Can correct deconfounding support causal brain-behavioural predictive modelling?

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Problem statement

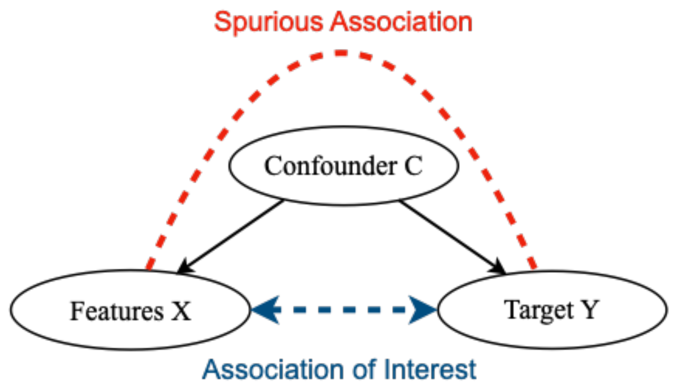
Why using predictive models?

- Uncover neurobiological mechanisms
- Clinical precision medicine tool

➡ Need for **generalizable** predictive results

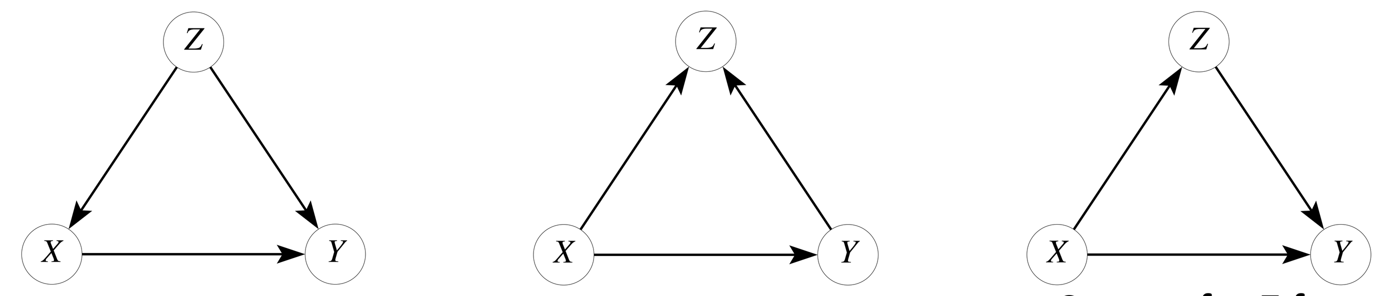
Confounders can bias models

→ not generalizable

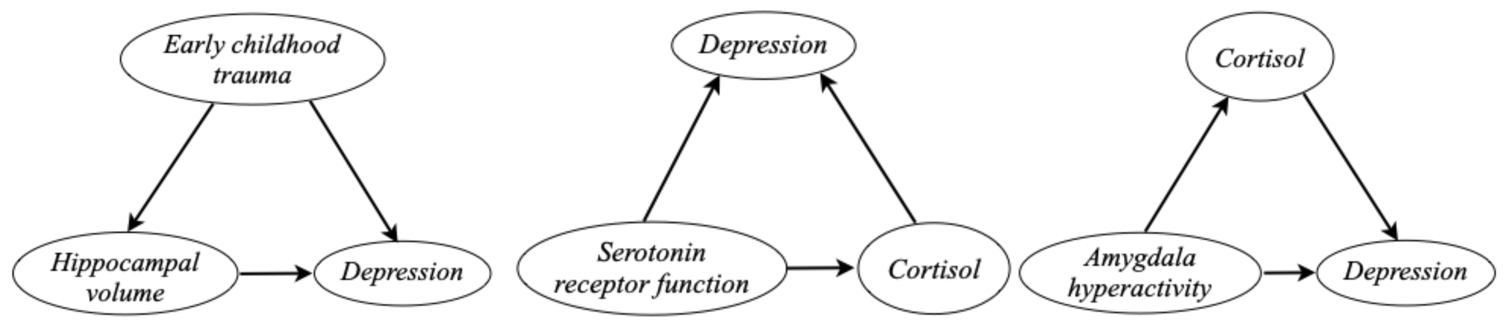


Background

Confounder | Collider | Mediator



Correct for Z | Do not correct for Z | Correct for Z for partial effect

