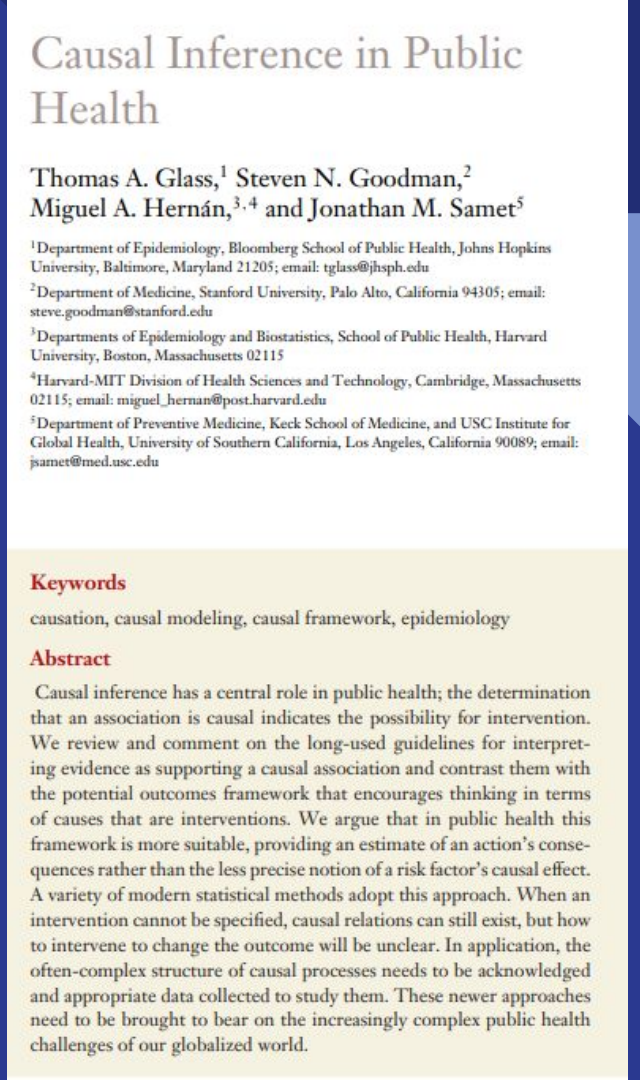
Causal inference 1.0

Frameworks and Randomized Controlled Trials



Causal Inference in Public Health

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causation, causal modeling, causal framework, epidemiology

Abstract

Causal inference has a central role in public health; the determination that an association is causal indicates the possibility for intervention. We review and comment on the long-used guidelines for interpreting evidence as supporting a causal association and contrast them with the potential outcomes framework that encourages thinking in terms of causes that are interventions. We argue that in public health this framework is more suitable, providing an estimate of an action's consequences rather than the less precise notion of a risk factor's causal effect. A variety of modern statistical methods adopt this approach. When an intervention cannot be specified, causal relations can still exist, but how to intervene to change the outcome will be unclear. In application, the often-complex structure of causal processes needs to be acknowledged and appropriate data collected to study them. These newer approaches need to be brought to bear on the increasingly complex public health challenges of our globalized world.

Why do we care if an association is “causal”?

