

Smoking in Women and Girls:

Kathleen Brady, MD, PhD

Distinguished University Professor

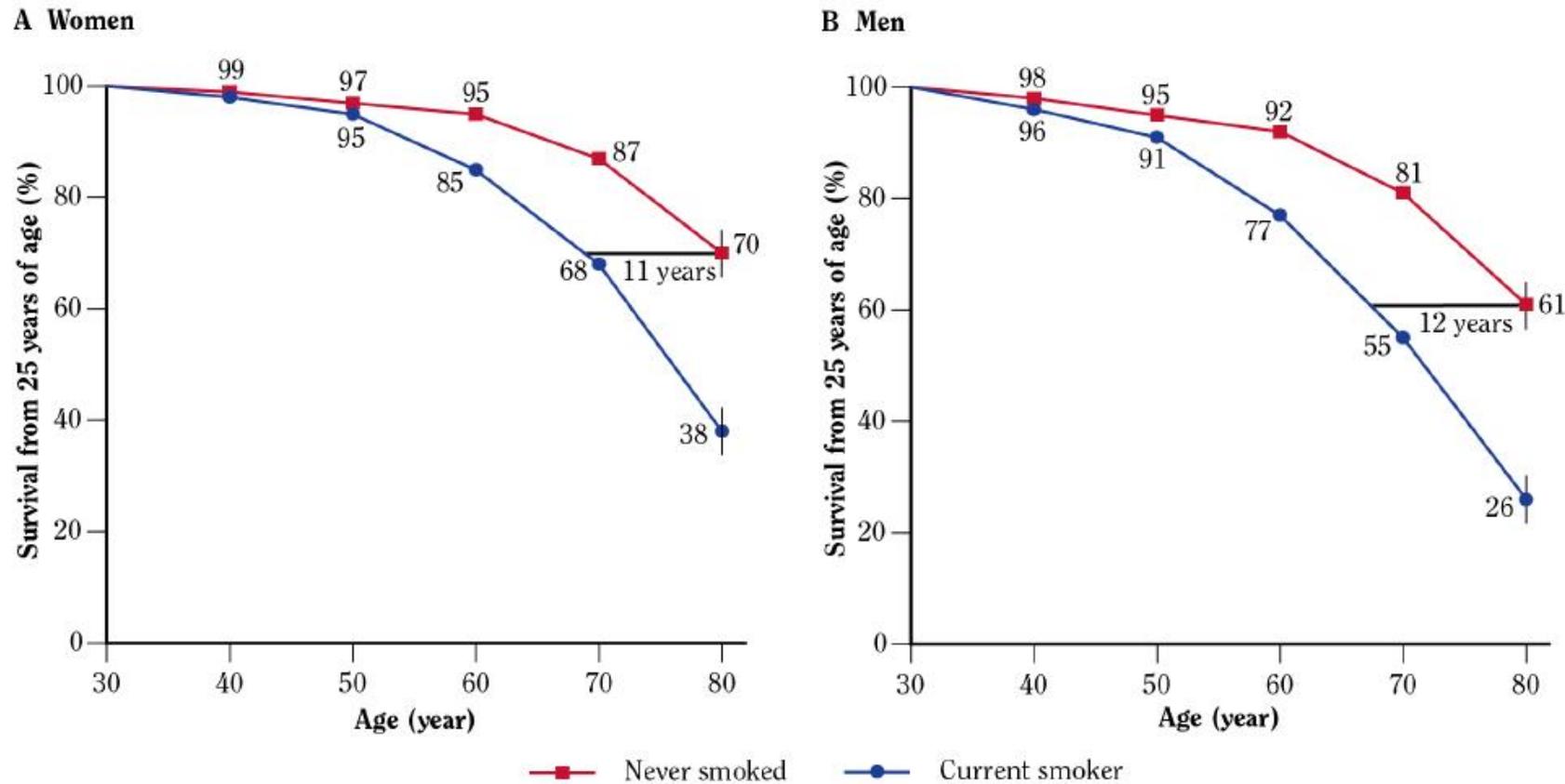
Medical University South Carolina



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Figure 11.6 Survival probabilities for current smokers and never smokers for women and men



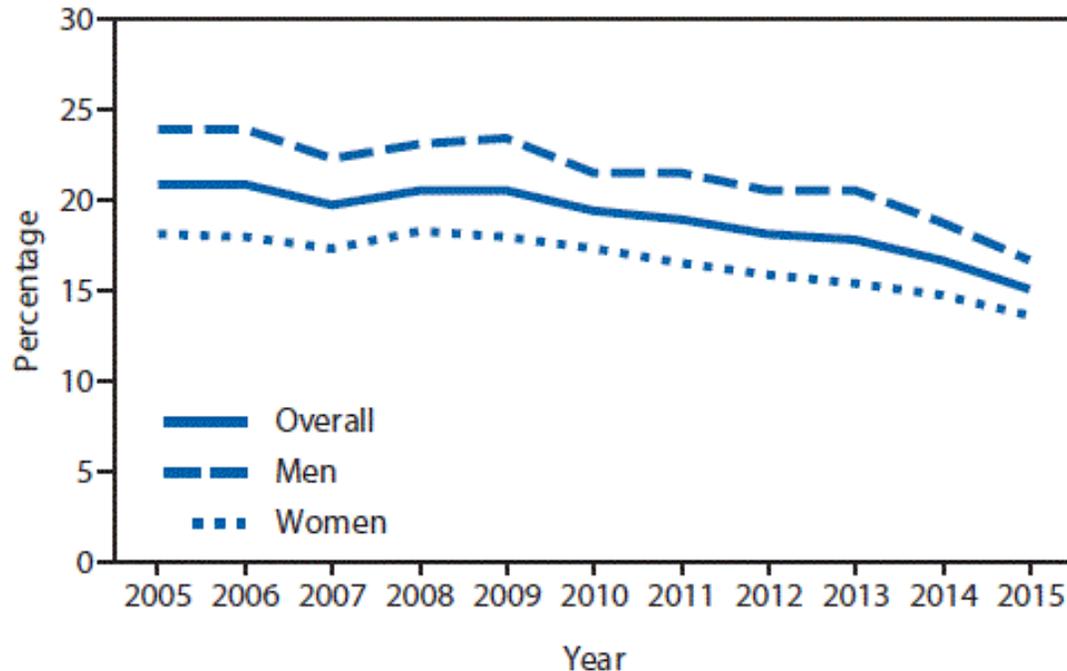
Source: Jha et al. 2013. Reprinted with permission from Massachusetts Medical Society, © 2013.

Note: Survival probabilities for current smokers and never smokers among men and women 25–80 years of age. The vertical lines at 80 years of age represent the 99% cumulative survival probabilities, as derived from the standard errors estimated with use of the jackknife procedure. Survival probabilities have been scaled from the National Health Interview Survey to the U.S. rates of death from all causes at these ages for 2004, with adjustments for differences in age, educational level, alcohol consumption, and adiposity (body mass index).

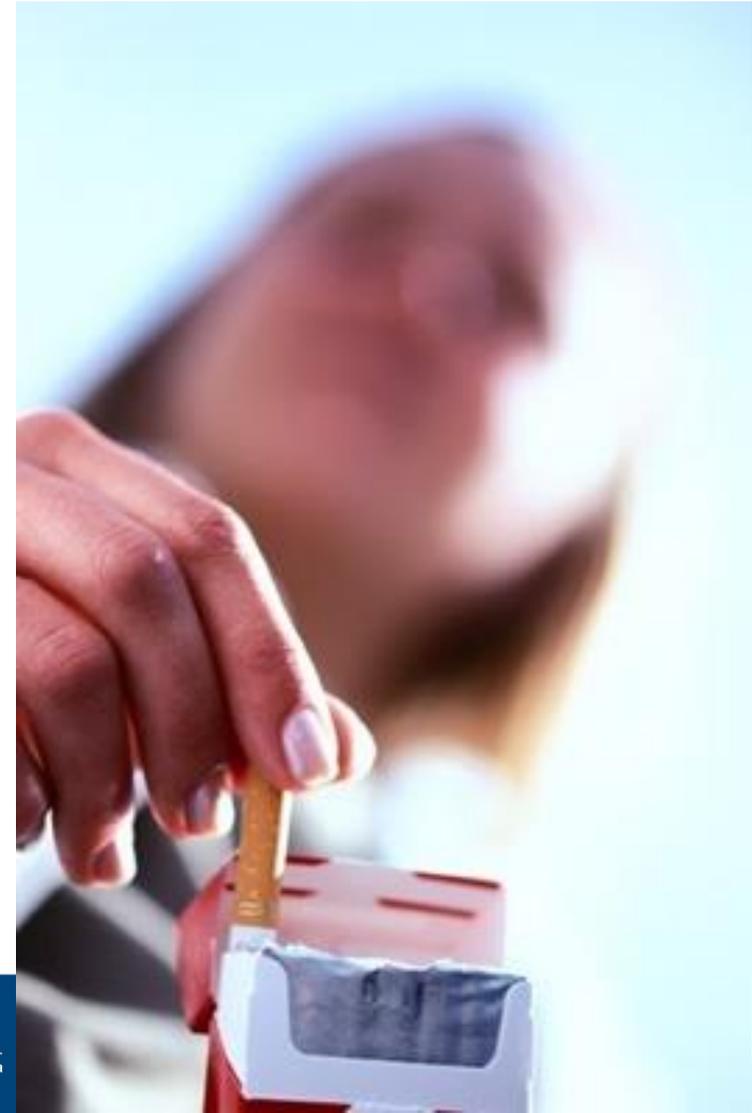


US Prevalence Rates

Percentage of adults who were current cigarette smokers,* overall and by sex – National Health Interview Survey, United States, 2005–2015



2021:
13.1% men
10.1% women



Substance Use Disorders: 2013 – 2019

National Survey on Drug Use and Health. (NSDUH)

Age (yrs)	Men 2013 (%)	Women 2013(%)	Ratio	Men 2019(%)	Women 2019(%)	Ratio
12+	10.8	5.8	2:1	9.4	5.5	1.7:1
18+	11.4	5.8	2:1	10.0	5.6	1.8:1
12-17	5.3	5.2	1:1	4.0	5.0	0.8:1



Male-to-Female Smoking Ratios by World Health Organization Region

	ADULTS	YOUTH
Africa	7.2 to 1	2.2 to 1
Americas	1.6 to 1	1.2 to 1
Eastern Mediterranean	8.8 to 1	4.3 to 1
Europe	1.8 to 1	1.2 to 1
Southeast Asia	11.0 to 1	4.2 to 1
Western Pacific	7.5 to 1	1.7 to 1



Cigarette Smoking Among Youth at the Intersection of Sexual Orientation and Gender Identity

(Wheldon et al, 2019)

