nature portfolio

Corresponding author(s): Nathan J. Palpant and Kirsty R. Short

Last updated by author(s): Mar 19, 2026

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	FACSDiva v9.0 software (BD Biosciences) for flow cytometry data acquisition; CardioExcyte Control96 (Nanion Technologies GmbH, v1.4.7.1) for cardiomyocyte contractility recordings; Vevo LAB v5.0 (VisualSonics) for echocardiography image acquisition; Witec Raman Alpha 300 software (WITec Suite SEVEN) for SERS tissue damage chip data acquisition; Instrument-integrated software associated with LC-MS/GC-MS metabolomics (LabSolutions Insight LCMS v4 sp2, LabSolutions Insight GCMS v3.7 SP3).
Data analysis	FlowJo v10.6.2 for flow cytometry analysis; ImageJ/Fiji v1.53q for image quantification (ORO staining, fibrosis); STAR aligner v2.7.11 for RNA-seq read alignment; htseq-count v2.0.3 for gene-level read quantification; EdgeR (R) v4.2.2 for RNA-seq normalization and differential expression analysis; LabSolutions Insight LCMS/GCMS for metabolomics peak integration and quantification; MetaboAnalyst 6.0 for metabolomics statistical analysis; GraphPad Prism v9.3.1 for statistical analysis and data visualization; R v3.6.0 for logistic regression, Cox proportional hazards models, and other statistical analyses.

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

The raw and processed bulk RNA sequencing data generated in this study have been deposited in the NCBI Gene Expression Omnibus database (GSE279917, [https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE279917]). The metabolomics data generated in this study have been deposited in the MetaboLights database (MTBLS11411, [https://www.ebi.ac.uk/metabolights/MTBLS11411]). Demographic characteristics of human participants are provided in Table 1 and Supplementary Data 1.

Individual-level human plasma measurements, clinical metadata, and continuous glucose monitoring (CGM) datasets contain potentially identifiable information and are therefore not publicly available. The authors affirm that all human research participants provided informed consent for publication of the de-identified demographic and clinical summary data presented. Access to individual-level human data may be granted upon reasonable request to the corresponding author and is subject to approval by the relevant human research ethics committees.

Individual-level UK Biobank data are available through application to the UK Biobank resource. Custom analysis scripts, phenotype definitions, and metadata required to reanalyse the data are available from the corresponding author upon reasonable request.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Biological sex was recorded for all human participants based on clinical records. Gender identity was not assessed. The study was not powered to detect sex-specific differences in the primary experimental outcomes, and results were therefore not stratified by sex. For the 32 Type 1 diabetes participants, sex was included as a covariate in descriptive comparisons of high versus low glycaemic variability. For the UK Biobank cohorts, sex was included as a covariate in all statistical models assessing MI risk in individuals with diabetes (n=6,010) and in control participants (n=344,476).
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were not primary variables in this study and were not used to stratify the human plasma or in vitro experimental analyses. Participant ethnicity was self-reported and is provided in Supplementary Data 1. UK Biobank analyses were restricted to individuals of Caucasian ancestry to minimize population stratification and confounding. The study was not designed or powered to assess race- or ethnicity-specific effects.
Population characteristics	Sample characteristics: For the 32 adults with Type 1 diabetes mellitus, age ranged 18–60 years; sex was recorded from clinical records (M/F distribution in Supplementary Data 1); ethnicity was self-reported (Supplementary Data 1); inclusion criteria included non-pregnant, non-smokers, diabetes duration ≥2 years, and no known immune disease requiring immunosuppressants. Data collected included blood, clinical data, and 2 weeks of CGM data. For the UK Biobank analyses, participants included 6,010 adults with Type 2 diabetes and 344,476 controls of Caucasian ancestry. The primary outcome was myocardial infarction (MI) risk, analyzed as low versus high biomarker levels (details in Methods).
Recruitment	The 32 Type 1 diabetes participants were recruited between 8 June 2021 and 11 November 2021 via clinic registry and advertisement, with inclusion and exclusion criteria applied at recruitment. UK Biobank participants were recruited between 2006–2010 as part of the UK Biobank study, with exclusions for non-Caucasian ancestry, prior MI, non-MI mortality, or diabetes type other than T2DM. Cohorts were analyzed to assess MI risk stratified by biomarker levels.
Ethics oversight	All human participant studies were approved by the Mater Human Research Ethics Committee (HREC/MML/55151 V2) and The University of Queensland Human Research Ethics Committee (UQ HREC #2019/HE002522). UK Biobank data access was approved under application at University of Queensland and conducted in accordance with the UK Biobank Ethics and Governance Framework. All participants provided written informed consent.

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	Sample sizes were determined based on prior literature, feasibility, and established standards for each experimental system; no formal a priori power calculations were performed. Human plasma studies included 32 adults with Type 1 diabetes, consistent with prior mechanistic plasma–cardiomyocyte studies. hiPSC-CM experiments used ≥3 independent differentiations (biological replicates) with 2–3 technical replicates per condition. Mouse studies used 11–12 animals per group, consistent with previous cardiac functional studies. UK Biobank

	analyses included all eligible participants meeting predefined criteria (6,010 with diabetes and 344,476 controls), providing substantial statistical power for epidemiological analyses.
Data exclusions	No mouse, hiPSC-CM, or human plasma samples were excluded post hoc. For UK Biobank analyses, individuals of non-Caucasian ethnicity, those with prior MI (for diabetes cohort), or mortality from non-MI causes were excluded according to pre-specified criteria.
Replication	Mouse studies: Each experiment was independently replicated in separate cohorts of mice. hiPSC-CM modelling: Experiments were performed using ≥3 biological replicates from independent hiPSC differentiations, each with 2–3 technical replicates per plasma sample. UK Biobank analyses: Epidemiological analyses were conducted on pre-defined diabetes and control cohorts; findings were internally validated through stratified analyses.
Randomization	Mouse studies: Mice were randomly assigned to experimental groups. hiPSC-CM studies: Cardiomyocytes from different differentiations and technical replicates were randomised across treatments. Human plasma participants and UK Biobank analyses: Randomisation is not applicable; analyses were observational and based on existing clinical or cohort data.
Blinding	Mouse studies: Investigators were blinded to group assignments during outcome assessment. hiPSC-CM studies: Experimenters were blinded to plasma sample identity during functional readouts and data analysis. Human plasma participant data and UK Biobank analyses: Blinding not applicable, as analyses were conducted on pre-collected or publicly available datasets.