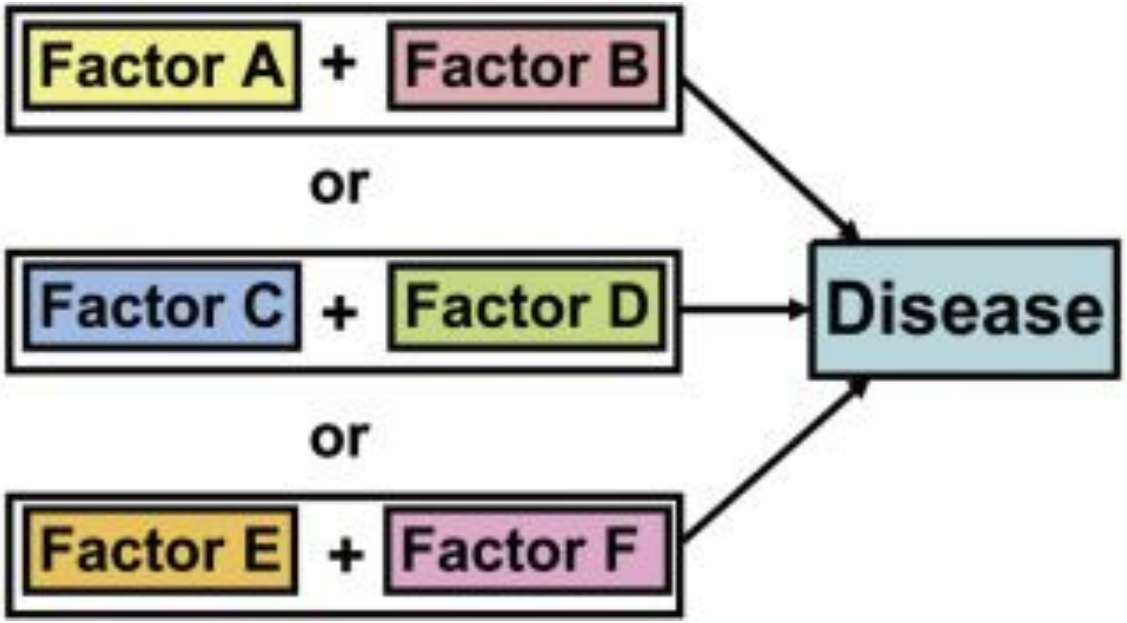
- **Primary justification for instituting policies, programs, regulations, treatments, etc.**
  - Safe levels of contaminants in drinking water and soil (and when they must be mitigated)
  - Limiting access to tobacco and exposure to second-hand smoke
  - Screening protocols (when, how often, for whom) for breast, colon, prostate cancer
  - Establishing new standards of care
  - Supplementing foods with nutrients (e.g., niacin, iodine) to prevent malnutrition
  - Putting children to bed on their back to prevent SIDS

- **Once programs, policies, regulations, treatments, etc. get established they become “sticky” - meaning it is more challenging to get them removed (the burden of proof is shifted to demonstrating that it *does not work* - which is still a *causal* claim!)**
  - DARE as an ineffective program for preventing drug abuse
  - Stents and bypass surgery as unnecessary for preventing mortality for stable patients
  - The Back to Sleep campaign didn’t come until decades of observational research demonstrating the benefits - showing the stickiness of existing beliefs given the lack of RTC data on back sleeping

Logic 101: Types of (abstract) causal relationships

- Necessary
  - A is a necessary cause of B if B never occurs in the absence of A
  - The presence of A does not inevitably lead to B
- Sufficient
  - A is a sufficient cause of B if the presence of A inevitable leads to B
  - A = the minimum set of factors/conditions that will produce B
- Necessary and sufficient
  - A is a N & S cause of B IFF B only occurs in the presence of A, and the presence of A is the minimum set of factors necessary to produce B
- Neither necessary nor sufficient

Illustration of causal relationships that are neither necessary nor sufficient



Different combinations of exposures (risk factors) can generate the same disease outcome.

This schematic is reasonable for almost all diseases, even those that have “necessary” components.

Why do we say experiments (randomized controlled trials) allow us to estimate a **causal** effect?

Before we get to that:
A reminder

For any given person, you can only observe one state of the world at a time (e.g., exposed or not, diseased or not).

That is: You can only observe what DID HAPPEN to them.

Where what DID (in fact) happen is:

They were exposed (or not)

They developed disease (or not)

Before we get to that:
A reminder

For **any given person**, you can **only observe one state of the world** at a time (e.g., exposed or not, diseased or not).

What we want to know:

What WOULD HAVE HAPPENED to them IF…

Where the “IF” is

“They had been exposed” ***(if they were, in fact, unexposed)***

OR

“They had not been exposed” ***(if they were, in fact, exposed)***

Got it.

One question: What does this have to do with randomized controlled trials/experiments?

- The **two arms of a RCT are** composed of individuals who are, on average, **similar in every way except for the fact** that one group got the **treatment (exposure)** and the other group got **placebo (unexposed).**
- They are similar on both observed and unobserved (unmeasured) characteristics...

Except for the “WHAT IF…”

Therefore, if the two groups differ at the end of the trial in their disease status, we infer that this is (only) because of the WHAT IF (treatment vs. placebo).

That is: the treatment CAUSED the difference in the outcome.

