Sex as a Biological Variable

Statistics in Medical Research Fall Series

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Introduction

- In 2016, the National Institutes of Health (NIH) implemented a policy requiring investigators to consider sex as a biological variable;
- The policy aimed to ensure equal representation of males and females in vertebrate research studies;
- It does not require investigators to power studies in order to determine sex differences nor does it ask investigators to analyze data by sex.

Introduction

- NIH policy was a consequence of a series of reports calling for the inclusion of females in research and describing the limitations of sex-biased studies starting in the 1990s until early 2000s.
- In 2011, Beery and Zucker conducted a systematic review to quantify the extension of sex-bias across several research areas. Out of 841, only 28% (n = 232) articles had inclusion of both sexes such that 50% (n = 131) of them presented analysis by sex.

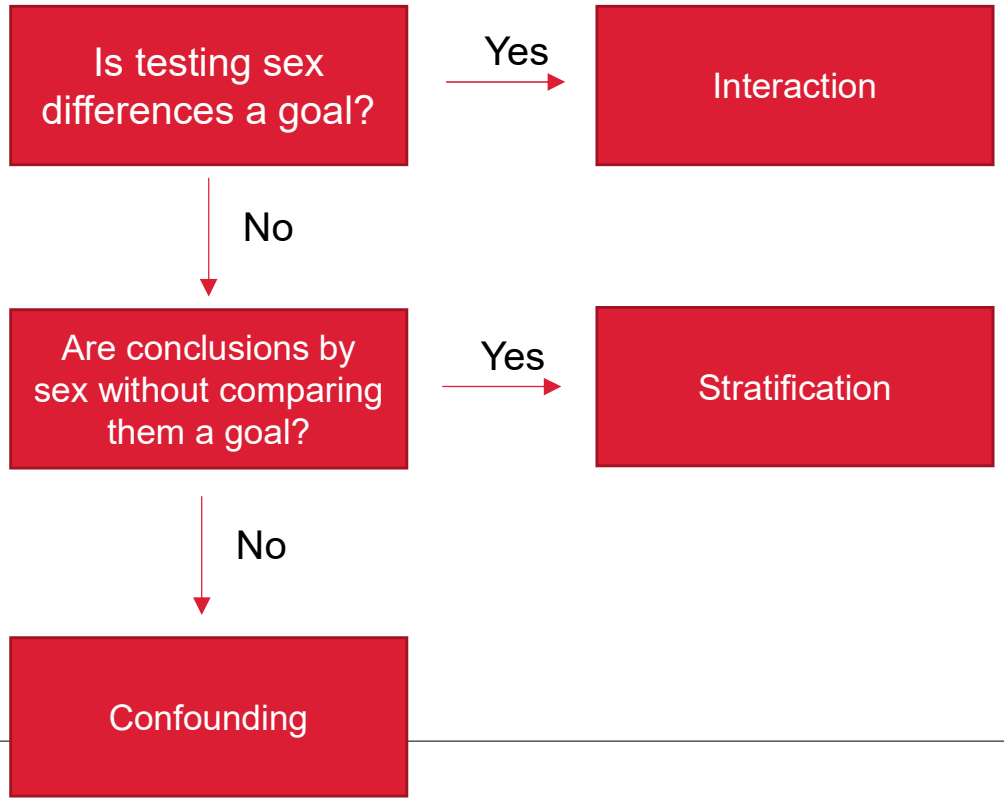
Beery, A.K. and Zucker, I., 2011. Sex bias in neuroscience and biomedical research. *Neuroscience & Biobehavioral Reviews*, *35*(3), pp.565-572.

Introduction

- The common justification for the exclusion of females that decreases experimental variability has been often refuted in the literature.
- The inclusion of females in research contributes to experimental rigor and reproducibility.
- Recently, Woitowich et al. (2020) did a follow-up study including 720 articles from 9 research areas (including PloS Biology, Science, Nature among others).
  - There was a large increase of sex-inclusive studies from 28% to 63%.
  - However, there is no improvement on analyses by sex from 50% to 42%.

Woitowich NC, Beery A, Woodruff T. Meta-research: a 10-year follow-up study of sex inclusion in the biological sciences. Elife. 2020 Jun 9;9:e56344.

