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Assessment of cardiometabolic phenotype

Cardiac MRI (cMRI) was conducted in 35,972 participants. Image acquisition was performed during a 20-min protocol using a 1.5T scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). [1] Currently only left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), left ventricular stroke volume (LVSV) and cardiac output data are available for the entire subpopulation. We indexed measurements to body surface area (BSA) and computed cardiac contractility index (CCI), which is SBP divided by indexed LVESV - a validated measure of myocardial contractility.[2]

Carotid artery ultrasound was performed in 41,442 participants (CardioHealth Station, Panasonic Healthcare, Newark, USA) with a 9 MHz linear array transducer.[3] Carotid intima-media thickness (CIMT) was assessed at two angles for each common carotid, giving a total of four CIMT measurements from which mean CIMT was calculated. PASI was measured in 162,029 participants using the PulseTrace PCA2 (CareFusion; San Diego, CA). PASI (in m/s) was calculated by dividing waveform standing height by the time between forward and reflected pulse waves detected from an infrared sensor on the index finger over 15 seconds. [4] SBP, DBP and heart rate were measured in the entire study population at recruitment using the Omron Digital blood pressure monitor (Omron, Kyoto, Japan). Two measurements were taken in each participant from which the mean was calculated.

Abdominal MRI was performed using a Siemens Aera 1.5T scanner (Syngo MR D13) (Siemens, Erlangen, Germany). The imaging protocol covered a 1.1m region from neck-to-knee region. A single 3D volume using an automated fat-water swap detection and correction procedure was calculated. [5] Visceral adipose tissue volume (VAT), subcutaneous adipose tissue volume (SAT) and total thigh fat-free muscle volume data were available for 9,407 participants. Total abdominal adipose tissue index (TAATI) was defined as VAT volume + abdominal SAT volume / BSA. Abdominal fat ratio (AFR) was defined as VAT volume + SAT volume / VAT volume + abdominal SAT volume + total thigh fat-free muscle volume.[6] Anthropometric data were available from 450,798 participants at baseline. Weight and bioimpedance were measured using the Tanita BC418ma bioimpedance device (Tanita, Tokyo, Japan), from which percentages of body fat and lean mass were defined. [7] Non-fasting venous blood was collected and processed at a central laboratory.

References for supplementary methods

1 Raisi-Estabragh Z, Harvey NC, Neubauer S, *et al.* Cardiovascular magnetic resonance imaging in the UK Biobank: a major international health research resource. *Eur Heart J Cardiovasc Imaging* 2021;**22**:251–8. doi:10.1093/ehjci/jeaa297

2 Gierula J, Paton MF, Lowry JE, *et al.* Rate-Response Programming Tailored to the Force-Frequency Relationship Improves Exercise Tolerance in Chronic Heart Failure. *JACC Heart Fail* 2018;**6**:105–13. doi:10.1016/j.jchf.2017.09.018

3 Coffey S, Lewandowski AJ, Garratt S, *et al.* Protocol and quality assurance for carotid imaging in 100,000 participants of UK Biobank: development and assessment. *Eur J Prev Cardiol* 2017;**24**:1799–806. doi:10.1177/2047487317732273

4 Zekavat SM, Aragam K, Emdin C, *et al.* Genetic Association of Finger Photoplethysmography-Derived Arterial Stiffness Index With Blood Pressure and Coronary Artery Disease. *Arterioscler Thromb Vasc Biol* 2019;**39**:1253–61. doi:10.1161/ATVBAHA.119.312626

5 Liu Y, Basty N, Whitcher B, *et al.* Genetic architecture of 11 organ traits derived from abdominal MRI using deep learning. *Elife* 2021;**10**. doi:10.7554/eLife.65554

6 Linge J, Borga M, West J, *et al.* Body Composition Profiling in the UK Biobank Imaging Study. *Obesity (Silver Spring)* 2018;**26**:1785–95. doi:10.1002/oby.22210

7 Tong TY, Key TJ, Sobiecki JG, *et al.* Anthropometric and physiologic characteristics in white and British Indian vegetarians and nonvegetarians in the UK Biobank. *Am J Clin Nutr* 2018;**107**:909–20. doi:10.1093/ajcn/nqy042

	Missing	No Diabetes			Diabetes		
		Normal (N=143 847)	Overweight (N=185 758)	Obese (N=99 589)	Normal (N=2290)	Overweight (N=7732)	Obese (N=12 429)
				Cardiometabolic medication			
Angiotensin converting enzyme inhibitor, *n (%)*	0	5482 (3.8)*†	13 125 (7.1)*†	11 430 (11.5)*†	621 (27.1)*†	2564 (33.2)*†	4701 (37.8)*†
Angiotensin receptor blocker, *n (%)*	0	2294 (1.6)*†	6451 (3.5)*†	6628 (6.7)*†	213 (9.3)*†	1093 (14.1)*†	2418 (19.5)*†
Beta-blocker, *n (%)*	0	4914 (3.4)*†	11 596 (6.2)*†	9651 (9.7)*†	251 (11.0)*†	1357 (17.6)*†	2873 (23.1)*†
Calcium channel blocker, *n (%)*	0	4864 (3.4)*†	11 868 (6.4)*†	10 415 (10.5)*†	346 (15.1)*†	1715 (22.2)*†	3441 (27.7)*†
Statin, *n (%)*	0	10 156 (7.1)*†	25 703 (13.8)*†	18 269 (18.3)*†	1425 (62.2)*†	5393 (69.8)*†	8927 (71.8)*†
Aspirin, *n (%)*	0	11 449 (8.0)*†	22 765 (12.3)*†	15 577 (15.6)*†	995 (43.5)*†	3974 (51.4)*†	6642 (53.4)*†
Clopidogrel, *n (%)*	0	496 (0.3)*†	1088 (0.6)*†	794 (0.8)*†	48 (2.1)*†	226 (2.9)*†	323 (2.6)*†
Warfarin, *n (%)*	0	739 (0.5)*†	1474 (0.8)*†	1248 (1.3)*†	30 (1.3)*†	133 (1.7)*†	326 (2.6)*†
Loop diuretic, *n (%)*	0	346 (0.2)*†	888 (0.5)*†	1713 (1.7)*†	65 (2.8)*†	241 (3.1)*†	957 (7.7)*†
Thiazide diuretic, *n (%)*	0	4641 (3.2)*†	11 890 (6.4)*†	11 337 (11.4)*†	201 (8.8)*†	1146 (14.8)*†	2591 (20.9)*†
				Diabetes medication			
Insulin, *n (%)*	0	<50 (0.0)*†	<50 (0.0)*†	<50 (0.0)*†	811 (35.4)*†	1501 (19.4)*†	2227 (17.9)*†
Metformin, *n (%)*	0	<50 (0.0)*†	54 (0.0)*†	86 (0.1)*†	861 (37.6)*†	4143 (53.6)*†	7968 (64.1)*†
Sulphonylurea , *n (%)*	0	<50 (0.0)†	<50 (0.0)†	(0.0)†	396 (17.3)*†	1682 (21.8)*†	2824 (22.7)*†
Thiazolidinediones, *n (%)*	0	<50 (0.0)*†	<50 (0.0)*†	<50 (0.0)*†	80 (3.5)*†	500 (6.5)*†	1525 (12.3)*†
Meglitinides, *n (%)*	0	<50 (0.0)†	<50 (0.0)†	<50 (0.0)†	<50 (0.5)†	<50 (0.5)†	71 (0.6)†

Table S1 - **Participant medications at study recruitment**. Participants stratified by diabetes status and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Categorical data presented as n (%). * represents chi^2 test ≤ 0.005 between BMI categories for categorical variables respectively within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from chi^2 test for categorical variables. Where fewer than 50 participants are within any group, UK Biobank requires that the specific number of participants is not listed to reduce the risk of de-anonymisation.

