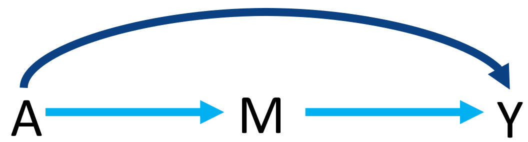
Mediation analysis: introduction to the methods

S. Ghazaleh Dashti, MPH, DDS, PhD candidate
Centre for Epidemiology and Biostatistics,
Melbourne School of Population and Global Health

Outline

- Setting and motivating example
- Traditional approaches to mediation analysis
- Causal mediation analysis and counterfactuals
- No confounding assumptions in mediation analysis
- Estimating the effects
- Mediation analysis with multiple mediators
- Study design

Mediation analysis: setting



Quantify the effect of exposure **A** on outcome **Y**:

Through the mediator **M;** ***<u>Indirect effect</u>***

Not through the mediator **M;** ***<u>direct effect</u>***

THE UNIVERSITY OF MELBOURNE

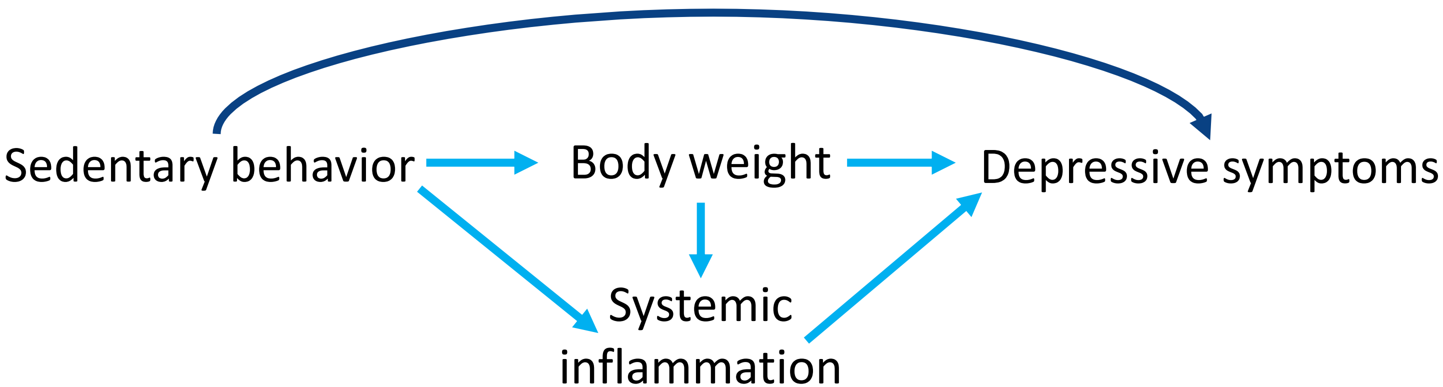
Motivating examples

Sedentary behavior → Systemic inflammation → Depressive syndrome

How much of the effect of sedentary behavior on depressive syndrome is mediated by systemic inflammation? *(indirect effect)*

How much of the effect is through other pathways? *(direct effect)*

Motivating examples

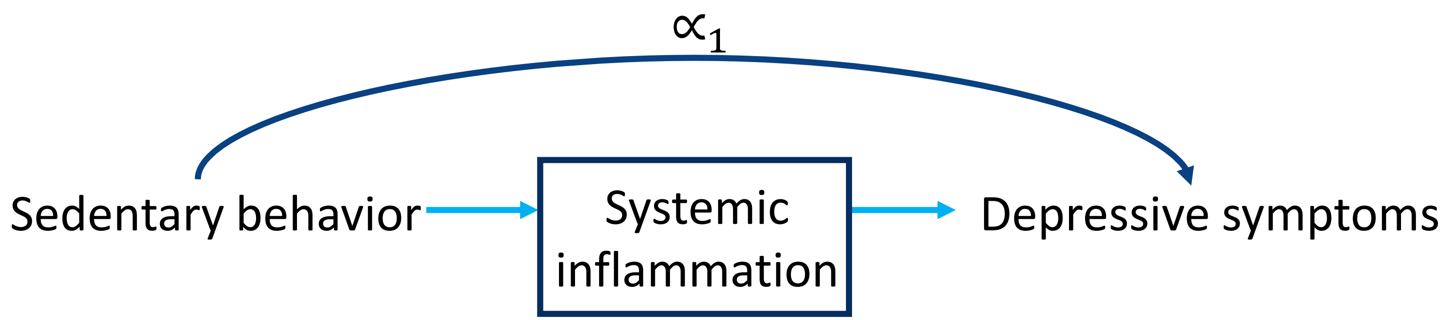


Traditional approaches to mediation analysis: Difference method

Sedentary behavior → Systemic inflammation → Depressive symptoms

$$E[Y|A,C] = \beta_0 + \beta_1 \mathrm{A} + \beta_3 \mathrm{C}$$

Traditional approaches to mediation analysis: Difference method



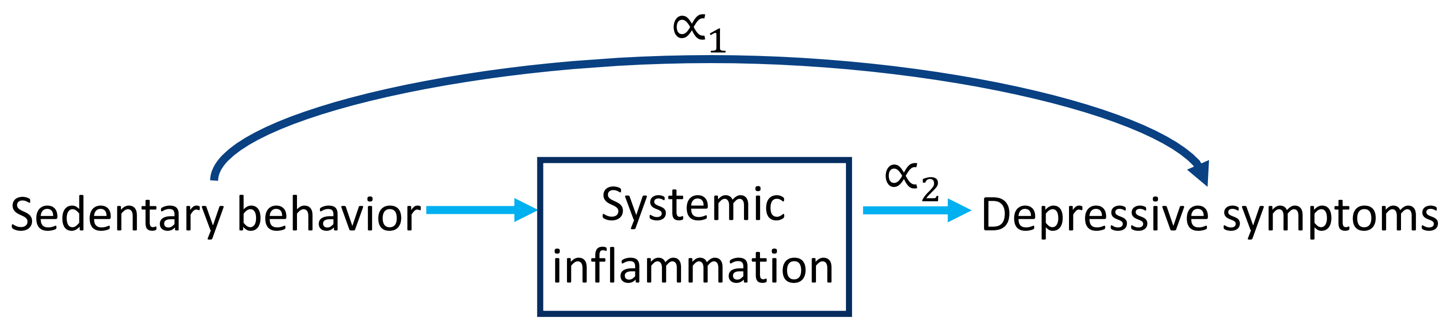
$$E[Y|A,C] = \beta_0 + \beta_1\mathrm{A} + \beta_3\mathrm{C}$$

$$E[Y|A,M,C] = \propto_0 + \propto_1\mathrm{A} + \propto_2\mathrm{M} + \propto_3\mathrm{C}$$