So you’re saying that I should abandon my research program of observational/survey research and start doing RCTs because otherwise I’ll never be able to say anything meaningful about the exposures/diseases I care about and want to prevent?

But RCTs can't answer all (or even most) of our questions about the causes of population health: Why not?

1. **Clinical Trials/Experiments are generally designed to only examine one outcome at a time.**
    a. Many most risk factors are SHARED across outcomes (e.g., smoking predicts cancer and CVD) and so if I only look at one outcome at a time, I am undoubtedly getting an INCOMPLETE PICTURE of the impact of that exposure as a determinant of population health.
2. **Trials are generally designed to estimate ACUTE effects**
    a. For many health conditions, the etiologic period is on the order of YEARS or DECADES, and so a trial would have to last many, many years to see an effect.
3. **We can only use experiments to evaluate exposures that we think would BENEFIT the individual.**
    a. For example, we could randomize people to exercise as a PREVENTIVE for depression, but we could not randomize them to stress.

Moving Causal Claims from Experimental to Observational Data: The Potential Outcomes Framework

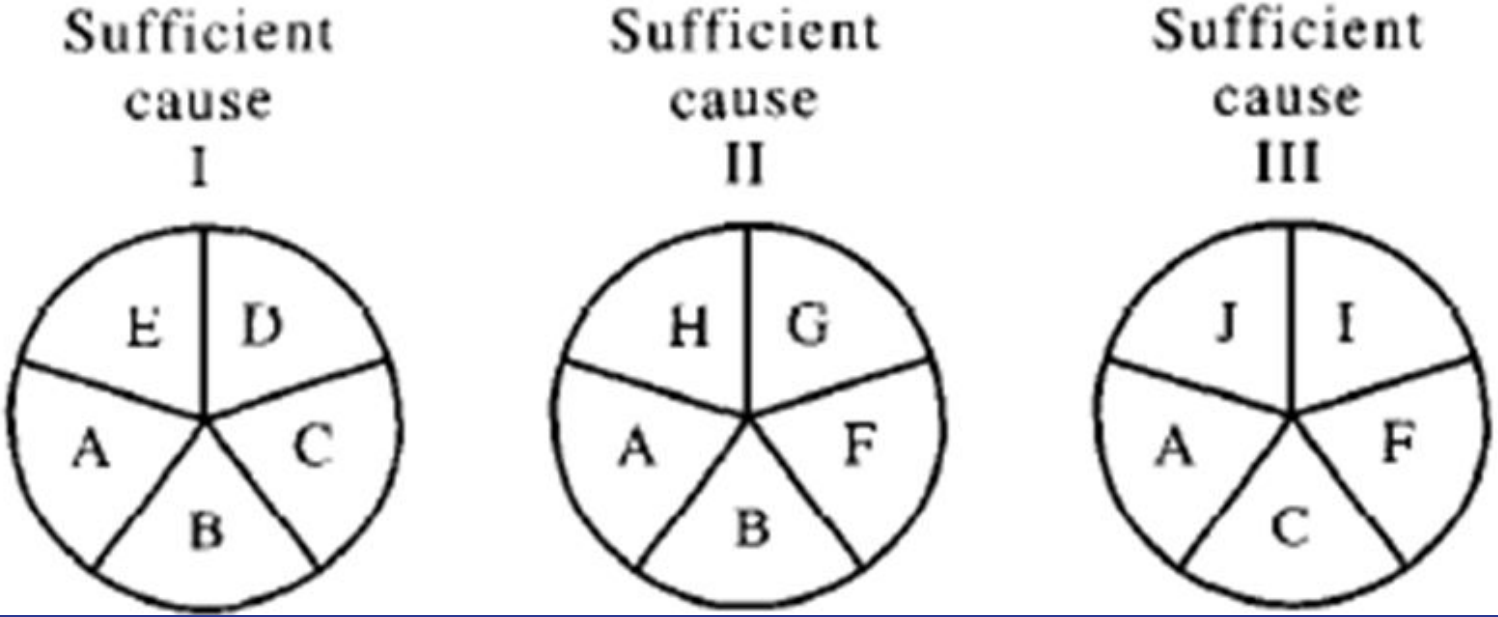
- **Main idea: To compare what was observed (what did happen) to what might have happened (what did not happen) - all other things being equal (controlling for all confounders)**
  - What would have happened to the people who got Treatment A (exposed) if they had gotten Treatment B (unexposed), given that they got Treatment A (exposed)?
- Implements the logic of the experimental design into observational data

So what should observational researchers do instead?