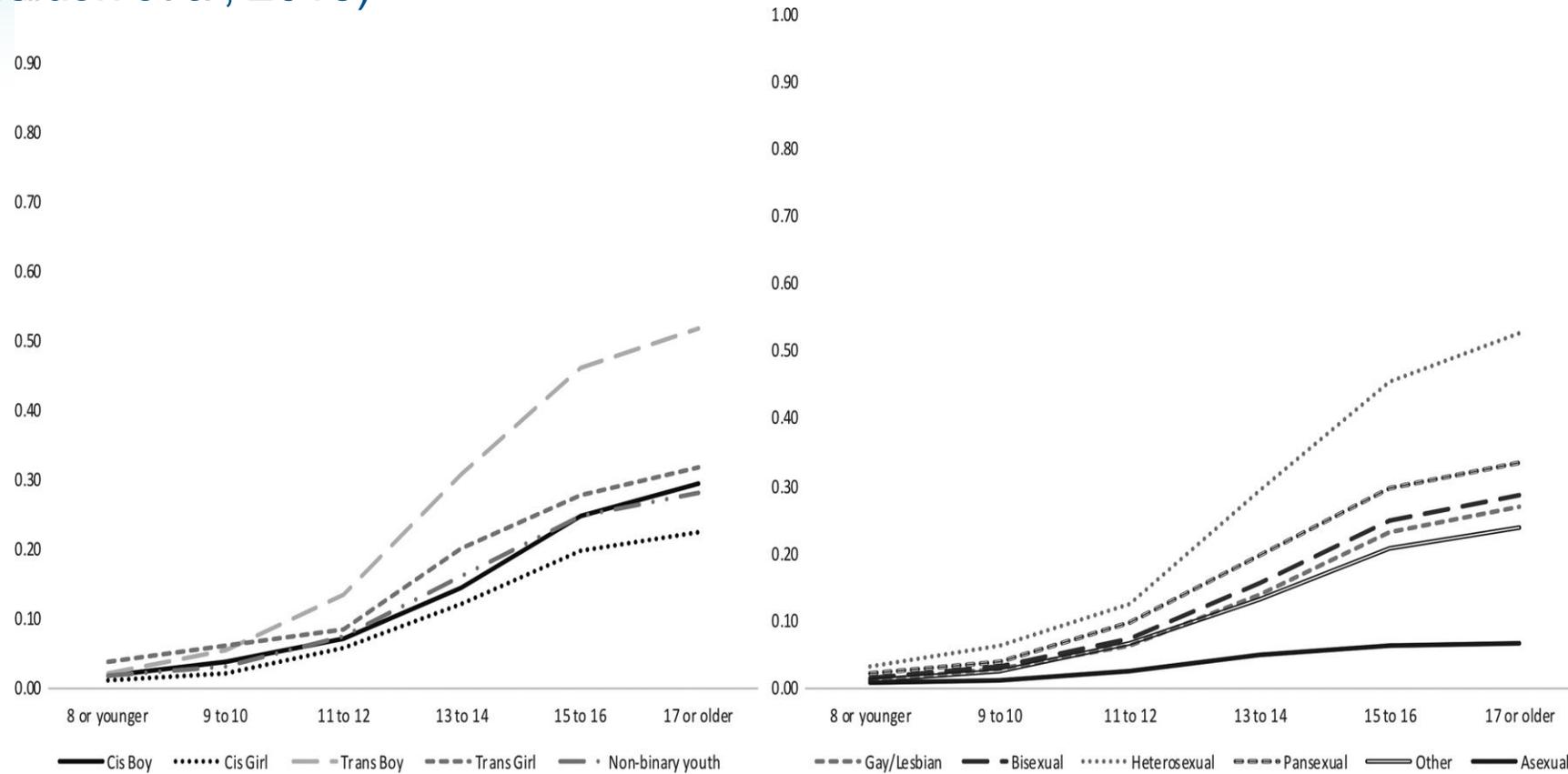


FIG. 2. Cumulative incidence plots of age at first cigarette smoking by gender identity and sexual identity: The LGBTQ National Teen Survey. Cis, cisgender; Trans, transgender.



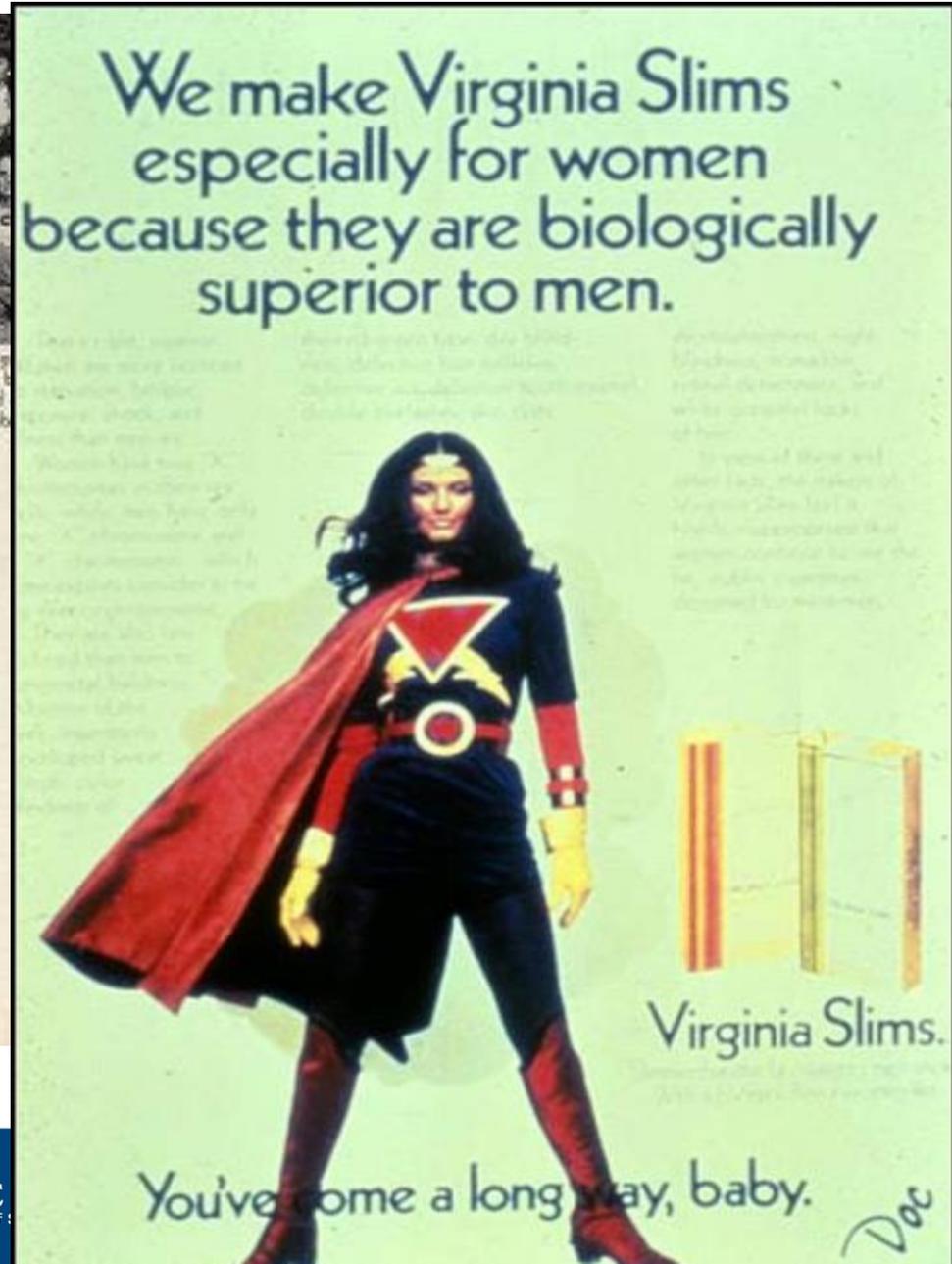
Gender differences in susceptibility to smoking among high school students

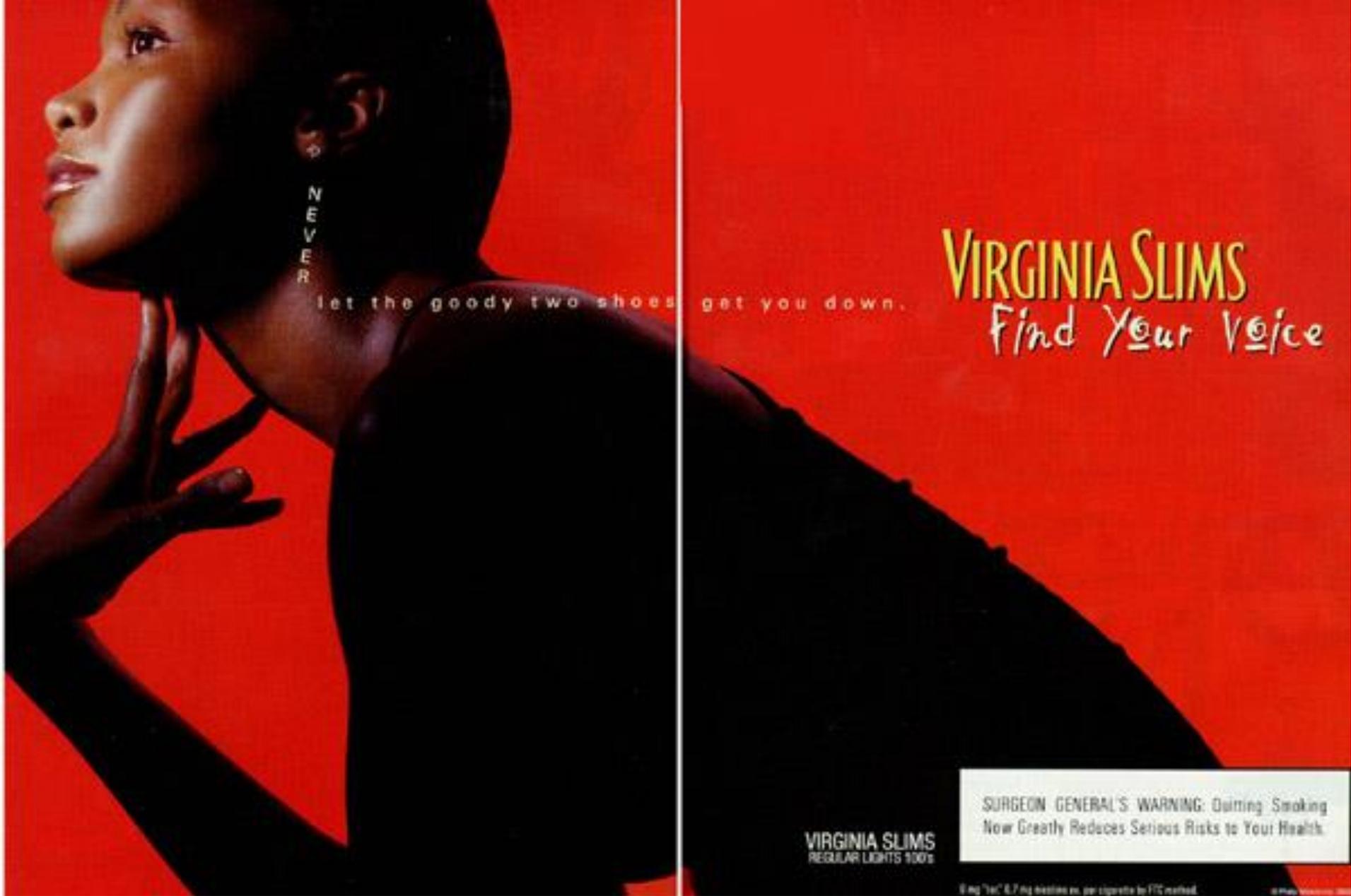
(Santano-Mogena et al., 2023)

Females:
greater cigarette use
greater alcohol use
more likely to have smoking friends



1 Mrs. Violet Anderson claims to have smoked her first cigarette on May 19, 1910... in the attic of her home in...
2 Cynthia Irene Bell smoked her first cigarette behind the old barn out back on Jan. 4, 1910...
3 Myra F. Phillips confesses she smoked March 4 or 5, 1911, out in the country, where only a squirrel could see her. The ladies offered "no comment." You've come a long way. Now there's a new slim for all your oves.