		All-cause mortality	Cardiovascular mortality	Myocardial infarction	Ischemic stroke
Total population					
	Normal	4.62 (4.52-4.72)	0.70 (0.66-0.74)	0.88 (0.84-0.93)	0.48 (0.44-0.51)
	Overweight	5.47 (5.37-5.57)	1.03 (0.98-1.07)	1.44 (1.40-1.50)	0.67 (0.63-0.70)
	Obese	7.21 (7.07-7.36)	1.65 (1.58-1.72)	1.85 (1.77-1.92)	0.87 (0.82-0.92)
No Diabetes					
	Normal	4.48 (4.38- 4.58)	0.66 (0.63-0.70)	0.86 (0.82-0.91)	0.46 (0.42-0.49)
	Overweight	5.15 (5.06-5.25)	0.92 (0.88-0.96)	1.37 (1.32-1.42)	0.62 (0.59-0.66)
	Obese	6.19 (6.05-6.33)	1.30 (1.23-1.36)	1.60 (1.53-1.68)	0.74 (0.69-0.79)
Diabetes					
	Normal	14.12 (12.74-15.65)	2.79 (2.23-3.50)	2.28 (1.77-2.95)	1.80 (1.35-2.41)
	Overweight	13.45 (12.70-14.24)	3.69 (3.31-4.11)	3.33 (2.97-3.74)	1.73 (1.48-2.03)
	Obese	15.75 (15.10-16.42)	4.54 (4.21-4.90)	3.91 (3.59-4.26)	1.94 (1.72-2.19)

Table S2 – Absolute unadjusted rates of all-cause mortality, cardiovascular mortality, myocardial infarction, and stroke per 1000 person-years of follow-up according to diabetes and ethnicity adjusted BMI category. Data are rates per 1000 person-years (95% CI). Abbreviations: body mass index (BMI); confidence interval (CI).

	Unadjusted	Model 1	Model 2	Model 3
	IRR (95% CI)	Adjusted IRR* (95% CI)	Adjusted IRR (95% CI)	Adjusted IRR* (95% CI)
Cardiovascular mortality				
Normal + non-diabetes	0.22 (0.18-0.29, p<0.001)	0.42 (0.33-0.52, p<0.001)	0.53 (0.42-0.67, p<0.001)	0.64 (0.50-0.82, p<0.001)
Overweight + non-diabetes	0.31 (0.25-0.40, p<0.001)	0.46 (0.36-0.58, p<0.001)	0.54 (0.43-0.68, p<0.001)	0.65 (0.51-0.82, p<0.001)
Obese + non-diabetes	0.45 (0.36-0.56, p<0.001)	0.69 (0.55-0.87, p=0.002)	0.72 (0.57-0.91, p<0.005)	0.82 (0.64-1.04, p=0.104)
Normal + diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + diabetes	1.30 (1.01-1.67, p=0.037)	1.18 (0.92-1.51, p=0.196)	1.07 (0.83-1.37, p=0.614)	1.10 (0.86-1.41, p=0.454)
Obese + diabetes	1.61 (1.27-2.04, p<0.001)	1.69 (1.33-2.14, p<0.001)	1.37 (1.08-1.74, p=0.010)	1.27 (1.00-1.61, p=0.055
All-cause mortality				
Normal + non-diabetes	0.32 (0.29-0.35, p<0.001)*	0.51 (0.46-0.56, p<0.001)	0.56 (0.50-0.62, p<0.001)	0.64 (0.57-0.71, p<0.001)
Overweight + non-diabetes	0.36 (0.33-0.40, p<0.001)*	0.49 (0.44-0.55, p<0.001)	0.53 (0.48-0.59, p<0.001)*	0.60 (0.54-0.67, p<0.001)
Obese + non-diabetes	0.44 (0.49-0.49, p<0.001)	0.62 (0.56-0.69, p<0.001)	0.63 (0.56-0.70, p<0.001)	0.70 (0.62-0.78, p<0.001)
Normal + diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + diabetes	0.95 (0.85-1.07, p=0.417)*	0.88 (0.78-0.99, p=0.035)	0.83 (0.74-0.93, p=0.002)*	0.86 (0.77-0.97, p=0.014)
Obese + diabetes	1.11 (1.00-1.25, p=0.055)*	1.16 (1.04-1.29, p=0.010)	1.04 (0.93-1.16, p=0.528)	1.02 (0.91-1.14, p=0.699)
Non-fatal myocardial infarction				
Normal + non-diabetes	0.38 (0.29-0.49, p<0.001)	0.63 (0.48-0.82, p=0.001)	0.72 (0.56-0.94, p=0.017)	0.83 (0.63-1.09, p=0.179)
Overweight + non-diabetes	0.60 (0.46-0.78, p<0.001)	0.80 (0.62-1.04, p=0.093)	0.88 (0.68-1.14, p=0.314)	1.01 (0.77-1.33, p=0.937)
Obese + non-diabetes	0.70 (0.54-0.91, p=0.008)	1.00 (0.77-1.30, p=0.981)	1.02 (0.79-1.33, p=0.873)	1.17 (0.89-1.54, p=0.263)
Normal + diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + diabetes	1.46 (1.10-1.94, p<0.009)	1.30 (0.98-1.72, p=0.070)	1.21 (0.91-1.61, p=0.179)	1.28 (0.96-1.69, p=0.093)
Obese + diabetes	1.71 (1.31-2.23, p<0.001)	1.79 (1.37-2.35, p<0.001)	1.56 (1.19-2.04, p<0.001)	1.59 (1.21-2.10, p=0.001)
Non-fatal ischemic stroke				
Normal + non-diabetes	0.25 (0.19-0.34, p<0.001)*	0.41 (0.30-0.55, p<0.001)	0.48 (0.36-0.65, p<0.001)	0.55 (0.40-0.75, p<0.001)
Overweight + non-diabetes	0.35 (0.26-0.46, p<0.001)*	0.47 (0.35-0.62, p<0.001)	0.53 (0.39-0.71, p<0.001)	0.59 (0.43-0.81, p=0.001)
Obese + non-diabetes	0.41 (0.31-0.55, p<0.001)	0.59 (0.44-0.80, p=0.001)	0.61 (0.45-0.82, p=0.001)	0.68 (0.49-0.93, p=0.016)
Normal + diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Overweight + diabetes	0.96 (0.69-1.33, p=0.805)*	0.89 (0.64-1.24, p=0.506)	0.83 (0.60-1.16, p=0.283)	0.87 (0.63-1.22, p=0.430)
Obese + diabetes	1.07 (0.79-1.47, p=0.653)*	1.14 (0.84-1.57, p=0.397)	0.99 (0.73-1.36, p=0.965)	0.98 (0.72-1.35, p=0.919)

Table S3 – Unadjusted and adjusted incidence rate ratios (IRR) for cardiovascular outcomes by diabetes and ethnicity adjusted BMI category with normal weight diabetes as the comparator. Data presented as incidence rate ratios (IRR) with 95% confidence intervals (CI) obtained from Poisson regression analysis. * represents p value <0.05 for interaction between diabetes status and BMI category. Model 1 = Unadjusted model + adjustment for sex, age, ethnicity, smoking status, and deprivation score. Model 2 = Model 1 + adjustment for chronic cardiac condition, hypertension, cancer, chronic respiratory condition, chronic liver disease, chronic renal disease, neurological disease. Model 3 = Model 2 + adjustment for calcium channel blocker, beta blocker, angiotensin receptor blocker, thiazide diuretic, loop diuretic, mineralocorticoid receptor antagonist, statin, ACE inhibitor, aspirin, clopidogrel, warfarin, insulin, and metformin. Abbreviations: body mass index (BMI); confidence interval (CI); incident rate ratio (IRR).

