

Sex as A Biological Variable: Program Update

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**Associate Director for Basic and Translational Research
Office of Research on Women's Health
National Institutes of Health**

**48th Meeting of the NIH Advisory Committee on Research on Women's Health
April 10, 2019**



SABV Policy in a Nutshell

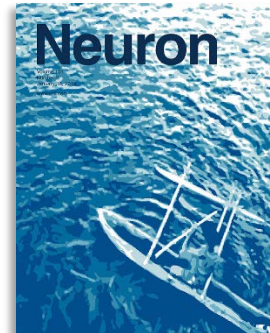
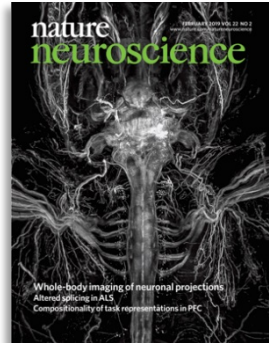
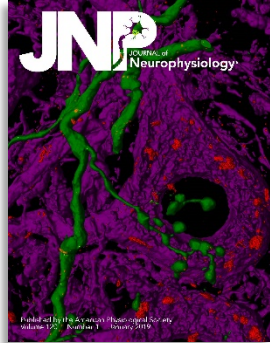


NOT-OD-15-102*: Consideration of Sex as a Biological Variable in NIH-funded Research

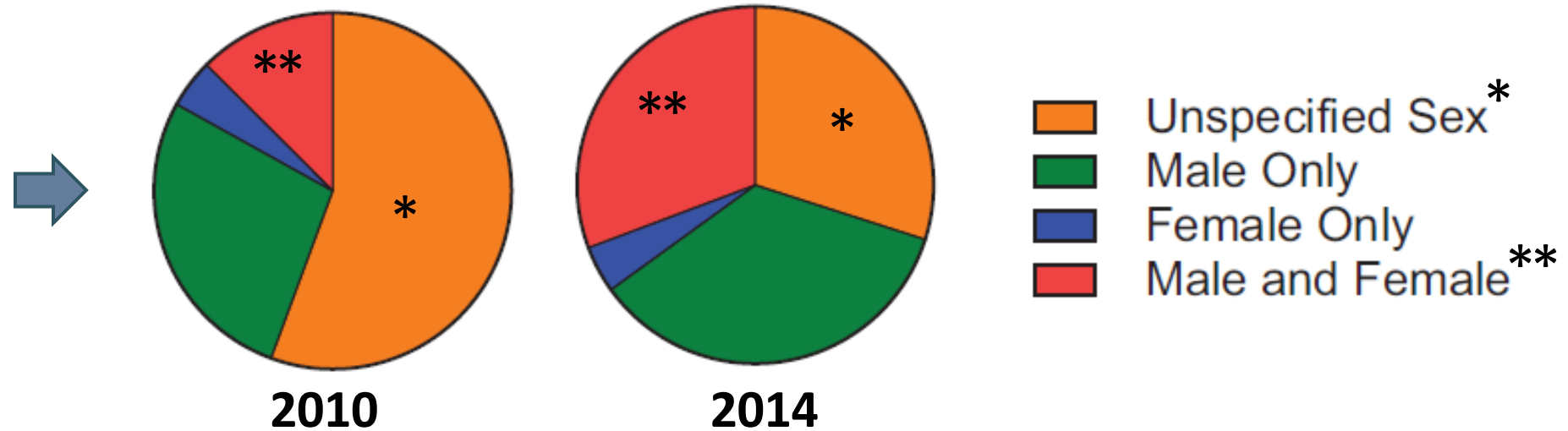
“NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.”

***January 25, 2016 (effective date)**

There has been slow progress on results reporting for preclinical research



Sex of rodents in 6,636 neuroscience papers from 6 top journals



Will et al., 2017. *eNeuro* 4 (6) e0278-17.2017: 1–10.

