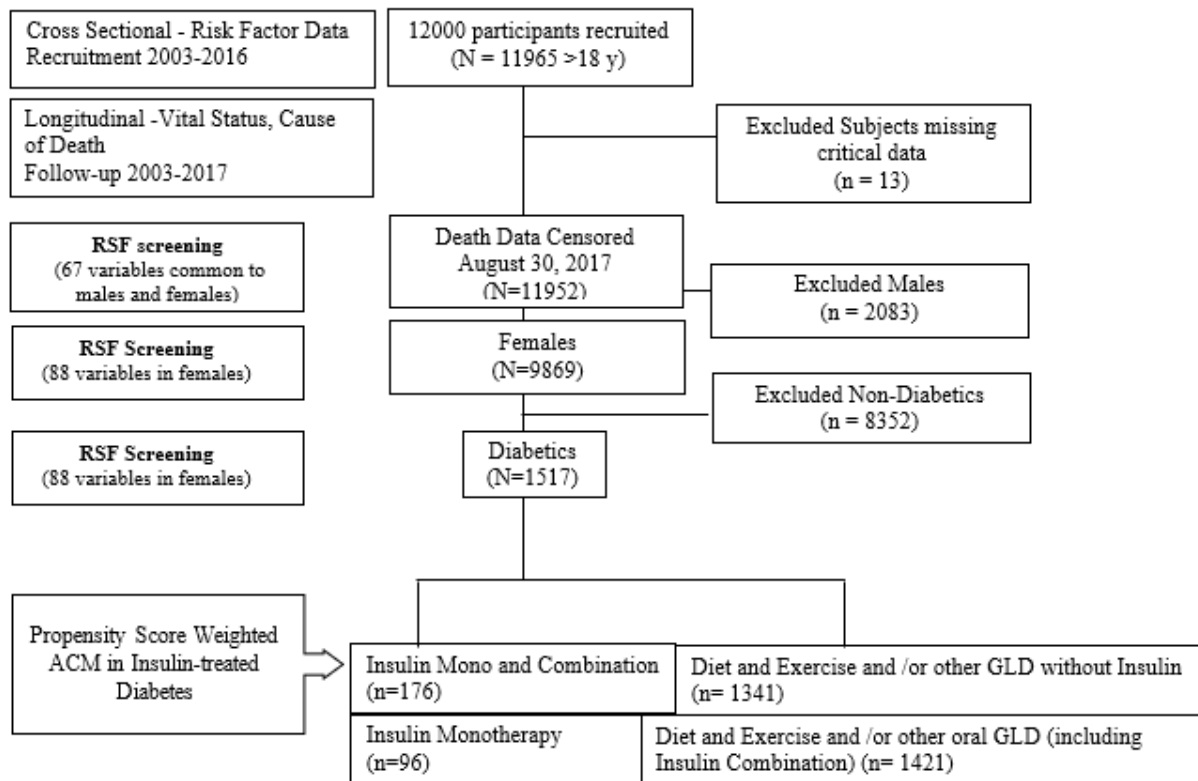
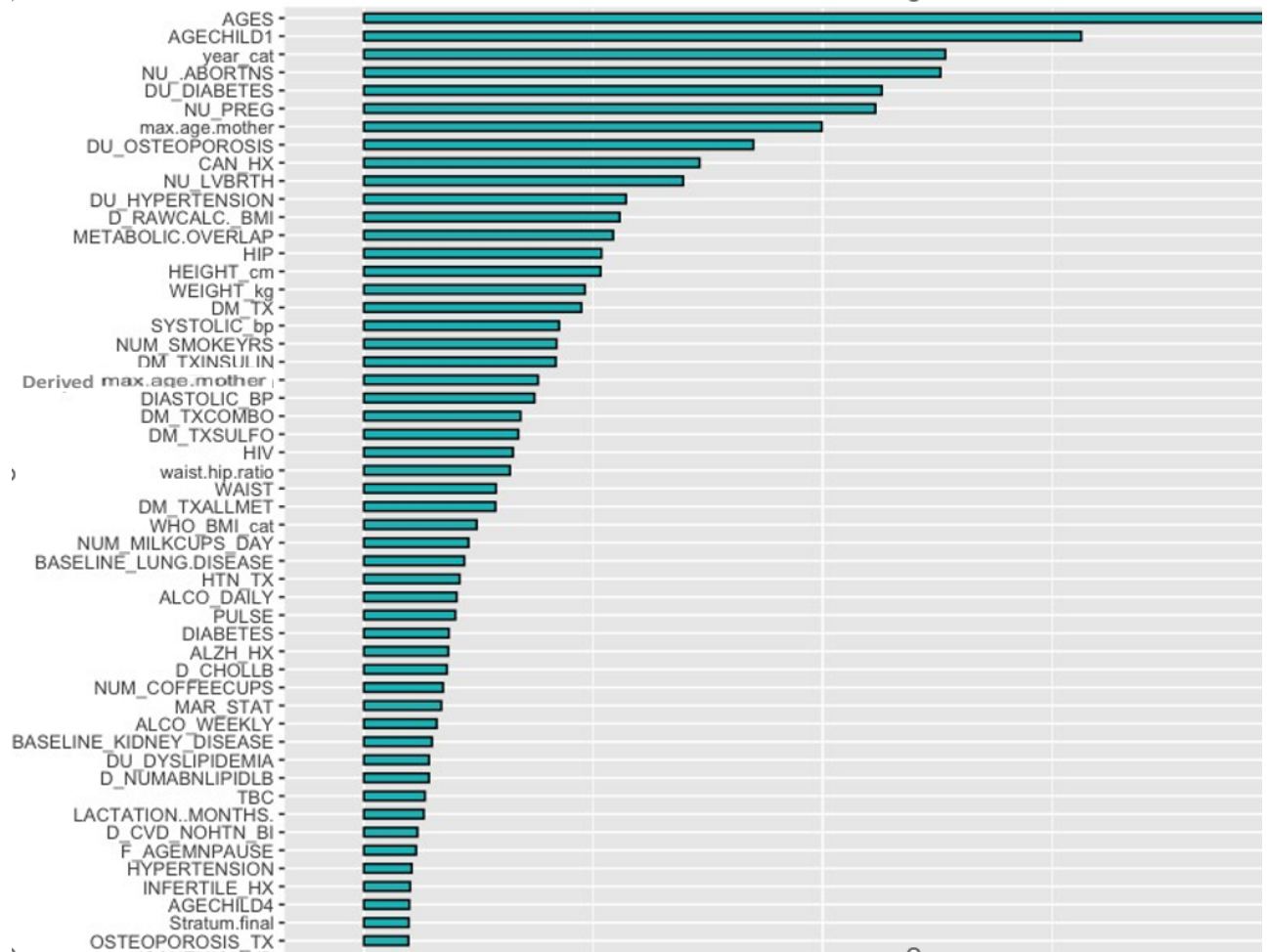
