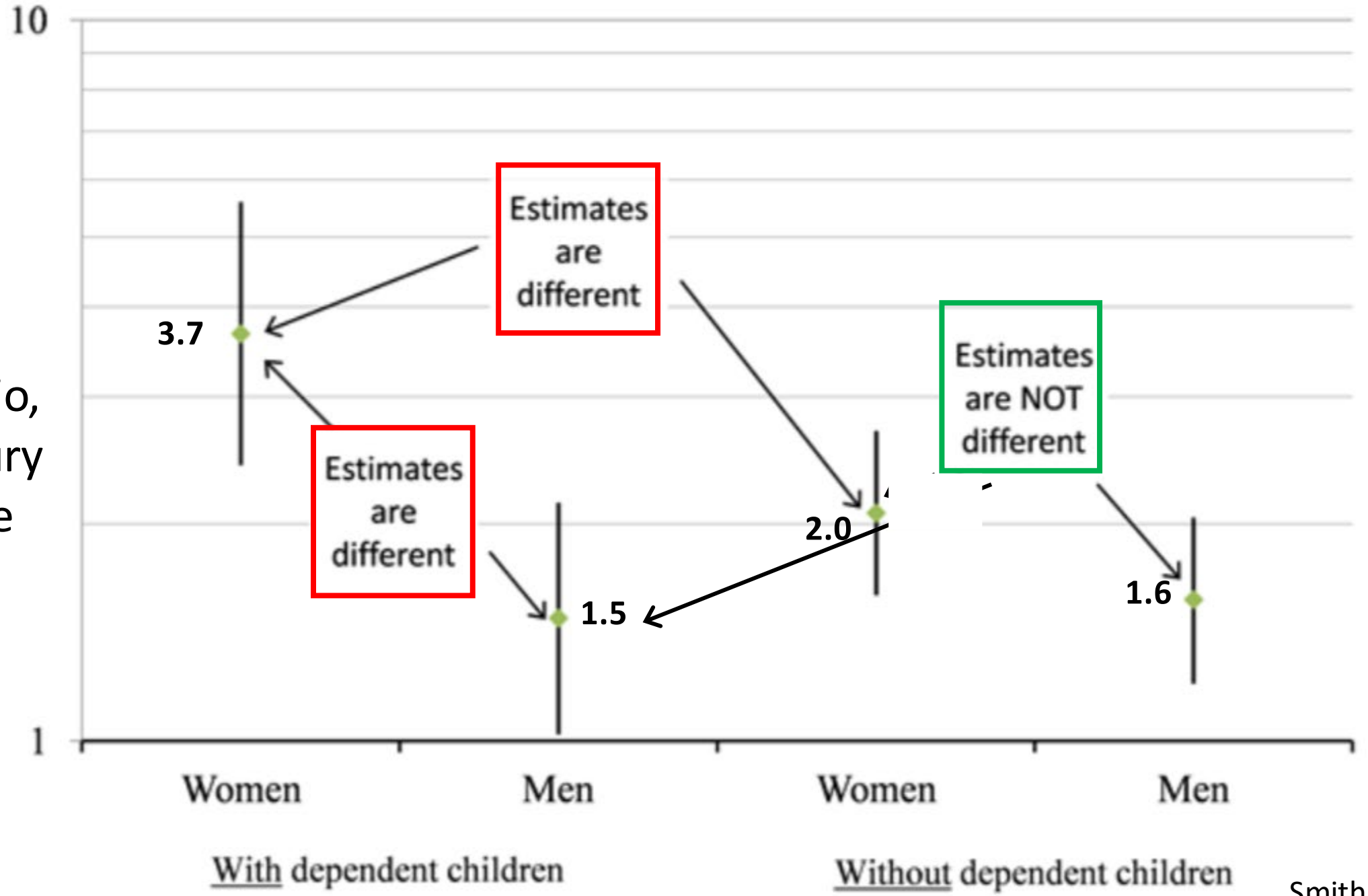
What type of subgroup analysis?



What type of subgroup analysis?



Odds ratio, work injury vs. none



Smith et al 2013

CIHR-IGH

Recommendations for Subgroup Analyses

- Identify why sex and/or gender should be considered in relation to your study objectives
    - Provide rationale (conceptual model) & hypotheses
- Stratified descriptive tables
- Interaction analyses
- Emphasize overall results (direction & magnitude of effects)

Aulakh and Anand. *Women's Health Issues* (2007) **17**:342-50; Yusuf et al. *JAMA* (1991) **266**:93-8.

