Evidence Map: Reporting of results by sex or gender in randomized controlled trials with women Veteran participants 2008-2018

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Acknowledgements

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I have no financial relationships to disclose.

The views expressed in this presentation are those of the authors and do not represent the views of the VA or the U.S. Government.
Evidence Map: Reporting of Results by Sex or Gender in Randomized, Controlled Trials with Women Veteran Participants (2008 to 2018)

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Poll Question #1

Let’s get to know who’s in the audience:
Select your main role(s)!

- Physician
- Nurse
- Research PI
- Research study staff
- Veteran
- Other (VA personnel, student, etc)
Overview

Background

Methods

Results

Key Findings and Conclusions
Poll Question #2

What’s the difference between Sex and Gender?

- There’s a difference?
- It’s simple: Sex refers to biological attributes, while Gender is a sociocultural construct
- Actually it’s a lot more complicated than that
Definitions

**Sex** = biological attributes

**Gender** = psychosocial or sociocultural

Do Sex and Gender matter for Health Research?

Have you considered the possibilities?

Learn more: [www.cihr-irsc.gc.ca/shapingscience.html](http://www.cihr-irsc.gc.ca/shapingscience.html)
Sex and Gender influences on pharmacological response

**Sex:** pharmacokinetics, pharmacodynamics

**Gender:** access to care, other health behaviors (i.e., smoking), placebo effect, medication adherence, education, socio-economic status, patient-physician dyad

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**Table 1. Some differences between men and women.**

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<tr>
<th>Differences</th>
<th>XX</th>
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<tbody>
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<tr>
<td>Infant mortality</td>
<td>+</td>
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<tr>
<td>Height</td>
<td>+</td>
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<td>Muscle</td>
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<tr>
<td>Fat</td>
<td>+</td>
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<td>Distribution of fat</td>
<td>Peripheral</td>
<td>Visceral</td>
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<td>Total water</td>
<td>+</td>
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<td>Intracellular water</td>
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<tr>
<td>Extracellular water</td>
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<td>Plasma</td>
<td>+</td>
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<td>Heart frequency</td>
<td>+</td>
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<tr>
<td>Average organ flow</td>
<td>+</td>
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<tr>
<td>Glomerular filtration rate</td>
<td>+</td>
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<td>Gastric pH (acidity)</td>
<td>+</td>
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<td>Gastrointestinal mobility</td>
<td>+</td>
<td></td>
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<tr>
<td>Gastric emptying</td>
<td>+</td>
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<tr>
<td>Acetylcholine esterase</td>
<td>+</td>
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<tr>
<td>Catechol-O-methyl transferase</td>
<td>+</td>
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<tr>
<td>CYP2D6</td>
<td>+</td>
<td></td>
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<tr>
<td>CYP3A4</td>
<td>+</td>
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<tr>
<td>P-glycoprotein</td>
<td>+</td>
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<tr>
<td>QTc interval</td>
<td>+</td>
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</tbody>
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Sex and Gender reporting in health research over time

- In 2001, the US government reported that 8 out of 10 drugs removed from the market in preceding years had more significant adverse effects for women than men

- The NIH and the National Academy of Medicine (formerly IOM) have called for increased participation of women in medical research
  - Now close to 50% female in NIH funded trials
Women Veterans

10% of all living Veterans are women
16% by 2040

7% of VA patients are women
175% increase in 15 years!

Younger than men
More diverse
42% racial/ethnic minority

Sourcebook Vol 4: Women Veterans in VHA, 2018
Previous Review

- Reviewed ALL the women Veterans’ health research from 2008-2015

- Excluded studies that didn’t explicitly report results for women
  - Over 350 studies excluded!

- Major gap: Need to improve reporting of results by sex or gender
Objectives

**Overall:** Evaluate attention to sex and gender in randomized controlled trials (RCTs) with women Veterans over the past decade (2008-18)
Overview

Background

Methods

Results

Key Findings and Conclusions
Systematic Review vs. Evidence Map

Annals of Internal Medicine

PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation

Andrea C. Tricco, PhD, MSc; Erin Lillie, MSc; Wasifa Zarin, MPH; Kelly K. O’Brien, PhD, BScPT; Heather Colquhoun, PhD; Danielle Levac, PhD, MSc, BScPT; David Moher, PhD, MSc; Micah D.J. Peters, PhD, MSc; Tanya Horsley, PhD; Laura Weeks, PhD; Susanne Hempel, PhD; Elie A. Akl, MD, PhD, MPH; Christine Chang, MD, MPH; Jessie McGowan, PhD; Lesley Stewart, PhD, MSc; Lisa Hartling, PhD, MSc, BScPT; Adrian Aldcroft, BA(Hons), BEd; Michael G. Wilson, PhD; Chantelle Garrity, MSc; Simon Lewin, PhD; Christina M. Godfrey, PhD, RN; Marilyn T. Macdonald, PhD, MSN; Etienne V. Langlais, PhD; Karla Soares-Weiser, MD, PhD; Jo Moriarty, MA; Tammy Clifford, PhD, MSc; Özge Tunçalp, MD, PhD, MPH; and Sharon E. Straus, MD, MSc

