Mediation Analysis: A Primer

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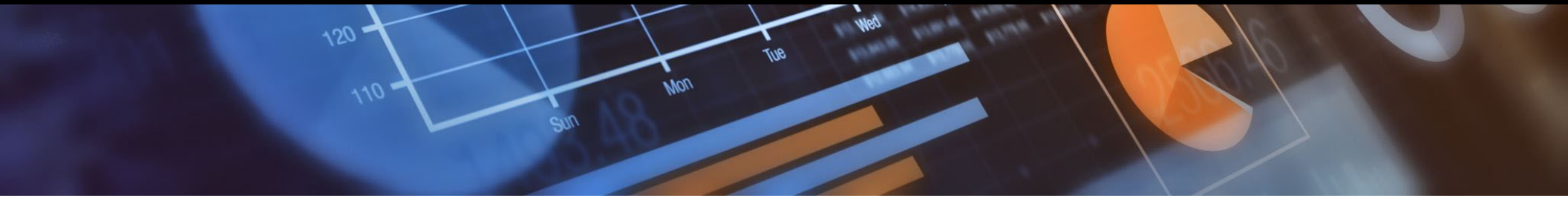


Outline

Section 1: Background

Section 2: Modern Approaches

Section 3: Real-World Example

Section 1: Background

What is mediation?

- A phenomenon that occurs when the effect of an exposure on an outcome is (at least partially) caused by the action of the exposure on a third factor (a mediator) that then itself affects the outcome.
- In other words, the exposure causes a change in the mediator, and the mediator then causes a change in the outcome.

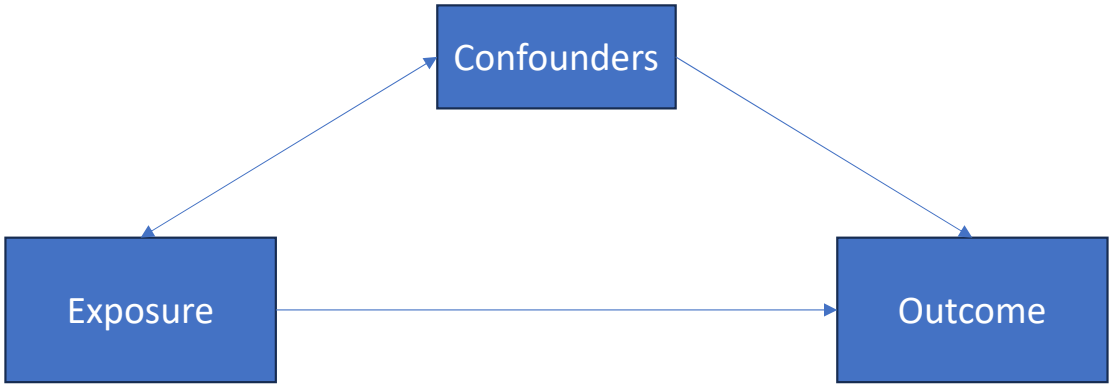
Why Does it Matter?

Understanding

New tools

Traditional Regression Approach

- Confounder: a covariate that is associated with both the exposure and the outcome but does not mediate the relationship.
  - (In other words, a confounder cannot lie on the causal pathway, or it is a mediator, not a confounder)
- We usually avoid controlling for mediators.

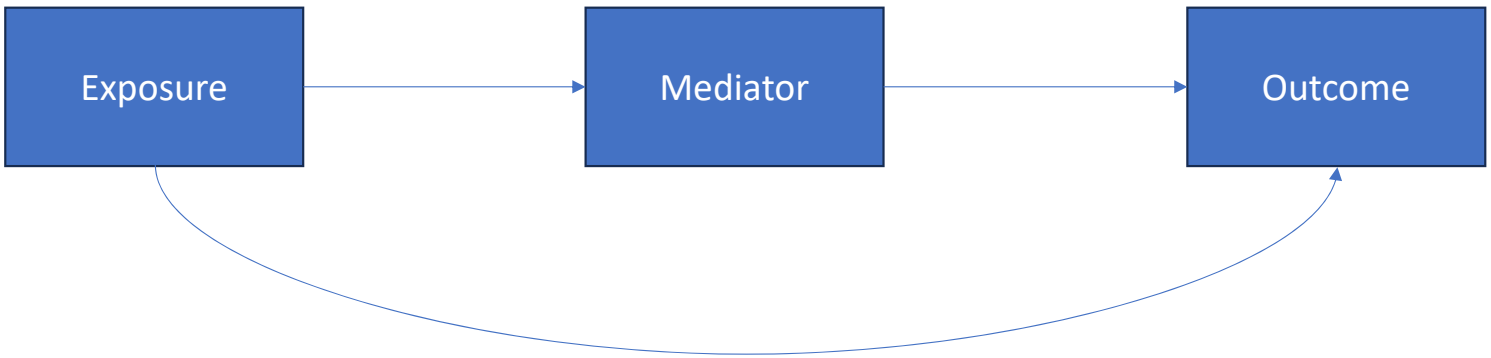


Total vs Partial Mediation

- Total mediation: the mediator is 100% responsible for the action of the exposure on the outcome.
- In the absence of the mediator, the exposure has no effect on the outcome.
- Rare

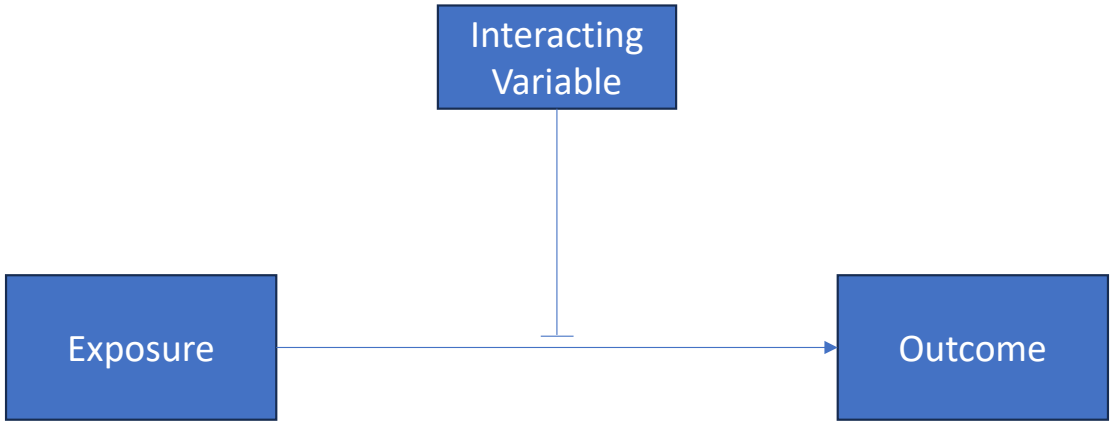
Total vs Partial Mediation

- Partial mediation: the mediator accounts for some but not all of the total effect of the exposure on the outcome.
- In the absence of the mediator, the exposure still affects the outcome, but not to the same degree.
- Common



