Mapping the Evidence: Sex & Gender Differences in Treatments for Depression, Diabetes, & Chronic Pain

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Durham VAMC Evidence-Based Synthesis Program, December 9th, 2015

Outline

I. Importance of Sex and Gender Differences

II. What is an Evidence Map?

III. Characteristics of Evidence Base

IV. Reporting of Sex Effects

V. Gaps in Evidence & Next Steps

Which of the following does not vary by gender?

A) Cardiovascular risk

B) Zolpidem dosing

C) First line anti-hypertensive medications

D) Indications for aspirin as primary prevention

E) Stroke risk with atrial fibrillation

Which best describes your experience with evidence synthesis?

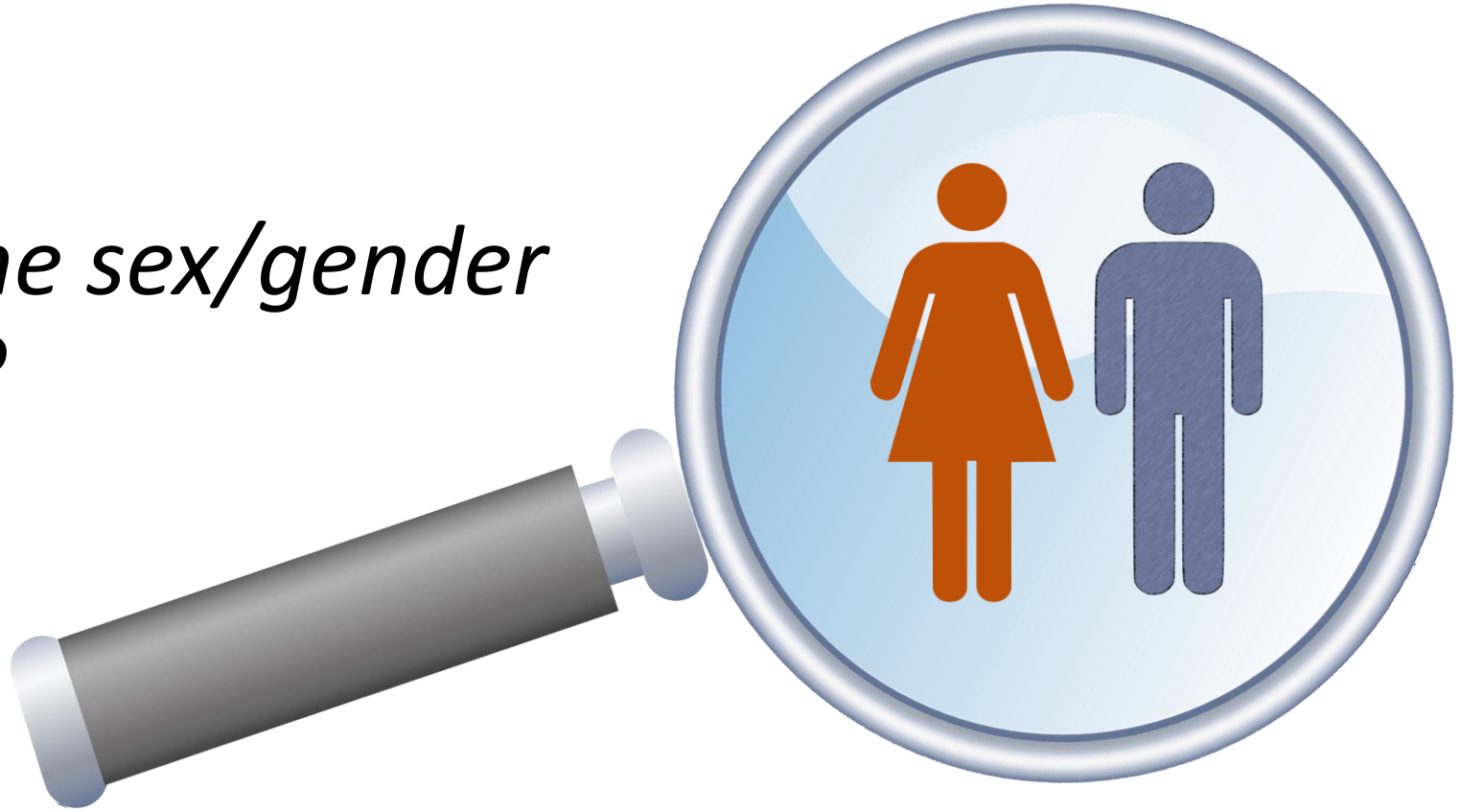
A) PI of evidence synthesis projects

B) Participated in conducting systematic reviews, etc.

