



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

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CCDOR

Acknowledgements

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Disclosures

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.



ELSEVIER

WOMEN'S
HEALTH ISSUES

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Article

Evidence Map: Reporting of Results by Sex or Gender in
Randomized, Controlled Trials with Women Veteran
Participants (2008 to 2018)



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[Click here for link to Full Article Online](#)

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?

GENDER

Socially-constructed roles, behaviours, expressions and identities of girls, women, boys, men and gender diverse people.



SEX

Biological attributes of humans and animals, including physical features, chromosomes, gene expression, hormones and anatomy.



Have you considered the possibilities?

Learn more: www.cihlrlsc.gc.ca/shapingscience.html



Canadian Institutes of Health Research

Instituts de recherche en santé du Canada

Canada

Sex and Gender influences on pharmacological response

Sex: pharmacokinetics, pharmacodynamics

Table 1. Some difference between men and women.

Differences	XX	XY
Birth and adult weight		+
Infant mortality		+
Height		+
Muscle		+
Fat	+	
Distribution of fat	Peripheral	Visceral
Total water		+
Intracellular water		+
Extracellular water		+
Plasma	+	
Heart frequency	+	
Average organ flow		+
Glomerular filtration rate		+
Gastric pH (acidity)		+
Gastrointestinal mobility		+
Gastric emptying		+
Acetylcholine esterase		+
Catechol-O-methyl transferase		+
CYP2D6		+
CYP3A4	+	
P-glycoprotein		+
QTc interval	+	

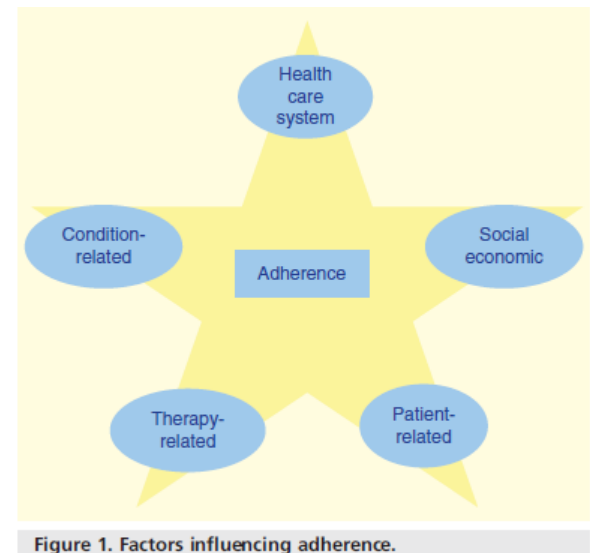


Figure 1. Factors influencing adherence.

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

Franconi F and Campesi I, Sex and gender influences on pharmacological response: an overview, *Expert Review of Clinical Pharmacology*, May 2014

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

S.1 - National Institutes of Health Revitalization Act of 1993

Subtitle B--Clinical Research Equity Regarding Women and Minorities

PART I--WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH

SEC. 131. REQUIREMENT OF INCLUSION IN RESEARCH.

Part G of title IV of the Public Health Service Act, as amended by section 101 of this Act, is amended by inserting after section 492A the following section:

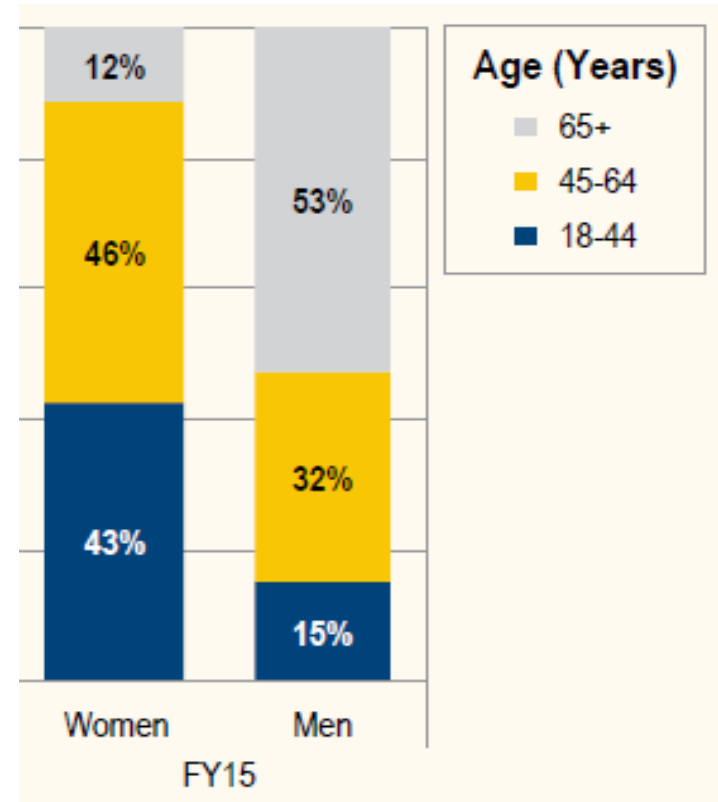
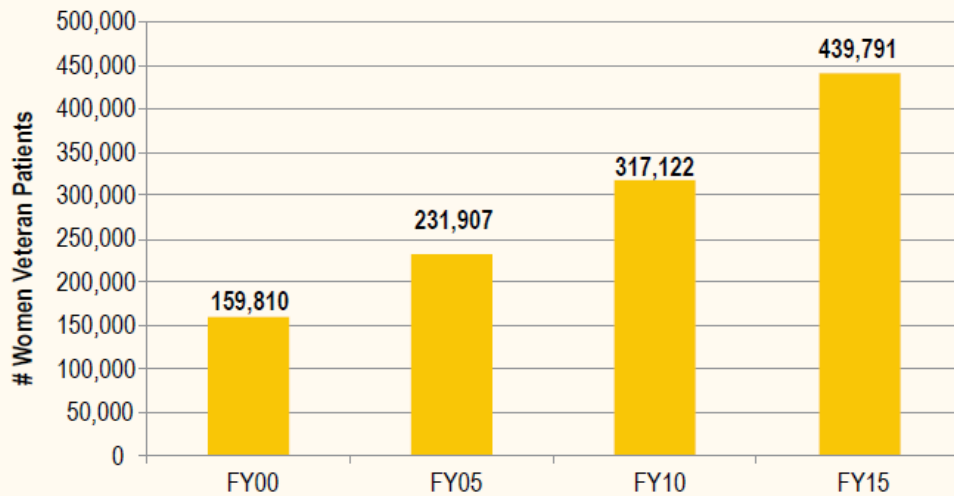
INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH

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

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

An Evidence Map of the Women Veterans' Health Research Literature (2008–2015)

Elisheva R. Danan, MD, MPH^{1,2}, Erin E. Krebs, MD, MPH^{1,2}, Kristine Ensrud, MD, MPH^{1,2}, Eva Koeller, BA¹, Roderick MacDonald, MS¹, Tina Velasquez, MS¹, Nancy Greer, PhD¹, and Timothy J. Wilt, MD, MPH^{1,2}

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BACKGROUND: Women comprise a growing proportion of Veterans seeking care at Veterans Affairs (VA) healthcare facilities. VA initiatives have accelerated changes in services for female Veterans, yet the corresponding literature has not been systematically reviewed since 2008. In 2015, VA Women's Health Services and the VA Women's Health Research Network requested an updated literature review to facilitate policy and research planning.

METHODS: The Minneapolis VA Evidence-based Synthesis Program performed a systematic search of research related to female Veterans' health published from 2008 through 2015. We extracted study characteristics including healthcare topic, design, sample size and proportion female, research setting, and funding source. We created an evidence map by organizing and presenting results within and across healthcare topics, and describing patterns, strengths, and gaps.

RESULTS: We identified 2276 abstracts and assessed each for relevance. We excluded 1092 abstracts and reviewed 1184 full-text articles; 750 were excluded. Of 440 included articles, 208 (47%) were related to mental health, particularly post-traumatic stress disorder (71 articles), military sexual trauma (37 articles), and substance abuse (20 articles). The number of articles addressing VA priority topic areas increased over time, including reproductive health, healthcare organization and delivery, access and utilization, and post-deployment health. Three or fewer articles addressed each of the common chronic diseases: diabetes, hypertension, depression, or anxiety. Nearly 400 articles (90%) used an observational design. Eight articles (2%) described randomized trials.

CONCLUSIONS: Our evidence map summarizes patterns, progress, and growth in the female Veterans' health and healthcare literature. Observational studies in mental health make up the majority of research. A focus on primary care delivery over clinical topics in primary care and a lack of sex-specific results for studies that include men and women have contributed to research that is not addressing common health issues for women.