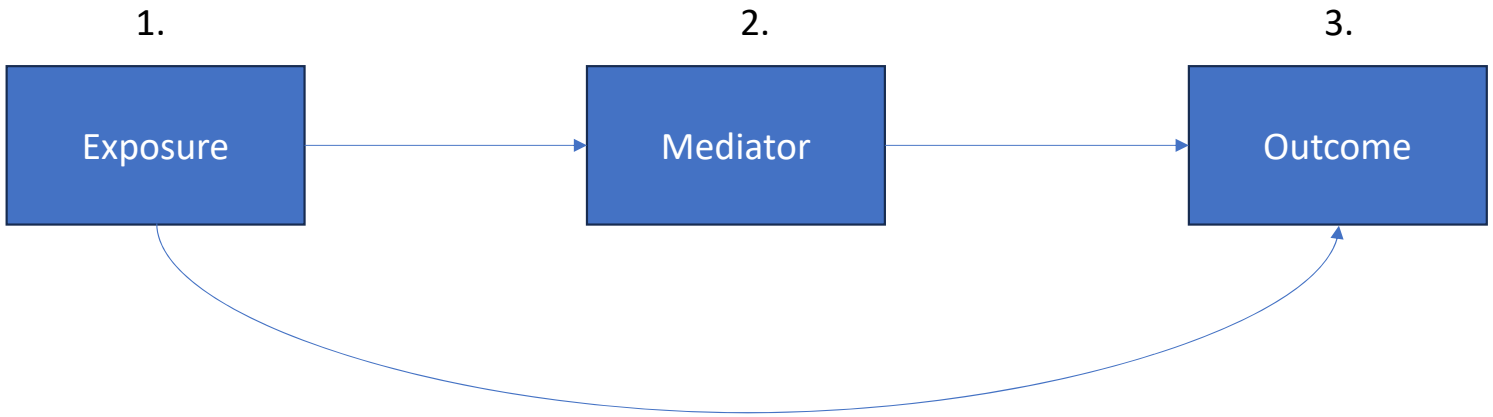
Mediation vs Interaction: Not the Same Thing

- Interaction: The total effect of the exposure varies depending on some external factor, e.g., by sex
  - Synonymous with the term “effect modification”
  - Moderation is a specific form of interaction



Assumptions for Mediation

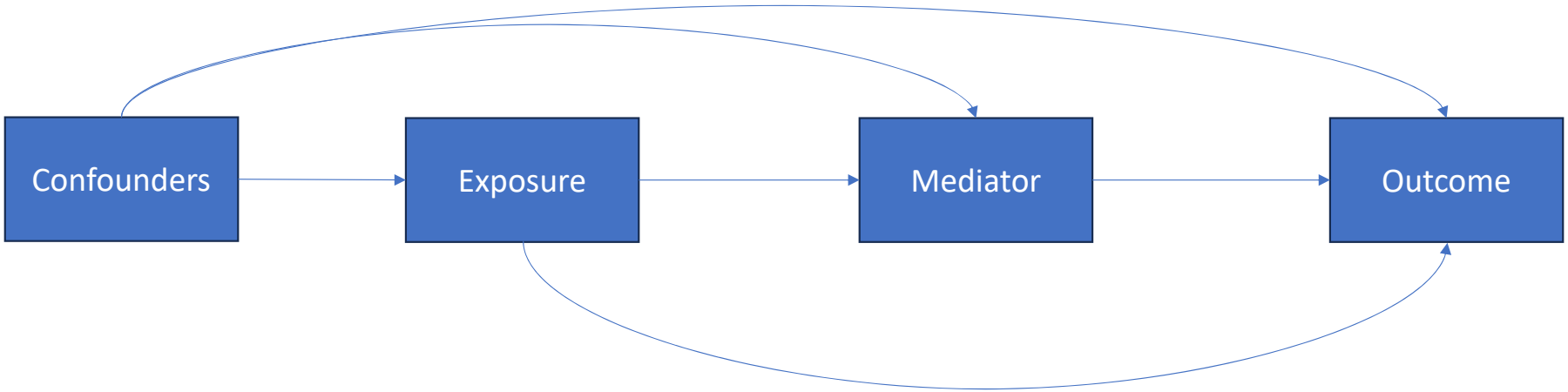
0. There is a temporal order to things. The exposure must occur first. The mediator happens later, and the outcome happens last.



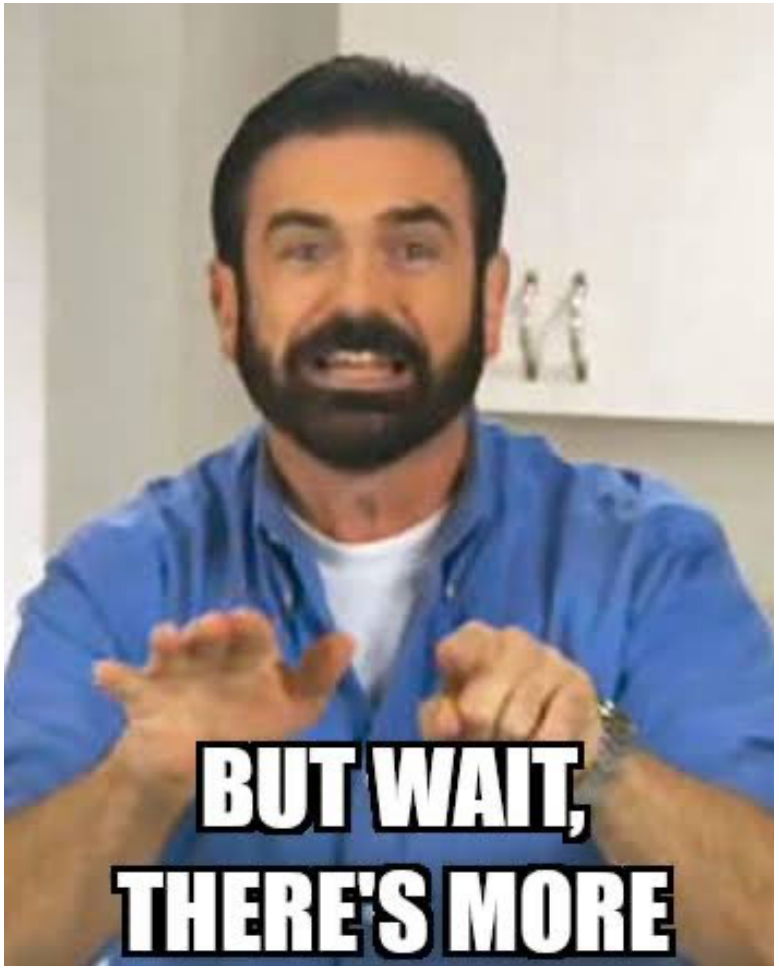
Assumptions for Mediation

From VanderWeele (2016):

1. Exposure-outcome confounding must be controlled.
2. Mediator-outcome confounding must be controlled.
3. Exposure-mediator confounding must be controlled.

