



Let's talk about sex: addressing misconceptions and barriers to including both sexes

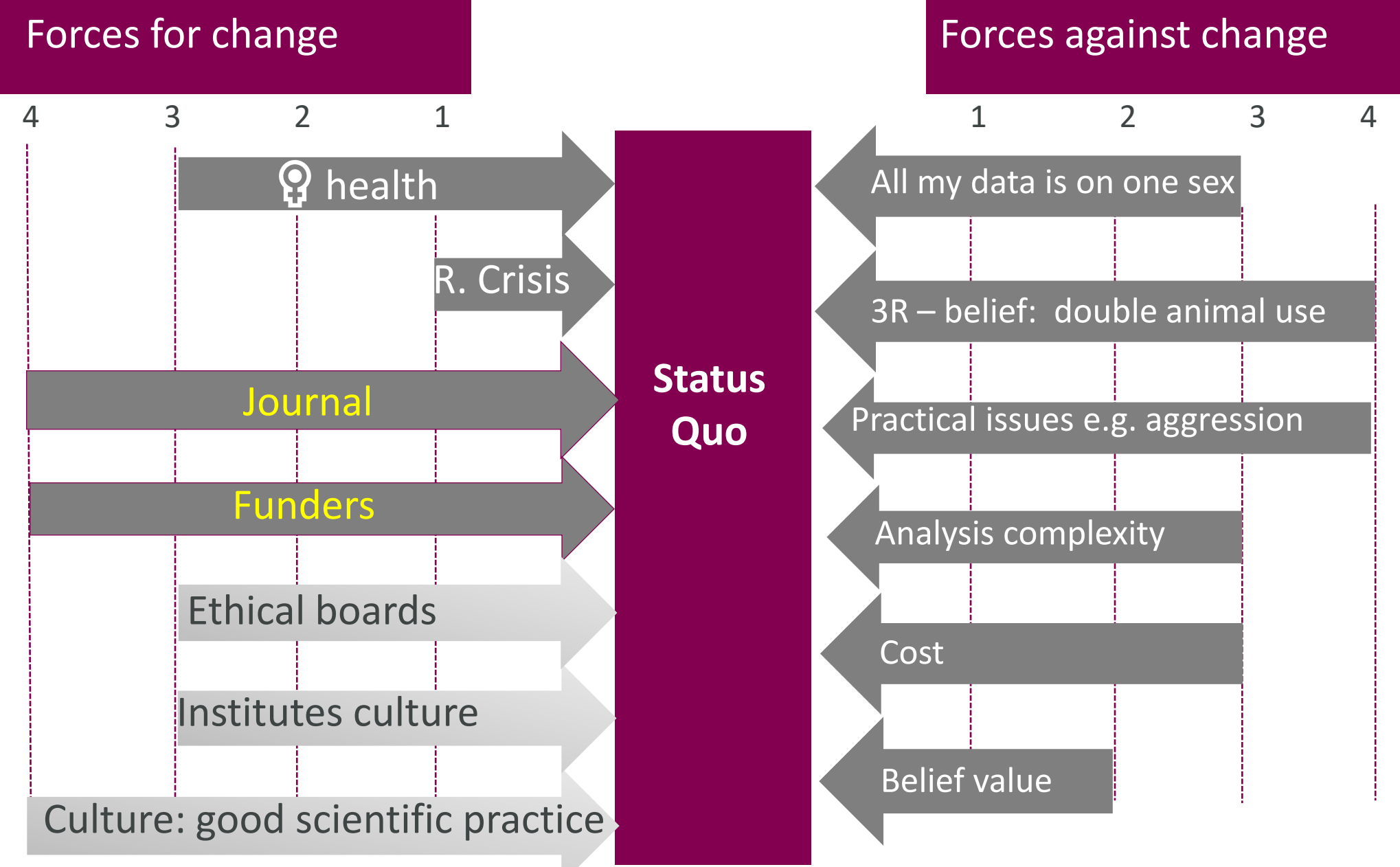
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Lewin's Force field analysis