Direct effect= $\propto_1$

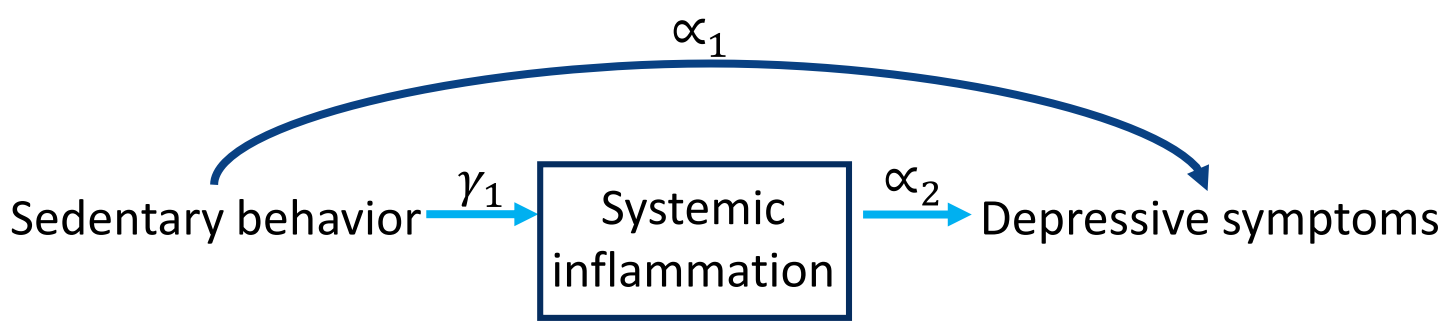
Indirect effect= β_1- $\propto_1$

Traditional approaches to mediation analysis: Product method



$$E[Y|A,M,C] = \propto_0 + \propto_1 \mathrm{A} + \propto_2 \mathrm{M} + \propto_3 \mathrm{C}$$

Traditional approaches to mediation analysis: Product method



$$E[Y|A, M, C] = \propto_0 + \propto_1 \mathrm{A} + \propto_2 \mathrm{M} + \propto_3 \mathrm{C}$$

$$E[M|A, C] = \gamma_0 + \gamma_1 \mathrm{A} + \gamma_3 \mathrm{C}$$

Direct effect= $\propto_1$

Indirect effect= $\beta_1 \times \propto_2$

Traditional approaches to mediation analysis: limitations

Presupposes no exposure-mediator interaction

Cannot [always] be used in nonlinear models

Cannot [always] handle multiple mediators

Suggested reading: VANDERWEELE, T. J. 2016. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health, 37, 17-32.

Causal mediation analysis and counterfactuals

Methods based on the counterfactual view of causation

Can be used when:

- there is exposure-mediator interaction
- models are non-linear (e.g. outcome is binary)

Clarified the no-confounding assumptions required for identifying effects

Extended to allow identifying indirect/direct effects with multiple mediators

THE UNIVERSITY OF MELBOURNE

Causal mediation analysis and counterfactuals: Notations and definitions

Sedentary behavior → Systemic inflammation → Depressive syndrome

Outcome (Y): depressive symptoms
Exposure (A): sedentary behaviour ≥9 vs. <9 hours/days
Mediator (M): systemic inflammation score

Y_1: depressive symptoms when sedentary behaviour ≥9 (A=1)
Y_0: depressive symptoms when sedentary behaviour <9 (A=0)
M_1: inflammation score when sedentary behaviour ≥9 (A=1)
M_0: inflammation score when sedentary behaviour <9 (A=0)