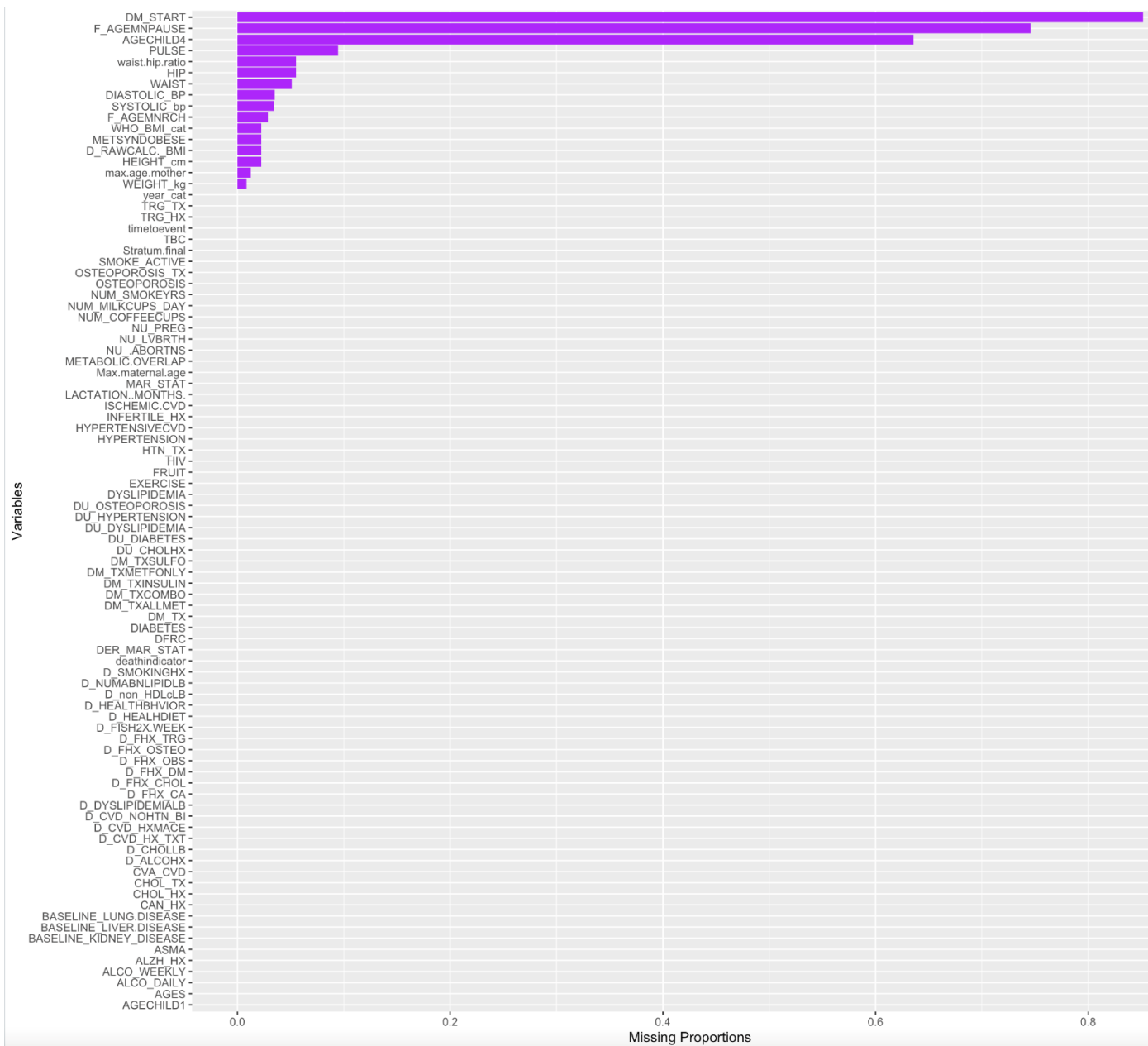