Original Articles

Implementation of the NIH Sex-Inclusion Policy: Attitudes and Opinions of Study Section Members

Nicole C. Weitowich, PhD¹ and Teresa K. Woodruff, PhD^{1,2}

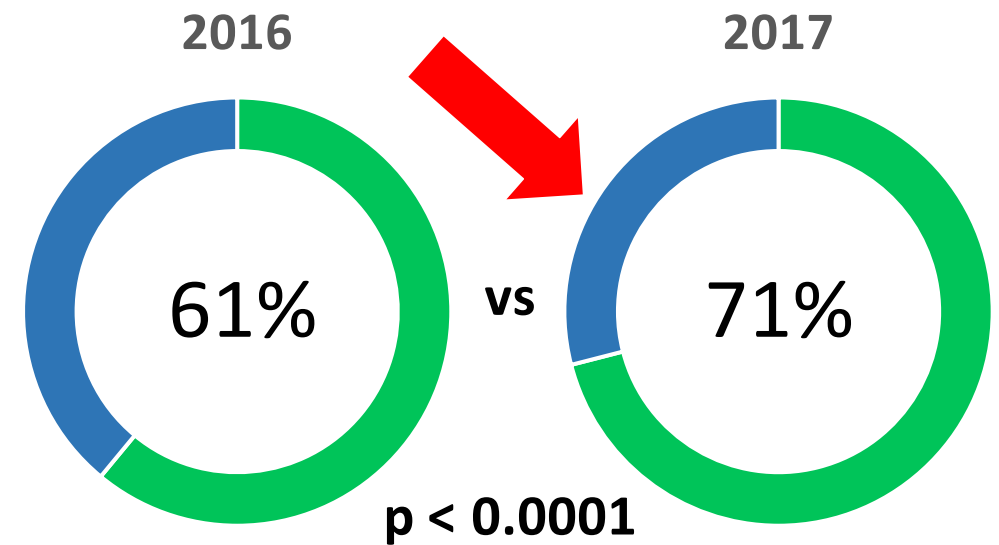
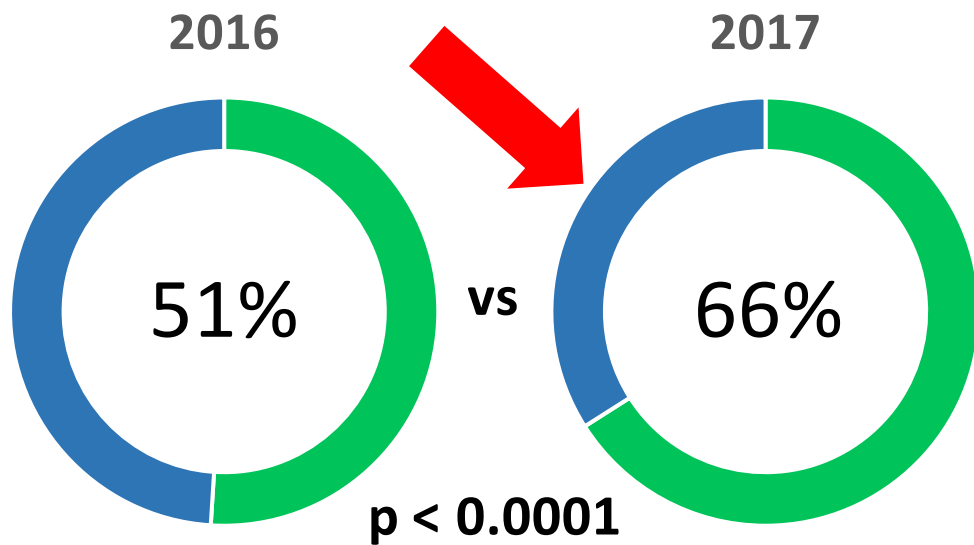
[Volume 28, Number 1, 2019](#)



From 2016 to 2017, surveyed NIH study section members perceived an increase in the consideration of SABV by applicants

Q: Did applicants adequately address the incorporation of SABV into their experimental design, analysis, and reporting?

Q: Did applications account for the consideration of SABV within the research strategy?



■ A: The majority of them did so. ■ A: Half or fewer of them did so.

Adapted from: Weitowich & Woodruff, 2019. Implementation of the NIH sex-inclusion policy: attitudes and opinions of study section members. *Journal of Women's Health* 28: 1–8.

