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

Reported disease phenotype in proud	Basis for definit ion (refere nce)	Column Variable for Derived Data definition	Data source	Constitue nt Variable	Column Variable for Additiona l 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	Questionnair e (medical, treatment and medication history) Metabolic substudy	DM_HX DM_TX DM_TXM ED DM_LB (0H=1, 2	DU_DM = duration of diabetes DM LB0HR
			OH glucose =>125 mg/dL 2H glucose =>200 mg/dL	HR =2, 0,2 HR=3) DM_LB	fasting hyperglyc emia DM_LB2 HR postprandi al hyperglyc emia
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)	Questionnair e (medical, treatment and medication history) Baseline	HTN_HX HTN_TX SYS BP	DU_HTN = duration of hypertensi on
		Hypertension binary y/n	blood pressure (systolic) (diastolic)	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	Questionnair e (medical, treatment and medication history)	CHOL_H X CHOL_T X TRG_HX TDG_TX	DU_DYS LIPIDEMI A
			Metabolic substudy (n=3845) Total cholesterol> =200 mg/dL	D_ABNLI PIDLB (number of abnormal tests 0-6)	D_CHOL LB (1918) D_TRGL B (1589) D_LOHD LLBGEN
			HDL <50 females and <40 males LDL=>130 mg/dL	D_ABNLI PIDLB binary y/n	DEK (1350) D_LDLL B (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_B MI Derived from data
metabolic syndrome	(21)	D_metsyn Binary yes/no	Composite of questionnaire and me history or random testin WAIST >94 cm males, DIABETES HYPERTENSION CHOLHXTXLB TRG HXTXLB HDLHXTXLB	anthropometrics, tabolic tests by g >90 females
Osteoporosis	(22)	D_penia/porosis osteoporosis	Questionnair POROS e (medical, _HXTX treatment PENIA and XTX medication history)	SIS DU_OST K EOPORO _H SIS
Uric acid disorders		URIC_HX	Questionnair URIC_] e (medical, URIC_' treatment and medication history)	HX DU_URIC TX

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

Phenot ype	Definition (and reported terms)	Database Source	(Variable name)
Cardio vascula r	Patient reported CVD: Coronary Myocardial Infarct Stroke	Clinic record	Coronary_HX MI_HX stroke _HX
(CVD)	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
Dement ia	Alzheimer's disease in questionnaire	Clinic record + Recorded Diagnosis	ALZH_HX
Respira tory 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
Tuberc ulosis	Patient reported diagnosis	Clinic	TBC_HX
Skin	r allont reported diagnosis	100014	SKIN_HX
Fractur			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.

