Metabolic profiling of different glycemic traits: a Two-sample Mendelian randomization study

Authors

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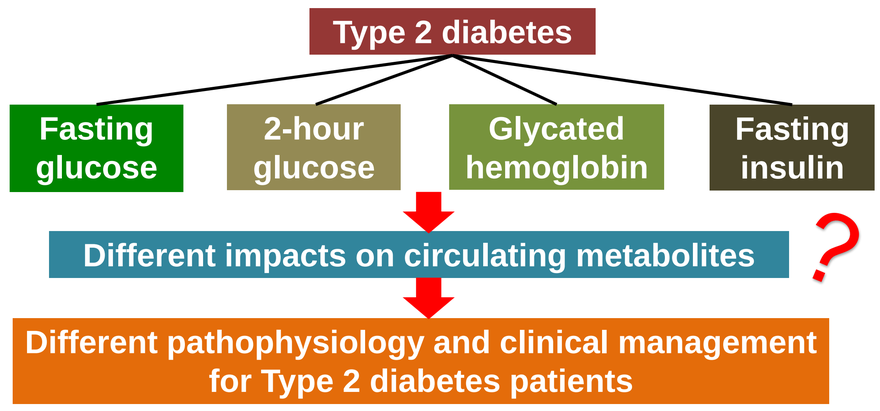
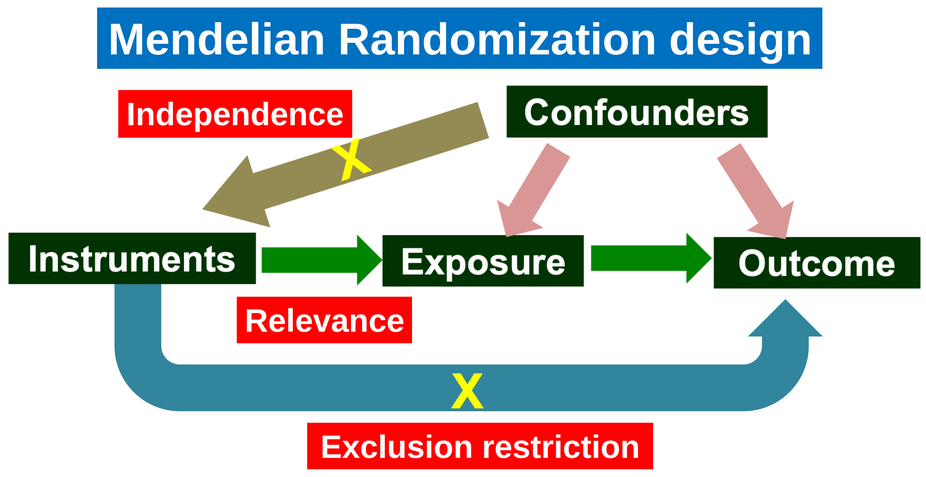
Background & Objectives

- Type 2 diabetes (T2D) is diagnosed based on different glycemic traits – fasting glucose (FG), 2-hour glucose (2hGlu), glycated hemoglobin (HbA_{1c}) and fasting insulin [1].
- A recent study suggested different roles of the four glycemic traits in atherosclerotic and thrombotic conditions [2].
- Clarifying the similarities and differences in the association with downstream metabolites (e.g., lipid subfractions and amino acids) of these glycemic traits and liability to T2D may help clarify the pathophysiology of these inter-related glycemic traits in various diseases, such as cardiovascular diseases [3].

