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

Luke W Johnston[1], Clemens Wittenbecher[3], Helene T Vistisen[2], Christina C Dahm[2], Daniel R Witte[1,2]
1. Steno Diabetes Center Aarhus, Denmark, 2. Aarhus University, Denmark, 3. Harvard University, USA
No relevant disclosures.

Contact:
Luke W. Johnston, MSc, PhD
Email: luke.johnston@rm.dk
0000-0003-4169-2616
posters.lwjohnst.com/2020/easd

Background:

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

Methods:

- Cross-sectional analysis of UK Biobank (Application ID 47673): n=367,838, without 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-C, HDL-C, 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-C-LDL-C-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:

- Adverse early childhood growth conditions (leading to shorter legs and shorter stature) may contribute to higher HbA1c 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)

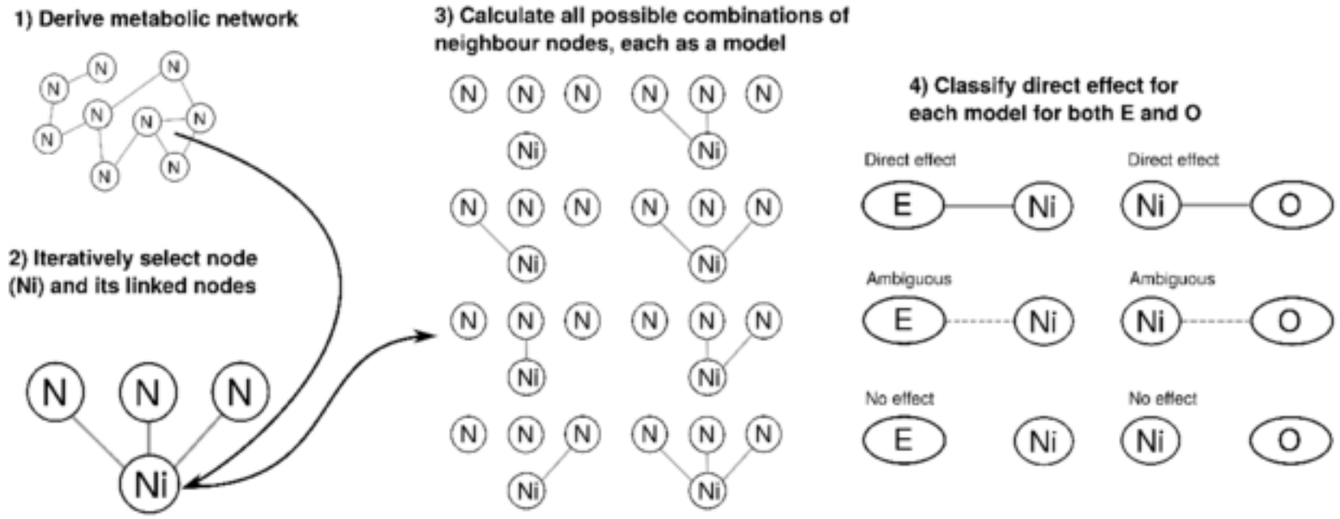
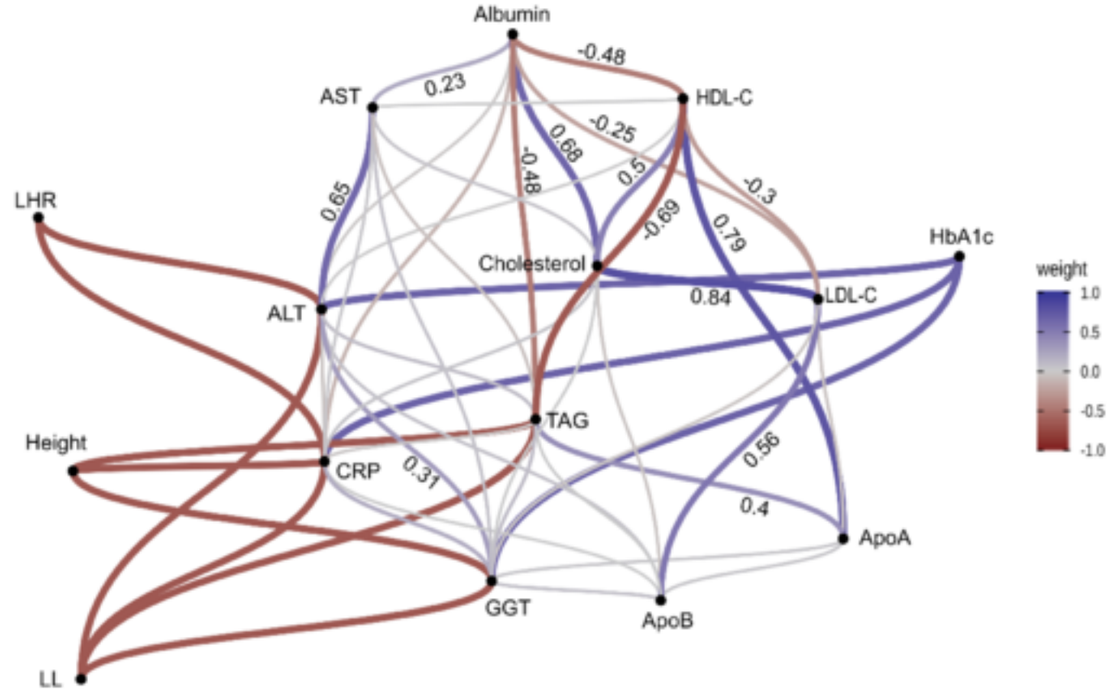


Figure 2: Pathways between stature, network, and HbA1c



Potential pathways identified from the NetCoupler algorithm. A darker blue link indicates a positive relationship, while a darker red one indicates a negative relationship. Grey lines between metabolic variables are the derived neighbours, but with weaker connections. Numbers between metabolic variables indicate the weights for the strong 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; while all other connections with metabolic variables had been classified as ambiguous, they were removed for better visual presentation.