PROUD STUDY DESIGN

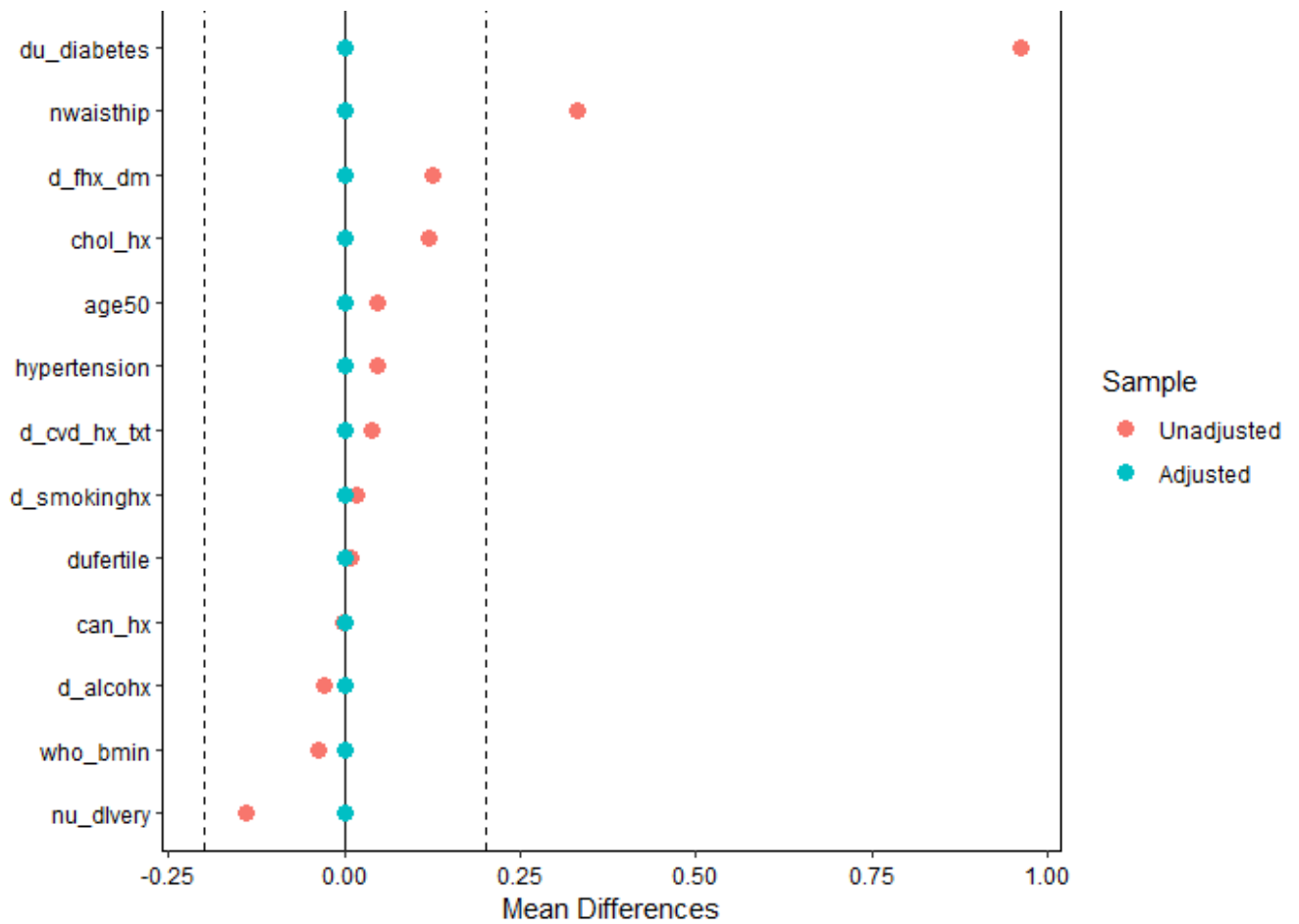


Supplemental Figure 1 Study design and flowchart for subjects enrolled in proud.