	Unadjusted model	Model 1	Model 2	Model 3
	IRR (95% CI)	Adjusted IRR (95% CI)	Adjusted IRR (95% CI)	Adjusted IRR (95% CI)
Cardiovascular death				
All people with diabetes (n = 22 451)				
Normal + diabetes	4.38 (3.47-5.23, p <0.001)	2.39 (1.90-3.02, p<0.001)	1.88 (1.49-2.37, p<0.001)	1.55 (1.21-1.98, p<0.001)
Overweight + diabetes	5.71 (5.06-6.44, p <0.001)	2.82 (2.49-3.19, p<0.001)	2.00 (1.76-2.27, p<0.001)	1.71 (1.47-1.98, p<0.001)
Obese + diabetes	7.05 (6.40-7.75, p<0.001)	4.05 (3.68-4.47, p<0.001)	2.57 (2.32-2.84, p<0.001)	1.96 (1.71-2.25, p<0.001)
People with diabetes diagnosed under 40 years & on insulin excluded (n = 20 695)				
Normal + diabetes	4.21 (3.24-5.46, p <0.001)	2.08 (1.60-2.70, p<0.001)	1.63 (1.26-2.13, p<0.001)	1.34 (1.03-1.76, p<0.001)
Overweight + diabetes	5.50 (4.84-6.24, p<0.001)	2.59 (2.28-2.95, p<0.001)	1.83 (1.60-2.09, p<0.001)	1.50 (1.29-1.74, p<0.001)
Obese + diabetes	6.76 (6.13-7.45, p<0.001)	3.79 (3.43-4.19, p<0.001)	2.39 (2.16-2.66, p<0.001)	1.71 (1.50-1.96, p<0.001)
Non-fatal myocardial infarction				
All people with diabetes (n = 22 451)				
Normal + diabetes	2.65 (2.04-3.44, p<0.001)	1.59 (1.22-2.07, p<0.001)	1.38 (1.06-1.80, p = 0.017)	1.21 (0.92-1.59, p=0.179)
Overweight + diabetes	3.87 (3.41-4.39, p<0.001)	2.07 (1.82-2.35, p<0.001)	1.67 (1.47-1.91, p<0.001)	1.41 (1.32-1.52, p<0.001)
Obese + diabetes	4.54 (4.11-5.01, p<0.001)	2.85 (2.58-3.16, p<0.001)	2.15 (1.93-2.39, p<0.001)	1.93 (1.67-2.23, p<0.001)
People with diabetes diagnosed under 40 years & on insulin excluded (n = 20 695)				
Normal + diabetes	2.74 (2.05-3.65, p<0.001)	1.52 (1.42-2.03, p=0.004)	1.32 (0.99-1.76, p=0.056)	1.16 (0.86-1.56, p=0.334)
Overweight + diabetes	3.77 (3.30-4.31, p<0.001)	1.94 (1.70-2.22, p<0.001)	1.57 (1.37-1.80, p<0.001)	1.39 (1.19-1.64, p<0.001)
Obese + diabetes	4.35 (3.92-4.81, p<0.001)	2.68 (2.42-2.98, p<0.001)	2.02 (1.81-2.25, p<0.001)	1.71 (1.48-1.97, p<0.001)
Non-fatal ischemic stroke				
All people with diabetes (n = 22 451)				
Normal + diabetes	3.96 (2.94-5.33, p<0.001)	2.45 (1.82-3.30, p<0.001)	2.06 (1.53-2.78, p<0.001)	1.83 (1.33-2.52, p<0.001)
Overweight + diabetes	3.80 (3.19-4.52, p<0.001)	2.19 (1.32-1.60, p<0.001)	1.72 (1.44-2.06, p<0.001)	1.60 (1.29-1.99, p<0.001)
Obese + diabetes	4.26 (3.70-4.89, p<0.001)	2.80 (2.43-3.23, p<0.001)	2.05 (1.77-2.37, p<0.001)	1.80 (1.48-2.21, p<0.001)
People with diabetes diagnosed under 40 years & on insulin excluded (n = 20 695)				
Normal + diabetes	3.84 (2.75-5.36, p<0.001)	2.16 (1.55-3.03, p<0.001)	1.82 (1.30-2.55, p<0.001)	1.61 (1.13-2.84, p=0.008)
Overweight + diabetes	3.65 (3.04-4.38, p<0.001)	2.02 (1.68-2.43, p<0.001)	1.58 (1.31-1.91, p<0.001)	1.41 (1.13-1.76, p=0.002)
Obese + diabetes	4.09 (3.54-4.72, p<0.001)	2.63 (2.28-3.05, p<0.001)	1.92 (1.65-2.23, p<0.001)	1.58 (1.29-1.93, p<0.001)

Table S4. Sensitivity analysis of cardiovascular outcomes with and without people with diabetes diagnosed under 40 and taking insulin excluded. Unadjusted and adjusted incidence rate ratios (IRR) for all-cause and cardiovascular mortality obtained from multivariable Poisson regression analysis in participants grouped ethnicity adjusted BMI category. Comparator group is normal weight non-diabetes. Model 1 = Unadjusted model + adjustment for sex, age, ethnicity, smoking status, and deprivation score. Model 2 = Model 1 + adjustment for chronic cardiac condition, hypertension, cancer, chronic respiratory condition, chronic liver disease, chronic renal disease, neurological disease. Model 3 = Model 2 + adjustment for calcium channel blocker, beta blocker, angiotensin receptor blocker, thiazide diuretic, loop diuretic, mineralocorticoid receptor antagonist, statin, ACE inhibitor, aspirin, clopidogrel, warfarin, insulin, and metformin. Abbreviations: cardiac contractility index (CCI), carotid intimal media thickness (cIMT); confidence interval (CI); incident rate ratio (IRR); left ventricular ejection fraction (LVEF), pulse wave arterial stiffness index (PASI).

	Unadjusted	Model 1	Model 2	Model 3
	IRR (95% CI)	**Adjusted IRR* (95% CI)**	**Adjusted IRR (95% CI)**	**Adjusted IRR* (95% CI)**
Cardiovascular mortality				
No central obesity + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Central obesity + non-diabetes	2.66 (2.50-2.83, p<0.001)	1.54 (1.44-1.65, p<0.001)	1.36 (1.27-1.46, p<0.001)	1.33 (1.24-1.43, p<0.001)
No central obesity + diabetes	5.06 (4.21-6.09, p<0.001)	3.36 (2.79-4.05, p<0.001)	2.56 (2.12-3.09, p<0.001)	2.01 (1.65-2.46, p<0.001)
Central obesity + diabetes	8.79 (8.09-9.54, p<0.001)*	3.94 (3.61-4.30, p<0.001)*	2.61 (2.38-2.86, p<0.001)*	2.08 (1.84-2.36, p<0.001)
Non-fatal myocardial infarction				
No central obesity + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Central obesity + non-diabetes	2.58 (2.45-2.73, p<0.001)	1.59 (1.50-1.69, p<0.001)	1.48 (1.39-1.56, p<0.001)	1.48 (1.40-1.57, p<0.001)
No central obesity + diabetes	3.26 (2.68-3.97, p<0.001)	2.36 (1.94-2.87, p<0.001)	2.00 (1.64-2.43, p<0.001)	1.74 (1.41-2.15, p<0.001)
Central obesity + diabetes	5.32 (4.89-5.78, p<0.001)*	2.69 (2.46-2.94, p<0.001)*	2.09 (1.91-2.29, p<0.001)*	1.86 (1.62-2.12, p<0.001)*
Non-fatal ischemic stroke				
No central obesity + non-diabetes	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Central obesity + non-diabetes	3.90 (3.07-4.96, p<0.001)	1.36 (1.26-1.48, p<0.001)	1.25 (1.16-1.36, p<0.001)	1.26 (1.16-1.36, p<0.001)
No central obesity + diabetes	1.99 (1.84-2.14, p<0.001)	2.82 (2.22-3.58, p<0.001)	2.32 (1.82-2.95, p<0.001)	2.02 (1.55-2.63, p<0.001)
Central obesity + diabetes	4.72 (4.21-5.30, p<0.001)*	2.62 (2.32-2.96, p<0.001)*	1.98 (1.75-2.25, p<0.001)*	1.78 (1.48-2.14, p<0.001)*

Table S5 – Unadjusted and adjusted incidence rate ratios (IRR) for cardiovascular mortality, non-fatal myocardial infarction and non-fatal ischemic stroke by diabetes and central obesity. Central obesity defined as a waist to hip ratio (WHR) ≥ 0.85 if female and ≥ 0.90 if. Data presented as incidence rate ratios (IRR) with 95% confidence intervals (CI) obtained from Poisson regression analysis. * represents p value <0.05 for interaction between diabetes status and central obesity category. Model 1 = Unadjusted model + adjustment for sex, age, ethnicity, smoking status, and deprivation score. Model 2 = Model 1 + adjustment for chronic cardiac condition, hypertension, cancer, chronic respiratory condition, chronic liver disease, chronic renal disease, neurological disease. Model 3 = Model 2 + adjustment for calcium channel blocker, beta blocker, angiotensin receptor blocker, thiazide diuretic, loop diuretic, mineralocorticoid receptor antagonist, statin, ACE inhibitor, aspirin, clopidogrel, warfarin, insulin, and metformin. Abbreviations: body mass index (BMI); confidence interval (CI); incident rate ratio (IRR).