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Systematic Reviews

RESEARCH

What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products

Isomi M. Miake-Lye^{1,2,*}, Susanne Hempel^{3}, Roberta Shanman^{3} and Paul G. Shekelle^{1,3,4}
Search strategy

MEDLINE search:
- MeSH terms: Women; Women’s health; Women’s Health Services; Transgendered persons; Veterans; Veterans health; Hospitals, Veterans
- English language
- 2008 to present

Exclusion Criteria:
- Not related to health/healthcare
- Does not include Female Veterans
- Not a randomized controlled trial
Key questions

**Q1:** How do RCTs that include women veterans and report results by sex or gender differ from RCTs that include women veterans but do not report results by sex or gender?

**Q2:** Among RCTs with women veterans that report results by sex or gender, do sex/gender analyses and reporting adhere to currently proposed best practices?

**Q3:** Among RCTs with women veterans that do not report results by sex or gender, how are sex/gender addressed in publications, if at all?

**Study characteristics:**
- Publication year
- Journal
- Health care topic
- Sample size
- Number women
- Proportion female
- Location
- Time to follow-up
- Intervention type
- Control type
- Outcome type
- Funding source

**Attention to sex/gender in:**
- Hypothesis
- Study design
- Statistical analysis
- Reporting
- Limitations acknowledged

**Any mention of sex/gender in:**
- Methods
- Results
- Discussion
Best practices for Sex and Gender reporting in research

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

- Created criteria for appraisal of attention sex and gender
- Intended to be descriptive

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Sex and Gender Equity in Research (SAGER) guidelines</th>
</tr>
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<tbody>
<tr>
<td><strong>General principles</strong></td>
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<tr>
<td>• Authors should use the terms sex and gender carefully in order to avoid confusing both terms.</td>
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<tr>
<td>• Where the subjects of research comprise organisms capable of differentiation by sex, the research should be designed and conducted in a way that can reveal sex-related differences in the results, even if these were not initially expected.</td>
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<tr>
<td>• Where subjects can also be differentiated by gender (shaped by social and cultural circumstances), the research should be conducted similarly at this additional level of distinction.</td>
<td></td>
</tr>
</tbody>
</table>

**Recommendations per section of the article**

| Title and abstract | If only one sex is included in the study, or if the results of the study are to be applied to only one sex or gender, the title and the abstract should specify the sex of animals or any cells, tissues and other material derived from these and the sex and gender of human participants. |
| Introduction | Authors should report, where relevant, whether sex and/or gender differences may be expected. |
| Methods | Authors should report how sex and gender were taken into account in the design of the study, whether they ensured adequate representation of males and females, and justify the reasons for any exclusion of males or females. |
| Results | Where appropriate, data should be routinely presented disaggregated by sex and gender. Sex- and gender-based analyses should be reported regardless of positive or negative outcome. In clinical trials, data on withdrawals and dropouts should also be reported disaggregated by sex. |
| Discussion | The potential implications of sex and gender on the study results and analyses should be discussed. If a sex and gender analysis was not conducted, the rationale should be given. Authors should further discuss the implications of the lack of such analysis on the interpretation of the results. |
Overview

Background

Methods

Results

Key Findings and Conclusions
Citations identified from 2008-2015 review

Previously eligible N=11
ROUTs N=8
Secondary analysis N=3

Previously ineligible N=424
Did not provide sex-specific results N=361
Did not include enough women N=63

Total Citations
N = 1885

Duplicates removed N = 65

Updated search 2015-2018

MEDLINE citations N=1461

Abstracts/Full-text reviewed
N = 163

Excluded abstracts N=1668
Not relevant to female veterans
Not an intervention study

Abstracts/Full-text reviewed
N = 163

Excluded articles N=98
Single-arm uncontrolled trial N=36
Implementation/evaluation study N=41
RCT-related articles N=17
VA clinician participants only N=2
Ineligible population N=2

Ineligible secondary analyses N=22

Missed by search:
Parent trials N=2

Included articles
N = 45
Evidence Map: RCTs with veteran participants, by proportion women, reporting of results by sex or gender, and publication year.