- Policy makers are primarily interested in understanding and addressing the **sufficient causes** of population health:
  - ***What is the probability that a healthy unexposed individual would have contracted the disease had she been exposed?*** This is different than asking: ***Was the exposure necessary to cause her illness?***
  - Think about this from the perspective of **Legal Responsibility or Culpability**: Should a company be held liable for harm incurred during the use of its product? If the answer is yes, what are you saying about the causal relationship between the product and the harm?
- **The parallel to public health is this**: It matters less whether an exposure was *necessary to cause disease*, just whether the evidence indicates it was ***sufficient*** *to cause disease*.

Component causes: Rothman's causal pies

- Reflects the fact that each "sufficient cause" has multiple components within it
- Each disease outcome has >1 "component causal pie" that can produce it



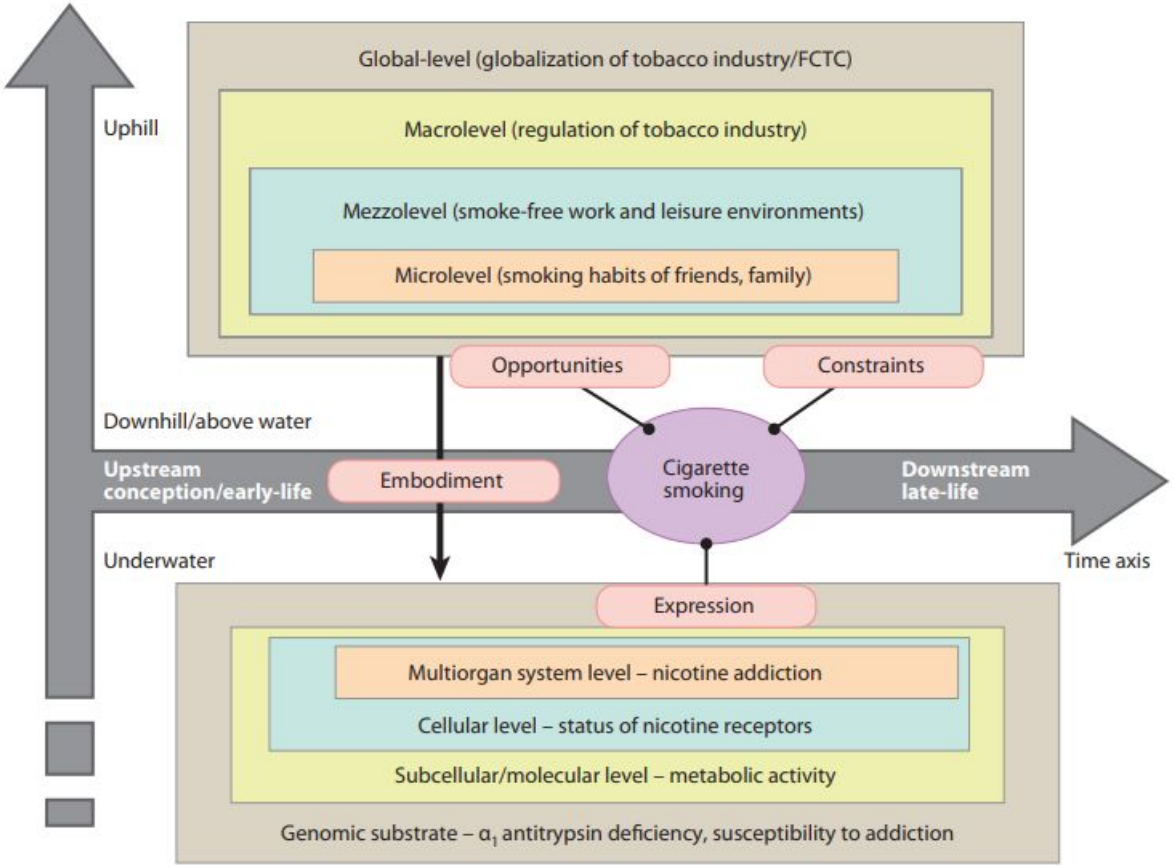


Figure 1

Axis of nested hierarchies for tobacco control. Reprinted with permission from Samet & Wipfli (65). FCTC, Framework Convention on Tobacco Control.

