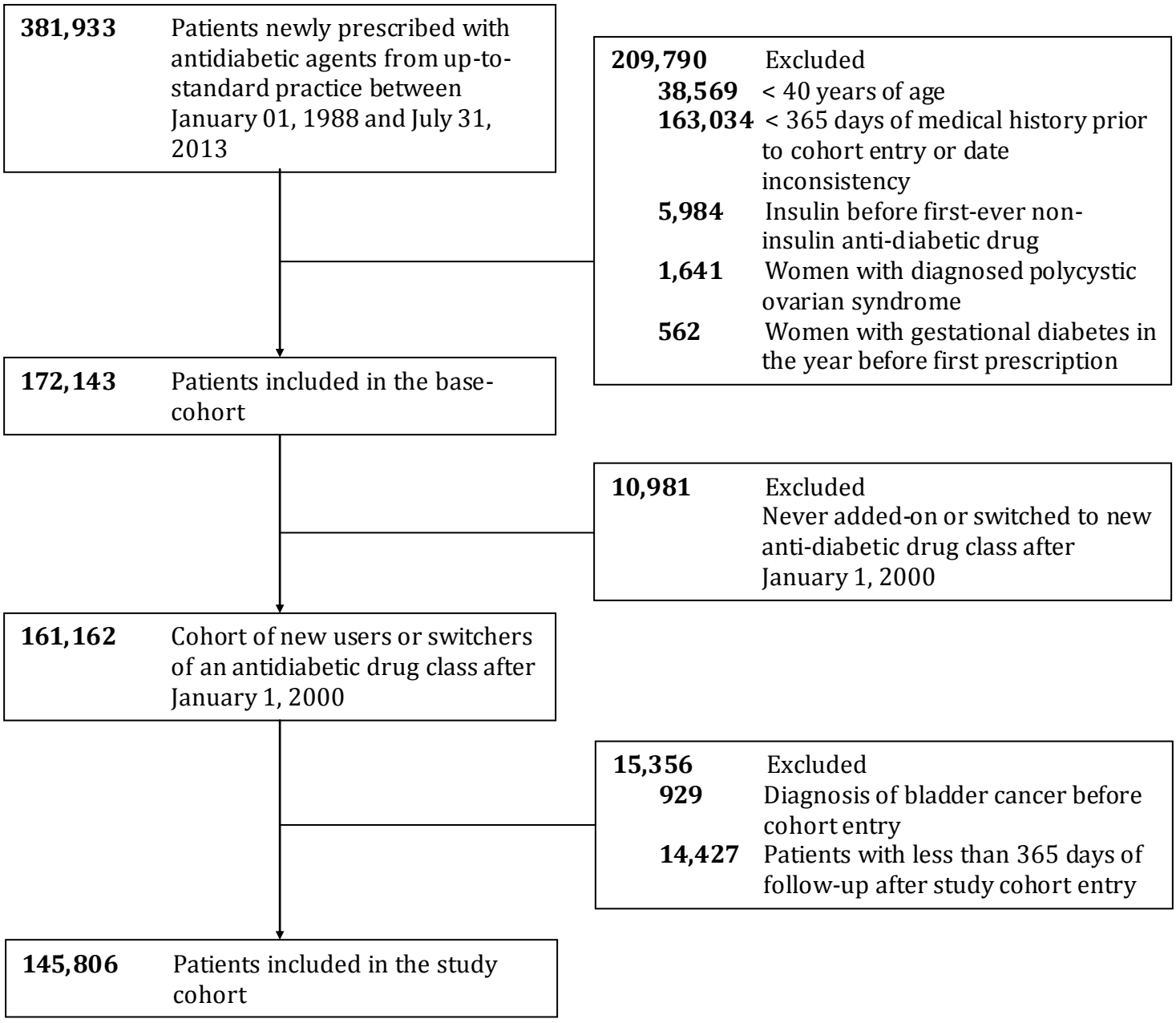
Pioglitazone use and bladder cancer risk: a population-based cohort study