	No Diabetes			Diabetes		
	Normal	**Overweight**	**Obese**	**Normal**	**Overweight**	**Obese**
			Male			
			Diabetes metrics			
Diabetes duration, *years*	-	-	-	8 (3-18)*	6 (2-11)*	6 (2-10)*
Age of diabetes diagnosis, *years*	-	-	-	52 (39-59)*	55 (46-60)*	53 (46-59)*
			Body composition			
BMI	23.5 (22.3-24.3)*†	27.2 (26.1-28.5)*†	31.1 (30.9-34.3)*†	23.7 (22.5)*†	27.7 (26.4-28.9)*†	33.5 (31.5-36.5)*†
Waist circumference, cm	86 (82-90)*†	96 (92-100)*†	108 (103-114)*†	88 (83-91)*†	98 (93-102)*†	113 (106-120)*†
Hip circumference, cm	97 (94-100)*†	103 (100-106)*†	110 (106-114)*†	96 (93-99)*†	102 (99-105)*†	111 (107-117)*†
Waist to hip ratio	0.88 (0.85-0.92)*†	0.93 (0.90-0.96)*†	0.98 (0.95-1.02)*†	0.91 (0.87-0.95)*†	0.96 (0.92-0.99)*†	1.01 (0.97-1.05)*†
Body fat percentage	19.7 (16.6-22.5)*†	25.1 (22.6-27.6)*†	30.8 (28.3-33.4)*†	20.6 (17.2-23.5)*†	26.3 (23.7-28.7)*†	32.4 (29.6-35.5)*†
Whole body fat mass, *kg*	14.3 (11.7-16.7)*†	21.1 (18.4-23.8)*†	30.4 (27.0-34.9)*†	14.7 (12.0-17.0)*†	21.9 (19.1-24.7)*†	32.9 (28.5-39.1)*†
Whole body impedance, *ohms*	580 (547-615)*	536 (507-566)*	489 (460-519)*†	578 (542-617)*	535 (503-569)*	478 (446-513)*†
			Lipids			
Serum Apolipoprotein A, *g/L*	1.5 (1.3-1.6)*†	1.4 (1.3-1.6)*†	1.3 (1.2-1.5)*†	1.4 (1.3-1.6)*†	1.3 (1.2-1.5)*†	1.3 (1.2-1.4)*†
Serum Apolipoprotein B, *g/L*	1.0 (0.8-1.1)*†	1.0 (0.9-1.2)*†	1.0 (0.9-1.2)*†	0.8 (0.7-0.9)*†	0.8 (0.7-0.9)*†	0.8 (0.7-1.0)*†
Serum total cholesterol, *mmol/L*	5.5 (4.8-6.2)*†	5.6 (4.9-6.3)*†	5.5 (4.7-6.3)*†	4.2 (3.7-4.9)†	4.2 (3.7-4.9)†	4.2 (3.6-4.8)†
Serum HDL cholesterol, *mmol/L*	1.4 (1.2-1.6)*†	1.2 (1.1-1.4)*†	1.1 (1.0-1.3)*†	1.3 (1.1-1.5)*†	1.1 (1.0-1.3)*†	1.0 (0.9-1.2)*†
Serum LDL cholesterol, *mmol/L*	3.4 (2.9-4.0)*†	3.6 (3.0-4.1)*†	3.5 (2.9-4.1)*†	2.4 (2.1-2.9)†	2.5 (2.1-3.0)†	2.5 (2.1-3.0)†
Serum lipoprotein A, *nmol/L*	20.2 (9.4-61.6)*†	20.2 (9.3-61.0)*	18.7 (8.7-63.1)*†	18.7 (8.4-58.6)*†	20.2 (8.8-67.3)*	16.7 (7.8-62.0)*†
Serum triglycerides, *mmol/L*	1.3 (0.9-1.8)*†	1.7 (1.2-2.5)*	2.1 (1.5-2.9)*	1.3 (0.9-1.8)*†	1.7 (1.2-2.5)*	2.1 (1.5-2.9)*
Triglyceride/HDL ratio	0.94 (0.62-1.45)*	1.39 (0.90-2.14)*†	1.83 (1.21-2.76)	0.96 (0.61-1.53)*	1.55 (0.99-2.42)*†	2.03 (1.35-3.06)*†
			Biochemistry			
Creatinine, *µmol/L*	78 (71-86)*†	81 (74-89)*†	81 (73-90)*†	76 (68-86)*†	78 (70-88)*†	79 (69-90)*†
Serum cystatin C, *mg/L*	0.88 (0.81-0.96)*†	0.91 (0.84-1.00)*†	0.96 (0.88-1.06)*†	0.90 (0.81-1.02)*†	0.93 (0.84-1.04)*†	0.98 (0.88-1.11)*†
Urinary microalbumin, *mg/L*	10.6 (8.1-17.2)*†	11.1 (8.3-18.6)*†	12.7 (8.8-23.3)*	15.1 (9.4-33.4)*†	15.4(9.9-34.7)*†	19.8 (10.9-51.6)*
Alanine aminotransferase, *U/L*	20 (16-25)*†	24 (19-31)*†	29 (22-39)*	22 (17-28)*†	25 (19-33)*†	29 (21-40)*
C-reactive protein, *mg/L*	0.8 (0.4-1.6)*	1.2 (0.7-2.3)*	2.0 (1.1-3.6)*†	0.8 (0.4-1.8)*	1.2 (0.6-2.3)*	2.0 (1.1-3.8)*†
			Diabetes related biomarkers			
Glucose, *mmol/L*	4.9 (4.5-5.2)*†	4.9 (4.6-5.3)*†	5.0 (4.6-5.4)*†	6.5 (5.2-9.5)*†	6.5 (5.3-8.7)*†	6.7 (5.4-9.2)*†
HbA1c, *mmol/mol*	34 (32-37)*†	35 (33-37)*†	36 (34-39)*†	49 (42-58)*†	50 (43-58)*†	51 (44-61)*†
HbA1c, %	5.3 (5.1-5.5)*†	5.4 (5.2-5.5)*†	5.4 (5.3-5.7)*†	6.6 (6.0-7.5)*†	6.7 (6.1-7.5)*†	6.8 (6.2-7.7)*†
IGF-1, *nmol/L*	22.0 (18.6-25.3)*†	22.2 (18.9-25.6)*†	21.0 (17.3-24.5)*†	21.3 (17.4-25.5)*†	21.2(17.1-25.0)*†	19.1(14.9-23.4)*†
			Abdominal MRI			
Abdominal fat ratio, *fraction*	0.37 (0.31-0.43)*	0.46 (0.41-0.51)*	0.54 (0.48-0.58)*†	0.42 (0.33-0.48)*	0.47 (0.44-0.54)*	0.57 (0.54-0.61)*†
Total abdominal adipose tissue index, L/m^2	2.2 (1.7-2.8)*	3.5 (2.9-4.1)*†	5.1 (4.3-5.9)*†	2.5 (1.8-3.2)*	3.7 (3.0-4.4)*†	5.6 (5.1-6.4)*†
			Female			
			Diabetes metrics			
Diabetes duration, *years*	-	-	-	7 (3-21)*	5 (2-12)*	5 (2-10)*
Age of diabetes diagnosis, *years*	-	-	-	52 (34-60)*	55 (45-60)*	54 (45-59)*
BMI	22.9 (21.6-24.0)*†	27.0 (25.9-28.3)*†	33.0 (31.2-35.9)*†	23.1 (21.9-24.1)*†	27.6 (26.3-28.8)*†	34.9 (32.2-38.9)*†
Waist circumference, cm	74 (70-79)*†	85 (80-90)*†	99 (93-105)*†	77 (72-82)*†	90 (85-94)*†	106 (99-114)*†
Hip circumference, cm	96 (92-99)*†	103 (100-107)*†	115 (110-121)*†	95 (91-98)*†	102 (98-106)*†	117 (110-125)*†
Waist to hip ratio	0.78 (0.74-0.82)*†	0.82 (0.78-0.87)*†	0.86 (0.82-0.90)*†	0.81 (0.76-0.87)*†	0.88 (0.83-0.93)*†	0.90 (0.86-0.95)*†
Body fat percentage	31.1 (27.8-34.1)*	38.0 (35.6-40.3)*	44.3 (41.8-46.8)*†	31.2 (27.6-34.3)*	38.1 (35.4-40.4)*	45.1 (42.3-48.0)*†
Whole body fat mass, *kg*	18.9 (16.0-21.6)*	27.0 (24.2-30.1)*	38.3 (34.1-43.9)*†	19.0 (15.6-21.7)*	27.1 (23.9-30.2)*	41.0 (35.1-48.2)*†