NEVER

let the goody two shoes get you down.

VIRGINIA SLIMS

Find Your Voice

VIRGINIA SLIMS
REGULAR LIGHTS 100's

SURGEON GENERAL'S WARNING: Quitting Smoking
Now Greatly Reduces Serious Risks to Your Health.

8 mg "tar" 0.7 mg nicotine av. per cigarette by FTC method.



A woman with dark skin and long black hair is smiling and looking to the right. She is wearing a colorful headwrap with red, blue, and yellow patterns, and a beaded necklace. She is carrying a large, wrapped bundle on her head. The background is a soft, out-of-focus green and yellow.

Kila mtu
ana uzuri
wake

NO SINGLE INSTITUTION OWNS THE COPYRIGHT
FOR BEAUTY.

VIRGINIA SLIMS
Find Your Voice

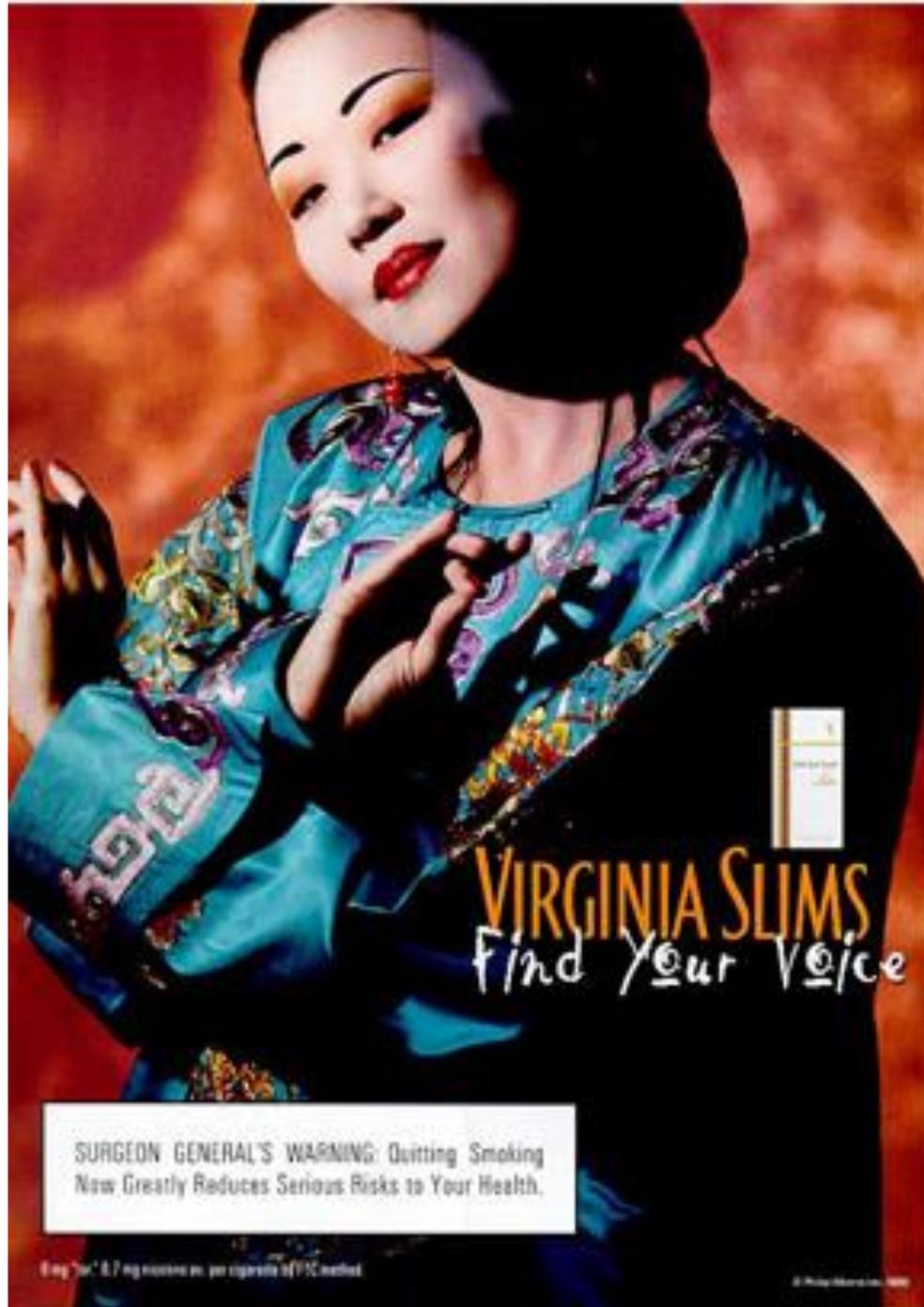
SURGEON GENERAL'S WARNING: Smoking
By Pregnant Women May Result in Fetal
Injury, Premature Birth, And Low Birth Weight.

VIRGINIA SLIMS
REGULAR LIGHTS 100%

1 mg "tar," 0.7 mg nicotine av. per cigarette by FTC method.

© 1999 B&W T Co.





VIRGINIA SLIMS
Find Your Voice

SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.

8 mg "tar," 0.7 mg nicotine av. per cigarette by FTC method.

© Philip Morris Inc. 1999

MY *voice*

REVEALS
THE HIDDEN POWER WITHIN

SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.

VIRGINIA SLIMS
REGULAR LIGHTS 100'S

8 mg "tar," 0.7 mg nicotine av. per cigarette by FTC method.



Women smokers have more difficulty quitting

Preventive Medicine 92 (2016) 135–140

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Sex/gender differences in smoking cessation: A review

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ABSTRACT

Data from treatment studies tends to show women are less likely to quit smoking than men, but these findings have been disputed, typically based on contradictory evidence from epidemiological investigations. The purpose of this review was to shed light on this conflict. We conducted a qualitative review in January 2016 to examine sources of variation in sex/gender differences for smoking cessation. We identified 214 sex/gender difference tests from 190 studies through Medline and studies were categorized into efficacy trials ($k = 37$), effectiveness trials ($k = 77$), prospective observational studies of cessation ($k = 40$; current smokers transitioning to former smokers), prospective observational studies of relapse ($k = 6$; former smokers transitioning to current smokers), cross-sectional investigations of former smoker prevalence ($k = 32$), and community-based interventions ($k = 4$). We also summarized evidence across time periods, countries, outcome assessments, study sample, and treatment. Evidence from efficacy and effectiveness trials, as well as prospective observational studies of relapse, demonstrated that women have more difficulty maintaining long-term abstinence than men. Findings from prospective observational studies and cross-sectional investigations were mixed and demonstrated that bio-psycho-social variation in samples across place and time may determine whether or not women or men are less likely to quit smoking. Based on these findings, we consider whether sex/gender differences in quitting meet criteria for a disparity and outline directions for further research.

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1. Main text

Cigarette smoking continues to be the leading cause of preventable death and disease in the United States (U.S.), killing approximately 556,000 Americans annually (Carter et al., 2015). While tobacco control efforts have had remarkable success in the past 50 years reducing the number of cigarettes smoked, the number of people who smoke has not declined proportionally. We refer to differences between women and men as “sex/gender” differences to incorporate the biological and social dimensions of sex and gender that are captured in investigations of smoking cessation.

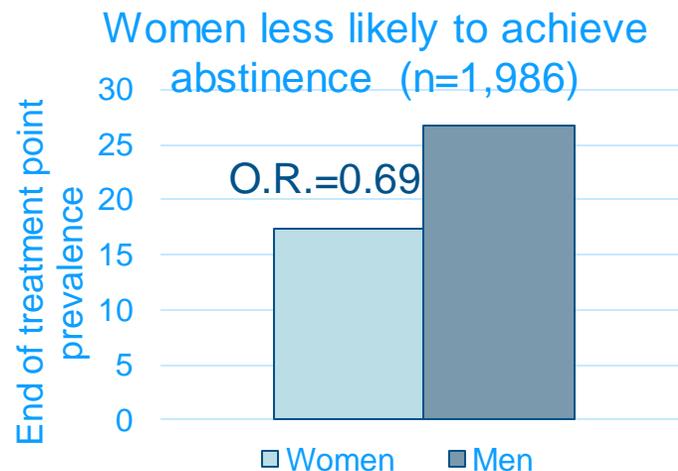
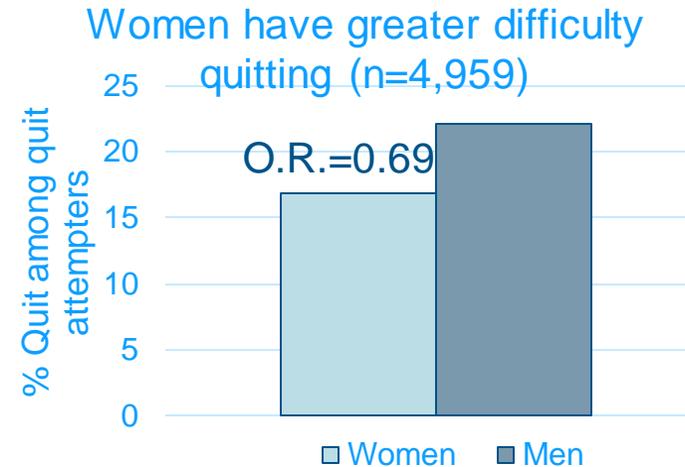
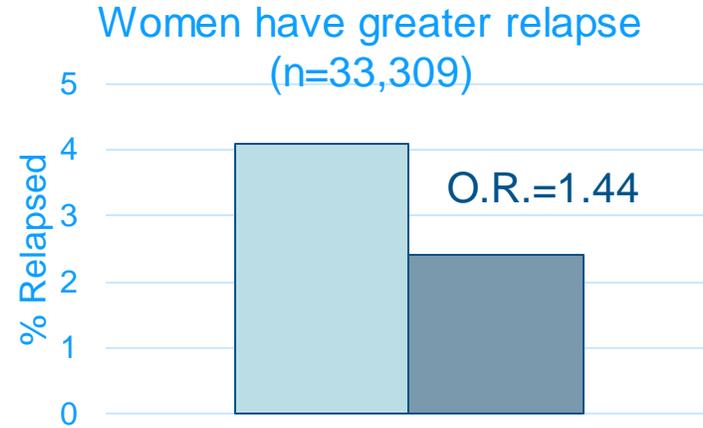
Observed differences between men and women in the success with which individuals achieve smoking cessation (e.g., Gritz et al., 1996; Taylor et al., 2003) have been consistently reported. For example, Taylor et al. (2003) reported that women were less likely to achieve long-term abstinence than men in a community-based intervention. In a meta-analysis of 190 studies, we found that women were less likely to achieve long-term abstinence than men in 190 studies.

Summarized 190 studies.

