Supplemental Table 1 Derived definition of metabolic disorders from the available data in PROUD

Reported disease phenotype in proud	Basis for definition (reference)	Column Variable for Derived Data definition	Data source	Constituent Variable	Column Variable for Additional derived data
Diabetes (DM)- self reported history (HX), treatment (TX) including medication name (MED) AND/OR Laboratory diagnosis (LB) in subset that consented to testing.	(17)	DM_HXTXLB Categorical (HXTX=1, LB=2, HXTXLB=3) DIABETES binary y/n	Questionnaire (medical, treatment and medication history)	DM_HX DM_TX DM_TXMED	DU_DM = duration of diabetes
			Metabolic substudy OH glucose =>125 mg/dL 2H glucose =>200 mg/dL	DM_LB (0H=1, 2 HR =2, 0,2 HR=3) DM_LB	DM _LB0HR fasting hyperglycemia DM_LB2HR postprandial hyperglycemia
Hypertension- self-reported history (HX), treatment (TX) including medication name (MED) AND/OR Baseline Systolic or Diastolic hypertension	(18)	D_HTN_HXBP Categorical (HTNHXTX=1, SYSBP=2, SYSBP+HXTX=3 DIASBP=4, DIASBP+HXTX=5 DIASBP+SYSBP=6) Hypertension binary y/n	Questionnaire (medical, treatment and medication history)	HTN_HX HTN_TX	DU_HTN = duration of hypertension
			Baseline blood pressure (systolic) (diastolic)	SYS_BP DIAS_BP	
Dyslipidemia self-reported history (HX), treatment (TX) of Cholesterol or Triglyceride disorder AND/OR Laboratory diagnosis (LB) in subset that consented to testing.	(18, 19)	Dyslipidemiahxtxlb (history or treatment of cholesterol or triglyceride disorder) dyslipidemia	Questionnaire (medical, treatment and medication history)	CHOL_HX CHOL_TX TRG_HX TDG_TX	DU_DYSLIPIDEMIA
			Metabolic substudy (n=3845) Total cholesterol> =200 mg/dL HDL <50 females and <40 males LDL=>130 mg/dL	D_ABNLIPIDLB (number of abnormal tests 0-6) D_ABNLIPIDLB binary y/n	D_CHOLLB (1918) D_TRGLB (1589) D_LOHDLLBGENDER (1350) D_LDLLB (1775) Other D_non_H

			Non-HDL=> 150 triglycerides =>299 mg/dL		DLcLB (565) D_VLDL LB (738)
Obesity Baseline anthropometrics	(20)	D_RAWCALC_BMI METSYNDOBESE BMI>= 30	RAW_BM Provided in database		CALC_BMI Derived from data
metabolic syndrome	(21)	D_metsyn Binary yes/no	Composite of anthropometrics, questionnaire and metabolic tests by history or random testing WAIST >94 cm males, >90 females DIABETES HYPERTENSION CHOLHXTXLB TRG HXTXLB HDLHXTXLB		
Osteoporosis	(22)	D_penia/porosis osteoporosis	Questionnaire (medical, treatment and medication history)	POROSIS_HXTX PENIA_HXTX	DU_OSTEOPOROSIS
Uric acid disorders		URIC_HX	Questionnaire (medical, treatment and medication history)	URIC_HX URIC_TX	DU_URIC

Supplemental Table 2 Derived definition of chronic noncommunicable disorders from the available data in proud The presence of these conditions was defined by documentation of one or more of these conditions in the patient questionnaire or their reported surgical and other medical diagnoses. The original terms were translated into English from Spanish, and for CVD, grouped in accordance with major ICD10 groupings or MACE terms

Phenotype	Definition (and reported terms)	Database Source	(Variable name)
Cardiovascular Disease (CVD)	Patient reported CVD: Coronary Myocardial Infarct Stroke	Clinic record	Coronary_HX MI_HX stroke _HX
	Surgical or medical diagnosis following ICD 10 major groupings: ischemic, cerebrovascular, hypertensive large vessel or peripheral vascular, other (inclusive of valvular, rhythm, myopathy etc)	Clinic record + Recorded Diagnosis	CVD_termsrgry CVD_otrosenfer N=1485 had no entries in any of the disease columns except fractures and could be missing or presumed to have no history of other illness
	Categorized according to 5 component MACE: MI, Stroke, Angina, Heart Failure, Coronary revascularization of revascularization in a subject with any of the above CVD diagnoses, history of surviving previous sudden cardiac death	Clinic record + Recorded Diagnosis	DERIVED D_CVD_HXMACE
Cancer	Detailed text for types of malignancy	Clinic record + Recorded Diagnosis@	CAN_HX
Dementia	Alzheimer's disease in questionnaire	Clinic record + Recorded Diagnosis	ALZH_HX
Respiratory Disease	asthma plus COPD (Chronic Bronchitis)	Clinic record + Recorded Diagnosis	ASMA_HX LUNG_DX
Liver Disease	Hepatitis, viral and unspecified, Fatty liver, cirrhosis, liver failure, transplantation	Recorded Diagnosis	LIVER_HX
Kidney Disease	Nephrolithiasis, nephritis, nephropathy, renal insufficiency, renal failure, nephrectomy, transplantation, various	Recorded Diagnosis	KIDNEY_DX
Tuberculosis	Patient reported diagnosis	Clinic record	TBC_HX
Skin Disease			SKIN_HX
Fracture			FRACTURE_HX
HIV			HIV_HX