Online supplementary material

Supplementary Figure 1: Study flow chart of patients initiating an antidiabetic drug between January 1, 1988 and July 31, 2013



Supplementary Table 1. Baseline characteristics of the cohort overall, and stratified by users and non-users of rosiglitazone at cohort entry

Characteristics	Entire cohort (n=145,806)	Rosiglitazone [a] (n=2127)	No TZD use [b] (n=142,758)
Male, n (%)	82,824 (56.8)	1167 (54.9)	81,114 (56.8)
Age (years), mean (SD)	63.7 (11.7)	64.3 (10.4)	63.7 (11.7)
Year of cohort entry, n (%)			
2000	8167 (5.6)	194 (9.1)	7970 (5.6)
2001	9445 (6.5)	381 (17.9)	8938 (6.3)
2002	9604 (6.6)	260 (12.2)	9224 (6.5)
2003	10,393 (7.1)	239 (11.2)	10,040 (7.0)
2004	12,141 (8.3)	379 (17.8)	11,624 (8.1)
2005	11,683 (8.0)	304 (14.3)	11,273 (7.9)
2006	11,126 (7.6)	232 (10.9)	10,810 (7.6)
2007	11,657 (8.0)	116 (5.5)	11,477 (8.0)
2008	11,731 (8.1)	14 (0.7)	11,664 (8.2)
2009	12,445 (8.5)	S*	12,391 (8.7)
2010	12,035 (8.3)	S*	11,995 (8.4)
2011	10,659 (7.3)	0 (0.0)	10,645 (7.5)
2012	10,110 (6.9)	0 (0.0)	10,101 (7.1)
2013	4610 (3.2)	0 (0.0)	4606 (3.2)
Body mass index, n (%)			
<30 kg/m^2	67,621 (46.4)	990 (46.5)	66,152 (46.3)
≥30 kg/m^2	76,627 (52.6)	1118 (52.6)	75,076 (52.6)
Unknown	1558 (1.1)	19 (0.9)	1530 (1.1)
Smoking, n (%)			
Ever	85,032 (58.3)	1167 (54.9)	83,342 (58.4)
Never	57,283 (39.3)	917 (43.1)	55,982 (39.2)
Unknown	3491 (2.4)	43 (2.0)	3434 (2.4)
Alcohol-related disorders, n (%)	15,491 (10.6)	171 (8.0)	15,240 (10.7)
Haemoglobin A1c, n (%)			
≤7.4 %	27,209 (18.7)	268 (12.6)	26,793 (18.8)
>7.4 %	68,309 (46.9)	1287 (60.5)	66,485 (46.6)
Unknown	50,288 (34.5)	572 (26.9)	49,480 (34.7)
Duration of treated diabetes (years), mean (SD)	0.3 (1.6)	4.4 (3.8)	0.3 (1.3)
Prior bladder conditions, n (%)	13,755 (9.4)	227 (10.7)	13,415 (9.4)
Cancer, n (%)	13,908 (9.5)	186 (8.7)	13,646 (9.6)
Urine protein test, n (%)	62,729 (43.0)	1166 (54.8)	61,072 (42.8)
Charlson comorbidity score [c], mean (SD)	2.0 (1.3)	2.0 (1.3)	2.0 (1.3)
Previous antidiabetic drug use, n (%) [d]			
Metformin	122,843 (84.3)	1581 (74.3)	120,765 (84.6)
Sulfonylureas	31,825 (21.8)	1175 (55.2)	30,217 (21.2)
Pioglitazone	921 (0.6)	0 (0.0)	0 (0.0)
Rosiglitazone	2127 (1.5)	2127 (100.0)	0 (0.0)
Incretin-based drugs	375 (0.3)	0 (0.0)	375 (0.3)
Insulins	1467 (1.0)	18 (0.9)	1435 (1.0)
Others	1406 (1.0)	144 (6.8)	1217 (0.9)

Abbreviations: S: suppressed; SD: standard deviation; TZDs: thiazolidinediones

Note: Patients exposed to pioglitazone alone or together with rosiglitazone are not displayed in the table.

*Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

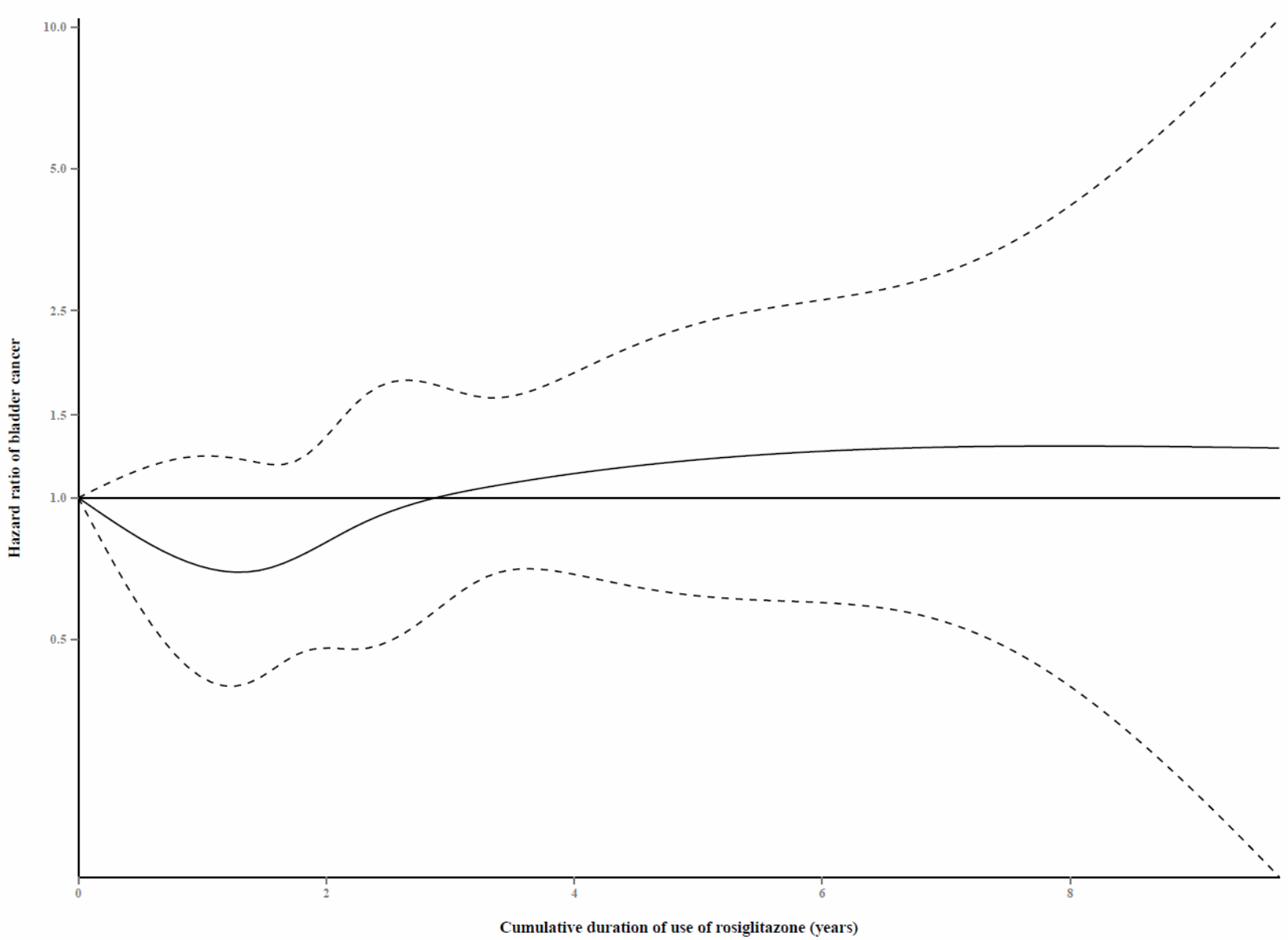
[a] Rosiglitazone only users at cohort entry

