



correlation analysis

LD score regression: VAT-T2D and glucose-related traits



Two-sample Mendelian Randomization

Data sources

Genetic instruments

221 SNPs associated with predicted VAT using UK Biobank data ($N = 325,153$)

Associations

SNP-VAT

MR analyses

Univariable MR

Inverse-variance weighted
Weighted median
MR-Egger regression
MR-RAPS
CAUSE
Bi-directional MR
GSMR

Outlier detection

MR-PRESSO
GSMR

Sensitivity analyses

Multivariable MR

Adjusted for BMI, WC, WHR and smoking

Outcomes

Type 2 diabetes

Discovery ($N = 159,208$)
Replication ($N = 70,127$)

Glucose-related traits

HbA1c ($N = 200,622$)
FG ($N = 200,622$)
2hGlu ($N = 200,622$)
FI ($N = 200,622$)

SNP-T2D and glucose-related traits



Transcriptome-wide association study

Reference data

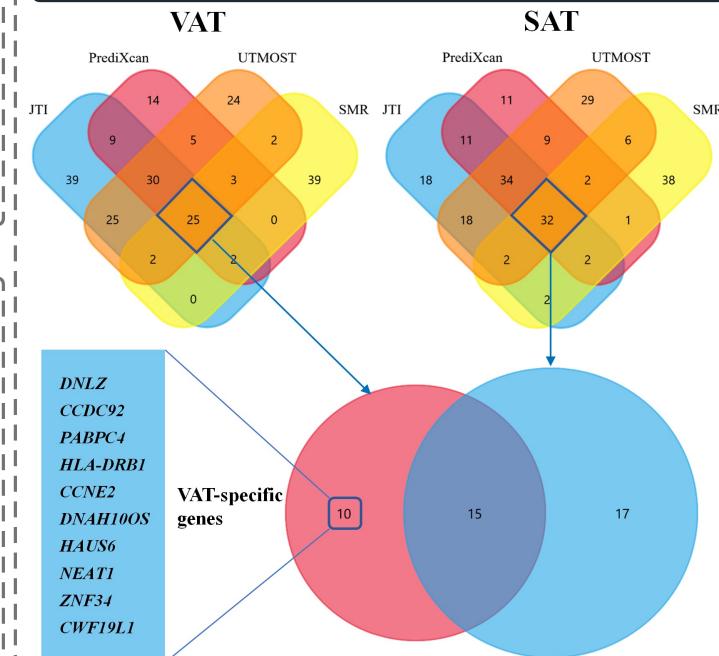
GTEX project transcriptome and genetic data VAT ($N = 581$) SAT ($N = 469$)

TWAS methods

Prediction Models

JTI
PrediXcan
UTMOST

VAT-specific genes



Summary-based TWAS

Gene expression imputation and association analyses with T2D
Large-scale GWAS for T2D (74,124 cases and 824,006 controls)

Identification of "causal gene"
SMR and colocalization

Enrichment analyses and clarifying cell-type specificity

FUMA GWAS and DEPICT software

Single-cell RNA-seq data from VAT in T2D (4888 cells) and non-T2D (8009 cells) individuals

Function validation

Knockdown experiments in 3T3-L1 pre-adipocytes

3T3-L1 pre-adipocytes

Transfection

- Empty vector
- Target gene shRNA
- Empty vector+insulin
- shRNA+insulin

Cell proliferation test

Inducing differentiation

3T3-L1 adipocytes

- Morphological features
- Lipid accumulation
- Glucose and energy metabolism
- Secretion function
- Insulin signalling

