

SUPPLEMENTARY DATA

Sex and BMI alter the benefits and risks of sulfonylureas and thiazolidinediones in type 2 diabetes: A framework for evaluating stratification using routine clinical and individual trial data

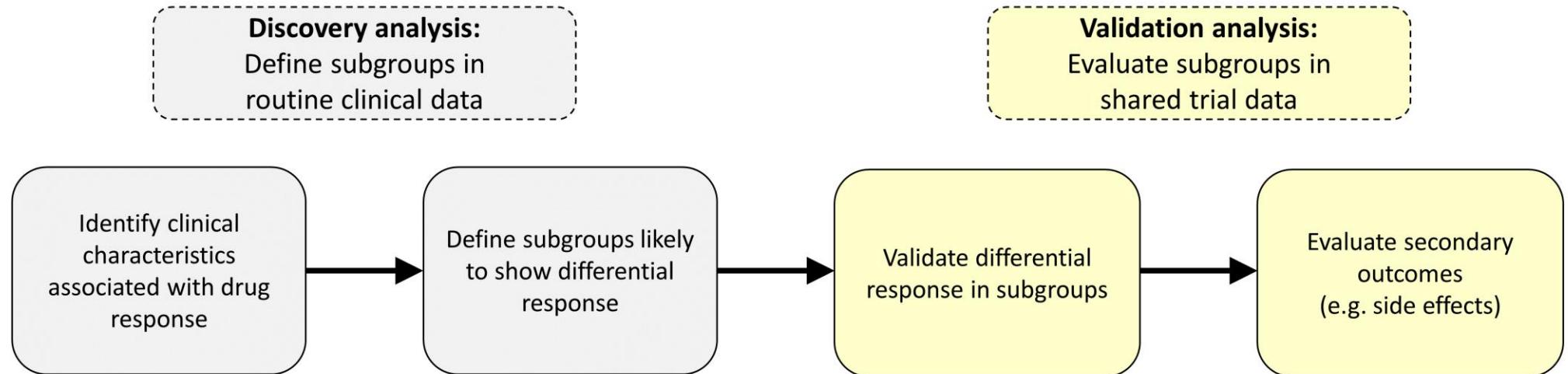
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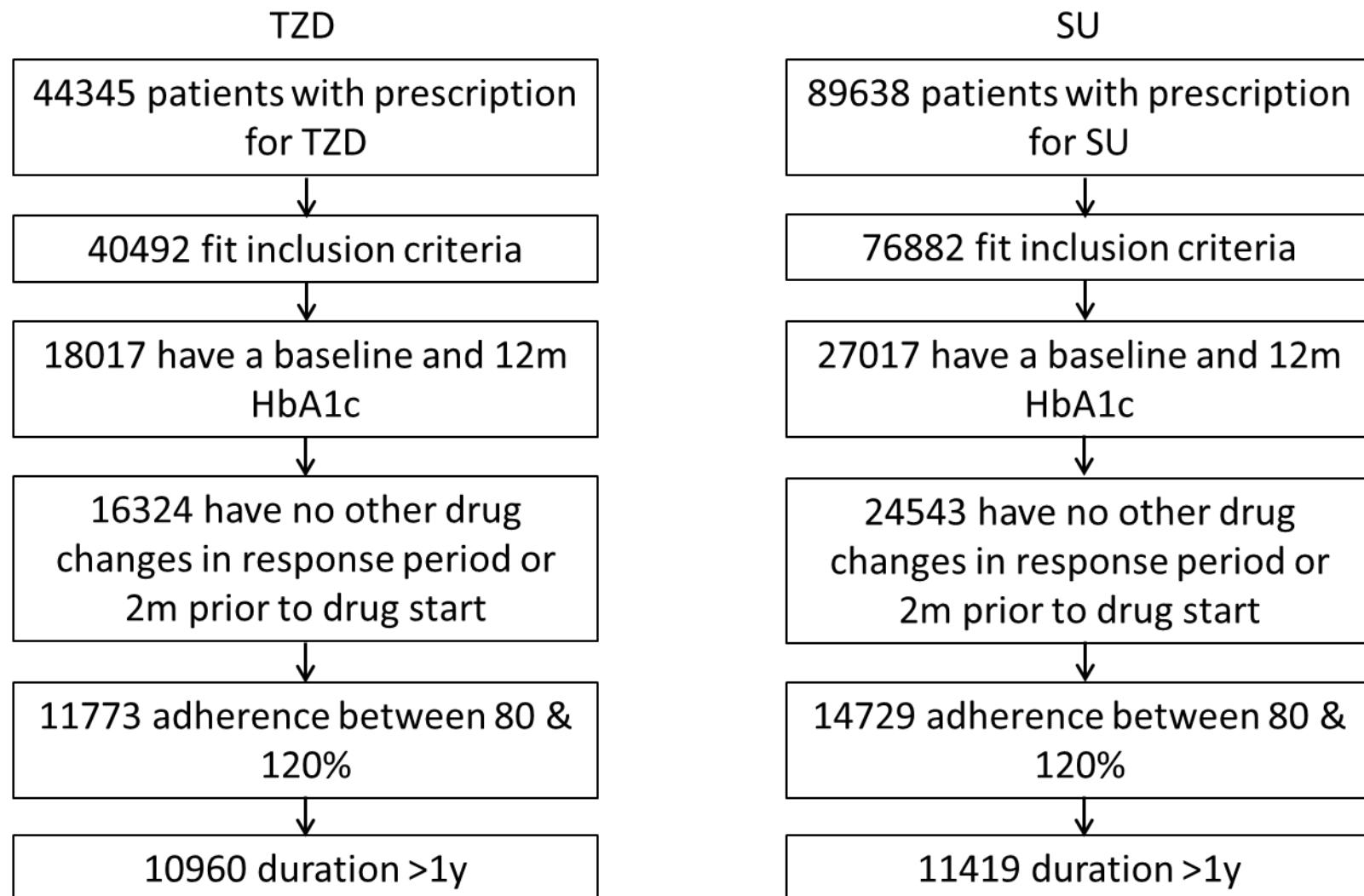
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Supplementary Figure S1. A framework for stratification research using routine clinical and shared trial data



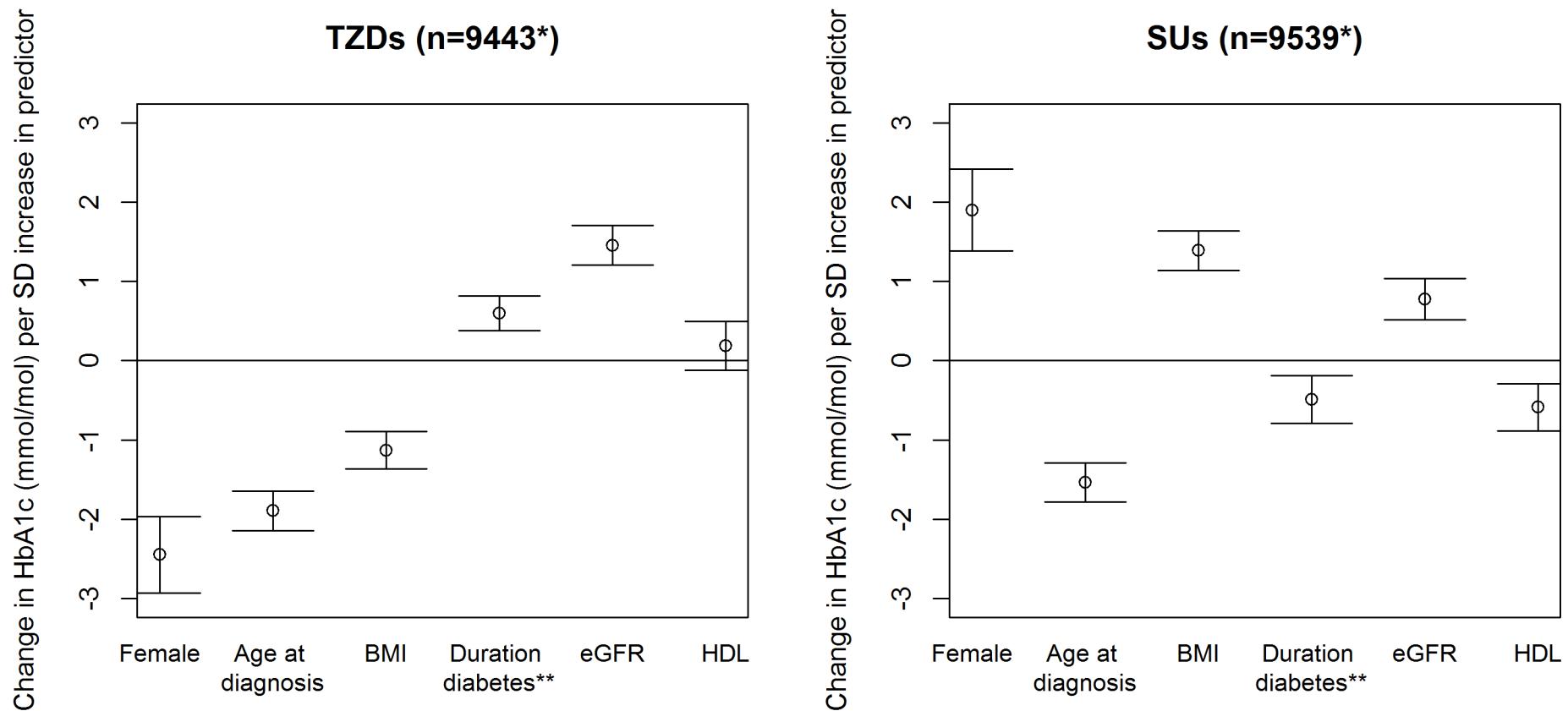
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Supplementary Figure S2. Flow diagram showing the determination of the final CPRD datasets used in analysis, based on patients treated with thiazolidinediones (TZD) or sulfonylureas (SU). Adherence measured by the medicine possession ratio.



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Supplementary Figure S3. Coefficients for predictors of one year response with thiazolidinediones (TZDs) or sulfonylureas (SUs) in CPRD. Data presented as beta coefficient from regression analysis (change in HbA1c per one unit increase in each predictor) with 95% confidence intervals as error bars. All predictors, except for baseline HbA1c, are adjusted for baseline HbA1c.

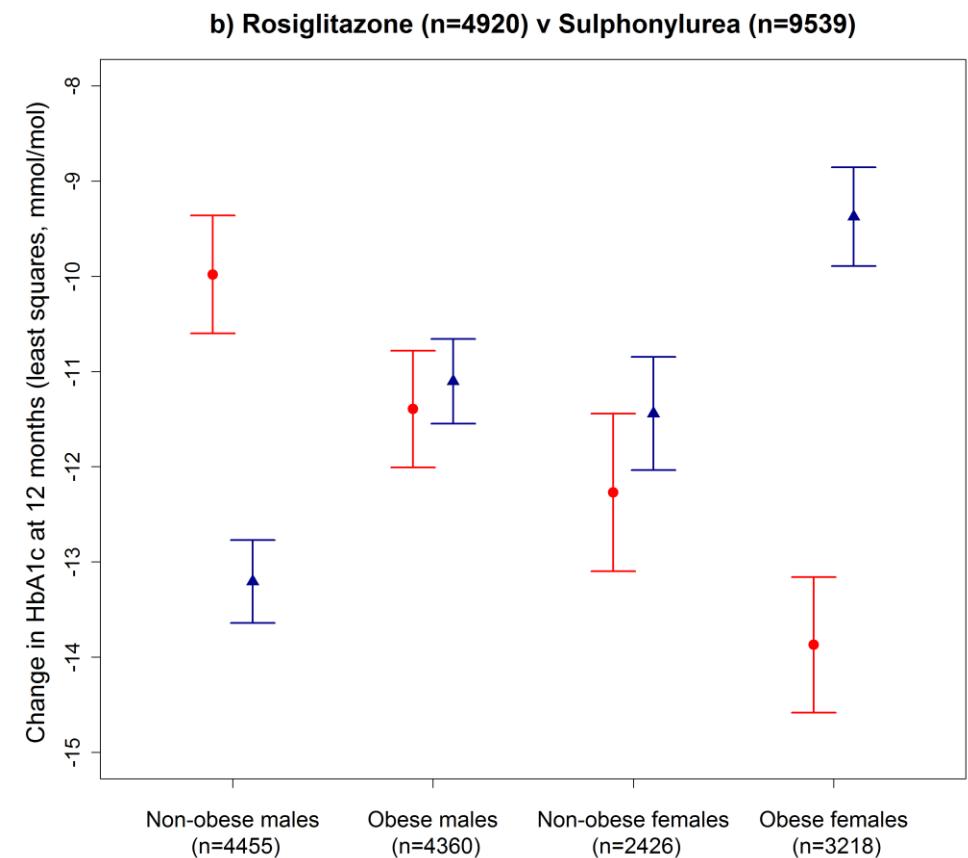
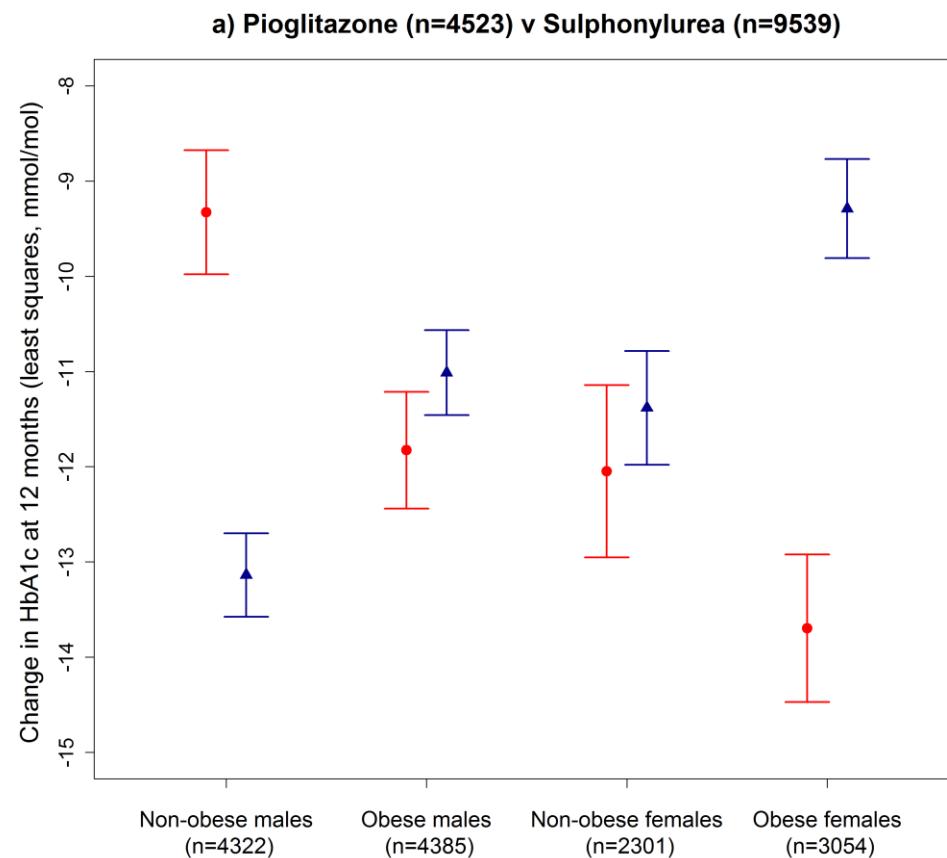


* TZD n=8291, SU n=8055 with valid baseline eGFR measure. TZD n=6184, SU n=5623 with valid baseline HDL measure.