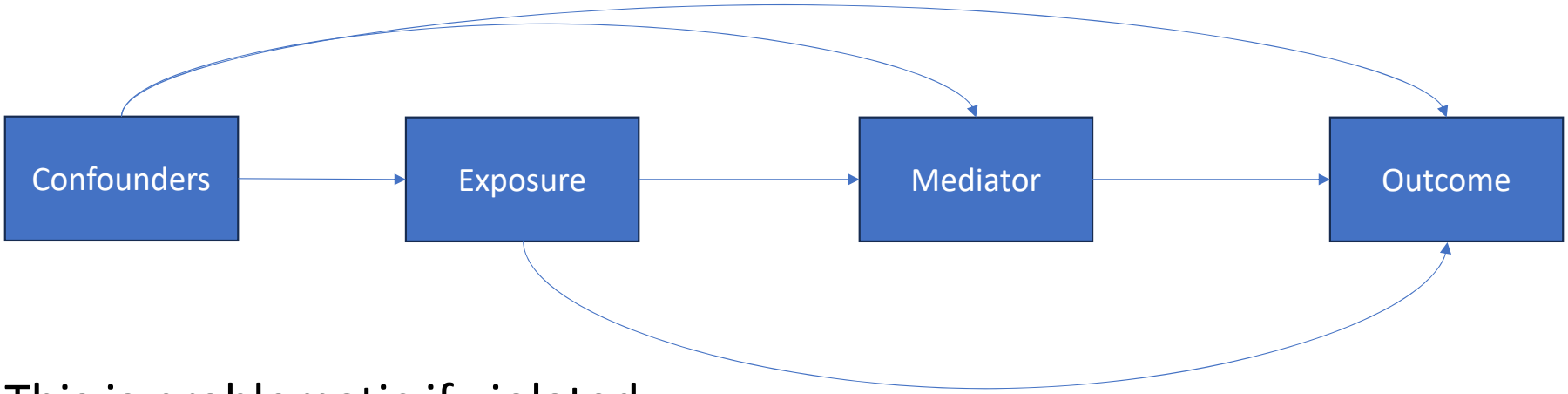


Assumptions for Mediation



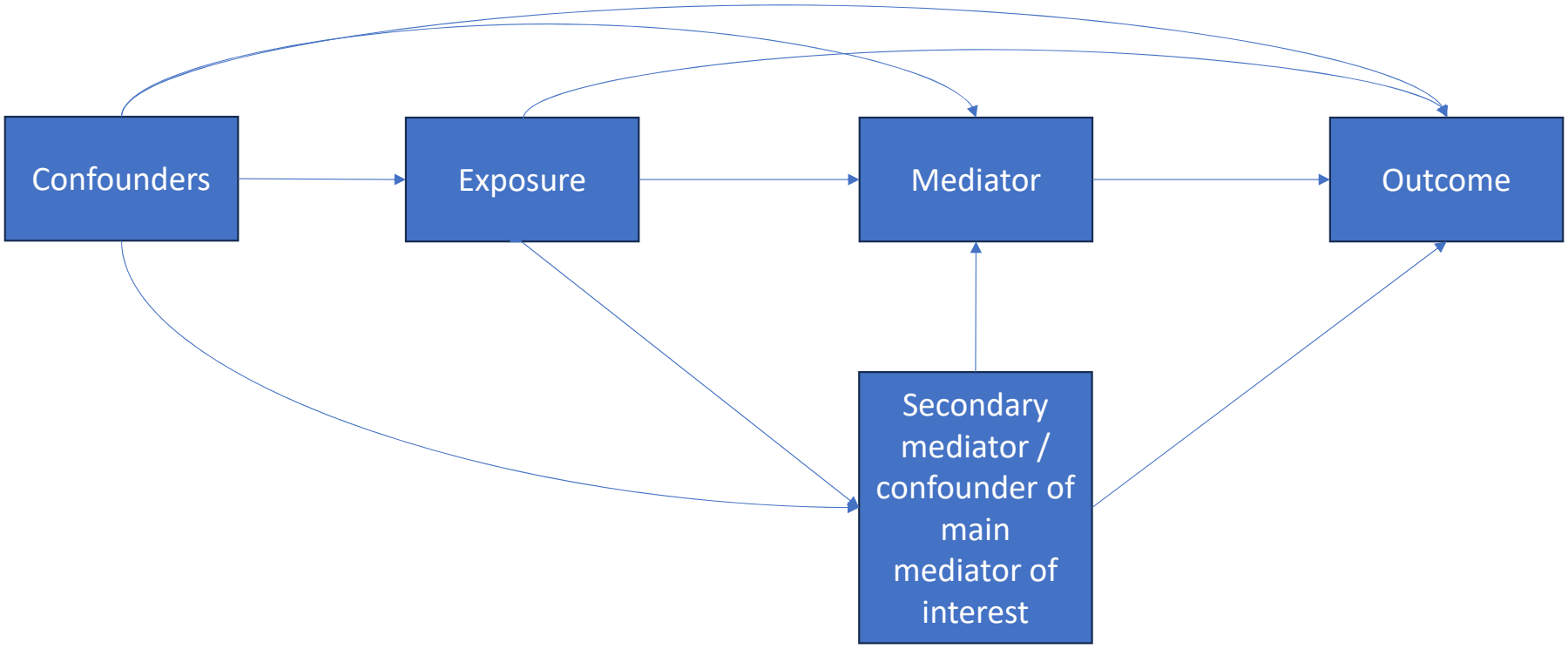
Assumptions for Mediation

4. None of the mediator-outcome confounders are themselves affected by the exposure.



This is problematic if violated.

Assumptions for Mediation



Section 2: Modern Approaches

Problems with the Traditional Approaches

It is unclear which approach is correct for binary outcomes.

No allowance for exposure-mediator interaction.

Too much emphasis on statistical significance.

Failure to detect mediation when the direct and indirect effects work in opposite directions.

Key Terms

Total Effect: The effect of an exposure on an outcome, including both mediated and unmediated effects.

Direct effect: the unmediated portion of the total effect (the exposure directly affects the outcome).