*28 subjects with Coronary HX had no MI or Stroke HX nor a recorded diagnosis

+138 subjects with a recorded diagnosis did not report a history of MI or Stroke (includes angina, heart failure, other)

@CIRURGIAS (67.3% [n=8046] of volunteers report surgical procedures and dates of procedures in a surgical history) and OTROS ENFERMES (42.5% [n=5084] of volunteers report other medical conditions, including food and drug allergies in the medical history).

Supplemental Table 3 Screening RSF model comparison (TOP) by missing imputation (BOTTOM), and final variable categories incorporated into PS weighting and the final Cox regression model.

TOP — Screening Random Survival Forest (Females w/ diabetes mellitus), Hyperparameter Tuning, Variable Importance Ranking

Variable Categories	model with no missing imputation, number of trees =1000, splitting rule= logrank	model with missing imputation, number of trees = 1000, splitting rule = logrank	model with no missing imputation, # trees = 1000, splitting rule = logrank, # random split points to split a node = 5	model with no missing imputation, # trees = 1000, splitting rule = logrank, # random split points to split a node =10	model with no missing imputation, number of trees is 1500, splitting rule is logrank	model with no missing imputation, number of trees is 800, splitting rule is logrank
	names.diabetes_imprank.	names.diabetes_imprank_im	names.diabetes_imprank_missing	names.diabetes_imprank_missin	names.diabetes_imprank	names.diabetes_imprank_800
Reproductive	NU_LVBRTH	D_RAWCALC._BMI	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH
Anthropometric, Demographic, Vital signs	D_RAWCALC._BMI	NU_LVBRTH	D_RAWCALC._BMI	D_RAWCALC._BMI	D_RAWCALC._BMI	D_RAWCALC._BMI
Diabetes and Related variables	WEIGHT_kg	DU_DIABETES	max.age.mother	WEIGHT_kg	WEIGHT_kg	WEIGHT_kg
Other metabolic disorders	max.age.mother	WEIGHT_kg	WEIGHT_kg	max.age.mother	max.age.mother	AGECHILD1
Cancer and major organ disease (CV, liver, renal)	AGECHILD1	AGECHILD1	WHO_BMI_cat	AGECHILD1	AGECHILD1	DU_DIABETES
Diet, Exercise and Social Habits	WAIST	max.age.mother	DU_DIABETES	WAIST	WAIST	WAIST
Communicable disease (TB, HIV)	DU_DIABETES	WAIST	AGECHILD1	DU_DIABETES	DU_DIABETES	max.age.mother
Year recruited	HEIGHT_cm	AGES	WAIST	HEIGHT_cm	AGES	HEIGHT_cm
	NU_PREG	NU_PREG	AGES	NU_PREG	HEIGHT_cm	NU_PREG
	AGES	HIP	NU_PREG	AGES	NU_PREG	AGES
	WHO_BMI_cat	HEIGHT_cm	DM_START	WHO_BMI_cat	WHO_BMI_cat	WHO_BMI_cat
	SYSTOLIC_bp	DM_START	HEIGHT_cm	SYSTOLIC_bp	DM_START	F_AGEMNRCH
	DM_START	WHO_BMI_cat	SYSTOLIC_bp	DM_START	SYSTOLIC_bp	HIP
	F_AGEMNRCH	SYSTOLIC_bp	HIP	F_AGEMNRCH	HIP	SYSTOLIC_bp
	HIP	F_AGEMNRCH	F_AGEMNRCH	HIP	F_AGEMNRCH	DM_START
	ALCO_WEEKLY	year_cat	ALCO_WEEKLY	ALCO_WEEKLY	ALCO_WEEKLY	ALCO_WEEKLY
	waist.hip.ratio	waist.hip.ratio	DU_HYPERTENSION	DIASTOLIC_BP	DIASTOLIC_BP	DIASTOLIC_BP