**Duration results presented but association was non-linear and showed poor model fit

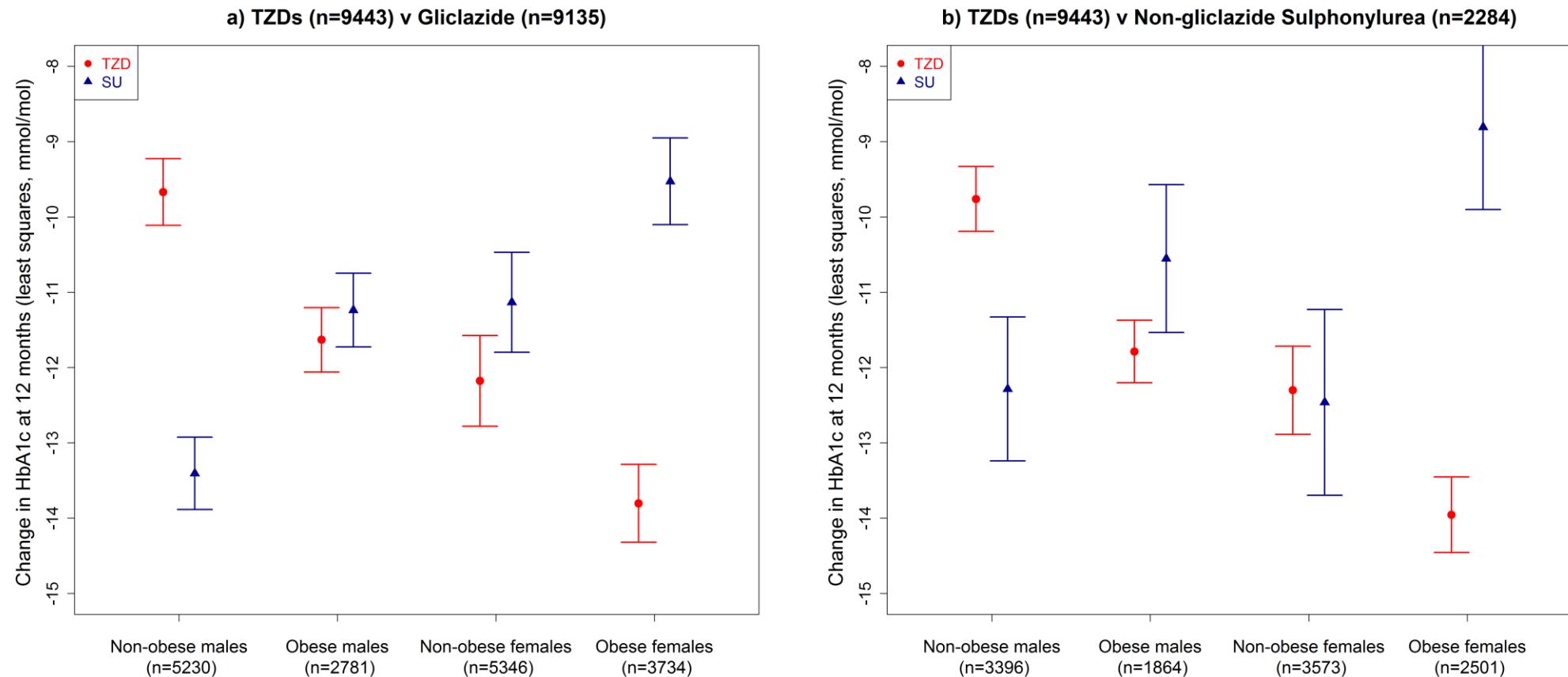
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Supplementary Figure S4a. CPRO one year response with a) Pioglitazone and b) Rosiglitazone (red dots), compared to sulfonylurea (blue triangles), by sex and obesity defined subgroups. Data are presented as baseline adjusted mean change in HbA1c \pm 95% CI



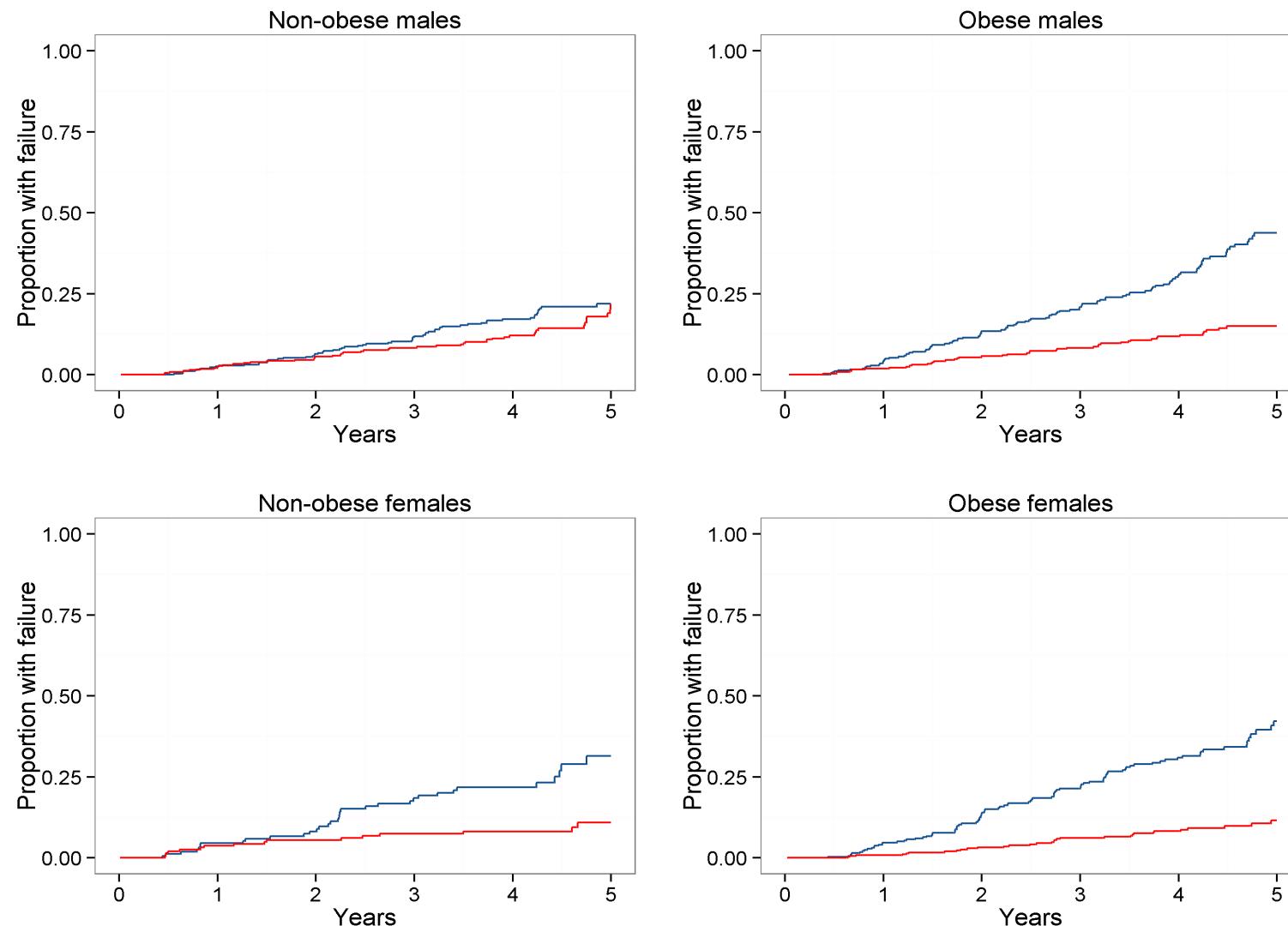
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Supplementary Figure S4b. CPRO one year response with a) Gliclazide and b) Non-gliclazide sulfonylureas (blue triangles), compared to thiazolidinediones (red dots), by sex and obesity defined subgroups. Data are presented as baseline adjusted mean change in HbA1c \pm 95% CI



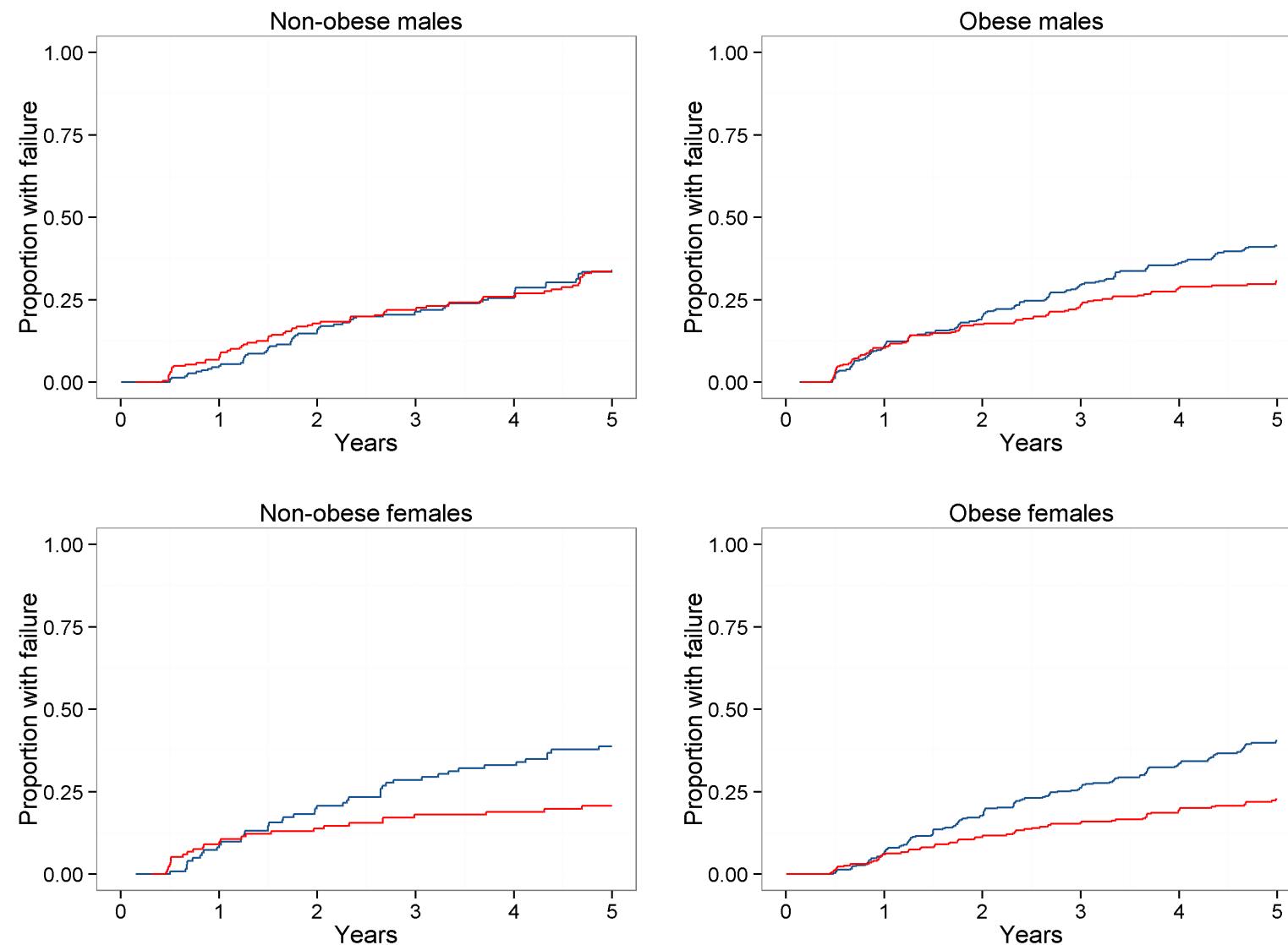
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Supplementary Figure S5. ADOPT Kaplan–Meier estimates of the cumulative incidence of monotherapy failure with thiazolidinediones (red) and sulfonylureas (blue) over 5 years by sex and obesity defined subgroup. Failure defined as confirmed fasting plasma glucose ≥ 180 mg/dl.