Indirect effect: the mediated portion of the total effect (the exposure indirectly affect the outcome through its action on the mediator)

Controlled Direct Effect (CDE)

$$Y_{am} - Y_{a^*m}$$

- The effect of the exposure on the outcome if you hold the mediator constant at value *m*.
- Only requires the first two assumptions to hold (control for exposure-outcome and mediator-outcome confounding)
- Special methods are still needed to assess CDE if the fourth assumption is violated (mediator-outcome confounder affected by the exposure).
- Useful for policy initiatives targeting the mediator to reduce the total effect.
- Cannot be used for effect decompositions.

Natural Direct Effect

$$Y_{aM_{a^*}} - Y_{a^*M_{a^*}}$$

- The effect of the exposure on the outcome when the mediator is fixed at the value it would naturally have in the absence of exposure.
- Equal to the controlled direct effect if the exposure and mediator do not interact.
- Can be used for a calculation of the proportion mediated.
- Can be used for an effect decomposition.

Natural Indirect Effect

$$Y_{aM_a} - Y_{aM_{a^*}}$$

- The difference between the effect of the exposure on the outcome allowing the mediator to assume whatever value it naturally would, and the effect of the exposure on the outcome setting the mediator to be whatever value it would naturally have in the absence of exposure.
- If the NIE is 0, then typically in the real world we do not observe evidence of mediation.
- Required for a calculation of the proportion mediated and an effect decomposition.

Other measures – Proportion mediated

- Simply put, indirect effect divided by total effect
- Can be a nice summary measure if the indirect and direct effects both move in the same direction.
- Can yield nonsensical proportions of >100% (or negative proportions) when the direct and indirect effects are of opposite signs.
- DO NOT USE AS EVIDENCE/NON-EVIDENCE OF MEDIATION ON ITS OWN!!!

Mediation vs Interaction Again

- What if some of the effect is due to both interaction AND mediation?
- 4-way effect decomposition (VanderWeele, 2014)
- Decomposes the total effect into four subcomponents:
  - Controlled direct effect (CDE)
    - The effect of the exposure on the outcome in the absence of the mediator
  - Reference interaction (INT_{REF})
    - The effect when the mediator is present in the absence of the exposure
  - Mediated interaction (INT_{MED})
    - An interactive effect that happens only when the exposure affects the mediator.
  - Pure indirect effect (PIE)
    - An effect that is only present when the mediator affects the outcome in the absence of the exposure, and the exposure itself affects the mediator.

$$TE = CDE + INT_{REF} + INT_{MED} + PIE$$

Mediation vs Interaction Interpretation

- Controlled direct effect: effect due neither to mediation nor interaction.
- Reference interaction: effect due only to interaction
- Mediated interaction: effect due to both interaction and mediation
- Pure indirect effect: effect due to mediation alone

More Handy Proportions

- Proportion of the total effect due to mediation $= \frac{INT_{MED} + PIE}{TE}$
- Proportion of the total effect due to interaction $= \frac{INT_{MED} + INT_{REF}}{TE}$
- THESE ONLY MAKE SENSE IF ALL OF THE COMPONENT EFFECTS ARE OF THE SAME SIGN AND THE TOTAL EFFECT IS NOT CLOSE TO ZERO!!!

Software Options

- SAS
  - PROC CAUSALMED
  - Capable of assessing mediation with continuous or binary outcomes
  - Can assess mediation in time-to-event settings
  - Can do a 4-way effect decomposition if desired
  - Automated bootstrapping procedure to generate confidence intervals
  - Parametric CIs also available (bootstrapping is preferred)
  - Can conduct mediation analysis in a case-control study paradigm
  - Cannot take complex survey designs into account
  - Unclear if it will work on data that has had missing values imputed using MI

Software Options

- R
  - `mediation` package
  - Capable of assessing mediation with continuous or binary outcomes
  - Can assess mediation in time-to-event settings
  - Automated bootstrapping procedure to generate confidence intervals (boot = TRUE)
  - Parametric CIs also available (bootstrapping is preferred – and required for some model types)
  - https://cran.r-project.org/web/packages/mediation/vignettes/mediation.pdf

Software Options

- Python
  - `stats.mediation.Mediation` function in the `Statsmodels` library
  - Capable of assessing mediation with continuous or binary outcomes
  - https://statsmodels.org/dev/generated/statsmodels.stats.mediation.Mediation.html
- Stata: mediate command
- SPSS: PROCESS macro

Other Approaches

- Marginal Structural Model approach (Lange, Vansteelandt, and Bekaert, 2012)
  - Flexible
  - Code available for implementation in SAS and R
  - Can be time-consuming to run
  - Available example code is limited to categorical exposures/mediators and binary/survival outcomes
  - Some debate in the literature regarding the appropriate way to compute standard errors (parametric vs bootstrapping)
  - Does not identify the controlled direct effect*

*That I am aware of.

Other Approaches

- Structural Equation Modeling (SEM)
  - Used often by the psychological sciences.
  - Can assess multiple mediators simultaneously.
  - Requires even stronger assumptions (assumptions 1-4 must hold for every single variable in the models, not just the exposure, mediator, and outcome).
  - Limited to continuous variables
  - All relationships in the model are subject to the same assumptions that linear regression is (linearity of relationship, normality and homoskedasticity of residuals, etc.)

Other Approaches

- Simulation-based approaches (Imai and Keele, 2010)
  - Parametric and nonparametric algorithms are available.
  - Can be adapted to virtually any scenario.
  - Computationally intensive.

Section 3: Real-World Example

Description of Study

- Purpose: to identify the risk of an Autism Spectrum Disorder (ASD) diagnosis from a maternal infertility treatment
- Study population: All singleton and multifetal deliveries in Ontario from 2006-2018
- Exposure of interest: Maternal infertility treatment
  - In-vitro fertilization/intracytoplasmic sperm injection[IVF/ICSI]
  - Ovulation induction/intrauterine insemination [OI/IUI]
  - Infertility diagnosis without fertility treatment (subfertile)
  - Spontaneous pregnancy [not infertile] referent
- Outcome: Diagnosis of ASD in baby at age 18 months or older
- Desired analytical paradigm: time-to-event

Description of Study

- Mediators: several pregnancy-related factors
  - Multifetal pregnancy
  - Pre-eclampsia
  - Preterm birth (<37 weeks gestational age)
  - Caesarian birth
    - Planned vs unplanned C-section examined as sub-analyses
  - Severe neonatal morbidity
- Covariates:
  - maternal age, parity, income quintile, rural residence, immigration status, smoking history, obesity, drug or alcohol use, maternal history of mental illness or ASD, chronic (non-gestational) diabetes, chronic hypertension
  - Infant sex
- Reference: Velez et al., 2023

