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Heterogeneity in phenotype, disease progression and drug response in type 2 diabetes

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Supplementary Table 1: Phenotypic characteristics of the study population in this analysis.

Variables	Tayside Scotland (SCI-DC) (N=23137)	UK Biobank (N=7332)	ADOPT trial (N=4150)
	Mean (SD)/N (%)	Mean (SD)/N (%)	Mean (SD)/N (%)
Males	13007 (56.2)	4359 (59.5)	2383 (57.4)
Age at diagnosis (year)	63.2 (11.7)	61.8 (7.6)	56.5 (10.0)
HDL-c (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Total cholesterol (mmol/L)	5.0 (1.2)	5.1 (1.2)	5.3 (1.0)
Triglycerides (mmol/L)	2.4 (1.5)	2.2(1.3)	2.1 (1.3)
HbA1c (%)	7.9 (1.9)	7.5 (1.8)	7.3 (0.9)
BMI (Kg/m ²)	32.2 (6.5)	31.8 (5.9)	32.1 (6.2)
SBP (mm of Hg)	138.8 (18.5)	136.5 (15.8)	132.8 (15.4)
DBP (mm of Hg)	80.2 (10.8)	80.1 (9.8)	79.6 (8.7)
ALT (IU/L)	35.1 (22.2)	36.6 (20.9)	26.7 (14.2)
Creatinine (mmol/L)	79.1 (22.5)	83.1(18.1)	71.1 (16.4)
C-peptide (nmol/l) (n=3604)	2.0(1.1)	-	-
Adiponectin (ng/ml) (n=965)	4552.3(3051.3)	-	-
Leptin (ng/ml) (n=742)	17549.3(15208.3)	-	-
HOMA2-B	-	-	72.6 (28.6)
HOMA2-IR	-	-	2.9 (1.2)

Supplementary Table 1 shows mean and standard deviation phenotypic variables of the study participants (in Scottish, UKBB and ADOPT data) at the time of T2D diagnosis (C-peptide, adiponectin and leptin measurements were not available at the time of diagnosis in Scottish data)

Supplementary table 2: Summary of GAM models predicting DDRTree Dimension1 and Dimension 2, fitted with cubic regression splines.

Variables	GAM for DDRTree Dimension1 (adj.R²=79.5%)				GAM for DDRTree Dimension2 (adj.R²=86.0%)			
Parametric Coefficient	Estimate	Std. Error	P value		Estimate	Std. Error	P value	
<i>Sex</i>	-0.071	0.004	<0.0001		0.218	0.003	<0.0001	
Smooth terms	edf	Ref.df	F	P value	edf	Ref.df	F	P value
<i>Age at diagnosis (year)</i>	7.72	8.40	1039.40	<0.0001	3.04	3.82	134.16	<0.0001
<i>HDL-c (mmol/L)</i>	7.26	8.14	696.05	<0.0001	8.53	8.90	2786.68	<0.0001
<i>Total cholesterol (mmol/L)</i>	5.15	6.64	377.70	<0.0001	6.39	7.53	674.20	<0.0001
<i>Triglycerides (mmol/L)</i>	7.81	8.57	1255.44	<0.0001	7.48	8.36	925.80	<0.0001
<i>HbA1c (%)</i>	7.39	8.21	497.27	<0.0001	4.89	5.91	95.84	<0.0001
<i>BMI (Kg/m²)</i>	7.76	8.55	476.17	<0.0001	5.48	6.65	818.97	<0.0001
<i>SBP (mm of Hg)</i>	6.40	7.58	603.05	<0.0001	6.51	7.67	1437.75	<0.0001
<i>DBP (mm of Hg)</i>	7.40	8.37	557.81	<0.0001	8.41	8.89	1139.93	<0.0001
<i>ALT (IU/L)</i>	7.18	8.00	368.41	<0.0001	6.83	7.71	109.21	<0.0001
<i>Creatinine (mmol/L)</i>	2.21	3.54	34.79	<0.0001	4.17	5.12	627.07	<0.0001

Supplementary table 3: Summary of competing risk models constructed with continuous covariates for diabetes outcomes (Insulin Initiation, MACE, CKD and DR) . Table shows sHR (sub Hazard Ratios) and 95% CI with p values generated from Fine Gray models of competing risk analysis.