This may be the logic model that you have in your mind when you are planning your research career…

…but when it comes to any specific study, you are only ever investigating a small portion of this multi-level, life-long process.

Bri's Minimum requirements* for investigating causal relationships from observational data

1. Longitudinal/panel data
    a. Initial/baseline appropriate for the causal process you are investigating
    b. Follow-up duration appropriate for the causal process you are investigating
    c. Follow-up frequency appropriate for the causal process you are investigating
2. Accurate assessment of exposure status over time
3. Accurate assessment of outcome status over time
4. Unbiased sampling/response rate (>75% of eligible)
5. Minimal attrition/loss to follow-up (~80-85% retention)
6. Information on measured confounders
7. Indicators of unmeasured/unmeasurable confounders
8. Appropriate statistical methods

*Subject to change without notice.

Causality 2.0: Analytic methods appropriate for assessing causality from observational data

- Directed Acyclic Graphs (DAGs) as a tool for visualizing causal relationships
- Propensity score matching/weighting techniques
- Marginal structural models
- Instrumental variable analyses
- Time-series and Difference-in-difference analyses
- Evaluating “Natural experiments” of **exogenous sources of variation**
  - Comparing identical twins
  - Policy changes that were implemented at different times/to different groups, etc. (see example at the end of this deck)
  - Accidents (e.g., randomly half of patients didn’t get a reminder letter they were supposed to because of a glitch in the mailroom)
  - Mendelian randomization

Summary

- Invoking causal language has powerful consequences, both good and bad.
- Strong experimental data isn't the only thing that informs policy changes, but its presence (and absence) is part of the conversation.
- There are costs to implementing programs based on research that has not sufficiently "kicked the tires" of causality - and it costs more to de-implement those programs once they get established.
- The logic model underlying your research guides hypothesis development, study design, interpretation of results, etc. but it is not directly testable by any single project.

For HRS users - working group!

Purpose: To provide dedicated time for early-career scientists who are working with the HRS data to learn from each other and problem solve data management and analytic issues as they arise.

Frequency and timing: 60 minutes, 1x per month on Wednesdays (9-10am EST)

Schedule for Winter/Spring 2022 (9-10am EST)

1/26
2/23
3/23
4/27
5/25

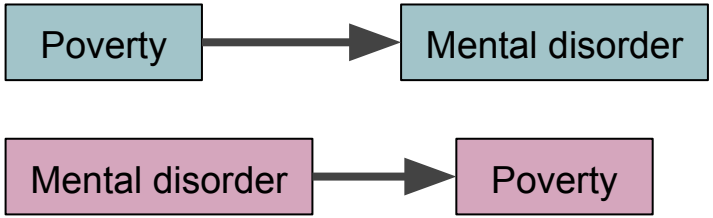
Format: The agenda for each month is open - scientists should come prepared to discuss their projects using HRS data, have questions they want to pose to the group, and engage in active dialogue about their ideas using this cohort.

Resources: There are some recommended readings in this Google Folder. Working group members are encouraged to add additional materials to this shared google folder.

Example of an actual “Natural experiment”