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REVIEW | VOLUME 396, ISSUE 10250, P565-582, AUGUST 22, 2020

Sex and gender: modifiers of health, disease, and medicine

Prof Franck Mauvais-Jarvis, MD • Prof Noel Bairey Merz, MD • Prof Peter J Barnes, MD • Prof Roberta D Brinton, PhD • Prof Juan-Jesus Carrero, PhD • Dawn L DeMeo, MD • et al. Show all authors

Published: August 22, 2020 • DOI: https://doi.org/10.1016/S0140-6736(20)31561-0 • Check for updates

Genders, sexes, and health: what are the connections—and why does it matter? FREE

Nancy Krieger

International Journal of Epidemiology, Volume 32, Issue 4, August 2003, Pages 652–657, https://doi.org/10.1093/ije/dyg156

November 8, 2016

Reporting Sex, Gender, or Both in Clinical Research?

Janine Austin Clayton, MD[1]; Cara Tannenbaum, MD, MS[2]

» Author Affiliations | Article Information

JAMA. 2016;316(18):1863-1864. doi:10.1001/jama.2016.16405

Sex and Gender Equity in Research: rationale for the SAGER guidelines and recommended use

Shirin Heidari, Thomas F. Babor, Paola De Castro, Sera Tort & Mirjam Curno

Research Integrity and Peer Review **1**, Article number: 2 (2016) | Cite this article

EDITORIAL | 18 May 2022

Nature journals raise the bar on sex and gender reporting in research

Authors will be prompted to provide details on how sex and gender were considered in study design.

August 31, 2022

Analysis of Sex and Gender Reporting Policies in Preeminent Biomedical Journals

Lorin A. Bibb, MD[1]; Brian D. Adkins, MD[2]; Garrett S. Booth, MD, MS[3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(8):e2230277. doi:10.1001/jamanetworkopen.2022.30277

- 34% stated a policy for reporting sex and/or gender reporting policy
- 24% explicitly distinguished between or defined sex and gender
- 16% required authors to report methods for determining sex and/or gender
- 2% required authors to collect both sex and gender characteristics

Table 2. Association Between Sex and Gender Reporting Policies and Journal Characteristics

	Stated sex and/or gender reporting policy			Distinguish between or define sex and gender			Require reporting of methods used to determine sex and/or gender			Require collection of both sex and gender		
Criteria	Yes[a]	No	Mean difference (95% CI)	Yes[a]	No	Mean difference (95% CI)	Yes[a]	No	Mean difference (95% CI)	Yes[a]	No	Mean difference (95% CI)
2020 IF,[b] mean (SD)	10.8 (13.1)	8.8 (10.3)	2.0 (−1.4 to 5.5)	12.1 (15.4)	8.7 (9.6)	3.4 (−0.4 to 7.2)	15.7 (17.7)	8.3 (9.2)	7.4 (3.1 to 11.7)	15.7 (12.4)	9.4 (11.3)	6.3 (−6.7 to 19.3)
Journal age, mean (SD), y	50.5 (46.1)	52.2 (41.2)	1.7 (−11.3 to 14.7)	46.6 (46.8)	53.3 (41.5)	6.7 (−7.6 to 21.0	47.6 (51.8)	52.4 (41.0)	4.8 (−11.8 to 21.4)	32.3 (8.4)	52.0 (43.1)	19.7 (−29.5 to 68.9)
Women EIC, No./No. (%)	15/70 (21.4)	16/139 (11.5)	*P* = .07	11/50 (22)	20/159 (12.6)	*P* = .11	10/34 (29.4)	21/175 (12)	*P* = .02	1/3 (33.3)	30/206 (14.6)	*P* = .38

Abbreviations: EIC, editor-in-chief; IF, impact factor.

[a] Includes journals that have an external link to a policy.

[b] Data from Journal Citation Reports.[5]

Communicate Results

Table. Suggested Approach for Reporting Demographic Characteristics of Study Participants and Outcome by Sex and Gender (N = 59)

Demographic Characteristics	
Total No.	59
Age range, y	18-90
Sex, No.[a]	
Male participant	27
Female participant	32
Gender, No.[b]	
Men	26
Women	33
Outcome, No. (%)[c]	50 (85)
Males	20 (40)
Females	30 (60)
Outcome, No. (%)[d]	
Male	20 (74)
Female	30 (94)

[a] Ascertained by genotyping of blood sample.

[b] Ascertained by self-report.

[c] The number (%) occurring in males and females of the total outcomes (n = 50).

[d] Number (%) of outcomes occurring within the subgroups of males (20/27) and females (30/32).