Causal mediation analysis and counterfactuals: Total causal effect

SB=1

SB=0

Causal mediation analysis and counterfactuals: Total causal effect

SB=1

SB=0

$$TCE = Y_1 - Y_0$$

Causal mediation analysis and counterfactuals: Total causal effect

SB=1 → inflammation score when SB=1

SB=0 → inflammation score when SB=0

$$TCE = Y_1 - Y_0$$

$$TCE = Y_{1M1} - Y_{0M0}$$

Causal mediation analysis and counterfactuals: Natural Indirect Effect

SB=1

inflammation score when SB=1

SB=0

inflammation score when SB=0

Causal mediation analysis and counterfactuals: Natural Indirect Effect

SB=1

inflammation score when SB=1

SB=1

inflammation score when SB=0

$$NIE = Y_{1M1} - Y_{1M0}$$

THE UNIVERSITY OF MELBOURNE

Causal mediation analysis and counterfactuals: Natural Direct Effect

SB=1

inflammation score when SB=1

SB=0

inflammation score when SB=0

Causal mediation analysis and counterfactuals: Natural Direct Effect

SB=1 → inflammation score when SB=0

SB=0 → inflammation score when SB=0

$$NDE = Y_{1M0} - Y_{0M0}$$

Causal mediation analysis and counterfactuals: Controlled Direct Effect

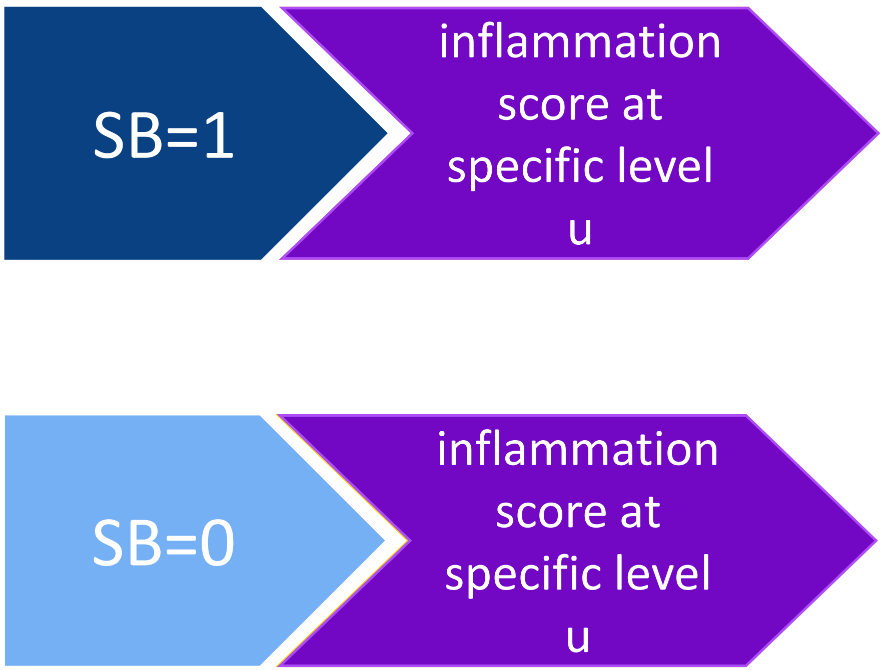
SB=1

inflammation score when SB=1

SB=0

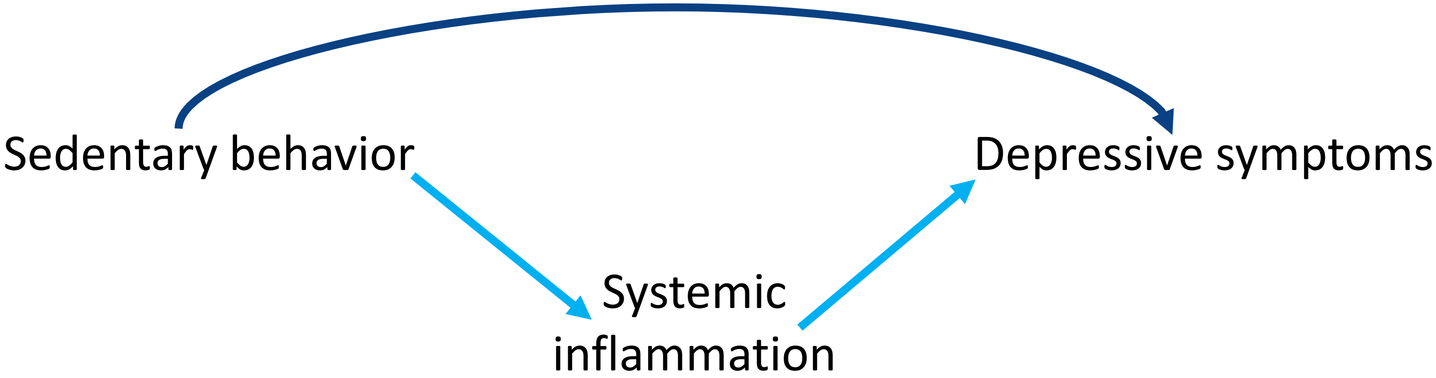
inflammation score when SB=0

Causal mediation analysis and counterfactuals: Controlled Direct Effect



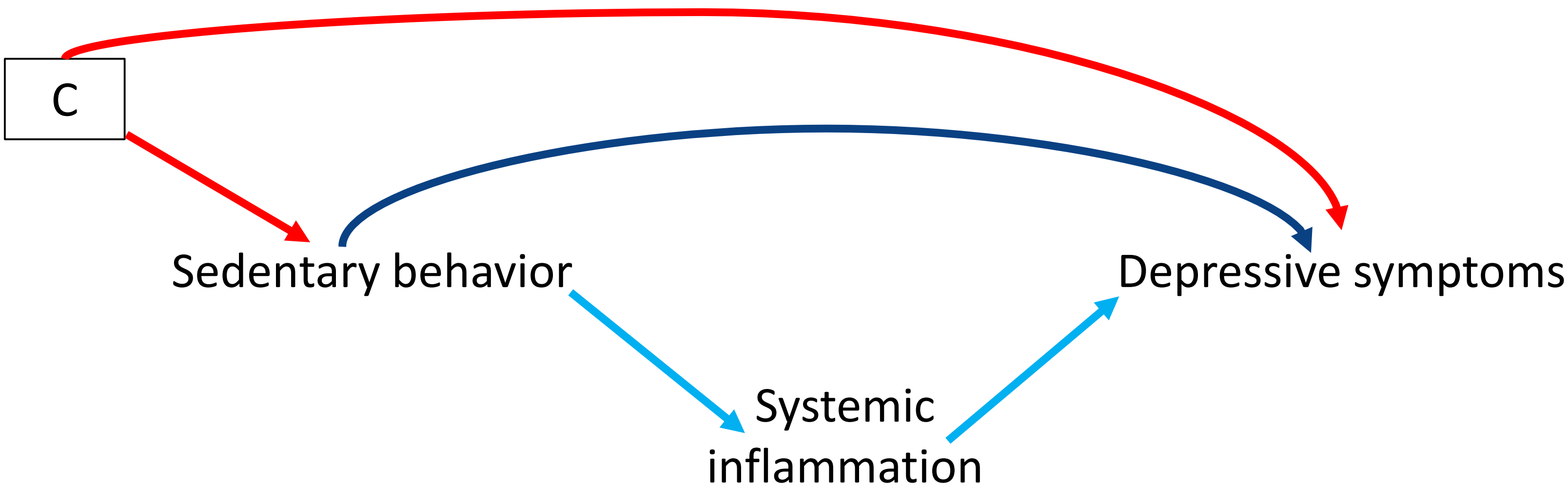
$$CDE = Y_{1Mu} - Y_{0Mu}$$

No confounding assumptions



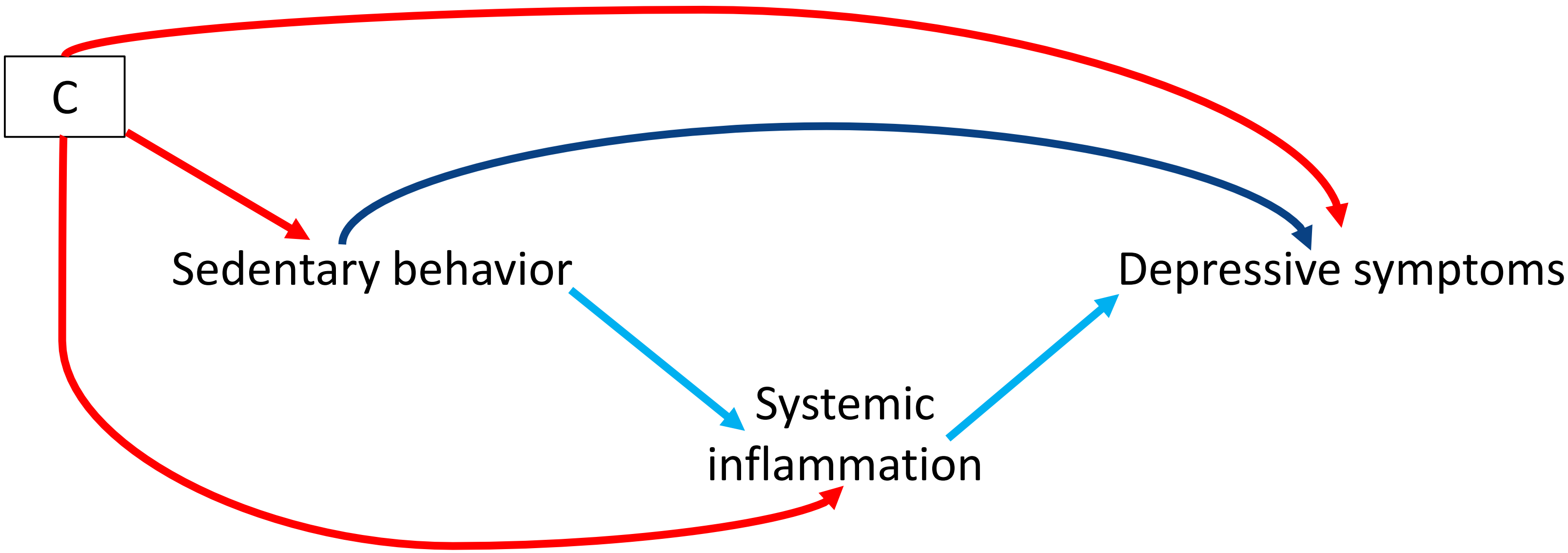
*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

No confounding assumptions



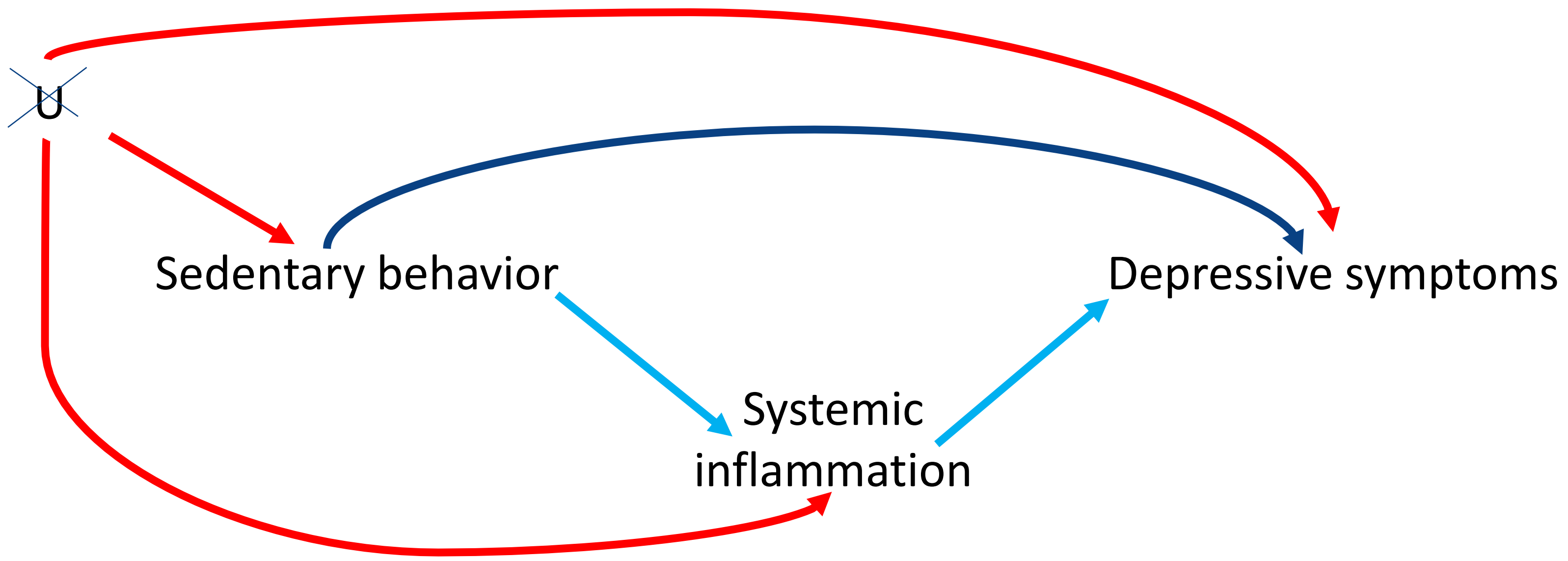
*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

