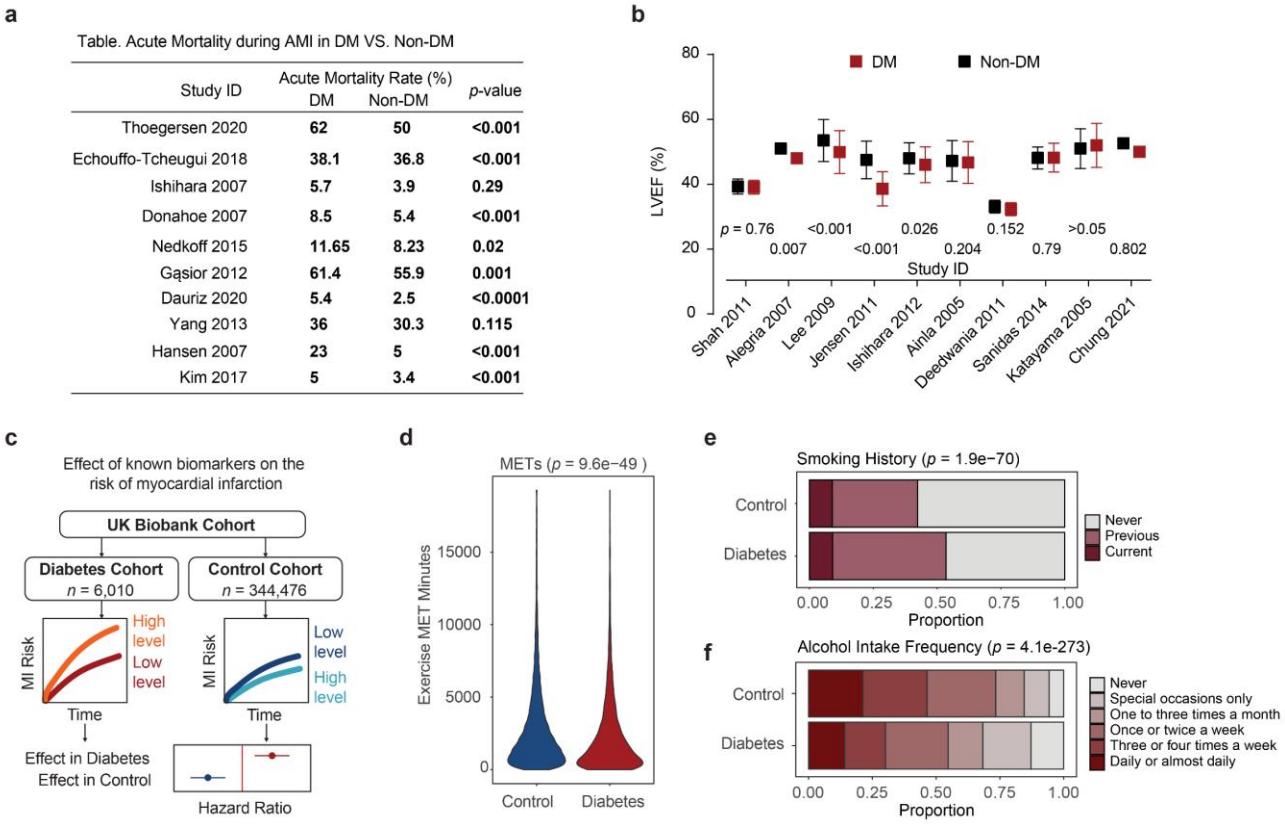
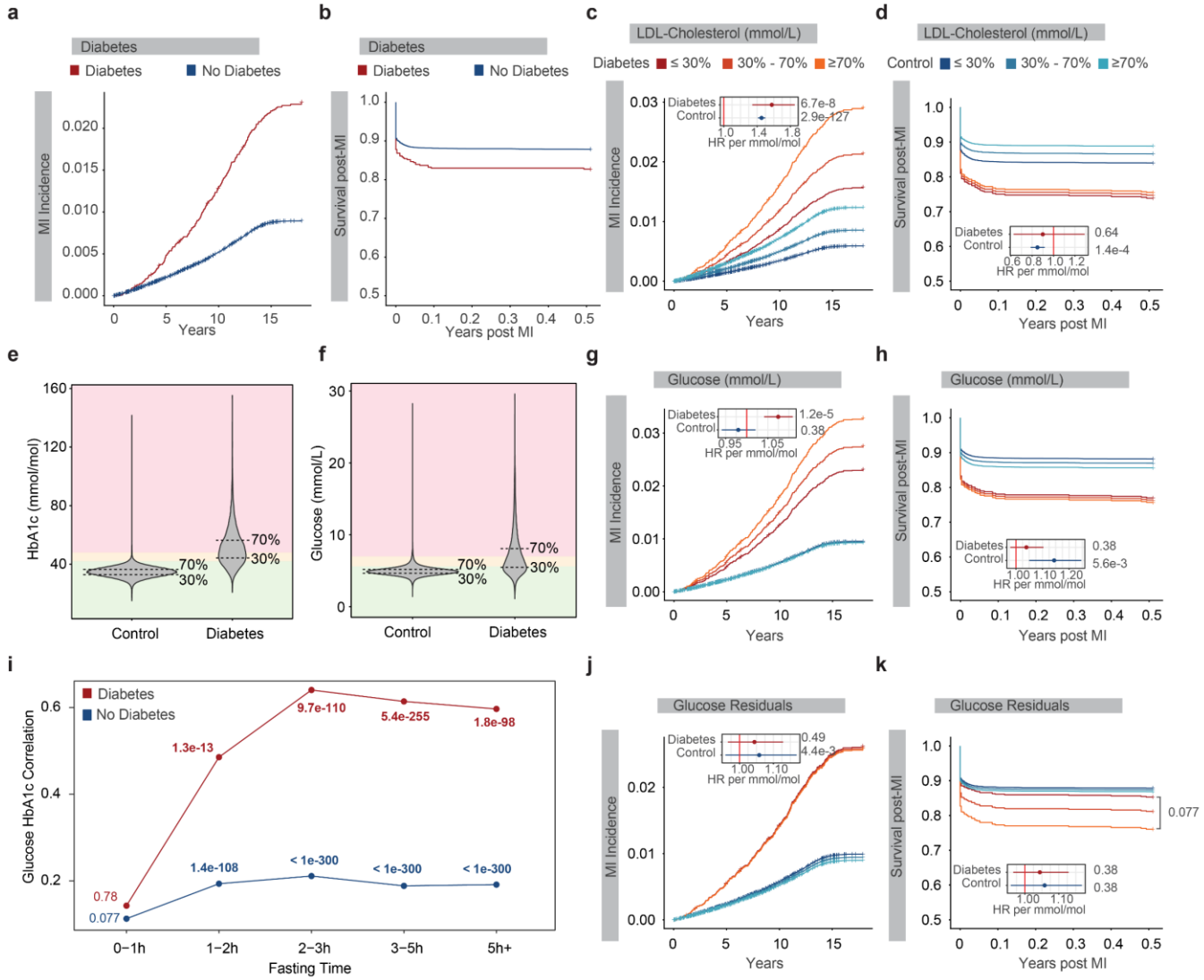
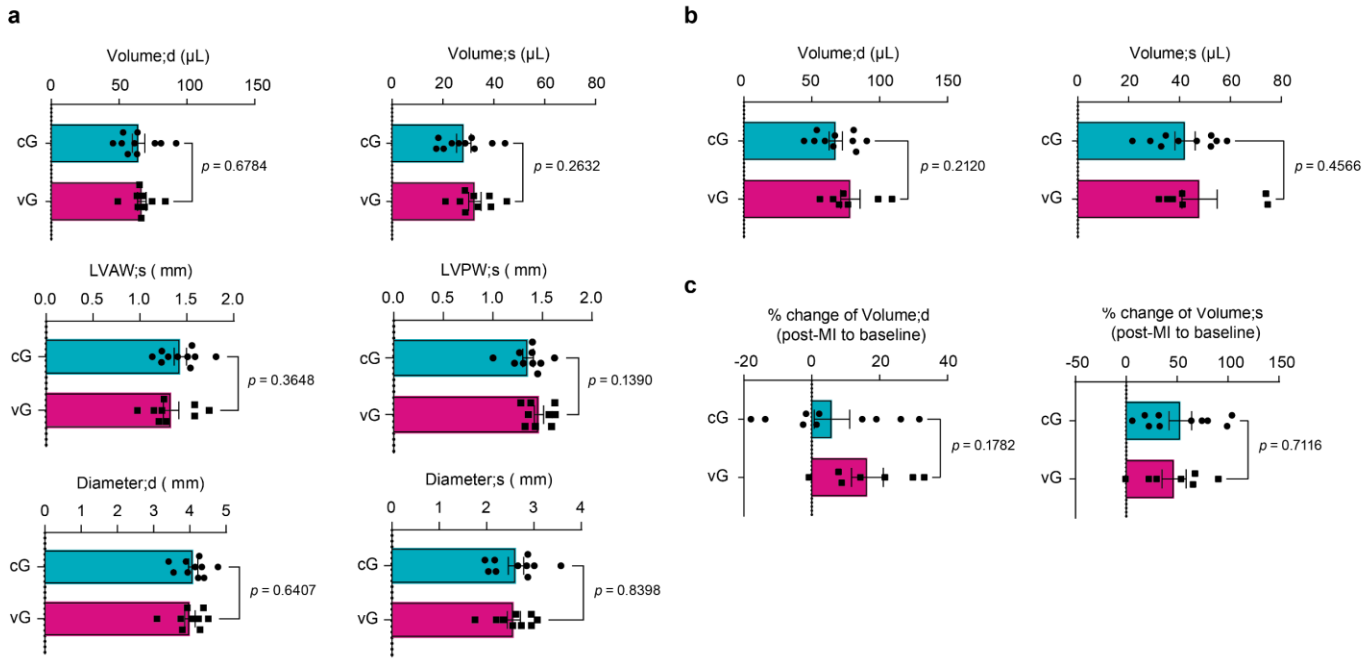
SUPPLEMENTARY FIGURES AND LEGENDS