No results by sex

Sex-specific results

>33% women

10-33% women

<10% women

100% women
Q1 Results: Compare characteristics or RCTs that do or do not report sex/gender results

<table>
<thead>
<tr>
<th>Trial characteristics</th>
<th>Women and men veteran participants</th>
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<tbody>
<tr>
<td></td>
<td>NO results by sex or gender (n=30)</td>
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<tr>
<td></td>
<td>median(IQR)</td>
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<td>n randomized participants</td>
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<td>% women participants</td>
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<td>Time to longest follow-up (days)</td>
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<td>Trial characteristics</td>
<td>Women and men veteran participants</td>
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<td>NO results by sex or gender (n=30)</td>
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<td>n(%) or median(IQR)</td>
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<td>Health care topic</td>
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<td>Mental health</td>
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<td>Physical health</td>
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<td>Health care delivery</td>
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<td>Access, Utilization, PDH</td>
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<td>Study location(s)</td>
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<td>Single site</td>
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<td>Multi-site</td>
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<td>VA Cooperative study</td>
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<td>WH PBRN study</td>
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<td>Non-VA or Community based</td>
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<td>Intervention type</td>
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<td>Pharmacologic</td>
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<td>Behavioral</td>
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<td>Health services</td>
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<td>Device or Physical treatment</td>
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</table>
### Q2 Results: Attention to Sex and Gender among those that DID report

<table>
<thead>
<tr>
<th>Publication Year</th>
<th>Article ID number</th>
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<tr>
<td></td>
<td>1 2 3 4 5 6 7 8 9 10</td>
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<td>2010 2015 2016 2017 2018</td>
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#### Hypothesis
- Explicitly stated hypothesis
- Suggested relationship or prior sex-specific findings cited

#### Study design
- Explicitly an article about sex/gender differences
- Oversampling or enhanced recruitment of women
- Sex/gender-specific inclusion/exclusion criteria
- Randomization stratified or blocked by sex
- Sex/gender balanced between treatment arms

#### Statistical analysis
- Power calculation for interaction
- Interaction test (sex/gender by treatment group)

#### Reporting
- Gender of patients lost/withdrawn post-randomization reported
- Sex/gender analysis described in introduction or methods
- Statistically significant sex/gender by treatment interaction
- Any differential treatment effect by sex/gender reported
- Full sex-disaggregated results reported for primary outcome

#### Limitations acknowledged
- Small proportion of women limits generalizability
- Sub-group analysis lacks power, interpret with caution, replicate
### Methods

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### Results

| Proportion of male/female participants reported |      |      |      |      |      |      |      |      |      |      |
| Balance of sex/gender across treatment arms reported |      |      |      |      |      |      |      |      |      |      |

### Discussion

| Mostly male population limits generalizability |      |      |      |      |      |      |      |      |      |      |
| Future research should study sex/gender effect |      |      |      |      |      |      |      |      |      |      |
| Mostly male population (descriptive) |      |      |      |      |      |      |      |      |      |      |
Overview

Background

Methods

Results

Key Findings and Conclusions
Participation of women Veterans

Studies that reported sex/gender results were:
- larger (n=344 vs. 126)
- included a higher proportion of women (17 vs. 11%)

Women are 10% of living Veterans; 7% of VA users
- only 1 of 13 trials with <10% women reported sex/gender results

VA ORD requires “special efforts... to include women Veterans”
- Since 2013, the number of women and men enrolled must be reported on ClinicalTrials.gov
- The WH PBRN may help improve recruitment
Reporting sex/gender results

25% of studies reported sex/gender results
- Similar to reviews of non-Veteran RCTs (13-48% women)
- Funders/Regulators (NIH/FDA) and Journals (ICMJE/Consort) can try to raise this proportion

Only 1 of 11 pharmacologic/device studies presented sex/gender results

CSP study at 12 VAMCs
N= 304
297 men
7 women (2%)

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Prazosin for Post-Traumatic Stress Disorder in Military Veterans

Improved attention to sex/gender

- An interaction test is great, but it’s not enough!
  - Power calculation
  - False positives/negatives

- Why do you think there might be a relationship between sex/gender and the intervention?

- Provide full results disaggregated by sex, regardless of interaction test results
Poll Question:

Have you ever received training on sex and gender research and analyses?

- Yes, I’m an expert – ask me anything!
- Just a bit, I need more training and experience
- Never – this is the first I’ve heard of it!
Opportunities to improve

VA Women’s Health Research Network:

Click here to learn more about the VA WHRN

Click here for NIH resources

The 4 Cs of Studying Sex to Strengthen Science

Consider
Design studies that take sex into account, or explain why it isn’t incorporated

Collect
Tabulate sex-based data

Characterize
Analyze sex-based data

Communicate
Report and publish sex-based data

Click here for online training modules from the CIH Research
Limitations

Search criteria specific to women

Likely overestimates the proportion that report sex/gender

Limited to published data and online supplements

Missed some data on ClinicalTrials.gov

Only included RCTs

Lots of single-arm pilots and implementation/evaluation projects
Conclusions

Women Veterans are increasingly participating in clinical trials

Reporting of results by sex/gender remains infrequent

Even those that do report sex/gender results often omit key information

Improving attention to sex/gender for research that includes women veterans will improve the applicability of knowledge gained from veteran research to the care of women
Questions?

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