The Metabolic Pathways Between Components of Stature and HbA1c: A Causal Structure Learning Approach in the UK Biobank

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No relevant disclosures.

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Background:

- Short adult leg length (LL) is a marker of early childhood conditions and is associated with higher risk for type 2 diabetes, but is not known how association is metabolically mediated.
- Aim: Identify how components of stature influence metabolic profile and consequent risk for diabetes through HbA1c.

Methods:

- Cross-sectional analysis of UK Biobank: n=367,838, not prevalent diabetes cases.
- Applied causal structure learning algorithm NetCoupler (R package at github.com/NetCoupler), tested on 100 resamples of 10% of dataset.
- Exposures: LL, leg-height ratio (LHR), and height; Outcome: HbA1c.
- Metabolic profile: gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), TAG, LDL, HDL, total cholesterol, C-reactive protein (CRP), apolipoprotein A and B, and albumin.
- Confounders: Age, sex, and waist circumference.

Results:

- Metabolic network links: e.g. HDL-LDL-Cholesterol-TAG (serum lipid profile) and GGT-ALT-AST (liver function).
- Network to HbA1c: Positive links with ALT, GGT, and CRP.
- Stature to network: Negative links between:
  - LL and height on CRP, GGT, and TAG.
  - LHR, LL on CRP and ALT.
- NetCoupler algorithm identified GGT, ALT, and CRP as likely metabolic link between stature components and HbA1c.

Conclusion:

- Suggest more adverse early childhood growth conditions (leading to shorter legs and shorter stature) may contribute to higher HbA1c (and higher risk for diabetes) through higher liver dysfunction (GGT and ALT) and higher inflammation (CRP).

Figure 1: NetCoupler algorithm (R package at github.com/NetCoupler) process, identifies potential pathways between exposure (E), metabolic network (N), and outcome (O)

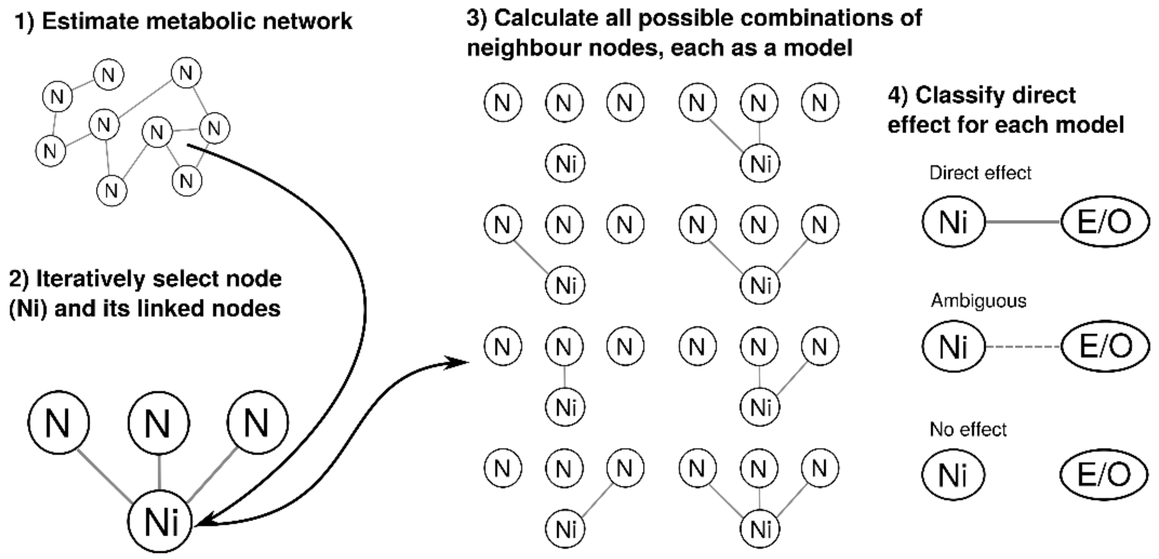
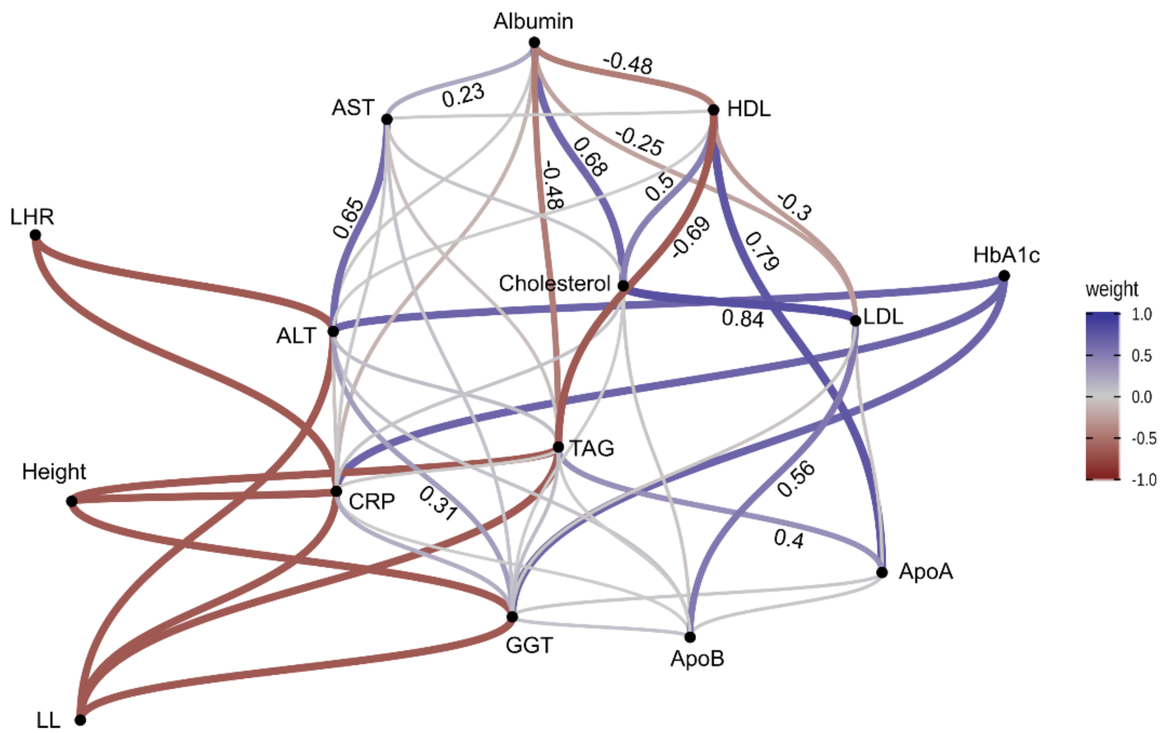


Figure 2: Pathways between stature, network, and HbA1c



Potential pathways identified from the NetCoupler algorithm. A darker blue link indicates a positive relationship, while a darker red one indicates a negative relationship. Numbers between metabolic variables indicate the weights for the links (a larger number suggests a stronger link). Links shown with the stature or HbA1c variables and the network variables were classified as direct effect links; all other linked had been classified as ambiguous.