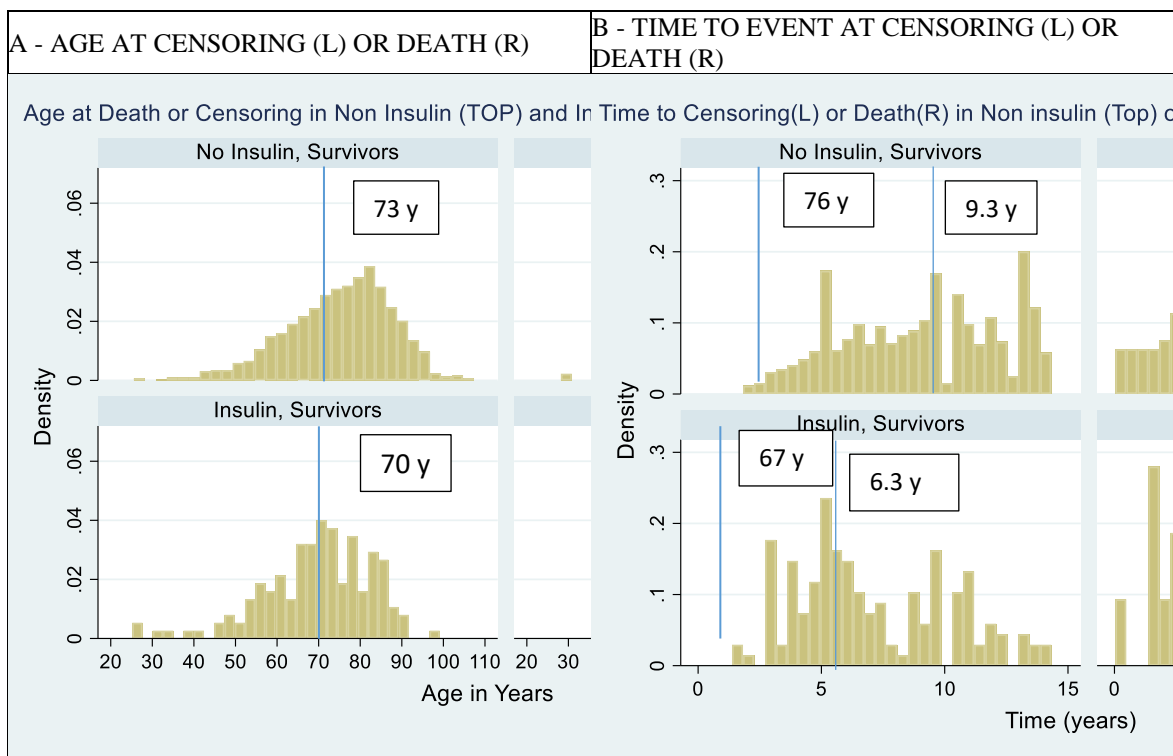
Supplemental Figure 2 RSF variables of importance (top) and evaluation of missing data and exclusion of variables with 50% missingness (bottom).



	Unweighted			p	SM D	PS Weighted		
	0	1				0	1	p
N	1182	151			113.1	113.1		
Smoking	278 (23.5)	38 (25.2)	0.729	0.03	28.4 (25.1)	28.4 (25.1)	1	<0.0 01
Duration of diabetes (y) (mean (SD))	6.62 (7.05)	14.26 (8.77)	<0.0 01	0.96 1	12.45 (10.11)	12.45 (7.89)	1	<0.0 01
Hypercholesterolemia	0.48 (0.50)	0.60 (0.49)	0.005	0.24 3	0.56 (0.50)	0.56 (0.50)	1	<0.0 01
Hypertension	1049 (88.7)	141 (93.4)	0.112	0.16 3	104.6 (92.5)	104.6 (92.5)	1	<0.0 01
Waist/hip ratio (mean (SD))"	0.88 (0.06)	0.90 (0.08)	<0.0 01	0.33	0.89 (0.06)	0.89 (0.06)	1	<0.0 01
Alcohol use	66 (5.6)	4 (2.6)	0.184	0.14 8	3.5 (3.1)	3.5 (3.1)	1	<0.0 01
Family history of diabetes	603 (51.0)	96 (63.6)	0.005	0.25 6	66.7 (59.0)	66.7 (59.0)	1	<0.0 01
WHO BMI category			0.17	0.25 7			1	<0.0 01
0	10 (0.8)	0 (0.0)			0.0 (0.0)	0.0 (0.0)		
1	282 (23.9)	37 (24.5)			27.3 (24.1)	27.3 (24.1)		
2	67 (5.7)	16 (10.6)			10.0 (8.8)	10.0 (8.8)		
3	23 (1.9)	2 (1.3)			1.5 (1.3)	1.5 (1.3)		
4	288 (24.4)	30 (19.9)			23.8 (21.0)	23.8 (21.0)		

