# Confounding of indirect effects in the "real world"

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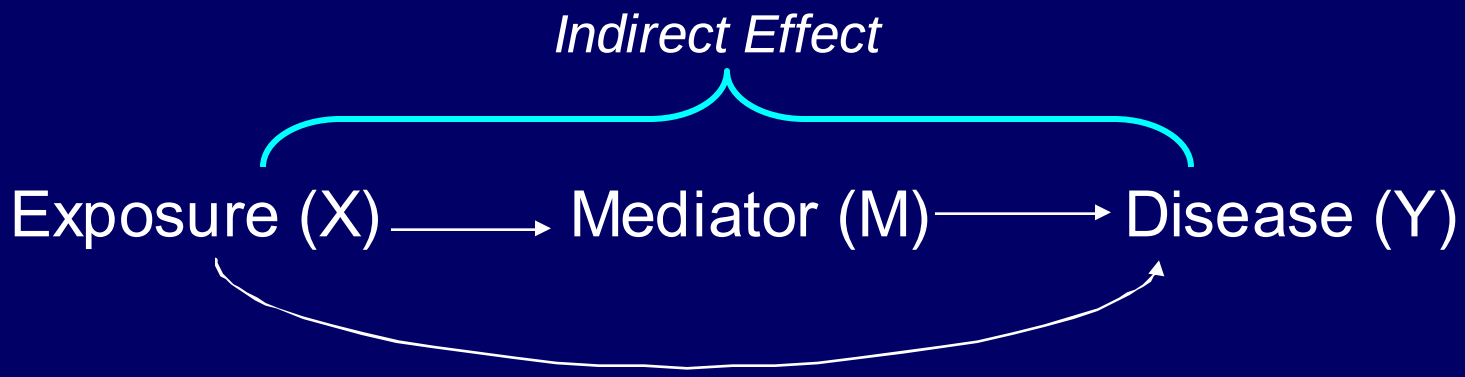
# What is an indirect effect?

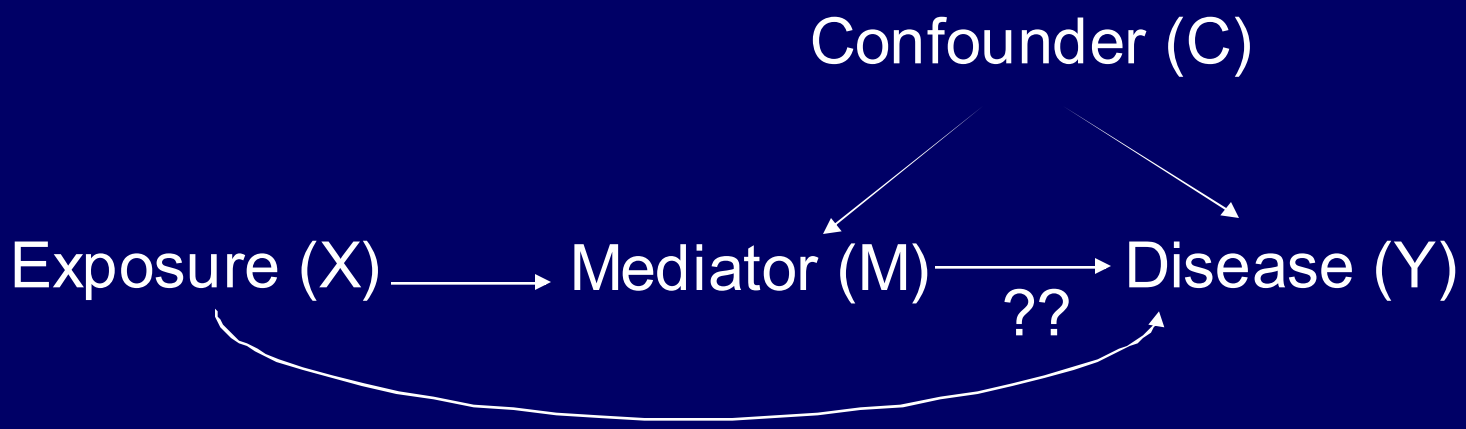
## Main Effect:

Exposure (X) ⟶ Disease (Y)

## Pathways that explain the main effect:



# Confounding of the mediator




- Biases the indirect and direct effects, but not the main effect
- Problematic even when exposure (X) is randomized

# “Real world” impact of confounding?

- A confounder of the mediator can cause bias (e.g. Cole and Hernan 2002)
- But how much bias? How much confounding would it take to explain the observed indirect effect??