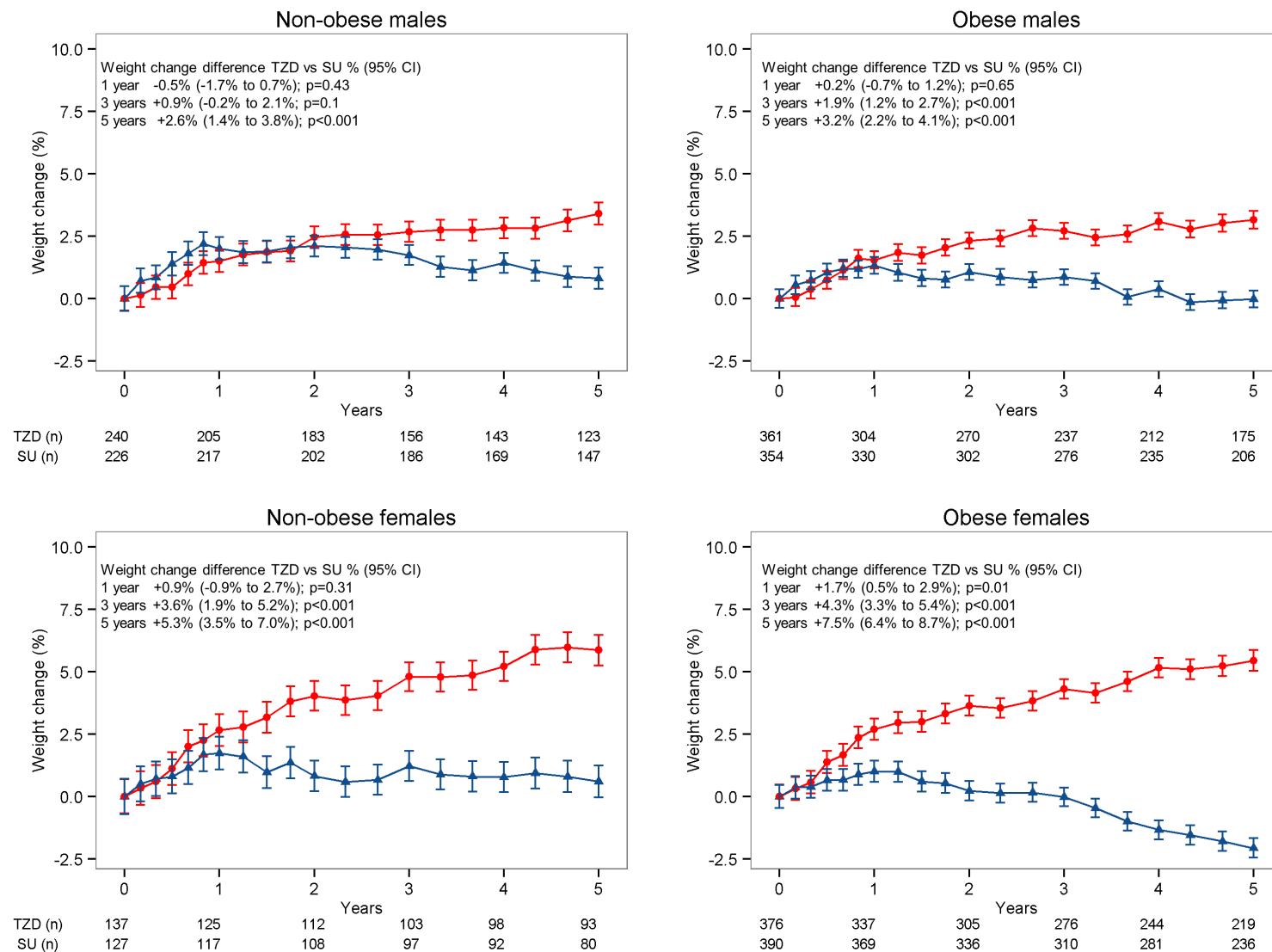
SUPPLEMENTARY DATA

Supplementary Figure S6. RECORD Kaplan–Meier estimates of the cumulative incidence of dual therapy failure with thiazolidinediones (red) and sulfonylureas (blue) over 5 years by sex and obesity defined subgroup. Failure defined as confirmed HbA1c $\geq 8.5\%$



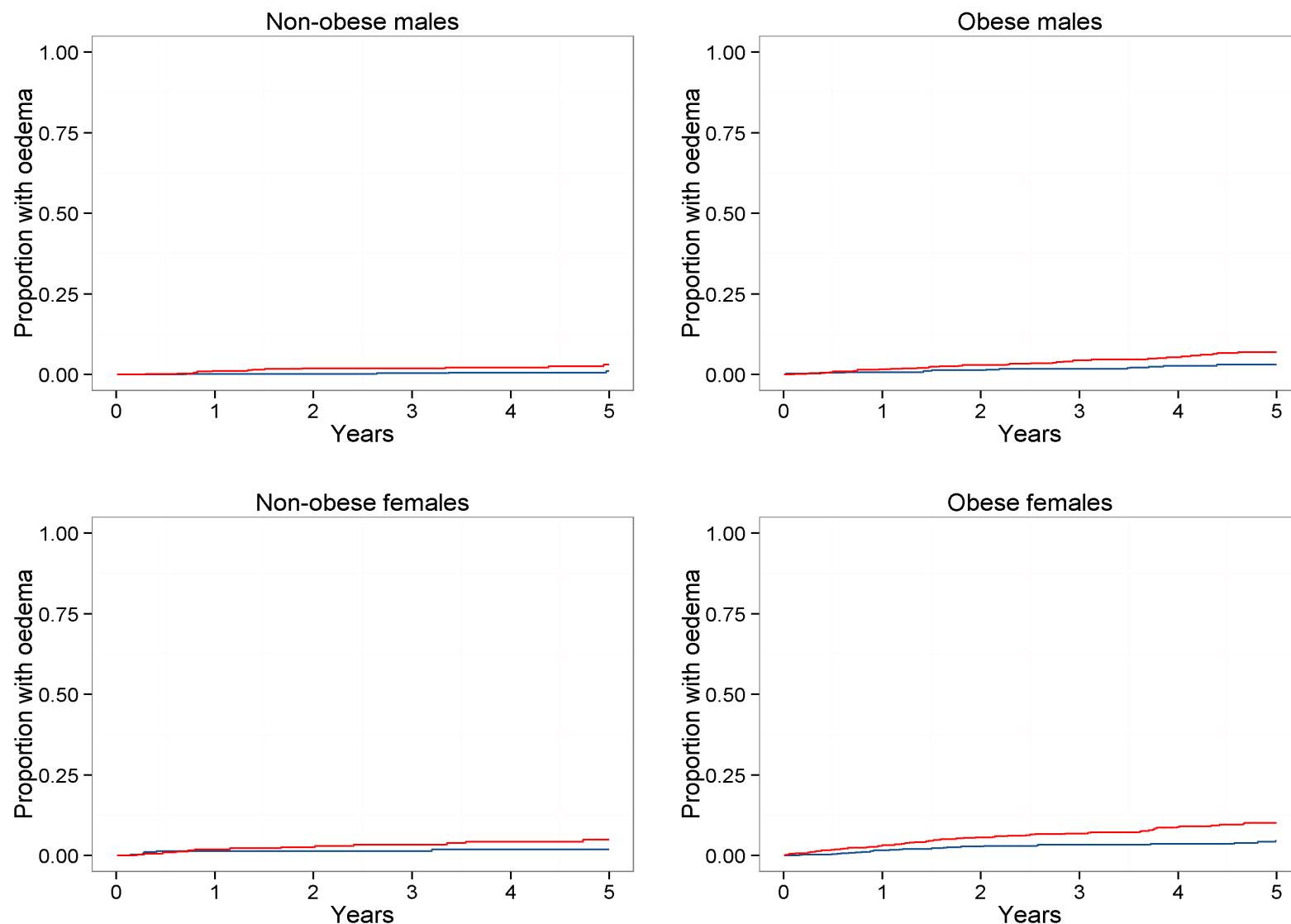
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Supplementary Figure S7. RECORD percentage weight change from baseline over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as means at each study visit \pm standard error from mixed effects models, adjusted for baseline weight. Number (n) per year presented below plots for each therapy and subgroup.



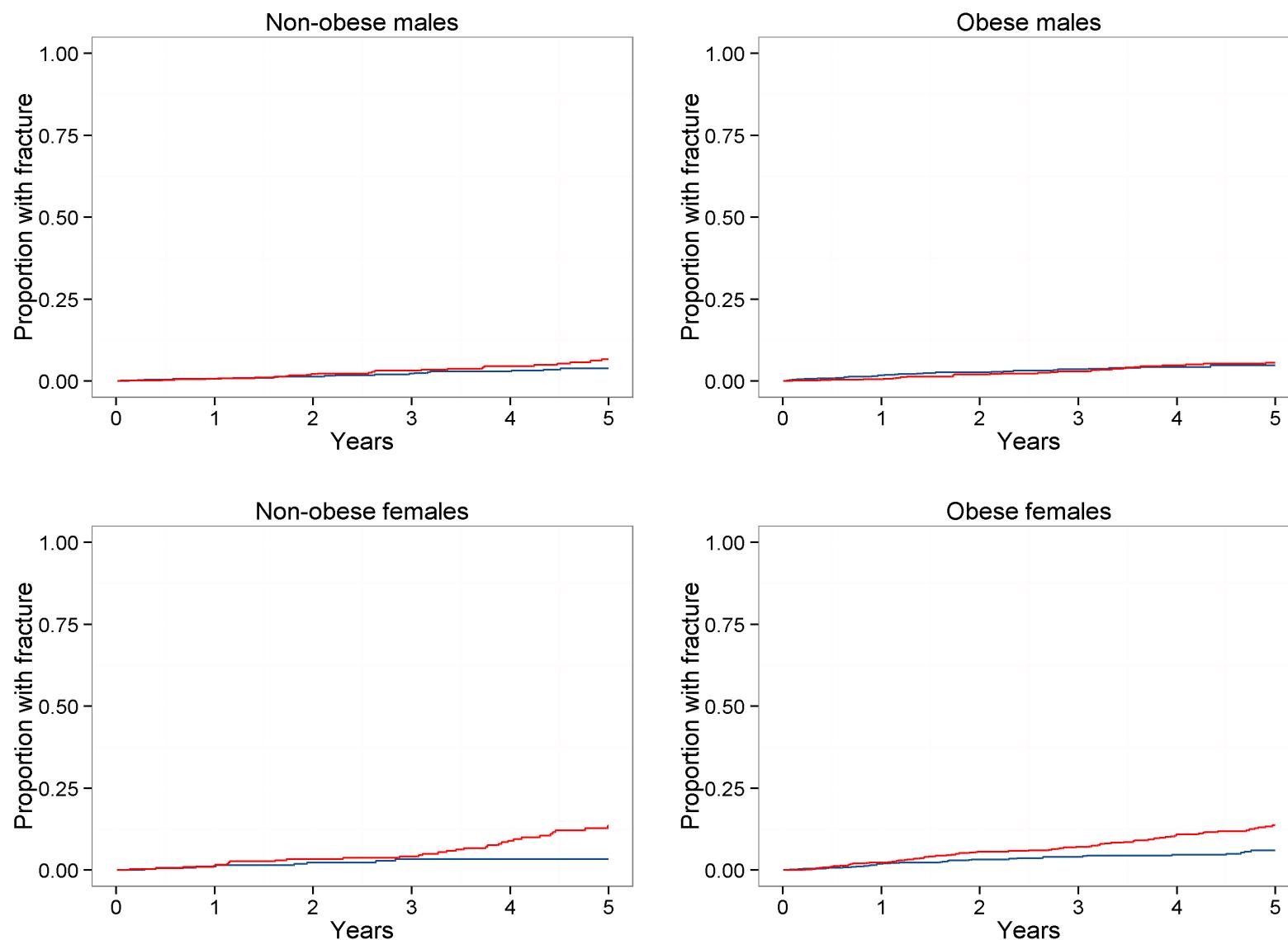
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Supplementary Figure S8. ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of moderate/severe oedema over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



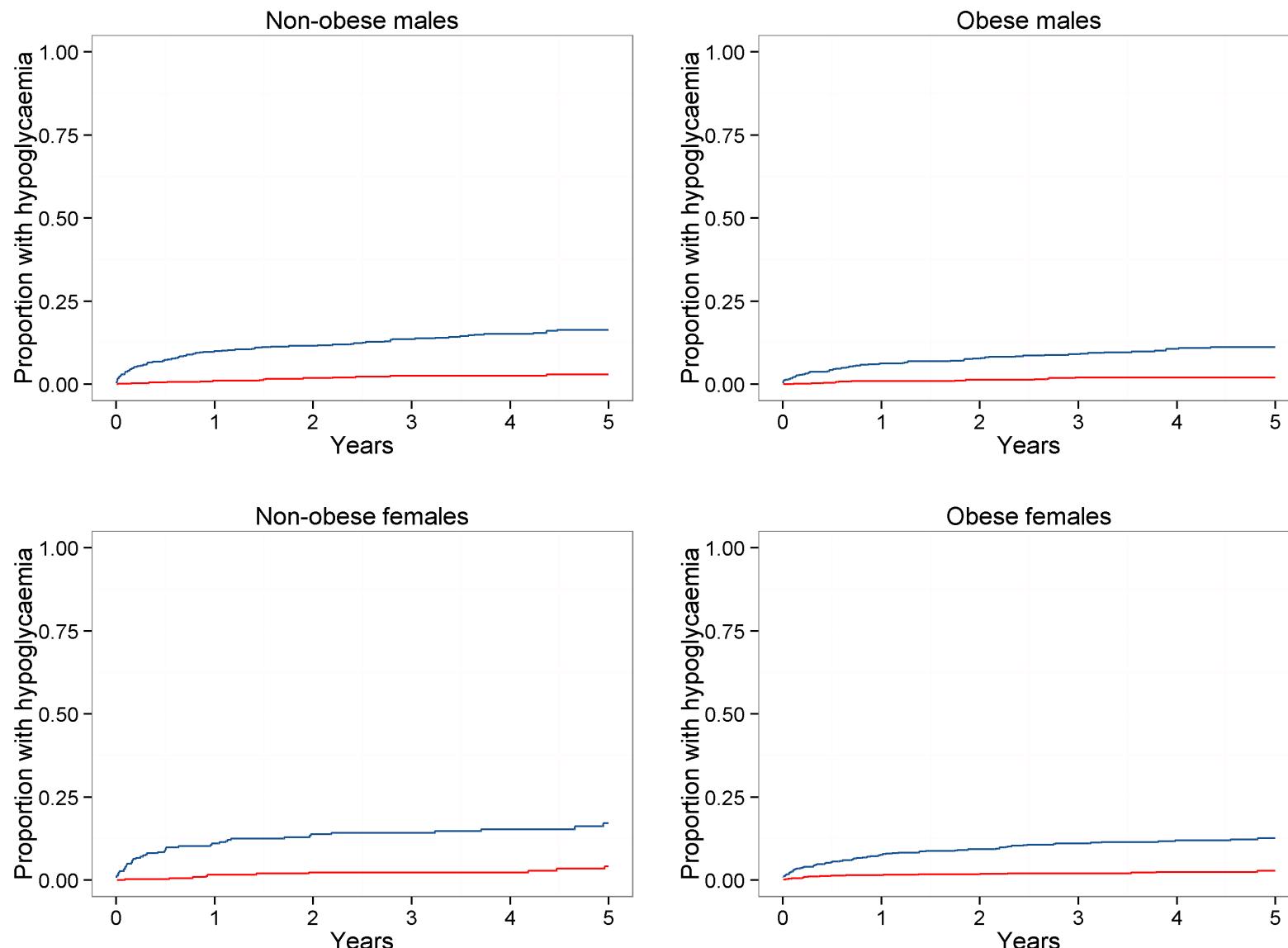
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Supplementary Figure S9. ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of fracture (any) over 5 years with thiazolidinediones (red) and sulfonylureas (blue).