C) Mainly use systematic reviews to guide clinical practice or policies

D) None

Why examine sex/gender differences?



Promoting Research on Sex/Gender Differences

NIH Revitalization Act:
Mandated inclusion of women and minorities

1986

1993

2001

2015

NIH: Women of reproductive age no longer excluded from clinical trials

IOM Report:
Does Sex Matter?

NIH: Call for balancing of sex in cell & animal studies

Mazure & Jones (2015) *BMC Womens Health* **15**:94.

More than 2 million Women Veterans

8% of VHA users

Doubled in last decade

Goals

1. Volume & Characteristics of Evidence Base
   →Representation of women

2. Whether & How Sex Effects are Reported

3. What are the Sex Effects?

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	Purpose	Depth of process
SYSTEMATIC REVIEW	Addresses a focused clinical question	
EVIDENCE MAP	Covers a broad topic area	

Adapted from Bragge et al. (2011) *BMC Med Res Methodol* **11**:92.

REVIEW

Annals of Internal Medicine

Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder

An Updated Meta-analysis

Gerald Gartlehner, MD, MPH; Richard A. Hansen, PhD, RPh; Laura C. Morgan, MA; Kylie Thaler, MD, MPH; Linda Lux, MPA; Megan Van Noord, MSIS; Ursula Mager, PhD, MPH; Patricia Thieda, MA; Bradley N. Gaynes, MD, MPH; Tania Wilkins, MSc; Michaela Strobelberger, MA; Stacey Lloyd, MPH; Ursula Reichenpfader, MD, MPH; and Kathleen N. Lohr, PhD

Background: Second-generation antidepressants dominate the management of major depressive disorder (MDD), but evidence on the comparative benefits and harms of these agents is contradictory.

Purpose: To compare the benefits and harms of second-generation antidepressants for treating MDD in adults.

conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-

Gartlehner et al (2011) *Ann Int Med* **155**:772.

An evidence map of psychosocial interventions for the earliest stages of bipolar disorder

Martine Vallarino, Chantal Henry, Bruno Etain, Lillian J Gehue, Craig Macneil, Elizabeth M Scott, Angelo Barbato, Philippe Conus, Stefanie A Hlastala, Mary Fristad, David J Miklowitz, Jan Scott