[b] No use of any TZD at cohort entry

[c] Including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes-related chronic complications, connective tissue disease, mild liver disease, hemiplegia or paraplegia, renal disease, moderate to severe liver disease, acquired immuno-deficiency syndrome (AIDS). Adapted to exclude cancer.

[d] Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

Supplementary Figure 2. Smooth restricted cubic spline curve of the adjusted hazard ratio of bladder cancer (solid line) and 95% confidence limits (dashed lines) as a function of the cumulative duration of use of rosiglitazone



Supplementary Table 2. Hazard ratios for the association between rosiglitazone use and the risk of bladder cancer

Exposure [a]	Events	Person-years	Incidence rate (95% CI) [b]	Age-and-sex-adjusted HR (95% CI)	Fully Adjusted HR (95% CI) [c]
Primary analysis					
No TZD use [d]	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	56	64,990	86.2 (65.1 to 111.9)	1.19 (0.90 to 1.58)	1.10 (0.83 to 1.47)
Cumulative duration					
≤ 1 year	17	18,142	93.7 (54.6 to 150.0)	1.34 (0.82 to 2.18)	1.23 (0.75 to 2.02)
1-2 years	10	17,718	56.4 (27.1 to 103.8)	0.78 (0.42 to 1.47)	0.71 (0.38 to 1.34)
> 2 years	29	29,130	99.6 (66.7 to 143.0)	1.36 (0.93 to 1.99)	1.27 (0.86 to 1.87)
p-trend				0.32	0.69
Cumulative dose					
≤ 2008 mg	21	21,456	97.9 (60.6 to 149.6)	1.37 (0.89 to 2.13)	1.26 (0.81 to 1.98)
2008-4960 mg	18	22,087	81.5 (48.3 to 128.8)	1.12 (0.70 to 1.80)	1.03 (0.64 to 1.66)
> 4960 mg	17	21,446	79.3 (46.2 to 126.9)	1.09 (0.67 to 1.78)	1.02 (0.62 to 1.67)
p-trend				0.34	0.72

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: thiazolidinediones.

[a] Users of pioglitazone and users of combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, year of cohort entry, sex, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] No use of pioglitazone or rosiglitazone.

Supplementary Table 3. Sensitivity analyses for the association between pioglitazone use and bladder cancer

Exposure [a]	Events	Person-years	Incidence rate [b] (95% CI)	Age-and-sex-adjusted HR (95% CI)	Fully Adjusted HR (95% CI)[c]
No lag period					
No TZD use	**606**	**689,797**	**87.9 (81.7 to 95.1)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**59**	**55,859**	**105.6 (80.4 to 136.2)**	**1.54 (1.17 to 2.03)**	**1.49 (1.13 to 1.97)**
2-year lag period					
No TZD use	**412**	**447,751**	**92.0 (83.3 to 101.3)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**44**	**34,481**	**127.6 (92.7 to 171.3)**	**1.77 (1.28 to 2.44)**	**1.73 (1.26 to 2.39)**
Stricter exposure definition [d]					
No TZD use	**518**	**579,348**	**89.4 (81.9 to 97.5)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**48**	**37,999**	**126.3 (93.1 to 167.5)**	**1.81 (1.33 to 2.46)**	**1.76 (1.29 to 2.39)**
Exclude and censor on bladder conditions [e]					
No TZD use [d]	**429**	**500,774**	**85.7 (77.8 to 94.2)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**49**	**38,886**	**126.0 (93.2 to 166.6)**	**1.78 (1.31 to 2.42)**	**1.73 (1.27 to 2.35)**
Additional censoring variables [f]					
No TZD use	**415**	**527,957**	**78.6 (71.2 to 86.5)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**46**	**42,695**	**107.7 (78.9 to 143.7)**	**1.77 (1.29 to 2.43)**	**1.72 (1.26 to 2.37)**
Censoring follow-up on December 31, 2010					
No TZD use	**300**	**332,524**	**90.2 (80.3 to 101.0)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**24**	**20,237**	**118.6 (76.0 to 176.5)**	**1.66 (1.08 to 2.53)**	**1.60 (1.05 to 2.46)**
Additional adjustment for antidiabetic drugs					
No TZD use	**497**	**558,924**	**88.9 (81.3 to 97.1)**	**1.00 [Reference]**	**1.00 [Reference]**
Pioglitazone	**54**	**44,618**	**121.0 (90.9 to 157.9)**	**1.68 (1.26 to 2.24)**	**1.56 (1.16 to 2.09)**