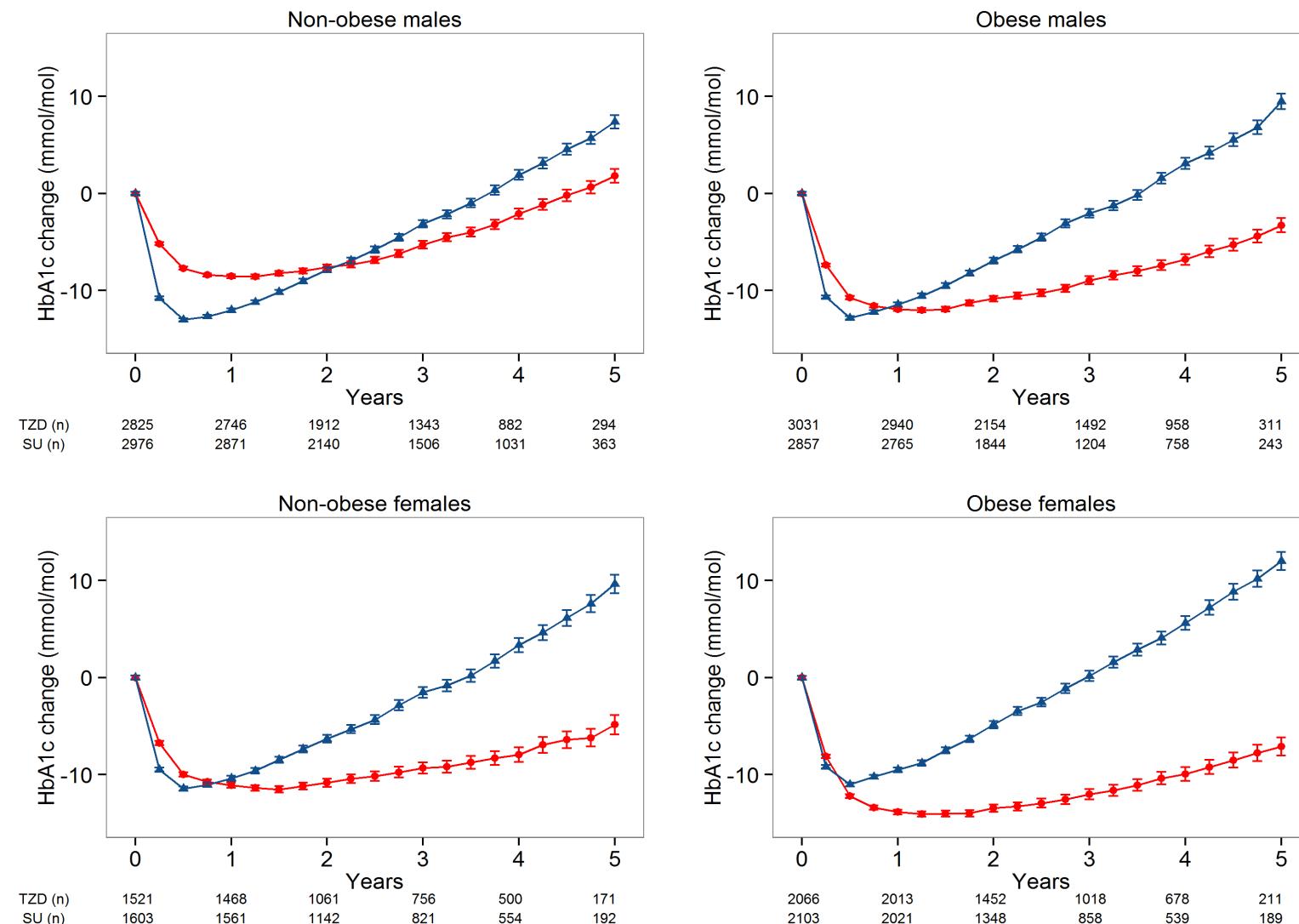
SUPPLEMENTARY DATA

Supplementary Figure S10. ADOPT & RECORD combined Kaplan–Meier estimates of the cumulative incidence of moderate/severe hypoglycaemia over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



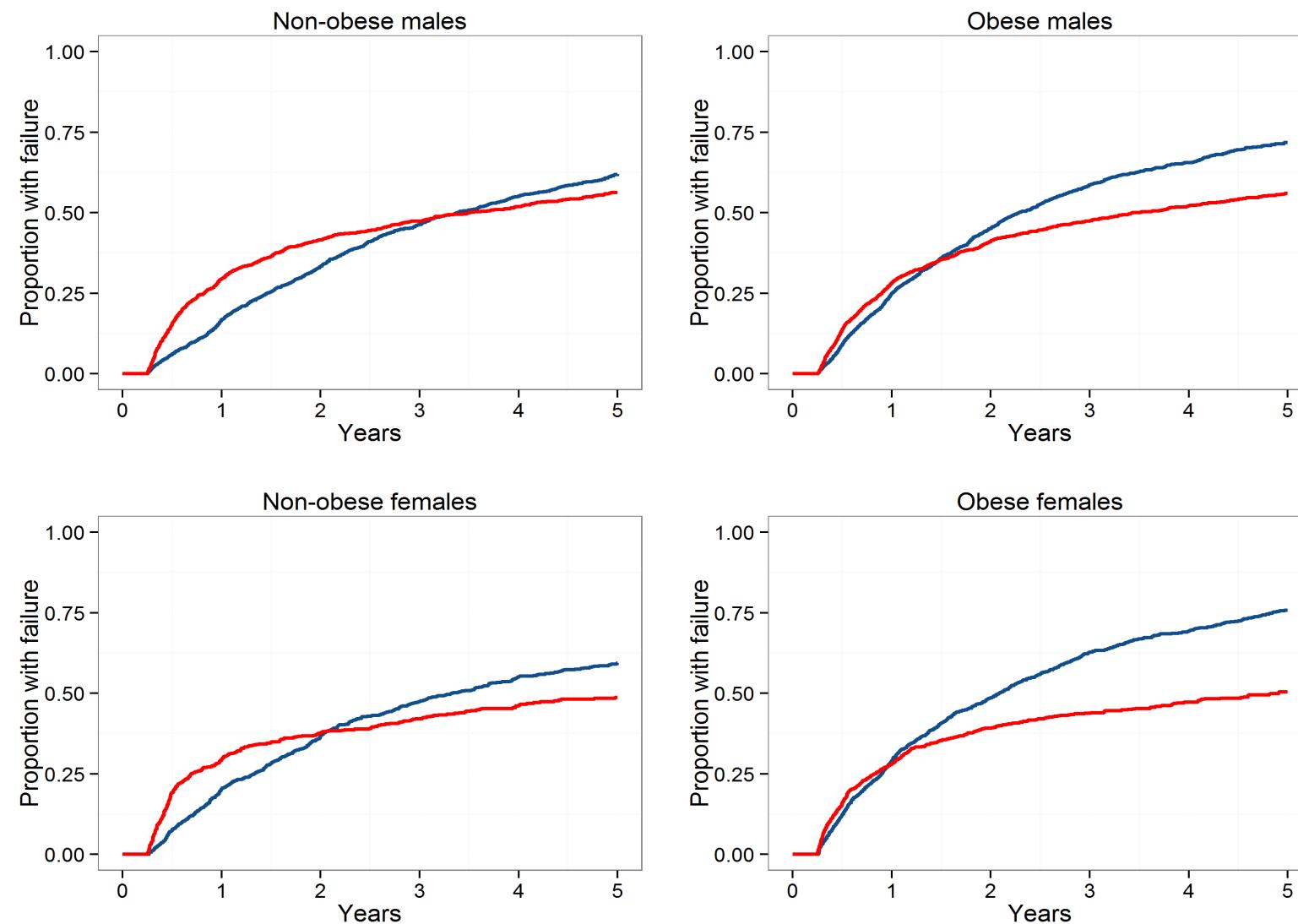
SUPPLEMENTARY DATA

Supplementary Figure S11. CPRD HbA1c over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 3 monthly means \pm standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



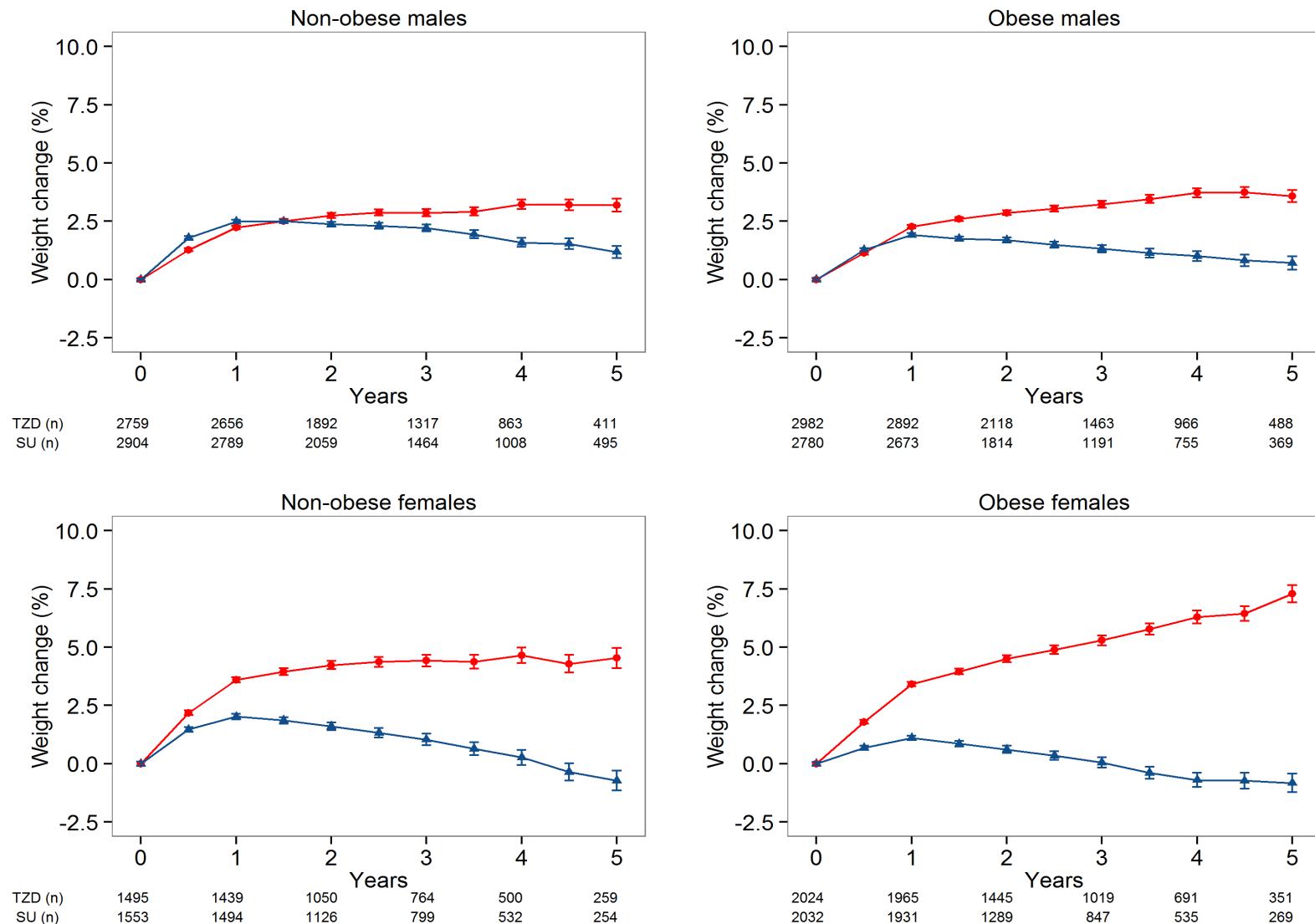
SUPPLEMENTARY DATA

Supplementary Figure S12. CPRD Kaplan–Meier estimates of the cumulative incidence of failure of therapy over 5 years with thiazolidinediones (red) and sulfonylureas (blue). Failure defined as two consecutive HbA1cs >8.5% or one HbA1c >8.5% followed by an additional oral hypoglycaemic agent being added.