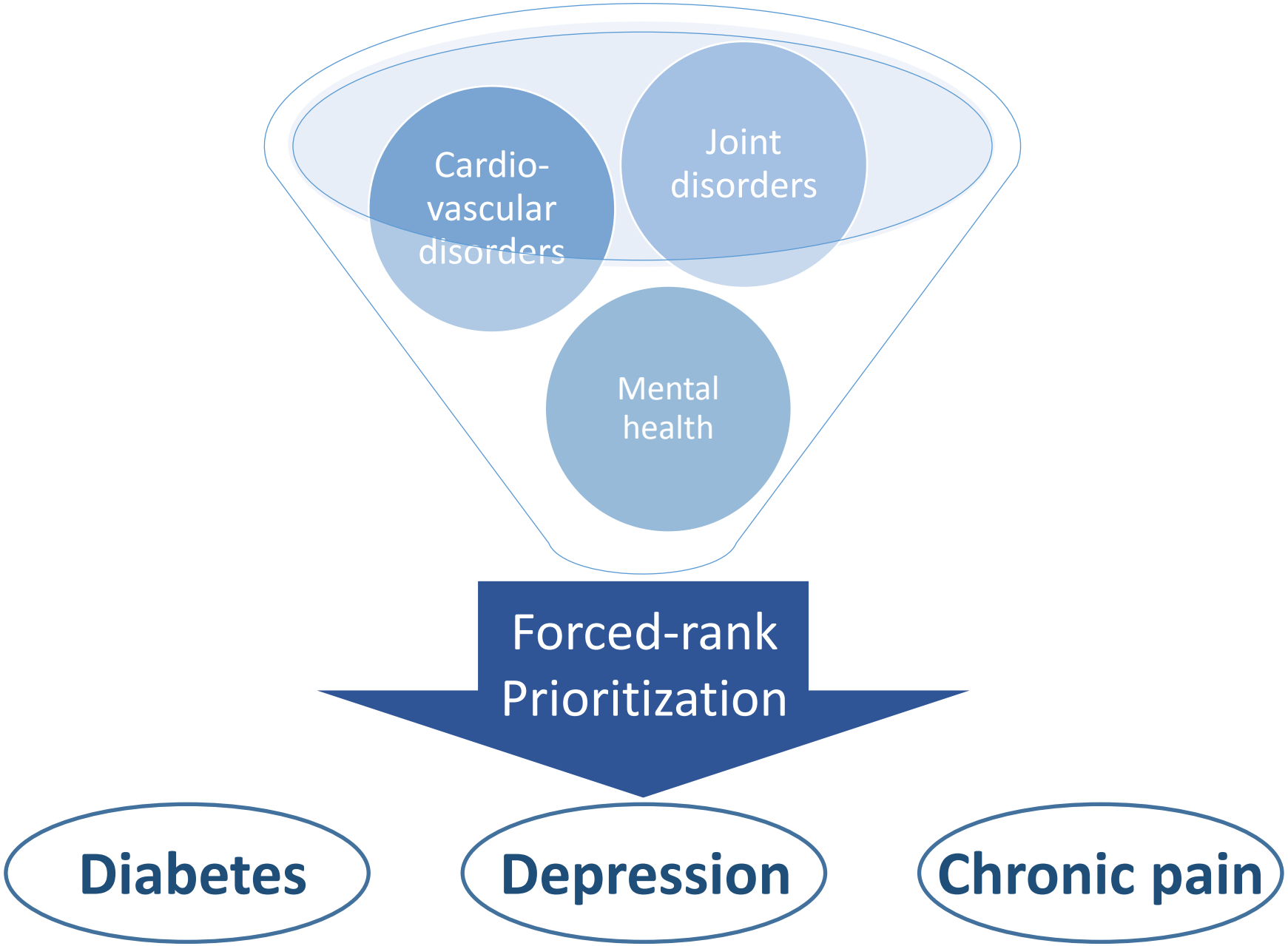
Lancet Psychiatry 2015; 2: 548–63

Depression, schizophrenia, and bipolar disorder are three of the four most burdensome problems in people aged under 25 years. In psychosis and depression, psychological interventions are effective, low-risk, and high-benefit

…we used evidence mapping to help us <u>identify the extent, distribution, and methodological quality of evidence</u>…

Epidemiology and Social Psychiatry, IRCCS Istituto di Ricerche Farmacologiche 'Mario Negri', Milan, Italy (M Vallarino, Prof A Barbato MD); Faculté de médecine, Université Paris Est, Créteil, France (Prof C Henry PhD, B Etain PhD); Pôle de Psychiatrie, APHP, Hôpital H Mondor—A Chenevier, Créteil, France

only slightly informative or appropriate. This strategy identified 29 studies in three target groups: ten studies in populations at high risk for bipolar disorder, five studies in patients with a first episode, and 14 studies in patients with early-onset bipolar disorder. Of the 20 completed studies, eight studies were randomised trials, but only two had sample sizes of more than 100 individuals. The main interventions used were family, cognitive behavioural, and interpersonal therapies. Only behavioural family therapies were tested across all of our three target groups. Although the available interventions were well adapted to the level of maturity and social environment of young people, few interventions target specific developmental psychological or physiological processes (eg, ruminative response style or delayed sleep phase), or offer detailed strategies for the management of substance use or physical health.


Cardio-vascular disorders
Joint disorders
Mental health
Forced-rank Prioritization
Diabetes
Depression
Chronic pain

	DEPRESSION	DIABETES	CHRONIC PAIN
Interventions	▪ Antidepressants ▪ Psychotherapy ▪ Exercise ▪ QI ▪ Guided self-help	▪ Insulin & oral meds ▪ Behavioral ▪ Exercise ▪ QI ▪ Bariatric surgery	▪ SSRI, etc. ▪ Behavioral ▪ Exercise ▪ QI ▪ Acupuncture ▪ Joint injections
Outcomes			

