Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries

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ABSTRACT

OBJECTIVE

To evaluate the association between pioglitazone use and bladder cancer risk in patients with type 2 diabetes.

DESIGN

Retrospective cohort study using propensity score matched cohorts.

SETTINGS

Healthcare databases from Finland, the Netherlands, Sweden, and the United Kingdom. Data comprised country specific datasets of linked records on prescriptions, hospitals, general practitioners, cancer, and deaths.

PARTICIPANTS

Patients with type 2 diabetes who initiated pioglitazone (n=56 337) matched with patients with type 2 diabetes in the same country exposed to diabetes drug treatments other than pioglitazone (n=317 109). Two matched cohorts were created, using a 1:1 fixed ratio (nearest match cohort) and a 1:10 variable ratio (multiple match cohort). Patients were matched on treatment history and propensity scores accounting for several variables associated with pioglitazone initiation.

MAIN OUTCOME MEASURES

Hazard ratios and 95% confidence intervals were estimated by Cox's proportional hazards model with adjustments for relevant confounders. To assess the robustness of the findings, several sensitivity and stratified analyses were performed.

RESULTS

In the cohort exposed to pioglitazone treatment, 130 bladder cancers occurred over a mean follow-up time of 2.9 years. In the nearest match and multiple match cohorts not exposed to pioglitazone treatment, 153 and 970 bladder cancers were recorded, with a mean follow-up time of 2.8 and 2.9 years, respectively. With regards to bladder cancer risk, the adjusted hazard ratio for patients ever exposed versus never exposed to pioglitazone was 0.99 (95% confidence interval 0.75 to 1.30) and 1.00 (0.83 to 1.21) in the nearest and multiple match cohorts, respectively. Increasing duration of pioglitazone use and increasing cumulative dose were not associated with risk of bladder cancer (>48 months of pioglitazone use, adjusted hazard ratio 0.86 (0.44 to 1.66); >40 000 mg cumulative dose, 0.65 (0.33 to 1.26) in the nearest match cohort).

CONCLUSIONS

This study shows no evidence of an association between ever use of pioglitzone and risk of bladder cancer compared with never use, which is consistent with results from other recent studies that also included a long follow-up period.

TRIAL REGISTRATION

Registered to the European Union electronic register of post-authorisation studies (EU PAS register no EUPAS3626).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many earlier epidemiological studies have reported an increased bladder cancer risk in patients with type 2 diabetes using pioglitazone

However, several of these early studies had little control of treatment allocation bias or had no information on known risk factors of bladder cancer

Recent large studies with longer follow-up have reported no association between pioglitazone exposure and bladder cancer risk

WHAT THIS STUDY ADDS

This analysis of datasets from Finland, Sweden, the Netherlands, and the UK shows no evidence of an association between ever use of pioglitazone and risk of bladder cancer, compared with never use

Results indicate that longer duration of pioglitazone use does not increase the risk of bladder cancer

These results provide additional important information on the safety of pioglitazone use in Europe

Introduction

Pioglitazone is a drug from the thiazolidinediones class that is used for the treatment of type 2 diabetes mellitus. Whether pioglitazone use causes an increased risk of developing bladder cancer has been debated for several years. In the two year, prospective, macrovascular events outcome clinical trial (PROactive), researchers observed an excess of bladder cancers among patients treated with pioglitazone versus placebo (14 *v* six).[1] However, 11 cancers in the pioglitazone group occurred during the first year of treatment, including two diagnosed 13 and 14 days into the trial, another at one month, a fourth at three months, and a fifth at four months. Increased risk of urothelial cancers requires long exposure to risk factors, thus it is considered not plausible that these early cancers could be due to pioglitazone.[2] Long term follow-up of the PROactive trial participants found no imbalance in bladder cancers between the pioglitazone versus placebo groups (23 *v* 22).[3]

Multiple epidemiological studies, and meta-analyses of these studies, have investigated pioglitazone use and

bladder cancer.[4-6] Most studies had short term exposure and follow-up but observed a positive association, and the meta-analyses show a pooled risk estimate of 1.2. Based on these early studies, some commentators have opined that it can confidently be assumed that pioglitazone increases the risk of bladder cancer.[7] A recent evaluation by the International Agency for Research on Cancer observed a positive association between pioglitazone and bladder cancer, but was unable to consistently rule out confounding, selection bias, detection bias, and bias related to indication or severity of disease in the populations studied as potential explanations for positive associations with the drug.[8]

More recently, second generation epidemiology studies have been undertaken, built on the knowledge and understanding of limitations of earlier studies. A large, long term prospective cohort study using the Kaiser Permanente Northern California (KPNC) database of health insurance claims was conducted at the request of the US Food and Drug Administration and European Medicines Agency. Increased risk of bladder cancer was observed in the KPNC study with at least two years of pioglitazone use at a five year interim analysis,[9] however, no increase was apparent in the 10 year analysis for ever exposure to pioglitazone or for duration or cumulative dose of pioglitazone.[10] Two large, long term cohort studies have also recently reported no association between bladder cancer and pioglitazone,[11 12] while one recent study has reported a positive association.[13]