Clayton JA, Tannenbaum C. Reporting Sex, Gender, or Both in Clinical Research? *JAMA*. 2016;316(18):1863–1864. doi:10.1001/jama.2016.16405

- Present the sex and/or gender of your participants – use correct terminology
- Report how information on sex and/ or gender was obtained
- Be transparent about limitations in data collection and generalizability, particularly with small numbers.
- Report all results: positive, negative, inconclusive

Your VA data adds value

- There is value in reporting data by sex / gender
  - Results from women and gender diverse Veterans (even exploratory):
    - provides valuable information on the health and efficacy of interventions
    - inform the direction of future studies
  - Stratified results provides valuable data that could be used in evidence maps and evidence synthesis projects
- Data sharing
  - Possibility of merging data sets with common measures (Wizeman, 2012).
  - Pooled data has the potential to increase statistical power and reach of studies with fewer women/ gender nonconforming Veterans enrolled. (Klap, 2019)

Conduct

Recruit and Retain women and/or gender diverse in VA trials

Consider

Think about how sex and/or gender may be relevant for your research question

Collect

Define and measure gender and/or sex in primary data collection

Characterize

Analyze your data with attention to sex and/or gender

Communicate

Report and publish sex and/or gender specific results; address limitations

Adapted from 4 C's, NIH ORWH at https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable.

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Research resources and trainings

- Canadian Institutes of Health Research: Institute of Gender and Health https://cihr-irsc.gc.ca/e/49347.html
- Stanford: Gendered Innovations http://genderedinnovations.stanford.edu/index.html
- Sex and Gender Equity in Research (SAGER) guidelines https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6
- Two-step method for assessing sex and gender in surveys https://genderedinnovations.stanford.edu/methods/surveys.html

VA resources

- VA Women's Health Research: https://www.research.va.gov/programs/womens_health/default.cfm
- Self-identified gender identity and birth sex in the medical record (VA intranet) https://dvagov.sharepoint.com/sites/vhava-lgbt-resources/HealthCareTopics/SitePages/Electronic-Health-Records.aspx
- Women's Enhanced Recruitment Process (WERP) Toolkit https://vhacdwdwhweb100.vha.med.va.gov/phenotype/index.php/WERP_Toolkit
- Comparison of methods for identifying transgender and gender-diverse veterans in CDW https://vaww.virec.research.va.gov/Notebook/RNB/RNB23-CDW-RN-Identifying-Transgender-Patients.pdf
- VA National LGBTQ+ Health Program Research resources https://dvagov.sharepoint.com/sites/vhava-lgbt-resources/SitePages/Research.aspx
- VA National LGBTQ+ Health Program Data Landing page https://dvagov.sharepoint.com/sites/vhava-lgbt-resources/HealthCareTopics/SitePages/LGBTQ+Data.aspx
- Join VA LGBTQ+ Research and Data listserv:
  - https://vaww.listserv.va.gov/scripts/wa.exe?INDEX : "LGBTQRESEARCHANDDATA"
- Contacts for LGBTQ+ Research Workgroup and LGBTQ+ Health Program:
  - Research: Alex McConnell (pronouns they/them/theirs), alex.mcconnell1@va.gov
  - Data: Dr. Wyatt Meriwether (he/they), wyatt.meriwether@va.gov

NIH resources

- Relevant policies https://grants.nih.gov/policy/inclusion/women-and-minorities.htm
- Office of Research on Women's Health (ORWH):
  - Trainings—https://orwh.od.nih.gov/orwh-courses
  - Funding opportunities and notices—https://orwh.od.nih.gov/research/funded-research-and-programs/funding-opportunities-and-notices
  - Administrative supplement for research on sex and gender differences—https://orwh.od.nih.gov/research/funded-research-and-programs/administrative-supplements

Subgroup analyses

- Klap R and Humphreys K. Designing studies for sex and gender analyses: How research can derive clinically useful knowledge for women's health. Women's Health Issues, 2019 June 25; 29:S12-14. https://doi.org/10.1016/j.whi.2019.05.002
- Aulakh AK, Anand SS. Sex and gender subgroup analyses of randomized trials. *Womens Health Issues.* 2007 Nov-Dec;17(6):342-50. doi: 10.1016/j.whi.2007.04.002.

- Institute of Medicine. *Sex-Specific Reporting of Scientific Research: A Workshop Summary.* Washington, DC: The National Academies Press. 2012. doi.org/10.17226/13307.
- Rothwell, Peter Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet*. 2005;365(9454):176-186. doi.org/10.1016/S0140-6736(05)17709-5
- Sun X, Ioannidis JPA, Agoritsas T, Alba AC, Guyatt G. How to Use a Subgroup Analysis: Users' Guide to the Medical Literature. *JAMA.* 2014;311(4):405–411. doi:10.1001/jama.2013.285063

Intersex and gender diversity resources and trainings

- Intersex support and advocacy groups https://interactadvocates.org/resources/intersex-organizations/
- Gender-diverse support and advocacy groups https://www.wpath.org/resources/general
- How sex development works, University of Toronto https://pie.med.utoronto.ca/htbw/module.html?module=sex-development
- Guidelines for transgender and gender-diverse care https://transcare.ucsf.edu/guidelines
- World Professional Association for Transgender Health (WPATH) https://www.wpath.org/

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