> “There is an urgent need for further methodological research that determines the likely magnitude and direction of bias in the estimation of direct and indirect effects” (Blakely 2002)

# Study Aims

- Question:

  How much of a threat does confounding of the mediator pose under “real world” circumstances?

- Basic Approach:
  - Develop sensitivity analysis program
  - Re-assess results from two well-known mediation studies

# Methods: Sensitivity Analysis

- Inputs
- Outputs

# Inputs: Observed Risks

- Risk of the Mediator
  - … in the unexposed: M0
  - … in the exposed: M1
- Risk of Disease
  - … in the unexposed, mediator-negative: Y00
  - … in the exposed, mediator-negative: Y10
  - … in the unexposed, mediator-positive: Y01
  - … in the exposed, mediator-positive: Y11

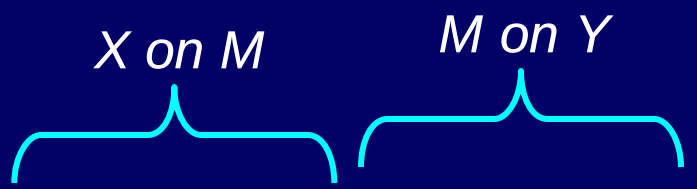
# Inputs: Confounder Characteristics

- Confounder Prevalence
  - Range of possible confounder prevalences tested
  - P(C=1) = .01, .2, .4, .8
- How much does the confounder interact with the exposure and the mediator?
  - No synergy
  - Perfect additivity
  - Perfect multiplicativity
  - Complete synergy

# Outputs: Observed Effects

- Main Effect = Y1 – Y0

- Indirect Effect




Pure Indirect Effect (PIE) = (M1-M0) x (Y01-Y00)

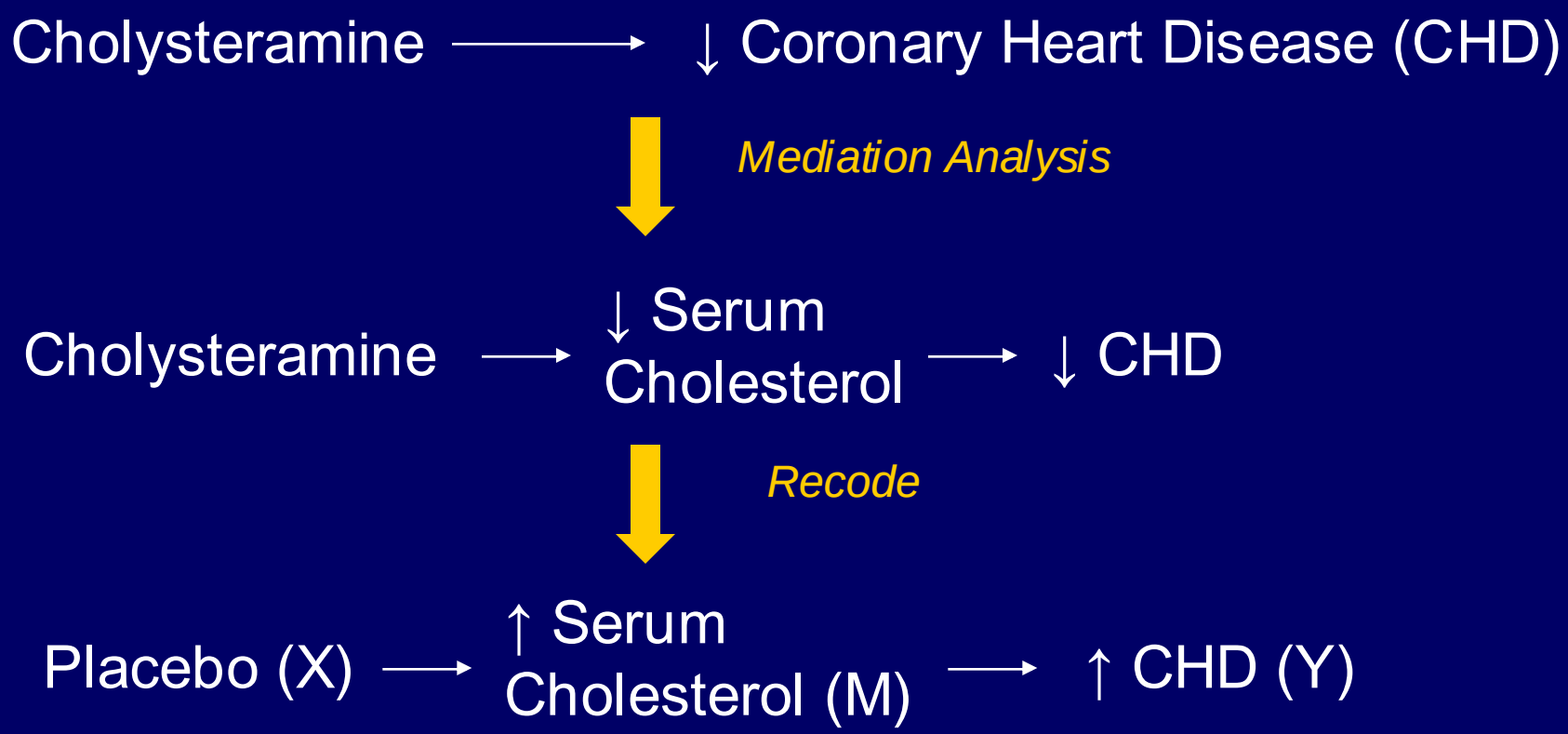
- Proportion Explained = Indirect Effect/Main Effect