Pharmacoepidemiology studies of drug effects are particularly prone to treatment allocation bias, which can result in detection of false associations. In Europe, pioglitazone is predominantly a second or third line treatment used particularly for overweight patients with diabetes who have failed to achieve or maintain good glycaemic control with metformin or a sulphonylurea. Thus, patients initiating pioglitazone treatment could have a longer diabetes duration, longer duration of poor glycaemic control, and more diabetic complications than other patients. These underlying characteristics could independently be associated with an increase in bladder cancer risk. Designs or statistical methods minimalising the effects of treatment allocation bias were not incorporated in several of the previous studies.

Most recent studies have observed no association between pioglitazone use and increased risk of bladder cancer, whereas several earlier studies have reported a positive association. To better understand whether the earlier reported association was real or due to confounding and bias, the European Medicines Agency requested a study. Our study was undertaken by a consortium of European pharmacoepidemiologists using healthcare data from Finland, the Netherlands, Sweden, and the UK. We present a propensity score matched cohort design in which patients initiating pioglitazone treatment have been matched to patients with a similar clinical history initiating alternative diabetic medications.

Methods

This study had a retrospective matched cohort design and was undertaken in six non-overlapping populations from four European countries: Finland, the Netherlands, Sweden, and the UK. We used the PHARMO database network for the Netherlands datasets, the Clinical Practice Research Datalink GOLD database for the UK general practitioner (GP) dataset, and Clinical Practice Research Datalink GOLD-Hospital Episode Statistics was used for the UK GP-hospital dataset. Table 1 presents used data sources and study periods, and the supplementary appendix provides further details. Drug use data were based on outpatient prescription data in the Netherlands GP, UK GP-hospital, and UK GP datasets, and based on outpatient dispensing data in the other datasets. Morbidity data were based solely on GP records in the Netherlands GP and UK GP datasets and on hospital records in the Finland, Sweden, and Netherlands hospital datasets, but based on both GP and hospital data in the UK GP-hospital dataset. Bladder cancer cases were identified from cancer registries in the Finland, Sweden, and UK GP-hospital datasets, from hospital records in the Netherlands hospital dataset, and from GP records in the Netherlands GP and UK GP datasets. For cancer registers, reporting is compulsory, with coverage close to 100%.[14-16] In the UK

Table 1 | Data sources used in each population. Start and end of follow-up together with dates on availability of morbidity and prescription data at baseline

Country, dataset	Data sources	Start of treatment and morbidity records	Earliest possible cohort entry date	End of follow-up
Finland	Linked national databases: Finnish prescription register, Finnish registry for reimbursed drug treatments, Finnish cancer registry, Finnish hospital care register (inpatient and outpatient), Finnish institutional care register, Finnish causes of death register	1 January 1998	1 January 2002	30 June 2011
Sweden	Linked national databases: Swedish prescribed drug register, Swedish cancer register, Swedish national patient register (inpatient and outpatient hospital visits), Swedish cause of death register, Swedish national diabetes register, Swedish total population register	1 July 2005	1 July 2006	30 June 2011
Netherlands, hospital	PHARMO outpatient pharmacy database linked to national medical registry from the Dutch Hospital Data Foundation (hospital admissions) and Central Bureau of Genealogy registry (mortality)	1 January 1995	1 January 2002	30 June 2011
Netherlands, GP	PHARMO GP database	1 January 2002	1 January 2003	30 June 2011
UK, GP-hospital	Portion of CPRD GOLD database with linkage to Hospital Episode Statistic data, cancer registry data, and death certificate data	1 January 1987	1 January 2000	31 December 2010
UK, GP	Remainder of CPRD GOLD database	1 January 1987	1 January 2000	30 June 2011

CPRD=Clinical Practice Research Datalink.

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GP dataset, a recent validation study reported over 91% coverage compared with the cancer registry data.[17]

We identified all patients with type 2 diabetes mellitus over age 40 years who initiated or switched to pioglitazone treatment (that is, pioglitazone exposed patients) or to any other diabetic treatment excluding pioglitazone (that is, non-exposed patients) during the study period. Patients' cohort entry dates among the exposed patients was the date of first pioglitazone prescription. Patients not exposed to pioglitazone could have initiated drugs at multiple time points during the study period, all of which were treated as possible cohort entry dates. To ensure that the patients were new initiators, a minimum 12 month membership in the treatment database with no pioglitazone exposure was required before the possible cohort entry date. We excluded all potential cohort entry dates associated with a shorter than 12 month membership in the treatment database. In addition, we excluded entry dates associated with any of the following histories:

- Diagnosis of malignant or benign bladder neoplasms
- Secondary malignancies of the bladder
- Neoplasms of uncertain or unknown behaviour of the bladder
- Partial or complete resection of the bladder
- Biopsy of bladder tumour or lesion.