3R ethical interpretation

Experiments isolate cause and effect by simplification

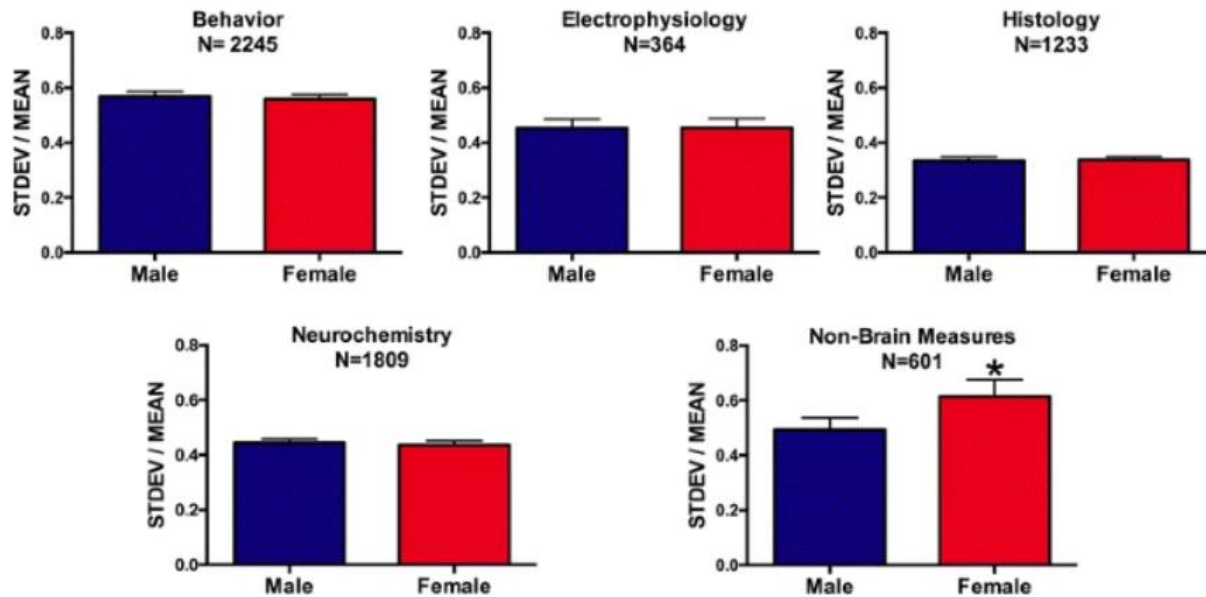
	Standard	Contemporary
Reduction	Methods which minimise the number of animals used per experiment	Appropriately designed and analysed animal experiments that are robust and reproducible, and truly add to the knowledge base

<https://www.nc3rs.org.uk/the-3rs>



Misconception: hormonal cycles: females more variable

Rats Becker 2016 BSD



“Female rats were not more variable at any stage of the estrous cycle than male rats.”

Mice Prendergast 2014 NNBR

- meta-analysis 293 published articles
- behavioral, physiological, morphological, and molecular traits
- CV distribution = no differences
- At trait level – for three types of traits males were more variable than females

“Randomly cycling female mice were no more variable than males on any trait.”



Data analysis skill gap leading to significant errors



RESEARCH ARTICLE



Reporting and misreporting of sex differences in the biological sciences

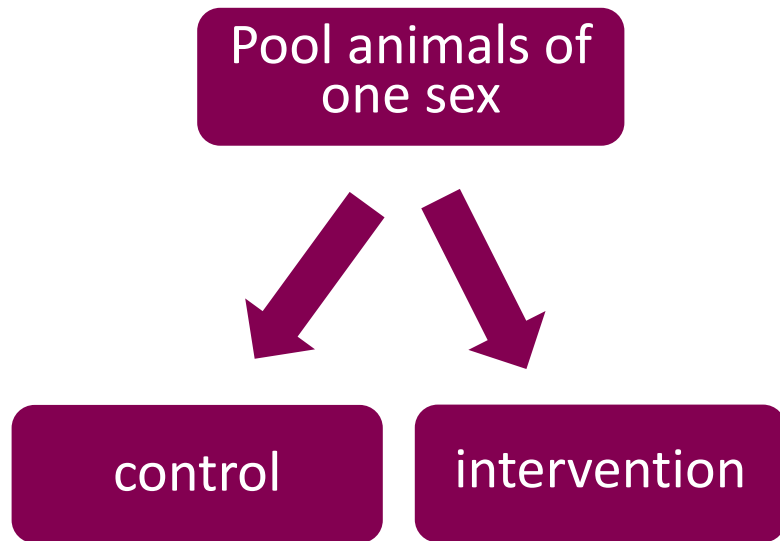
Yesenia Garcia-Sifuentes¹, Donna L Maney^{1,2*}