# Outputs: True Indirect Effects

- For each possible confounding scenario...
  - Confounder Prevalence
  - Interaction Model
  - Confounder-mediator risk ratio
  - Confounder-disease risk ratio

  ... determine true indirect effect consistent with observed results
- Which confounding scenarios would change our interpretation of observed results?

# Example 1: CHD
(Freedman et al. 1992)



# CHD Example: Observed Risks and Effects

- Observed Risks

| X | M0 | M1 | Y00 | Y01 | Y10 | Y11 |
|---|---|---|---|---|---|---|
| .5 | .193 | .392 | .064 | .090 | .074 | .109 |

- Observed Effects

| Main Effect | Indirect Effect (PIE) | Proportion Explained |
|---|---|---|
| .0187 | .0053 | 28% |

# CHD Example: True Indirect Effects

Question: *Could confounding plausibly explain the observed indirect effect?*

Answer: *Yes*

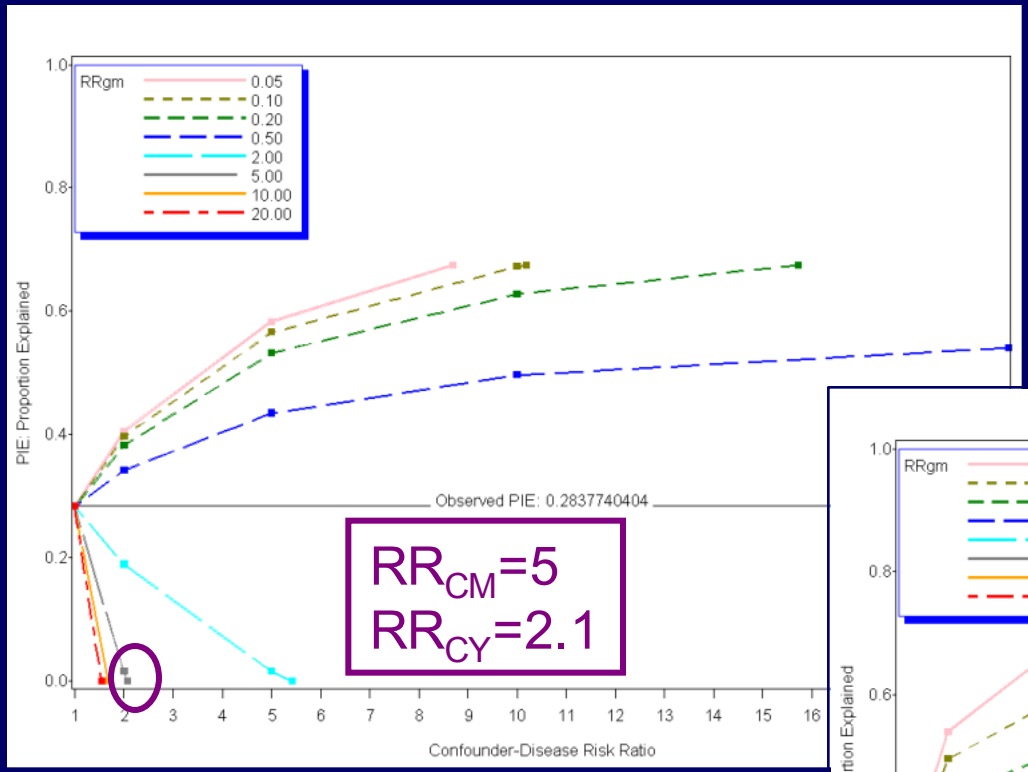
Question: *How strong would such a confounder have to be?*