Outline

- SABV policy uptake and adoption is not complete
- **New impetus for assessment of SABV policy uptake**
- New partnerships for SABV resource development
- Other SABV resources
- SABV application to the science

Trans- NIH SABV Working Group

Established: September 11, 2014

Mandate: To inform SABV Policy development

Chair: ORWH Director

Members: Senior IC staff nominated by IC Director

Meetings: Quarterly

ORWH Staff contacts:

- **Rebecca DelCarmen-Wiggins, Ph.D.**
- **Elena Gorodetsky MD., Ph.D.**
- **Chyren Hunter, Ph.D.**

Trans-NIH SABV Working Group Members

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Ron Adkins
Lee Alekel
Sally Amero
Inna Belfer
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Nancy Boudreau
Patricia Brown
Liza Bundesen
Ricardo Cibotti
Valerie Durrant
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OD/OLAW
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CSR
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NHGRI
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NIA
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NIAID
NCCIH
NCATS
NHLBI
NEI
NIGMS
CSR
OD/OSP
NIDCD
NIDDK
NIA

Sammie Sanchez
Thaddeus Schug
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Candace Tingen
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Barbara Woynarowska
Steve Zullo
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NIEHS
NINDS
NLM
NCCIH
NICHD
OD/OER
NIDCR
OD/OLAW
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NIDDK
NIBIB

21st Century Cures Act – Enhancing the Rigor and Reproducibility of Scientific Research – ACD Recommendations

- 1) Resources on rigor
- 2) Clarify scientific premise
- 3) Examples of authentication plans
- 4) Training in rigor scored
- 5) Outcomes evaluation

Public Law 115-135

One Hundred Fifteenth Congress of the United States of America

AT THE SECOND SESSION

*Began and held at the City of Washington on Wednesday,
the third day of January, two thousand and eighteen*

An Act

To amend titles 5 and 44, United States Code, to require Federal evaluation activities, improve Federal data management, and for other purposes.

*Be it enacted by the Senate and House of Representatives of
the United States of America in Congress assembled,*

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) **SHORT TITLE.**—This Act may be cited as the “Foundations for Evidence-Based Policymaking Act of 2018”.

(b) **TABLE OF CONTENTS.**—The table of contents for this Act is as follows:

Sec. 1. Short title; table of contents.

TITLE I—FEDERAL EVIDENCE-BUILDING ACTIVITIES

Sec. 101. Federal evidence-building activities.

TITLE II—OPEN GOVERNMENT DATA ACT

Sec. 201. Short title.

Sec. 202. OPEN Government data.

TITLE III—CONFIDENTIAL INFORMATION PROTECTION AND STATISTICAL EFFICIENCY

Sec. 301. Short title.

Sec. 302. Confidential information protection and statistical efficiency.

Sec. 303. Increasing access to data for evidence.

TITLE IV—GENERAL PROVISIONS

Sec. 401. Rule of construction.

Sec. 402. Use of existing resources.

NATIONAL SECURITY

BUDGET

IMMIGRATION

THE OPIOID CRISIS

STATEMENTS & RELEASES

Bill Announcement

Issued on: January 14, 2019



On Monday, January 14, 2019, the President signed into law:

H.R. 672, the “Combating European Anti-Semitism Act of 2017,” which expresses the sense of the Congress that it is in the United States national interest to combat anti-Semitism at home and abroad;

H.R. 4174, the “Foundations for Evidence-Based Policymaking Act of 2018,”

Strengthening Federal Agency evaluation capacity

efforts; and improving access to data for statistical purposes while protecting confidential information;

H.R. 7279, the “Water Infrastructure Improvement Act,” which amends the Federal Water Pollution Control Act to provide for the use of green infrastructure to reduce stormwater flows;

H.R. 7318, which eliminates the deadline for the appointment of members to

signed into law
January 14, 2019

New OD Office of Evaluation boosts NIH goal for evidenced-based evaluation of SABV policy implementation

Office of Evaluation, Performance, and Reporting, DPCPSI

Mission: To better capture, communicate, and enhance the value of NIH research through strategic planning, performance monitoring, evaluation, and reporting.



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ORWH and NIGMS establish a new partnership to develop a primer for SABV

PARTNERSHIP

- ✓ An interactive, e-learning course to enhance and improve the core of SABV in research design, analyses, and reporting
- ✓ A resource for designing research studies, preparing NIH grant applications, and training the next generation of investigators
- ✓ Audience: researchers of any level, from predoctoral trainees to senior faculty
- ✓ Developed by an ORWH-designated contractor with the input of NIH and NIH-designated subject matter experts
- ✓ Designed as independent, interrelated modules, with an instructor guide, glossary and references



SABV Primer – Goal:

To enhance the consideration of SABV in the context of conducting rigorous research to improve the reproducibility of data.