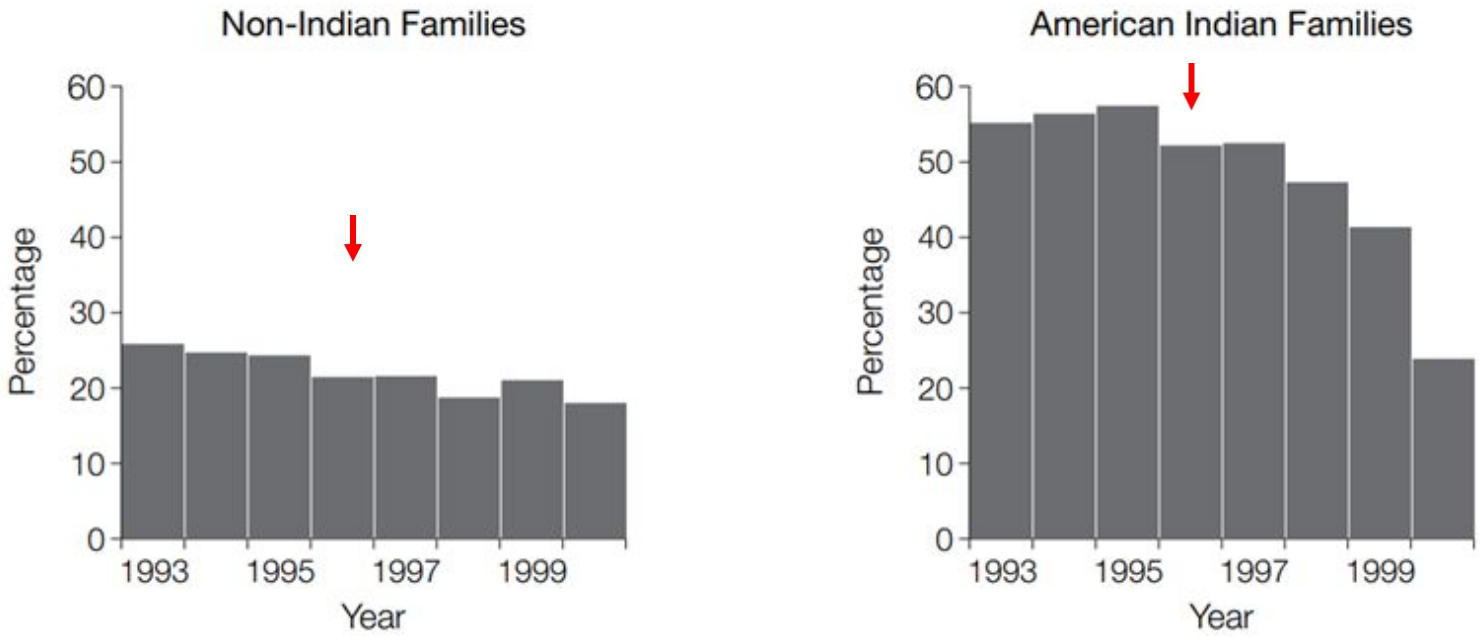
- Most mental disorders are more common among lower socioeconomic status (SES) groups relative to higher
- Two causal models could explain this patterning
  - Model 1: Low SES (poverty, low education, etc.) increases risk of mental disorders
  - Model 2: Persons with psychopathology drift into (or fail to move out of) lower SES
- **Need to manipulate SES in order to determine the causal nature of the relationship between SES and mental health**

Two potential models of the causal relationship between poverty and mental health



“Natural experiment” manipulation of SES: Opening of a casino

Figure. Annual Percentage of Non-Indian and Indian Families Below the Poverty Line



Three groups: (1) Never poor, (2) Persistently poor, and (3) Formally poor. The difference between 2 and 3 = effect of relieving poverty on mental health.

Behavioral problems in children: Pre- to Post-Casino

	Before Casino	After Casino	Contrast Before vs After Casino, OR (95% CI)*
Persistently poor, mean (SD)	2.41 (2.69)	2.91 (3.80)	0.80 (0.64-1.01), $P = .06$
Ex-poor, mean (SD)	2.25 (2.65)	1.34 (2.07)	1.66 (0.97-2.83), $P = .07$
Never poor, mean (SD)	1.30 (2.11)	1.37 (1.93)	0.95 (0.62-1.44), $P = .80$
Contrast persistently vs ex-poor*			
OR (95% CI)	1.07 (0.70-1.64)	2.21 (1.24-3.95)	
P value	.75	.007	
Contrast persistently vs never poor*			
OR (95% CI)	1.86 (1.25-2.78)	2.19 (1.47-3.28)	
P value	.002	<.001	
Contrast ex- vs never poor*			
OR (95% CI)	1.73 (1.03-2.91)	0.99 (0.53-1.86)	
P value	.04	.98	

Abbreviations: CI, confidence interval; OR, odds ratio.
*See Table 1 for explanation.

Observation 1: Both persistently poor and ex-poor are different after the casino (but in opposite directions)

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Observation 2: No difference in persistently poor vs. ex-poor PRE-CASINO, but they are different AFTER the casino opens.