Answer: *It depends on...*

- Confounder Prevalence
- Interaction Model

# Confounder Prevalence

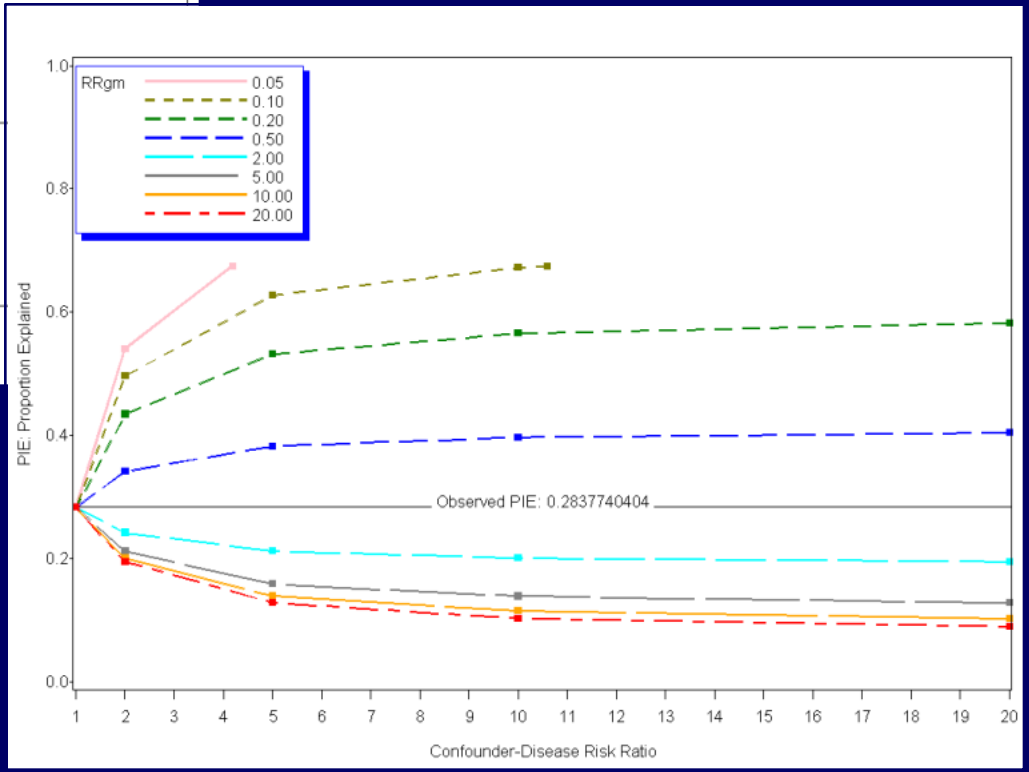
C=.2




$RR_{CM}=5$
$RR_{CY}=2.1$

No Synergy

C=.8



# Example 2: Vision Loss
(Buyse & Mohlenbergs 1998)

Interferon-α ⟶ Vision Loss @ 12 mo.

