

Causal Language To use or not to use....

Annette Flanagin

Executive Managing Editor

JAMA Network

Causal Language – why do we care?

- When authors/researchers use causal language in reports of studies, they are reporting that X causes Y, which can generally only be determined with specific study designs
- In high-profile medical journals, reporting X causes Y, when it may not do so, can be misleading to readers, clinicians, and other researchers - and can be potentially harmful to patients
- JAMA Network journals have editorial policies and guidance for authors regarding appropriate use of causal language for reports of research

When is causal language acceptable?

- Randomized clinical trials (RCTs)
- Laboratory experimental studies (JAMA Network journals rarely publish these)
- All JN journal Instructions for Authors indicate: “Causal language (including use of terms such as effect and efficacy) should be used only for randomized clinical trials. For all other study designs (including meta-analyses of randomized clinical trials), methods and results should be described in terms of association or correlation and should avoid cause-and-effect wording.”

<https://jamanetwork.com/journals/jama/pages/instructions-for-authors#SecUseOfCausalLanguage>

Casual language is not acceptable

- For secondary analyses of RCTs (in most cases and unless prespecified in the trial protocol)
- For observational studies
 - Cohort
 - Case-control
 - Cross-sectional
 - Case series
 - Meta-analysis - even a MA of RCTs
 - GWAS

Trigger words and substitutions for non-RCT titles, abstracts, methods, results

CAUSAL WORD	NONCAUSAL SUBSTITUTE
Effect (of or on)	Associated with, association between
Efficacy (different than effectiveness)	Associated with, association between
Directional words (eg, increased or reduced)	Associated with an increase in, associated with a reduction in
Related to or relationship	Associated with, association between

Do not replace “effect” with impact, influence, etc

When to use “correlated”

- When a statistical test is used to show correlation (eg, Pearson product moment, Spearman rank)
- *correlation*: “description of the strength of an association among 2 or more variables, each of which has been sampled by means of a representative or naturalistic method from a population of interest. The strength of the association is described by the correlation coefficient.” (From Glossary of Statistical Terms in *AMA Manual of Style*)
- r , r^2 , R , R^2

When to use “prediction” and “predictors”

- When the manuscript reports the results of a formal prediction model
- Includes appropriate statistics to predict an outcome
- Avoid use of the words “predict” and “predictive of” for reports of observational studies assessing independent and dependent variables, unless the **study design is a diagnostic/prognostic study and has used an appropriate approach to quantifying predictive performance such as use of validation samples**
- Note: a diagnostic or prognostic study type – alone – may not be sufficient

When to use “prediction” and “predictors”

- Study is diagnostic/prognostic AND a test/measure of quantifying predictive performance is used (look for validation samples)
- See reporting guidelines: [STARD](#) or [TRIPOD](#)
- Example: **Machine Learning–Based Prediction of Clinical Outcomes for Children During Emergency Department Triage**
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2720586>
- Otherwise, need to rephrase
 - “Factors (variables) associated with x” instead of “predictors for” or “x predicted y”

When some modified causal language may be acceptable

- Mendelian randomization with instrumental variable analysis
- Mediation analysis
- Helps if these analyses were prespecified in a clinical trial protocol

Mendelian randomization with instrumental variable analysis

- ***Mendelian randomization***: “a research method that provides evidence about putative causal relations between modifiable risk factors and disease, using genetic variants as natural experiments”
- ***Instrumental variables***: variables (such as a genetic variants) “that are associated with the risk factor of interest, that are not related to confounders, and that affects the outcome only through the risk factor”
 - *BMJ*. 2018. doi: <https://doi.org/10.1136/bmj.k601>
 - Podcast: Mendelian Randomisation for the Moderately Intelligent <https://www.bmj.com/content/362/bmj.k601>

Mendelian randomization

- “Mendelian randomization uses genetic variants to determine if an observational association between a risk factor and an outcome is **consistent with a causal effect.**”
- “relies on natural, random assortment of genetic variants during meiosis yielding a random distribution of genetic variants in a population” (eg, a gene variant that raises LDL cholesterol levels or an inflammatory marker for risk of schizophrenia)
- “Individuals who carry the variant and those who do not are followed up for the development of an outcome of interest.”
- “Because these genetic variants are typically unassociated with confounders, differences in the outcome between those who carry the variant and those who do not can be attributed to the difference in the risk factor.”