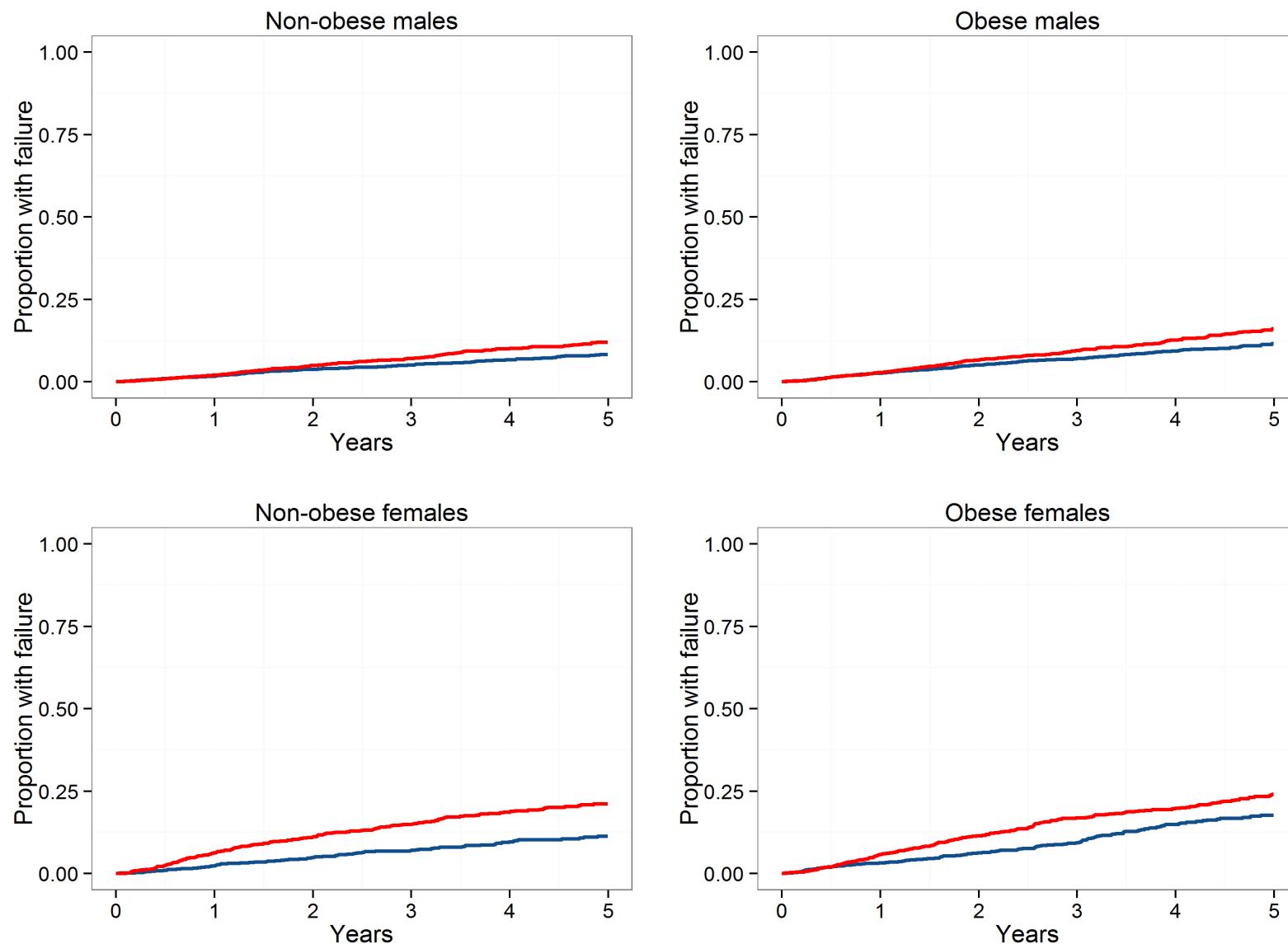
SUPPLEMENTARY DATA

Supplementary Figure S13. CPROD percentage weight change from baseline over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 6 monthly means \pm standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



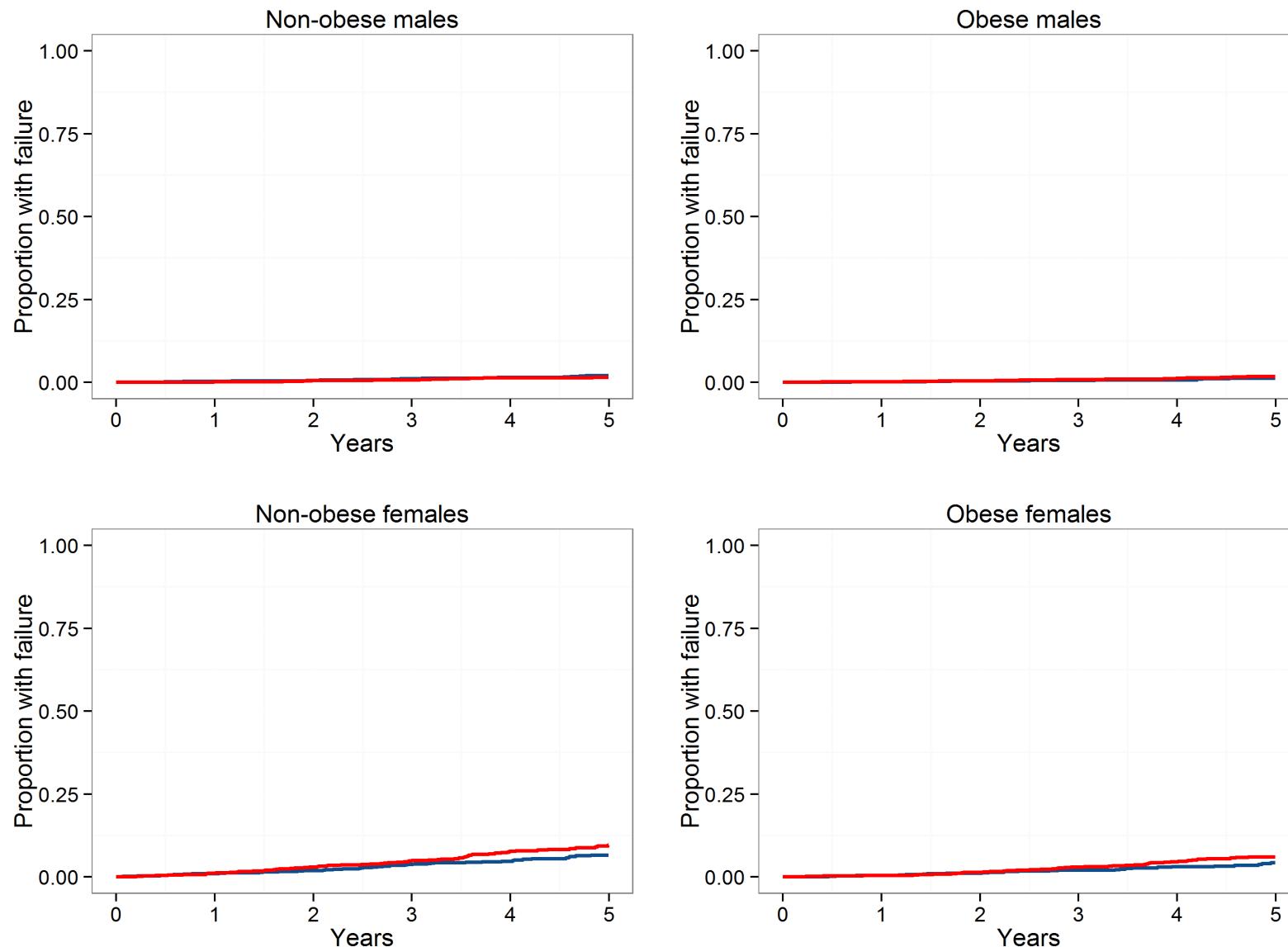
SUPPLEMENTARY DATA

Supplementary Figure S14. CPRD Kaplan–Meier estimates of the cumulative incidence of oedema over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



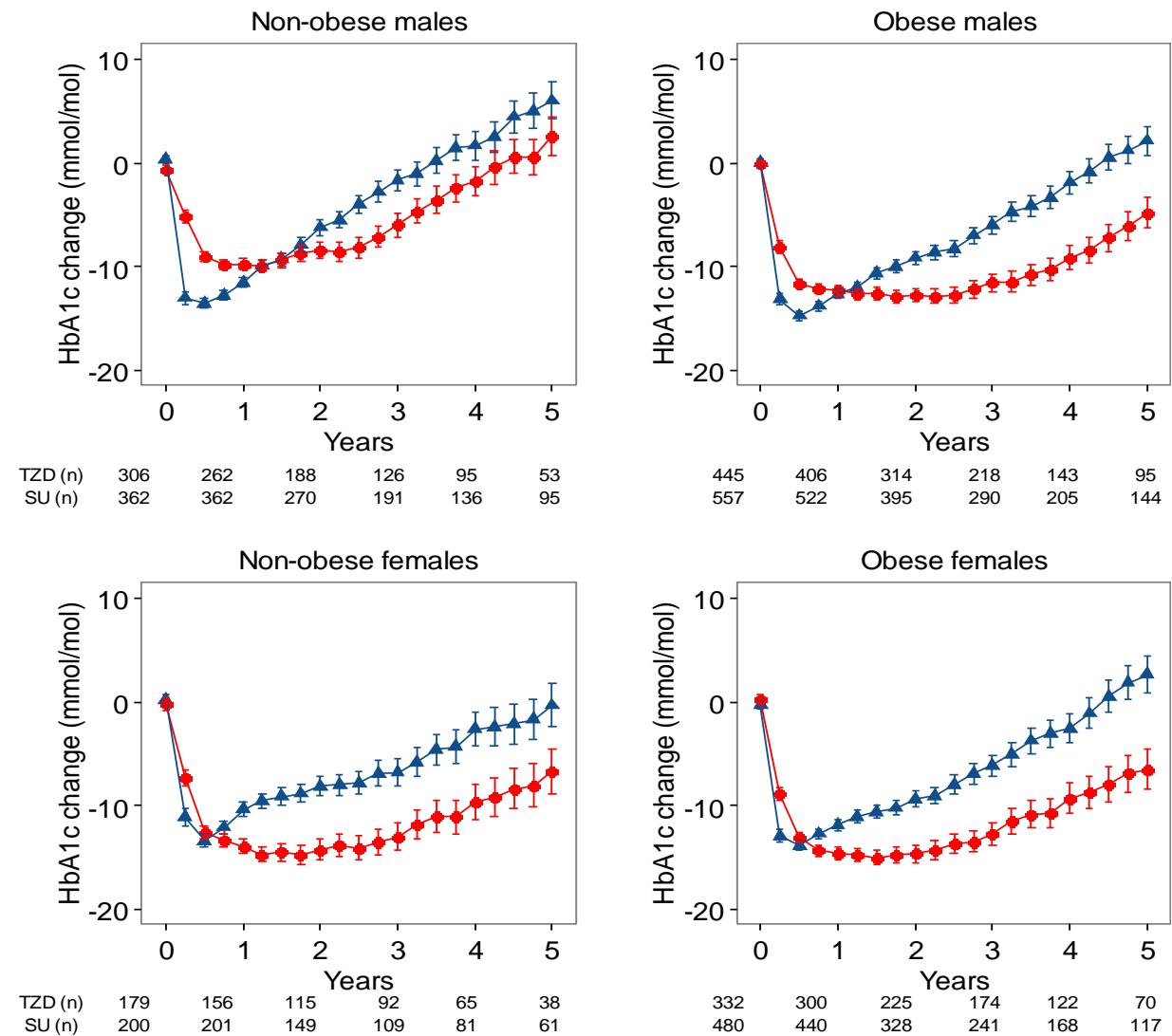
SUPPLEMENTARY DATA

Supplementary Figure S15. CPRO Kaplan-Meier estimates of the cumulative incidence of fracture (any) over 5 years with thiazolidinediones (red) and sulfonylureas (blue)



SUPPLEMENTARY DATA

Supplementary Figure S16. GoDARTs HbA1c over 5 years with thiazolidinediones (red dots) and sulfonylureas (blue triangles), by sex and obesity defined subgroup. Data are presented as 3 monthly means \pm standard error from mixed effects models, adjusted for baseline HbA1c. Number (n) per year presented below plots for each therapy and subgroup.



SUPPLEMENTARY DATA

Supplementary Table S1. CPRD population baseline characteristics split by cohorts treated with thiazolidinediones (TZD) and sulfonylureas (SU). Data presented for the whole group and 4 subgroups defined by obesity ($BMI > 30\text{kg}/\text{m}^2$) and sex.

	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
TZDs	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Age diag (y)	10960	57.0 (9.9)	2825	57.6 (9.7)	1521	61.1 (9.9)	3030	54.7 (9.3)	2064	56.1 (9.7)
Age (y)	10960	63.7 (10.4)	2825	65.3 (10.0)	1521	68.6 (10.1)	3030	60.6 (9.6)	2064	62.0 (10.0)
Duration Diabetes* (y)	10960	5.4 (2.6, 10.9)	2825	6.2 (3.0, 12.8)	1521	6.0 (2.9, 12.4)	3030	4.8 (2.4, 9.4)	2064	4.7 (2.4, 9.4)
BMI* (kg/m^2)	9443	30.9 (25.8, 37.0)	2825	26.7 (24.4, 29.2)	1521	26.2 (23.6, 29.1)	3030	34.6 (30.9, 38.8)	2064	35.9 (31.3, 41.3)
Male (%)	10960	62%	2825	100%	0	0%	3030	100%	0	0%
Dose (weighted mean % max)**	10703	50 (50, 66.7)	2761	50 (50, 66.7)	1488	50 (49.8, 66.7)	2963	50 (50, 66.7)	2011	50 (50, 66.7)
Adherence (%)	10960	101.1 (8.0)	2825	101.0 (8.0)	1521	101.4 (7.9)	3030	100.9 (8.1)	2064	101.2 (7.9)
HbA1c (mmol/mol)	10960	71.0 (14.2)	2825	69.4 (13.0)	1521	70.7 (14.8)	3030	71.8 (14.4)	2064	71.6 (15.0)
	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
SUs	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Age diag (y)	11419	59.3 (10.8)	2976	60.2 (10.4)	1603	64.5 (10.9)	2856	55.6 (9.6)	2103	57.8 (10.2)
Age (y)	11419	64.6 (10.8)	2976	65.8 (10.3)	1603	69.7 (10.8)	2856	60.7 (9.9)	2103	62.9 (10.3)
Duration Diabetes* (y)	11419	4.2 (2.1, 8.5)	2976	4.4 (2.1, 9.1)	1603	4.2 (2.1, 8.4)	2856	4.2 (2.2, 8.1)	2103	4.2 (2.1, 8.2)
BMI* (kg/m^2)	9539	30.6 (25.4, 36.8)	2976	26.5 (24.1, 29.1)	1603	26.0 (23.3, 29.1)	2856	34.6 (30.9, 38.8)	2103	36.0 (31.4, 41.2)
Male (%)	11419	61%	2976	100%	0	0%	2856	100%	0	0%
Dose (weighted mean % max)**	10958	25 (25, 44.5)	2853	25 (25, 37.8)	1541	25 (23.9, 33.2)	2745	25 (25, 50)	2011	25 (25, 47.7)
Adherence (%)	11419	101.0 (8.6)	2976	100.7 (8.4)	1603	101.4 (8.5)	2856	100.8 (8.7)	2103	101.4 (8.7)
HbA1c (mmol/mol)	11419	70.7 (16.0)	2976	69.4 (15.7)	1603	68.4 (15.0)	2856	71.9 (15.5)	2103	71.3 (16.1)

*skewed data so presented as geometric mean (SD range). **Dose presented as median (IQR)

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Supplementary Table S2. Baseline characteristics for patients in the ADOPT trial, by sex and obesity defined subgroup and therapy. Data presented as mean (SD) or *median (IQR)