SCREENING Random Survival Forest	model with no missing	model with missing	model with no missing	model with no missing	model with no	model with no missing	Category representation in	Multivariable
Females w/ diabetes mellitus	imputation, number of	imputation, number of	imputation, # trees = 1000,	imputation, # trees = 1000,	missing imputation,	imputation, number of	final propensity score model	Regression
Hyperparameter Tuning	trees =1000, splitting	trees = 1000, splitting	splitting rule = logrank, #	splitting rule = logrank, #	number of trees is	trees is 800, spliting		
Variable Importance Ranking	rule- logrank	rule – logrank	a node = 5	a node =10	is logrank	rule is logrank		
Variable Categories	names.diabetes_imprank.	names.diabetes_imprank_im	names.diabetes_imprank_missin	names.diabetes_imprank_missin	names.diabetes_imprank	names.diabetes_imprank_80	Age	Osteoporosis
Reproductive	NU_LVBRTH	D_RAWCALCBMI	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH	NU_LVBRTH	Year of recruitment‡ Repreductive lifespan‡	Active smoking
Diabetes and Related variables	WEIGHT_kg	DU_DIABETES	max.age.mother	WEIGHT_kg	WEIGHT_kg	WEIGHT_kg	Number of deliveries	Kidney disease
Other metabolic disorders	max.age.mother	WEIGHT_kg	WEIGHT_kg	max.age.mother	max.age.mother	AGECHILD1	Duration of diabetes WHO BMI extension	
Diet, Exercise and Social Habits	WAIST	max.age.mother	DU_DIABETES	WAIST	WAIST	WAIST	Waist Hip ratio	
Communicable disease (TB, HIV)	DU_DIABETES HEIGHT_om	WAIST	AGECHILD1 WAIST	DU_DIABETES HEIGHT om	DU_DIABETES	max.age.mother HEIGHT_om	History of cigarette smoking	
A FAI IFCIDILED	NU_PREG	NU_PREG	AGES	NU_PREG	HEIGHT_cm	NU_PREG	Hypertension	
	AGES WHO BML cat	HIP HEIGHT om	NU_PREG DM_START	AGES WHO BML cat	NU_PREG WHO BML cat	AGES WHO BML cat	Cancer Ischemic CVD	
	SYSTOLIC_bp	DM_START	HEIGHT_cm	SYSTOLIC_bp	DM_START	F_AGEMNRCH	Ischennic CVD	
	DM_START	WHO_BMI_cat SYSTOLIC_bp	SYSTOLIC_bp HIP	DM_START F_ACEMNRCH	SYSTOLIC_bp HIP	HIP SYSTOLIC bo		
	HIP	DIASTOLIC_BP	F_AGEMNRCH	HIP	F_AGEMNRCH	DM_START	*age at menopause - age at menarch	ie
	waist.hip.ratio	F_AGEMNRCH year_cat	waist.hip.ratio	waist.hip.ratio	DIASTOLIC_BP	DIASTOLIC_BP		
	DIASTOLIC_BP	waist.hip.ratio	DU_HYPERTENSION	DIASTOLIC_BP	waist.hip.ratio	DU_HYPERTENSION		
	METABOLIC.OVERLAP	ALCO_WEEKLY	D_CVD_NOHTN_BI	METABOLIC.OVERLAP	D_CVD_NOHTN_BI	LACTATIONMONTHS.		
	LACTATIONMONTHS.	LACTATIONMONTHS. PULSE	CAN_HX SMOKE_ACTIVE	LACTATIONMONTHS.	METABOLIC.OVERLA	D_CVD_NOHTN_BI		
-	PULSE	DU_HYPERTENSION	LACTATIONMONTHS.	PULSE	LACTATION. MONTH	METABOLIC.OVERLAP		
	NU_ABORTNS	METABOLIC.OVERLAP	NU_ABORTNS	NU_ABORTNS	PULSE	PULSE		
	D_CVD_NOHTN_BI	D CVD NOHTN BI	PULSE NUM MILKCUPS DAV	D_CVD_NOHTN_BI	SMOKE_ACTIVE	NUABORTNS ISCHEMIC CVD		
	ISCHEMIC.CVD	SMOKE_ACTIVE	NUM_SMOKEYRS	ISCHEMIC.CVD	NUM_MILKCUPS_DA	SMOKE_ACTIVE		
	D_FHX_DM NUM_COFFEECUPS	ISCHEMIC.CVD NUM_COFFEECUPS	BASELINE_KIDNEY_DISEASE METSYNDOBESE	D_FHX_DM NUM_COFFEECUPS	DU_DYSLIPIDEMIA ISCHEMIC.CVD	D_FHX_DM year_cat		
	NUM_MILKCUPS_DAY	D_NUMABNLIPIDLB	FRUIT	NUM_MILKCUPS_DAY	D_FHX_DM	FRUIT		
	METSYNDOBESE	BASELINE_LIVER.DISEAS	S_PHA_DM	METSYNDOBESE	FRUIT	DU_OSTEOPOROSIS		
	DU_OSTEOPOROSIS	DU_OSTEOPOROSIS	NUM_COFFEECUPS	DU_OSTEOPOROSIS	BASELINE_KIDNEY_I	METSYNDOBESE BASELINE KIDNEY DISE	ASE	
	DM_TXINSULIN	D_DYSLIPIDEMIALB	DU_DYSLIPIDEMIA	DM_TXINSULIN	OSTEOPOROSIS	NUM_COFFEECUPS		
	ASMA BASELINE KIDNEY DISE	NUM_SMOKEYRS	year_cat CVA_CVD	ASMA BASELINE_KIDNEY_DISEAS	DU_OSTEOPOROSIS EBASELINE_LIVER.DIS	NUM_MILKCUPS_DAY		
	BASELINE_LIVER.DISEAS	E OSTEOPOROSIS_TX	OSTEOPOROSIS	BASELINE_LIVER.DISEASE	D_CVD_HX_TXT	D_CVD_HX_TXT		
	D_CVD_HX_TXT	BASELINE_KIDNEY_DISE	OSTEOPOROSIS_TX	D_CVD_HX_TXT	OSTEOPOROSIS_TX	DM_TXINSULIN		
	year_cat OSTEOPOROSIS TX	METSYNDOBESE NUM MILKCUPS DAY	DM_TXINSULIN D CVD HX TXT	year_cat OSTEOPOROSIS TX	year_cat D CVD HXMACE	OSTEOPOROSIS_TX D FHX TRG		
	D_FHX_TRG	OSTEOPOROSIS	ASMA	D_FHX_TRG	NUM_COFFEECUPS	D_CVD_HXMACE	-	
	D_NUMABNLIPIDLB DU_CHOLHX	D_CVD_HXMACE	D_CHOLHX D_FHX_TRG	DU_CHOLHX	DU_CHOLHX DYSLIPIDEMIA	DASELINE_LIVER DISEAS. OSTEOPOROSIS	<u>E</u>	
	OSTEOPOROSIS	DYSLIPIDEMIA	D_CVD_HXMACE	OSTEOPOROSIS	DM_TXINSULIN	D_ALCOHX		
	DYSLIPIDEMIA	DM_TXSULFO	D_NUMABNLIPIDLB	DYSLIPIDEMIA	CVA_CVD	D_FHX_CA		
among the top 50, common variable selected	CVA CVD	MAR STAT	D HEALTHBHVIOR model1 vs model3	CVA CVD model1 vs model4	D DYSLIPIDEMIALB	DYSLIPIDEMIA modell vs model6		
anong the top so, common variable offected		model i va model 2	mootra to mootra	modell vs model4	modeli va modelo	incours to incours		
anong me top 50, common variable objecto		45	49	50	49	48		
model	model with no missing	45 model 1 vs model 2	49 del with multiple imputa	50 tion: multiple imputatio	n by chained equa	48 tion		
model	model with no missing imputation, number of trees is 1000 colities relation	45 mooth 2 45	del with multiple imputa	tion: multiple imputatio	n by chained equa	48 tion		
model	model with no missing imputation, number of trees is 1000, splitting rule is	micel names.imprank_1000mice.	del with multiple imputa mice2 names.imprank_1000mice1	tion: multiple imputatio mice3 names.imprank_1000mice2	n by chained equa mice4 names.imprank_1000mi	48 tion mice5 names.imprank_1000mice.4		
model	model with no missing imputation, number of trees is 1000, splitting rule is 1	micel micel names.imprank_1000mice. D_RAWCALC_BMI NU LVBRTH	del with multiple imputa mice2 names.imprank_1000mice.1 D_RAWCALC_BMI NU LVBRTH	mice3 names imprank_1000mice.2 D_RAWCALC_BMI NU_LVBRTH	mice4 mice4 names.imprank_1000mi D_RAWCALC_BMI NU LVBRTH	48 tion mice5 names.imprank_1000mice.4 D_RAWCALC_BMI NU LVBRTH		
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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 fem	ales 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.	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	2021;9(1):e001950. 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/s 13098-015-0055-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
AgeinsulintherapyantihypertensivetherapyBMIdiastolicbloodpressureLDL,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	Reclassificatio n for variable selection, training and validation across registries, Cox proportional hazards regression on pooled dataset