- Clarify the SABV policy
 - What is required and what is not ?
- Create better buy-in and compliance
 - myth-busting
 - address perceived challenges
- Help investigators better apply the policy to their research
 - research design / analysis / reporting
 - basic / pre-clinical / clinical / population health

Building Interdisciplinary Research Careers in Women's Health (BIRCWH) Annual Meeting – November 28, 2018

Expert Panel on SABV Curriculum Development

Major questions posed to the BIRCWH PI Panel:

- ✓ *Do scientists understand how to incorporate SABV principles into scientific thinking?*
- ✓ *How do we teach incorporation of these principles in order to change existing paradigms?*
- ✓ *How do researchers incorporate both sexes and/or genders into their research within cost and time constraints?*



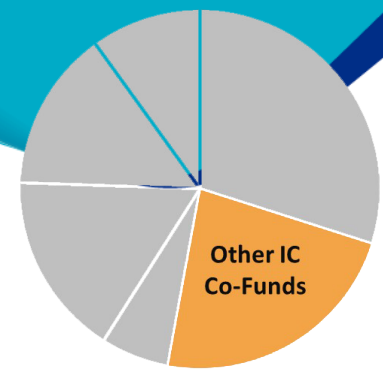
Speakers: BIRCWH PIs & Program Directors from Mayo Clinic, U of CO, U of PENN, & ORWH

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ORWH co-funds field-specific training on SABV

RFA GM-18-002 : Training Modules to Enhance the Rigor and Reproducibility of Biomedical Research (R25 Clinical Trial Not Allowed)



GOALS:

To develop exportable training modules in areas with the potential to enhance data reproducibility and to provide for communication and coordination of the development and deployment of such modules.

It is expected that the proposed training modules will identify deficiencies and teach best practices in the following general areas:

- Scientific culture and principles
- Good laboratory practices and record keeping
- Experimental design and analysis



The ORWH Sex and Gender infographic is now available in Spanish

Cómo el SEXO y el GÉNERO influyen sobre la salud y la enfermedad

El sexo y el género pueden influir en la salud de formas importantes. Si bien el sexo y el género son conceptos distintos, su influencia generalmente está inextricablemente relacionada. Los estudios científicos que generan los datos más completos consideran las influencias de sexo y/o género en el diseño de estudios, recopilación y análisis de datos, e informe de resultados.

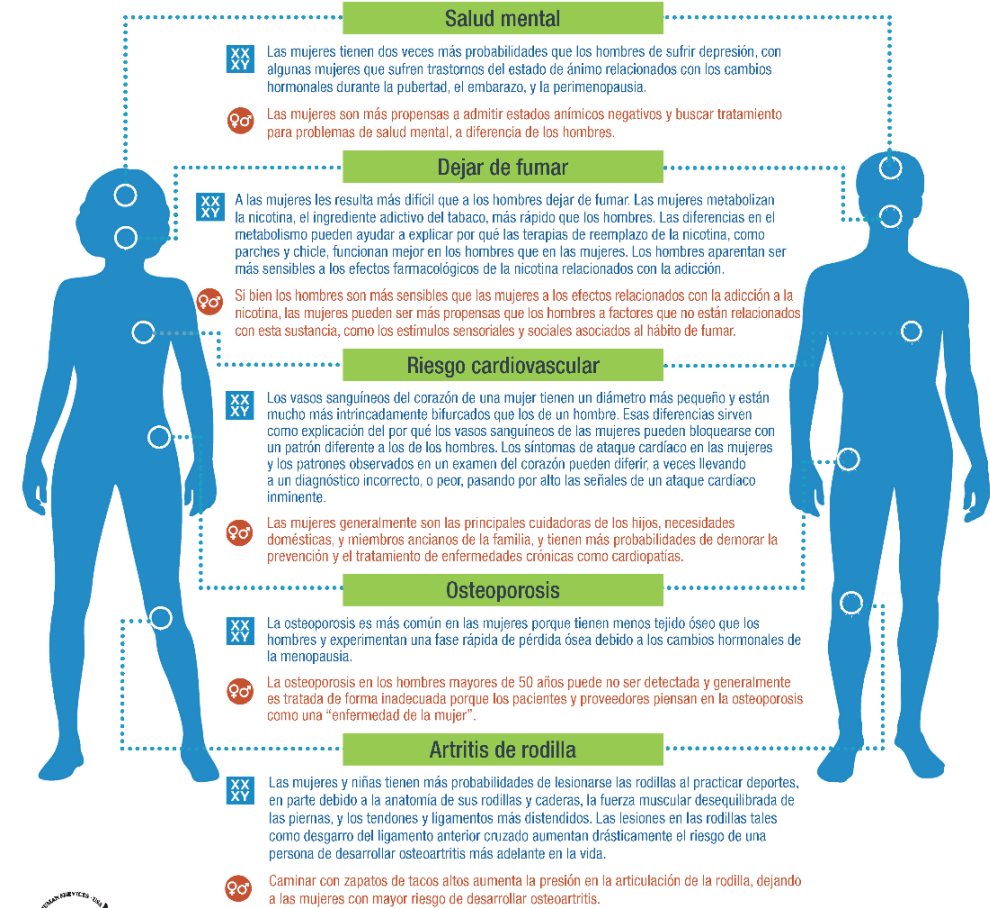
Sexo es una clasificación biológica, codificado en nuestro ADN. Los hombres tienen cromosomas XY, y las mujeres tienen cromosomas XX. El sexo nos hace hombres o mujeres. Cada célula de nuestro cuerpo tiene un sexo—conformando tejidos y órganos, como la piel, el cerebro, corazón, y estómago. Cada célula es masculina o femenina según usted sea hombre o mujer.