INTRODUCTION

Despite serving in or alongside the US military since the Revolutionary War, women have experienced unequal access to Veterans Affairs (VA) benefits, and few women used the VA healthcare system prior to the early 1980s.¹ In the subsequent 30 years, clinical, research, and policy initiatives have sought to improve the quality and accessibility of evidence-based healthcare for female Veterans.² Today, women are the fastest-growing population of US Veterans receiving VA healthcare.³

When the literature related to female Veterans' health and healthcare was last reviewed in 2008,⁴⁻⁶ the authors encountered a rapidly emerging field of research. They described growth in research related to access, utilization, and organizational quality, but identified gaps in research related to chronic physical and mental health conditions, complex combinations of disease, pregnancy and aging, traumatic brain injury, co-managed mental and physical preventive care, and post-deployment transitional health. Subsequently, the VA women's health landscape has changed substantially. In 2008, the national Women's Health Services (WHS) program was established to oversee clinical initiatives, such as the provision of comprehensive women's healthcare (including general and gender-specific care) at a single site from a single provider.³ The VA Women's Health Research Network (WHRN) was created in 2010 to fill knowledge gaps in the evidence base related to female Veterans' health and healthcare.⁷ Based in part on the results of the previous review,⁵ the WHRN prioritized research on six key topic areas: (1) mental health, (2) primary care and prevention, (3) reproductive health, (4) complex chronic conditions/aging and long-term care, (5) access to care and rural health, and (6) post-deployment health.

CALL FOR SUBMISSIONS

To a Special Supplement to *Women's Health Issues*
Topic: Examining Sex/Gender Differences in VA Clinical and Health Services Research

Evidence-based Synthesis Program (ESP)



Objectives

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

Overview

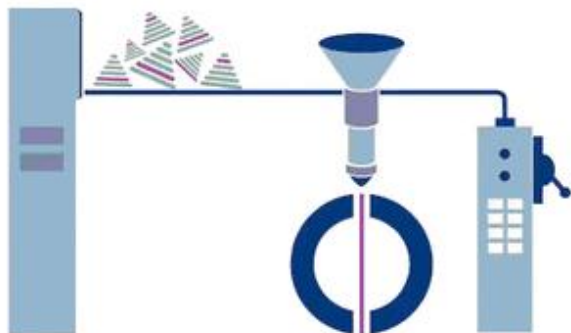
Background

Methods

Results

Key Findings and Conclusions

Systematic Review vs. Evidence Map



Annals of Internal Medicine RESEARCH AND REPORTING METHODS

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, MA(Q); 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 Garritty, MSc; Simon Lewin, PhD; Christina M. Godfrey, PhD, RN; Marilyn T. Macdonald, PhD, MSN; Etienne V. Langlois, PhD; Karla Soares-Weiser, MD, PhD; Jo Moriarty, MA; Tammy Clifford, PhD, MSc; Özge Tunçalp, MD, PhD, MPH; and Sharon E. Straus, MD, MSc

Miake-Lye *et al. Systematic Reviews* (2016) 5:28
DOI 10.1186/s13643-016-0204-x

Systematic Reviews

RESEARCH

Open Access

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 Hempel³, Roberta Shanman³ 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