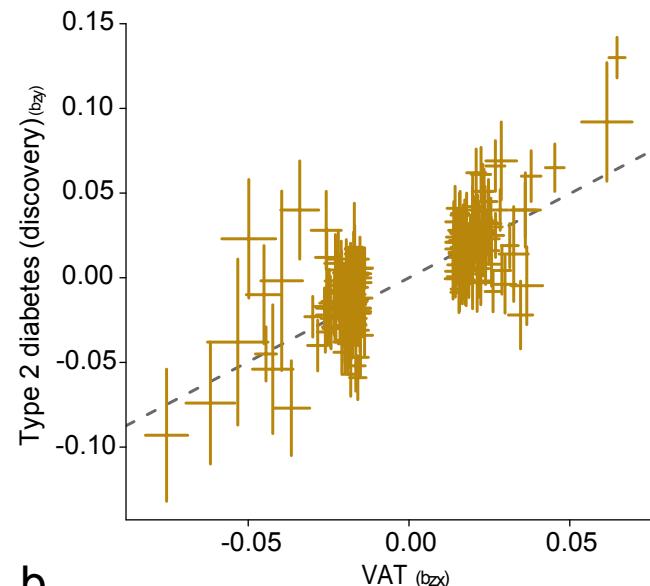
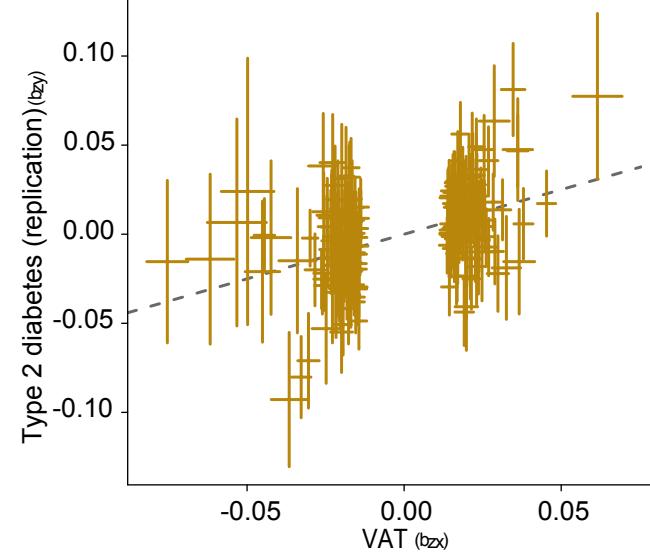
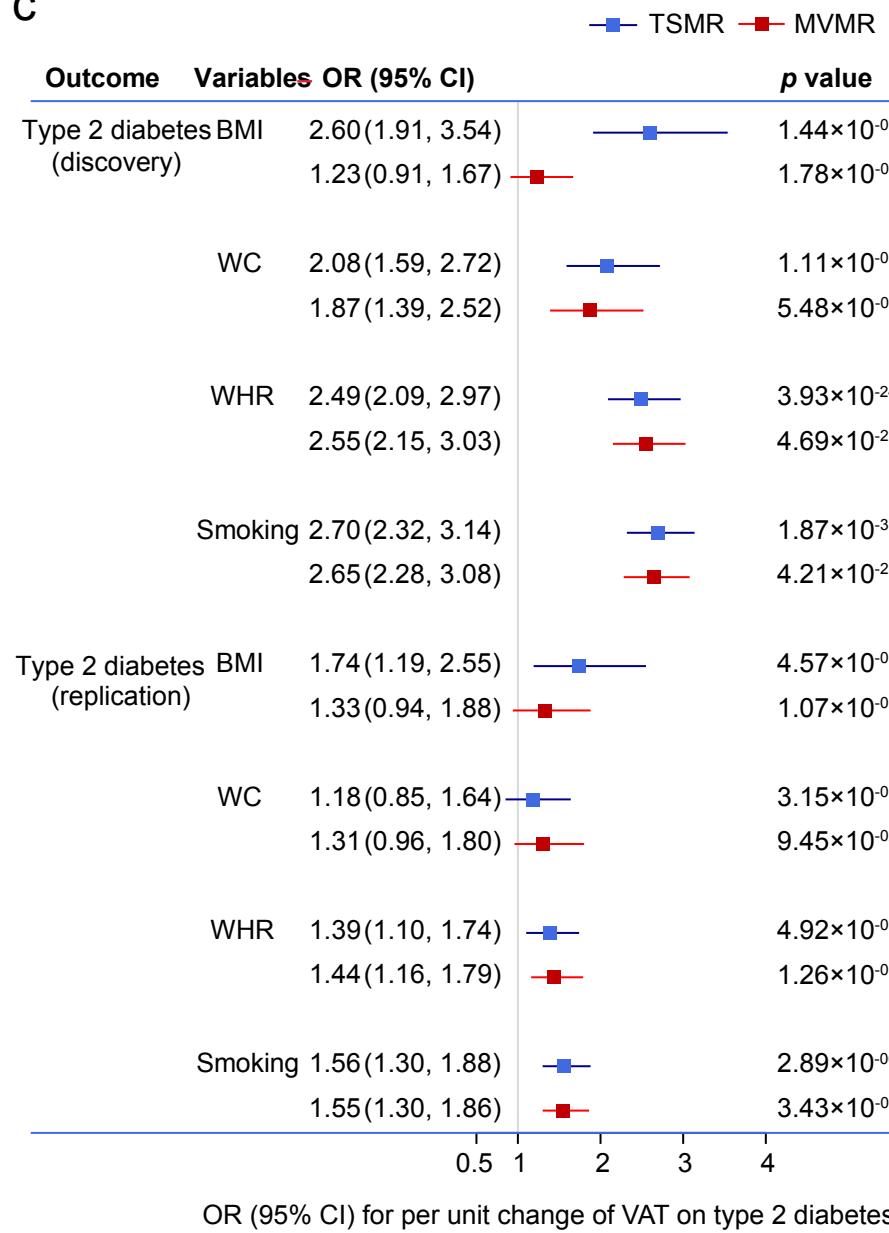
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Fig. 2
Colour