Género se refiere a los roles, las conductas, expresiones, e identidades socialmente construidas de niñas, mujeres, niños, hombres, y personas de género diverso. Influye en cómo las personas se perciben a sí mismas y entre sí, y cómo actúan e interactúan. El género usualmente está conceptualizado como binario (niña/mujer y niño/hombre), aunque existe una diversidad considerable en cómo las personas y los grupos lo entienden, experimentan, y expresan.

Visite NIH.gov/women para conocer cómo el estudio del sexo y género fortalece a la ciencia.

Available on the ORWH website under Downloadable Resources or in the NIH Salud Spanish Health Information portal.

Ejemplos de influencias del SEXO y del GÉNERO



NIH National Institutes of Health
Office of Research on Women's Health

NIH.gov/women  [@NIH_ORWH](https://twitter.com/NIH_ORWH) [#HexinScience](https://twitter.com/HexinScience)

Fuentes: Institute of Medicine, Canadian Institutes of Health Research, World Health Organization, National Institute on Drug Abuse, NIH Osteoporosis and Related Bone Diseases National Resource Center, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Kerrigan, D.C.; Johansson, J.I.; Bryant, M.G.; Bozic, J.A.; Della Croce, U.; & Riley, P.O. (2009). Moderate heeled shoes and knee joint torques relevant to the development and progression of knee osteoarthritis. Archives of Physical Medicine and Rehabilitation, 86(5), 871-875.

SABV Application to the Science



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Emerging Research on Alcohol and Women's Health: What Do We Know and Where Do We Go from Here?

George F. Koob, PhD
Director,
National Institute
on Alcohol Abuse
and Alcoholism

NIH Coordinating Committee
on Women's Health March 13, 2019



Women and Alcohol

Women's drinking patterns are different from men's—especially when it comes to type of beverage, amounts, and frequency. Women's bodies also react differently to alcohol than men's bodies. As a result, women face particular health risks and realities.

Women should be aware of the health risks associated with drinking alcohol, especially because most women drink at least occasionally, and many women drink a lot.

Why do women face higher risk?

Women feel the immediate effects of alcohol more quickly and for a longer time than men do. Due to natural differences in body composition, hormones, and rate of alcohol metabolism, women retain more alcohol in their blood than men. They also break down and get rid of alcohol more slowly than men do. As a result, women are more susceptible to alcohol's health risks.

What are the health risks?

Liver Damage:

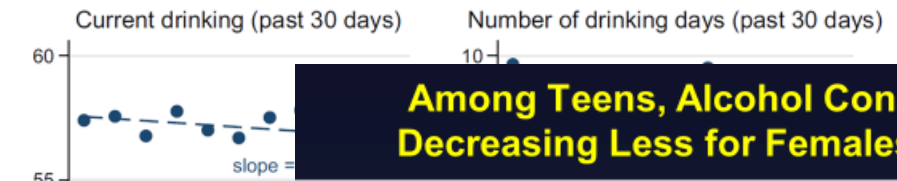
Women who drink are more likely to develop alcoholic hepatitis (liver inflammation) than men who drink the same amount of



More Women are Drinking and They are Drinking More Often

George F. Koob, PhD
 Director,
 National Institute
 on Alcohol Abuse
 and Alcoholism

Among Teens, Alcohol Consumption Is Decreasing Less for Females than Males



The Brain Undergoes Widespread Sexual Differentiation During Adolescence – Implications?