No confounding assumptions



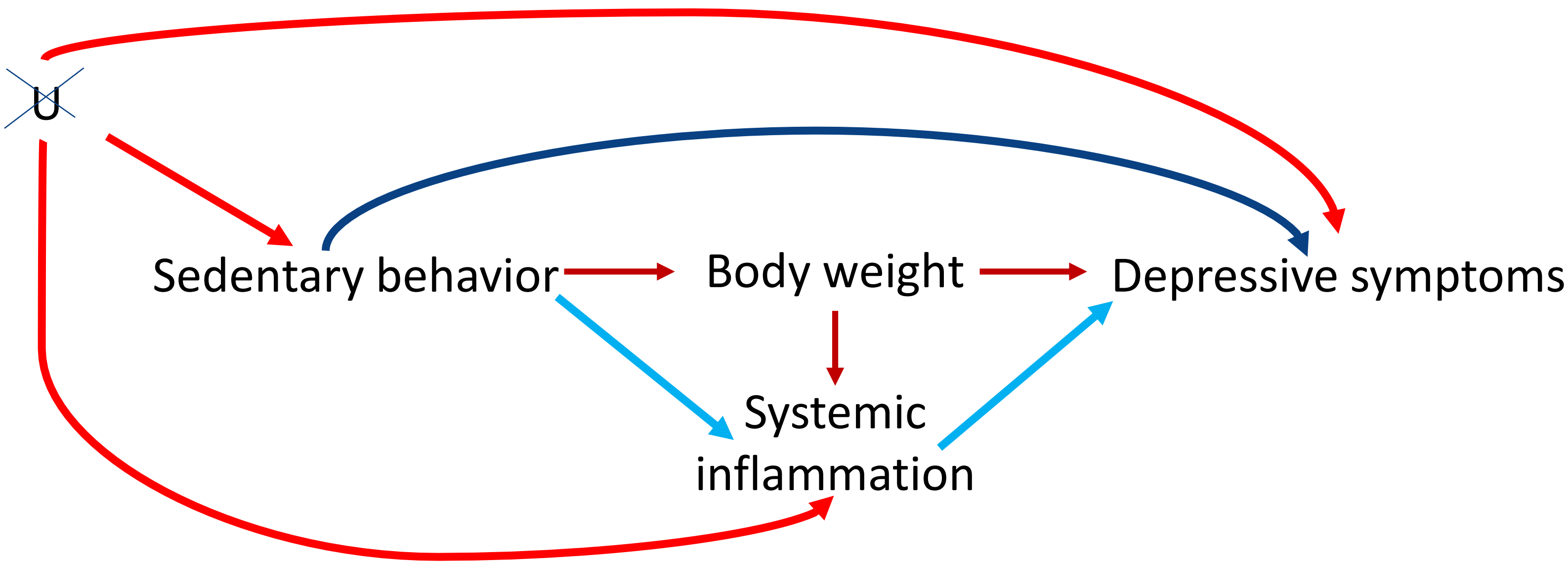
*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

No confounding assumptions



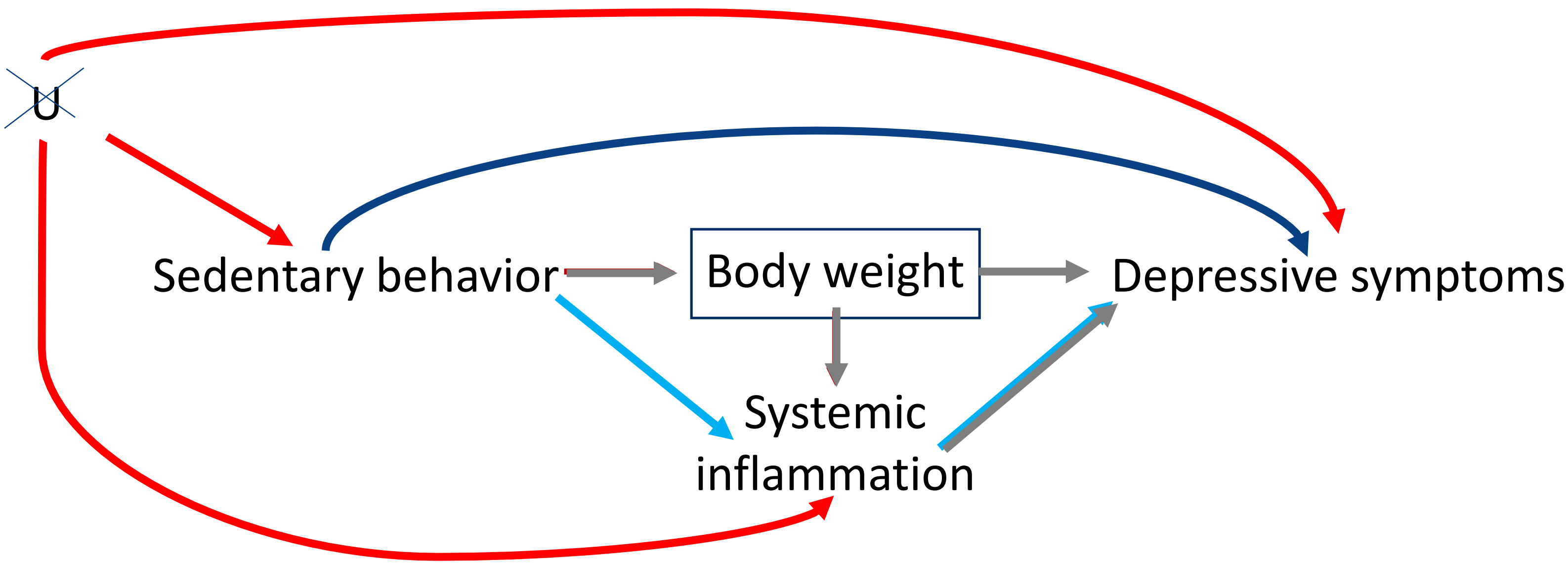
*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

No confounding assumptions



*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

No confounding assumptions



*For CDE, only no unmeasured confounding of exposure-outcome exposure-mediator is required.