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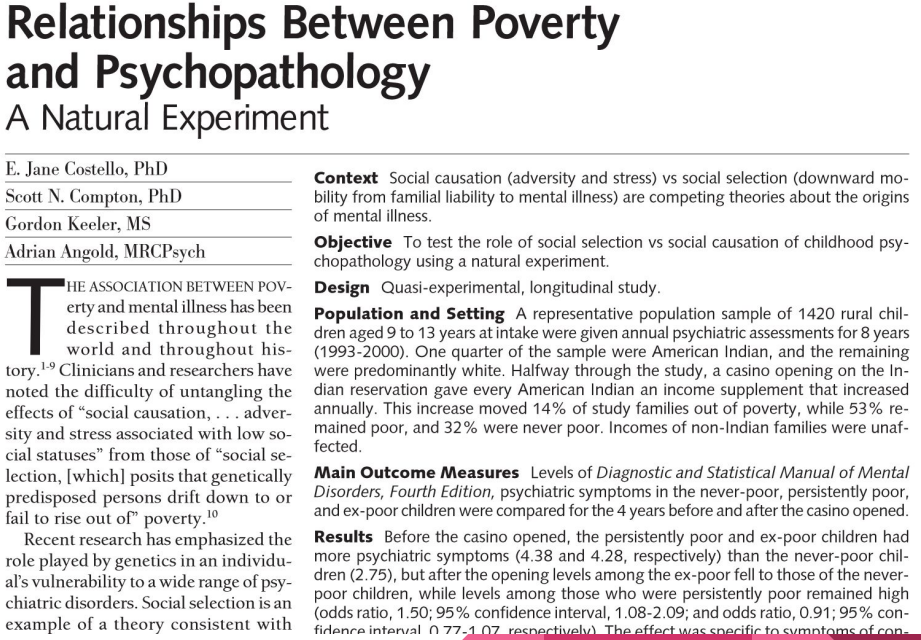
Abbreviations: CI, confidence interval; OR, odds ratio.
*See Table 1 for explanation.

Observation 3: Significant difference in never vs. ex-poor PRE-CASINO but no difference AFTER CASINO

Summary

- The casino caused a subset of families to have higher income
- Higher income translated into improved behavioral health outcomes for the children in those families that gained SES.
- *What did you think Costello and company hypothesized as to the mechanism?*



Relationships Between Poverty and Psychopathology

A Natural Experiment

E. Jane Costello, PhD
Scott N. Compton, PhD
Gordon Keeler, MS
Adrian Angold, MRCPsych

THE ASSOCIATION BETWEEN POVerty and mental illness has been described throughout the world and throughout history.[1-9] Clinicians and researchers have noted the difficulty of untangling the effects of "social causation, . . . adversity and stress associated with low social statuses" from those of "social selection, [which] posits that genetically predisposed persons drift down to or fail to rise out of" poverty.[10]

Recent research has emphasized the role played by genetics in an individual's vulnerability to a wide range of psychiatric disorders. Social selection is an example of a theory consistent with

Context Social causation (adversity and stress) vs social selection (downward mobility from familial liability to mental illness) are competing theories about the origins of mental illness.

Objective To test the role of social selection vs social causation of childhood psychopathology using a natural experiment.

Design Quasi-experimental, longitudinal study.

Population and Setting A representative population sample of 1420 rural children aged 9 to 13 years at intake were given annual psychiatric assessments for 8 years (1993-2000). One quarter of the sample were American Indian, and the remaining were predominantly white. Halfway through the study, a casino opening on the Indian reservation gave every American Indian an income supplement that increased annually. This increase moved 14% of study families out of poverty, while 53% remained poor, and 32% were never poor. Incomes of non-Indian families were unaffected.

Main Outcome Measures Levels of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition,* psychiatric symptoms in the never-poor, persistently poor, and ex-poor children were compared for the 4 years before and after the casino opened.

Results Before the casino opened, the persistently poor and ex-poor children had more psychiatric symptoms (4.38 and 4.28, respectively) than the never-poor children (2.75), but after the opening levels among the ex-poor fell to those of the never-poor children, while levels among those who were persistently poor remained high (odds ratio, 1.50; 95% confidence interval, 1.08-2.09; and odds ratio, 0.91; 95% confidence interval, 0.77-1.07, respectively). The effect was specific to symptoms of con-