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: Thiazolidinediones.

[a] Users of rosiglitazone and users of combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

[c] Adjusted for age, sex, year of cohort entry, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] Exposure defined by at least 4 prescriptions in a 12 months window

[e] Bladder conditions includes

[f] Benign bladder lesions, in situ bladder cancer, heart failure, liver failure.

Supplementary Table 4: Sensitivity analyses for the association between rosiglitazone use and bladder cancer					
Exposure [a]	**Events**	**Person-years**	**Incidence rate** [b] **(95% CI)**	**Age-and-sex-adjusted HR (95% CI)**	**Fully Adjusted HR (95% CI)** [c]
No lag period					
No TZD use	606	689,797	87.9 (81.0 to 95.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	57	73,552	77.5 (58.7 to 100.4)	1.10 (0.84 to 1.45)	1.02 (0.77 to 1.36)
2-year lag period					
No TZD use	412	447,751	92.0 (83.3 to 101.3)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	52	56,743	91.6 (68.4 to 120.2)	1.27 (0.95 to 1.71)	1.16 (0.85 to 1.57)
Stricter exposure definition [d]					
No TZD use d	518	579,348	89.4 (81.9 to 97.5)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	44	57,047	77.1 (56.0 to 103.5)	1.10 (0.80 to 1.51)	1.01 (0.73 to 1.39)
Exclude and censor on bladder conditions [e]					
No TZD use [d]	429	500,774	85.7 (77.8 to 94.2)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	50	56,573	88.4 (65.6 to 116.5)	1.25 (0.93 to 1.69)	1.16 (0.85 to 1.58)
Additional censoring variables [f]					
No TZD use	415	527,957	78.6 (71.2 to 86.5)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	45	61,310	73.4 (53.5 to 98.2)	1.19 (0.87 to 1.63)	1.10 (0.79 to 1.52)
Censoring follow-up on December 31, 2010					
No TZD use	300	332,524	90.2 (80.3 to 101.0)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	38	49,736	76.4 (54.1 to 104.9)	1.08 (0.77 to 1.53)	1.02 (0.72 to 1.44)
Additional adjustment for antidiabetic drugs					
No TZD use	497	558,924	88.9 (81.3 to 97.1)	1.00 [Reference]	1.00 [Reference]
Rosiglitazone	56	64,990	86.2 (65.1 to 111.9)	1.19 (0.90 to 1.58)	1.07 (0.80 to 1.42)

Abbreviations: CI: confidence interval; HR: hazard ratio; TZDs: Thiazolidinediones

[a] Users of pioglitazone and users of combination of pioglitazone and rosiglitazone are not displayed in the table, but were considered in the regression model for proper estimation of treatment effects.

[b] Per 100,000 person-years.