5	500 (42.3)	63 (41.7)			48.3 (42.7)	48.3 (42.7)		
6	12 (1.0)	3 (2.0)			2.3 (2.0)	2.3 (2.0)		
Cancer	35 (3.0)	4 (2.6)	1	0.01	3.0 (2.7)	3.0 (2.7)	1	<0.001
Cardiovascular history	94 (8.0)	18 (11.9)	0.134	0.13	11.4 (10.1)	11.4 (10.1)	1	<0.001
Age >50 years	1009 (85.4)	136 (90.1)	0.15	0.14	100.3 (88.7)	100.3(88.7)	1	<0.001
Number of deliveries (mean SD))	4.85 (2.97)	4.46 (2.54)	0.128	0.14	4.48 (2.71)	4.48 (2.57)	1	<0.001
Duration of fertility (y)(mean SD))	46.18(12.64)	46.29(12.27)	0.919	0.00	46.25(12.56)	46.25(12.28)	1	<0.001

Supplemental Figure 3 Standard mean difference in covariates between the Insulin treated and untreated females cohorts in the diabetes PROUD substudy.²³

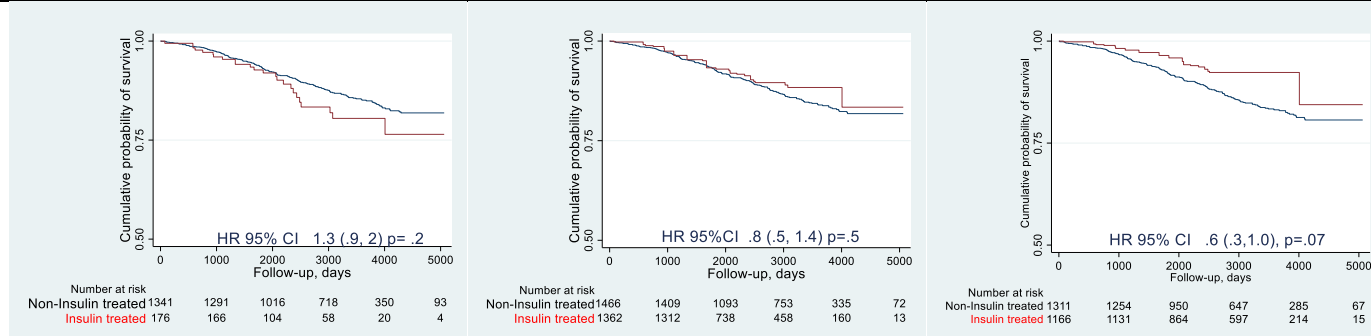


Supplemental Figure 4 Age (PANEL A) or Time to Event (PANEL B) in Insulin (BOTTOM) and Non-Insulin (TOP) treated females with diabetes mellitus in the proud study.

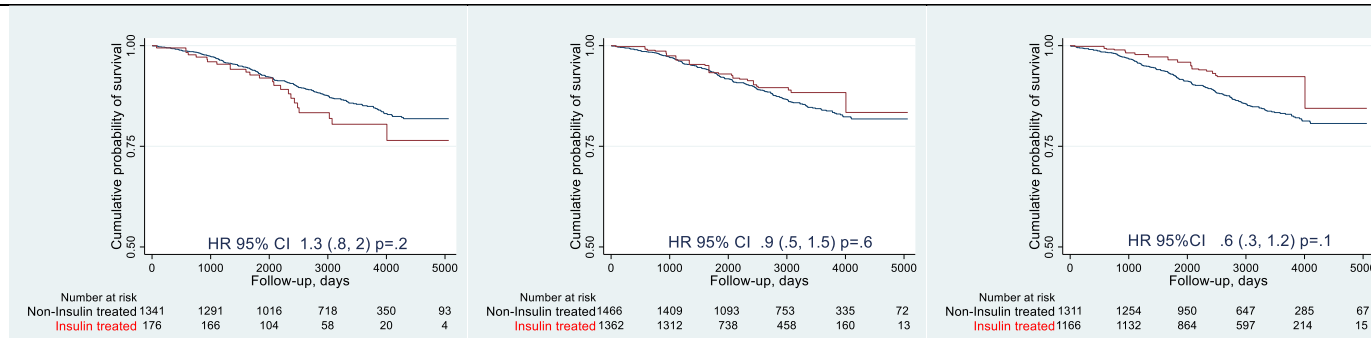
Kaplan Meier survival curves for all-cause mortality in females with diabetes mellitus