Significant errors in analysis

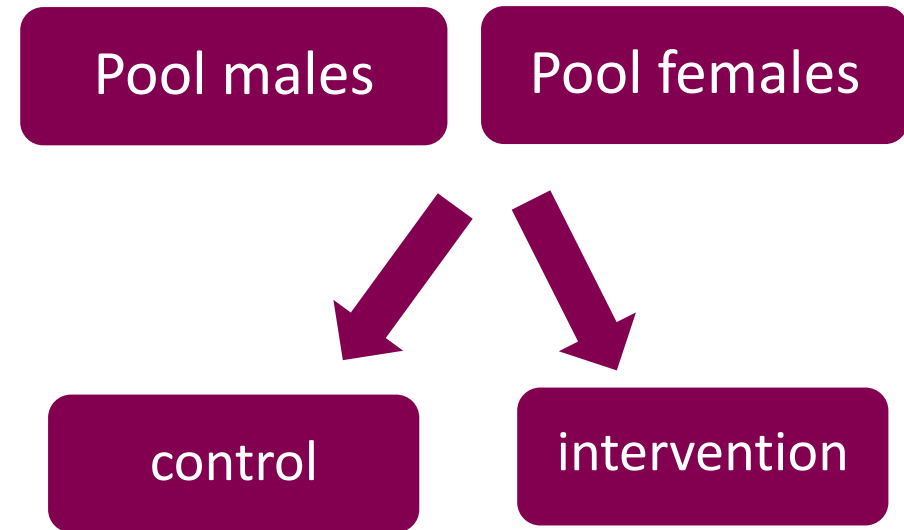
- 25% of papers reporting a sex differences had disaggregating data and not testing for a sex differences
- 33% articles pooled sexes but did not test for sex differences
- 20% compared males and females within the treatment gps to conclude sex effect