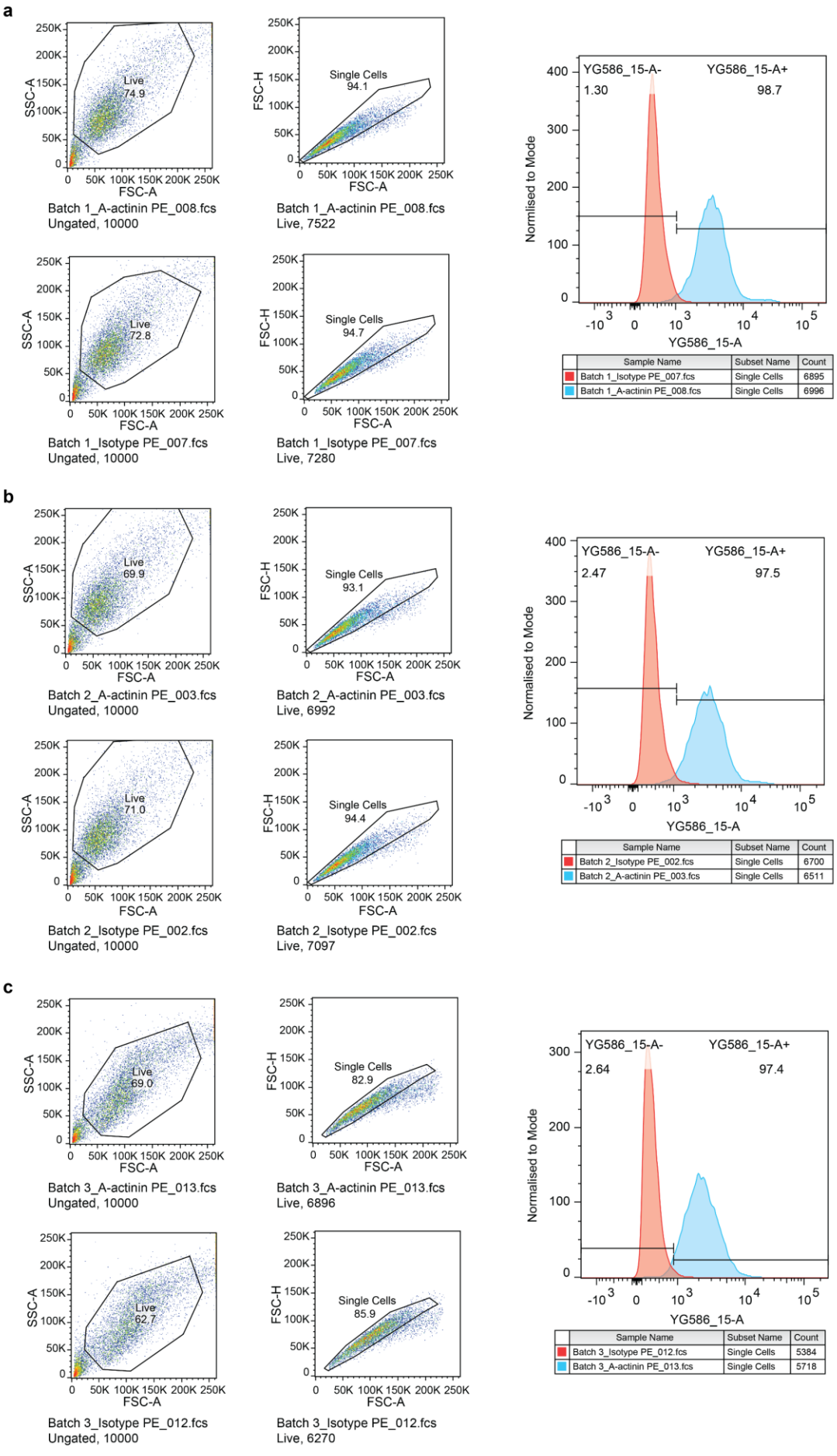
Supplementary Figure 1: Risk of MI and mortality from MI in DM and non-DM individuals in clinical, epidemiological data and in the UK Biobank Cohort. (**a**) Clinical and epidemiological summaries of acute mortality rates during AMI in DM and non-DM[1-10]. (**b**) Clinical and epidemiological summaries of heart dysfunction on LVEF changes post-AMI in DM and non-DM[11-20]. (**c**) Summary of analyses to characterise the association of blood biomarkers in individuals with and without diabetes to the incidence and mortality of MI in the UK Biobank. (**d-f**) The lifestyle differences, including exercise (**d**), smoking (**e**) and alcohol (**f**) between DM individuals and non-DM individuals. DM, diabetes mellitus; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction. Wilcoxon signed rank test used for **d** and chi-squared tests for **e-f**. Source data are provided as a Source Data file.