Women have more difficulty maintaining long-term abstinence than men



Women smokers have more difficulty quitting



- Similar findings in quit behavior across large population-based studies, pooled clinical trial findings, and international samples of naturalistic quitting

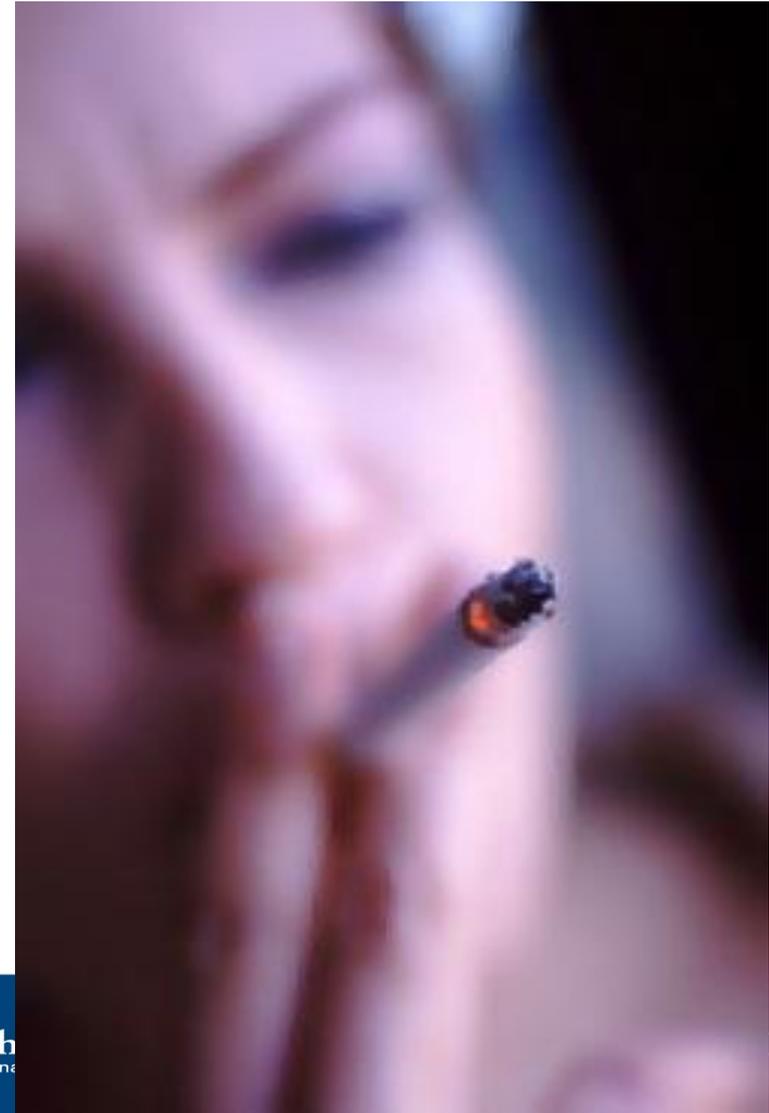
Weinberger...McKee, 2014; Smith...McKee, 2015, McKee et al., 2015

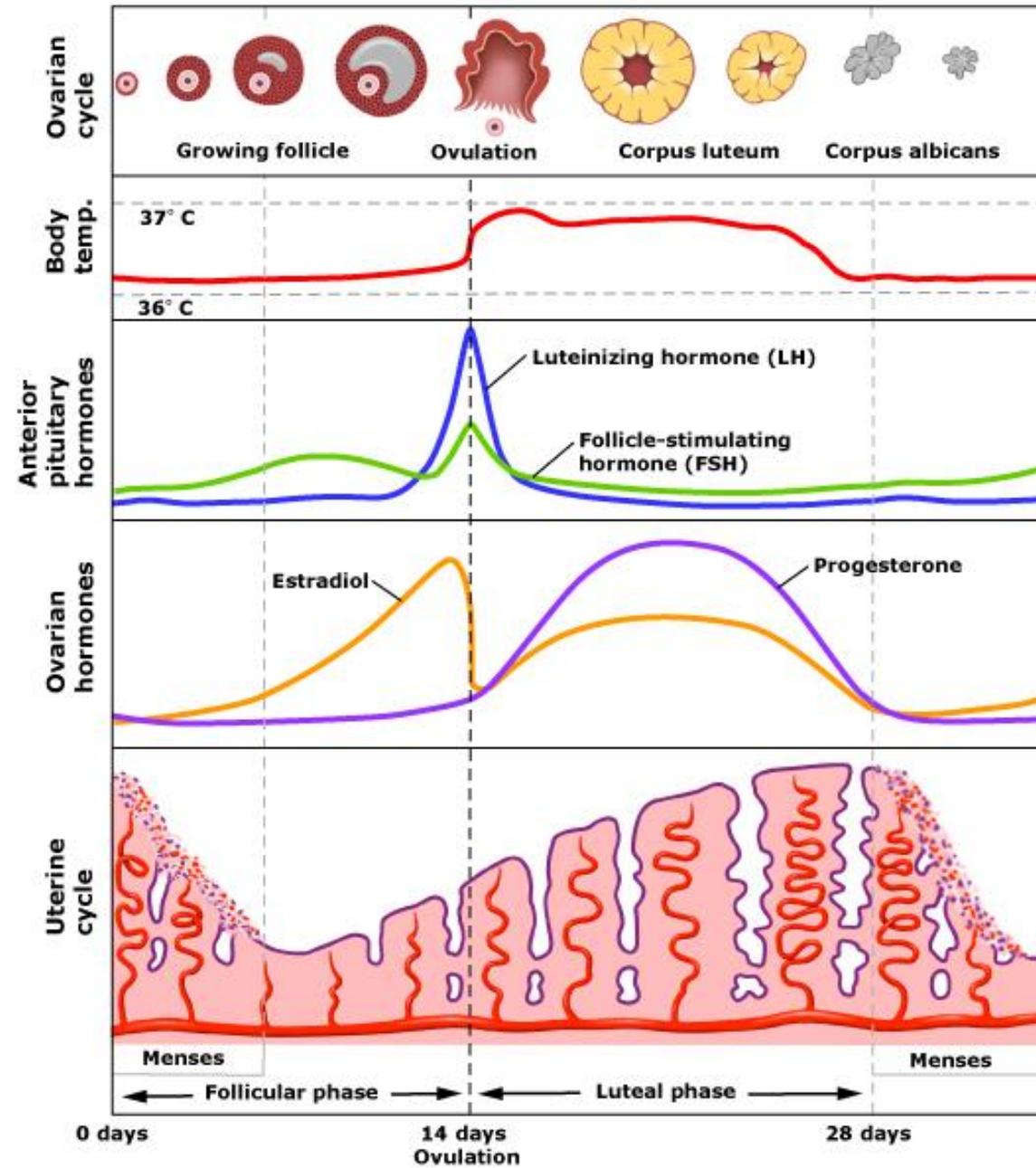


Why do women have more difficulty quitting smoking?

Factors underlying poor treatment response in women

- ❑ reproductive status & hormones
 - ❑ psychiatric co-morbidities
 - ❑ weight management
 - ❑ stress & negative affect
- › medication response





Animal Literature

Fairly substantial animal literature

However, most studies involve non-nicotine reinforcers

- › especially cocaine

A few notable generalizations from this literature are

- › (see reviews by: Lynch, Roth, & Carroll, 2002; Anker & Carroll, 2010; Carroll & Anker, 2010; Hudson & Stamp, 2011)
- › **Estradiol** enhances drug reward and facilitates reinstatement
- › **Progesterone** dampens drug-seeking behavior



Human Laboratory research

Administration of progesterone vs. placebo

- › Progesterone attenuated craving in response to smoking and...
- › Trend level evidence of reduced smoking during self-administration task (Sofuoglu, Babb, & Hatsukami, 2001)

- › Progesterone decreased self-report 'liking' of IV nicotine and increased self-report 'bad effects' (Sofuoglu, Mitchell, & Mooney, 2009)

- › Progesterone reduced ambient craving & increased cognitive performance (Stroop task; Sofuoglu et al., 2011)



Reproductive status & hormones

Nicotine & Tobacco Research, 2015, 407–421
doi:10.1093/ntr/ntu249
Review

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Review

Systematic and Meta-Analytic Review of Research Examining the Impact of Menstrual Cycle Phase and Ovarian Hormones on Smoking and Cessation

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Abstract

Introduction: To determine the effect of ovarian hormones on smoking, we conducted a systematic review of menstrual cycle effects on smoking (i.e., ad lib smoking, smoking topography, and subjective effects) and cessation-related behaviors (i.e., cessation, withdrawal, tonic craving, and cue-induced craving).

Methods: Thirty-six papers were identified on MEDLINE that included a menstrual-related search term (e.g., menstrual cycle, ovarian hormones), a smoking-related search term (e.g., smoking, nicotine), and met all inclusion criteria. Thirty-two studies examined menstrual phase, 1 study measured hormone levels, and 3 studies administered progesterone.

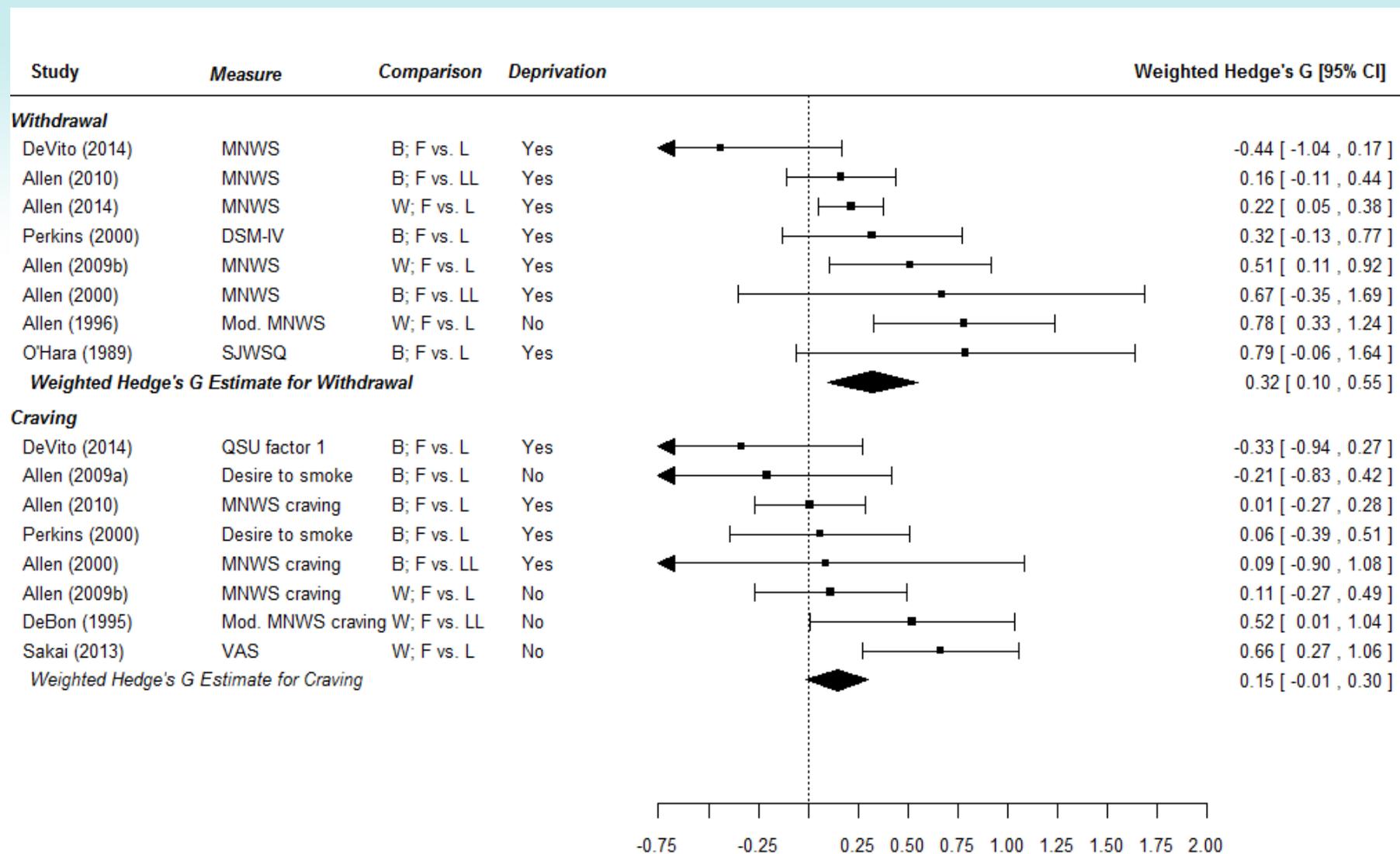
Results: Sufficient data were available to conduct meta-analyses for only 2 of the 7 variables: withdrawal and tonic craving. Women reported greater withdrawal during the luteal phase than during the follicular phase, and there was a nonsignificant trend for greater tonic craving in the