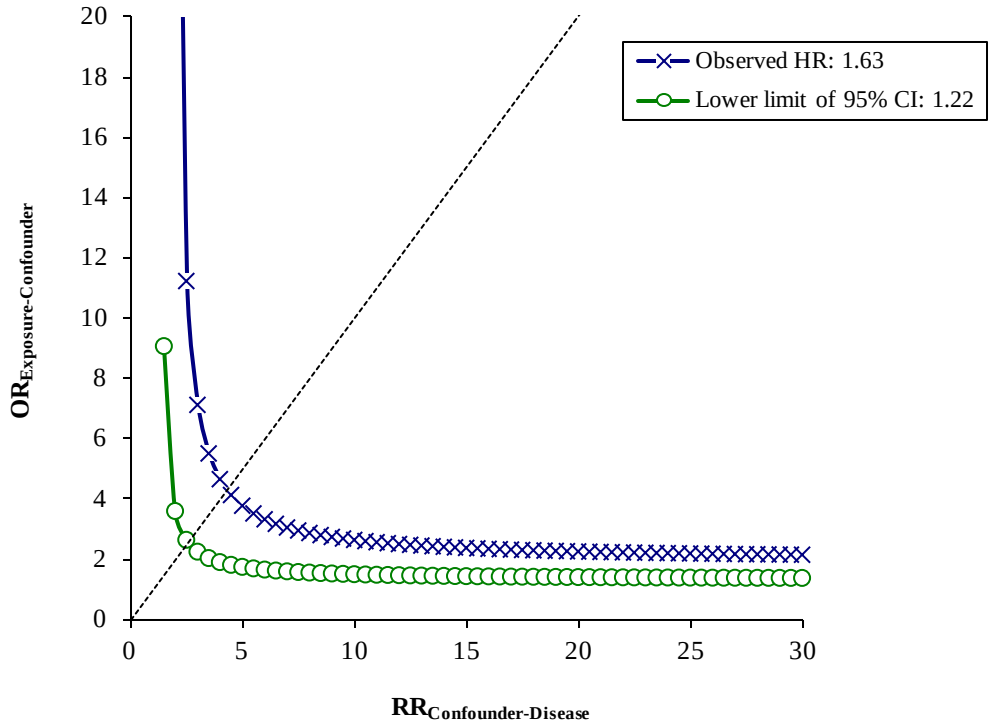
[c] Adjusted for age, sex, year of cohort entry, alcohol-related disorders, smoking status, obesity, haemoglobin A1c, previous cancer, bladder conditions, Charlson comorbidity score, duration of treated diabetes, urine protein test.

[d] Exposure defined by at least 4 prescriptions in a 12 months window

[e] Bladder conditions includes

[f] Benign bladder lesions, in situ bladder cancer, heart failure, liver failure.