Supplementary Figure 2: Risk of MI and mortality from MI in DM and non-DM individuals in clinical, epidemiological data and in the UK Biobank Cohort. (**a-b**) Incidence of MI (**a**) and post-MI mortality (**b**) due to the MI in DM individuals compared to non-DM individuals, along with lifestyle differences between them. (**c-d**) Effects of known MI biomarker (LDL-Cholesterol) on time to MI incidence (**c**) and mortality (**d**). Individuals stratified by diabetes diagnosis and further into the high quantile (top 30%), middle quantile (30%–70%), and bottom quantile (bottom 30%) of the biomarker levels. (**e**) DM and non-DM individuals are to be diabetic state with higher HbA1c levels compared to those with lower HbA1c levels. (**f-i**) Stratifying DM individuals by random blood glucose, which can capture glycaemic variability not represented by HbA1c shows a non-significant stratification in post-MI mortality. (**j-k**) Deviation in blood glucose after accounting for fasting time and HbA1c as a proxy for glycaemic variability, finding a larger, though still non-significant stratification in post-MI mortality only in DM individuals. DM, diabetes mellitus; MI, myocardial infarction; LDL, low-density lipoprotein. Data are presented as mean with 95% confidence intervals, and statistical analysis by Cox proportional hazards regression is used to determine hazard ratios and statistical significance (**c-d**, **g-k**). Source data are provided as a Source Data file.