Statistics Analyses for SABV



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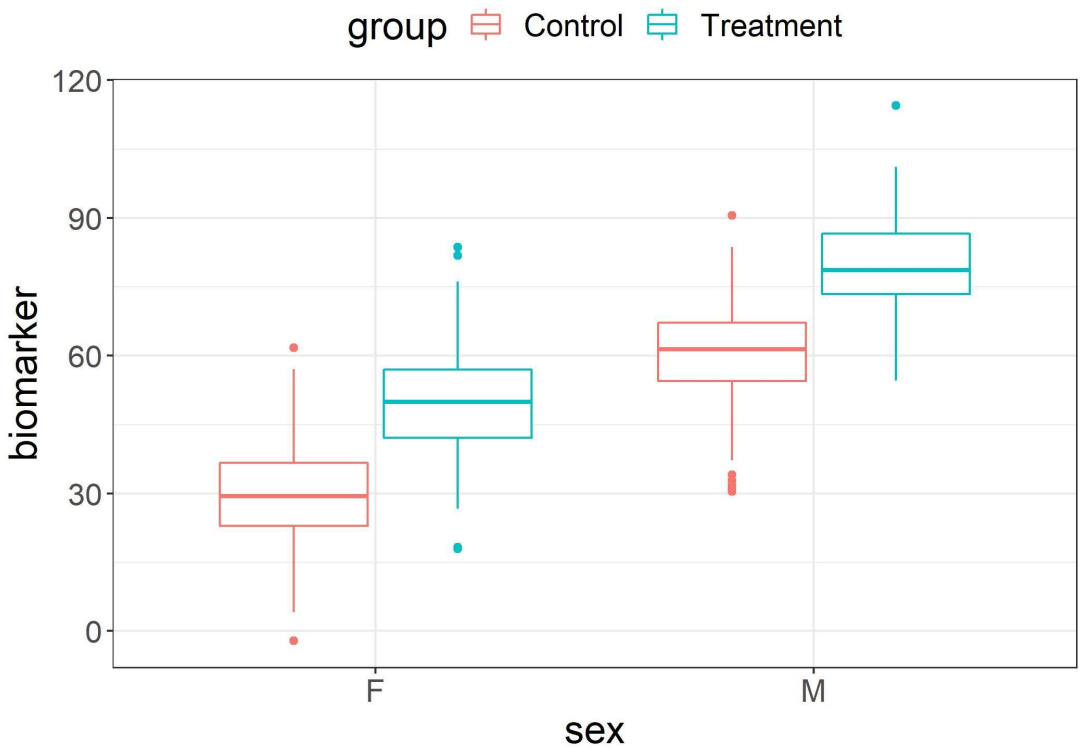
Confounding



- Confounding assumes that the treatment effect (treatment – control) is the same for both sexes, except for shift;
- It suggests no interest in how the outcomes might differ by sex.