	DIASTOLIC_BP	NU_.ABORTNS	METABOLIC.OVERLAP	DU_HYPERTENSION	waist.hip.ratio	DU_HYPERTENSION
	DU_HYPERTENSION	ALCO_WEEKLY	D_CVD_NOHTN_BI	METABOLIC.OVERLAP	DU_HYPERTENSION	waist.hip.ratio
	METABOLIC.OVERLAP	LACTATION..MONTHS.	CAN_HX	LACTATION..MONTHS.	METABOLIC.OVERLAP	D_CVD_NOHTN_BI
	LACTATION..MONTHS.	DU_HYPERTENSION	SMOKE_ACTIVE	CAN_HX	LACTATION..MONTH	CAN_HX
	CAN_HX	CAN_HX	DIASTOLIC_BP	PULSE	CAN_HX	METABOLIC.OVERLAP
	PULSE	METABOLIC.OVERLAP	NU_.ABORTNS	NUM_SMOKEYRS	NUM_SMOKEYRS	NUM_SMOKEYRS
	NUM_SMOKEYRS	HYPERTENSIVECVD	PULSE	NU_.ABORTNS	PULSE	PULSE
	NU_.ABORTNS	D_CVD_NOHTN_BI	NUM_MILKCUPS_DAY	D_CVD_NOHTN_BI	SMOKE_ACTIVE	NU_.ABORTNS
	D_CVD_NOHTN_BI	SMOKE_ACTIVE	NUM_SMOKEYRS	SMOKE_ACTIVE	NU_.ABORTNS	ISCHEMIC.CVD
	SMOKE_ACTIVE	ISCHEMIC.CVD	BASELINE_KIDNEY_DISEASE	ISCHEMIC.CVD	NUM_MILKCUPS_DA	SMOKE_ACTIVE
	ISCHEMIC.CVD	NUM_COFFEECUPS	METSYNDOBESE	D_FHX_DM	ISCHEMIC.CVD	D_FHX_DM
	D_FHX_DM	D_NUMABNLIPIDLB	FRUIT	NUM_COFFEECUPS	D_FHX_DM	year_cat
	NUM_COFFEECUPS	DU_DYSLIPIDEMIA	D_FHX_DM	NUM_MILKCUPS_DAY	METSYNDOBESE	FRUIT
	NUM_MILKCUPS_DAY	BASELINE_LIVER.DISEAS	ISCHEMIC.CVD	DU_DYSLIPIDEMIA	FRUIT	DU_CHOLHX
	DU_DYSLIPIDEMIA	DU_OSTEOPOROSIS	METSYNDOBESE	METSYNDOBESE	BASELINE_KIDNEY_I	DU_OSTEOPOROSIS
	METSYNDOBESE	DM_TXINSULIN	NUM_COFFEECUPS	DU_OSTEOPOROSIS	HYPERTENSIVECVD	METSYNDOBESE
	DU_OSTEOPOROSIS	D_DYSLIPIDEMIALB	DU_DYSLIPIDEMIA	FRUIT	OSTEOPOROSIS	BASELINE_KIDNEY_DISEASE
	FRUIT	D_FHX_DM	DU_OSTEOPOROSIS	DM_TXINSULIN	DU_OSTEOPOROSIS	NUM_COFFEECUPS
	DM_TXINSULIN	OSTEOPOROSIS_TX	DU_DYSLIPIDEMIA	ASMA	DU_OSTEOPOROSIS	NUM_MILKCUPS_DAY
	ASMA	DU_CHOLHX	CVA_CVD	BASELINE_KIDNEY_DISEASE	BASELINE_LIVER.DISI	HYPERTENSIVECVD
	BASELINE_KIDNEY_DISEA	BASELINE_KIDNEY_DISE	OSTEOPOROSIS	BASELINE_LIVER.DISEASE	ASMA	D_CVD_HX_TXT
	BASELINE_LIVER.DISEASE	OSTEOPOROSIS_TX	BASELINE_LIVER.DISEASE	HYPERTENSIVECVD	OSTEOPOROSIS_TX	DU_DYSLIPIDEMIA
	HYPERTENSIVECVD	DU_CHOLHX	OSTEOPOROSIS_TX	D_CVD_HX_TXT	year_cat	DM_TXINSULIN
	D_CVD_HX_TXT	METSYNDOBESE	DM_TXINSULIN	year_cat	DYSLIPIDEMIA	OSTEOPOROSIS_TX
	year_cat	NUM_MILKCUPS_DAY	ASMA	OSTEOPOROSIS_TX	NUM_COFFEECUPS	D_FHX_TRG
	OSTEOPOROSIS_TX	OSTEOPOROSIS	D_FHX_TRG	D_FHX_TRG	DYSLIPIDEMIA	D_CVD_HXMACE
	D_FHX_TRG	BASELINE_LUNG.DISEAS	D_NUMABNLIPIDLB	D_NUMABNLIPIDLB	DM_TXINSULIN	BASELINE_LIVER.DISEASE
	D_NUMABNLIPIDLB	D_CVD_HXMACE	DU_CHOLHX	DU_CHOLHX	D_FHX_TRG	OSTEOPOROSIS
	DU_CHOLHX	DYSLIPIDEMIA	OSTEOPOROSIS	OSTEOPOROSIS	CVA_CVD	D_ALCOHX
	OSTEOPOROSIS	TBC	D_CVD_HXMACE	D_CVD_HXMACE	D_FHX_TRG	CVA_CVD
	D_CVD_HXMACE	DM_TXSULFO	HYPERTENSIVECVD	DYSLIPIDEMIA	D_DYSLIPIDEMIALB	D_FHX_CA
	DYSLIPIDEMIA	MAR_STAT	DYSLIPIDEMIA	CVA_CVD		DYSLIPIDEMIA
	CVA_CVD		D_HEALTHBHVIOR			
among the top 50, common variable selected	model 1 vs model 2	model1 vs model3	model1 vs model4	model1 vs model5	model1 vs model6	
	45	49	50	49	48	