Indirect and Direct Effect: continuous outcome

$$TCE = Y_{1M1} - Y_{0M0} = \underbrace{Y_{1M1} - Y_{1M0}}_{NIE} + \underbrace{Y_{1M0} - Y_{0M0}}_{NDE}$$

$$\text{Proportion mediated} = \frac{NIE}{TCE} = \frac{NIE}{NIE+NDE}$$

Suggested reading: VANDERWEELE, T. J. 2016. Mediation Analysis: A Practitioner's Guide. Annu Rev Public Health, 37, 17-32.

Indirect and Direct Effect: binary outcome

Possible to estimate effects on the odds ratio scale: assumes rare outcome

$$\text{TCE}^{\text{OR}} = \text{NIE}^{\text{OR}} \times \text{NDE}^{\text{OR}}$$

$$\text{Proportion mediated} = \frac{\text{NDE}^{\text{OR}}(\text{NIE}^{\text{OR}} - 1)}{\text{NDE}^{\text{OR}} \times \text{NIE}^{\text{OR}} - 1}$$

Suggested reading: VANDERWEELE, T. J. & VANSTEELANDT, S. 2010. Odds ratios for mediation analysis for a dichotomous outcome. Am J Epidemiol, 172, 1339-48

Estimating the effects

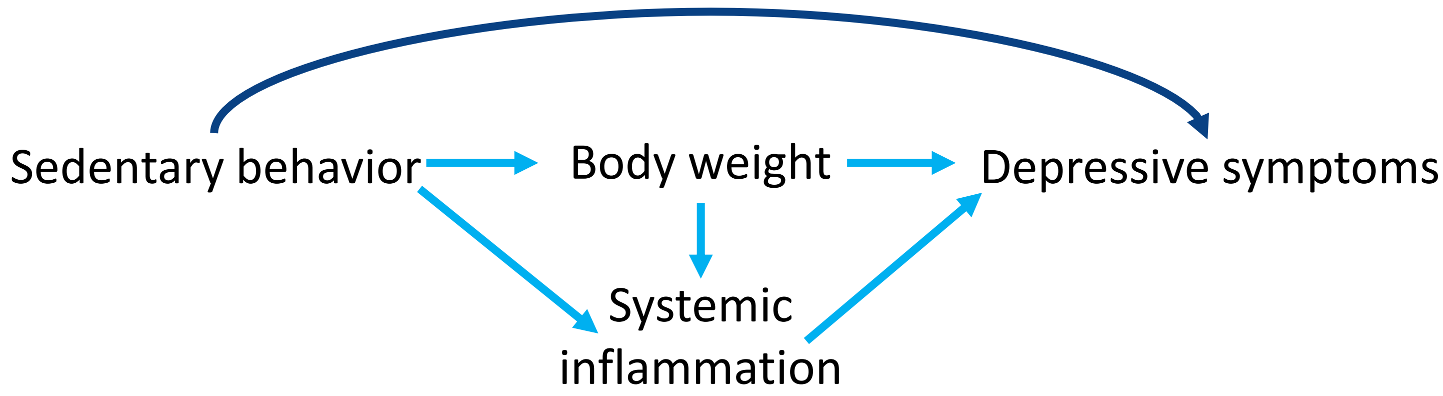
Parametric regression-based approach, based on:

- A regression model for the mediator given the exposure and covariates
- A regression model for the outcome given the exposure, mediator, and covariates

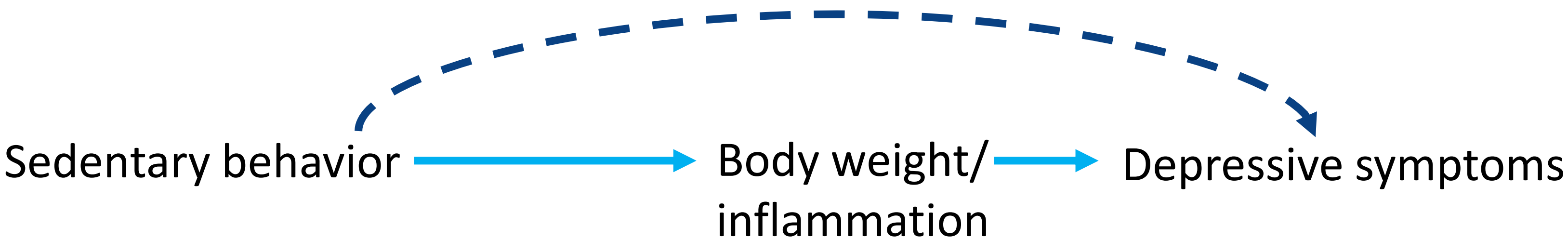
Macros available in most statistical packages

THE UNIVERSITY OF MELBOURNE

Mediation analysis with multiple mediators



Mediation analysis with multiple mediators: Joint mediation analysis



Mediation analysis with multiple mediators: Joint mediation analysis

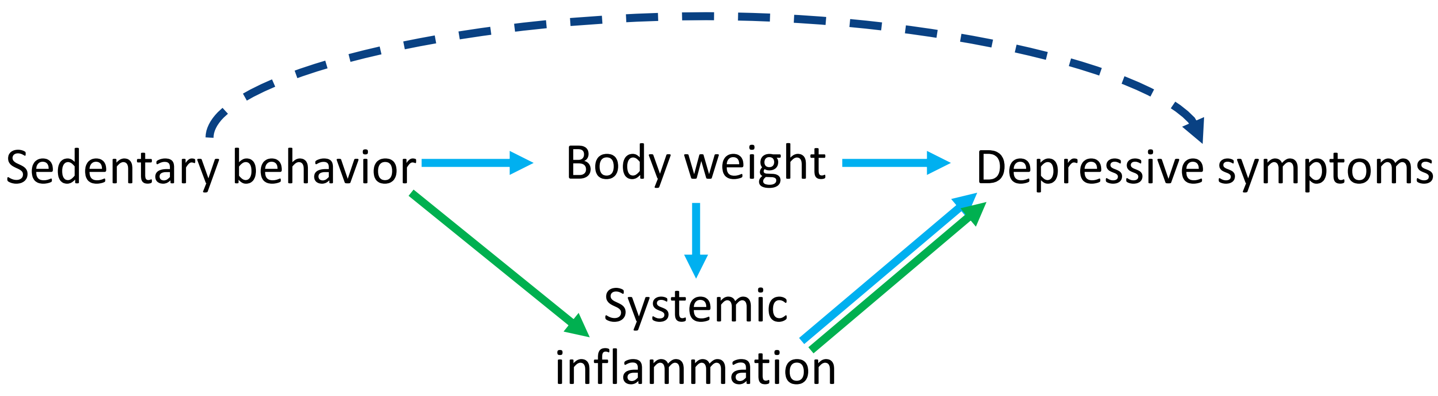
Different from estimating mediating effect for one mediator at a time