Whole body impedance, *ohms*	690 (650-732)*†	649 (612-688)*†	590 (630-667)*†	679 (636-721)*†	635 (595-677)*†	564 (520-608)*†
			Lipids			
Serum Apolipoprotein A, *g/L*	1.7 (1.5-1.9)*†	1.6 (1.4-1.8)*†	1.5 (1.4-1.7)*†	1.6 (1.4-1.8)*†	1.5 (1.4-1.7)*†	1.4 (1.3-1.6)*†
Serum Apolipoprotein B, *g/L*	1.0 (0.8-1.1)*†	1.1 (0.9-1.2)*†	1.1 (0.9-1.2)*†	0.8 (0.7-0.9)*†	0.8 (0.7-1.0)*†	0.9 (0.7-1.0)*†
Serum total cholesterol, *mmol/L*	5.8 (5.1-6.5)*†	6.0 (5.2-6.7)*†	5.9 (5.1-6.6)*†	4.7 (4.1-5.4)*†	4.7 (4.0-5.3)*†	4.6 (4.0-5.2)*†
Serum HDL cholesterol, *mmol/L*	1.7 (1.5-2.0)*†	1.5 (1.3-1.8)*†	1.4 (1.2-1.6)*†	1.6 (1.3-1.9)*†	1.3 (1.1-1.6)*†	1.2 (1.1-1.4)*†
Serum LDL cholesterol, *mmol/L*	3.5 (2.9-4.0)*†	3.7 (3.1-4.3)*†	3.7 (3.1-4.3)*†	2.6 (2.2-3.1)*†	2.7 (2.2-3.2)*†	2.7 (2.3-3.2)*†
Serum lipoprotein A, *nmol/L*	20.8 (9.5-59.7)*	22.9 (10.2-62.1)*	24.0 (10.4-65.4)*†	21.4 (9.7-63.8)	23.7 (9.6-67.2)	20.9 (9.2-62.5)†
Serum triglycerides, *mmol/L*	1.1 (0.8-1.5)*	1.4 (1.0-2.0)*†	1.7 (1.2-2.3)*†	1.1 (0.8-1.7)*	1.7 (1.1-2.4)*†	1.9 (1.4-2.6)*†
Triglyceride/HDL ratio	0.64 (0.45-0.94)*†	0.91 (0.62-1.39)*†	1.22 (0.83-1.81)*†	0.71 (0.44-1.21)*†	1.28 (0.76-1.97)*†	1.58 (1.07-2.30)*†
			Biochemistry			
Creatinine, *µmol/L*	62 (56-69)*†	64 (58-71)*†	64 (58-72)*†	60 (54-68)*†	62 (55-70)*†	62 (55-72)*†
Serum cystatin C, *mg/L*	0.82 (0.75-0.89)*†	0.86 (0.79-0.95)*†	0.92 (0.84-1.03)*†	0.84 (0.76-0.94)*†	0.90 (0.80-1.02)*†	0.96 (0.85-1.09)*†
Urinary microalbumin, *mg/L*	10.7 (8.2-16.5)*†	10.7 (8.2-16.5)*†	11.7 (8.6-19.2)*†	13.5 (9.1-24.4)†	13.7 (9.6-26.3)†	14.6 (9.5-29.2)†
Alanine aminotransferase, *U/L*	16 (13-20)*†	18 (14-23)*†	21 (16-27)*†	19 (15-25)*†	21 (16-29)*†	23 (17-32)*†
C-reactive protein, *mg/L*	0.8 (0.4-1.5)*†	1.5 (0.8-2.8)*†	3.1 (1.7-5.7)*†	0.9 (0.5-2.0)*†	1.6 (0.8-3.3)*†	3.3 (1.7-6.5)*†
			Diabetes related biomarkers			
Glucose, *mmol/L*	4.8 (4.5-5.2)*†	4.9 (4.6-5.3)*†	5.0 (4.7-5.4)*†	6.3 (5.1-9.4)*†	6.3 (5.2-8.4)*†	6.4 (5.2-8.7)*†
HbA1c, *mmol/mol*	34 (32-37)*†	35 (33-37)*†	36 (34-39)*†	51 (44-60)*†	50 (43-59)*†	51 (45-60)*†
HbA1c, %	5.3 (5.1-5.5)*†	5.4 (5.2-5.5)*†	36 (34-39)*†	6.8 (6.2-7.6)*†	6.7 (6.1-7.5)*†	6.8 (6.3-7.6)*†
IGF-1, *nmol/L*	21.5 (17.8-25.1)*†	21.0 (17.3-24.7)*†	19.2 (15.5-23.2)*†	20.4 (16.4-24.7)†	20.1 (16.0-24.2)†	17.6 (13.7-21.8)†
			Abdominal MRI			
Abdominal fat ratio, *fraction*	*0.48 (0.41-0.54)**	0.58 (0.53-0.62)*	0.65 (0.62-0.68)*†	0.49 (0.39-0.54)*	0.60 (0.55-0.62)*	0.68 (0.65-0.71)*†
Total abdominal adipose tissue index, *L/m²*	2.7 (2.1-3.4)*	4.4 (3.7-5.1)*	6.3 (5.5-7.4)*†	3.1 (1.9-3.8)*	4.5 (3.8-5.2)*	7.0 (6.0-8.3)*†

Table S6 – **Metabolic phenotypes of study participants stratified by sex**. Participants are stratified by diabetes status, sex and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Continuous data presented as median with 25th and 75th centile. Categorical data presented as n (%). * represents Kruskal-Wallis p value or chi^2 test <0.005 between BMI categories for continuous variables and categorical variables respectively within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from Mann-Whitney U tests for continuous variables and chi^2 test for categorical variables. Total abdominal adipose tissue index is defined as VAT volume + abdominal SAT volume / body surface area. Abdominal fat ratio is defined as VAT volume + abdominal SAT volume / VAT volume + abdominal SAT volume + total thigh fat-free muscle volume. Abbreviations: body mass index (BMI); subcutaneous adipose tissue (SAT); visceral adipose tissue (VAT).

	Obese non-diabetes	Normal weight diabetes	Mann Whitney U test p value
Mean carotid IMT, *μm*	685 (611-779)	725 (642-791)	0.0062
LVEF, *%*	56 (52-60)	57 (54-60)	0.1243
Cardiac contractility index (SBP/LVESVi)	4.5 (3.8-5.5)	4.7 (4.0-5.5)	0.2737
Pulse wave arterial stiffness index	9.6 (7.5-11.4)	9.2 (6.9-11.4)	0.0075

Table S7 – Cardiometabolic phenotypes of obese non-diabetics vs normal weight diabetics according to ethnicity adjusted BMI category. . Continuous data presented as median with 25th and 75th centile Abbreviations: body mass index (BMI), intimal media thickness (IMT), left ventricular ejection fraction (LVEF), left ventricular end systolic volume indexed for body surface area (LVESVi), systolic blood pressure (SBP).

	All people with diabetes *(n = 22 451)*			***People with diabetes diagnosed under 40 years old & on insulin excluded (n = 20 695)***		
	Normal	Overweight	Obese	Normal	Overweight	Obese
Mean carotid IMT, *μm*	725 (642-791)	720 (629-810)	703 (639-794)	725 (657-779)	722 (630-814)	703 (639-794)
LVEF, *%*	57 (54-60)*	54 (49-58)*	55 (50-58)*	57 (54-59)*	54 (49-58)*	55 (50-58)*
Cardiac contractility index (SBP/LVESVi)	4.7 (4.0-5.5)	4.5 (3.7-5.5)	4.8 (3.9-5.8)	4.8 (4.1-5.5)	4.5 (3.8-5.5)	4.8 (3.9-5.9)
Pulse wave arterial stiffness index	9.2 (6.9-11.4)*	9.9 (7.7-11.9)*	9.7 (7.9-11.5)*	9.3 (7.0-11.4)*	10.1 (7.8-12.0)*	9.7 (7.9-11.5)*

Table S8 - Sensitivity analysis of cardiovascular phenotypic measures with and without people with diabetes diagnosed under 40 years of age and taking insulin at recruitment excluded. Participants stratified by ethnicity adjusted BMI category. Continuous data presented as median with 25th and 75th centile. * represents Kruskal Wallis p value <0.005 between BMI categories. Abbreviations: cardiac contractility index (CCI), carotid intimal media thickness (cIMT); left ventricular ejection fraction (LVEF), left ventricular end systolic volume indexed to body surface area (LVESVi), pulse wave arterial stiffness index (PASI), systolic blood pressure (SBP).