Category representation in final propensity score model / Multivariable Regression

Category representation in final propensity score model	Multivariable Regression
Age	Osteoporosis
Year of recruitment‡	Active smoking
Reproductive lifespan*	Race
Number of deliveries	Kidney disease
Duration of diabetes	
WHO BMI categories	
Waist Hip ratio	
History of cigarette smoking	
Hypercholesterolemia	
Hypertension	
Cancer	
Ischemic CVD	

*age at menopause - age at menarche

BOTTOM — model with multiple imputation: multiple imputation by chained equation

(model with no missing imputation, number of trees is 1000, splitting rule is)

#	mice1 (names.imprank_1000mice.)	mice2 (names.imprank_1000mice..1)	mice3 (names.imprank_1000mice..2)	mice4 (names.imprank_1000mi)	mice5 (names.imprank_1000mice..4)
1	D_RAWCALC._BMI	D_RAWCALC._BMI	D_RAWCALC._BMI	D_RAWCALC._BMI	D_RAWCALC._BMI
2	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH
3	DU_DIABETES	WEIGHT_kg	DU_DIABETES	DU_DIABETES	WEIGHT_kg
4	WEIGHT_kg	DU_DIABETES	max.age.mother	WEIGHT_kg	DU_DIABETES
5	max.age.mother	AGECHILD1	WEIGHT_kg	AGECHILD1	max.age.mother
6	AGECHILD1	max.age.mother	AGECHILD1	max.age.mother	AGECHILD1
7	WAIST	WAIST	WAIST	WAIST	WAIST
8	AGES	NU_PREG	AGES	NU_PREG	NU_PREG
9	NU_PREG	DM_START	NU_PREG	AGES	DM_START
10	DM_START	AGES	DM_START	DM_START	WHO_BMI_cat
11	HIP	HIP	WHO_BMI_cat	WHO_BMI_cat	HIP
12	WHO_BMI_cat	WHO_BMI_cat	HIP	HIP	WHO_BMI_cat
13	HEIGHT_cm	HEIGHT_cm	HEIGHT_cm	HEIGHT_cm	HEIGHT_cm
14	SYSTOLIC_bp	SYSTOLIC_bp	SYSTOLIC_bp	SYSTOLIC_bp	SYSTOLIC_bp
15	DIASTOLIC_BP	F_AGEMNRCH	DIASTOLIC_BP	F_AGEMNRCH	DIASTOLIC_BP
16	year_cat	DIASTOLIC_BP	F_AGEMNRCH	DIASTOLIC_BP	year_cat
17	F_AGEMNRCH	NU_.ABORTNS	ALCO_WEEKLY	year_cat	NU_.ABORTNS
18	NU_.ABORTNS	year_cat	year_cat	year_cat	waist.hip.ratio
19	waist.hip.ratio	waist.hip.ratio	NU_.ABORTNS	DU_HYPERTENSION	PULSE
20	ALCO_WEEKLY	DU_HYPERTENSION	DU_HYPERTENSION	CAN_HX	F_AGEMNRCH
21	DU_HYPERTENSION	CAN_HX	LACTATION..MONTHS.	LACTATION..MONTH	LACTATION..MONTHS.
22	CAN_HX	ALCO_WEEKLY	PULSE	ALCO_WEEKLY	DU_HYPERTENSION
23	PULSE	LACTATION..MONTHS.	CAN_HX	waist.hip.ratio	ALCO_WEEKLY
24	LACTATION..MONTHS.	PULSE	waist.hip.ratio	METABOLIC.OVERLA	METABOLIC.OVERLAP