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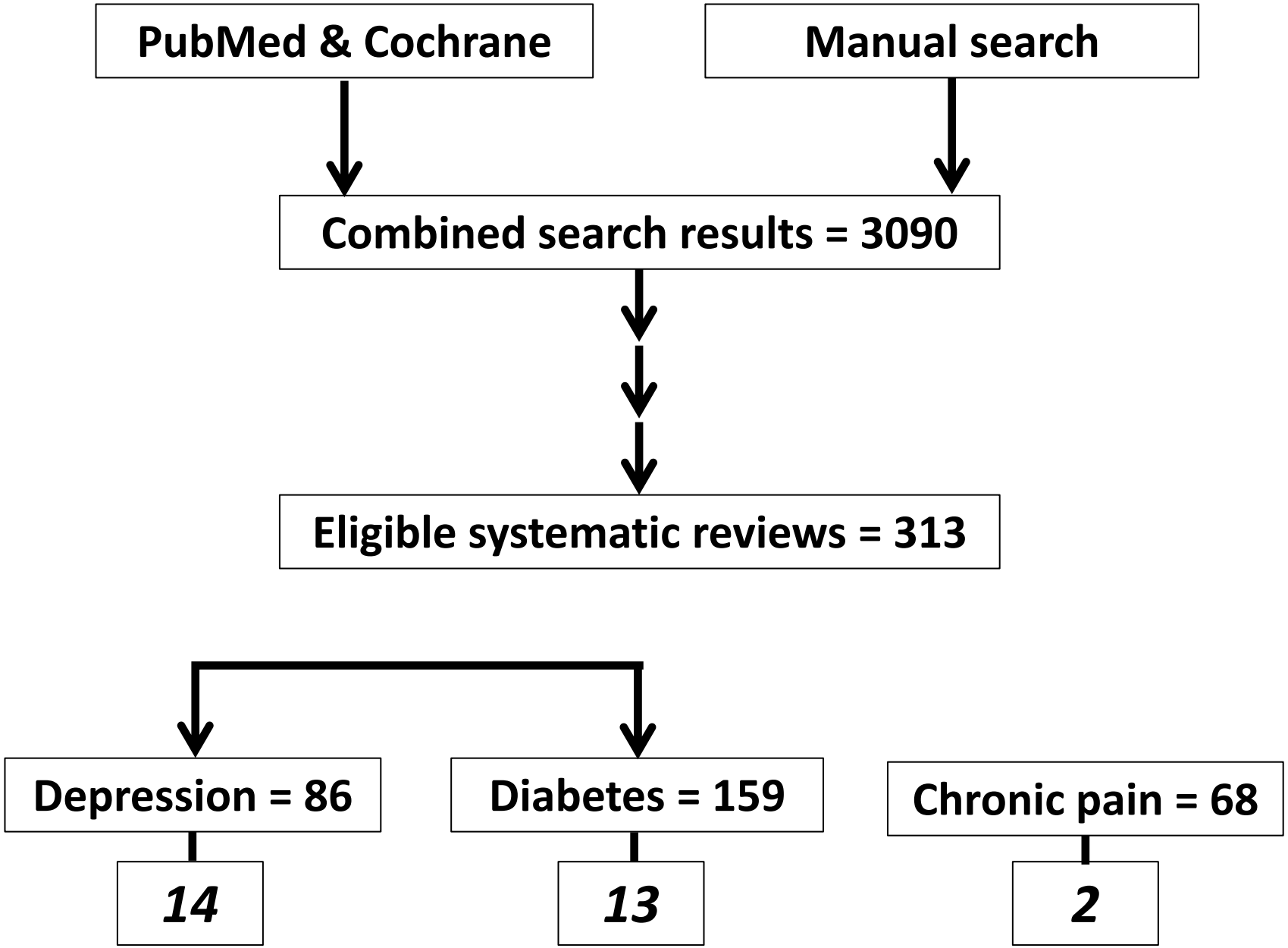
PubMed & Cochrane
Manual search
Combined search results = 3090
Eligible systematic reviews = 313
Depression = 86
Diabetes = 159
Chronic pain = 68
14
13
2