	No Diabetes			Diabetes		
	Normal	**Overweight**	**Obese**	**Normal**	**Overweight**	**Obese**
			Male			
			Vital signs			
Systolic blood pressure, *mmHg*	136 (125-149)*†	142 (130-154)*†	145 (133-157)*†	139 (127-154)*†	143 (132-156)*†	144 (133-156)*†
Diastolic blood pressure, *mmHg*	80 (73-87)*†	84 (77-91)*†	87 (81-94)*†	77 (71-84)*†	81 (74-88)*†	83 (76-90)*†
Resting heart rate, *bpm*	65 (58-73)*†	66 (60-74)*†	70 (62-79)*†	70 (62-80)*†	71 (63-80)*†	74 (65-83)*†
			Carotid intima-media thickness			
Mean carotid IMT, *μm*	672 (597-771)*†	698 (613-796)*†	710 (626-814)*	728 (645-834)†	729 (642-834)†	713 (646-811)
			Cardiac MRI			
LVEF, *%*	55 (51-58)	55 (51-59)†	55 (50-58)†	55 (53-59)	54 (49-58)†	53 (48-57)†
LVEDV, *ml*	151 (131-172)*†	154 (135-175)*†	159 (138-183)*†	131 (114-145)*†	139 (116-165)*†	144 (124-172)*†
LVESV, *ml*	67 (57-80)*†	69 (58-81)*†	72 (61-86)*†	55 (49-67)*†	64 (52-77)*†	68 (56-84)*†
LVSV, *ml*	82 (71-94)*†	84 (72-96)*†	86 (73-100)*†	72 (61-83)†	73 (61-88)†	77 (62-88)†
LVEDV / BSA, *ml/m²*	80 (70-90)*†	77 (68-87)*†	74 (65-84)*†	71 (60-77)†	71 (62-81)†	68 (59-79)†
LVESV / BSA, *ml/m²*	36 (31-42)*†	34 (29-40)*†	33 (28-40)*†	28 (26-36)†	32 (27-38)†	32 (26-38)†
LVSV / BSA, *ml/m²*	43 (38-49)*†	42 (36-48)*†	40 (35-47)*†	39 (33-45)†	37 (31-43)†	35 (30-41)†
Cardiac output, L/min^{-1}	4.8 (4.2-5.5)*	5.0 (4.4-5.7)*†	5.3 (4.5-6.1)*	4.6 (4.1-5.4)*	4.8 (4.0-5.5)*†	5.1 (4.4-5.9)*
Cardiac index, L/min^{-1}/m^2	2.5 (2.2-2.9)*	2.5 (2.2-2.8)*†	2.5 (2.1-2.8)*	2.5 (2.2-3.0)	2.4 (2.1-2.8)†	2.4 (2.1-2.8)
Cardiac contractility index (SBP/LVESVi)	3.8 (3.1-4.6)*†	4.1 (3.4-4.9)*†	4.3 (3.6-5.2)*†	4.7 (4.1-5.1)†	4.3 (3.6-5.3)†	4.5 (3.7-5.6)†
			Photoplethysmography derived arterial stiffness			
Pulse wave arterial stiffness index	9.0 (7.1-11.4)*†	9.8 (7.7-12.0)*†	10.2 (8.4-12.0)*	9.5 (7.5-11.7)*†	10.3 (8.3-12.2)*†	10.0 (8.5-11.7)*
			Female			
			Vital signs			
Systolic blood pressure, *mmHg*	130 (118-145)*†	137 (124-151)*†	140 (128-154)*†	138 (125-152)*†	141 (129-154)*†	142 (131-154)*†
Diastolic blood pressure, *mmHg*	77 (70-84)*†	81 (74-88)*†	85 (78-92)*†	75 (69-82)*†	79 (72-85)*†	82 (76-89)*†
Resting heart rate, *bpm*	68 (62-75)*†	69 (63-76)*†	72 (65-80)*†	73 (65-80)*†	74 (67-83)*†	77 (68-86)*†
			Carotid intima-media thickness			
Mean carotid IMT, *μm*	639 (576-715)*†	654 (590-735)*	663 (600-744)*†	715 (631-767)†	680 (611-742)	684 (624-762)†
			Cardiac MRI			
LVEF, *%*	57 (54-61)	57 (54-61)†	57 (54-61)	58 (56-61)	56 (51-58)†	56 (52-60)
LVEDV, *ml*	117 (103-132)*	119 (105-135)*†	128 (112-145)*†	108 (93-129)	109 (97-127)†	120 (98-136)†
LVESV, *ml*	50 (43-58)*	51 (43-59)*	54 (46-63)*†	45 (36-55)	48 (41-58)	51 (42-60)†
LVSV, *ml*	67 (58-75)*	68 (59-77)*†	73 (63-83)*†	63 (53-73)	60 (52-68)†	66 (55-75)†
LVEDV / BSA, *ml/m²*	71 (63-79)*	68 (61-76)*†	68 (60-75)*†	65 (57-78)	64 (55-72)†	61 (54-69)†
LVESV / BSA, *ml/m²*	30 (26-35)*	29 (25-33)*†	29 (25-33)*	27 (23-34)	28 (23-33)	26 (22-31)†
LVSV / BSA, *ml/m²*	40 (36-45)*	39 (34-44)*†	39 (33-43)*†	39 (33-44)	34 (29-39)†	35 (29-39)†
Cardiac output, L/min^{-1}	4.1 (3.6-4.7)*	4.3 (3.7-4.9)*	4.6 (4.0-5.3)*	4.2 (3.5-4.7)	4.2 (3.5-4.6)	4.4 (3.9-5.2)
Cardiac index, L/min^{-1}/m^2	2.5 (2.2-2.8)*	2.4 (2.1-2.8)*	2.4 (2.1-2.7)*	2.6 (2.1-2.7)	2.3 (2.1-2.6)	2.3 (2.1-2.6)
Cardiac contractility index (SBP/LVESVi)	4.2 (3.5-5.1)*†	4.6 (3.8-5.6)*	4.8 (4.0-5.8)*†	5.0 (4.0-5.8)†	5.0 (4.1-6.0)	5.3 (4.3-6.2)†
			Photoplethysmography derived arterial stiffness			
Pulse wave arterial stiffness index	7.7 (6.1-9.9)*†	8.4 (6.3-10.6)*†	8.9 (6.7-10.9)*	8.4 (6.4-10.8)†	9.0 (6.6-11.2)†	9.1 (7.0-11.1)

Table S9 – **Phenotypic measurements of cardiovascular disease stratified by sex**. Participants are stratified by diabetes status, sex and then by ethnicity adjusted BMI category. Normal: BMI ≥18.5kg/m^2 to <25 kg/m^2 *or* ≥18.5kg/m^2 to <23 kg/m^2 if south Asian ethnicity; Overweight: ≥25kg/m^2 to <30 kg/m^2 *or* ≥23kg/m^2 to <27.5 kg/m^2 if south Asian ethnicity; Obese: ≥30kg/m^2 *or* ≥27.5kg/m^2 if south Asian ethnicity. Continuous data presented as median with 25th and 75th centile. Categorical data presented as n (%). * represents Kruskal-Wallis p value or chi^2 test <0.005 between BMI categories for continuous variables and categorical variables respectively within diabetes or non-diabetes groups. † represents p value <0.005 between each BMI category in diabetes participants and their respective BMI category in non-diabetes participants from Mann-Whitney U tests for continuous variables and chi^2 test for categorical variables. Total abdominal adipose tissue index is defined as VAT volume + abdominal SAT volume / body surface area. Abdominal fat ratio is defined as

VAT volume + abdominal SAT volume / VAT volume + abdominal SAT volume + total thigh fat-free muscle volume. Abbreviations: body mass index (BMI) body surface area (BSA), intima media thickness (IMT), left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular end-systolic volume indexed to body surface area (LVESVi), left ventricular stroke volume (LVSV), systolic blood pressure (SBP).