agemalesexCaucasianracesystolicanddiastolicbloodpressurehypertensionmedicationOralGLDinsulinBMIheartfailureheartdiseaseaspirin, clopidogrelcurrentsmoking TIA, stoke history,GFR(ml/Minute)<60HbA1c,HDL,LDL,Note:	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
AGE, BMI, UACR, insulin therapy related to ACM 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	US prospective study in type 2 diabetes mellitus managed care setting, medical record, and administrative data from 8,733 participants, 4-year mortality	measures Cox proportional hazards models
	patients with diabetes: the Translating Research Into Action for Diabetes (TRIAD) Study. Diabetes Care. 2007;30(7):1736-41.		
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 lifespa	an and risk for cardiovasc	ular disease and mortality in fem	ales (regardless
Shorter reproductive life span (RLS) is associated with a higher mortality risk (HR 1.10 to 1.21, varying by quartile)	of diabetes 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	Status) 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	15. Ley SH, Li Y,	US 73, 814 prospective cohort in	Multivariable
Life Span, Age at Menarche,	Tobias DK, Manson JE,	the Nurses' Health Study without	time dependent
and Age at Menopause and	Rosner B, Hu FB, et al.	baseline CVD, with biennial	Cox
their association with Fatal	JAHA 6:11. 2	questionnaire follow-up to	proportional
MI or Fatal Stroke as part of	November 2017	occurrence of CVD, death, or	hazards models
CVD outcomes	doi:10.1161/JAHA.117.	end of follow up on June 2022.	found shorter
	006713		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		Std error	P value	Odds Ratio		Std error
	(95% CI)				(95% CI)		
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	Р	Odds Ratio	Std
		error	value		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

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 7,98	86,607	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		

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