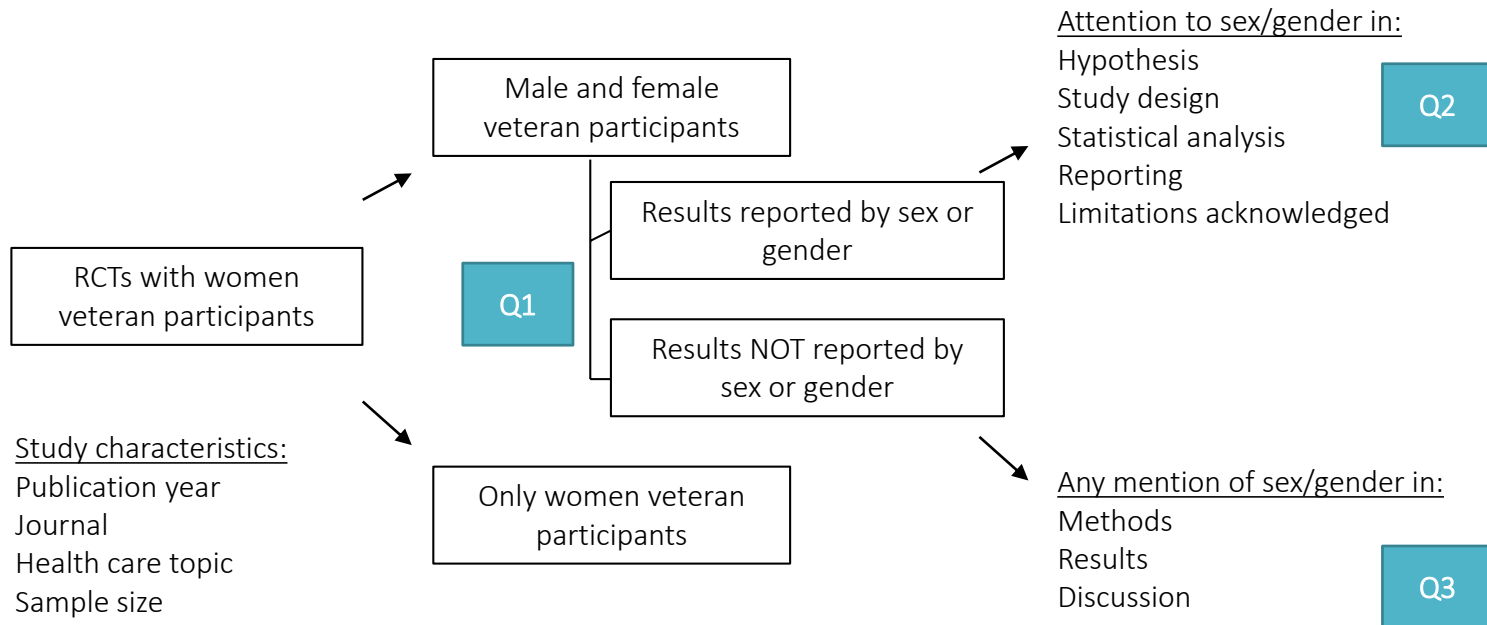
Exclusion Criteria:

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?

Best practices for Sex and Gender reporting in research

REVIEW

Open Access

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

Shirin Heidari¹, Thomas F. Babor^{2*}, Paola De Castro³, Sera Tort⁴ and Mirjam Curno⁵



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

Table 1 Sex and Gender Equity in Research (SAGER) guidelines

General principles

- Authors should use the terms *sex* and *gender* carefully in order to avoid confusing both terms.
- 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.
- 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.

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.