Unweighted	PS weighted	RSF enriched PS weighted
All insulin (monotherapy and combination)		
1517 observations 1517 subjects, 202 deaths 4,606,501 days at risk	1459 observations 2828 subjects, 322 deaths 7,795,073 days at risk	1309 observations 2477 subjects, 281 deaths 7,326,512 days at risk

Univariate



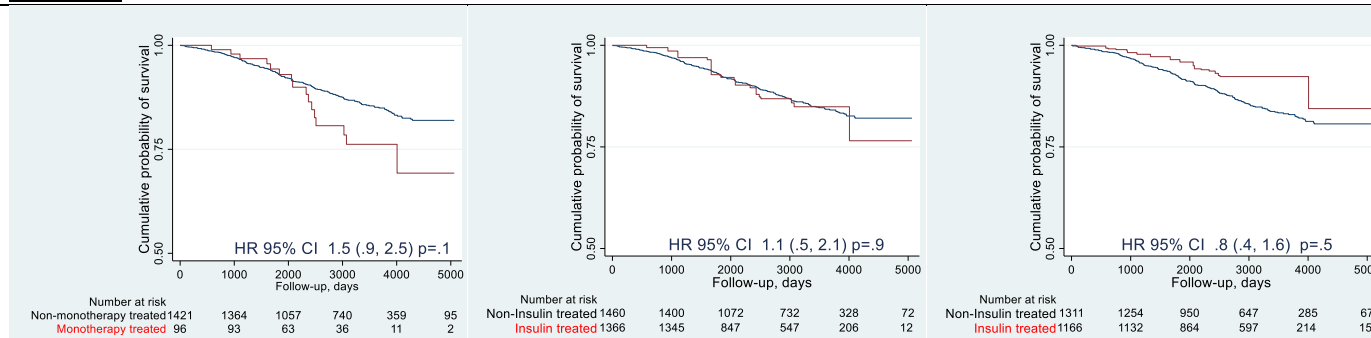
Multivariable



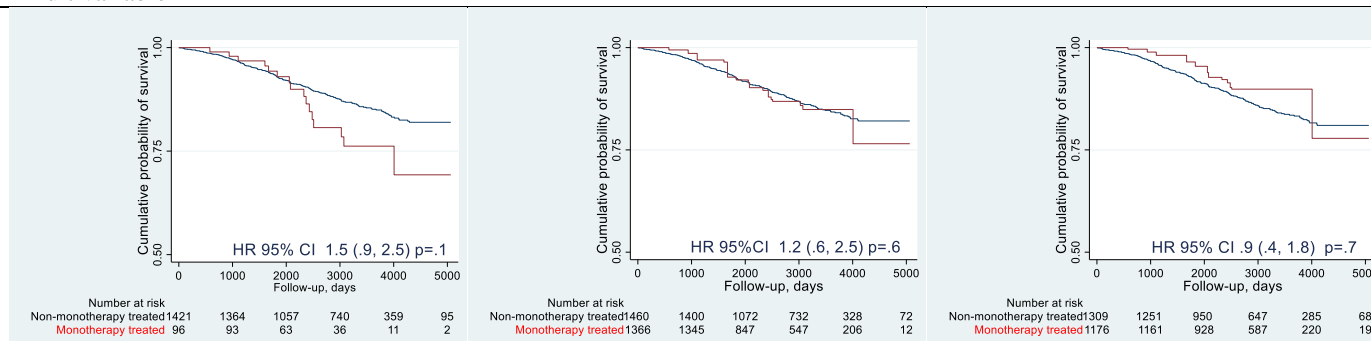
Sensitivity insulin monotherapy

1517 subjects, 202 deaths 4,606,501 days at risk	<u>Subjects 2826 Deaths 360</u> <u>Time at risk 7,986,607</u>	<u>Subjects 2485 Deaths 312</u> <u>Time at risk 7,397,680</u>
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Univariate



Multivariable



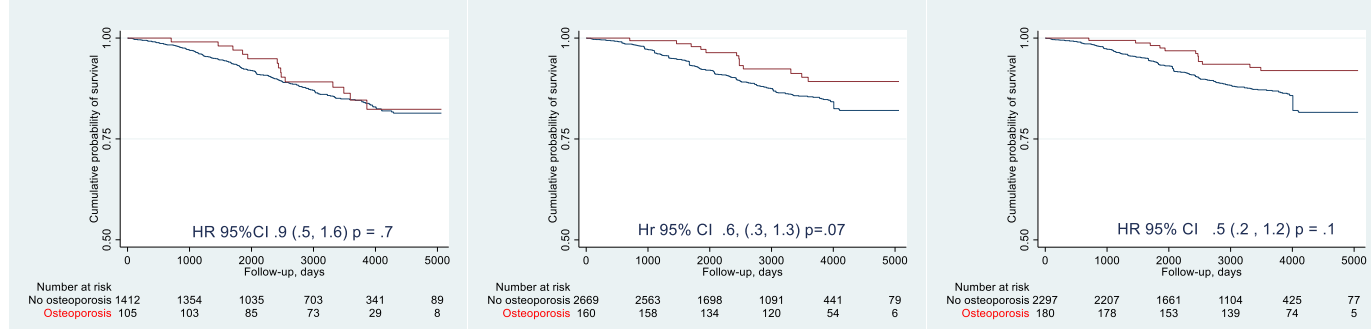
The cumulative probability of survival in the all insulin treated (red line) vs the no insulin group (blue line) for the monotherapy and combination insulin group (TOP panel, univariate and multivariable analyses).