Medications

Behavioral & Psychotherapy

Exercise

Quality Improvement

Depression

Diabetes

Chronic Pain Conditions

- Chronic Low Back Pain
- Fibromyalgia
- Knee Osteoarthritis

Studies in Largest Reviews

- > 100
- 81-100
- 61-80
- 41-60
- 21-40
- 1-20

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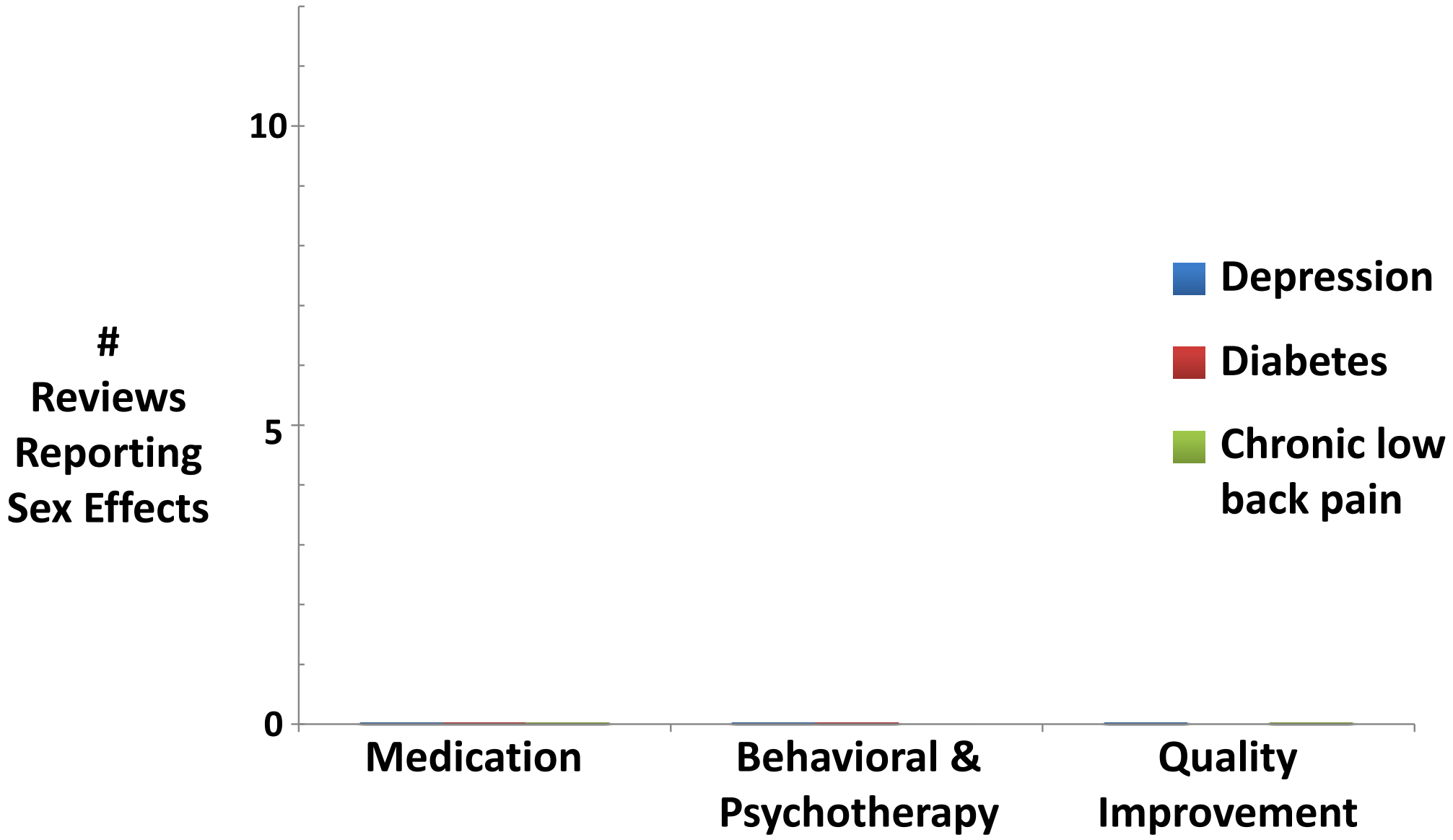
Reviews Reporting Sex Effects
10
5
0
Medication
Behavioral & Psychotherapy
Quality Improvement
Depression
Diabetes
Chronic low back pain

Intervention	Outcome	Analysis Method	Sex Effect	Industry Funding?	Considered Power?

Calati *et al.* (2013) *J Affect Disord* **147**:1.