*Mediation Analysis*

Interferon-α (X) ⟶ Vision Loss @ 6 mo. (M) ⟶ Vision Loss @ 12 mo. (Y)

# Vision Loss Example: Observed Risks and Effects

- Observed Risks

| X | M0 | M1 | Y00 | Y01 | Y10 | Y11 |
|---|---|---|---|---|---|---|
| .46 | .369 | .540 | .139 | .790 | .225 | .809 |

- Observed Effects

| Main Effect | Indirect Effect (PIE) | Proportion Explained |
|---|---|---|
| .161 | .111 | 69% |

# Vision Loss Example: True Indirect Effects

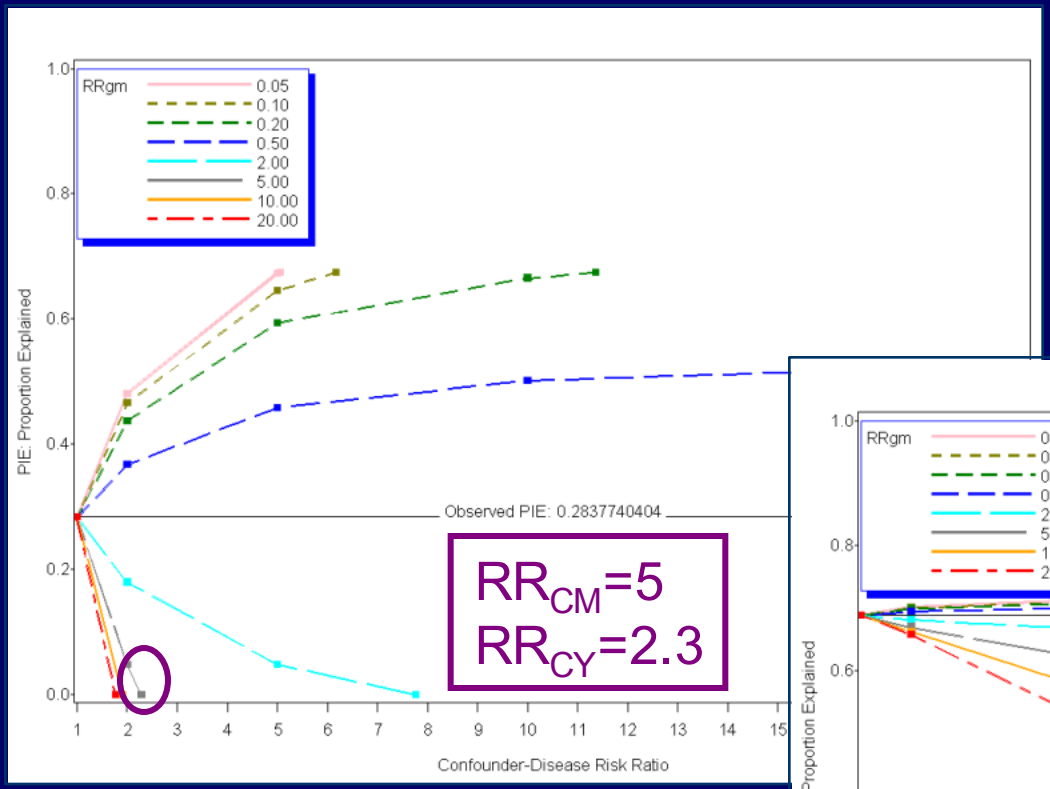
Question: *Could confounding plausibly explain the observed indirect effect?*

Answer: *Only under very limited conditions…*

- Interaction model (No synergy, perfect additivity)
- Confounder prevalence (C=.4)
- Strong risk ratios (>10)