Supplemental Figure 5 KM survival analysis for all subjects on insulin UNWEIGHTED (left), PS WEIGHTED (middle) and PS weighted with RSF novel variables (right) in subjects receiving Insulin (monotherapy and combination) vs. non-insulin treatment (Top) and as sensitivity analysis, in subjects receiving insulin monotherapy vs. comparator (bottom).

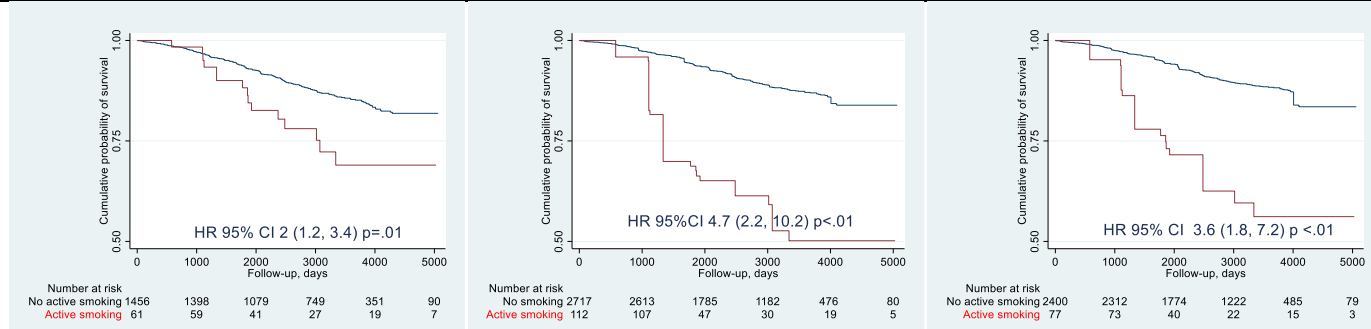
Kaplan Meier survival curves for all-cause mortality in females with diabetes mellitus

Unweighted	PS weighted	RSF enriched PS weighted
1517 observations 1517 subjects, 202 deaths 4,606,501 days at risk	1459 observations 2828 subjects, 322 deaths 7,795,073 days at risk	1309 observations 2477 subjects, 281 deaths 7,326,512 days at risk