25	METABOLIC.OVERLAP	METABOLIC.OVERLAP	METABOLIC.OVERLAP	PULSE	CAN_HX
26	HYPERTENSIVECVD	NUM_COFFEECUPS	HYPERTENSIVECVD	HYPERTENSIVECVD	ISCHEMIC.CVD
27	ISCHEMIC.CVD	ISCHEMIC.CVD	ISCHEMIC.CVD	DU_DYSLIPIDEMIA	D_CVD_NOHTN_BI
28	SMOKE_ACTIVE	D_CVD_NOHTN_BI	D_CVD_NOHTN_BI	ISCHEMIC.CVD	NUM_COFFEECUPS
29	NUM_COFFEECUPS	HYPERTENSIVECVD	SMOKE_ACTIVE	NUM_COFFEECUPS	HYPERTENSIVECVD
30	D_CVD_NOHTN_BI	DU_DYSLIPIDEMIA	NUM_COFFEECUPS	SMOKE_ACTIVE	SMOKE_ACTIVE
31	DU_DYSLIPIDEMIA	SMOKE_ACTIVE	NUM_SMOKEYRS	D_CVD_NOHTN_BI	DU_DYSLIPIDEMIA
32	DU_OSTEOPOROSIS	DU_OSTEOPOROSIS	DU_DYSLIPIDEMIA	D_NUMABNLIPIDLB	DU_OSTEOPOROSIS
33	DM_TXINSULIN	D_DYSLIPIDEMIALB	DU_OSTEOPOROSIS	DM_TXINSULIN	NUM_SMOKEYRS
34	BASELINE_LIVER.DISEAS	D_NUMABNLIPIDLB	D_DYSLIPIDEMIALB	NUM_SMOKEYRS	D_NUMABNLIPIDLB
35	D_FHX_DM	NUM_MILKCUPS_DAY	DM_TXINSULIN	D_DYSLIPIDEMIALB	DM_TXINSULIN
36	OSTEOPOROSIS_TX	OSTEOPOROSIS_TX	METSYNDOBESE	METSYNDOBESE	BASELINE_LIVER.DISEASE
37	D_DYSLIPIDEMIALB	DM_TXINSULIN	BASELINE_LIVER.DISEASE	DU_OSTEOPOROSIS	OSTEOPOROSIS_TX
38	METSYNDOBESE	D_FHX_DM	NUM_MILKCUPS_DAY	BASELINE_LIVER.DISI	D_DYSLIPIDEMIALB
39	NUM_SMOKEYRS	BASELINE_LIVER.DISEASE	OSTEOPOROSIS_TX	NUM_MILKCUPS_DA'	D_FHX_DM
40	D_NUMABNLIPIDLB	METSYNDOBESE	DU_CHOLHX	DU_CHOLHX	METSYNDOBESE
41	NUM_MILKCUPS_DAY	BASELINE_KIDNEY_DISEASE	D_FHX_DM	OSTEOPOROSIS_TX	NUM_MILKCUPS_DAY
42	BASELINE_KIDNEY_DISE	NUM_SMOKEYRS	BASELINE_KIDNEY_DISEASE	METSYNDOBESE	DU_CHOLHX
43	OSTEOPOROSIS	DU_CHOLHX	DU_CHOLHX	BASELINE_KIDNEY_I	DYSLIPIDEMIA
44	DU_CHOLHX	OSTEOPOROSIS	DYSLIPIDEMIA	OSTEOPOROSIS	BASELINE_LUNG.DISEASE
45	DYSLIPIDEMIA	BASELINE_LUNG.DISEASE	D_CVD_HXMACE	TBC	FRUIT
46	D_CVD_HX_TXT	D_CVD_HXMACE	OSTEOPOROSIS	DYSLIPIDEMIA	ASMA
47	TBC	DYSLIPIDEMIA	ASMA	D_CVD_HXMACE	OSTEOPOROSIS
48	D_FHX_TRG	TBC	TBC	D_CVD_HX_TXT	OSTEOPOROSIS
49	FRUIT	D_FHX_TRG	Max.maternal.age	Max.maternal.age	MAR_STAT
50	D_CVD_HXMACE	DM_TXSULFO	DM_TXSULFO	FRUIT	TBC
among the top 50, common variable selected	model1 vs mice1	model1 vs mice2	model1 vs mice3	model1 vs mice4	model1 vs mice5
	48	47	46	47	46

Supplemental Table 4 RSF identified variables (bolded) in published ACM risk scores in all subjects with diabetes mellitus - Panel A and in published Cardiovascular mortality in general populations of female subjects (Panel B)