Parametric regression-based approach

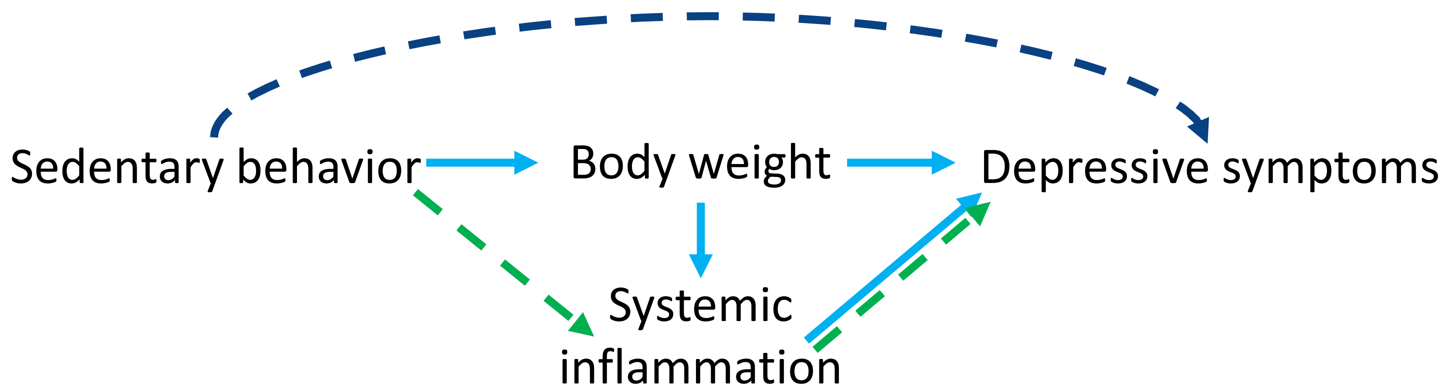
Weighted-based approach

Suggested reading: VANDERWEELE, T. J. & VANSTEELANDT, S. 2014. Mediation Analysis with Multiple Mediators. Epidemiol Method, 2, 95-115.

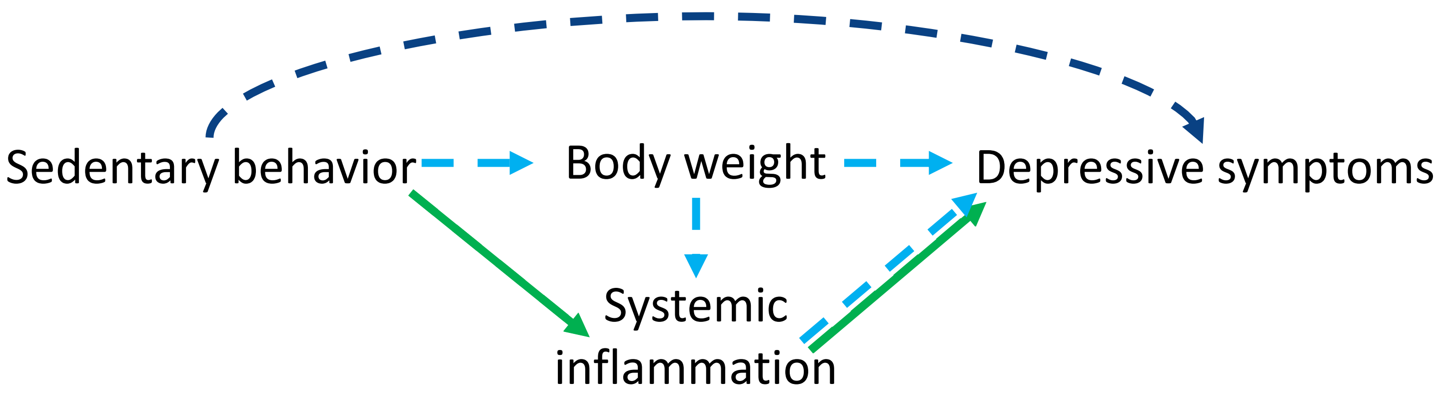
Mediation analysis with multiple mediators: Sequential mediation analysis



Mediation analysis with multiple mediators: Sequential mediation analysis



Mediation analysis with multiple mediators: Sequential mediation analysis



Mediation analysis with multiple mediators: Sequential mediation analysis

Requires making assumptions about the sequence of mediators:

Assumes no unmeasured mediator-mediator confounding

Parametric regression-based approach

Weighted-based approach *(VANDERWEELE, T. J. & VANSTEELANDT, S. 2014. Epidemiol Method, 2, 95-115.)*