	Non-obese Male		Obese Male		Non-obese Female		Obese Female	
	TZD	SU	TZD	SU	TZD	SU	TZD	SU
Patients (n)	373	395	402	387	208	174	407	379
Age (years)	57.8 (10.0)	57.9 (9.9)	55.2 (9.5)	55.4 (9.3)	58.2 (10.1)	59.7 (10.4)	55.0 (9.9)	54.7 (10.6)
Ethnic origin (white)	330 (88%)	362 (92%)	358 (89%)	347 (90%)	173 (83%)	161 (93%)	356 (87%)	326 (86%)
Time since diagnosis	0.80 (0.89)	0.89 (0.91)	0.80 (0.88)	0.84 (0.89)	0.85 (0.85)	0.86 (1.23)	0.79 (0.83)	0.77 (0.82)
Weight (kg)	81.9 (9.3)	82.6 (9.8)	106.7 (17.7)	108.1 (17.8)	68.7 (8.4)	69.2 (7.9)	97.2 (17.2)	97.1 (18.4)
BMI	26.9 (2.1)	27.0 (2.0)	34.9 (4.7)	35.2 (4.6)	26.6 (2.5)	26.5 (2.5)	37.2 (6.0)	37.2 (5.9)
Waist to hip ratio	0.97 (0.06)	0.96 (0.08)	1.00 (0.08)	1.00 (0.06)	0.89 (0.09)	0.89 (0.09)	0.90 (0.08)	0.90 (0.08)
HbA1c (mmol/mol)	56.7 (11.0)	56.2 (11.2)	57.1 (10.1)	57.3 (9.5)	57.6 (10.3)	56.7 (10.3)	56.8 (9.1)	57.2 (9.3)
Fasting glucose (mmol/l)	8.4 (1.6)	8.4 (1.4)	8.5 (1.5)	8.6 (1.6)	8.4 (1.3)	8.5 (1.8)	8.4 (1.3)	8.4 (1.4)
Insulin sensitivity HOMA-S (%)[*]	46 (31-64)	45 (32-63)	28 (20-39)	28 (20-39)	43 (32-59)	41 (29-56)	27 (19-39)	26 (20-36)
Beta-cell function HOMA-B (%)[*]	59 (46-79)	59 (47-73)	75 (59-95)	74 (57-94)	58 (46-73)	64 (46-81)	74 (58-91)	76 (59-94)
Triglycerides (mmol/l)[*]	1.7 (1.2-2.4)	1.6 (1.1-2.4)	2.0 (1.4-3.0)	1.9 (1.4-2.7)	1.7 (1.2-2.3)	1.6 (1.2-2.3)	1.9 (1.4-2.6)	1.8 (1.4-2.4)
LDL cholesterol (mmol/l)[*]	3.1 (2.5-3.7)	3.0 (2.5-3.6)	3.1 (2.5-3.6)	3.1 (2.5-3.7)	3.3 (2.6-3.9)	3.4 (2.7-4.0)	3.2 (2.7-3.8)	3.1 (2.6-3.8)
HDL cholesterol (mmol/l)[*]	1.2 (1.0-1.4)	1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.1 (0.9-1.3)	1.4 (1.2-1.6)	1.4 (1.2-1.6)	1.3 (1.1-1.5)	1.3 (1.1-1.5)

SUPPLEMENTARY DATA

Supplementary Table S3. Baseline characteristics for patients in the RECORD trial, by sex and obesity defined subgroup and therapy. Data presented as mean (SD) or *median (IQR)

	Non-obese Male		Obese Male		Non-obese Female		Obese Female	
	TZD	SU	TZD	SU	TZD	SU	TZD	SU
Patients (n)	240	228	361	356	137	127	379	394
Age (years)	58.2 (8.4)	57.9 (8.5)	55.5 (7.8)	55.7 (8.0)	59.1 (7.7)	59.2 (8.2)	56.9 (7.8)	57.5 (7.8)
Ethnic origin (white)	237 (99%)	223 (98%)	359 (99%)	351 (99%)	135 (99%)	122 (96%)	374 (99%)	391 (99%)
Time since diagnosis	6.4 (4.4)	6.9 (4.4)	5.7 (3.7)	6.0 (4.4)	6.9 (4.9)	7.1 (4.7)	6.1 (4.2)	6.1 (4.3)
Weight (kg)	85.7 (8.2)	86.2 (8.2)	106.6 (14.8)	106.0 (14.4)	72.9 (7.2)	73.1 (7.3)	93.4 (13.1)	92.4 (14.1)
BMI	27.8 (1.5)	27.8 (1.5)	34.7 (3.9)	34.3 (4)	27.7 (1.5)	27.6 (1.7)	36.0 (4.4)	35.8 (4.9)
Waist to hip ratio	0.97 (0.05)	0.98 (0.06)	1.01 (0.06)	1.01 (0.06)	0.90 (0.07)	0.91 (0.07)	0.92 (0.07)	0.92 (0.07)
HbA1c (mmol/mol)	61.4 (7.3)	61.2 (7.2)	62.1 (7.5)	62.9 (7.7)	61.5 (7.3)	62.0 (6.8)	62.4 (7.3)	62.0 (6.7)
Fasting glucose (mmol/l)	9.5 (2.0)	9.4 (2.0)	9.6 (2.3)	9.9 (2.2)	9.1 (2.0)	9.1 (1.9)	9.4 (1.9)	9.5 (2.2)
Insulin sensitivity HOMA-S (%)*	87 (60-131)	93 (60-123)	52 (38-74)	52 (34-77)	80 (55-127)	79 (57-130)	58 (41-79)	58 (39-83)
Beta-cell function HOMA-B (%)*	29 (21-39)	30 (20-42)	42 (30-60)	42 (25-58)	33 (23-42)	32 (22-47)	40 (30-54)	41 (28-57)
Triglycerides (mmol/l)*	1.8 (1.3-2.5)	1.8 (1.2-2.7)	2.2 (1.7-3.0)	2.1 (1.4-3.1)	1.8 (1.3-2.7)	1.8 (1.3-2.3)	2.1 (1.6-2.7)	2.0 (1.5-2.8)
LDL cholesterol (mmol/l)*	3.2 (2.6-3.6)	3.2 (2.6-3.7)	3.0 (2.5-3.6)	3.0 (2.4-3.6)	3.3 (2.8-3.9)	3.3 (2.8-3.9)	3.3 (2.7-3.9)	3.3 (2.6-3.9)
HDL cholesterol (mmol/l)*	1.1 (1.0-1.3)	1.2 (1-1.3)	1.1 (0.9-1.2)	1.1 (0.9-1.2)	1.3 (1.1-1.5)	1.3 (1.1-1.5)	1.2 (1.1-1.4)	1.2 (1.1-1.4)

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Supplementary Table S4. ADOPT absolute and relative risk of side effects over 5 years with thiazolidinediones (TZD) and sulfonylureas (SU), by sex and obesity defined subgroup. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU.

Side effect	No. of patients		No. of events		Absolute 5 year risk (%)		Hazard ratio*	p value
	TZD	SU	TZD	SU	TZD	SU		
Non-obese males								
Oedema	367	392	16	12	6%	5%	1.44 (0.68-3.03)	0.34
Oedema (Moderate/Severe)	367	392	6	3	2%	2%	2.16 (0.54-8.63)	0.28
Fracture	373	395	12	12	4%	5%	1.06 (0.48-2.37)	0.88
Hypoglycaemia (All)	373	395	33	161	10%	49%	0.18 (0.12-0.25)	<0.01
Hypoglycaemia (Moderate/Severe)	373	395	12	74	4%	22%	0.16 (0.09-0.29)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Obese males								
Oedema	379	363	52	34	19%	13%	1.33 (0.86-2.05)	0.20
Oedema (Moderate/Severe)	379	363	13	10	5%	4%	1.10 (0.48-2.51)	0.83
Fracture	402	387	18	14	6%	5%	1.09 (0.54-2.20)	0.81
Hypoglycaemia (All)	402	387	36	120	11%	40%	0.23 (0.16-0.33)	<0.01
Hypoglycaemia (Moderate/Severe)	402	387	8	52	2%	16%	0.13 (0.06-0.28)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Non-obese females								
Oedema	203	166	31	12	19%	9%	2.07 (1.06-4.03)	0.03
Oedema (Moderate/Severe)	203	166	10	4	6%	3%	1.94 (0.61-6.19)	0.26
Fracture	208	174	19	4	18%	3%	3.42 (1.16-10.07)	0.03
Hypoglycaemia (All)	208	174	20	64	13%	52%	0.20 (0.12-0.33)	<0.01
Hypoglycaemia (Moderate/Severe)	208	174	6	34	3%	26%	0.13 (0.05-0.31)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							
Obese females								
Oedema	370	352	78	46	29%	20%	1.36 (0.94-1.96)	0.10
Oedema (Moderate/Severe)	370	352	32	19	12%	11%	1.30 (0.74-2.31)	0.36
Fracture	407	379	41	14	16%	9%	2.17 (1.18-3.98)	0.01
Hypoglycaemia (All)	407	379	50	137	15%	45%	0.26 (0.19-0.36)	<0.01
Hypoglycaemia (Moderate/Severe)	407	379	14	59	5%	19%	0.19 (0.10-0.33)	<0.01
Hypoglycaemia (Severe)	24 events total across all 4 subgroups with both therapies - 21 SU, 3 TZD							

SUPPLEMENTARY DATA

Supplementary Table S5. RECORD absolute and relative risk of side effects over 5 years with thiazolidinediones (TZD) and sulfonylureas (SU), by sex and obesity defined subgroup. Relative risks presented as hazard ratios (95% CI) for TZD compared to SU.

Side effect	No. of patients		No. of events		Absolute 5 year risk (%)		Hazard ratio*	p value*
	TZD	SU	TZD	SU	TZD	SU		
Non-obese males								
Oedema	240	228	13	9	7%	5%	1.59 (0.68-3.71)	0.29
Oedema (Moderate/Severe)	240	228	7	1	4%	1%	7.84 (0.96-63.7)	0.05
Fracture	240	228	14	6	9%	3%	2.66 (1.02-6.94)	0.04
Hypoglycaemia (All)	240	228	5	38	2%	18%	0.12 (0.05-0.31)	<0.01
Hypoglycaemia (Moderate/Severe)	240	228	2	16	1%	8%	0.12 (0.03-0.54)	<0.01
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Obese males								
Oedema	361	356	48	21	17%	7%	2.61 (1.56-4.35)	<0.01
Oedema (Moderate/Severe)	361	356	24	6	9%	2%	4.45 (1.82-10.90)	<0.01
Fracture	361	356	12	14	5%	5%	0.94 (0.43-2.03)	0.88
Hypoglycaemia (All)	361	356	10	51	3%	16%	0.19 (0.10-0.38)	<0.01
Hypoglycaemia (Moderate/Severe)	361	356	5	18	2%	6%	0.29 (0.11-0.79)	0.015
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Non-obese females								
Oedema	137	127	17	4	15%	4%	4.13 (1.39-12.2)	0.01
Oedema (Moderate/Severe)	137	127	3	1	3%	1%	2.77 (0.29-26.60)	0.38
Fracture	137	127	12	4	11%	3%	2.86 (0.92-8.88)	0.07
Hypoglycaemia (All)	137	127	3	26	3%	22%	0.10 (0.03-0.31)	<0.01
Hypoglycaemia (Moderate/Severe)	137	127	4	10	4%	9%	0.36 (0.11-1.3)	0.08
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							
Obese females								
Oedema	379	394	75	20	23%	6%	4.37 (2.67-7.16)	<0.01
Oedema (Moderate/Severe)	379	394	28	6	9%	2%	5.16 (2.14-12.46)	<0.01
Fracture	379	394	36	19	12%	5%	2.12 (1.21-3.70)	<0.01
Hypoglycaemia (All)	379	394	14	73	4%	21%	0.19 (0.11-0.34)	<0.01
Hypoglycaemia (Moderate/Severe)	379	394	4	24	1%	7%	0.17 (0.06-0.50)	<0.01
Hypoglycaemia (Severe)	10 events total across all 4 subgroups with both therapies - 10 SU, 0 TZD							

SUPPLEMENTARY DATA

Supplementary Table S6. GoDARTs population baseline characteristics, split by cohorts treated with thiazolidinediones (TZD) and sulfonylureas (SU). Data presented for the whole group and 4 subgroups defined by obesity ($BMI > 30\text{kg/m}^2$) and sex.