Considerations

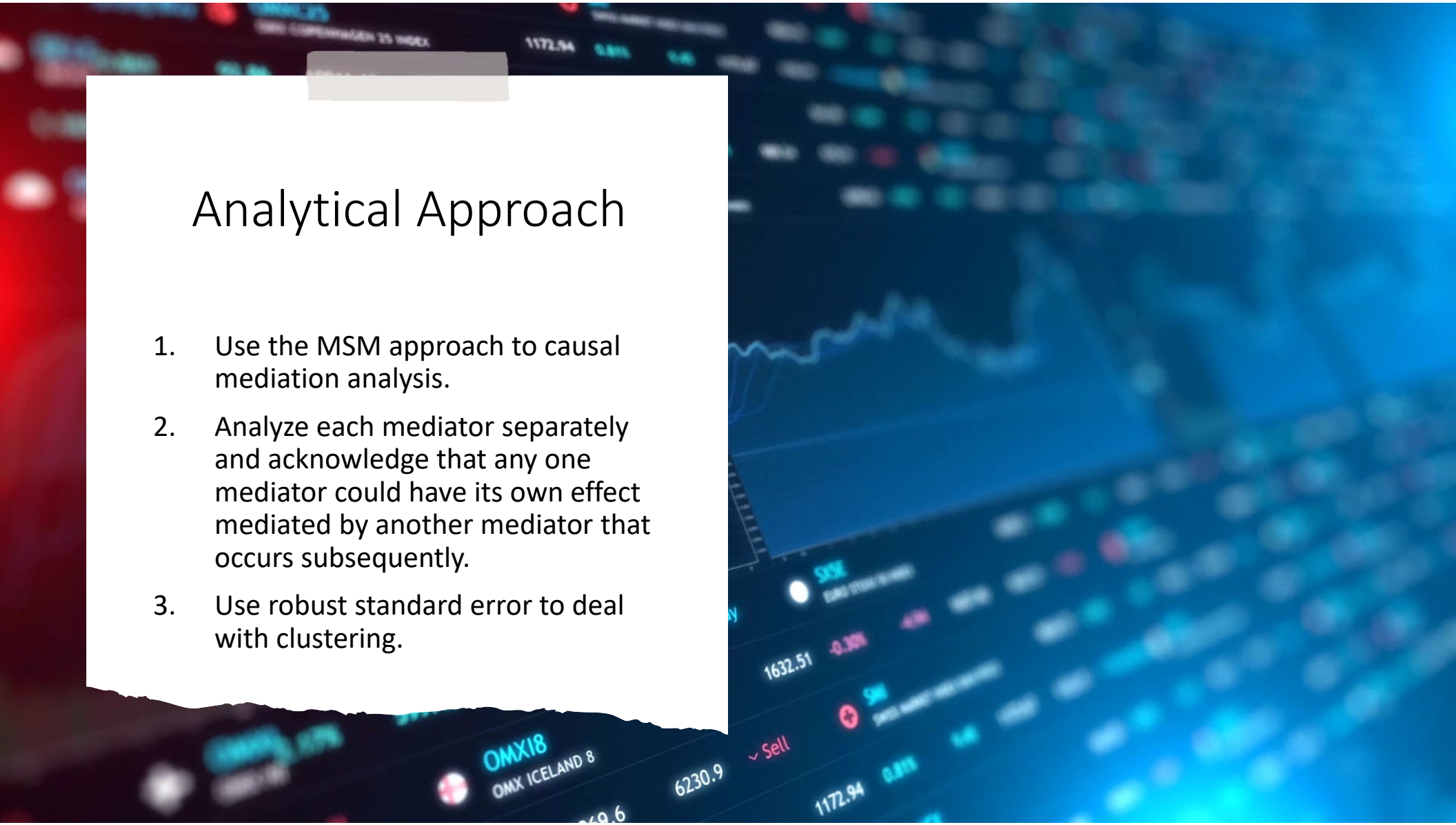
Multiple mediators

Very high likelihood that all mediators are causally linked to each other and affected by the exposure (4th assumption is violated)

Software limitations

At the time PROC CAUSALMED could not be applied to time-to-event models

Clustering due to multiple observations per mother



Analytical Approach

1. Use the MSM approach to causal mediation analysis.
2. Analyze each mediator separately and acknowledge that any one mediator could have its own effect mediated by another mediator that occurs subsequently.
3. Use robust standard error to deal with clustering.

Results

Table 2. Risk of Autism Spectrum Disorder (ASD) by Mode of Conception

Mode of conception	No. with ASD/No. at risk	Rate of ASD per 1000 person-years	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Analysis among all 1 370 152 live-born children (main model)				
Unassisted conception	18 689/1 185 024	1.93	1 [Reference]	1 [Reference]
Subfertility	2858/141 180	2.49	1.29 (1.24-1.34)	1.20 (1.15-1.25)
Ovulation induction or intrauterine insemination	404/20 429	2.72	1.31 (1.18-1.45)	1.21 (1.09-1.34)
In vitro fertilization or intracytoplasmic sperm injection	458/23 519	2.71	1.29 (1.17-1.43)	1.16 (1.04-1.28)
Analysis limited to 185 128 live-born children of individuals with infertility				
Subfertility	2858/141 180	2.49	1 [Reference]	1 [Reference]
Ovulation induction or intrauterine insemination	404/20 429	2.72	1.01 (0.91-1.12)	1.02 (0.92-1.14)
In vitro fertilization or intracytoplasmic sperm injection	458/23 519	2.71	1.00 (0.90-1.11)	0.94 (0.84-1.05)
Analysis limited to 23 519 live-born children of individuals who underwent in vitro fertilization or intracytoplasmic sperm injection				
In vitro fertilization	408/20 968	2.70	1 [Reference]	1 [Reference]
Intracytoplasmic sperm injection	50/2551	2.77	1.01 (0.75-1.37)	1.05 (0.77-1.42)

Results

Table 3. Mediation Analysis of the Effect of Selected Adverse Pregnancy Outcomes on the Association Between Mode of Conception and Autism Spectrum Disorder