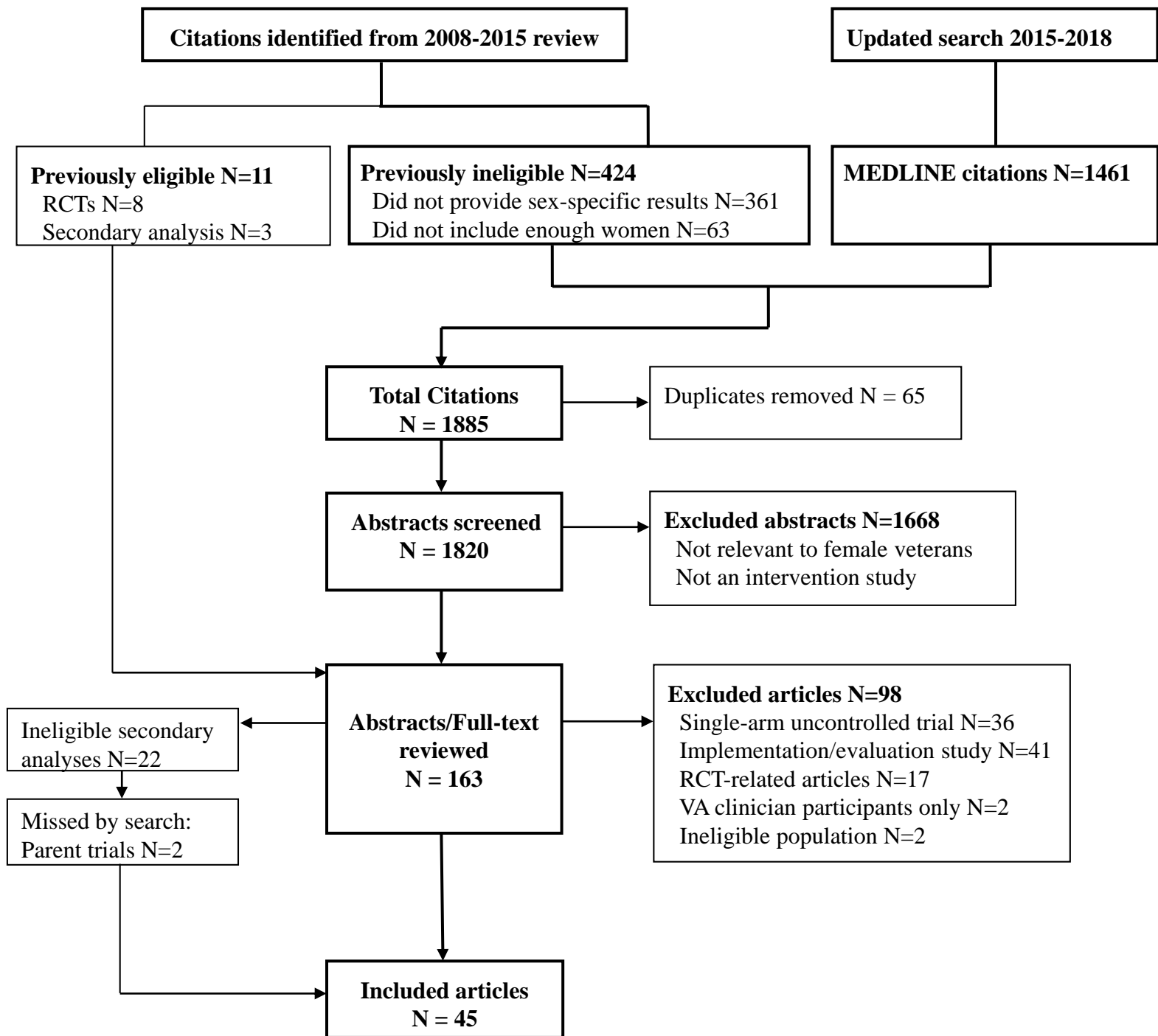
Overview

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Q1 Results: Compare characteristics of RCTs that do or do not report sex/gender results

Trial characteristics	Women and men veteran participants	
	NO results by sex or gender (n=30) median(IQR)	Results by sex or gender (n=10) median(IQR)
n randomized participants		
% women participants		
Time to longest follow-up (days)		

Trial characteristics

Women and men veteran participants

NO results by sex or
gender (n=30)
n(%) or median(IQR)

Results by sex or gender
(n=10)
n(%) or median(IQR)

Health care topic

Mental health

Physical health

Health care delivery

Access, Utilization, PDH

Study location(s)

Single site

Multi-site

VA Cooperative study

WH PBRN study

Non-VA or Community based

Intervention type

Pharmacologic

Behavioral

Health services

Device or Physical treatment

Q2 Results: Attention to Sex and Gender among those that DID report

	Article ID number									
	1	2	3	4	5	6	7	8	9	10
Publication Year	2010	2015		2016			2017			2018
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										

	Article ID number																													
	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Publication Year	2008		2009			2011		2012		2013			2014			2015			2016		2017					2018				
Methods																														
Randomization stratified by sex/gender																														
Sex specific eligibility criteria (pregnancy related)																														
Sex specific eligibility criteria (non pregnancy)																														
Potential participant pool described as mostly male																														
Men and women eligible for study																														
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

ESTABLISHED IN 1812

FEBRUARY 8, 2018

VOL. 378 NO. 6

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

M.A. Raskind, E.R. Peskind, B. Chow, C. Harris,* A. Davis-Karim, H.A. Holmes, K.L. Hart, M. McFall, T.A. Mellman, C. Reist, J. Romesser, R. Rosenheck, M.-C. Shih, M.B. Stein, R. Swift, T. Gleason, Y. Lu, and G.D. Huang

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](#)



Are you a VA investigator who is planning to submit a proposal to
VA HSR&D in June 2019?

Can we help you meet requirements to include women in your
study?

[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

A screenshot of the Canadian Institutes of Health Research (CIHR) website. The header includes the CIHR logo and navigation links. The main content area features a banner for 'IGH LEARNING' with the text 'Learning about Sex and Gender - Video'. Below the banner, there is a section for 'Online Training Modules: Integrating Sex & Gender in Health Research' and a specific course titled 'Course 1: Sex and Gender in Biomedical Research' with buttons for 'Start course' and 'More information'.

[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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