Systematic review & meta-analysis of menstrual cycle and ovarian hormone effects on smoking

ad-lib smoking, cessation, relapse, withdrawal, and craving

36 studies identified

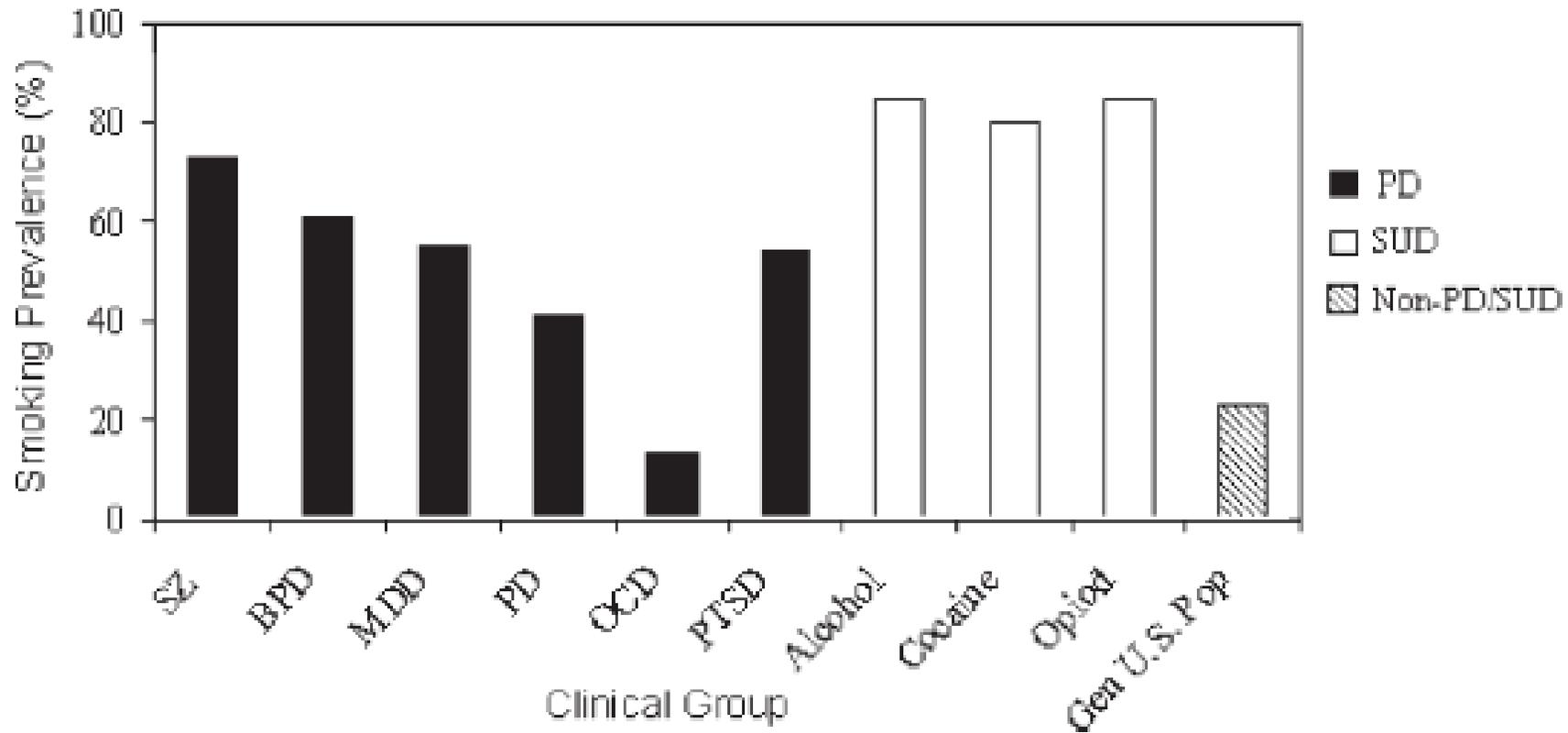




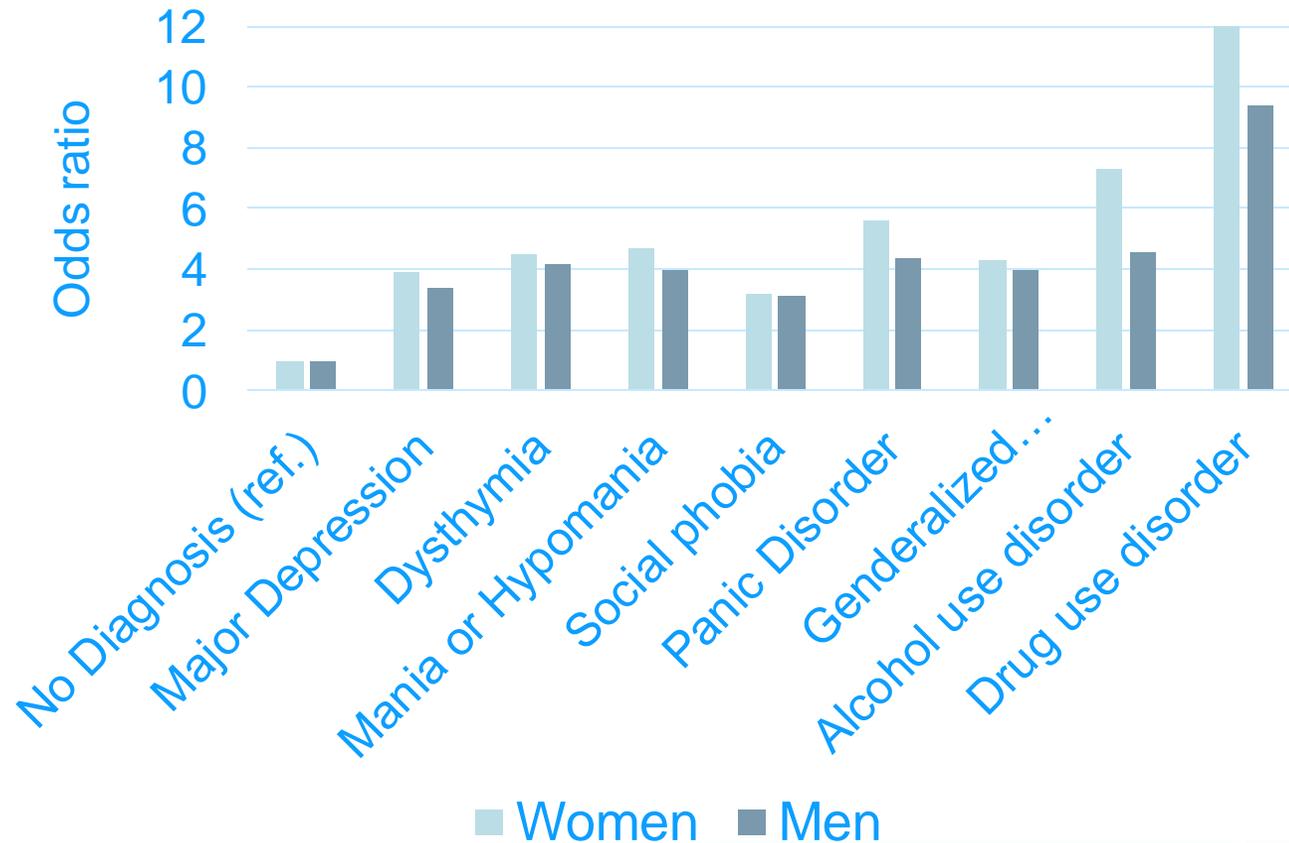
Women reported greater withdrawal and craving during the luteal phase compared to the follicular phase.



Smoking and Psychiatric Illness



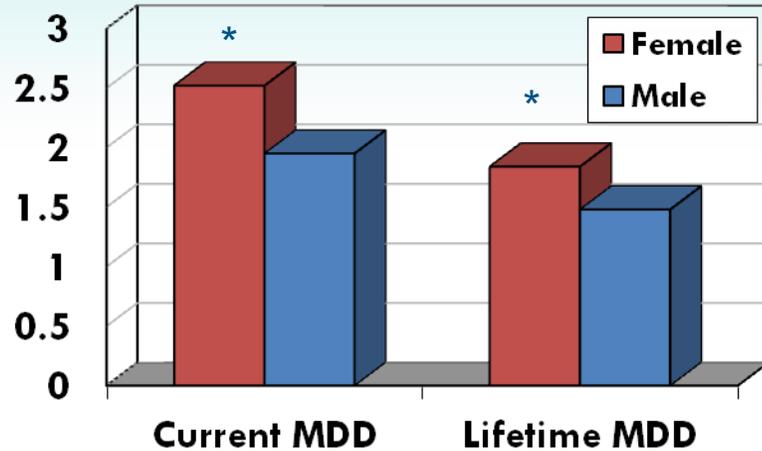
Psychiatric co-morbidities



Past-year psychiatric diagnoses more strongly associated with past-year smoking among women compared to men

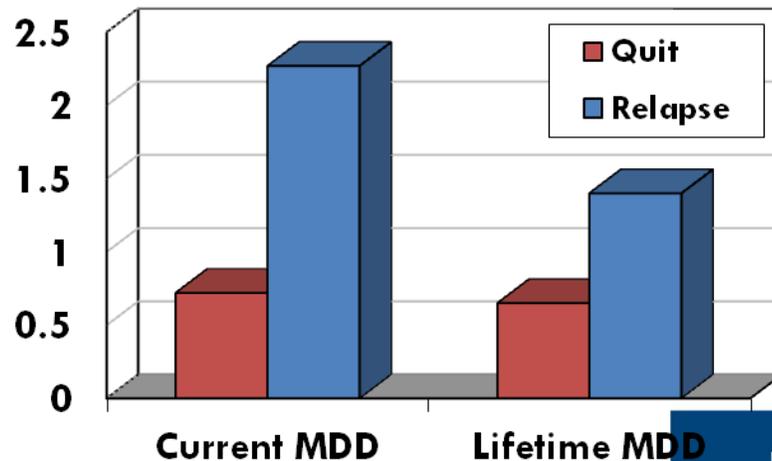


Odds ratios of daily smoking status by depression diagnosis by gender, n=43,093



Husky et al, 2008, DAD

Odds ratios of transitions in smoking status by depression diagnosis, n=34,653



Weinberger et al., 2012, Addiction

Women vs men

- are 2x more likely to present with current MDD (16% vs. 7.9%)