Adverse pregnancy outcome mediator assessed and mode of conception[b]	Adjusted hazard ratio (95% CI)[a]			Proportion mediated (%)
	Total effect	Natural direct effect	Natural indirect effect	
Preeclampsia				
Subfertility	1.19 (1.16-1.23)	1.19 (1.17-1.22)	1.00 (0.98-1.02)	1.2
Ovulation induction or intrauterine insemination	1.20 (1.14-1.27)	1.20 (1.14-1.26)	1.01 (0.99-1.03)	4.0
In vitro fertilization or intracytoplasmic sperm injection	1.16 (1.10-1.22)	1.14 (1.09-1.20)	1.01 (0.99-1.03)	8.7
Cesarean birth				
Subfertility	1.20 (1.16-1.23)	1.18 (1.16-1.21)	1.01 (0.99-1.03)	7.4
Ovulation induction or intrauterine insemination	1.21 (1.14-1.27)	1.19 (1.13-1.25)	1.02 (1.00-1.04)	10.6
In vitro fertilization or intracytoplasmic sperm injection	1.14 (1.09-1.20)	1.10 (1.05-1.16)	1.04 (1.02-1.06)	28.9[c]
Planned cesarean birth[d]				
Subfertility	1.18 (1.14-1.21)	1.16 (1.14-1.19)	1.01 (0.99-1.03)	7.1
Ovulation induction or intrauterine insemination	1.18 (1.11-1.26)	1.16 (1.09-1.23)	1.02 (1.00-1.04)	12.0
In vitro fertilization or intracytoplasmic sperm injection	1.12 (1.05-1.20)	1.08 (1.02-1.15)	1.04 (1.02-1.06)	34.7[c]
Unplanned Caesarian birth[e]				
Subfertility	1.19 (1.16-1.23)	1.19 (1.16-1.21)	1.01 (0.99-1.03)	4.2
Ovulation induction or intrauterine insemination	1.21 (1.14-1.29)	1.20 (1.13-1.27)	1.01 (0.99-1.03)	5.8
In vitro fertilization or intracytoplasmic sperm injection	1.12 (1.05-1.19)	1.09 (1.03-1.15)	1.02 (1.00-1.05)	22.7[c]

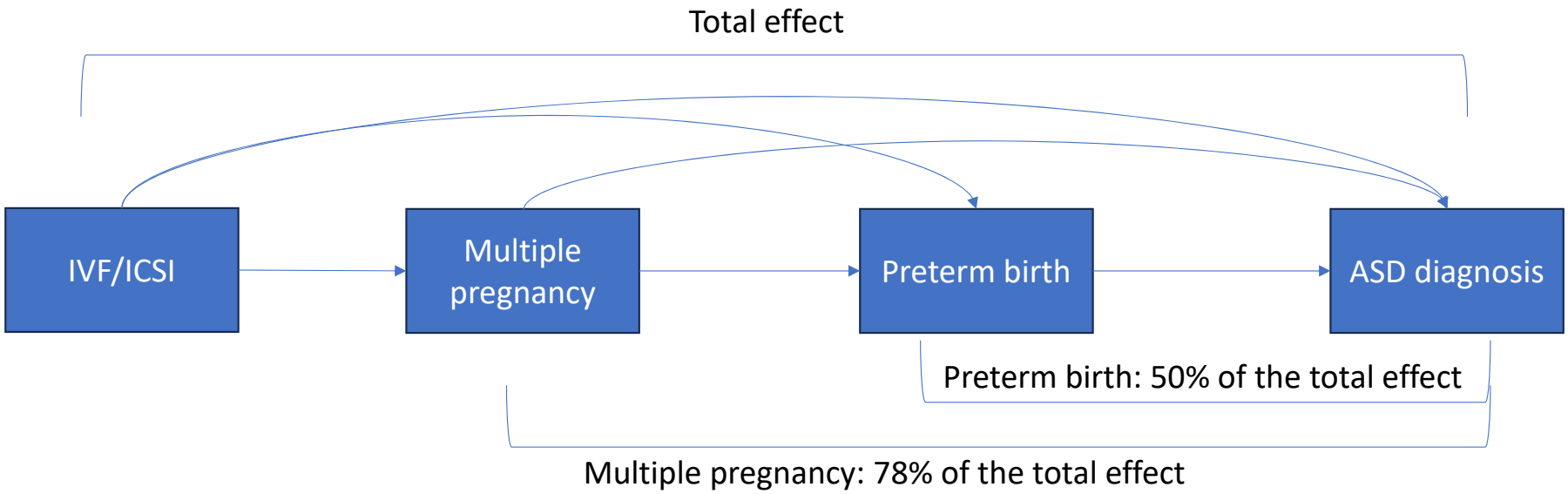
Results

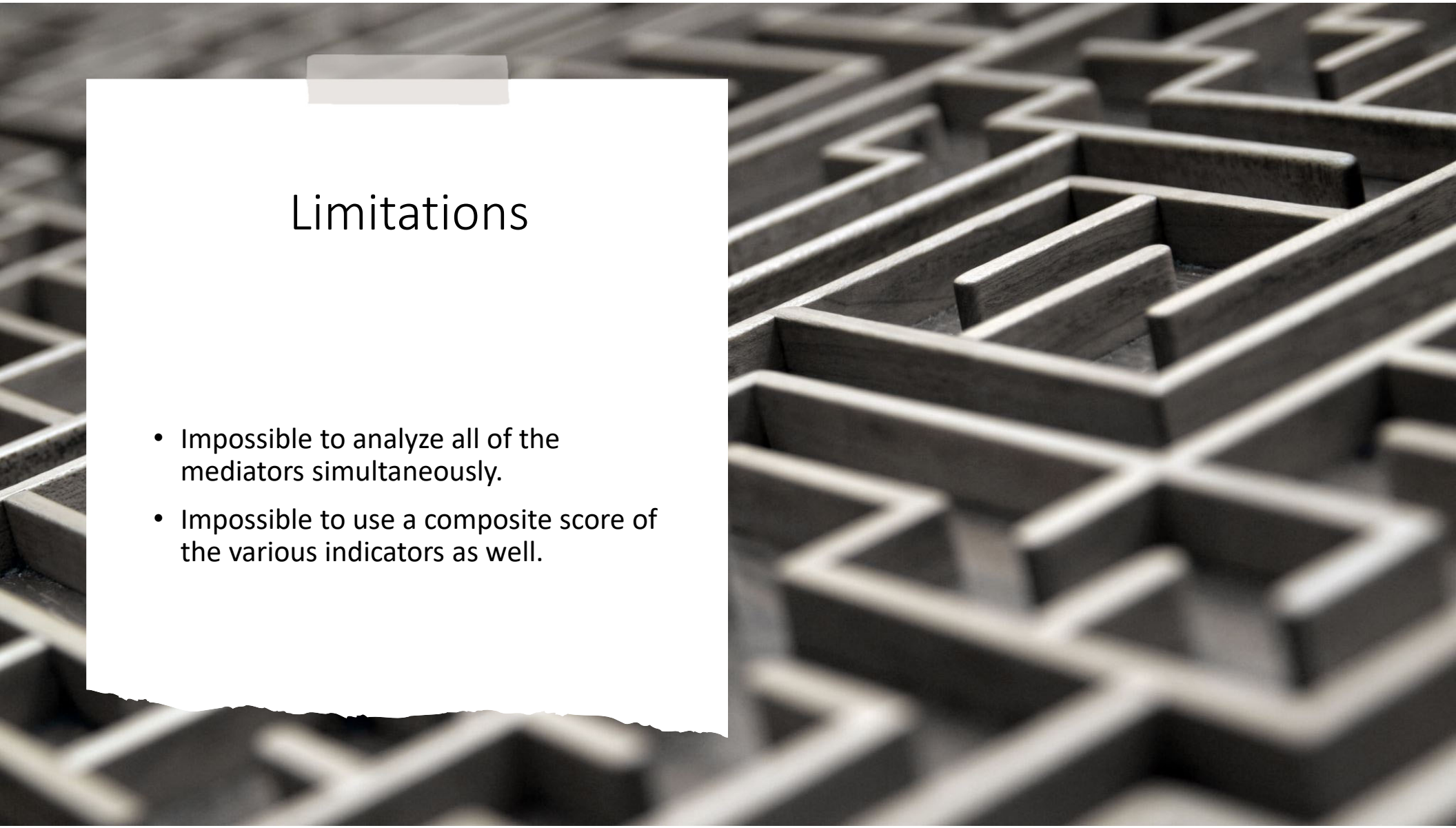
Table 3. Mediation Analysis of the Effect of Selected Adverse Pregnancy Outcomes on the Association Between Mode of Conception and Autism Spectrum Disorder