Moving from complete randomised to factorial design



outcome \sim Intervention
E.g. T-test

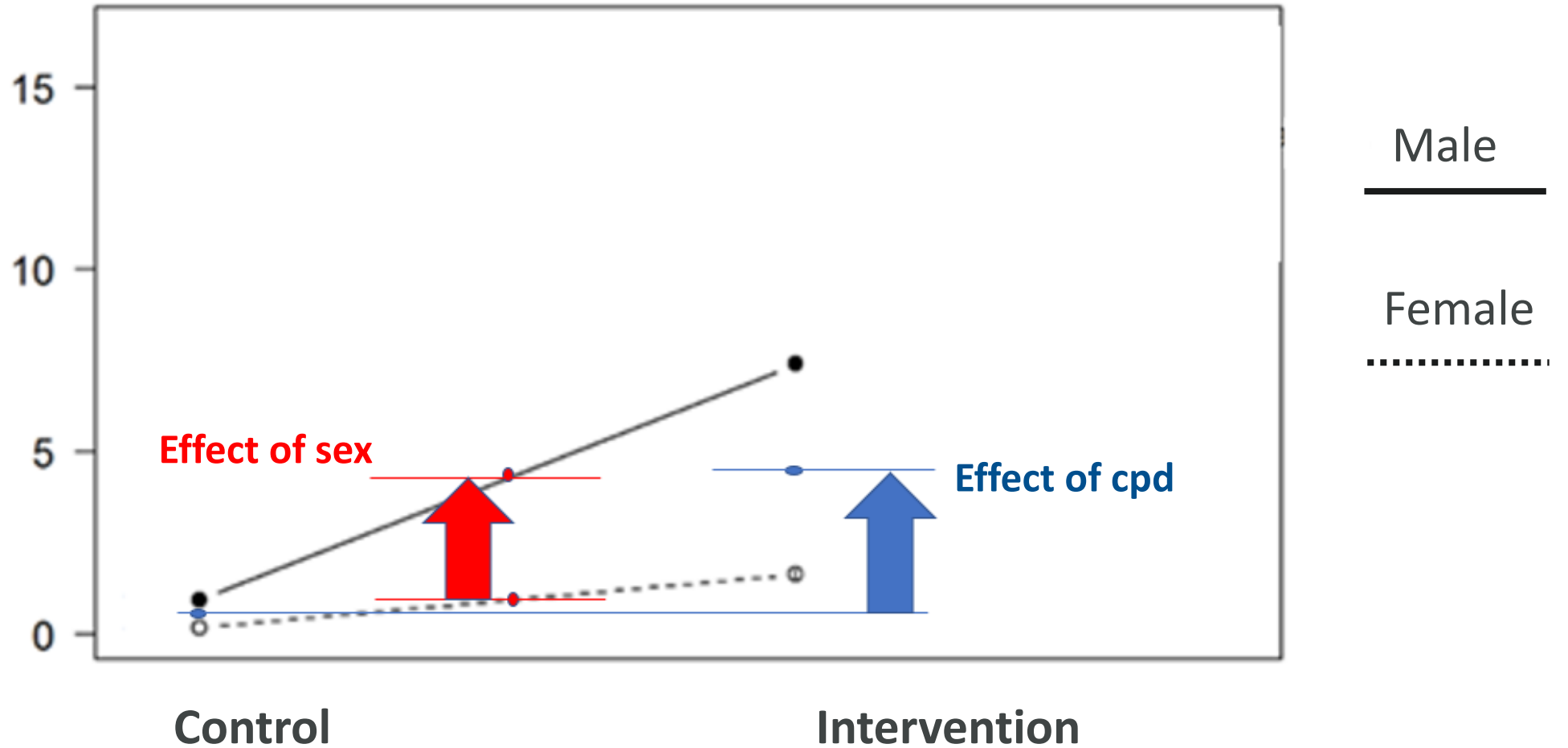


outcome \sim Intervention + sex + Intervention*sex
E.g. two way anova

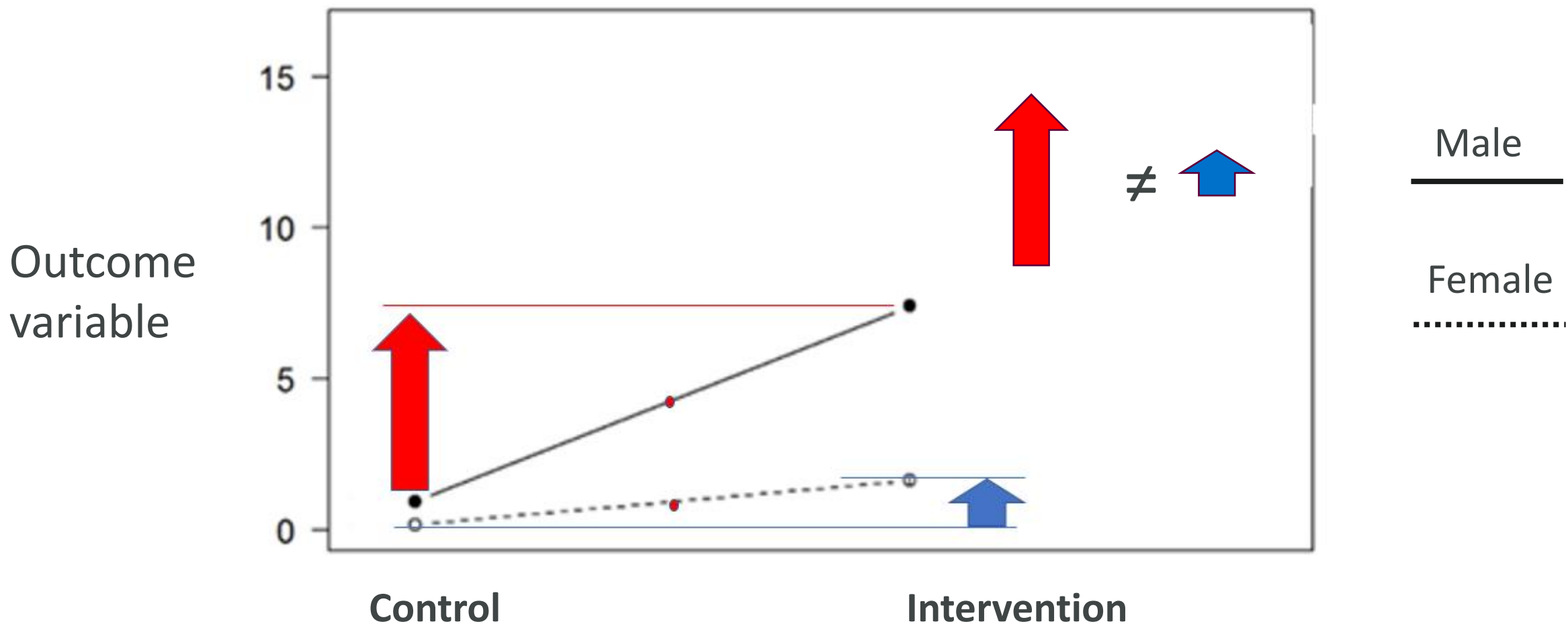


Testing the main effects: intervention and sex

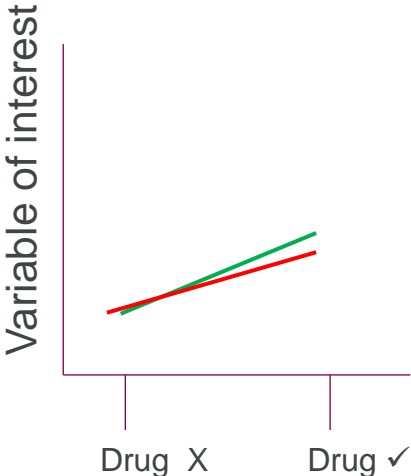
Outcome variable



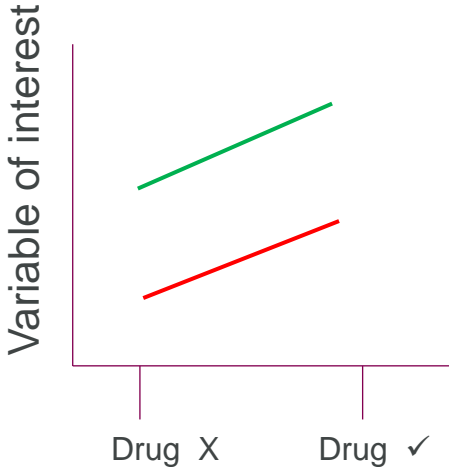
Testing the interaction: comparison of differences



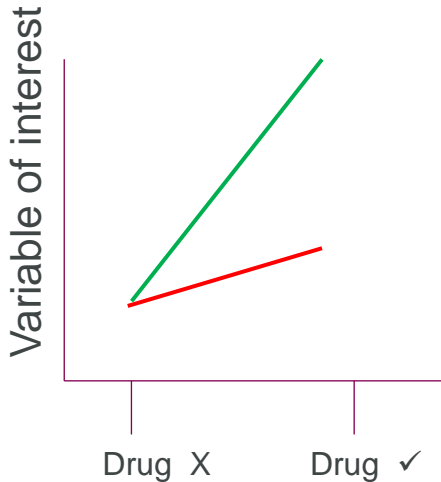
Some examples



Effect	Significant
Sex	X
Drug	✓
Interaction	X



Effect	Significant
Sex	✓
Drug	✓
Interaction	X



Effect	Significant
Sex	✓
Drug	✓
Interaction	✓

— Male
— Female



Misconception: It will DOUBLE my animal usage

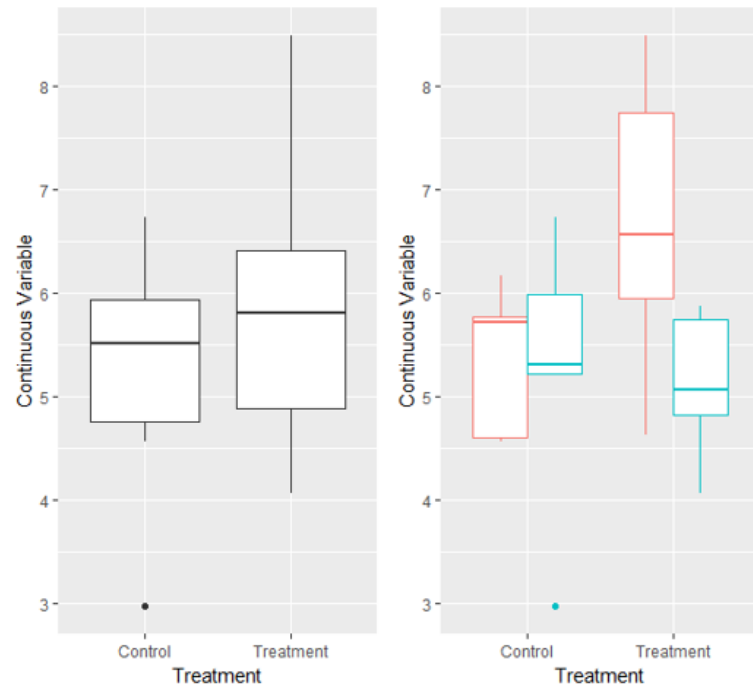
“Keep doing what you are already doing but change half the animals in your study to female”

McCarthy 2015 Schizophrenia Bulletin



Data analysis errors

Pooling



Disaggregation – analyse independently

- Loss of power
- Doesn't test for interaction



Practical issues – 2 sexes increase complexity and can have welfare challenges



Conclusions

- Misconceptions are significant part of the barrier to inclusion.
 - Female hormonal cycle does not mean that females are inherently more variable than male animals
 - Including both sexes does not increase variability and does not mean a doubling of your sample size
- It does require embracing new ways of analysing and visualising data.



References

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- Becker, Jill B., Brian J. Prendergast, and Jing W. Liang. "Female rats are not more variable than male rats: a meta-analysis of neuroscience studies." *Biology of sex differences* 7.1 (2016): 1-7.
- Prendergast, Brian J., Kenneth G. Onishi, and Irving Zucker. "Female mice liberated for inclusion in neuroscience and biomedical research." *Neuroscience & Biobehavioral Reviews* 40 (2014): 1-5.



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