- have stronger associations between smoking and MDD

- depression is associated with decreased ability to quit and increased likelihood of relapse



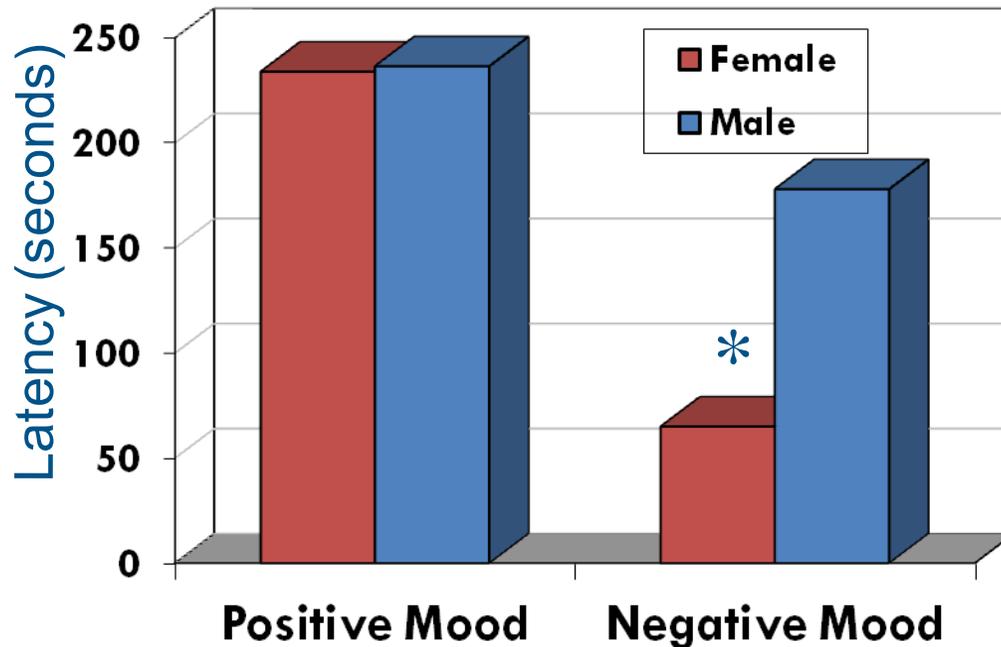
Stress & smoking

- ❑ Stress is a primary mechanism involved in the maintenance of *(Ikard et al., 1969)*, and relapse to smoking *(Shiffman et al. 2004)*
- ❑ Smokers (35% to 100%) identify stress as a causal factor in accounts of relapse *(Marlatt & Gorden, 1980; Brandon, 1994; Shiffman, 1982)*
- ❑ Smokers believe that smoking will alleviate negative affect *(Brandon & Baker, 1991)*
- ❑ Smoking lapse, triggered by stress, progress more quickly to relapse *(Shiffman et al., 1996)*



Negative affect & stress

Negative mood reduces latency (seconds) to smoke in females



Across several laboratory studies, smoking in women vs men more likely to be negatively influenced by stress and negative affect



Gender Differences in Craving and Cue Reactivity to Smoking and Negative Affect/Stress Cues

(Saladin et al., 2014)

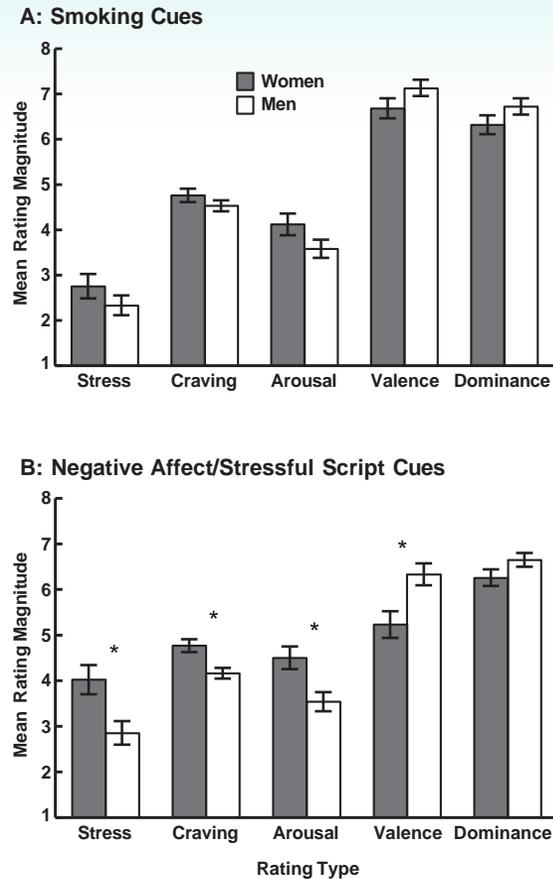


FIGURE 1. Panels A and B depict the mean stress, craving, arousal, valence and dominance rating magnitudes of women versus men smokers in response to smoking cues (A) and negative affect/stressful script cues (B). Means are adjusted for (i) response to control cues (neutral in vivo cues for smoking cues and relaxed script cues for negative affect/stress script cues), (ii) order of smoking versus script cues presentation, and (iii) level of nicotine dependence (as measured by the Fagerstrom Test for Nicotine Dependence (FTND)). * $p < .01$.

Sex Differences in Subjective and Behavioral Responses to Stressful and Smoking Cues Presented in the Natural Environment of Smokers

(Tomko et al., 2018)

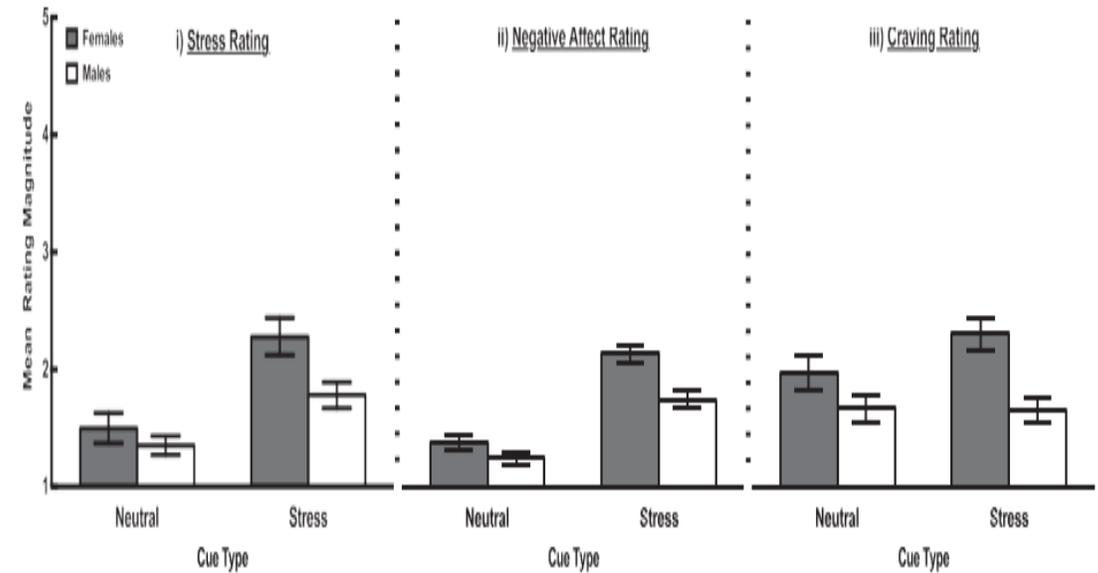


Figure I. Stress (i), negative affect (ii), and craving (iii) ratings of female and male smokers in response to stress versus neutral cues.

To keep a slender figure
No one can deny...



Reach
for a
LUCKY
instead of a
sweet



"It's toasted"
No Throat Irritation—No Cough.

"THE SHADOW
which pursues us all"

John Greenleaf Whittier, 1807-1893

"COMING EVENTS CAST
THEIR SHADOWS BEFORE"
Thomas Campbell, 1761-1841



**AVOID THAT
FUTURE SHADOW**

by refraining from over-
indulgence, if you would
maintain the modern fig-
ure of fashion

We do not represent that
smoking **Lucky Strike** Ciga-
rettes will bring modern figures
or cause the reduction of flesh.
We do declare that when tempt-
ed to do yourself too well, if
you will "Reach for a **Lucky**"
instead, you will thus avoid
over-indulgence in things that
cause excess weight and, by
avoiding over-indulgence, main-
tain a modern, graceful form.

When Tempted
Reach
for a
LUCKY
instead
"It's toasted"



Your Throat Protection—against irritation—against cough.

Women & Weight Gain

- ❑ Smoking controls weight (*Brandon & Baker, 1991*).
- ❑ Concerned about post-cessation weight gain (*Pirie et al., 1991*)
- ❑ Fear of weight gain inhibits quit attempts
- ❑ Identify weight gain as a cause for relapse to smoking (*Swan et al., 1993*)
- ❑ Perkins et al., 2001 – accepting small weight gain improves smoking cessation outcomes