JAMA. 2017; 318(19):1925-1926. doi: 10.1001/jama.2017.17219

Mendelian randomization

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Mendelian Randomization

Connor A. Emdin, DPhil^{1,2}; Amit V. Khera, MD^{1,2}; Sekar Kathiresan, MD^{1,2}

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JAMA. 2017;318(19):1925-1926. doi:10.1001/jama.2017.17219

- Ed Livingston's JAMA Network Podcast

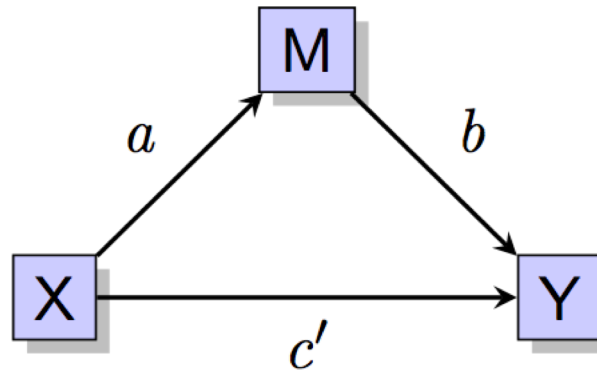
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Mendelian randomization analysis examples

- Hartwig FP, Borges MC, Horta BL, Bowden J, Davey Smith G. **Inflammatory Biomarkers and Risk of Schizophrenia: A 2-Sample Mendelian Randomization Study.** *JAMA Psychiatry.* 2017;74(12):1226–1233. doi:10.1001/jamapsychiatry.2017.3191
<https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2660057>
- Byrne EM, Yang J, Wray NR. **Inference in Psychiatry via 2-Sample Mendelian Randomization—From Association to Causal Pathway?** *JAMA Psychiatry.* 2017;74(12):1191–1192. doi:10.1001/jamapsychiatry.2017.3162
<https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2660056>

Mediation analysis

- “a hypothesized ‘causal chain’ in which 1 variable affects a second variable that, in turn, affects a third variable. The intervening variable, M , is the **mediator**”
- M mediates the relationship between X and Y