TZD	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Age diag (y)	719	55.6 (9.3)	176	56.7 (9.2)	97	59.9 (8.5)	267	52.9 (9.0)	174	56.1 (9.1)
Age (y)	719	63.7 (9.6)	176	65.9 (9.0)	97	69.0 (8.8)	267	60.7 (9.3)	174	63.3 (9.3)
Duration Diabetes (y)	719	8.2 (5.1)	176	9.2 (5.9)	97	9.2 (5.2)	267	7.8 (4.9)	174	7.2 (4.0)
BMI (kg/m^2)	714	32.2 (5.7)	176	27.3 (2.0)	97	26.8 (2.5)	267	34.9 (4.6)	174	36.0 (5.6)
Male (%)	719	62	176	100	97	0	267	100	174	0
Dose (weighted mean % max)	686	50 (23)	170	51 (25)	95	49 (22)	252	51 (23)	164	48 (22)
Adherence (%)	719	97 (5)	176	97 (5)	97	98 (3)	267	97 (5)	174	97 (5)
HbA1c (mmol/mol)	719	73.1 (12.5)	176	70.8 (12.0)	97	71.0 (11.6)	267	74.3 (12.5)	174	74.6 (13.0)
SU	All		Non Obese Male		Non Obese Female		Obese Male		Obese Female	
	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Age diag (y)	1258	58.8 (10.4)	350	59.8 (10.0)	219	64.0 (10.5)	336	56.1 (9.6)	285	57.2 (10.3)
Age (y)	1258	64.6 (10.2)	350	66.0 (9.9)	219	69.3 (9.8)	336	61.9 (9.6)	285	62.9 (10.3)
Duration Diabetes (y)	1258	5.8 (3.9)	350	6.2 (4.4)	219	5.4 (3.5)	336	5.8 (3.7)	285	5.7 (3.7)
BMI (kg/m^2)	1190	31.2 (5.5)	350	27.1 (2.1)	219	26.4 (2.5)	336	34.6 (4.1)	285	35.8 (4.8)
Male (%)	1258	57	350	100	219	0	336	100	285	0
Dose (weighted mean % max)	1167	29 (22)	330	26 (14)	202	24 (14)	307	30 (15)	268	37 (31)
Adherence (%)	1258	96 (6)	350	96 (6)	219	96 (6)	336	96 (5)	285	97 (5)
HbA1c (mmol/mol)	1258	70.9 (14.5)	350	68.8 (14.3)	219	69.0 (12.8)	336	71.4 (13.8)	285	72.9 (14.9)

SUPPLEMENTARY DATA

CPRD – data supplement

Therapy records

Medcodes for prescriptions of sulfonylureas and thiazolidinediones were identified using BNF codes and keyword searches of “product name” and “drug substance name”. Records matching the following medcodes in the Therapy file were extracted:

Prod-code	productname	drugsubstancename
Thiazolidinediones		
469	Rosiglitazone 4mg tablets	Rosiglitazone maleate
548	Pioglitazone 15mg tablets	Pioglitazone hydrochloride
5227	Rosiglitazone 8mg tablets	Rosiglitazone maleate
9662	Avandia 4mg tablets (GlaxoSmithKline UK Ltd)	Rosiglitazone maleate
9699	Pioglitazone 30mg tablets	Pioglitazone hydrochloride
10051	Pioglitazone 45mg tablets	Pioglitazone hydrochloride
13628	Romozin 400mg Tablet (Glaxo Wellcome UK Ltd)	Troglitazone
15232	Avandia 8mg tablets (GlaxoSmithKline UK Ltd)	Rosiglitazone maleate
19472	Actos 45mg tablets (Takeda UK Ltd)	Pioglitazone hydrochloride
20287	Actos 15mg tablets (Takeda UK Ltd)	Pioglitazone hydrochloride
20889	Actos 30mg tablets (Takeda UK Ltd)	Pioglitazone hydrochloride
37617	Rosiglitazone 2mg tablet	Rosiglitazone Maleate
48120	Avandia 2mg Tablet (GlaxoSmithKline UK Ltd)	Rosiglitazone Maleate
48139	Pioglitazone 30mg tablets (A A H Pharmaceuticals Ltd)	Pioglitazone hydrochloride
56208	Pioglitazone 15mg tablets (A A H Pharmaceuticals Ltd)	Pioglitazone hydrochloride
56376	Rosiglitazone 4mg with glimepiride 4mg tablet	Rosiglitazone Maleate
56831	Troglitazone 200mg Tablet	
Sulfonylureas		
32	Gliclazide 80mg tablets	Gliclazide
547	Glipizide 2.5mg tablets	Glipizide
1253	Chlorpropamide 100mg tablets	Chlorpropamide
1254	Glibenclamide 5mg tablets	Glibenclamide
1847	Chlorpropamide 250mg tablets	Chlorpropamide
1964	Diamicron 80mg tablets (Servier Laboratories Ltd)	Gliclazide
1965	Tolbutamide 500mg tablets	Tolbutamide
2219	Glibenclamide 2.5mg tablets	Glibenclamide
4862	Diabetamide 2.5mg tablets (Ashbourne Pharmaceuticals Ltd)	Glibenclamide
5276	Glimepiride 1mg tablets	Glimepiride
5316	Glimepiride 4mg tablets	Glimepiride
5353	Glimepiride 2mg tablets	Glimepiride
5627	Gliclazide 30mg modified-release tablets	Gliclazide
5636	Glipizide 5mg tablets	Glipizide
6337	Glimepiride 3mg tablets	Glimepiride
7284	Amaryl 2mg tablets (Zentiva)	Glimepiride
7332	Amaryl 1mg tablets (Zentiva)	Glimepiride
7409	Amaryl 3mg tablets (Zentiva)	Glimepiride

SUPPLEMENTARY DATA

7744	Daonil 5mg tablets (Sanofi)	Glibenclamide
7912	Semi-Daonil 2.5mg tablets (Sanofi)	Glibenclamide
8034	Diabinese 100mg Tablet (Pfizer Ltd)	Chlorpropamide
8168	Diabinese 250mg Tablet (Pfizer Ltd)	Chlorpropamide
8976	Euglucon 2.5mg tablets (Aventis Pharma)	Glibenclamide
9108	TOLBUTAMIDE 250 MG TAB	
10427	Tolazamide 250mg Tablet	Tolazamide
11284	Amaryl 4mg tablets (Zentiva)	Glimepiride
11695	Diamicron 30mg MR tablets (Servier Laboratories Ltd)	Gliclazide
11946	Tolbutamide 50mg/ml Injection	Tolbutamide
12245	Glutril 25mg Tablet (Roche Products Ltd)	Glibornuride
12259	Glibornuride 25mg Tablet	Glibornuride
12455	Rastinon 500mg Tablet (Hoechst Marion Roussel)	Tolbutamide
12513	Glibenese 5mg tablets (Pfizer Ltd)	Glipizide
13331	Euglucon 5mg tablets (Sanofi)	Glibenclamide
15374	Gliclazide 40mg/5ml oral suspension	Gliclazide
16211	TOLBUTAMIDE 100 MG TAB	
16602	Calabren 2.5mg Tablet (Berk Pharmaceuticals Ltd)	Glibenclamide
17343	Gliclazide 80mg tablets (A A H Pharmaceuticals Ltd)	Gliclazide
17698	Minodiab 5mg tablets (Pfizer Ltd)	Glipizide
17706	Minodiab 2.5mg tablets (Pfizer Ltd)	Glipizide
19336	Tolazamide 100mg Tablet	Tolazamide
21424	Glibenclamide 5mg/5ml oral suspension	Glibenclamide
21489	Tolanase 250mg Tablet (Pharmacia Ltd)	Tolazamide
21564	Gliclazide 80mg tablets (Wockhardt UK Ltd)	Gliclazide
21832	Diabetamide 5mg tablets (Ashbourne Pharmaceuticals Ltd)	Glibenclamide
21892	Diaglyk 80mg tablets (Ashbourne Pharmaceuticals Ltd)	Gliclazide
22145	Tolanase 100mg Tablet (Pharmacia Ltd)	Tolazamide
22614	DAONIL 10 MG TAB	
22636	TOLBUTAMIDE 1 GM TAB	
22858	Acetohexamide 500mg tablets	Acetohexamide
24848	Glymidine sodium 500mg Tablet	Glymidine Sodium
25636	Libanil 2.5mg Tablet (Approved Prescription Services Ltd)	Glibenclamide
26118	Dimelor 500mg Tablet (Eli Lilly and Company Ltd)	Acetohexamide
26218	Calabren 5mg Tablet (Berk Pharmaceuticals Ltd)	Glibenclamide
27969	Glymese 250mg Tablet (DDSA Pharmaceuticals Ltd)	Chlorpropamide
28708	Malix 2.5mg Tablet (Lagap)	Glibenclamide
29326	Glipizide 5mg tablets (Generics (UK) Ltd)	Glipizide
29939	Gliclazide 80mg tablets (Generics (UK) Ltd)	Gliclazide
30460	Malix 5mg Tablet (Lagap)	Glibenclamide
31212	Gliclazide 80mg tablets (Actavis UK Ltd)	Gliclazide
31474	Libanil 5mg Tablet (Approved Prescription Services Ltd)	Glibenclamide
33562	Duclazide 80mg Tablet (Dumex Ltd)	Gliclazide
33673	Tolbutamide 500mg tablets (Actavis UK Ltd)	Tolbutamide
34399	Gliclazide 80mg tablets (IVAX Pharmaceuticals UK Ltd)	Gliclazide
34507	Glibenclamide 2.5mg tablets (Wockhardt UK Ltd)	Glibenclamide

SUPPLEMENTARY DATA

34563	Glibenclamide 5mg tablets (Wockhardt UK Ltd)	Glibenclamide
34676	Glibenclamide 2.5mg tablets (A A H Pharmaceuticals Ltd)	Glibenclamide
34706	Glibenclamide 2.5mg tablets (IVAX Pharmaceuticals UK Ltd)	Glibenclamide
34802	Glipizide 5mg tablets (IVAX Pharmaceuticals UK Ltd)	Glipizide
34932	Gliclazide 80mg tablets (Genus Pharmaceuticals Ltd)	Gliclazide
34957	Tolbutamide 500mg tablets (A A H Pharmaceuticals Ltd)	Tolbutamide
36856	Gliclazide 80mg tablets (Sandoz Ltd)	Gliclazide
40365	Glimepiride 1mg tablets (Actavis UK Ltd)	Glimepiride
40425	Nazdol MR 30mg tablets (Teva UK Ltd)	Gliclazide
41558	Glibenclamide 5mg tablets (Teva UK Ltd)	Glibenclamide
41559	Glibenclamide 5mg tablets (A A H Pharmaceuticals Ltd)	Glibenclamide
41593	Glibenclamide 2.5mg tablets (Teva UK Ltd)	Glibenclamide
42790	Gliclazide 80mg Tablet (Merck Generics (UK) Ltd)	Gliclazide
43065	Gliclazide 40mg tablets	Gliclazide
43465	Zicron 40mg tablets (Bristol Laboratories Ltd)	Gliclazide
44304	Glyconon 500mg Tablet (DDSA Pharmaceuticals Ltd)	Tolbutamide
44473	Edicil MR 30mg tablets (Ratiopharm UK Ltd)	Gliclazide
44738	Niddaryl 1mg tablets (Dee Pharmaceuticals Ltd)	Glimepiride
45215	Gliclazide 80mg Tablet (Neo Laboratories Ltd)	Gliclazide
45831	Dacadis MR 30mg tablets (Generics (UK) Ltd)	Gliclazide
46927	Tolbutamide 500mg tablets (Teva UK Ltd)	Tolbutamide
47074	Gliclazide 80mg/5ml oral suspension	Gliclazide
47894	Nazdol MR 30mg tablets (Consilient Health Ltd)	Gliclazide
48056	Gliclazide 80mg tablets (Sovereign Medical Ltd)	Gliclazide
51955	Gliclazide 80mg tablets (Accord Healthcare Ltd)	Gliclazide
53288	Gliclazide 30mg modified-release tablets (A A H Pharmaceuticals Ltd)	Gliclazide
54764	Gliclazide 80mg tablets (Arrow Generics Ltd)	Gliclazide
55862	Gliclazide Oral solution	Gliclazide
56008	Gliclazide 80mg tablets (Almus Pharmaceuticals Ltd)	Gliclazide
56437	Gliclazide 60mg modified-release tablets	Gliclazide

For combined metformin and thiazolidinedione medications, the doses of each medication were extracted separately. Where there were two prescriptions for the same medication on the same date, the mean of the non-zero quantities was taken.

SUPPLEMENTARY DATA

HbA1cs

Records matching the following HbA1c-related medcodes were extracted:

medcode	readcode
5717	42W..11
9958	42W..00
13597	42W1.00
13604	42W3.00
14049	42WZ.00
14050	42c..00
14051	44TB.00
14052	42W..12
14053	42W4.00
19807	42c3.00
27040	44TC.00
29218	42W2.00
37035	66Ae.00
39205	44TL.00
40463	42c1.00
42360	42c0.00
46079	42c2.00
96968	42W5.00
101208	66Ae000

SUPPLEMENTARY DATA

Oedema

Oedema was identified using clinical codes relating to keywords associated with oedema, swelling etc. Two researchers independently searched the medical code database and compared results. The full list of codes is below:

medcode	readcode	description
387	N247013	Swollen legs
1284	22C3.00	O/E - oedema of feet
1906	22C2.11	O/E - ankle oedema
2140	183..12	Swelling - oedema - symptom
3158	183..00	Oedema
4950	R023.00	[D]Oedema
5889	1832.11	Ankle swelling symptom
5919	1833.11	Leg swelling symptom
6047	183..11	Oedema - symptom
6585	22C4.11	O/E - leg oedema
6651	22C..11	O/E - swelling - oedema
6764	22C8.11	O/E - scrotal oedema
7106	22C3.11	O/E - foot oedema
7122	1832	Ankle swelling
9108	1837	Pitting oedema
9392	22C7.00	O/E - sacral oedema
10931	22C..00	O/E - oedema
14702	R023z00	[D]Oedema NOS
15047	1833	Leg swelling
15477	R023z11	[D]Dependent oedema
19358	22C4.00	O/E - oedema of legs
19714	22C5.11	O/E - thigh oedema
20301	R023000	[D]Oedema, generalized
20553	22C2.00	O/E - oedema of ankles
22500	8E95.00	Reduction of oedema
22734	1838	Sacral oedema
28107	L161.00	Oedema or excessive weight gain in pregnancy no hypertension
28419	22CZ.00	O/E - oedema NOS
29565	L161.13	Gestational oedema
30309	183Z.00	Oedema NOS
36394	L16C.00	Pregnancy induced oedema+proteinuria without hypertension
37201	L16C100	Gestational oedema with proteinuria
43618	G581.12	Pulmonary oedema - acute
49411	22C8.00	O/E - genital oedema
53921	L161000	Oedema or excessive weight gain in pregnancy, unspecified
61224	22C5.00	O/E - oedema of thighs
61563	L161300	Oedema or excessive weight gain in pregnancy - not delivered
61835	L161z00	Oedema or excessive weight gain in pregnancy NOS
92998	Lyu1.00	[X]Oedema,proteinuria+hypertens in pregnancy,childbrth,puerp
98612	1839	Oedema of calf

SUPPLEMENTARY DATA

103579	183C.00	Reduction in peripheral oedema
558	H584.00	Acute pulmonary oedema unspecified
5155	23E1.00	O/E - pulmonary oedema
5293	H584z00	Acute pulmonary oedema NOS
7321	H541z00	Pulmonary oedema NOS
24552	SN27.00	Heat oedema
26082	H541000	Chronic pulmonary oedema
39706	H584000	Postoperative pulmonary oedema
48466	H584.11	Acute oedema of lung, unspecified
102627	183B.00	Worsening pulmonary oedema
102720	183A.00	Worsening peripheral oedema