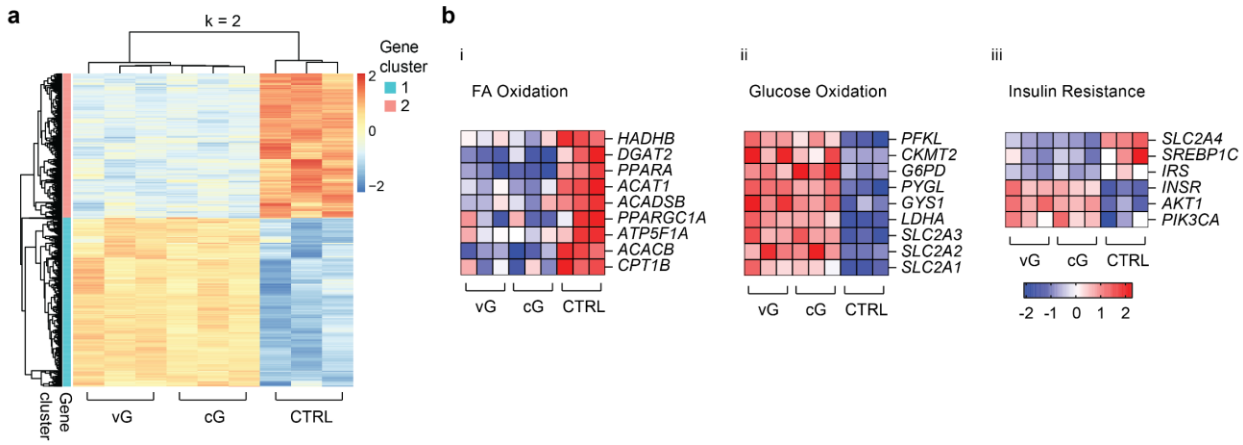


Supplementary Figure 3: Baseline pre-MI and post-MI echocardiographic analysis in an *in vivo* model of diabetes. **(a)** Baseline (pre-MI) echocardiographic assessment of heart function based on volume-derived systolic function and ventricular dimensions. **(b)** Post-MI echocardiographic assessment of heart function based on volume-derived systolic function. (**c**) Percentage change in end-diastolic volume and end-systolic volume relative to their respective baseline values. For *in vivo* studies, n = 11-12 per group. MI=myocardial infarction; Volume;d=left ventricular end-diastolic volume (LVEDV); Volume;s=left ventricular end-systolic volume (LVESV); LVAW;s=left ventricular anterior wall thickness at end-systole; LVPW;s=left ventricular posterior wall thickness at end-systole; Diameter;d=left ventricular internal diameter at end-diastole (LVIDd); Diameter;s=left ventricular internal diameter at end-systole (LVIDs). Data are presented as mean ± SEM. Statistical analysis by two-tailed student's *t*-test (**a-c**). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. Source data are provided as a Source Data file.