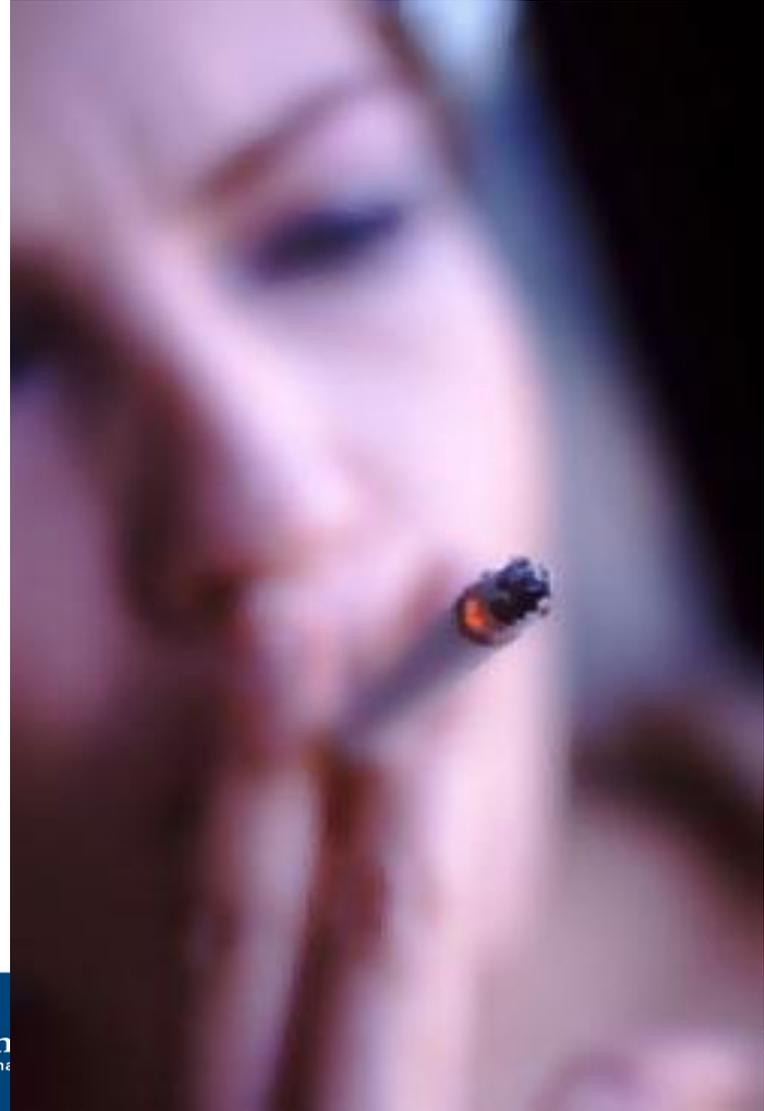
Medication Response

FDA approved medications for smoking cessation

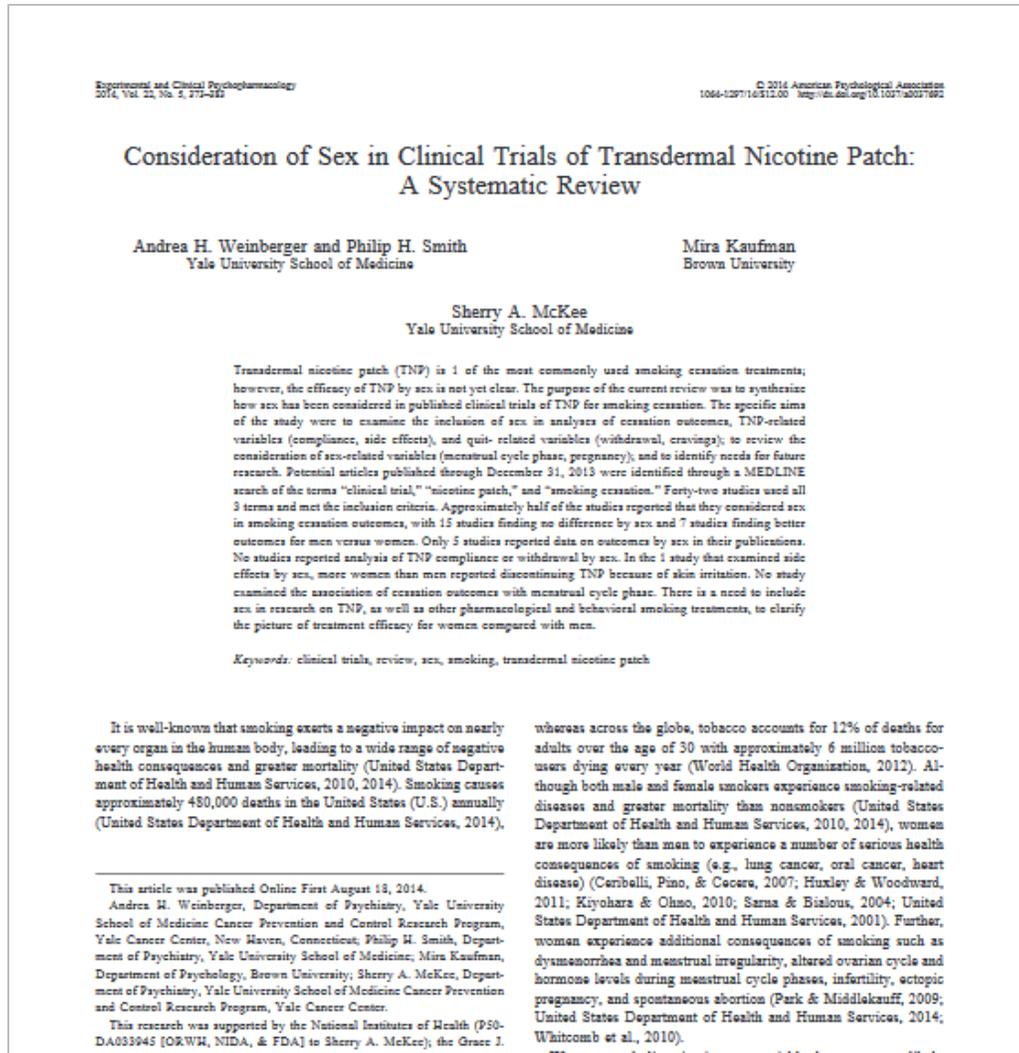
Nicotine replacement (various forms)

Bupropion (Zyban, Wellbutrin)

Varenicline (Chantix)



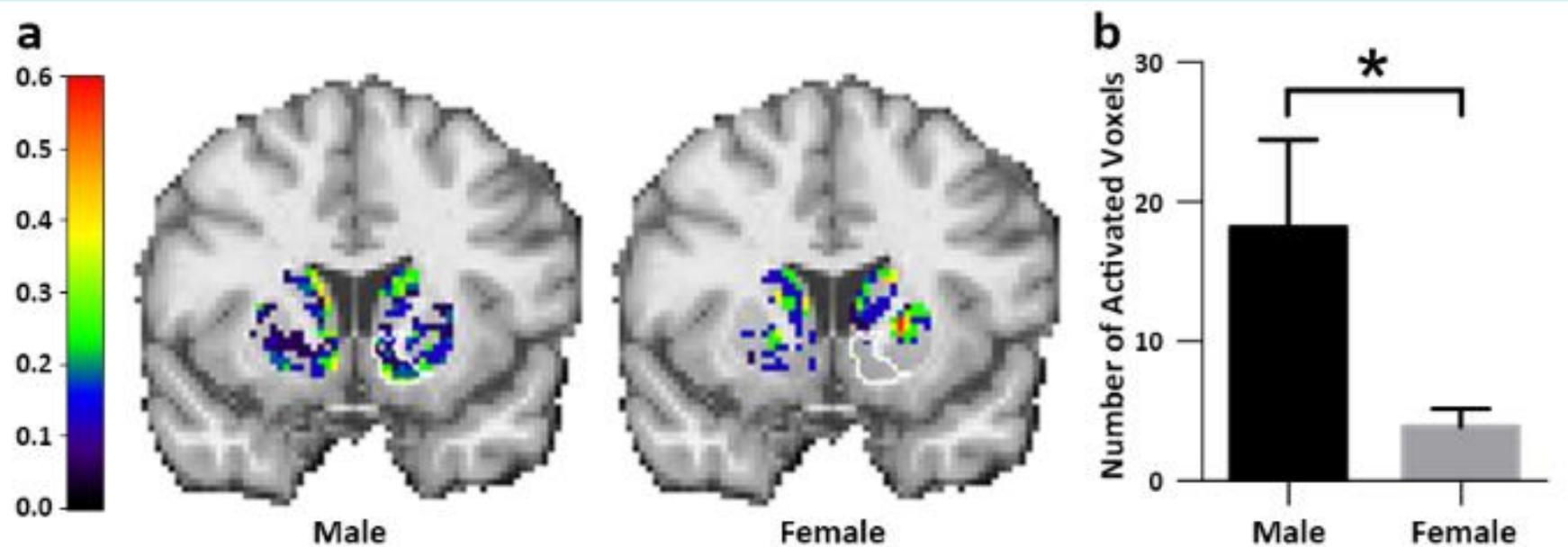
Analysis of nicotine replacement efficacy by sex



- ❑ 42 placebo-controlled clinical trials were identified
- ❑ 22 articles (52.4%) reported examining treatment outcomes by sex
- ❑ When men and women differed, women did poorer than men
- ❑ Virtually no data on differences in compliance, side effects, withdrawal or cravings



Why might women smokers have poorer response to NRT?



a. The probability of activation maps for male and female smokers. The most striking difference between male and female smokers is in the right ventral striatum.

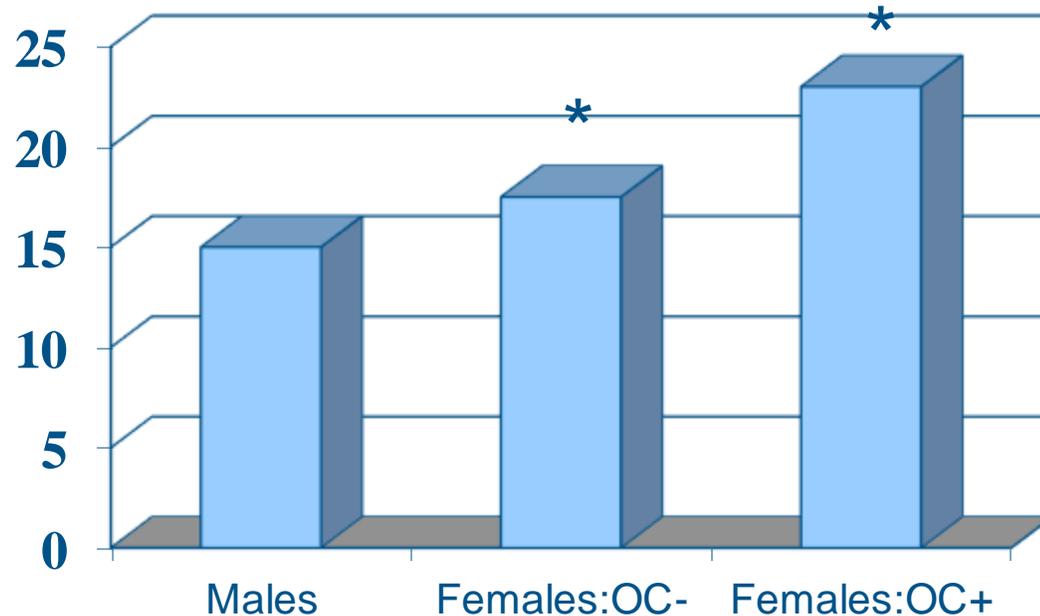
b. The mean and (and standard error) number of voxels activated during smoking in the right ventral striatum for male and female smokers (* $p = 0.01$).

Cosgrove et al., J of Neuroscience,
2014



Why might women smokers have poorer response to NRT?