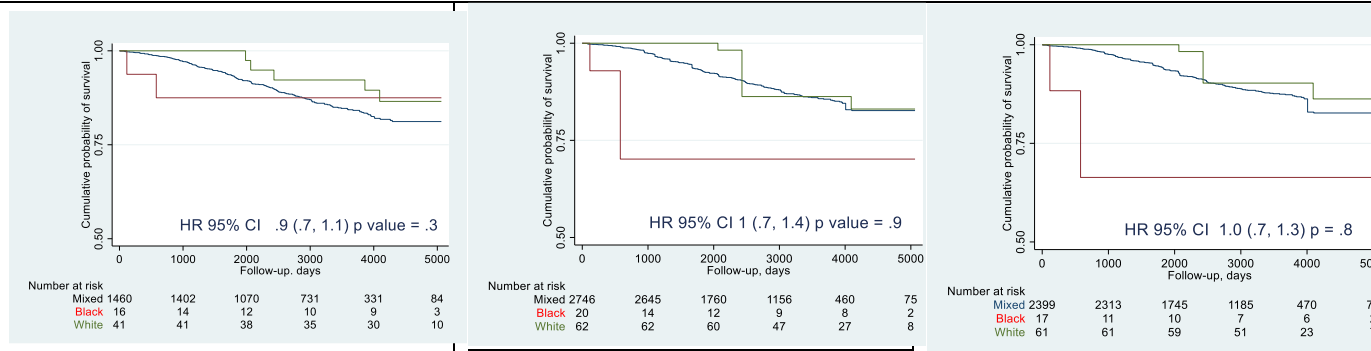
Osteoporosis



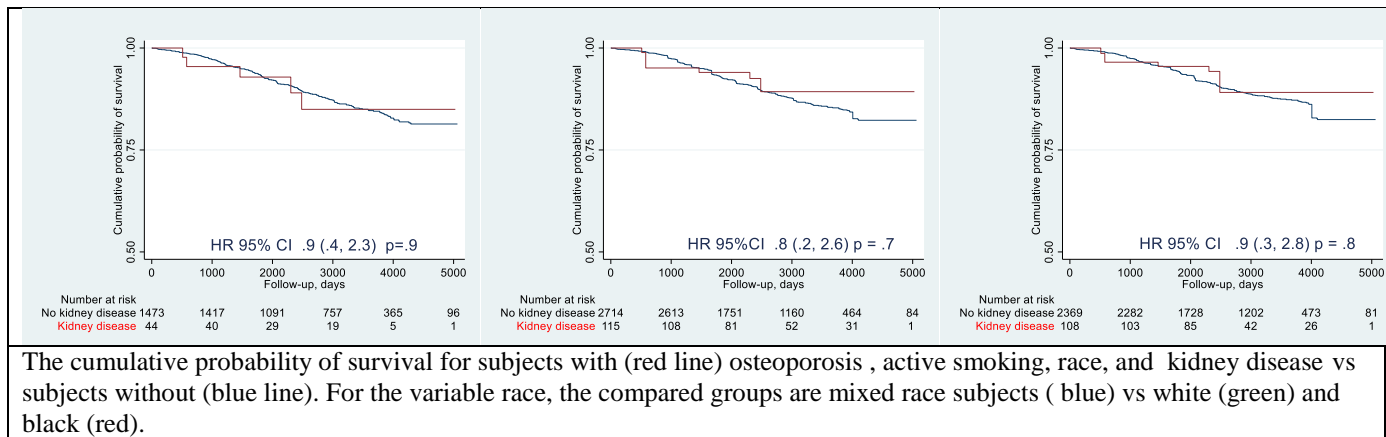
Active smoking



Race



Kidney disease



Supplemental Figure 6 KM survival analysis for all subjects on insulin UNWEIGHTED (left), PS WEIGHTED (middle) and PS weighted with RSF novel variables (right) for subjects with osteoporosis, active smoking, by race category or with kidney disease vs their comparator cohorts without that factor.

Supplemental Figure 3
Covariate balance:

	Unweighted				PS Weighted			
	0	1	p	SM D	0	1	p	SMD
N	1182	151			113.1	113.1		
Smoking	278 (23.5)	38 (25.2)	0.72	0.03	28.4 (25.1)	28.4 (25.1)	1	<0.001
Duration of diabetes (y) (mean (SD))	6.62 (7.05)	14.26 (8.77)	<0.001	0.96	12.45 (10.11)	12.45 (7.89)	1	<0.001
Hypercholesterolemia	0.48 (0.50)	0.60 (0.49)	0.00	0.24	0.56 (0.50)	0.56 (0.50)	1	<0.001
Hypertension	1049 (88.7)	141 (93.4)	0.11	0.16	104.6 (92.5)	104.6 (92.5)	1	<0.001
Waist/hip ratio (mean (SD))"	0.88 (0.06)	0.90 (0.08)	<0.001	0.33	0.89 (0.06)	0.89 (0.06)	1	<0.001
Alcohol use	66 (5.6)	4 (2.6)	0.18	0.14	3.5 (3.1)	3.5 (3.1)	1	<0.001
Family history of diabetes	603 (51.0)	96 (63.6)	0.00	0.25	66.7 (59.0)	66.7 (59.0)	1	<0.001
WHO BMI category			0.17	0.25			1	<0.001
0	10 (0.8)	0 (0.0)		7	0.0 (0.0)	0.0 (0.0)		
1	282 (23.9)	37 (24.5)			27.3 (24.1)	27.3 (24.1)		
2	67 (5.7)	16 (10.6)			10.0 (8.8)	10.0 (8.8)		
3	23 (1.9)	2 (1.3)			1.5 (1.3)	1.5 (1.3)		
4	288 (24.4)	30 (19.9)			23.8 (21.0)	23.8 (21.0)		
5	500 (42.3)	63 (41.7)			48.3 (42.7)	48.3 (42.7)		
6	12 (1.0)	3 (2.0)			2.3 (2.0)	2.3 (2.0)		
Cancer	35 (3.0)	4 (2.6)	1	0.01	3.0 (2.7)	3.0 (2.7)	1	<0.001
Cardiovascular history	94 (8.0)	18 (11.9)	0.13	0.13	11.4 (10.1)	11.4 (10.1)	1	<0.001
Age >50 years	1009 (85.4)	136 (90.1)	0.15	0.14	100.3 (88.7)	100.3 (88.7)	1	<0.001

Number of deliveries (mean (SD))"	4.85 (2.97)	4.46 (2.54)	0.12 8	0.14	4.48 (2.71)	4.48 (2.57)	1	<0.0 01
Duration of fertility (y) (mean (SD))"	46.18 (12.64)	46.29 (12.27)	0.91 9	0.00 9	46.25 (12.56)	46.25 (12.28)	1	<0.0 01