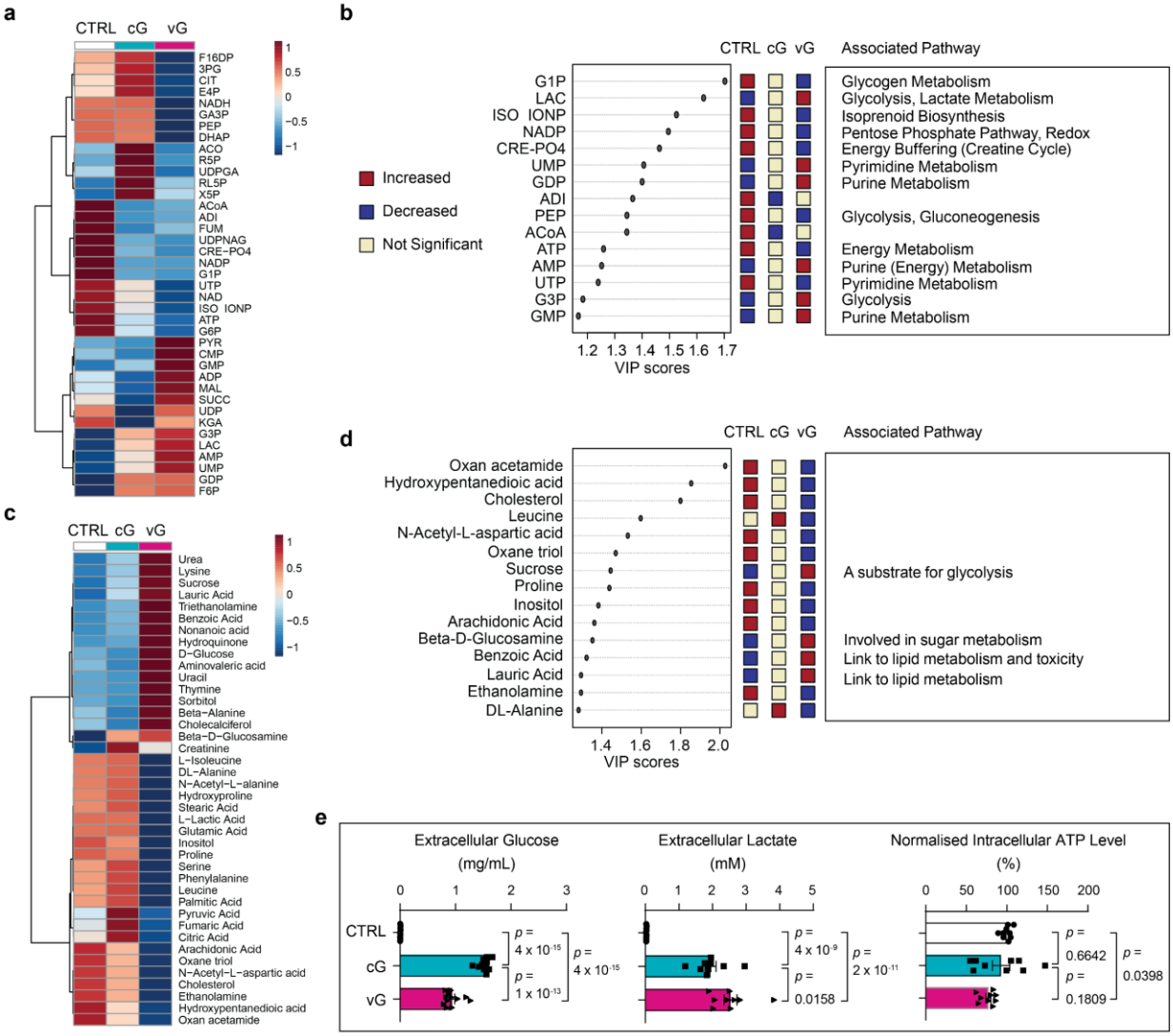


Supplementary Figure 4: Flow cytometry characterisation of the cardiac purity of hiPSC-CMs. (**a-c**) Representative raw data and gating strategy for assessing cardiomyocyte purity by flow cytometry in differentiated