Continuing Concerns About Alcohol, Fetal and Maternal Health

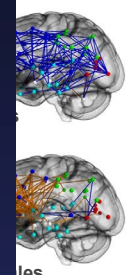
- Drinking during pregnancy is a threat to both the mother and child
 - In 2017, **nearly 1 in 4 (23.5%) women** in the 1st trimester of pregnancy drank alcohol in the prior 30 days, while **12.5% engaged in binge drinking** (SAMHSA NSDUH, 2017)
 - An NIAAA-funded study of 6,639 children in four communities found the **prevalence of FASD was 1-5%** (May et al, 2018)
 - Current NIAAA portfolio on FASD consists of roughly 100 active grants
- Drinking during breast feeding can be dangerous
 - An NIAAA-funded study suggests drinking while breastfeeding was associated with lower body weight and verbal IQ in kids at age 7 (May et al., 2016)

Do moms need too much wine? Women's drinking habits spark concern

September is National Recovery Month. Women are at greater risk for some of the negative effects of alcohol, but their drinking is catching up to men. Today.com



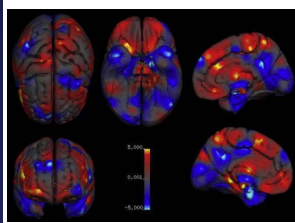
Females develop more spherication
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et al (2014) Sex
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 828

Females and males develop different densities of gray matter in cortical areas

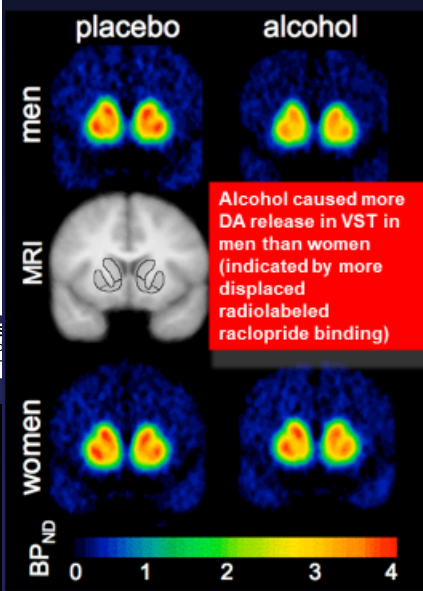
Areas with more gray matter in female (RED) or in male (BLUE) adult brains



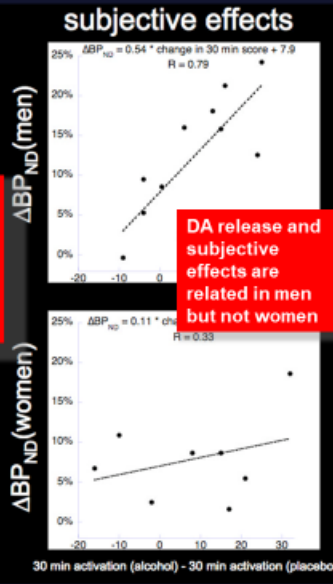
Source: Ruigroka et al (2014) A meta-analysis of sex differences in human brain structure. Neurosci Biobehav Reviews, 39, 34-50

Females have more functional brain connectivity

Alcohol Induces More Dopamine Release in Male than Female Nucleus Accumbens



Alcohol caused more DA release in VST in men than women (indicated by more displaced radiolabeled raclopride binding)



DA release and subjective effects are related in men but not women

(PET) imaging using the D2/3 radiotracer [¹¹C] raclopride.
 Delta BP = relative reduction in DA D2/3 receptor availability for [¹¹C] raclopride binding.
 Decreased D2/3 binding reflects displacement by endogenously released dopamine
 From: Urban NBL et al, Biol Psychiatry 68(8): 689-696 (2010).