	No Diabetes		**Diabetes Mellitus**	
	No central obesity (n=224 088)	**Central obesity (n = 204 816)**	**No central obesity (n=3982)**	**Central obesity (n=18 469)**
Mean carotid IMT, *μm*	652 (585-737)*†	690 (612-788)*†	693 (626-782)†	717 (641-812)†
LVEF, %	57 (53-60)*	55 (51-59)*	57 (52-60)*	54 (49-58)*
Cardiac contractility index (SBP/LVESVi)	4.2 (3.5-5.0)*†	4.4 (3.6-5.3)*†	4.6 (3.9-5.6)†	4.6 (3.8-5.7)†
Pulse wave arterial stiffness index	8.1 (6.4-10.4)*†	9.7 (7.6-11.7)*†	8.8 (6.8-11.1)*†	9.9 (7.9-11.8)*†

Table S10. Cardiovascular phenotypic measures of the population stratified by central obesity (defined by WHR) and diabetes. Central obesity defined as a WHR ≥ 0.85 if female and ≥ 0.90 if male. Continuous data presented as median with 25th and 75th centile. * represents Kruskal Wallis p value <0.005 between central obesity categories for continuous variables within diabetes or non-diabetes groups. † represents p value <0.005 between each central obesity category in diabetes participants and their respective central obesity category in non-diabetes participants from Mann-Whitney U tests for continuous variables. Abbreviations: cardiac contractility index (CCI), carotid intimal media thickness (cIMT); left ventricular ejection fraction (LVEF), left ventricular end systolic volume indexed to body surface area (LVESVi), pulse wave arterial stiffness index (PASI), systolic blood pressure (SBP), waist to hip ratio (WHR).

	cIMT (Per 25 unit increase)		LVEF (Per 1 unit increase)		CCI (Per 1 unit increase)		PASI (Per 2.5 unit increase)	
	IRR (95% CI)	Diabetes interaction	IRR (95% CI)	Diabetes interaction	IRR (95% CI)	Diabetes interaction	IRR (95% CI)	Diabetes interaction
Cardiovascular death								
Unadjusted model	1.09 (1.06-1.13, p<0.001)	0.512	0.95 (0.93-0.97, p<0.001)	0.572	0.83 (0.63-0.99, p=0.049)	0.762	1.03 (1.02-1.03, p<0.001)	0.456
Model 1	1.05 (1.01-1.09, p=0.019)	0.450	0.96 (0.94-0.99, p=0.006)	0.732	0.74 (0.62-0.89, p=0.001)	0.834	1.02 (1.01-1.03, p<0.001)	0.800
Model 2	1.05 (1.01-1.09, p=0.021)	0.342	0.97 (0.94-0.99, p=0.014)	0.713	0.76 (0.63-0.92, p=0.004)	0.932	1.02 (1.01-1.03, p<0.001)	0.974
Model 3	1.05 (1.01-1.09, p=0.017)	0.507	0.97 (0.95-0.99, p=0.026)	0.633	0.77 (0.64-0.93, p=0.007)	0.934	1.02 (1.01-1.03, p<0.001)	0.640

Table S11. Association of cardiovascular phenotypic measures with cardiovascular death presented with p values for interaction of diabetes status. Data presented as incidence rate ratios (IRR) with 95% confidence intervals (CI) and p values for interaction by diabetes status shown. Model 1 = Unadjusted model + adjustment for sex, age, ethnicity, smoking status, and deprivation score. Model 2 = Model 1 + adjustment for chronic cardiac condition, hypertension, cancer, chronic respiratory condition, chronic liver disease, chronic renal disease, neurological disease. Model 3 = Model 2 + adjustment for calcium channel blocker, beta blocker, angiotensin receptor blocker, thiazide diuretic, loop diuretic, mineralocorticoid receptor antagonist, statin, ACE inhibitor, aspirin, clopidogrel, warfarin, insulin, and metformin. Abbreviations: cardiac contractility index (CCI), carotid intimal media thickness (cIMT); confidence interval (CI); incident rate ratio (IRR); left ventricular ejection fraction (LVEF), pulse wave arterial stiffness index (PASI).

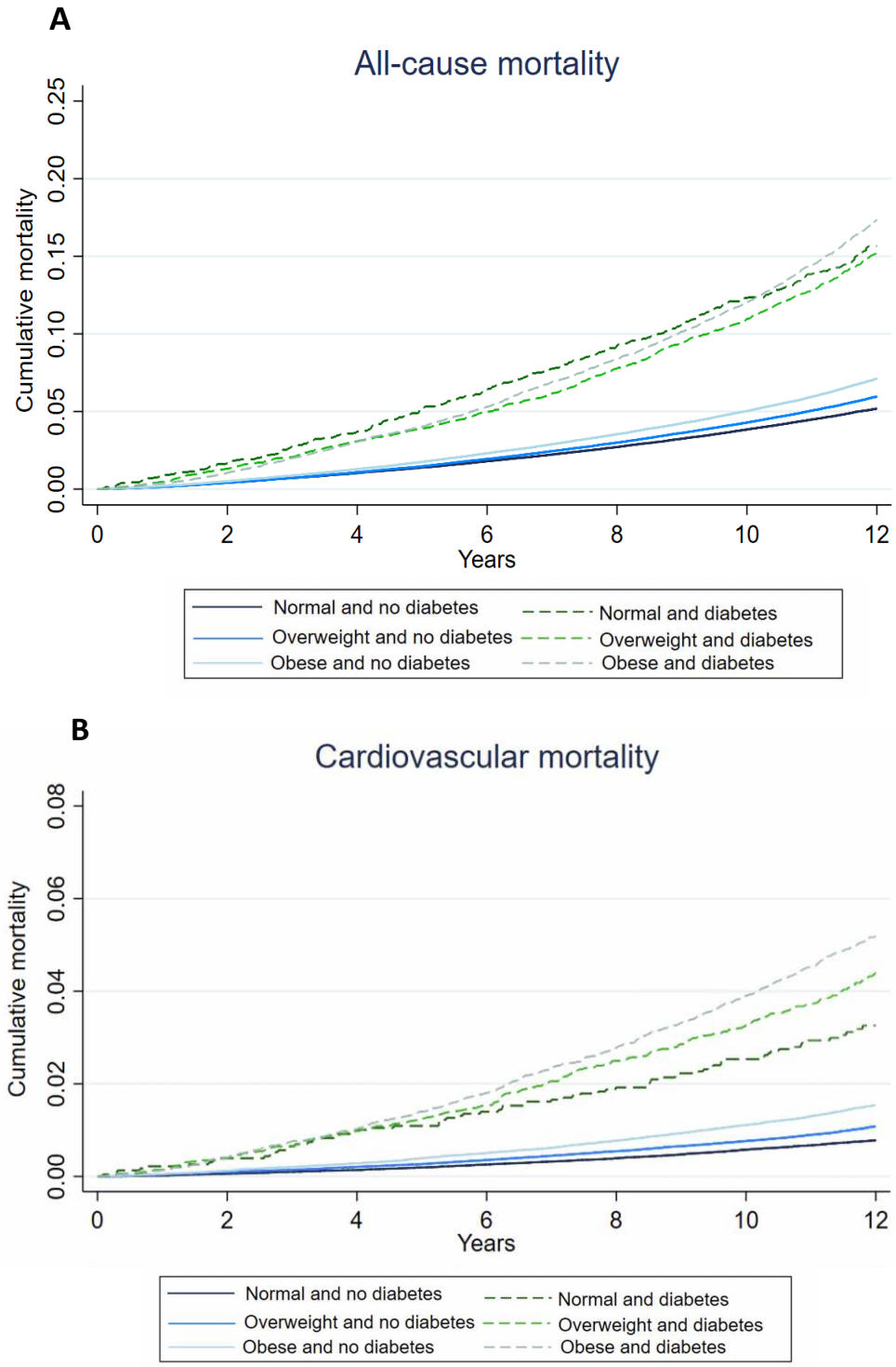

Figure S1. All-cause and cardiovascular mortality. Kaplan-Meier mortality curves illustrating cumulative all-cause (A) and cardiovascular (B) mortality stratified by ethnicity-adjusted BMI category and diabetes status.