# Comparison: CHD vs. Vision Loss (1)

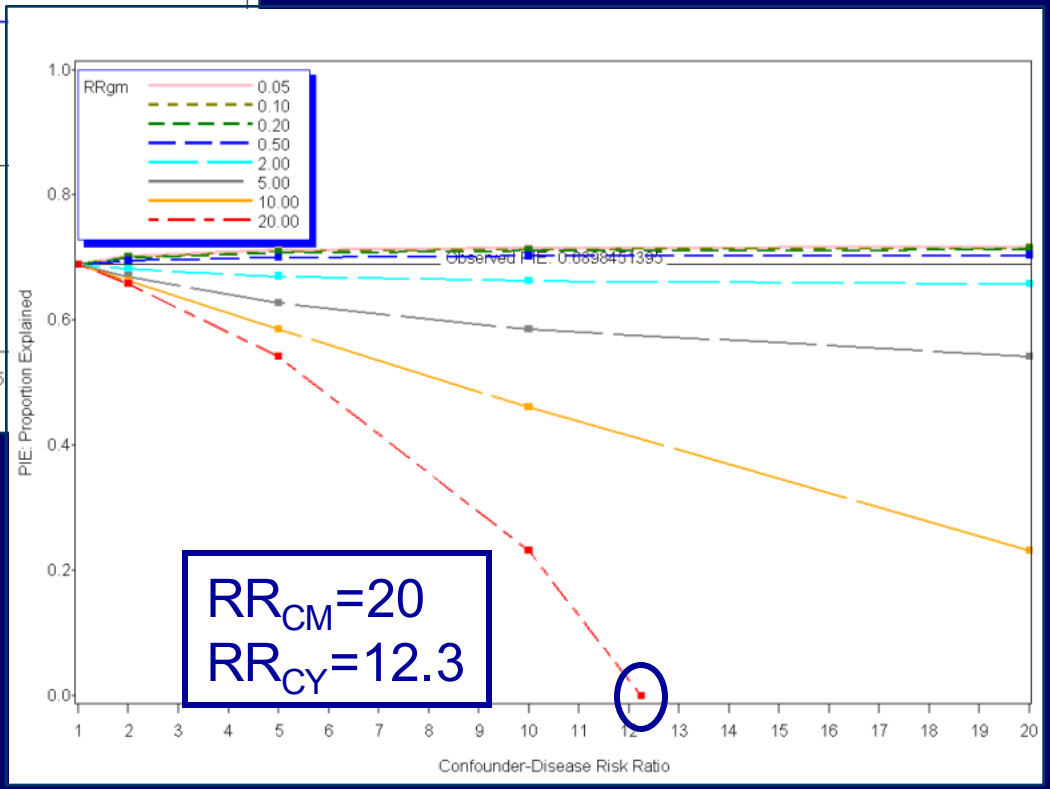
CHD




$RR_{CM}$=5
$RR_{CY}$=2.3

No Synergy
C=.4

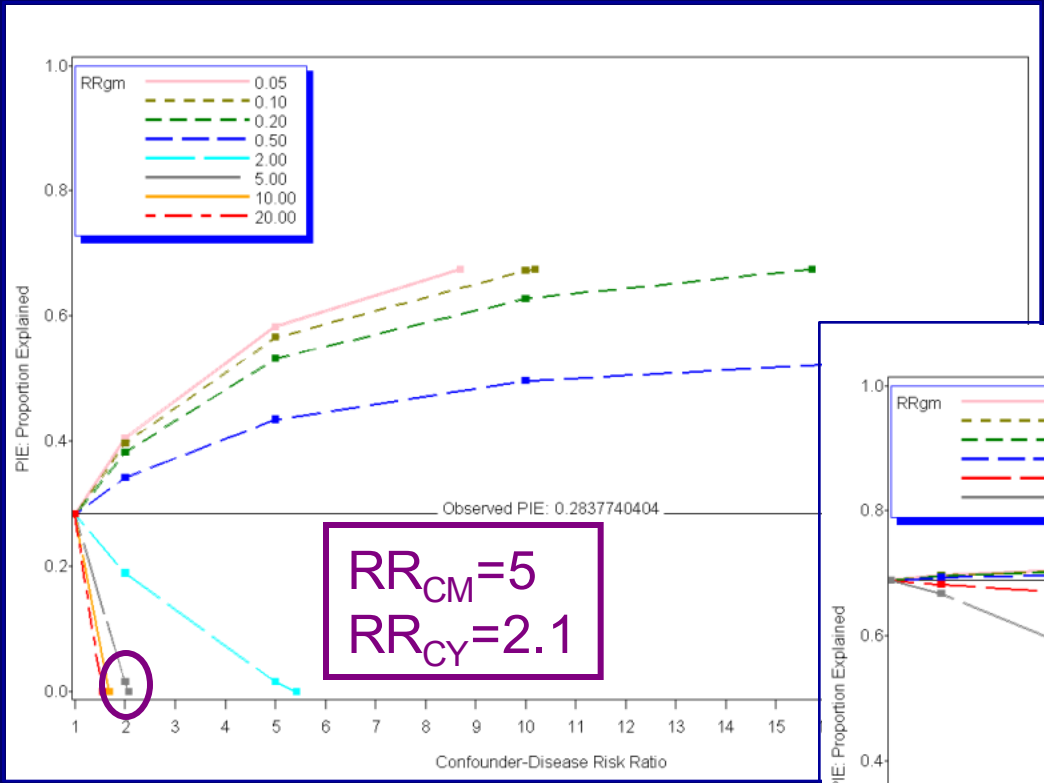
Vision Loss




$RR_{CM}$=20
$RR_{CY}$=12.3

# Comparison: CHD vs. Vision Loss (2)

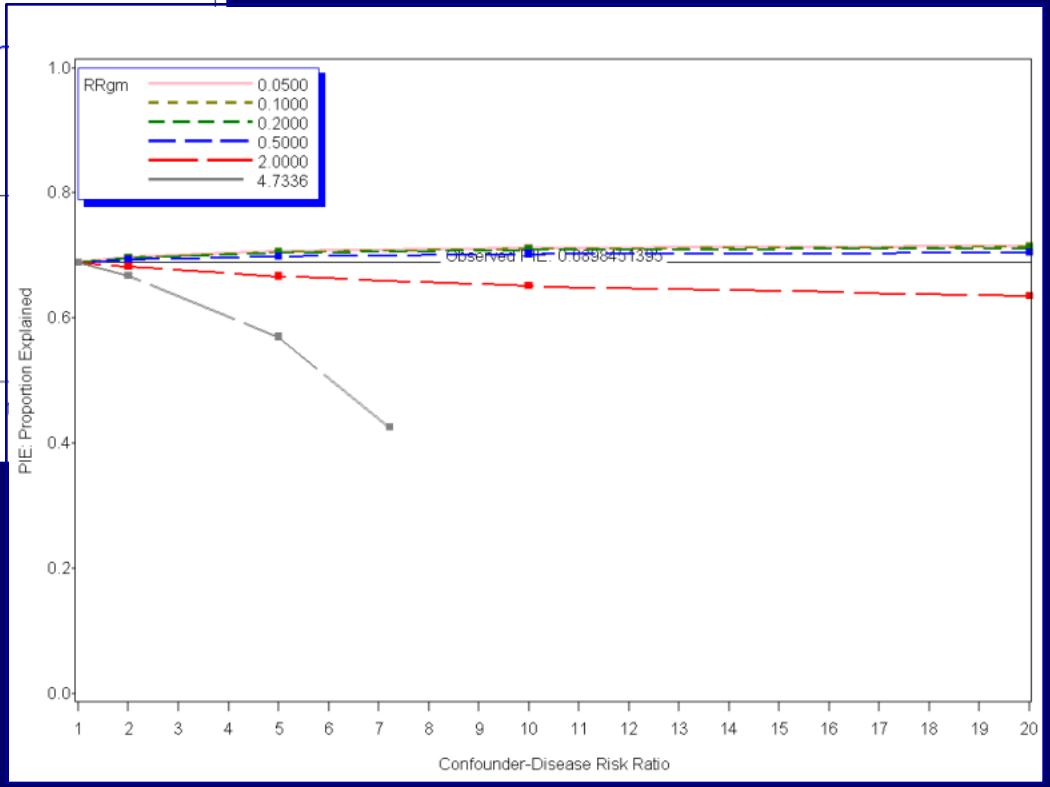
CHD




$RR_{CM}$=5
$RR_{CY}$=2.1

No Synergy
C=.2

Vision Loss



# Results: Summary

- CHD Example
  - Confounding is a plausible alternative explanation

    (e.g. G=.2, $RR_{CM}$=5, $RR_{CY}$=2.5)
  - *Note:* Main effect even more vulnerable to confounding

    (e.g. G=.2, $RR_{CX}$=2, $RR_{CY}$=2)

- Vision Loss Example
  - Confounding is not a plausible alternative explanation

    (e.g. G=.4, $RR_{CM}$=20, $RR_{CY}$=12.3)

# Conclusions

- Assessment of mediation is not hopeless
- Main effect more vulnerable to confounding than the indirect effect
- Confounding represents a viable alternative explanation in some situations, but not others
- Investigators should consider the role that confounding might play in their assessment of mediation

# Acknowledgements

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