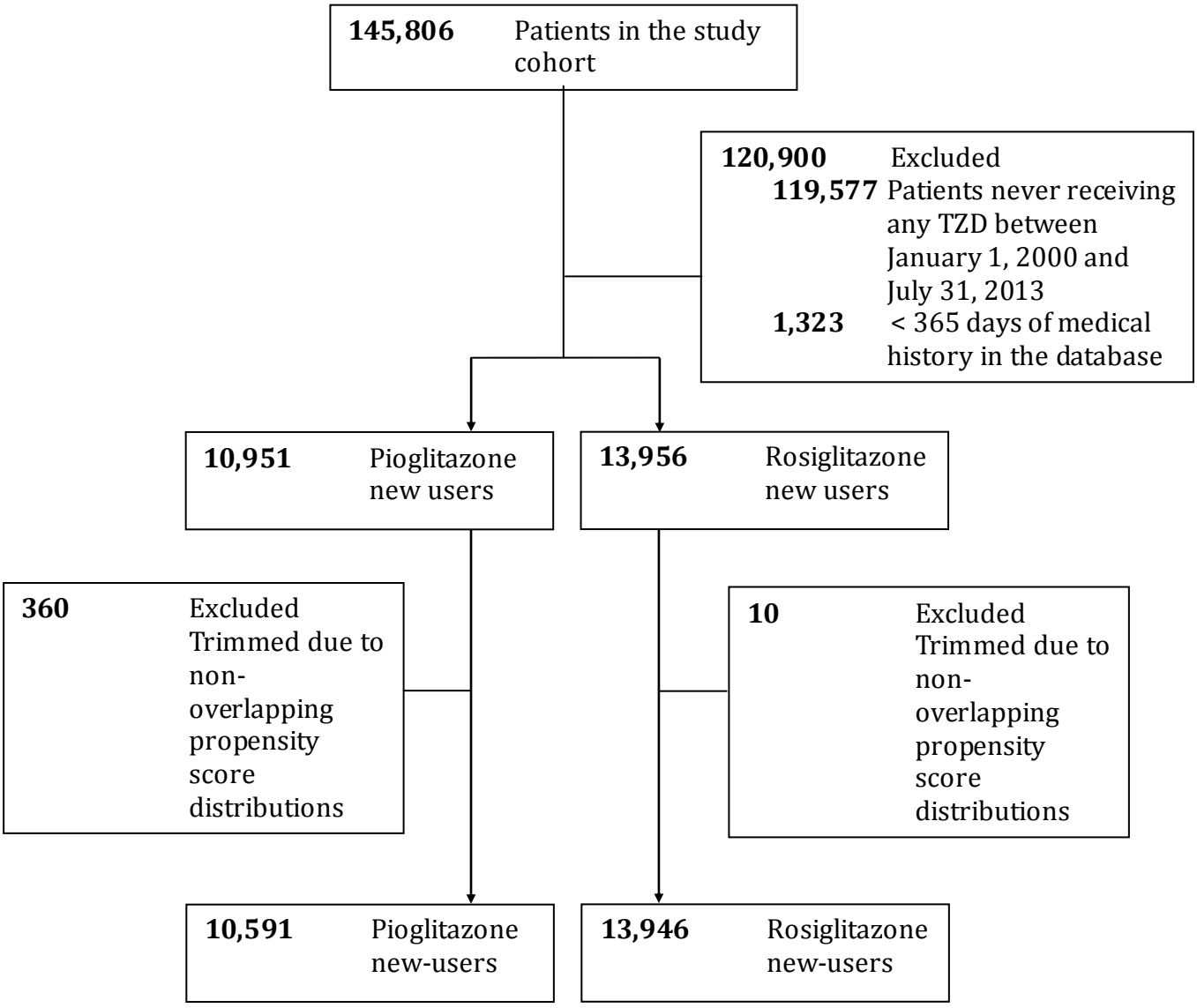
Supplementary Figure 3: Sensitivity analysis, strength of an unmeasured confounder needed to move the HR to the null.



Based on an observed HR of 1.63, a pioglitazone exposure prevalence of 7.3%, and a confounder prevalence of 20%. Blue line: observed hazard ratio (HR); Green line: lower bound of the confidence intervals. $OR_{Exposure\text{-}Confounder}$: odds ratio for the exposure-confounder association; $RR_{Confounder\text{-}Disease}$: relative risk for the confounder-disease association.

Exposure-confounder and confounder-disease associations to the right of the curves would be necessary to bring the association down to the null.

Supplementary Figure 4: Flowchart for the pioglitazone and rosiglitazone head-to-head comparison