Risk Predictors	Citation	Population	Methods
Panel A. ACM in males and females with diabetes mellitus			
age male sex **baseline comorbidities** anemia, neutrophil-to-lymphocyte ratio, HDL, TC, TRG, HbA1c and FBG and their variability	2. Lee S, Zhou J, Leung KSK, Wu WKK, Wong WT, Liu T, et al. Development of a predictive risk model for all-cause mortality in patients with diabetes in Hong Kong. BMJ Open Diabetes Research and Care. 2021;9(1):e001950.	Hong Kong, retrospective cohort of 273, 678 subjects with type 2 diabetes mellitus from public in- and outpatient centers with data from diagnosis in 1/2009 to follow up to 12/2019	COX estimates of c-statistic improved with RSF and Deep survival- 5-fold cross validation
Age BMI comorbidities (congestive heart failure, metastatic cancer, end-stage liver disease) serum creatinine Note: urine albumin to-creatinine ratio (UACR) in 10-year mortality, generally males	3. Griffith KN, Prentice JC, Mohr DC, Conlin PR. Predicting 5- and 10-Year Mortality Risk in Older Adults With Diabetes. Diabetes Care. 2020;43(8):1724-31.	US retrospective cohort of older adults, >65 years in 2006, with type 2 diabetes mellitus with data from Veteran's Administration database 2004 to 2015 (baseline predictors from 2004 to 2005) 5-, 10-year mortality	LASSO for variable identification, regression with 10-fold cross validation
Age Smoking antihypertensive therapy insulin lipid lowering therapy BMI systolic blood pressure TC/ HDL ratio HBA1c; UACR; eGFR, Note: in females: **Duration of diabetes lipid-lowering treatment**	4. Wan EYF, Fong DYT, Fung CSC, Yu EYT, Chin WY, Chan AKC, et al. Prediction of five-year all-cause mortality in Chinese patients with type 2 diabetes mellitus - A population-based retrospective cohort study. J Diabetes Complications. 2017;31(6):939-44.	Hong Kong Retrospective cohort out of 132, 462 patients with type 2 diabetes mellitus recruited from primary care clinics in 2010 and followed for 5-year mortality.	Cox proportional hazards regression validation cohort
Age Sex current smoking insulin use educational attainment Coronary artery calcified plaque UACR	5. Raffield LM, et al. Diabetol Metab Syndr 7, 58 (2015). https://doi.org/10.1186/s13098-015-0055-y	US Diabetes Heart Study prospective cohort of 1022 European Americans with type 2 diabetes mellitus without advanced renal insufficiency, from 476 DHS families from 1998 - 2005 western North Carolina, mortality follow-up to 2013	Variables significant in univariate analyses selected in Cox proportional hazards models with sandwich-based variance estimation
Age insulin therapy antihypertensive therapy BMI diastolic blood pressure LDL, HDL, triglycerides, UACR	6. De Cosmo S, Copetti M, Lamacchia O, Fontana A, Massa M, Morini E, et al. Development and validation of a predicting model of all-cause mortality in patients with type 2 diabetes. Diabetes Care. 2013;36(9):2830-5.	Southern Italy prospective cohort of 679 + 936 White subjects with type 2 diabetes mellitus from 2 registries (recruited 2000 to 2005 and 2002-2008, followed for 7.4+ 2 and 4.5 +1.6 years, respectively) 2-, 4-year mortality	Reclassification for variable selection, training and validation across registries, Cox proportional hazards regression on pooled dataset

age male sex Caucasian race systolic and diastolic blood pressure hypertension medication Oral GLD insulin BMI heart failure heart disease aspirin, clopidogrel current smoking TIA, stoke history, GFR (ml/Minute) <60 HbA1c, HDL, LDL, Note: AGE, BMI, UACR, insulin therapy related to ACM	7. Wells BJ, Jain A, Arrigain S, Yu C, Rosenkrans WA, Jr., Kattan MW. Predicting 6-year mortality risk in patients with type 2 diabetes. Diabetes Care. 2008;31(12):2301-6.	US retrospective cohort of 33,067 patients with type 2 diabetes mellitus from Cleveland Clinic electronic health record from 1998 to 2006 treated with an oral glucose lowering drug 6-year mortality	Cox proportional hazards 10-fold cross validation incorporates treatment variable selection using reclassification measures
Age Male sex income diabetes duration BMI Smoking nephropathy, macrovascular disease Charlson index	8. McEwen LN, Kim C, Karter AJ, Haan MN, Ghosh D, Lantz PM, et al. Risk factors for mortality among patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care. 2007;30(7):1736-41.	US prospective study in type 2 diabetes mellitus managed care setting, medical record, and administrative data from 8,733 participants, 4-year mortality	Cox proportional hazards models
Age Sex BMI blood pressure CVD, albuminuria and CKD HbA1c Note: Type 1 diabetes	9. Eliasson B, Lyngfelt L, Strömblad SO, Franzén S, Eeg-Olofsson K. The significance of chronic kidney disease, heart failure and cardiovascular disease for mortality in type 1 diabetes: nationwide observational study. Sci Rep. 2022;12(1):17950.	Treated only with insulin and diagnosed with type 2 diabetes mellitus before 30 years of age (n = 36,303) Swedish National Diabetes Register - January 1, 2015 - December 31, 2017 - followed until December 31, 2018, mean follow-up 3.3 years, (119,800 patient years of observation and 1127 deaths for a crude overall mortality of 0.92% deaths/year	Cox regression analyses

Panel B. reproductive lifespan and risk for cardiovascular disease and mortality in females (regardless of diabetes status)