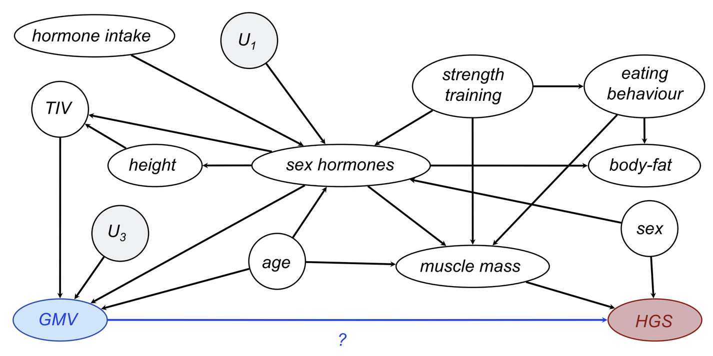
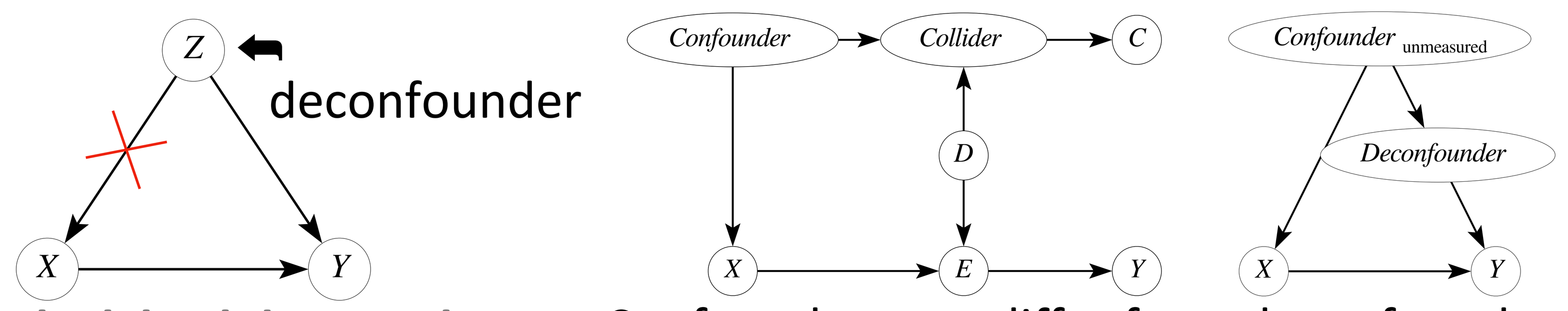
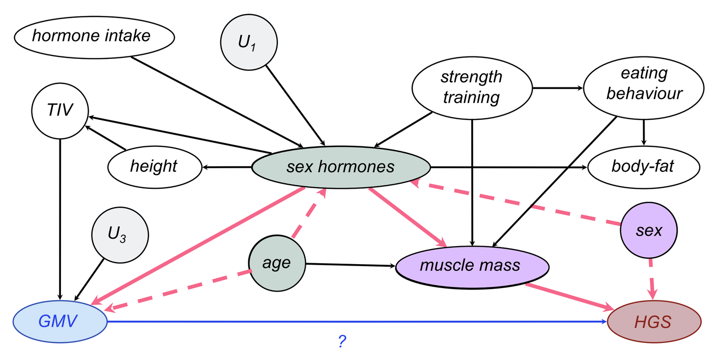
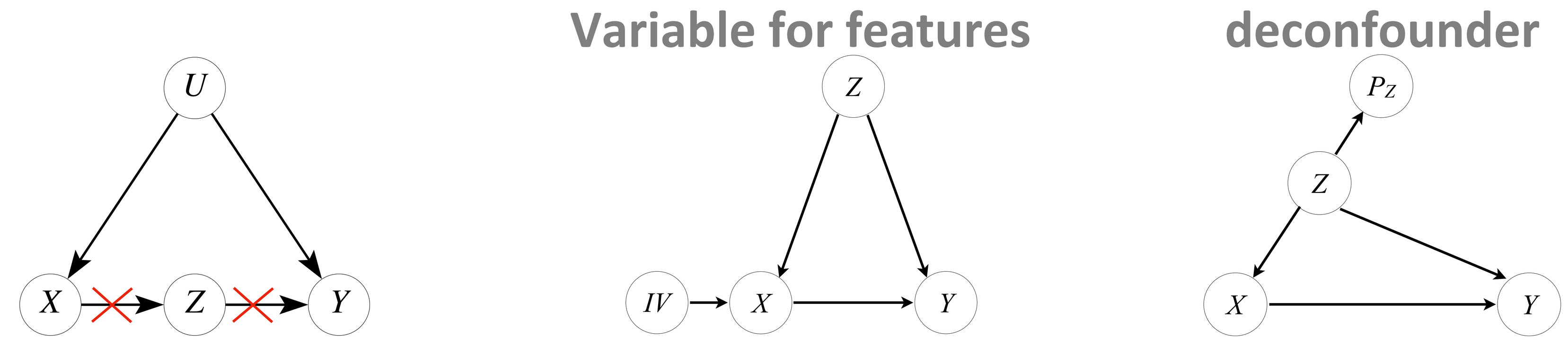
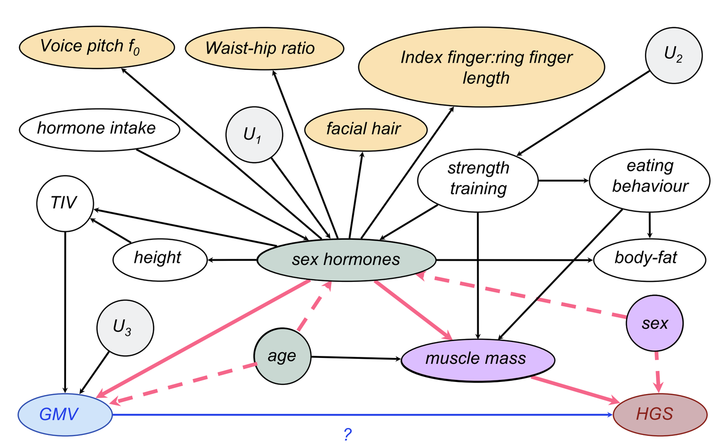
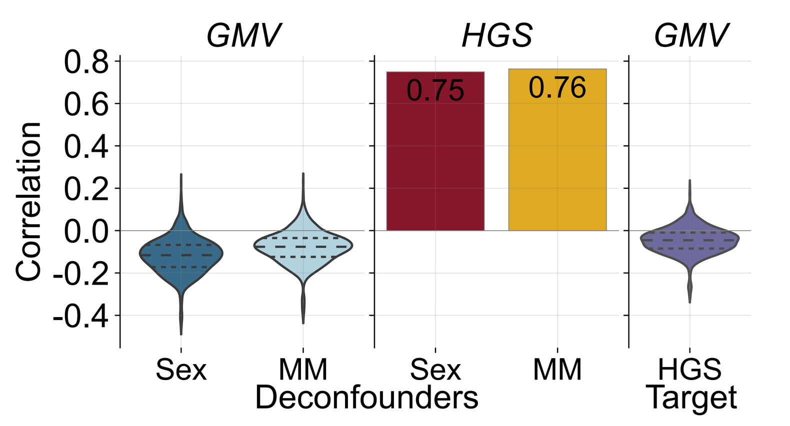
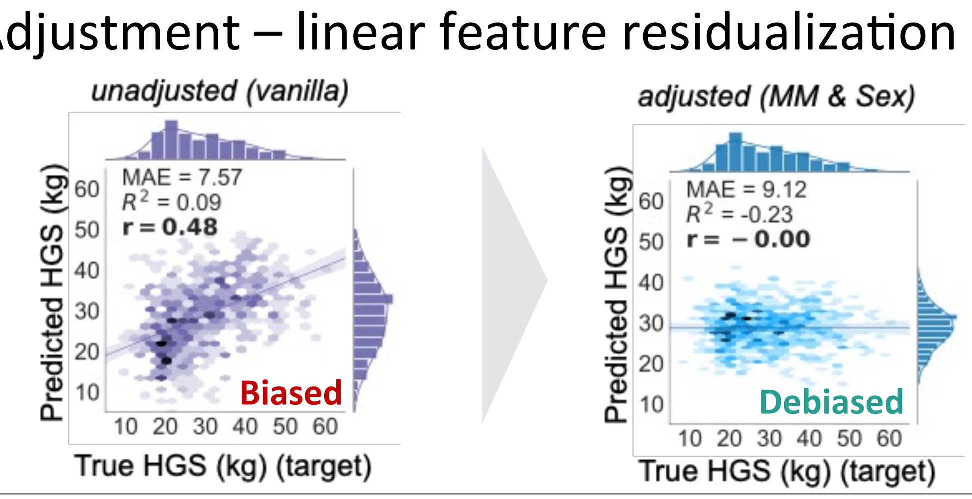
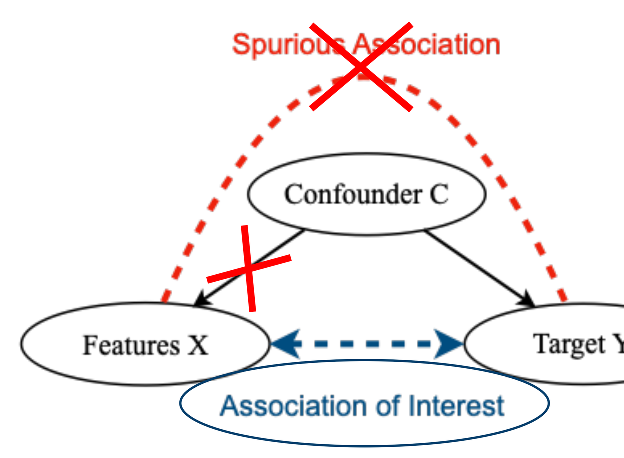