Adverse pregnancy outcome mediator assessed and mode of conception[b]	Adjusted hazard ratio (95% CI)[a]			Proportion mediated (%)
	Total effect	Natural direct effect	Natural indirect effect	
Multiple pregnancy				
Subfertility	1.17 (1.13-1.21)	1.15 (1.12-1.18)	1.01 (0.99-1.03)	8.5
Ovulation induction or intrauterine insemination	1.20 (1.13-1.27)	1.13 (1.07-1.19)	1.06 (1.04-1.09)	35.8[c]
In vitro fertilization or intracytoplasmic sperm injection	1.14 (1.08-1.21)	1.03 (0.98-1.09)	1.11 (1.08-1.14)	78.3[c]
Preterm birth <37 wk				
Subfertility	1.19 (1.16-1.23)	1.17 (1.15-1.20)	1.02 (1.00-1.03)	9.2
Ovulation induction or intrauterine insemination	1.19 (1.13-1.26)	1.14 (1.09-1.20)	1.04 (1.02-1.06)	25.6[c]
In vitro fertilization or intracytoplasmic sperm injection	1.16 (1.10-1.23)	1.08 (1.03-1.14)	1.07 (1.05-1.10)	49.8[c]
Severe neonatal morbidity				
Subfertility	1.20 (1.16-1.23)	1.19 (1.16-1.21)	1.01 (0.99-1.03)	5.1
Ovulation induction or intrauterine insemination	1.20 (1.14-1.27)	1.17 (1.11-1.23)	1.02 (1.00-1.04)	13.9[c]
In vitro fertilization or intracytoplasmic sperm injection	1.16 (1.10-1.22)	1.12 (1.07-1.18)	1.04 (1.02-1.06)	25.0[c]

Interpretation

- Proportions mediated add up to >100%. Can we trust this?
- YES!!!



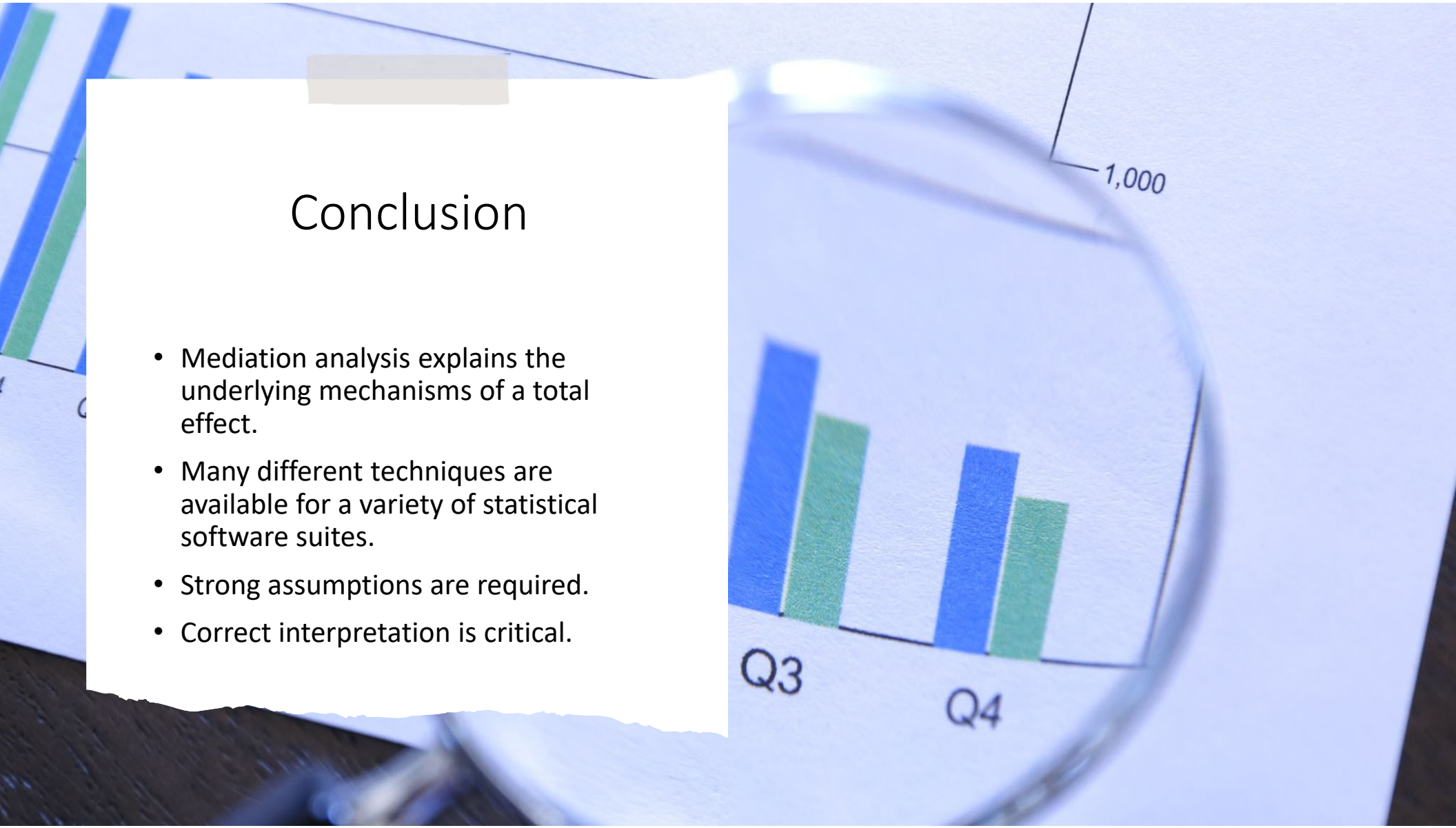


Limitations

- Impossible to analyze all of the mediators simultaneously.
- Impossible to use a composite score of the various indicators as well.