Using the *Adolescent Brain and Cognitive Development (ABCD)* data set, study finds relationship between sex, sports activity and mental health in preadolescents

Findings

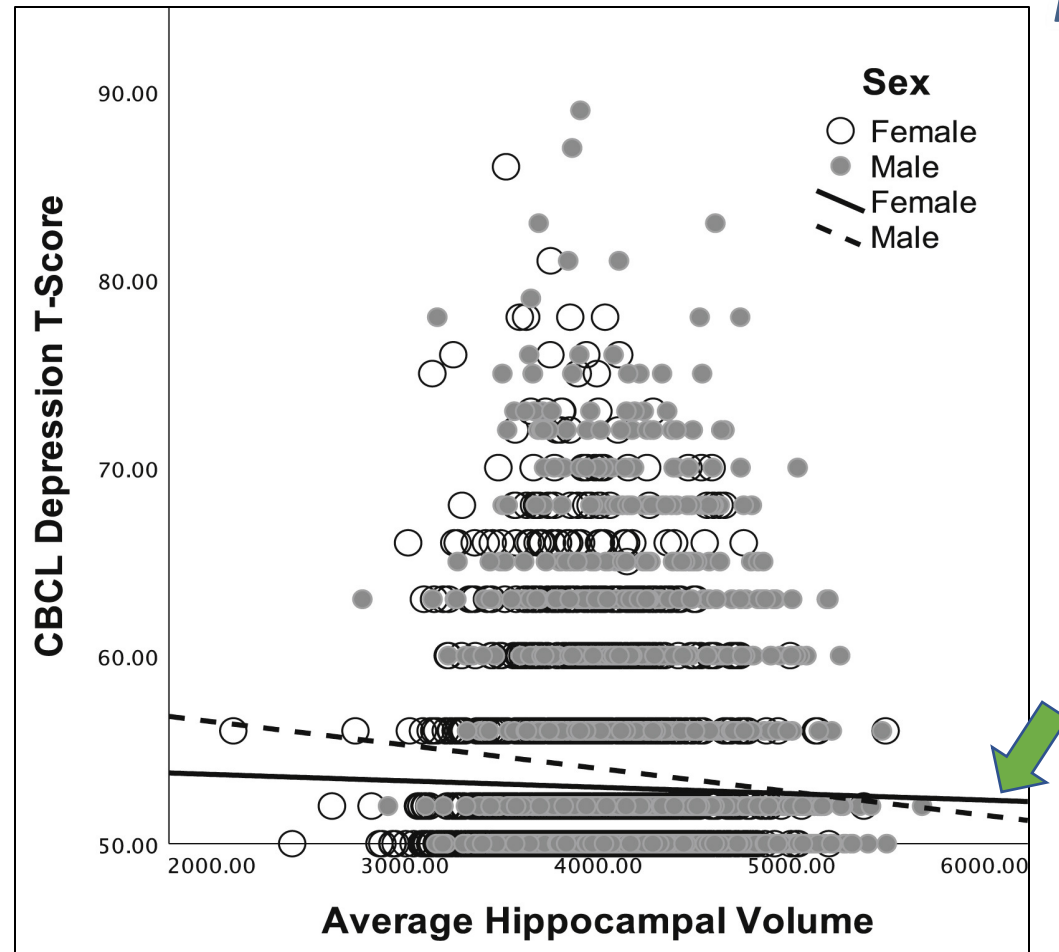
- Greater sports involvement, but not non sport activity involvement, was associated with less depression in boys
- Involvement in all types of sports except for individual sports and non-sport activities was related to hippocampal volume in both boys and girls.
- **Hippocampal volume was associated with depression in boys only**



Adolescent Brain Cognitive Development®
Teen Brains. Today's Science. Brighter Future.

