nature portfolio

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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	GraphPad Prism 9.4.0
Data analysis	TOPMed reference panel via the TOPMed imputation server [Das, S. et al. Next-generation genotype imputation service and methods. Nat Genet 48, 1284-1287 (2016); Taliun, D. et al. Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. Nature 590, 290-299 (2021)] GloWGR, a distributed version of the REGENIE whole-genome regression method [Mbatchou, J. et al. Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet 53, 1097-1103 (2021)] GraphPad Prism 9.4.0 Skyline (version 21.1.0.278)

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

All original data are available from the corresponding author upon request.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex but not gender of healthy human monocyte donors was considered for this study. The findings include both sexes. The sex of the donor was self-reported and consent for study participation was acquired before the study procedures. No sex- and gender-based analysis has been performed due to the study design. Human monocytes were collected and pooled together before treatment to account for potential differences between sex and genders and to de-identify the samples.
Population characteristics	Population characteristics for the genetic study were briefly described in the method section and as previously described. [Sudlow, C. et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 12, e1001779 (2015).] Population characteristics for the individuals with type 1 diabetes were described in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) as previously reported [Shao, B. et al. Pulmonary surfactant protein B carried by HDL predicts incident CVD in patients with type 1 diabetes. J Lipid Res 63, 100196 (2022).] Healthy human monocyte donors were recruited from our local department. Healthy subjects were between the age of 18 and 65 without any co-morbidities or regular medication use.
Recruitment	Healthy subjects were recruited by the investigators via study recruitment flyers and an email listserv. No subjects were excluded. Any relevant selection bias can be excluded.
Ethics oversight	Experiments were approved by the Institutional Review Board at the University of Washington and were performed according to local ethics regulations and NIH guidelines. Informed consent was obtained from each participant.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Power calculation was used to predetermine the sample size as described in the extended method section.
Data exclusions	The data for each figure were analyzed with the robust regression and outlier removal (ROUT) method with Q=0.1% to remove outliers as indicated in the figure legends and supporting information. For the genetic study, the analyses were conducted on 452,401 individuals of broadly European ancestry and on rs138326449 (IVS2 + 1G-A), a rare (MAF = 0.002) APOC3 splice donor variant that results in APOC3 loss-of-function as indicated in the supporting information.
Replication	All experiments were independently repeated as indicated in the figure legends and could be successfully replicated. Successfully replicated results are included in the manuscript. The key findings of the manuscript were verified using different technological approaches as described throughout the manuscript.
Randomization	Samples were assigned to various groups by block randomization with a block size of 2-4 (depending on the experiment).
Blinding	Data collection and analysis were performed blind to the conditions of the experiments.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	Antibodies from commercially available ELISAs were used. The information on the ELISAs is included in the method section.
Validation	Antibody validation and species reactivity were based on the information provided by manufacturers' official websites. Moreover, the mouse APOC3 ELISA was validated in a previous study. [Kanter, J.E. et al. Increased apolipoprotein C3 drives cardiovascular risk in type 1 diabetes. J Clin Invest 129, 4165-4179 (2019)].

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Adult (8-12 weeks old) female and male LDL receptor-deficient (Ldlr-/-) mice with or without a lymphocytic choriomeningitis virus (LCMV) glycoprotein transgene (GPTg) under control of the rat insulin promoter on a C57BL/6J background were used for part of this study [Renard, C.B. et al. Diabetes and diabetes-associated lipid abnormalities have distinct effects on initiation and progression of atherosclerotic lesions. J Clin Invest 114, 659-668 (2004)]. Male mice carrying a human APOC3 transgene were purchased from The Jackson Laboratory (B6;CBA-Tg(APOC3)3707Bres/J; JAX stock #006907). All mice were housed in a specific pathogen-free facility and kept in a temperature-controlled room set to a light and dark cycle of 12 hours each. The mice had ad libitum access to standard mouse chow (LabDiet, catalog#5053), or a low-fat diet [Renard et al. 2004], and water during the study.
Wild animals	This study did not involve wild animals.
Reporting on sex	Female and male mice were used in this study as indicated in the figure legends. If a specific sex of the mice was used, it was determined based on the investigators' previous experience with respective models and experiments.
Field-collected samples	This study did not involve samples collected in the field.
Ethics oversight	All animal procedures were reviewed and approved by the Institutional Animal Care and Use Committee of the University of Washington (protocol 3154-01) or by the Ionis Institutional Animal Care and Use Committee, and were conducted in conformity with the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

Note that full information on the approval of the study protocol must also be provided in the manuscript.