Shorter reproductive life span (RLS) is associated with a higher mortality risk (HR 1.10 to 1.21, varying by quartile)	13. Carlqvist E, Johnson L, Nilsson PM. Shorter reproductive life span is associated with increased cardiovascular risk and total mortality in Swedish women from an observational, population-based study. Maturitas. 2022;164:69-75.	Population based observational study in 12.101 middle-aged Swedish women (mean age 60 years with maximum 28-year follow-up to 2019	Cox regression models across quintiles of lifespan in years, with longest RLS as referent
≥40 reproductive years + favorable lifestyle (odds ratio, 0.28; 95% CI, 0.23–0.35) at lower ACM risk than with <40 reproductive years + unfavorable lifestyle	14. Li X, Wang S, Dunk M, Yang W, Qi X, Sun Z, et al. Association of life-course reproductive duration with mortality: a population-based twin cohort study. American Journal of Obstetrics and Gynecology. 2022;227(5):748.e1-.e13.	Population based observational study of 11,669 women from Swedish Twin Registry w/ questionnaire data linked to death registry, to 19 yrs follow-up	Generalized estimating model and conditional regression

Duration of Reproductive Life Span, Age at Menarche, and Age at Menopause and their association with Fatal MI or Fatal Stroke as part of CVD outcomes	15. Ley SH, Li Y, Tobias DK, Manson JE, Rosner B, Hu FB, et al. JAHA 6:11. 2 November 2017 doi:10.1161/JAHA.117. 006713	US 73, 814 prospective cohort in the Nurses' Health Study without baseline CVD, with biennial questionnaire follow-up to occurrence of CVD, death, or end of follow up on June 2022.	Multivariable time dependent Cox proportional hazards models found shorter duration of reproductive life span is associated with higher risk of composite endpoint

Supplemental Table 5 Logistic regression for all insulin treatment (PANEL A) and for insulin monotherapy (PANEL B) with and without novel RSF identified variables (year recruited, parity and reproductive lifespan)

A. Primary Analysis All Insulin	With Variables RSF			Without Variables RSF	
Baseline Variable	**Odds Ratio (95% CI)**	**Std error**	**P value**	**Odds Ratio (95% CI)**	**Std error**
Age >50	1.1(.6, 2.3)	0.4	0.7	.7 (.4, 1.2)	0.2
Diabetes duration	1.1(1.1, 1.2)	0.01	<.01	1.1 (1.1, 1.1)	0.01
Family history of diabetes	1.2 (.8, 1.8)	0.2	0.5	1.5 (1.0, 2.1)	0.3
WHO BMI	.96 (.9, 1.1)	0.06	0.5	.98 (.9, 1.1)	0.05
Waist Hip ratio	166 (7, 3905)	268	<.01	458 (28, 7380)	650
History of alcohol use	.66 (.2, 2.0)	0.4	0.4	.9 (.4, 2.2)	0.4
Smoking history	1.0 (.6, 1.6)	0.2	0.9	.9 (.6, 1.4)	0.2
Cardiovascular disease	1.4 (.7, 2.6)	0.4	0.3	1.1 (.6, 2)	0.3
Hypercholesterolemia	1.2 (.8, 1.8)	0.2	0.3	1.4 (.99, 2)	0.2
Hypertension	1.2 (.6, 2.5)	0.5	0.6	1.3 (.7, 2.6)	0.4
Cancer	.7 (.2, 2.2)	0.4	0.5	1.1 (.4, 2.9)	0.5
Parity	.9 (.9, 1.0)	0.04	0.1		
Reproductive lifespan	.99 (.97, 1.0)	0.01	0.2		
Year recruited					
2004	.3 (.06, 1.8)	0.2	0.2		
2005	.6 (.16, 2.4)	0.4	0.5		
2006	.7 (.2, 2.3)	0.4	0.5		
2007	.7 (.2, 2.3)	0.4	0.5		
2008	.5 (.2, 1.9)	0.3	0.3		
2009	.2 (.03, 1.0)	0.2	0.06		
2010	.5 (.13, 1.8)	0.3	0.3		
2011	2.1 (.7, 6.6)	1.2	0.2		
2012	1.4 (.4, 4.5)	0.8	0.5		
2013	2.5 (.7, 8.7)	1.6	0.1		
2014	2.5 (.7, 9.4)	1.7	0.2		
2015	1.4 (.2, 10.7)	1.4	0.7		
B. Insulin Monotherapy	With Variables RSF			Without Variables RSF	