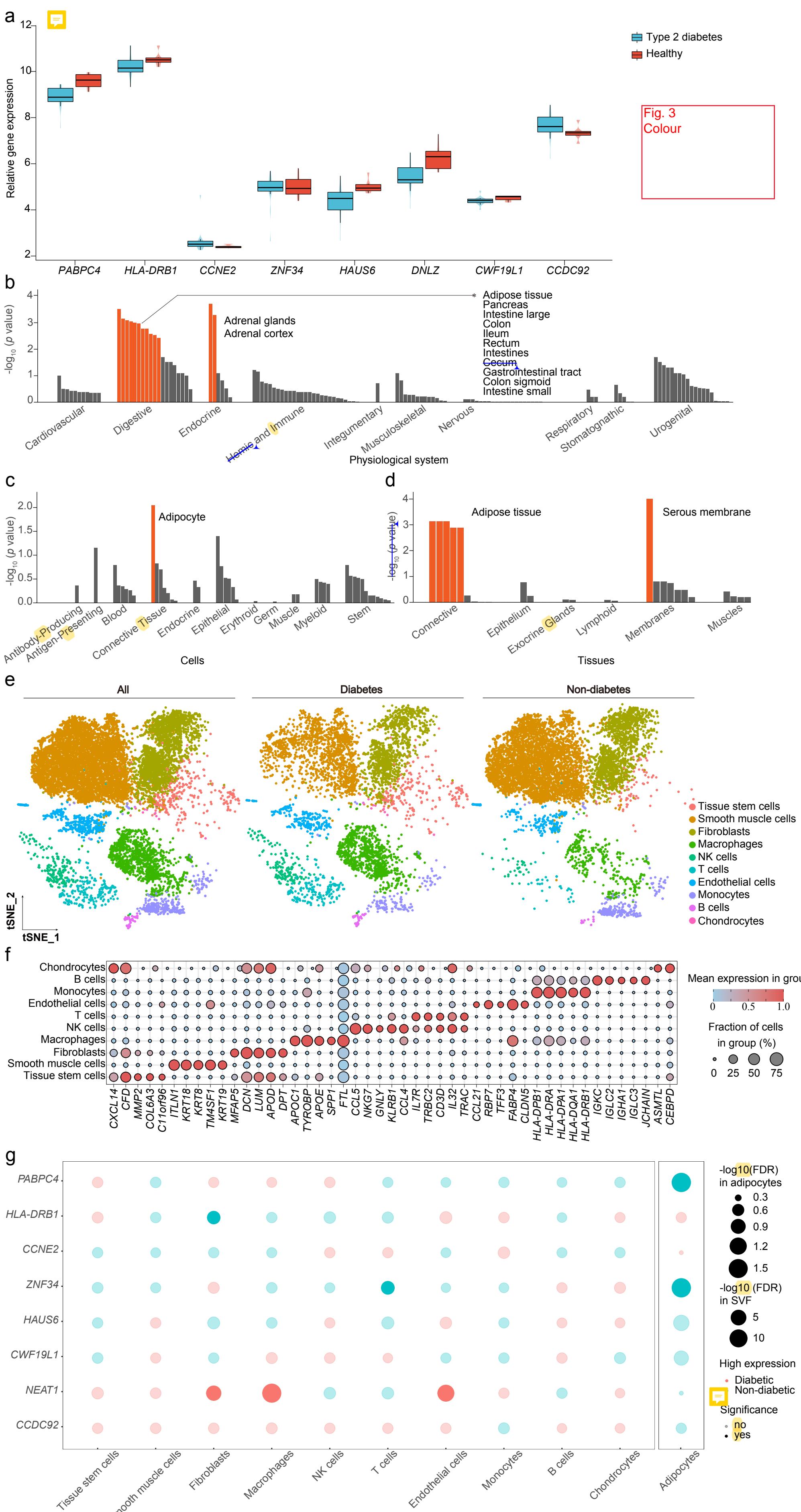


Fig. 4
Colour

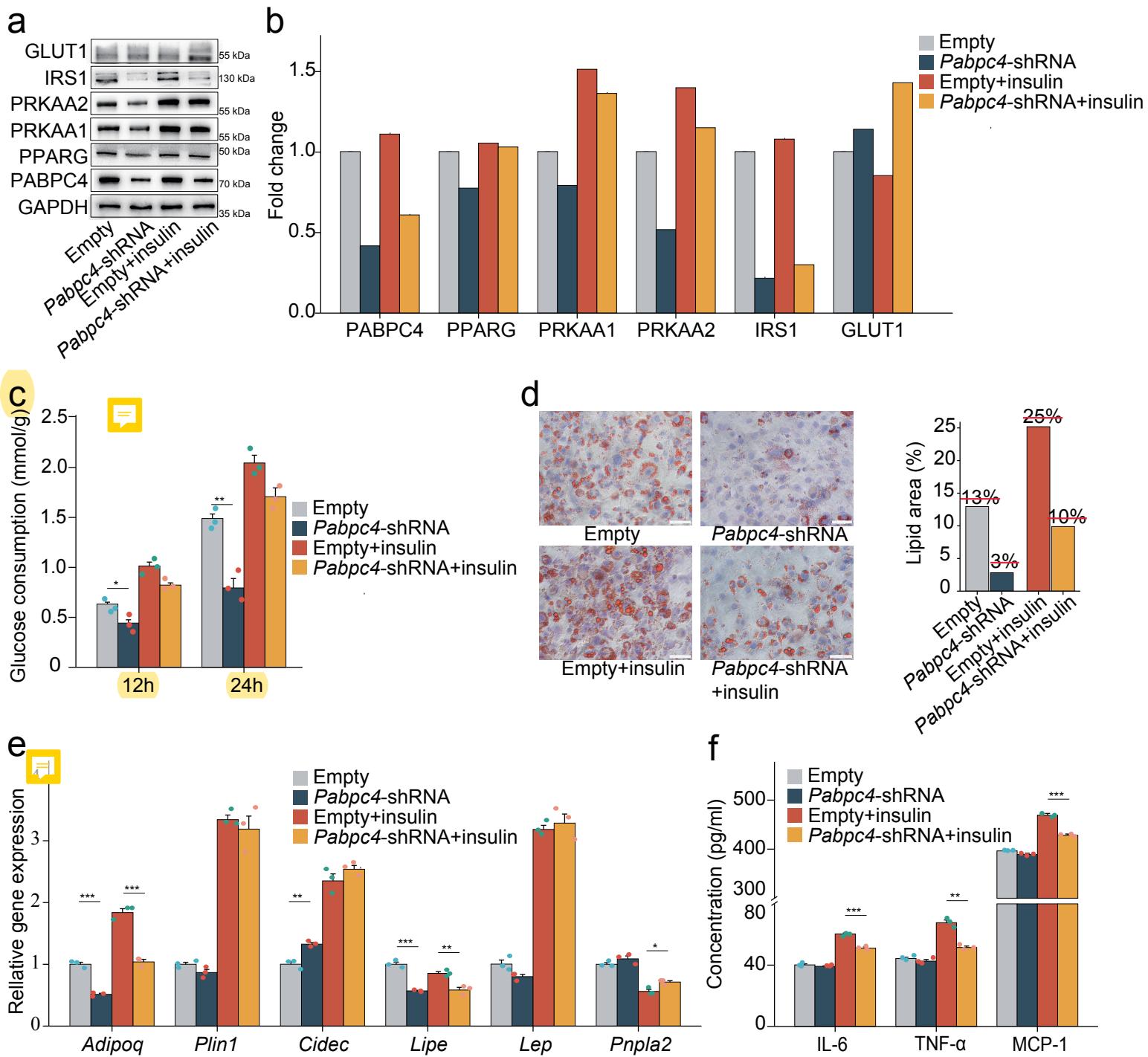


Fig. 1
Colour
No changes

23/0430 Mokhtar

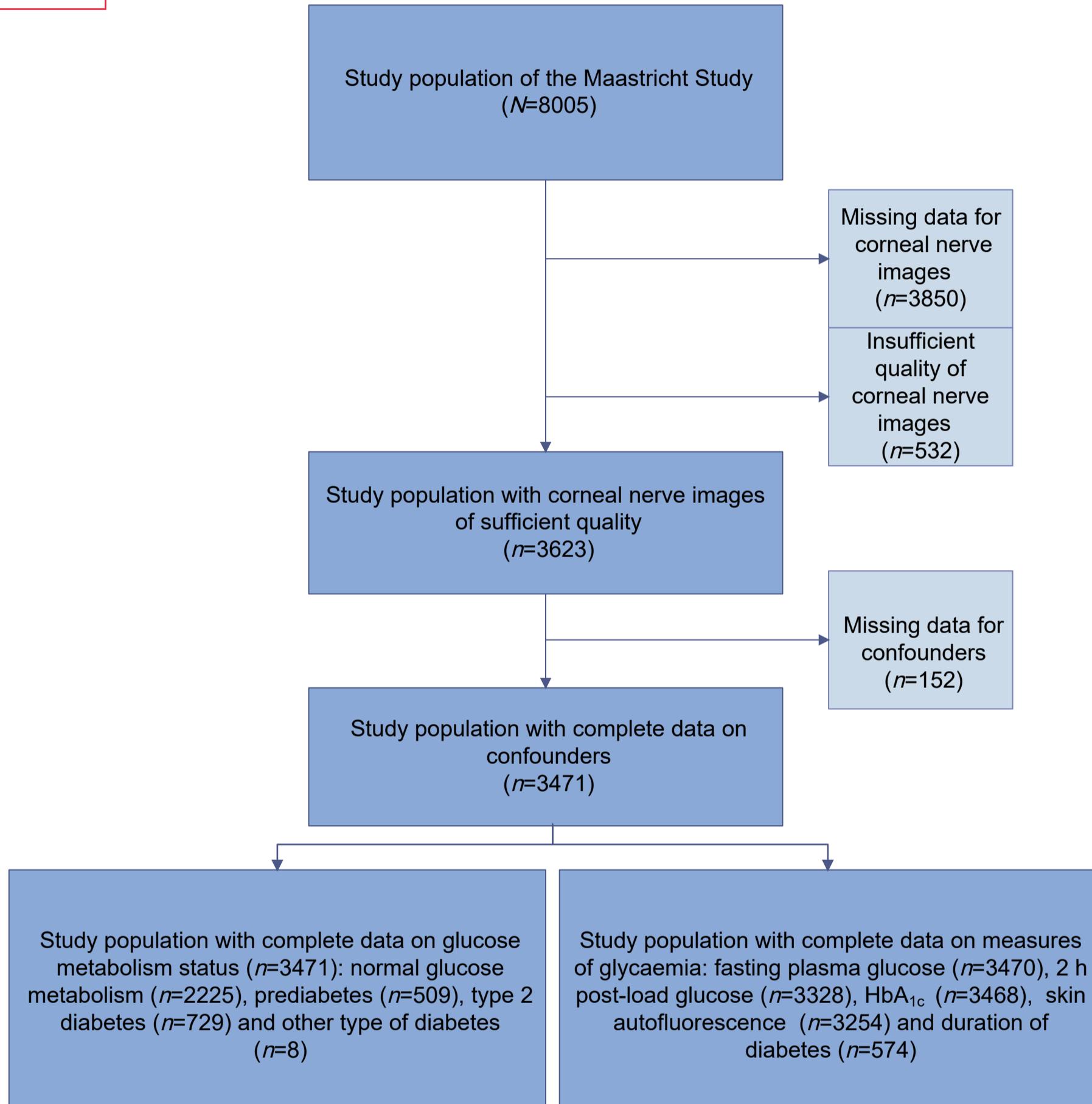


Fig. 2

GM status



n = 3471

Standardized β (95% CI)

Reference

Prediabetes versus NGM status



-0.08 (-0.17, 0.03)

Type 2 diabetes versus NGM status



-0.14 (-0.25, -0.04)*

Measures of glycemia

Fasting plasma glucose, per SD



n = 3470

-0.09 (-0.13, -0.05)*

2-Hour post-load glucose, per SD



n = 3328

-0.07 (-0.11, -0.03)*

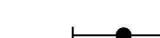
HbA1c, per SD



n = 3468

-0.08 (-0.11, -0.04)*

Skin autofluorescence, per SD



n = 3254

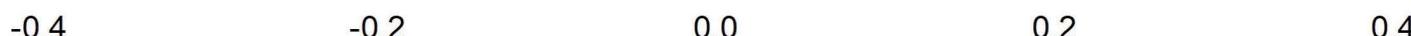
-0.05 (-0.08, -0.01)*

Duration of diabetes, per SD



n = 574

-0.09 (-0.17, -0.00)*



Composite Z-score of corneal nerve fiber measures

Indicates that a greater measure of the determinant is associated with a lower composite Z-score corneal nerve fiber measures

Indicates that a greater measure of the determinant is associated with a greater composite Z-score corneal nerve fiber measures