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
☒	☐ Plants

Methods

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

Antibodies

Antibodies used	Cardiac Troponin T anti-human antibody (Thermo Fisher Scientific, Cat. #MA5-12960); PE-conjugated sarcomeric α-actinin anti-human antibody (Miltenyi Biotec, Cat. #130-123-773); PE-conjugated anti-human IgG isotype control (Miltenyi Biotec, Cat. #130-119-964).
Validation	All antibodies were validated by the manufacturers for specificity and were used according to the manufacturers' recommended protocols. Cardiac troponin T and sarcomeric α-actinin antibodies specifically label cardiomyocytes and were validated for application in flow cytometry in human cardiomyocytes by the manufacturers (Thermo Fisher and Miltenyi websites). The PE-conjugated anti-human IgG isotype control was used to assess non-specific antibody binding and confirm staining specificity (Miltenyi websites).

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s)	WTC WT-11 hiPSCs (Gladstone Institute of Cardiovascular Research, UCSF; karyotype: 46, XY; RRID: CVCL_Y803), generated as previously described (PMID:24509632), were used to generate human iPSC-derived cardiomyocytes and to produce bulk RNA-seq datasets for diabetic disease modelling.
Authentication	WTC WT-11 hiPSC lines were authenticated by karyotyping prior to maintenance and differentiation according to established protocols. Donor identity and differentiation capacity were confirmed based on supplier documentation and routine cardiomyocyte differentiation performance.
Mycoplasma contamination	All iPSC lines were tested for mycoplasma and confirmed negative.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines used in the study.

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	Male C57BL/6J mice were obtained from the Animal Resources Centre (Australia). Mice were housed under standard specific pathogen–free conditions with controlled temperature, humidity, and a 12 h light–dark cycle, with ad libitum access to food and water. Experimental group sizes were n = 11–12 mice per group.
Wild animals	This study did not involve wild animals.
Reporting on sex	Only male mice were used in this study. Sex was selected to minimize variability and because the study was not powered to detect sex-specific effects.
Field-collected samples	This study did not involve field-collected animal samples.
Ethics oversight	All animal experiments were approved by the University of Queensland's Human Research Ethics Committee (HREC, approval #2022/AE000203) and were conducted in accordance with relevant institutional guidelines and national regulations for the care and use of laboratory animals.

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	This study did not involve a prospective interventional clinical trial and therefore was not registered as a clinical trial. Human plasma samples and associated clinical data were collected as part of an observational research study approved by institutional ethics committees. All human plasma studies were approved by the Mater Human Research Ethics Committee (HREC/MML/55151 V2) and the UQ HREC (approval #2019/HE002522).
Study protocol	A predefined study protocol describing participant eligibility criteria, sample collection procedures, and data acquisition was approved by the Mater Human Research Ethics Committee and The University of Queensland Human Research Ethics Committee. The protocol is described in the Methods section of this manuscript.
Data collection	Blood samples, clinical characteristics, and two weeks of prior continuous or flash glucose monitoring (CGM) data were collected at a single study visit at the time of recruitment. Plasma was isolated by centrifugation and used for downstream in vitro cardiomyocyte assays. Data collection was performed without intervention or modification of participants' standard clinical care.
Outcomes	The primary outcomes were in vitro cardiomyocyte functional responses, including contractile parameters measured using the CardioExcyte 96 system following exposure to human plasma samples. Secondary outcomes included associations between clinical glycaemic variability metrics derived from CGM data and cardiomyocyte functional readouts.

Plants

Seed stocks	No plants used in this study.
Novel plant genotypes	No plants used in this study.
Authentication	No plants used in this study.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	At day 15 of differentiation, a subset of cells (~1 × 10^6 cells) was collected at the time of replating for assessment of cardiomyocyte purity. Cells were fixed with 4% paraformaldehyde and permeabilised with 0.75% saponin. Fixed and permeabilised cells were stained with PE-conjugated sarcomeric α-actinin, cardiac troponin T, or a PE-conjugated anti-human IgG isotype control according to manufacturer protocols prior to acquisition.
Instrument	Flow cytometry was performed using a BD FACSCanto II flow cytometer (BD Biosciences).
Software	Data acquisition was performed using FACSDiva software v9.0 (BD Biosciences). Data analysis was conducted using FlowJo software v10.6.2 (BD Biosciences).
Cell population abundance	Cardiomyocyte purity was assessed based on the percentage of sarcomeric α-actinin–positive or cardiac troponin T–positive cells. For all experiments, only differentiated cell preparations exhibiting >80% cardiomyocyte purity were used for downstream analyses.
Gating strategy	Cells were initially gated based on forward and side scatter to exclude debris. Cardiomyocyte populations were identified by PE fluorescence corresponding to sarcomeric α-actinin or cardiac troponin T staining. Gates were defined using matched PE-conjugated anti-human IgG isotype controls, and population thresholds were applied consistently across experiments. Gating strategy was provided in Supplementary Figure 4.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.