Same correlation matrix (Wysocki et al, 2022)

Requires causal definition for distinction

Question-specific DAG

Which variables to adjust for to deconfound biased models?

Steps	Explanation	Take Away
1 Causal analysis (creating the DAG)	**"What are known or conceivable causes of…"** the target and recursively added variables (include features as potential cause) — Bottom-up build DAG — Example: 	Build informed DAG instead of using default confounders.
2 Identify stuiable set of deconfounders	**Option 1 – Backdoor criterion** — **Backdoor paths** := Paths from X to Y that start with arrow pointing into X —  deconfounder — Block backdoor paths — Confounders can differ from deconfounders — Example:  — Consider alternative paths in case of unmeasured variables — *Set of deconfounders 1* — *Set of deconfounders 2* — Two example confounding paths	Use DAG to identify confounding pathways. Adjust for variables blocking these pathways.
Deconfounder Sufficient subset of confounders whose adjustment blocks all confounding pathways (Pearl, 1995); (Angrist et al., 1996); (Miao et al., 2018)	**Option 2 – Alternatives for unmeasured deconfounders** — Block frontdoor paths — Use Instrumental Variable for features — Two proxies for the deconfounder —  — → hard to find in biological context — → cannot be verified — Example: 	Alternatives hinge on the availability of measured "high-quality" variables.
3 Statistical evaluation and adjustment	Statistical evaluation  — Adjustment – linear feature residualization  	Statistical confounder-feature/target association also matters.

Consequences - Predictive modeling for causal insights?

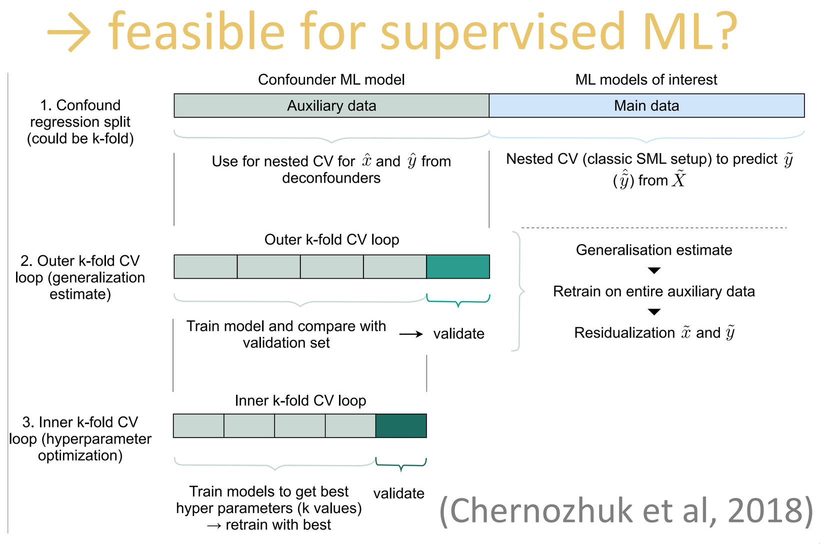
Limitations of linear (feature) residualization

1. Parametric linear model
   → Residual non-linear signal
2. Adjustment applied to either features or target, not both
   → Residual confounding in f/t

Double ML for the rescue?

ML to deconfound causal treatment effect estimation → assumed linear treatment-outcome relationship

→ feasible for supervised ML?



(Chernozhuk et al, 2018)

Deconfounded models for causal insights?

Traditional ML – Learn P(Y|X)
→ Associative prediction

Causal ML – Learn P(Y|do(X))
→ Interventional prediction

Deconfounded traditional ML

- Aims for mechanistic f-t insights
- ≠ causal ML (treatment effects)
- Causality assumptions would still need to be fulfilled

→ causal claims require further justifications

Conclusions

1. **DAG-informed confounder identification** instead of „default" adjustments
2. Linear (f/t) residualization has limitations
3. Deconfounded models do **not** directly allow for causal claims but are biologically more informative

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