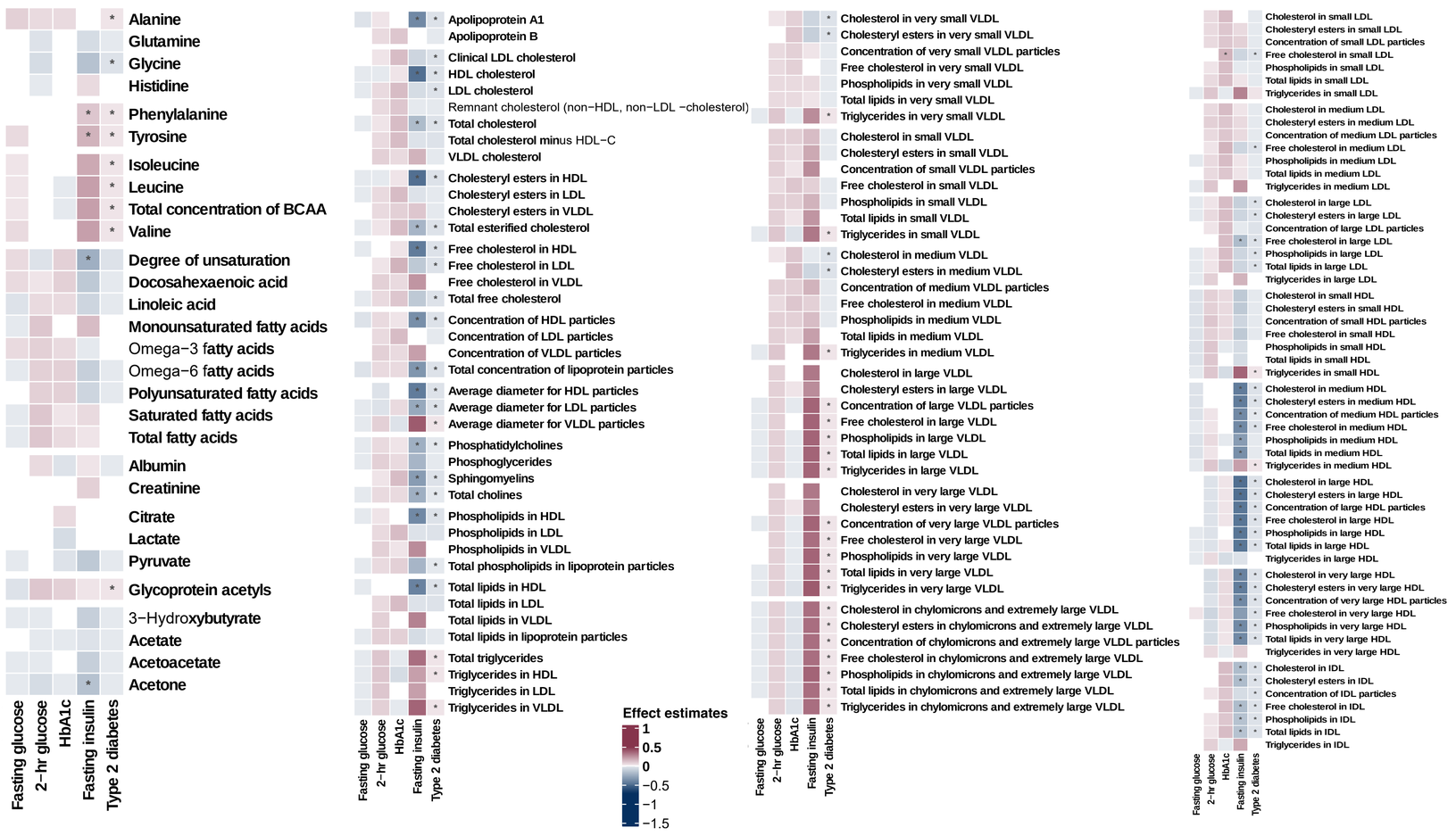


Methods

- We assessed the causal relation of four glycemic traits and liability to T2D with 167 metabolites using Mendelian randomization (MR) design.
- We extracted instruments (SNPs) for four glycemic traits from MAGIC (n = 200,622), and liability to T2D from a meta-analysis of multiple cohorts (148,726 cases, 965,732 controls) in Europeans.
- Outcome data were from summary statistics of 167 metabolites from the UK Biobank (n=115,078).
- Main analysis: Inverse variance weighted (IVW) estimates
- Sensitivity analyses: Median weighted estimates, MR-Egger estimates and Reverse MR.
- Correcting for multiple comparison, statistical significance was set at $p < 0.0004$.



Results



- Based on F statistics (>10), there was little evidence of weak instrument bias.
- FG and 2hGlu were not associated with any metabolite. Higher HbA_{1c} was associated with higher free cholesterol in small low-density lipoprotein (LDL).
- FI were associated with 42 circulating metabolites (2 positive associations, 40 inverse associations).
- T2D were associated with 88 circulating metabolites (34 positive associations, 54 inverse association), including most FI-associated signals (38 out of 42), except for degree of unsaturation in fatty acids, acetone, phospholipids in medium HDL, and total lipids in medium HDL.
- In the reverse MR analyses, linoleic acid was associated with HbA_{1c}; HDL-cholesterol and cholesteryl ester in HDL were associated with FI. Ten circulating metabolites were associated with T2D risk, suggesting potential reverse causation.

Discussion & Conclusion

- Our study used an MR design, which is less susceptible to confounding.
- However,

1. Valid causal inference depends on core instrumental assumptions, and fully assessing pleiotropy is challenging.
2. Genetic instruments for glycemic traits excluded participants with T2D, which reduces the likelihood of reverse causation, but may inevitably introduce possible selection bias.
3. Our study utilized data from European populations only, our findings may not generalize to other populations.
4. Instruments used for NMR measured traits could be pleiotropic (violation of exclusion restriction assumption).

- This is one of the largest MR studies exploring the metabolomic signatures of different glycemic traits and liability to T2D.
- Our study adds by showing that metabolomic signatures associated with liability to T2D resemble the signatures for FI, which implies that signals of liability to T2D cannot be solely explained by hyperglycemia but is likely more related to the consequence of elevated insulin.
- These findings indicate hyperglycemia-independent patterns and highlight the role of insulin in T2D development.
- Further studies should evaluate these glycemic traits in T2D diagnosis and clinical management.

We declared there is no conflict of interest.

Acknowledgements

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References

1. American Diabetes Association Professional Practice C. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2021;45(Supplement_1):S17-S38. doi: 10.2337/dc22-S002
2. Emerging Risk Factors, C., N. Sarwar, P. Gao, S.R. Seshasai, R. Gobin, S. Kaptoge, E. Di Angelantonio, E. Ingelsson, D.A. Lawlor, E. Selvin, M. Stampfer, C.D. Stehouwer, S. Lewington, L. Pennells, A. Thompson, N. Sattar, I.R. White, K.K. Ray, and J. Danesh. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375(9733), 2215-22. https://doi.org/10.1016/S0140-6736(10)60484-9
3. Yuan, S., A.M. Mason, S. Burgess, and S.C. Larsson. Differentiating Associations of Glycemic Traits With Atherosclerotic and Thrombotic Outcomes: Mendelian Randomization Investigation. Diabetes. 2022; 71(10), 2222-2232. https://doi.org/10.2337/db21-0905