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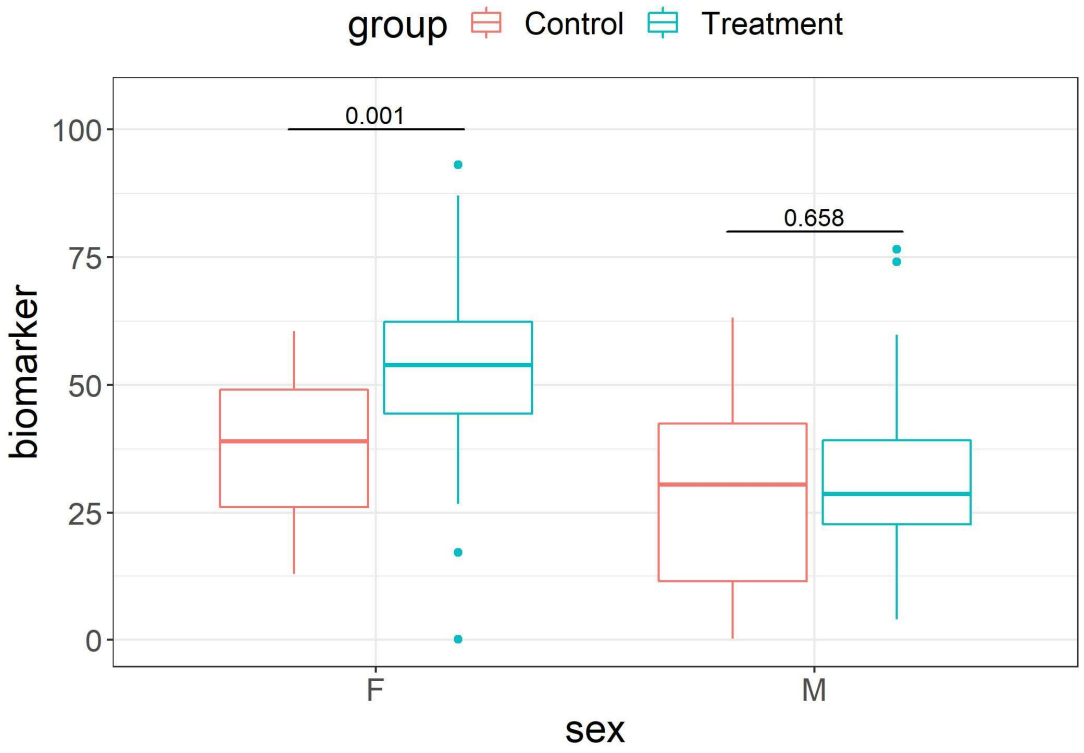
Stratification



- Stratification assumes that treatment effect (treatment – control) might be different by sex;
- It does not compare the treatment effect between sexes;
- It is the recommended approach for study designs that include an equal number of both sexes, and the main goal is not to find sex differences.

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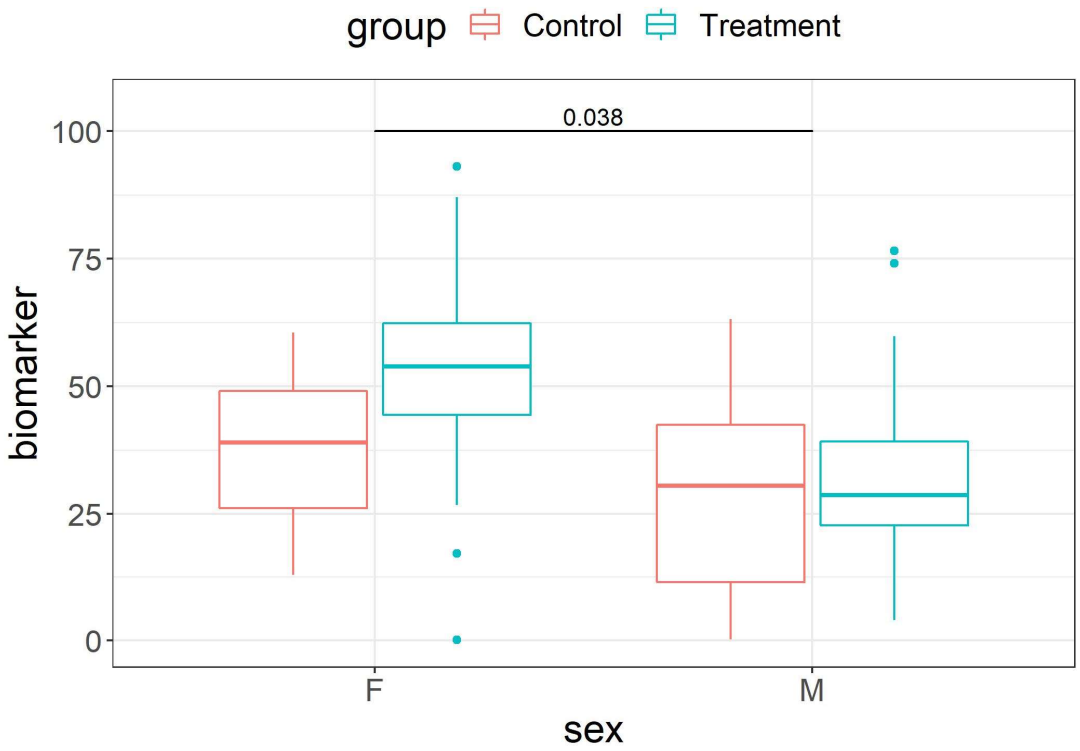
Interaction