ABCD data set = 4191 children ages 9-11

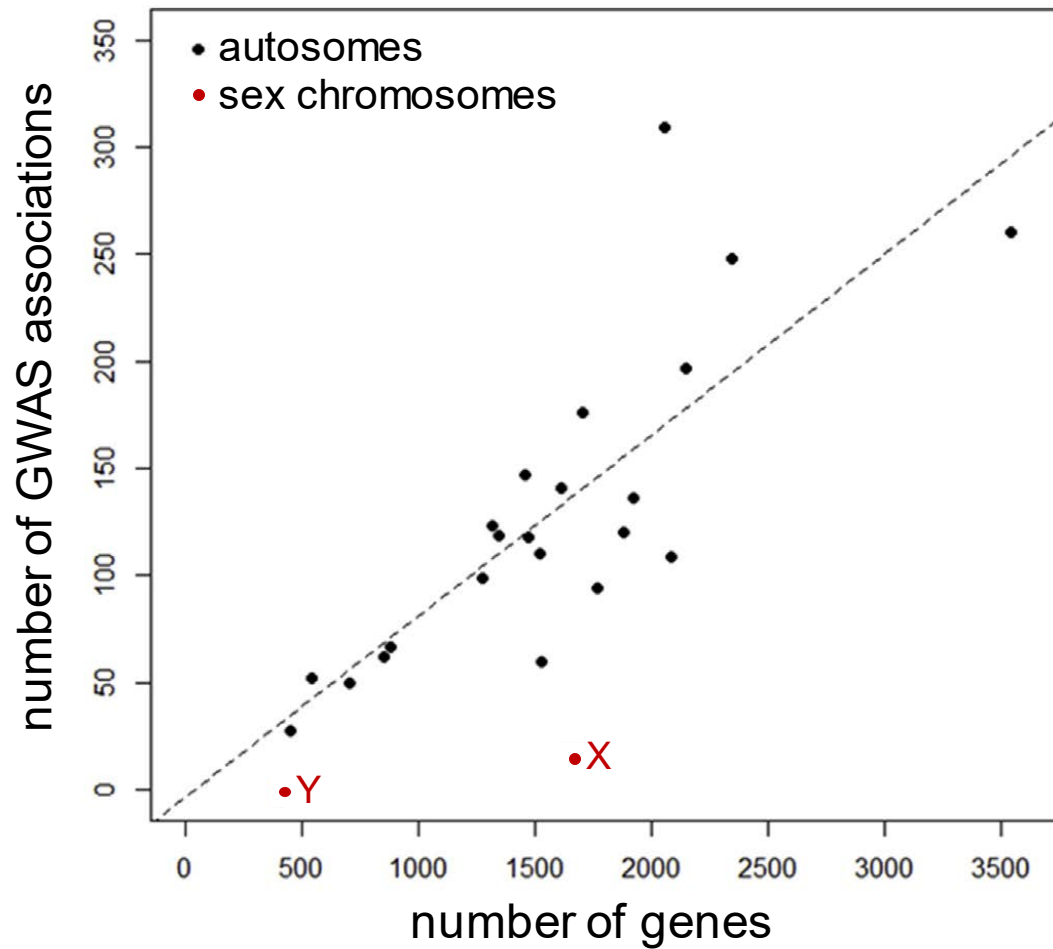
NIH National Institutes of Health
Office of Research on Women's Health



Involvement in Sports, Hippocampal Volume, and Depressive Symptoms in Children

Lisa S. Gorham, Terry Jernigan, Jim Hudziak, and Deanna M. Barch :Biological Psychiatry: Cognitive Neuroscience and Neuroimaging - 2019 In Press

ORWH hosted a *GWAS, Sex & Chromosomes Think Tank* on Feb. 27, 2019, which was attended by 15 NIH ICOs



- What factors explain underrepresentation of sex chromosomes in GWAS results?
- How much info is lost when sex is controlled for statistically, but the influence of sex is not reported?
- Are there emerging solutions to these issues?
- To what extent can historical GWAS datasets be re-examined to achieve a more thorough consideration of sex?
- How should additional information (e.g., menopausal, hormonal status) be incorporated?

Coming Soon! A Think Tank summary will be posted on the ORWH website

Gender and the Genome Core

Co-Chairs

Jamie White Matt Arnegard

Members

Rajeev Agarwal Elena Gorodetsky

Advisor

Chyren Hunter

Wise et al. 2013. *Am. J. Hum. Genet.* **92**: 643-647.

Winham et al. 2015. *Artherosclerosis* **241**: 219-228.

Khramtsova et al. 2019. *Nat. Rev. Genet.* **20**: 173-190.



**The Organization for the Study of Sex Differences / International Society for Gender Medicine
Joint Meeting
May 5 – May 8, 2019
Washington Marriott Georgetown**

ORWH 'SCORES' at OSSD / IGM 2019:

Current SCORE U54 Principal Investigators

Session 5: Sex differences in immune function and disease

Sex differences in vaccine-induced immunity against influenza

Sabra Klein, PhD, Johns Hopkins Bloomberg School of Public Health

Session 8: Sex differences in prescription, efficacy, and adverse drug reactions of commonly prescribed drugs

Sex hormones and adverse drug reactions

Virginia Miller, PhD, Mayo Clinic

Prior SCOR P50 Principal Investigator

Session 4: Sex differences in nicotine and smoking: From brain and behavior to smoking cessation

Chairs: Cora Lee Wetherington, PhD, National Institute on Drug Abuse,

Sherry McKee, PhD, Yale School of Medicine