Rates of Nicotine Clearance (ml/min/kg)



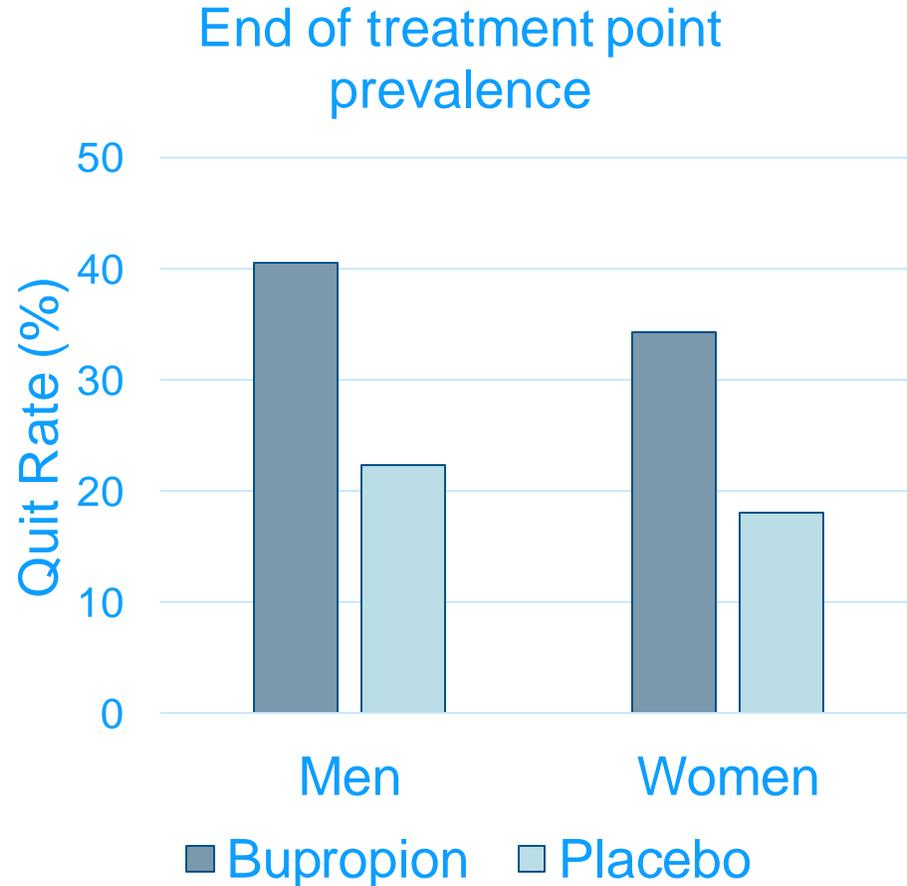
Women clear nicotine from their systems faster than men.

Women taking oral contraceptives containing estrogen clear nicotine the fastest.

OC: oral contraceptives



Meta-analysis of bupropion by sex (n=4,421 smokers)



Bupropion increased rates of quitting in women and men

□ Men O.R.=2.53

□ Women O.R. = 2.47

However, rates of quitting lower in women overall, regardless of treatment condition

□ women were 21% less likely to quit



Meta-analysis of varenicline by sex

Nicotine & Tobacco Research, 2016, 1002–1011
doi:10.1093/ntr/ntv207
Original investigation
Advance Access publication October 6, 2015



OXFORD

Original investigation

Sex Differences in Varenicline Efficacy for Smoking Cessation: A Meta-Analysis

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Abstract

Introduction: Women have lower rates of quitting than men with both bupropion and nicotine replacement. It is unknown whether varenicline demonstrates differential efficacy for men and women. The purpose of this study was to conduct the first comprehensive meta-analysis of clinical trial data examining sex differences in the efficacy of varenicline for smoking cessation.

Methods: Searching MEDLINE, EMBASE, and PsychINFO, 17 of 43 clinical trials of varenicline for smoking cessation published through December 31, 2014 were low-bias randomized double-blind placebo-controlled trials. Data ($n = 6710$ smokers, 34% female, $n = 16$ studies, 96% of available data) was analyzed with Metafor program in R. Outcome endpoints were 7-day point-prevalence (PP) and continuous-abstinence (CA) at week 12 (end of treatment), week 24 (6-month follow-up), and week 52 (12-month follow-up).

Results: Using placebo, women were less likely than men to quit (PP-12, CA-24; $P < .05$ for sex). Using varenicline, similar rates of abstinence for men and women were demonstrated for all six outcomes (eg, PP-12 abstinence rates were 53% in both women and men). Varenicline versus placebo outcomes demonstrated that varenicline was more effective for women for short and intermediate outcomes (PP-12, CA-12, CA-24; $P < .05$ sex \times medication interaction). For end-of-treatment PP, varenicline was 46% more effective for women. For continuous abstinence, varenicline was 34% (CA-12) and 31% (CA-24) more effective for women.

2 large studies published in JAMA indicated no sex differences in smoking cessation outcomes (*Jorenby et al., 2006; Gonzales et al., 2006*)

No published data presented by sex

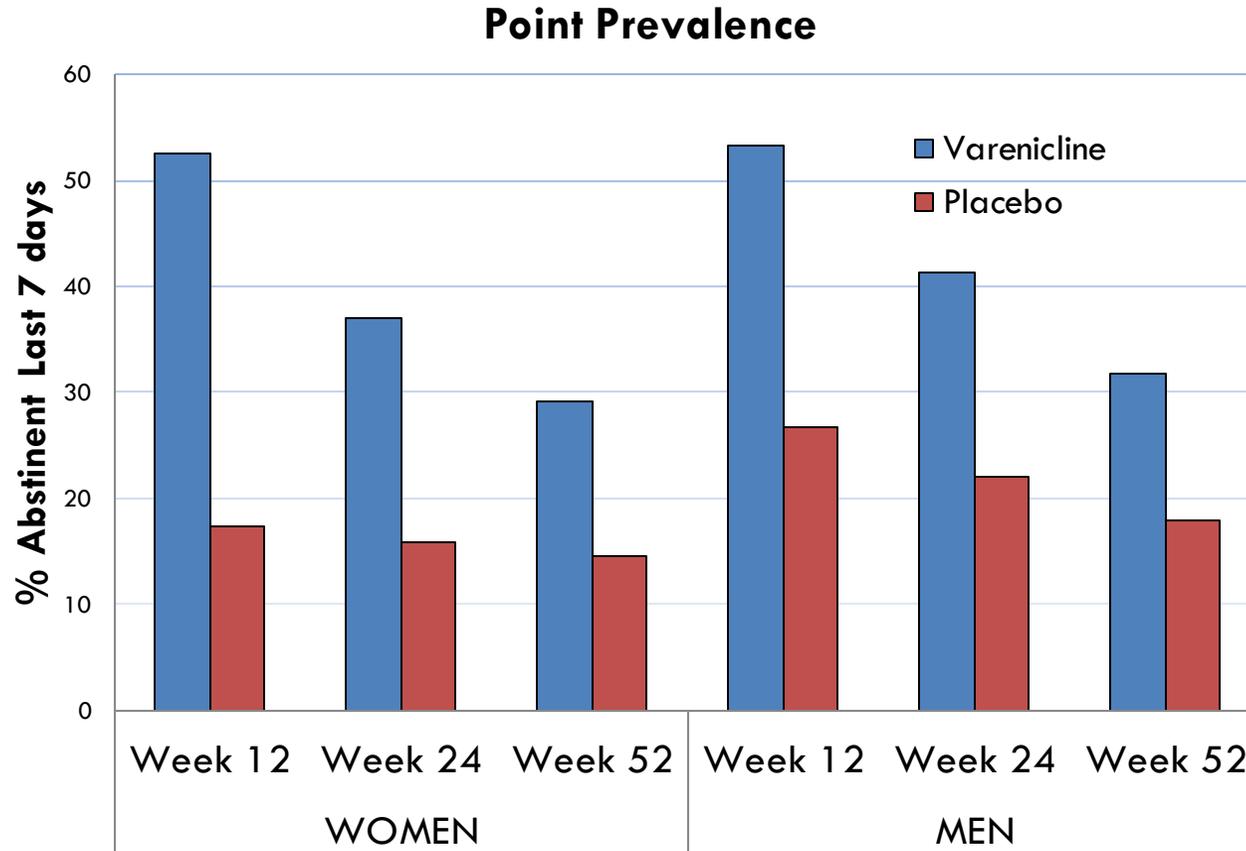
Meta-analysis:

pooling data from 10,641 smokers, representing 98% of all Phase II & III data

- data obtained from Pfizer & academic investigators



Meta-analysis of varenicline efficacy by sex

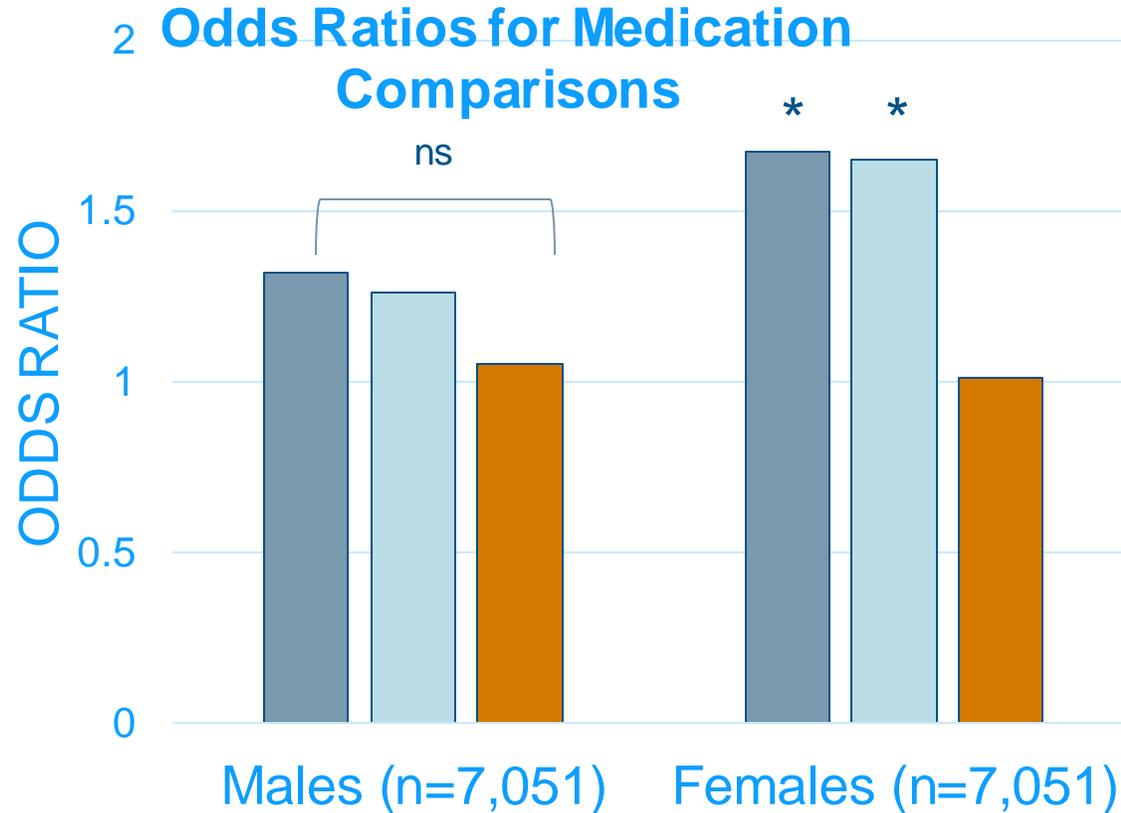


Placebo
responding
lower in women

Varenicline
increased rates
of abstinence in
women to
similar levels
vs. men



Network analysis of medication efficacy by sex



- Varenicline vs Nicotine Replacement
- Varenicline vs Bupropion
- Nicotine Replacement vs Bupropion

Head to head comparisons of medication by sex

Men
(VAR=BUP=PATCH)

Women
(VAR>BUP=PATCH)



Gender-informed approaches to smoking cessation

- To improve smoking cessation rates for women, effective strategies need to address factors that maintain smoking
- Targeting stress-reactivity



Take home message....

Women smokers face critical health disparities

Women smokers have more difficulty quitting smoking

Smoking cessation medications can help women quit smoking

Clinical care guidelines should be updated to reflect current knowledge

Medication development needs to target factors underlying key sex differences in smoking maintenance