SUPPLEMENTARY DATA

Fracture

Fracture codes were identified from read codes associated with fracture, as identified as part of another study of fragility fractures (Erwin J. Research Associate. Personal communication. 8th Dec 2015. List based on: Staa TPV, Geusens P, Bijlsma JWJ, Leufkens HGM, Cooper C: Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis & Rheumatism* 2006;54:3104-3112). The full list of read codes is below:

medcode	readcode	description
11503	N331M00	Fragility fracture due to unspecified osteoporosis
93497	N331N00	Fragility fracture
23803	S301800	Open fracture proximal femur, subcapital, Garden grade III
29145	S302200	Closed fracture proximal femur, subtrochanteric
33957	S300700	Closed fracture proximal femur, subcapital, Garden grade II
34078	S300900	Closed fracture proximal femur, subcapital, Garden grade IV
34351	S300600	Closed fracture proximal femur, subcapital, Garden grade I
36599	S300800	Closed fracture proximal femur, subcapital, Garden grade III
38489	S300.00	Closed fracture proximal femur, transcervical
38878	S301500	Open fracture proximal femur, subcapital, Garden grade unspec
45141	S302100	Closed fracture proximal femur, intertrochanteric, two part
49209	S300y00	Closed fracture proximal femur, other transcervical
51999	S301900	Open fracture proximal femur, subcapital, Garden grade IV
52194	S300300	Closed fracture proximal femur, basicervical
137	S23x111	Fracture of radius NOS
199	S23B.00	Fracture of lower end of radius
203	S234.11	Wrist fracture - closed
280	S120.00	Closed fracture rib
343	S234100	Closed Colles' fracture
358	S3z..11	Fracture NOS
455	S3z0000	Greenstick fracture
517	S22..00	Fracture of humerus
520	S31z.00	Fracture of femur, NOS
553	S242000	Fracture of scaphoid
738	S13..00	Fracture or disruption of pelvis
835	S10B200	Fracture of coccyx
868	S4...13	Fracture dislocations and fracture subluxations
909	S23z.00	Fracture of radius and ulna, NOS
1073	S23x211	Fracture of ulna NOS
1177	S21..00	Fracture of scapula
1250	S224.11	Elbow fracture - closed
1548	S228.00	Fracture of lower end of humerus
1591	S130.00	Closed fracture acetabulum
1700	S352.11	March fracture
1742	S234200	Closed fracture of the distal radius, unspecified
1857	S354.00	Fracture of calcaneus

SUPPLEMENTARY DATA

1994	S30..11	Hip fracture
2101	S226.00	Fracture of upper end of humerus
2225	S30..00	Fracture of neck of femur
2303	S237.00	Fracture of upper end of radius
2328	S10B500	Fracture of pubis
2442	S355.00	Fracture of talus
2461	S01..00	Fracture of base of skull
2603	S3...11	Leg fracture
2662	S230300	Closed Monteggia's fracture
3025	S3z2.00	Stress fracture
3288	S10A.00	Fracture of neck
3573	S10x.00	Closed fracture of spine, unspecified,
3675	S10B100	Fracture of sacrum
3748	S233.00	Open fracture of radius and ulna, shaft
3888	S104.00	Closed fracture lumbar vertebra
3983	S122.00	Closed fracture sternum
4013	N331L00	Collapse of vertebra due to osteoporosis NOS
4359	S23x300	Closed fracture of the radius and ulna
4409	S10..12	Fracture of vertebra without spinal cord lesion
5301	S302.00	Closed fracture of proximal femur, pectrochanteric
5332	S312300	Closed fracture distal femur, supracondylar
5381	S15..00	Fracture of thoracic vertebra
5841	N331J00	Collapse of lumbar vertebra due to osteoporosis
6213	S23C.00	Fracture of lower end of both ulna and radius
6320	S312100	Closed fracture of femoral condyle, unspecified
6667	S132100	Closed fracture pelvis, multiple pubic rami - stable
6825	S23..00	Fracture of radius and ulna
6868	S310.00	Closed fracture of femur, shaft or unspecified part
6893	S224100	Closed fracture distal humerus, supracondylar
7004	S132000	Closed fracture pelvis, single pubic ramus
7009	S230600	Closed fracture radius, head
7636	S231600	Open fracture radial head
7660	S230700	Closed fracture radius, neck
7988	S239.00	Fracture of shaft of radius
8040	S31..00	Other fracture of femur
8056	S242.00	Fracture at wrist and hand level
8243	S305.00	Subtrochanteric fracture
8255	S10..00	Fracture of spine without mention of spinal cord injury
8266	S104100	Closed fracture lumbar vertebra, wedge
8382	S238.00	Fracture of shaft of ulna
8410	S231B00	Open fracture olecranon, intra-articular
8589	S315.00	Fracture of lower end of femur
8613	S10B600	Multiple fractures of lumbar spine and pelvis

SUPPLEMENTARY DATA

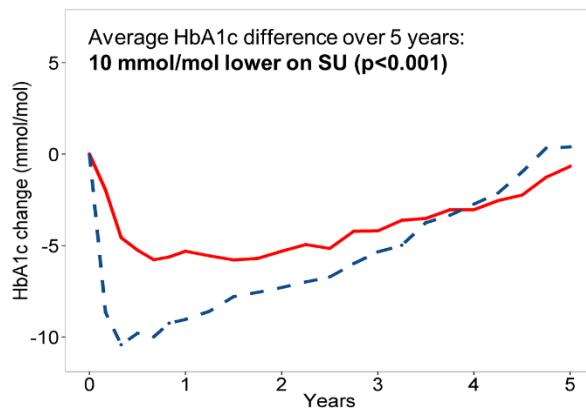
Subgroup Data summary

Summary for males BMI ≤30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

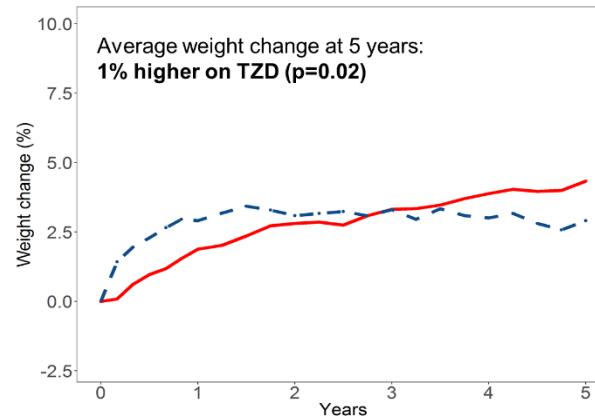
Males with a BMI ≤30

■ Thiazolidinedione ■ Sulfonylurea

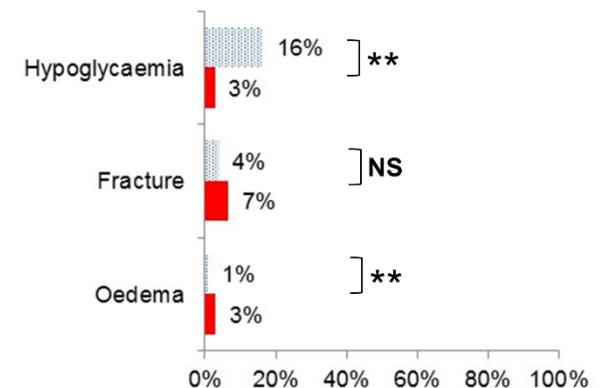
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



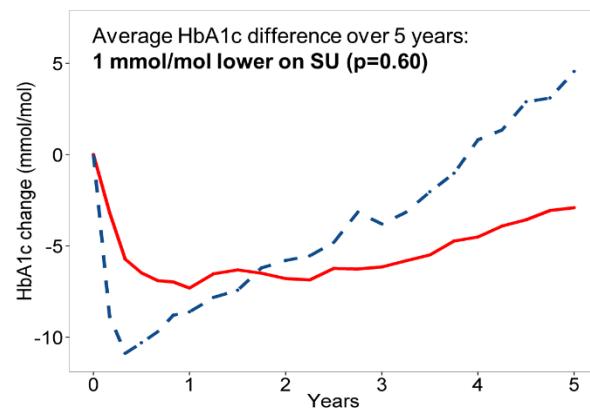
SUPPLEMENTARY DATA

Summary for males BMI >30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

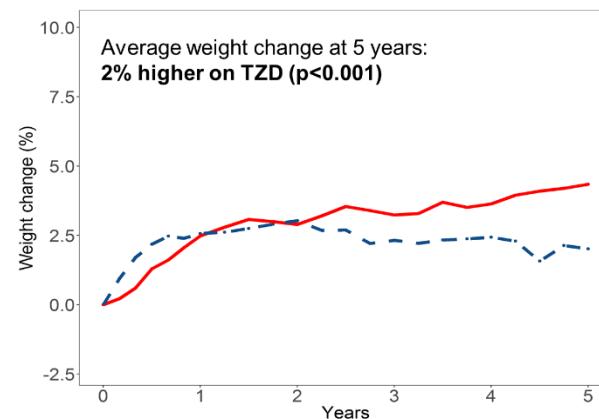
Males with a BMI >30

■ Thiazolidinedione ■ Sulfonylurea

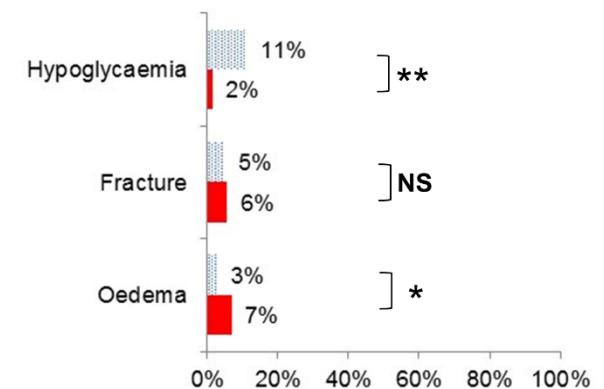
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



* = $p<0.05$, ** = $p <0.01$, NS = no significant difference

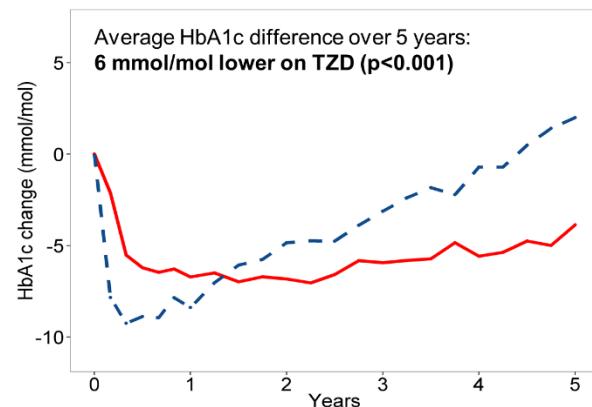
SUPPLEMENTARY DATA

Summary for females BMI ≤ 30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

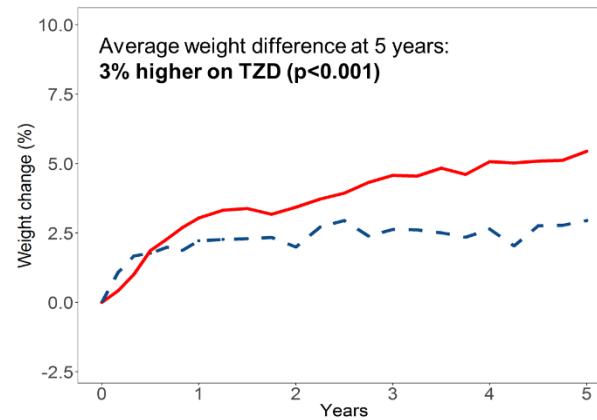
Females with a BMI ≤ 30

■ Thiazolidinedione ■ Sulfonylurea

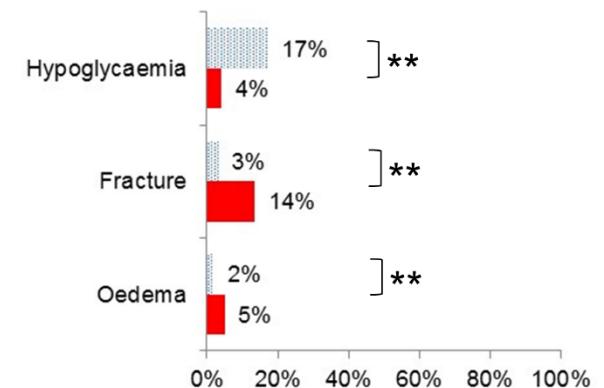
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



* = $p < 0.05$, ** = $p < 0.01$, NS = no significant difference

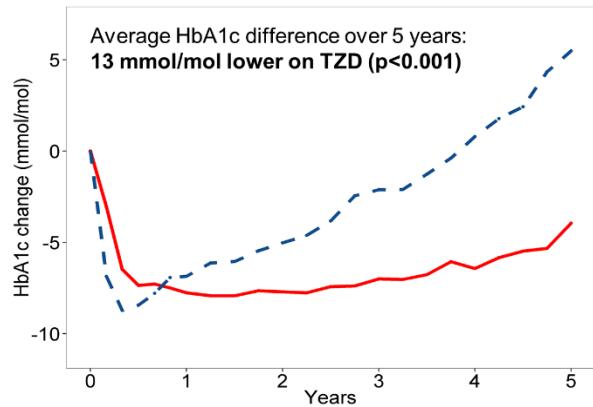
SUPPLEMENTARY DATA

Summary for females BMI >30 on thiazolidinedione (red) and sulfonylurea (blue dotted/dashed). HbA1c and weight data from ADOPT, side effects from ADOPT and RECORD.

Females with a BMI >30

■ Thiazolidinedione ■ Sulfonylurea

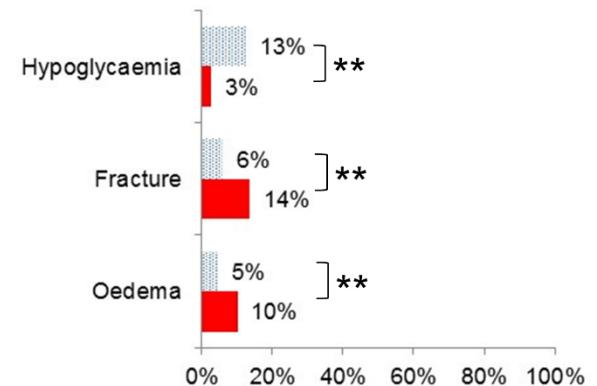
Average change in HbA1c from baseline



Average change in weight as a % of initial weight



Frequency of side effects at 5 years



* = $p<0.05$, ** = $p <0.01$, NS = no significant difference