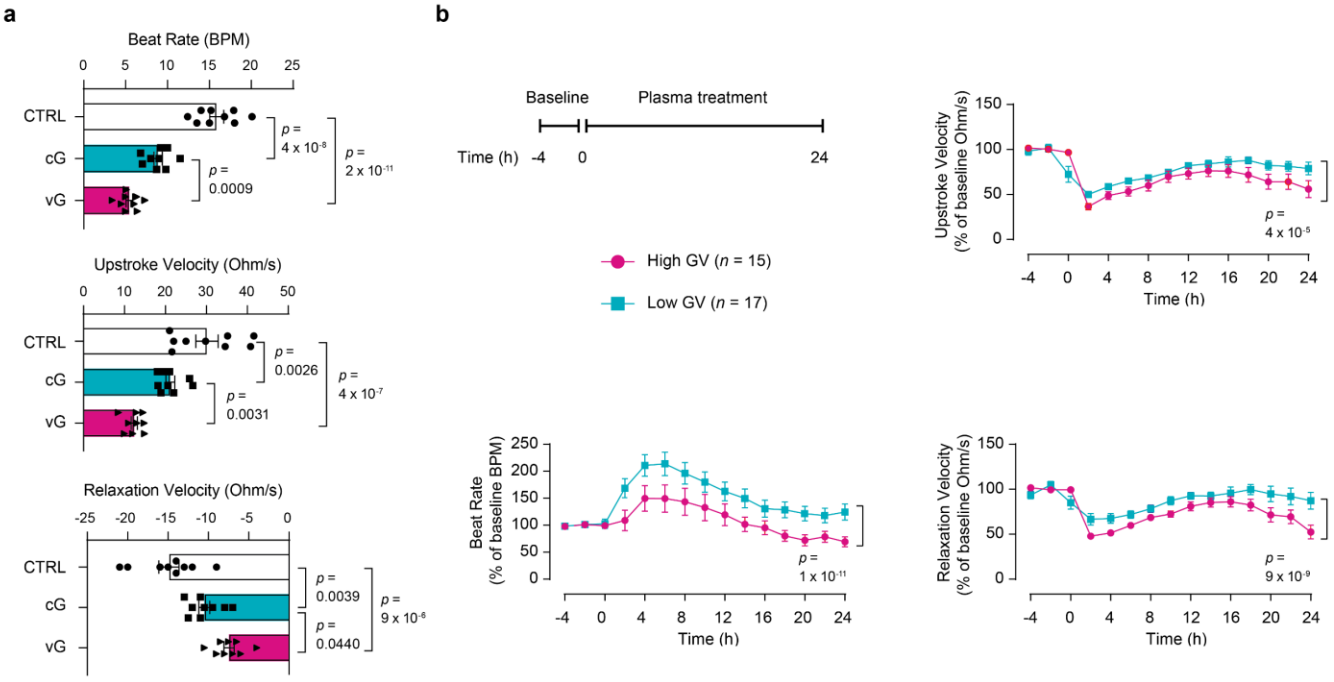
hiPSC-CMs (minimal 3 independent differentiations). Cells were stained with phycoerythrin (PE)-conjugated anti-sarcomeric α-actinin (cardiac purity marker) and compared to PE-conjugated anti-human IgG isotype control (no-staining control) at day 15 of differentiation. Representative phenotyping illustrating cell preparations at day 15 shows that more than 80% sarcomeric α-actinin-positive cardiac population were obtained (3 biological replicates, each with 3 technical replicates). hiPSC-CM=human induced pluripotent stem cell-derived cardiomyocytes. Source data are provided as a Source Data file.



Supplementary Figure 5: RNA sequencing analysis of control, cG and vG cardiomyocytes. (**a**) RNA-seq of differentially expressed (DE) genes identified two gene clusters among the three groups. (**b**) Diabetes-associated gene programs (i-iii) in the hallmark of diabetes-related cardiomyopathy. For RNA-seq assay, $n = 3$ biological replicates, each with 3 technical replicates. DE genes were identified based on an adjusted $p < 0.05$ after multiple testing correction (Benjamini–Hochberg FDR). Gene clusters were determined using hierarchical clustering with Euclidean distance and complete-linkage method, grouping transcripts according to shared expression dynamics across control, cG, and vG conditions. Source data are provided as a Source Data file.



Supplementary Figure 6: Metabolomics and metabolic analysis of control, cG and vG cardiomyocytes. (**a-b**) LC-MS analysis of the differential concentration of metabolites among control, cG and vG conditions in a heatmap (**a**) and unsupervised MS analysis of compounds associated with metabolic pathways (**b**). (**c-d**) GC-MS analysis of the differential concentration of metabolites among control, cG and vG conditions in a heatmap (**c**), and the relative concentrations of the corresponding metabolites in each group under study linked to metabolic pathways (**d**). (**e**) Metabolic analysis of glucose uptake, lactate secretion, and ATP production. $n = 3$; 3 biological replicates, each with 2 (**a-d**) or a minimum of 3 (**e**) technical replicates. Data are presented as mean ± SEM. Statistical analysis by hierarchical clustering analysis (**a**, **c**) or partial least squares-discriminant analysis (**b**, **d**), or One-Way ANOVA (**e**). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. Source data are provided as a Source Data file.



