Metabolites and metabolomics

Examples from the literature

University of BRISTOL
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Metabolomics for prediction

- Widespread metabolic changes are known to be associated with many diseases
- The evaluation of metabolite profiles might help us to understand biochemical basis of disease and we can use these for prediction
- Developing sensitive prediction and prognostic tools is important – to improve identification of high risk individuals and to customize treatment with specific strategies to maximise resources

Metabolomics for prediction of Type 2 diabetes

Metabolomics
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Metabolomics based markers predict type 2 diabetes in a 14-year follow-up study

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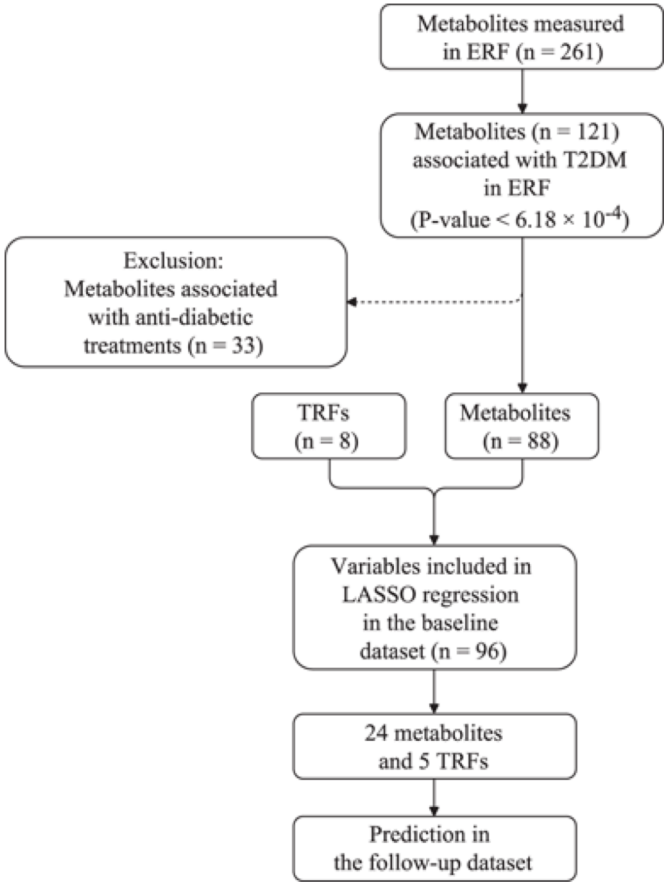
- The incidence of type 2 diabetes (T2D) is increasing worldwide
- It is often diagnosed with a fasting glucose test (FGT)
- Specificity is poor for low risk groups
- This study found that when evaluating FGT, traditional risk factors (TRF) and metabolites:
  - a combined model predicted future T2D with the best discrimination
  - a metabolomic prediction model outperformed the FGT for predicting future T2D in certain subpopulations

Metabolomics for prediction

- Erasmus Rucephen Family (ERF) study
- N=2,776, 1,571 followed up for (mean) 11.3 years
- 137 developed T2D, 1,434 did not
- Metabolite predictors = 261 markers measured either by NMR or MS
- 24 of these selected by LASSO as independent T2D metabolomic predictors
- TRF predictors: age, sex, family history, BMI, waist circumference, hypertension, HDL-cholesterol, and triglycerides



Flowchart showing metabolite selection
https://doi.org/10.1007/s11306-017-1239-2

Results for all groups

- Model performance assessed by area under the curve (AUC (95% CI)) and receiver operator characteristics (ROC) curves and continuous Net Reclassification Improvement (NRI)
- Combined model performs best

Model	AUC (95% ci)
ERF metabolites	0.81 (0.77, 0.85)
Fasting glucose	0.84 (0.81, 0.88)
ERF metabolites + fasting glucose	0.88 (0.84, 0.91)
ERF metabolites + fasting glucose + TRF's	**0.89 (0.86, 0.92)**

Results

However when populations were stratified by age, sex or weight, the AUC of the metabolite model is higher in females, those of normal weight and individuals <50 years

Group	Model	AUC (95% ci)
Females	ERF metabolites	**0.88 (0.83, 0.92)**
	Fasting glucose	0.84 (0.79, 0.90)
Males	ERF metabolites	0.78 (0.72, 0.84)
	Fasting glucose	0.83 (0.79, 0.88)
Normal BMI	ERF metabolites	**0.85 (0.75, 0.95)**
	Fasting glucose	0.80 (0.66, 0.93)
Overweight or obese	ERF metabolites	0.81 (0.76, 0.85)
	Fasting glucose	0.83 (0.79, 0.87)
Age <50	ERF metabolites	**0.86 (0.78, 0.94)**
	Fasting glucose	0.77 (0.67, 0.87)
Elderly	ERF metabolites	0.83 (0.78, 0.87)
	Fasting glucose	0.84 (0.80, 0.88)

Take home

- A combined model of metabolites, TRFs and FGT = best predictor of future T2D
- Metabolite models predict future T2D better than FGT in female, normal weight and < 50 years individuals
- LASSO method supports previous evidence suggesting *isoleucine* and *tyrosine* are independent predictors of T2D

- Opens up new opportunities for testing causal inference using Mendelian randomization
- Potential bias coming from some individuals taking lipid-lowering medication (although this was controlled for in each analysis)
- Needs validation