Conclusion

- Mediation analysis explains the underlying mechanisms of a total effect.
- Many different techniques are available for a variety of statistical software suites.
- Strong assumptions are required.
- Correct interpretation is critical.



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Questions

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Appendix Slides

Traditional Approaches

Some Key Notation to Understand

For an outcome Y, a mediator M, an exposure A, and a set of covariates C, consider these equations:

Model for the outcome, conditioned on the exposure and the covariates only: $E[Y|a,c] = \phi_0 + \phi_1 a + \phi_4' c$

Model for the outcome, conditioned on the exposure, the mediator, and covariates: $E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$

Model for the mediator, conditioned on the exposure and covariates: $E[M|a,c] = \beta_0 + \beta_1 a + \beta_4' c$

Traditional Approaches: Difference Method

- Fit two of the models mentioned previously:

$$E[Y|a,c] = \phi_0 + \phi_1 a + \phi_4' c$$
$$E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$$

ϕ_1 is the total effect of A on Y, including both direct (unmediated) and indirect (mediated) effects.

If θ_1 is considerably different, then it may be taken as evidence of mediation, if certain assumptions are met.

If the assumptions hold, then the indirect effect (IE) is $\phi_1 - \theta_1$ and the direct effect (DE) is θ_1

Traditional Approaches: Product Method

- Popularized by Baron & Kenny (1986).
- Fit two of the models mentioned previously:

$$E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_4' c$$
$$E[M|a,c] = \beta_0 + \beta_1 a + \beta_4' c$$

The direct effect, again, is θ_1.

The indirect effect is $\beta_1 \times \theta_2$ (the exposure coefficient in the mediator model times the mediator coefficient in the outcome model).

Counterfactual Framework

Counterfactual Framework

- Let a be the presence of an exposure (e.g., heart failure = 1 or SBP = 180) and a^* be the absence of exposure (heart failure = 0 or SBP = 120).
- Let Y_a be the natural outcome if an exposure A was set to value a (e.g., if the exposure is MI and set to a value of 1, then an outcome of death would probably naturally be 1).

Counterfactual Framework

- Let M_a be the natural value of the mediator if an exposure A was set to value a and M_{a^*} be the natural value of the mediator if exposure A was set to a^*
- e.g., for an exposure of MI=1, systemic blood circulation would naturally be a low value, whereas it would be much higher if MI=0.

Counterfactual Framework

- Let Y_{am} be the value of the outcome if an exposure A was set to value *a* and a mediator M was set to some counterfactual value *m*.
- E.g., what is the outcome if MI=1 and we somehow boosted circulation back up to normal levels by performing CPR?
- Given the above, we can now evaluate three effects: the controlled direct effect, the natural direct effect, and the natural indirect effect.

Counterfactual Mediation Analysis Manual Procedure

Counterfactual Mediation Analysis Procedure

- Somewhat different depending on the form of the outcome and mediator (i.e., binary vs continuous).
- There are actually four different scenarios to consider, but I will only go into two of them; see VanderWeele (2016) for a full listing of model types for various scenarios.

Continuous Outcome and Mediator

- a = exposure [exposed value], a* = exposure [unexposed value], m = mediator, c = set of confounders
- Two linear regression models:

$$E[Y|a,m,c] = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$
$$E[M|a,c] = \beta_0 + \beta_1 a + \beta_2' c$$

- Then:

$$DE = \{\theta_1 + \theta_3(\beta_0 + \beta_1 a^* + \beta_2' c)\}(a - a^*)$$
$$IE = (\beta_1\theta_2 + \beta_1\theta_3 a)(a - a^*)$$

If there is no exposure-mediator interaction (i.e., $\theta_3 = 0$) then these reduce to $DE = \theta_1(a - a^*)$ and $IE = \beta_1\theta_2(a - a^*)$

Binary Outcome and Mediator

- Two logistic regression models*:

$$logit\{P(Y=1|a,m,c)\} = \theta_0 + \theta_1 a + \theta_2 m + \theta_3 am + \theta_4' c$$
$$logit\{P(M=1|a,c)\} = \beta_0 + \beta_1 a + \beta_2' c$$

- Then:

$$OR^{DE} \cong \frac{\exp(\theta_1 a)\{1+\exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a^* + \beta_2' c)\}}{\exp(\theta_1 a^*)\{1+\exp(\theta_2 + \theta_3 a^* + \beta_0 + \beta_1 a^* + \beta_2' c)\}}$$

$$OR^{IE} \cong \frac{\{1+\exp(\beta_0 + \beta_1 a^* + \beta_2' c)\}\{1+\exp(\theta_2 + \theta_3 a + \beta_0 + \beta_1 a + \beta_2' c)\}}{\{1+\exp(\beta_0 + \beta_1 a + \beta_2' c)\}\{1+\exp(\theta_2 + \theta_3 a + \beta_1 a^* + \beta_2' c)\}}$$

*Actually almost any log-linear model will work, e.g., Poisson. The effect estimates will be on the RR scale instead of the OR scale if not using logistic regression.

Standard Errors / Confidence Intervals

- BOOTSTRAP
  - Resample the original cohort with replacement. 1000-2000 resamples should be more than sufficient
  - Be sure to replicate the original sampling strategy, i.e., if originally sampled using a two-stage cluster sampling strategy, sample the lowest-level cluster first, then sample the second-level cluster (then randomly sample if there was random sampling of individual participants at the level of the second cluster; if a cohort study with repeat observations, keep all observations for each resampled participant).
  - Run the same series of models as previously described for each replicant
  - Combine the coefficients from the models as described to get a point estimate of each effect for each resample
  - 95% CI is the 2.5^{th} and 97.5^{th} percentile value of the distribution of point estimates among the resamples
  - The estimate itself is the point estimate computed from the original sample
  - THIS IS THE PREFERRED WAY OF DOING IT IF YOU HAVE A SMALL SAMPLE

Standard Errors / Confidence Intervals

- DELTA METHOD
  - I STRONGLY RECOMMEND YOU DO NOT COMPUTE THIS MANUALLY!
  - But if you insist, there is a method for computing it based on covariance matrices in the online supplement to Valeri and Vanderweele (2013):
  - Supplemental Material for Mediation Analysis Allowing for Exposure–Mediator Interactions and Causal Interpretation: Theoretical Assumptions and Implementation With SAS and SPSS Macros (apa.org)