Supplementary Figure 7: Impedance-based contractility analysis under glycaemic stress and plasma treatment conditions. (**a**) Analysis of beat rate and relaxation velocity in control, cG, and vG hiPSC-CM using the CardioExcyte 96 platform. (**b**) Analysis on beat rate, upstroke velocity and relaxation velocity comparing plasma samples with high versus low GV. hiPSC-CM=human induced pluripotent stem cell-derived cardiomyocytes; GV=glycaemic variability. For *in vitro* glycaemic stress assay, n = 3 biological replicates, each with 3 technical replicates. For human plasma samples assay, n = 3 independent biological cardiomyocyte replicates, each with 2 technical replicates. Data are presented as mean ± SEM, with statistical analysis by One-Way ANOVA (**a**) or Two-Way ANOVA (**b**). Two-way ANOVA (group × time) revealed no significant interaction for beat rate (p = 0.5286), but significant interactions for velocities (upstroke, p = 0.0087; relaxation, p = 0.0055); time effects were significant for all plots (beat rate, $p = 1 \times 10^{-15}$; upstroke, $p < 1 \times 10^{-15}$; relaxation, $p < 1 \times 10^{-15}$); group effects were significant for all plots (beat rate, $p = 1 \times 10^{-11}$; upstroke, $p = 4 \times 10^{-5}$; relaxation, $p = 9 \times 10^{-9}$). *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. Source data are provided as a Source Data file.

SUPPLEMENTARY TABLES

Supplementary Table 1: Acute mortality rates during AMI in patients living with diabetes (DM) versus non-diabetic counterparts (non-DM)*.

Study ID	Reference	Study Period	Study Design	Patient Population	Sample Size	Diabetes Definition	AMI definition	Follow-up Period	30-Day Mortality Rate (%)
1	Thoegersen et al. 2020	2010-2017	Retrospective Cohort	AMI complicated by CS	1716	Previous physician's diagnosis	Fourth Universal Definition	30 days	62% (DM) vs. 50% (Non-DM), $P < 0.001$
2	Echouffo-Tcheugui et al. 2018	2012-2014	Retrospective Cohort	National Inpatient Sample, aged ≥18 years	1332530	Clinically diagnosed	International Classification of Diseases, Ninth Edition.	In-hospital	In-hospital mortality 38.1% (DM) vs. 36.8% (Non-DM), $P < 0.001$
3	Ishihara et al. 2007	1996-2003	Retrospective Cohort	Patients with AMI undergoing PCI	802	Clinically diagnosed	Persistent chest pain, lasting >30 minutes with ECG changes, and CK >2x normal limit.	Up to 3 years	5.7% (DM) vs. 3.9% (Non-DM), $P = 0.29$
4	Donahoe et al. 2007	1997-2006	Randomised Clinical Trials	Patients with ACS	62036	Clinically diagnosed	Systolic BP, heart rate, creatinine clearance, infarction location (if STEMI), Killip class, and TIMI risk index.	30 days and 1 year	8.5% (DM) vs. 5.4% (Non-DM), $P < 0.001$
5	Nedkoff et al. 2015	1998-2010	Retrospective Cohort	35-84 year olds with hospitalised incident MIs	26610	International Classification of Diseases, Ninth Edition.	International Classification of Diseases, Ninth Edition.	30 days	1998-2001 11.65% (DM) vs. 8.23% (Non-DM), $P = 0.02$; 2008-2010 3.96% (DM) vs. 4.02% (Non-DM), $P > 0.05$
6	Gąsior et al. 2012	2003-2006	Retrospective Cohort	Hospitalised patients with ACS	4144	Previous physician's diagnosis	Non-ST elevation MI (NSTEMI) and ST elevation MI (STEMI)	In-hospital and 3 years	In-hospital mortality 61.4% (DM) vs. 55.9% (Non-DM), $P = 0.001$

7	Dauriz et al. 2020	2001-2014	Retrospective Cohort	Hospitalised patients with ACS	28225	Previous physician's diagnosis	Previous physician's diagnosis	In-hospital	In-hospital mortality 5.4% (DM) vs. 2.5% (Non-DM), $P < 0.0001$
8	Yang et al. 2013	2005-2010	Prospective Cohort	STEMI patients with CS	816	Previous DM history treated with insulin or lifestyle modification	ST-elevation ≥1mm in two leads, new LBBB, positive necrosis marker, and cardiogenic shock.	30-day mortality	36% (DM) vs. 30.3% (Non-DM), $P = 0.115$
9	Hansen et al. 2007	2001-2003	Retrospective Cohort	Hospitalised patients with ACS	334	Not specified	S- segment changes with elevated cardiac troponin T above 0.10 ug/L	In-hospital and 4 years	In-hospital mortality 23% (DM) vs. 5% (Non-DM), $P < 0.001$
10	Kim et al. 2017	2011-2015	Prospective Cohort	Hospitalised patients with AMI	12625	History or new diagnosis per ADA guideline	Elevated biomarkers, symptoms, ECG changes, and imaging evidence of myocardial damage/abnormality.	In-hospital	In-hospital mortality 5% (DM) vs. 3.4% (Non-DM), $P < 0.001$

*AMI, Acute myocardial infarction; CS, Cardiogenic shock; PCI, Percutaneous coronary intervention; ECG, Electrocardiogram; CK, Creatine kinase; ACS, Acute coronary syndromes; BP, Blood pressure; ADA, American Diabetes Association.