Conditions	Outcomes	SEX EFFECTS		
		Meta-regression	IPD Meta-analysis and Subgroup Analysis	Qualitative Synthesis

ions

	Possible differences in sex effects between men and women	Possibly no differences in effects between men and women
Depression	• SSRIs in older adults • Duloxetine • Cognitive behavioral therapy • *Paroxetine*	• Combined meds & psychotherapy • QI • Self-help • *Antidepressants, overall*

Primary RCTs for Selected Interventions

DEPRESSION	DIABETES	CHRONIC PAIN
▪ Psychotherapy	▪ Diet	▪ Exercise
▪ Collaborative care	▪ Mixed behavioral	▪ Behavioral
	▪ Psychoeducation	

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Gaps in Evidence

- 9% of reviews reported sex or gender differences
  →**70% use meta-regression**

- Lack of info on sex distribution of studies

- Lack of adequately large RCTs
  → **Few report analyses or effects**

How should we prioritize?

- ❑ **Basic science, preclinical, and or early-phase clinical studies**
- ❑ **Observational studies or small RCTs**
- ❑ **Unique biological events**
- ❑ **Conceptual models about behavioral & sociocultural factors**

Steps in the Near Future?

Systematic Reviews:

- Report sex distribution of included trials
- Engage trial collaboratives to access individual patient data

Limitations

- No formal quality evaluation
- Only reviews published since 2009
- Industry-funded reviews that lacked systematic searches

Thank you!

- Supported by:
  - VHA QUERI (VA-ESP Project No. 09-009; 2015)
  - VA Office of Academic Affiliations (No. TPP 21-022)
- Key stakeholder groups:
  - HSR&D Center for the Study of Healthcare Innovation
  - Women's Health Research Network
  - Women's Health Services
  - Mental Health Services
- DVAMC ESP team members:
  - Jennifer McDuffie
  - Jaime M. Hughes
  - Megan E. B. Clowse
  - Ruth Klap
  - Varsha Masilamani
  - Nancy M. Allen LaPointe
  - Avishek Nagi

VA Women's Health Research Network

SDR 10-012 (PIs: Yano/Frayne/Hamilton)

Consortium

- Train/educate, foster research-clinical partnerships
- Technical consultation, mentorship, dissemination
  - e.g.: Consultation on WH Research
  - e.g.: Consultation on WH QI

Elizabeth Yano, PhD, MSPH
Director, VA Women's Health Consortium
Director, Center for the Study of Healthcare Innovation, Implementation and Policy (CSHIIP)
VA Greater Los Angeles Healthcare System
Adjunct Professor, UCLA School of Public Health

Practice-Based Research Network (PBRN)

- Ready-to-use infrastructure of 60 VA sites facilitating multi-site interventions and implementation projects
  - Represents more than 1 in 2 Women Veterans nationally (i.e.; about 200,000 women veterans)

Susan Frayne, MD, MPH
Director, VA Women's Health Practice-Based Research Network
Center for Innovation to Implementation (Ci2i)
VA Palo Alto Health Care System
Professor, Stanford University School of Medicine