- It assumes that treatment effect (treatment – control) might be different by sex;
- It compares the treatment effect (treatment – control) between sexes;

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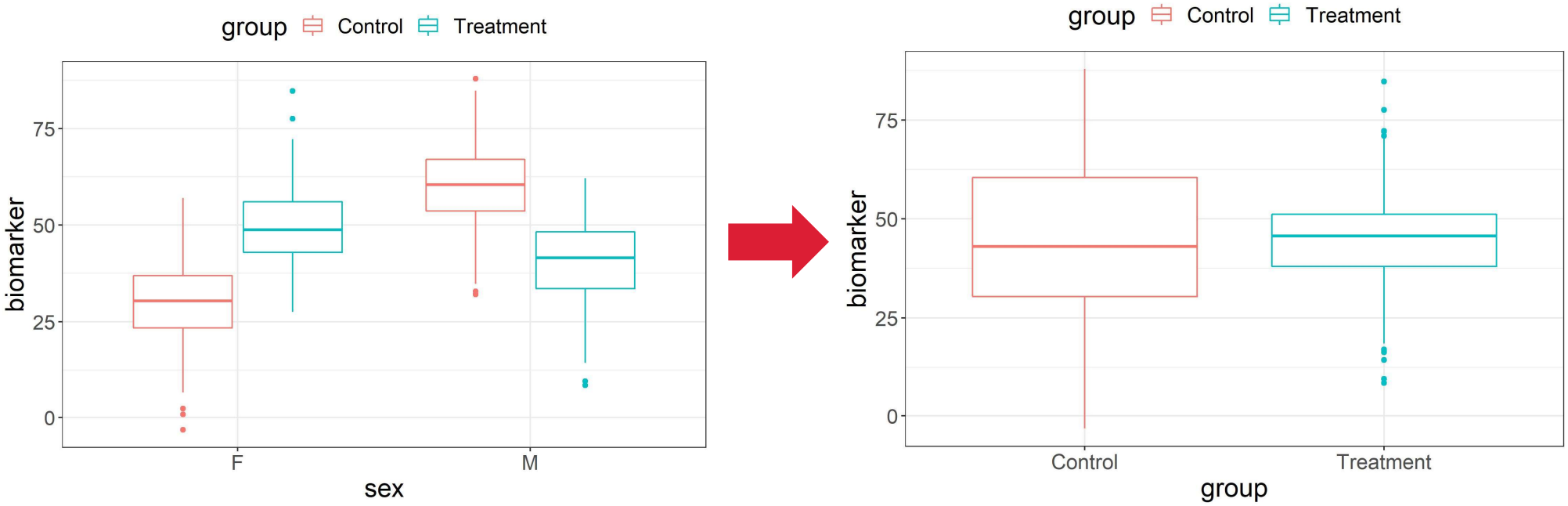
Common errors: Interaction vs. Confounding

- If there is a sex interaction effect, but interaction is not evaluated, then the treatment effect will be the average treatment effect in both sexes:



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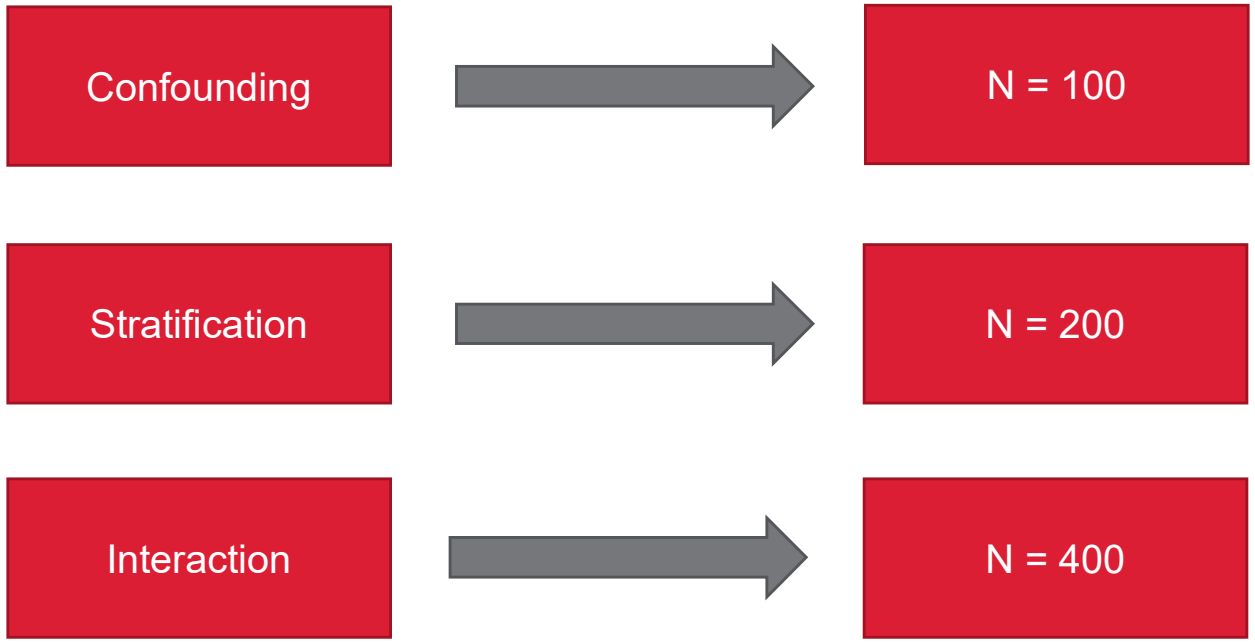
Common errors: Interaction vs. Stratification

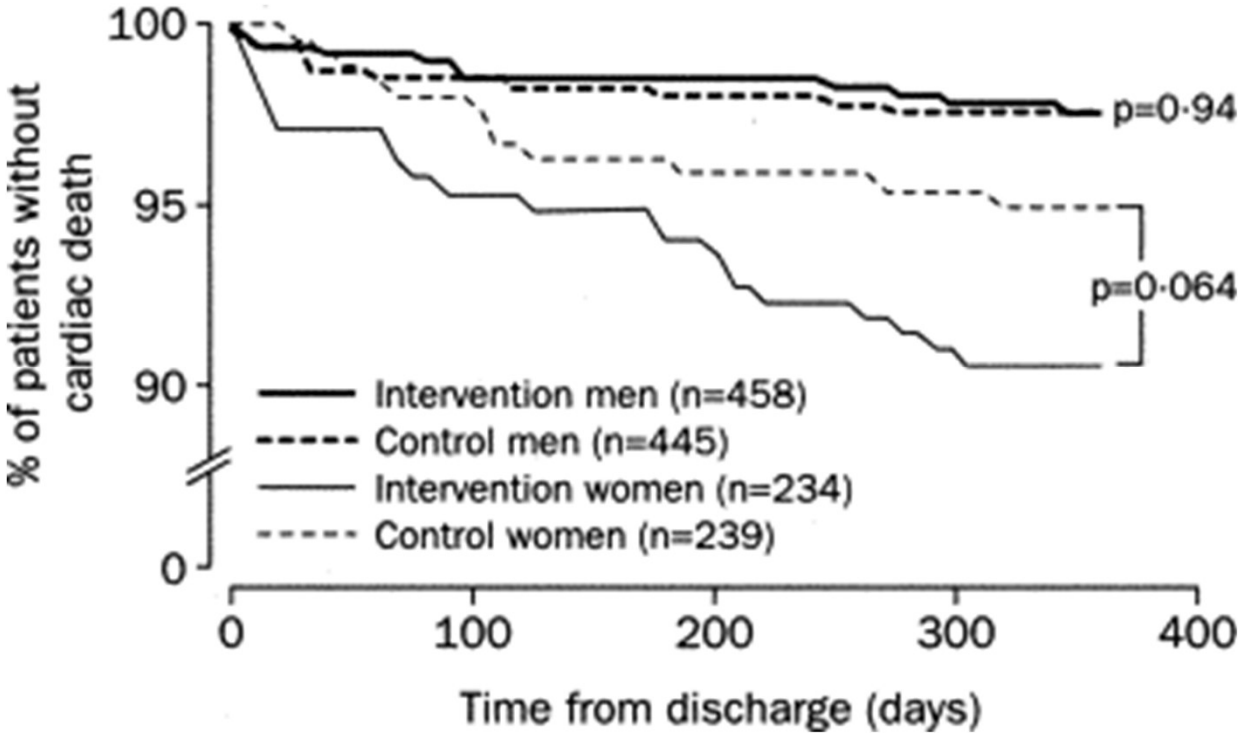
- Different treatment effects by sex when stratifying **does not** imply to sex differences;
- Comparing sexes within a treatment arm **does not** imply into sex-specific effects;
- Finding sex-differences (testing the interaction) requires a larger sample size than analyzing results separated by sex (stratification). Therefore, the lack of sex-specific effects when testing interaction might be lack of power.