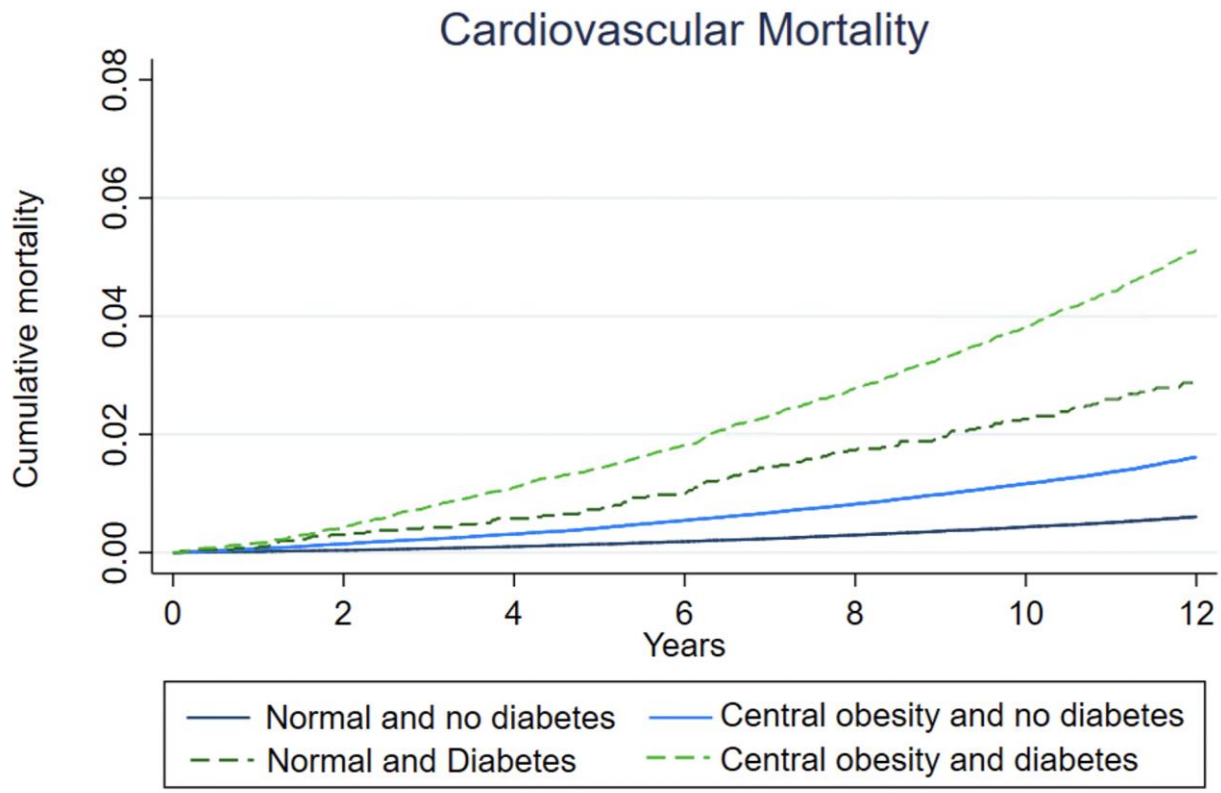

Figure S2 - Kaplan-Meier mortality curves illustrating cumulative cardiovascular mortality stratified by central obesity (defined as a waist to hip ratio (WHR) ≥ 0.85 if female and ≥ 0.90 if male) and diabetes status.

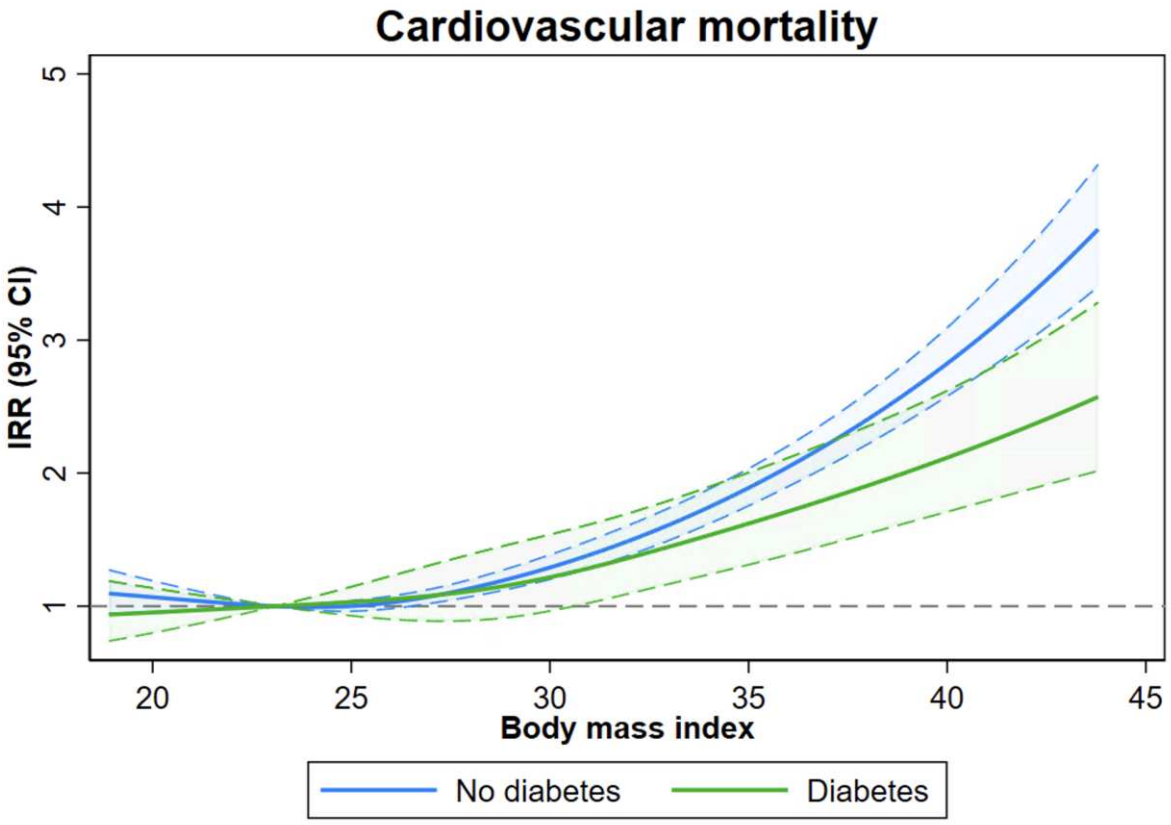

Figure S3. Cardiovascular mortality according to body mass index and diabetes status. Incidence rate ratios (IRR) and 95% confidence intervals (95% CI) for cardiovascular mortality according to body mass index (BMI) and diabetes status modelled using restricted cubic spline regression with 4 knots; the reference knot is at BMI 23.4 (median value of cohort). Solid lines represent IRR and shaded areas represent 95% CIs. Spline curves were truncated at the 1st and 99nd centile.

A – No Diabetes

	PASI	CIMT	LVEF	CCI
DM duration	.	.	.	.
HbA1c	0.08*	0.12*	-0.03*	0.09*
WHR	0.19*	0.20*	-0.16*	0.00
Cystatin C	0.11*	0.18*	-0.10*	0.07*
hsCRP	0.05*	0.03*	-0.01*	0.06*
HDL	-0.11*	-0.09*	0.11	0.04*
TG	0.12*	0.11*	-0.06*	0.08*
ALT	0.09*	0.06*	-0.05*	0.04*
Body fat %	-0.02*	-0.05*	0.12*	0.22*
AFR	0.04	-0.03*	0.07*	0.25*

B – Diabetes

	PASI	CIMT	LVEF	CCI
DM duration	-0.01	0.06	0.08	-0.02
HbA1c	0.02	0.03	-0.05	-0.02
WHR	0.09*	0.11*	-0.18*	-0.06
Cystatin C	0.01	0.06	-0.03	0.14*
hsCRP	0.01	0.03	-0.01	0.01
HDL	-0.07*	-0.07	0.09	-0.02
TG	0.05*	-0.03	-0.03	0.09
ALT	0.06*	-0.04	-0.04	0.05
Body fat %	-0.06*	-0.13*	0.04	0.17*
AFR	0.20	-0.19	0.08	0.25*

Figure S4. Correlation of cardiovascular imaging phenotypes with biomarkers of metabolic phenotype stratified by diabetes status. Numbers represent Pearson's correlation coefficient with * indicating $p<0.005$. AFR is defined as visceral adipose tissue (VAT) + abdominal subcutaneous adipose tissue volume (SAT) / VAT volume + abdominal SAT volume + total thigh fat-free muscle volume. CCI is defined as systolic blood pressure / left ventricular end-systolic volume indexed to body surface area. Abbreviations: abdominal fat ratio (AFR); alanine aminotransferase (ALT); body surface area (BSA); cardiac contractility index (CCI); carotid intima media thickness (CIMT); diabetes mellitus (DM); glycated hemoglobin (HbA1c); high density lipoprotein (HDL); high sensitivity c-reactive protein (hsCRP); left ventricular ejection fraction (LVEF); pulse wave arterial stiffness index (PASI); subcutaneous adipose tissue (SAT); triglycerides (TG); visceral adipose tissue (VAT); waist to hip ratio (WHR).