Discussant:
Elizabeth Yano, PhD, MSPH

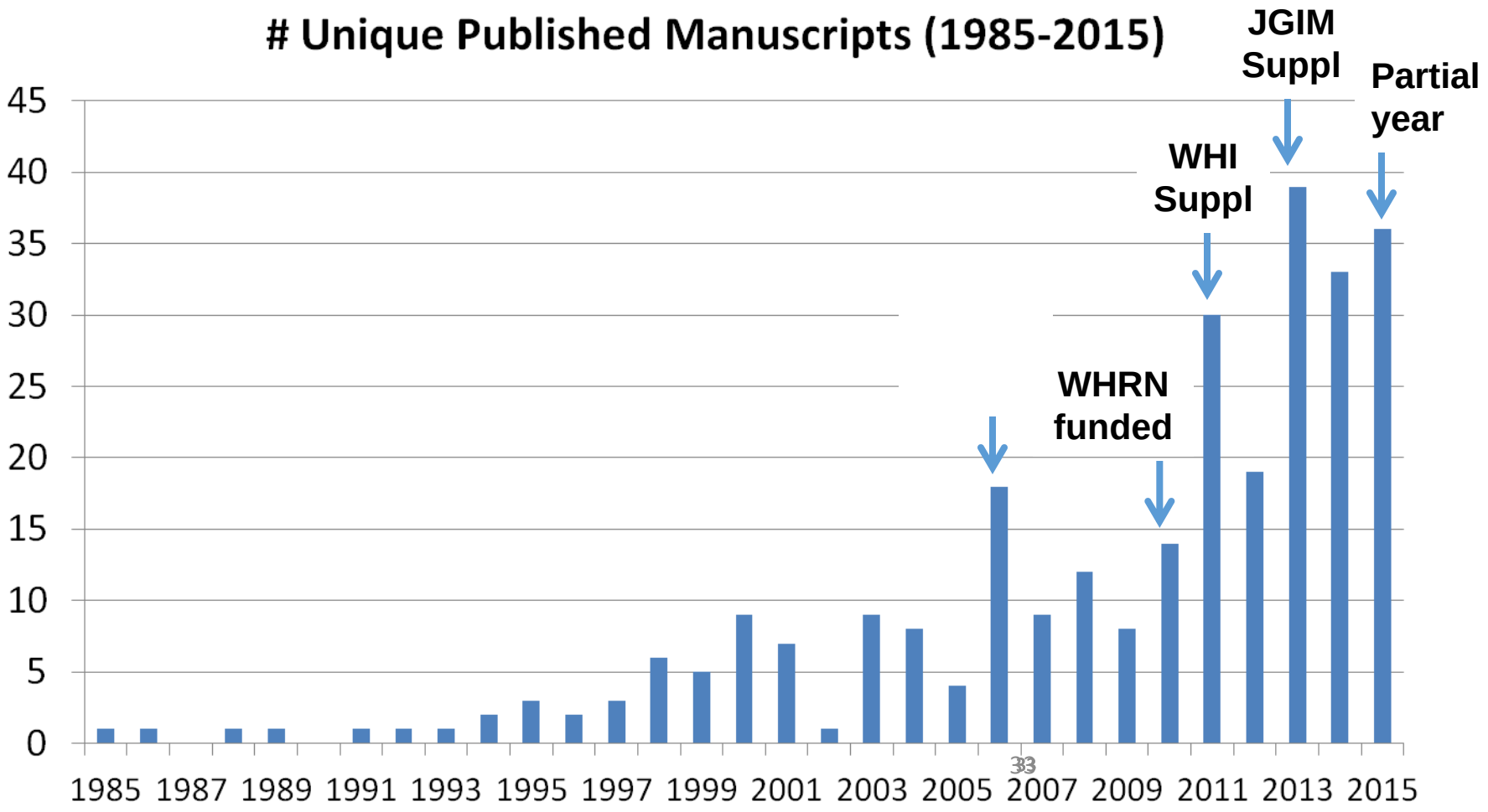
WHRN Goal of Increasing Dissemination: *Evidence Reviews and Updates*

- **Systematic reviews (knowledge synthesis)**
  - 1st systematic review (Goldzweig, JGIM, 2006)
  - 2nd systematic review (Bean-Mayberry, WHI, 2011)
    - "More articles published in the past 5 years than the previous 25 years combined…" (thru 2008)
  - Evidence map (Durham ESP, today's presentation)
    - Can we capitalize on knowledge of gender differences outside VA research?
  - 3rd systematic review *underway* (Minneapolis ESP)
    - Seven years since last review…will focus on overview (not RCTs)

CSHIIP
Center for the Study of Healthcare Innovation, Implementation & Policy

CONSORTIUM • PBRN
VA WOMEN'S HEALTH RESEARCH NETWORK
Supporting Practice and Research Collaboration

Dissemination: *Growth of Published Research Literature on Women Veterans*



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Importance of Durham's Evidence Map of Sex & Gender Differences for VA

- Durham ESP review notes major shifts in scientific policy to record *and enforce* evaluation of sex and gender differences
- Major gaps in reporting of sex/gender differences
  - Often adjusted for, not reported out, if analyzed at all
  - Applicability of available scientific evidence to women not always clear
- In VA, means women Veterans do not equitably benefit from VA's investment in research
  - Need to evaluate sex/gender differences and determine when interventions should be tailored to meet needs

Resources & References

- VHA ESP report http://www.hsrd.research.va.gov/publications/esp
- HSR&D Women's Health Research http://www.hsrd.research.va.gov/for_researchers/womens_health/
- NIH Office of Research on Women's Health http://orwh.od.nih/gov/resources
- Methods:
  - Bragge et al. (2011) *BMC Med Res Methodol* **11**:92.
  - Riley et al. (2010) *BMJ* **340**:c221
  - *AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (2015) http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318

Questions?