Supplementary Table 2: Changes in LVEF during AMI in patients with and without diabetes (DM versus Non-DM)*.

Study ID	Reference	Study Period	Study Design	Patient Population	Sample Size	Diabetes Definition	AMI definition	ECHO assessment period	ECHO findings
11	Shah et al. 2011	2005	Randomised controlled trial	Hospitalised patients with AMI	604	Known history or newly diagnosed based on medication use	AMI (12 hrs - 10 days) with HF signs or LV dysfunction	0.5 - 10 days after MI	LVEF (%) 39.1±5.4 (DM) vs. 39.3±5.8 (Non-DM), $P = 0.76$
12	Alegria et al. 2007	2003	Randomised controlled trial	Hospitalised patients with AMI	2948	Patient history	AMI and ≥1 mm STE in at least 2 contiguous leads or LBBB	6 – 16 days after MI	LVEF (%) 48% (DM) vs. 51% (Non-DM), $P = 0.007$
13	Lee et al. 2009	2005-2006	Prospective Cohort	Hospitalised patients with AMI	2233	Fasting glucose ≥126 mg/dL, random glucose ≥200 mg/dL, or medication history	Symptomatic, elevated troponin/CK-MB, and ischemic changes on ECHO	Up to 1 year	LVEF (%) 49.9±13.2 (DM) vs. 53.5±12.1 (Non-DM), $P < 0.001$
14	Jensen et al. 2011	2011	Retrospective Cohort	Hospitalised patients with AMI	107	Blood glucose > 7.8 mmol/l	STEMI treated by primary PCI	3 days after MI	LVEF (%) 38.6±13.7 (DM) vs. 47.5±12.2 (Non-DM), $P < 0.001$
15	Ishihara et al. 2012	2001-2003	Retrospective Cohort	Hospitalised patients with AMI	5325	Blood glucose 6.1-11 mmol/l	AMI treated by primary PCI	Up to 3 years	LVEF (%) 46±12 (DM) vs. 48±10 (Non-DM), $P = 0.026$
16	Ainla et al. 2005	2001-2002	Retrospective Cohort	Hospitalised patients with AMI	905	Blood glucose > 11 mmol/l and patient history	AMI and ≥1 mm STE in at least 2 contiguous leads or LBBB	Up to 180 days	LVEF (%) 46.7±13.8 (DM) vs. 47.2±13.3 (Non-DM), $P = 0.204$

17	Deedwania et al. 2014	1999-2001	Retrospective Cohort	Hospitalised patients with AMI	6632	Patient history	Electrocardiographic changes, symptoms, or elevated cardiac biomarkers	Within 14 days after MI	LVEF (%) 32.3±6.2 (DM) vs. 33.1±5.9 (Non-DM), $P = 0.152$
18	Sanidas et al. 2014	2009-2013	Randomised controlled trial	Hospitalised patients with AMI	451	Patient history	Anterior STEMI, occluded LAD, primary PCI	Within 5 days after MI	LVEF (%) 48.2±9.2 (DM) vs. 48.1±7 (Non-DM), $P = 0.79$
19	Katayama et al. 2005	2000-2004	Retrospective Cohort	Hospitalised patients with AMI	327	Insulin/medication use, fasting glucose ≥126mg/dL, random glucose ≥200mg/dL, or A1C ≥6.5%	Chest pain, ST elevation or new LBBB, and elevated creatine kinase	Soon after recanalisation	LVEF (%) 52±13 (DM) vs. 51±12 (Non-DM), $P > 0.05$
20	Chung et al. 2021	2005-2016	Retrospective Cohort	Hospitalised patients with AMI	1593	ADA guidelines*	Positive cardiac marker and symptoms or imaging evidence indicate myocardial infarction	Within 30 days after MI	LVEF (%) 50% (DM) vs. 52.6% (Non-DM), $P = 0.802$

*LVEF, Left ventricular ejection fraction; AMI, Acute myocardial infarction; STE, ST-segment elevation; LBBB, Left bundle branch block; PCI, Percutaneous coronary intervention; ACS, Acute coronary syndromes; ADA, American Diabetes Association.

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