Baseline Variable	Odds Ratio	Std error	P value	Odds Ratio	Std error
	(95% CI)			(95% CI)	
Age >50	1.2 (.5, 3.0)	0.6	0.7	.9 (.4, 1.9)	0.3
Diabetes duration	1.1 (1.1, 1.1)	0.02	<.01	1.1 (1.1, 1.1)	0.01
Family history of diabetes	1.1 (.7, 1.8)	0.3	0.7	1.5 (.9, 2.3)	0.3
WHO BMI	.93 (.8, 1.1)	0.07	0.3	.9 (.8, 1.1)	0.06
Waist Hip ratio	61 (2, 2192)	111	0.02	88 (3.4, 2276)	146
History of alcohol use	.6 (.1, 2.4)	0.4	0.4	.98 (.3, 2.8)	0.5
Smoking history	1.2 (.7, 2.1)	0.3	0.5	1.1 (.7, 1.9)	0.3
Cardiovascular disease	1.5 (.7, 3.2)	0.6	0.2	1.2 (.6, 2.5)	0.4
Hypercholesterolemia	1.0 (.6, 1.7)	0.3	0.9	1.2 (.7, 1.8)	0.3
Hypertension	1.0 (.4, 2.6)	0.5	0.9	1.1 (.5, 2.5)	0.4
Cancer	.7 (.2, 3.2)	0.5	0.6	1.0 (.3, 3.7)	0.7
Parity	.96 (.9, 1.0)	0.05	0.4		
Reproductive lifespan	.99 (.97, 1.0)	0.01	0.02		
Year recruited					
2004	.3 (.05, 2.3)	0.3	0.3		
2005	.7 (.1, 3.1)	0.5	0.6		
2006	.7 (.2, 3.0)	0.5	0.7		
2007	.7 (.2, 3.1)	0.5	0.7		
2008	.4 (.1, 1.8)	0.3	0.2		
2009	.1 (.01, 1.4)	0.2	0.1		
2010	.3 (.06, 1.6)	0.3	0.2		
2011	1.3 (.3, 5.0)	0.9	0.7		
2012	.9 (.2, 3.4)	0.6	0.8		
2013	1.8 (.4, 7.6)	1.3	0.4		
2014	1.3 (.2, 6.8)	1.1	0.7		
2015	.8 (.06, 10.5)	1	0.9		

Supplemental Table 6 Cox proportional model estimates for ACM for insulin (top) in all subjects on insulin: unweighted (left), PS weighted (middle) and PS weighted with RSF novel variables (right) and for other variables (bottom)

Insulin					
Analyses	**Unweighted**		**PS weighted**		**PS weighted with RSF**
Population	Subjects 1517		Subjects 2823		Subjects 2477
	Deaths 202		Deaths 322		Deaths 281
	Time at risk 4, 606, 501		Time at risk 7,795,073		Time at risk 7,326,513
Estimate	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Univariate	1.32 (.9, 2)	0.2	.83 (.5, 1.4)	0.5	.56 (.3, 1.0)	0.07
Multivariable	1.30 (.8, 2)	0.2	.90 (.5, 1.5)	0.6	.61 (.3, 1.2)	0.1
Other variables						
Osteoporosis	.90 (.5, 1.6)	0.7	.61 (.3, 1.3)	0.2	.49 (.2, 1.2)	0.1
Active Smoking	2.0 (1.1, 3.4)	0.01	4.7 (2.2, 10.2)	<.01	3.6 (1.8, 7.2)	<.01
Race	.89 (.7, 1.1)	0.3	1.0 (.7, 1.4)	0.9	1.0 (.7, 1.3)	0.8
Kidney Disease	.93 (.4, 2.3)	0.9	.76 (.2, 2.6)	0.7	.90 (.3, 2.8)	0.8

Supplemental Table 7 Cox proportional model estimates (SENSITIVITY ANALYSIS) for ACM for INSULIN Monotherapy (top) and for OTHER VARIABLES (bottom) in UNWEIGHTED (left), PS WEIGHTED (middle) and PS weighted with RSF novel variables (right) analyses

Insulin monotherapy						
Analyses	**Unweighted**		**PS weighted**		**PS weighted with RSF**	
Population	Subjects 1517		Subjects 2826		Subjects 2485	
	Deaths 202		Deaths 360		Deaths 312	
	Time at risk 4, 606, 501		Time at risk 7,986,607		Time at risk 7,397,680	
Estimate	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Univariate	1.50 (.9, 2.5)	0.1	1.06 (.5, 2.1)	0.9	.77 (.4, 1.6)	0.5
Multivariable	1.48 (.9, 2.5)	0.1	1.21 (.6, 2.5)	0.6	.85 (.4, 1.8)	0.7
Other variables						
Osteoporosis	.89 (.5, 1.5)	0.7	.37 (.1, 1.1)	0.07	.36 (.1, 1.1)	0.07
Active Smoking	1.97 (1.2, 3.3)	0.01	4.46 (1.7, 11.5)	<.01	3.64 (1.7, 8.0)	<.01
Race	.90 (.7, 1.1)	0.3	.98 (.6, 1.5)	0.9	.92 (.6, 1.4)	0.7
Kidney Disease	.91 (.4, 2.2)	0.8	.62 (.1, 3.0)	0.6	1.10 (.3, 3.9)	0.9