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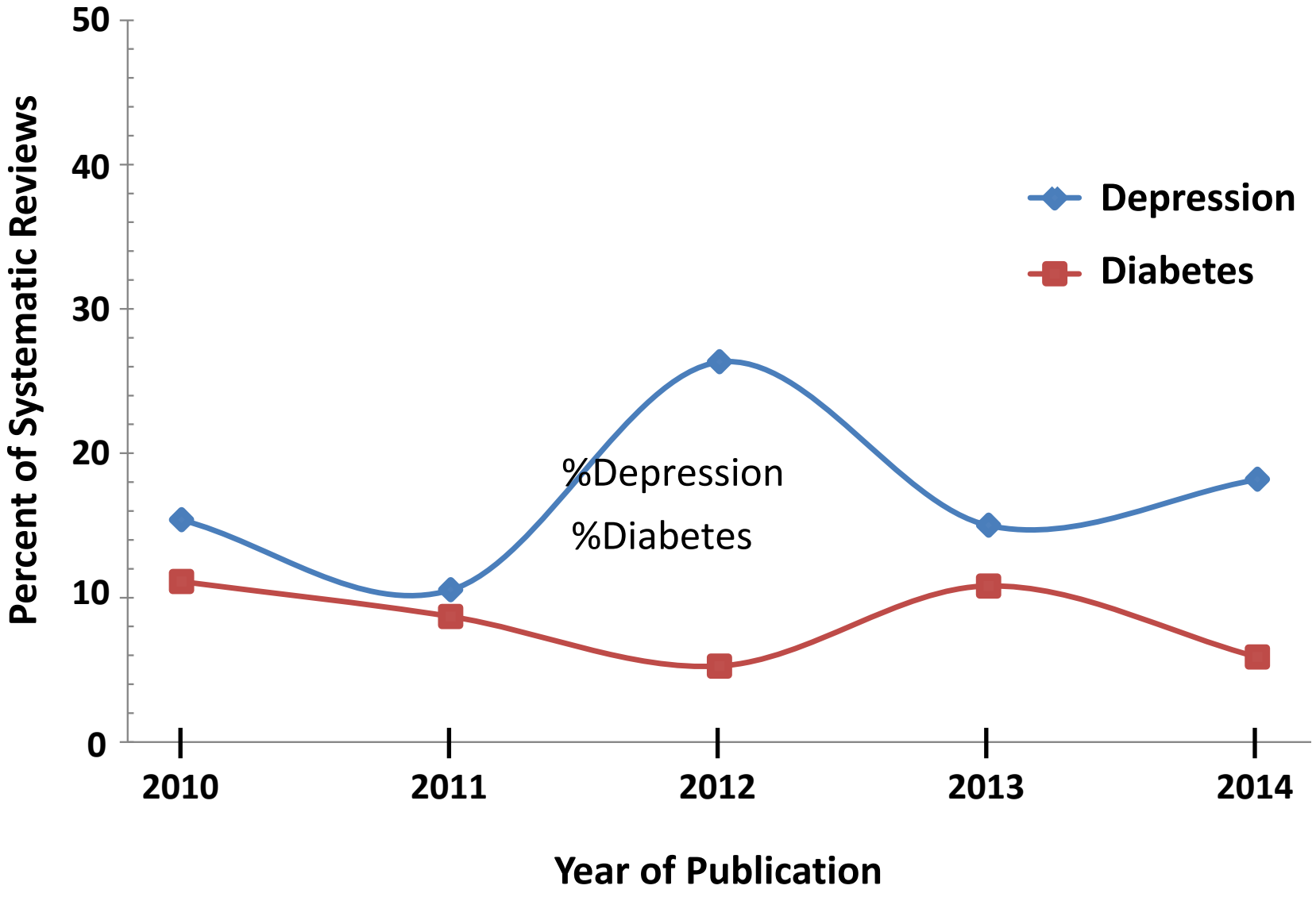
Percent of Systematic Reviews
50
40
30
20
10
0
2010
2011
2012
2013
2014
Year of Publication
Depression
Diabetes
%Depression
%Diabetes