Flexible approach *(STEEN, J., et al. 2017. Am J Epidemiol, 186, 184-193.)*

Causal mediation analysis and counterfactuals: Interventional Indirect Effect

SB=1

distribution of inflammation score in those with SB=1

SB=1

distribution of inflammation score in those with SB=0

$$\text{IntIE} = Y_{1G1|C} - Y_{1G0|C}$$

Causal mediation analysis and counterfactuals: Interventional Direct Effect

SB=1

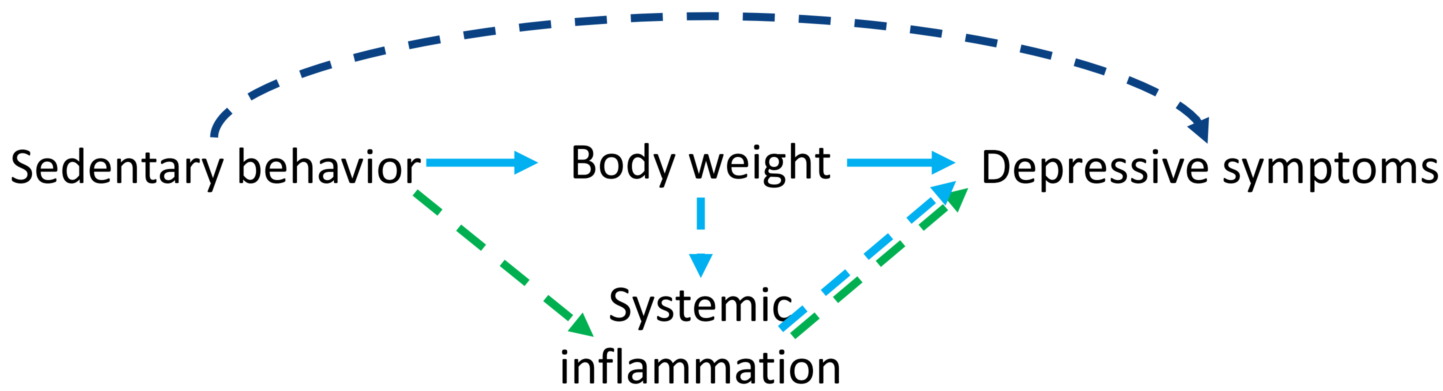
distribution of inflammation score in those with SB=0

SB=0

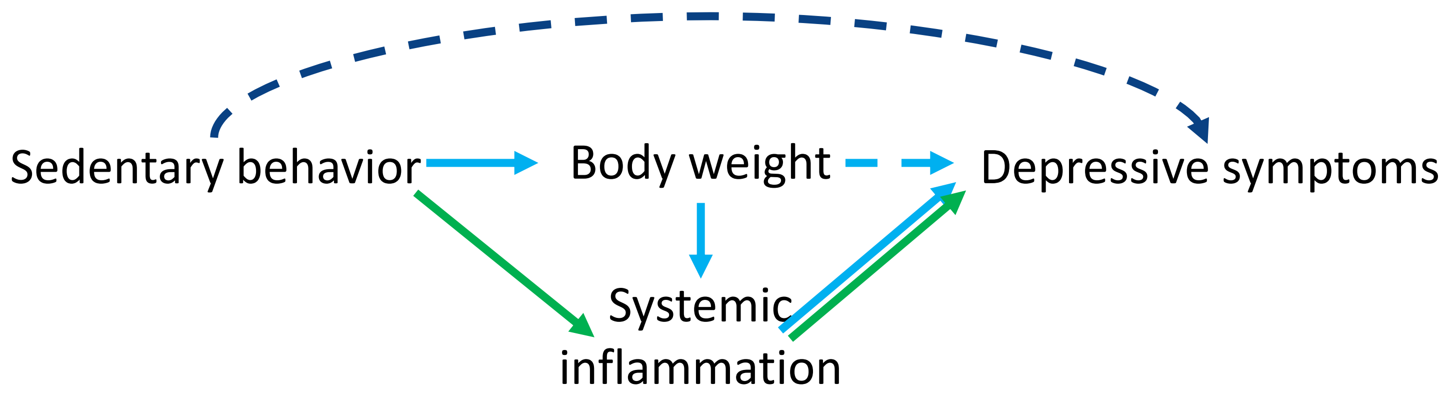
distribution of inflammation score in those with SB=0

$$\text{IntDE} = Y_{1G0|C} - Y_{0G0|C}$$

Mediation analysis with multiple mediators: Mediation analysis based on interventional effects



Mediation analysis with multiple mediators: Mediation analysis based on interventional effects



Mediation analysis with multiple mediators: Mediation analysis based on interventional effects

Estimation of effects does not rely on unobservable cross-world assumptions

Less reliant on the assumed sequence

The product of interventional indirect and direct effects does not always match the total causal effect

Mediation analysis with multiple mediators: Mediation analysis based on interventional effects

Standardized approach (weighted) *(VANDERWEELE, T. J., et. al. 2014. Epidemiology, 25, 300-6)*

Multiple-mediator approach (based on Monte Carlo simulations)
(VANSTEELANDT, S. & DANIEL, R. M. 2017. Epidemiology, 28, 258-265.)

G-formula approaches for handling time-varying exposure, mediator, confounders, and survival outcome becoming available

(LIN, S. H., et al. 2017. Epidemiology, 28, 266-274.
LIN, S. H., et. 2017. Stat Med, 36, 4153-4166.
VANDERWEELE, T. J. & TCHETGEN TCHETGEN, E. J. 2017. J R Stat Soc Series B Stat Methodol, 79, 917-938.)

Other suggested reading: MORENO-BETANCUR, M. & CARLIN, J. B. 2018. Understanding Interventional Effects: A More Natural Approach to Mediation Analysis? Epidemiology, 29, 614-617.

Study design

Methods developed for cohort studies

Complications when applying methods for case-control or nested case-cohort studies: How to get unbiased estimates for exposure or mediator models?

Suggested reading: VANDERWEELE, T. J. & TCHETGEN TCHETGEN, E. J. 2016. Mediation Analysis With Matched Case-Control Study Designs. Am J Epidemiol, 183**,** 869-70.

Other

What is the best approach to mediation analysis?

Some point to consider:

Research question

Causal structure of exposure, outcome, mediators, and covariates:

Worth spending time on developing the causal diagram

Study design

Assumptions of each approach

Type of variables

suggested reading: VANDERWEELE, T. 2015. *Explanation in causal inference: methods for mediation and interaction,* New York, Oxford Univ. Press.

Thank you