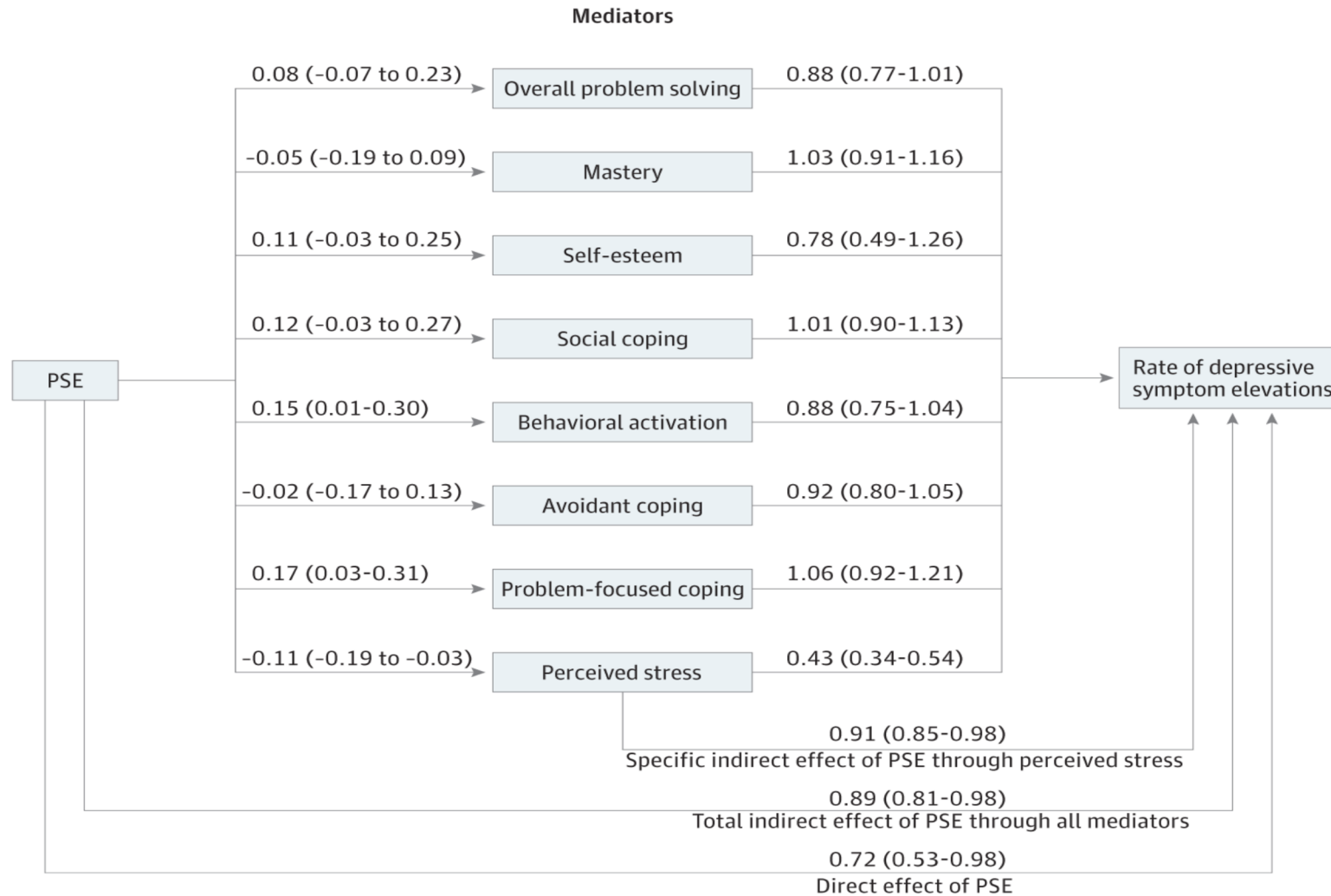


<http://davidakenny.net/cm/mediate.htm>

Mediation analysis example 1

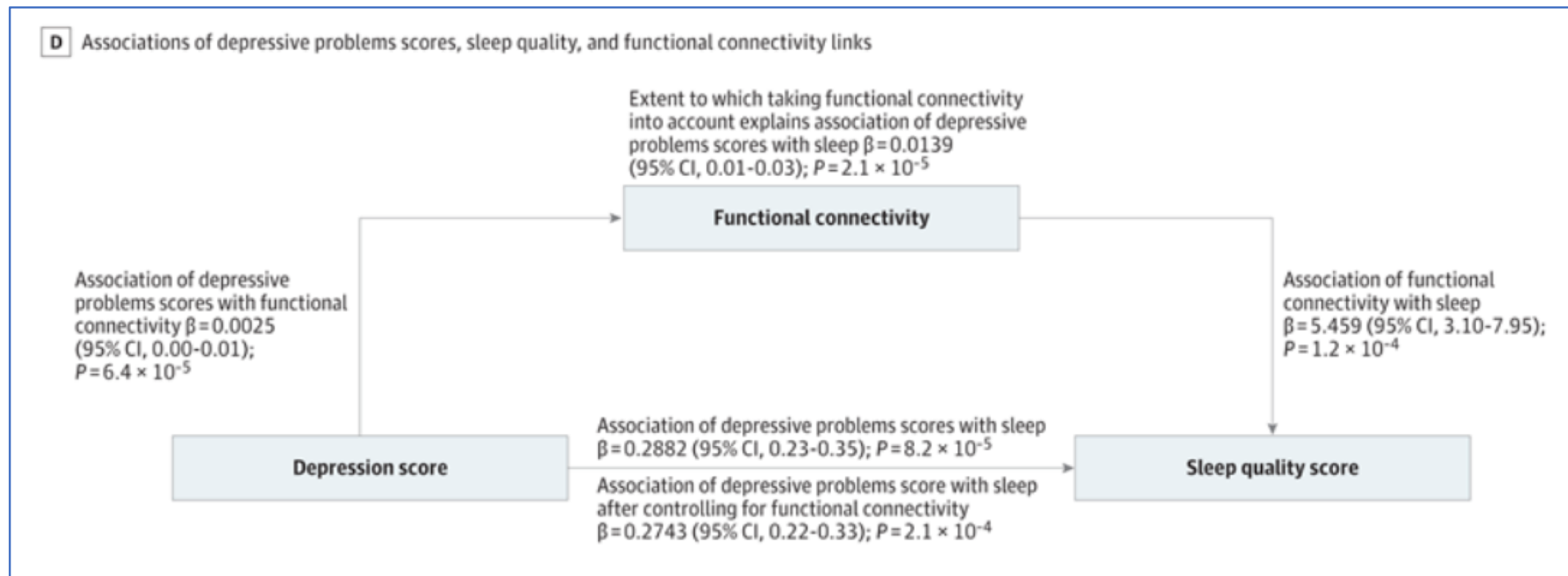
- Silverstein M, Cabral H, Hegel M, et al. Problem-Solving Education to Prevent Depression Among Low-Income Mothers: A Path Mediation Analysis in a Randomized Clinical Trial. *JAMA Netw Open*. 2018;1(2):e180334.
doi:10.1001/jamanetworkopen.2018.0334
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2686036>

Mediation analysis example 1



Mediation analysis example 2

- Cheng W, Rolls ET, Ruan H, Feng J. Functional Connectivities in the Brain That Mediate the Association Between Depressive Problems and Sleep Quality. *JAMA Psychiatry*. 2018;75(10):1052–1061. doi:10.1001/jamapsychiatry.2018.1941. <https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2688429>



Mediation analysis

JAMA Guide to Statistics and Methods

January 25, 2019

Mediation Analysis

- Lee H, Herbert RD, McAuley JH. Mediation Analysis. *JAMA*. Published online January 25, 2019. doi:10.1001/jama.2018.21973.
<https://jamanetwork.com/journals/jama/fullarticle/2723293>