Variables	Competing risk models							
	Time to Insulin		Time to MACE		Time to CKD		Time to DR	
N	22595		18239		19956		22759	
Event of Interest (n(%))	3954 (17.5)		3261 (17.9)		3160 (15.8)		540 (2.4)	
Competing event (n(%))	3627 (16.1)		1483 (8.1)		2320 (11.6)		4131 (18.2)	
	sHR 95% CI	P value	sHR 95% CI	P value	sHR 95% CI	P value	sHR 95% CI	P value
Sex	0.80 (0.74-0.86)	<0.0001	1.24 (1.14-1.35)	<0.0001	0.35 (0.31-0.39)	<0.0001	1.28 (1.05-1.58)	<0.01
Age at diagnosis (year)	0.96 (0.96-0.96)	<0.0001	1.02 (1.02-1.03)	<0.0001	1.06 (1.05-1.06)	<0.0001	***	
HDL-c (mmol/L)*	-		0.61 (0.52-0.72)	<0.0001	-		-	
Total cholesterol (mmol/L)	0.91 (0.88-0.94)	<0.0001	-		-		***	
Triglycerides (mmol/L)*	1.21 (1.13-1.30)	<0.0001	-		1.13 (1.03-1.24)	<0.0001	-	
HbA1c (%)	**		1.02 (1.00-1.03)	0.03	1.06 (1.03-1.08)	<0.0001	1.22 (1.18-1.22)	<0.0001
BMI (Kg/m ²)	***		1.01(1.00-1.02)	0.0001	***		***	
SBP (mm of Hg)	-		***		1.01 (1.01-1.01)	<0.0001	1.01 (1.01-1.01)	<0.0001
DBP (mm of Hg)	-		***		-		-	
ALT (IU/L)*	-		0.77 (0.74-0.84)	<0.0001	0.81 (0.75-0.88)	<0.0001	0.90 (0.87-0.95)	<0.0001
Creatinine (mmol/L)*	1.01 (1.00-1.01)	<0.0001	1.42 (1.18-1.71)	0.0001	**		-	
Year of Diagnosis (Year)	0.97 (0.97-0.98)	<0.0001	0.96 (0.95-0.96)	<0.0001	0.96 (0.95-0.97)	<0.001	0.91 (0.89-0.93)	
Statin use	-		1.24 (1.12-1.36)	<0.0001	0.86 (0.79-0.95)	<0.0001	0.64 (0.50-0.83)	<0.0001
Antihypertensive medication	0.84 (0.78-0.91)	<0.0001	1.11 (1.03-1.14)	<0.01	0.76 (0.70-0.82)	<0.0001	0.56 (0.46-0.68)	0.001

*Log transformed, **Stratified analysis, ***Spline function, - Nonsignificant effect

Supplementary Table 4: Performance of competing risk models, ROC AUC at 5 years follow up.

Model	ROC AUC (95% CI) 9 continuous clinical variables + age and sex+ drugs + year of T2D Diagnosis Internal validation	ROC AUC (95% CI) 9 continuous clinical variables+ age and sex+ drugs + year of T2D Diagnosis External validation	ROCAUC (95% CI) DDRTree Dimensions + age and sex	ROCAUC (95% CI) DDRTree Dimensions (Spline) + age and sex	ROCAUC (95% CI) 9 continuous clinical variables + DDRTree Dimensions + Age and Sex+ drugs + year of T2D Diagnosis
Insulin Initiation model	0.72 (0.71-0.73)	0.74 (0.71-0.77)	0.65 (0.64-0.67)	0.66 (0.64-0.67)	0.74 (0.72-0.75)
CKD Model	0.78 (0.77-0.80)	0.73 (0.70-0.76)	0.74 (0.73-0.76)	0.75 (0.73-0.76)	0.83 (0.82-0.85)
DR Model	0.72 (0.69-0.75)	--	0.58 (0.55-0.62)	0.60 (0.56-0.63)	0.72 (0.69-0.75)
MACE model	0.68 (0.66-0.69)	0.65 (0.62-0.68)	0.66 (0.65-0.68)	0.66 (0.65-0.68)	0.68 (0.66-0.69)

**drugs: statin and antihypertension drugs at the time of T2D diagnosis*

Supplementary Table 5: ICD codes used to identify MACE from SMR and GRO database in Tayside and Fife data.

ICD 10 / ICD 9 codes	
ICD 10 codes	I2000,I2001,I2002,I2009,I201,I208,I209,I21,I21.A1,I21.A9 ,I210,I2100,I2101,I2109,I211 ,I2110,I2111, I2119,I212 ,I2120,I2121,I213 ,I2130,I2139,I214,I2140,I219,I2190,I2191,I2199,I22 ,I229, I220,I2201, I221 ,I2210,I2211,I228 , I2280,I2281,I229,I2290,I2291,I23 ,I230 , I231 ,I232,I232 , I233 ,I234 , I238,I240,I241,I248,I249,I252,I25,I250,I251,I252 ,I253,I254 ,I255 ,I256 ,I258,I259,I46,I460,I461,I469,
ICD 9 codes	410,4101,4102,4103,4104,4105,4106,4107,4108,4109,411,4110,4111,4118,412,4297, 413,4130,4131,4139,4141,415,4150,4151
CABG_ICD10_OPCODES	K40,K401,K402,K403,K404,K408,K409,K41,K411,K412,K413,K414,K418,K419,K42,K421, K422,K423,K424,K428,K429,K43,K431,K432,K433,K434,K438,K439,K44,K441,K442,K448, K449,K45,K451,K452,K453,K454,K455,K456,K458,K459,K46,K461,K462,K463,K464,K465, K468,K469,K47,K471,K472,K473,K474,K475,K478,K479,K48,K481,K482,K483,K484,K488,K489
CABG_ICD9_OPCODES	304,3041,3042,3043,3044.
PCI_ICD10_OPCODES	K49,K491,K492,K493,K494,K498,K499,K50,K501,K502,K503,K504,K508,K509,K75,K751, K752,K753,K754,K758,K759.
PCI_ICD9_OPCODES	884,8841,8842,8843,8844.