Supplementary Table 5: Characteristics of patients initiating pioglitazone versus rosiglitazone		
Characteristics	**Pioglitazone[a] (n=10,591)**	**Rosiglitazone [b] (n=13,946)**
Male, n (%)	6246 (59.0)	7838 (56.2)
Age (years), mean (SD)	62.6 (10.5)	62.6 (10.6)
Year of cohort entry, n (%)		
2000	S*	282 (2.0)
2001	S*	751 (5.4)
2002	377 (3.6)	905 (6.5)
2003	485 (4.6)	1333 (9.6)
2004	750 (7.1)	2312 (16.6)
2005	794 (7.5)	2794 (20.0)
2006	854 (8.1)	3099 (22.2)
2007	1102 (10.4)	1859 (13.3)
2008	1456 (13.8)	315 (2.3)
2009	1604 (15.1)	211 (1.5)
2010	1470 (13.9)	85 (0.6)
2011	958 (9.1)	0 (0.0)
2012	369 (3.5)	0 (0.0)
2013	125 (1.2)	0 (0.0)
Body mass index, n (%)		
<30 kg/m^2	4662 (44.0)	6189 (44.4)
≥30 kg/m^2	5907 (55.8)	7711 (55.3)
Unknown	22 (0.2)	46 (0.3)
Smoking, n (%)		
Ever	6152 (58.1)	7635 (54.8)
Never	4186 (39.5)	5723 (44.4)
Unknown	253 (2.4)	588 (4.2)
Alcohol-related disorders, n (%)	844 (8.0)	955 (6.9)
Haemoglobin A1c, n (%)		
≤7.4 %	1208 (11.4)	1318 (9.5)
>7.4 %	5814 (54.9)	7283 (52.2)
Unknown	3569 (33.7)	5345 (38.3)
Duration of treated diabetes (years), mean (SD)	3.5 (3.0)	2.9 (2.7)
Prior bladder conditions, n (%)	918 (8.7)	1200(8.6)
Cancer, n (%)	806 (7.6)	1064 (7.6)
Urine protein test, n (%)	4862 (45.9)	6258 (44.9)
Charlson co-morbidity score [c], mean (SD)	1.7 (1.0)	1.6 (1.0)

Abbreviation: S: suppressed; SD: standard deviation

* Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

[a] Pioglitazone users at cohort entry.

[b] Rosiglitazone users at cohort entry.

[c] Including myocardial infarction, congestive heart failure, peripheral vascular disease, chronic pulmonary disease, cerebrovascular disease, dementia, peptic ulcer disease, diabetes-related chronic complications, connective tissue disease, mild liver disease, hemiplegia or paraplegia, renal disease, moderate to severe liver disease, acquired immuno-deficiency syndrome (AIDS). Adapted to exclude cancer.

Supplemental Method: Marginal structural Cox proportional hazards model sensitivity analysis.

We conducted a marginal structural Cox proportional hazards model to address potential residual time-dependent confounding over the 14.5-year follow-up period, a method designed to adjust for time-dependent confounding associated with time-varying exposures.[1 2] It first involved fitting two pooled logistic regression models to estimate the conditional probability of being exposed to pioglitazone and rosiglitazone given previous treatment history at each 30-day intervals during follow-up; one for the numerator and the other for the denominator of the stabilized inverse-probability-of-treatment weights (IPTWs). The numerator model included baseline covariates (age, sex, year of cohort entry, body mass index, smoking status, alcohol-related disorders, haemoglobin A1c, duration of treated diabetes, prior bladder conditions, history of cancer [other than non-melanoma skin cancer], the presence of a urine protein test, and Charlson comorbidity score) and follow-up time. The second denominator model included covariates (age, year of cohort entry, body mass index, smoking status, alcohol-related disorders, haemoglobin A1c, bladder conditions, cancer [other than non-melanoma skin cancer], the presence of a urine protein test, and Charlson comorbidity score) measured at each time interval and follow-up time. In both treatment models, the follow-up time variable was modelled using a restricted cubic spline with five knots to reduce bias due to model misspecification from linearity assumptions.[3] We also estimated inverse probability of censoring weights (IPCWs) in a similar fashion. Stabilized IPTW and IPCW for each patient were computed using the predicted probabilities from the two treatment and censoring models. The product of these stabilized IPTWs and IPCWs was then used to reweight the cohort, in which we estimated the hazard ratios of bladder cancer associated with the use of pioglitazone and rosiglitazone, with 95% confidence intervals calculated using robust variance estimators.[2]

References

(1) Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-60.

(2) Hernan MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology* 2000;11:561-70.

(3) Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168:656-64.