Gelman A, Stern H. The difference between “significant” and “not significant” is not itself statistically significant. The American Statistician. 2006 Nov 1;60(4):328-31.

Sample size - Implications



Randomized trial of home-based psychological nursing intervention for patients recovering from myocardial infarction: Does the intervention effect on cardiac death differ by sex?



It suggests that psycho-social nursing intervention after myocardial infarction appears to adversely affect cardiac mortality in women but not in men.

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Frasure-Smith N, Lesperance F, Prince RH, Verrier P, Garber R, Juneau M, Wolfson C, Bourassa M. Randomised trial of home-based psychological nursing intervention for patients recovering from myocardial infarction. Lancet 1997; 350:473–479

Does the Intervention Impact on Cardiac Death Differ by Sex? Why different conclusions by stratum do not imply interaction

Sex	Control	Intervention	Odds ratio (95% CI)	P-value by stratum	P-value Interaction
F	12 (5.0%)	22 (9.4%)	**1.96 (0.90 ; 4.46)**	0.064	**0.21**
M	11 (2.4%)	11 (2.5%)	**0.97 (0.37 ; 2.50)**	0.94	

- **P-values by stratum** ONLY indicate that there is evidence to state the Intervention arm has a negative impact when comparing with the Control arm for females;
- **P-value Interaction** indicates that there is NOT enough evidence to state that the intervention impact on cardiac death differs by sex.

Pocock, S. J., Assmann, S. E., Enos, L. E., & Kasten, L. E. (2002). Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practiceand problems. *Statistics in medicine*, *21*(19), 2917-2930.

How often do authors declare sex-specific effects without testing interaction?

- Recently, Garcia-Sifuentes and Maney (2021) evaluated 151 articles that had analyzed sex as a confounding variable, stratification and interaction among selected papers from Woitowich et al. (2020).
- Among those 151 articles, 91 (60%) planned an equal number of females and males in their studies;

Current sex-based analyses

- Among those 91 articles, 61 (67%) claimed sex differences but 40 (65%) did not test the interaction effect.

- Among those 40 articles,
  - 24 (60%) based their conclusions on the stratified analysis;
  - 12 (30%) based their conclusions on the comparisons between sex within a treatment arm;
  - 4 (10%) based their conclusions on the aggregated analysis.

Garcia-Sifuentes Y, Maney DL. Reporting and Misreporting of Sex Differences in the Biological Sciences. bioRxiv. 2021 Jan 1.

Current sex-based analyses

- Among the 31 articles that tested the interaction:
  - 15 (48%) found sex differences;
  - 5 (16%) did not report interaction p-values although claimed to have performed the analysis;
  - 1 (3%) claimed sex difference even though the interaction was not statistically significant;
  - 10 (32%) did not find sex differences.

Garcia-Sifuentes Y, Maney DL. Reporting and Misreporting of Sex Differences in the Biological Sciences. bioRxiv. 2021 Jan 1.

Reproducibility?

- Although the scientific community improved their study design by including in larger extent an equal number of females and males after NIH policy, there is still a lot of room for improvement.
- There is a lack of adequate statistical analysis presenting results by sex and the literature is full of misleading claims of sex differences based on wrong interpretation of p-values.