We also excluded cohort entry dates that occurred during the use of any other drug from the thiazolidinedione group.

Each pioglitazone exposed patient was matched with the closest corresponding non-exposed patients (that is, who were not exposed to pioglitazone) to a 1:1 fixed ratio (nearest match cohort) and 1:10 variable ratio (multiple match cohort).[18] For many pioglitazone exposed patients, fewer than 10 matches were identified and included. Patients were matched on the basis of propensity scores and on the following exact matching variables: antidiabetic treatment immediately before the cohort entry date, whether the treatment change at the cohort entry date was an add-on or switch-in treatment, and use of thiazolidinediones before the cohort entry date. The propensity score was based on the exact matching variables and the following baseline variables:

- Duration of treated diabetes
- Duration of prescription database membership
- Number of different diabetes treatments used before the cohort entry date
- Calendar year of the cohort entry date
- History of myocardial infarction
- Stroke
- Heart failure
- Diabetic complications, as follows: retinopathy or maculopathy, severe lower limb complications, renal complications, ketoacidosis, and hyperosmolar or ketoacidotic coma.

In all countries, the propensity score and matching were based on the same variables. Because the number of available matched patients not exposed to pioglitazone varied between countries, the primary analysis was based on the nearest match cohort.

Each patient was followed from cohort entry date to the date of diagnosis of the first incident bladder cancer, end of database membership, death, start of treatment with another thiazolidinedione, or end of study period. Use of diabetic drugs were treated as time updating variables. We determined drug exposure periods on the basis of the dispended amount and dose. Pioglitazone exposure was measured by three different variables: never versus ever exposed, cumulative duration of exposure, and cumulative dose. Other relevant comorbidities and other drug treatments (supplementary table 3) were each treated as time dependent binary (ever *v* never) variables. The country specific cohorts were ultimately pooled and analysed as a single dataset. In a sensitivity analysis, cumulative duration of insulin exposure, glycated haemoglobin (HbA1C), smoking, and body mass index were included as categorical variables.

Statistical methods

Propensity scores (the probabilities to initiate pioglitazone treatment at the cohort entry date) were estimated using logistic regression. The covariates included in the model are listed above and in supplementary table 2. We fitted the propensity score model by using baseline characteristics at the cohort entry date for the pioglitazone exposed patients and those at the potential cohort entry dates of the non-exposed patients.

Matching was based on both exact matching variables and distance within a caliper in the propensity score. The first round of matching was used as the 1:1 fixed ratio matched cohort, and the full matching resulted in the 1:10 variable ratio matched cohort. Details on the matching variables and algorithm are provided in the supplementary material.

We used descriptive statistics to characterise the study cohorts. Differences were quantified using standardize differences, with a score under 10 indicating good balance. Crude bladder cancer incidence rates with 95% confidence intervals were calculated.

To generate hazard ratios, we used Cox's proportional hazards model, adjusted for baseline and time dependent covariates. The base model included the ever versus never exposed to pioglitazone variable and a dataset population categorical variable. The adjusted model included age, sex, diabetic drug treatments, exact matching variables, groups based on quintiles of propensity scores, all variables used in the propensity score, plus possible confounding variables.[18 19] The propensity score variables that are indicators of comorbidities enter the model as time dependent variables (supplementary table 2). Confounders were defined as those variables that caused a minimum 10% shift in the hazard ratio for pioglitazone exposure.

For the multiple match cohort, the imbalance due to varying matching ratio was accounted for by the use of balancing weights corresponding to the 1:10 variable ratio matching in the Cox's proportional hazards analysis and in calculations of standardised differences.[18]

We did a meta-analysis of the population specific hazard ratios by using a fixed effect model and a random effects model, with the assumption that each dataset has its own effect. Heterogeneity was quantified by the I^2 statistic.[20]

Data on smoking, body mass index, and HbA1C were not available for the Finland population and the Netherlands hospital population. Therefore, we did not adjust primary analyses for these variables. Sensitivity analyses were undertaken in the remaining four populations to assess potential confounding. Missing values of available variables were treated as a separate category. Several preplanned sensitivity analyses evaluated robustness of the results with respect to outcome, exposure, and follow-up definitions, and many stratified analyses assessed risk modification. We undertook all sensitivity analyses using the nearest match cohort. Further details on the methodology are provided in the supplementary material.

Patient involvement

Our study was a secondary data analysis and did not include patients as study participants. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results, nor will we disseminate results directly to the patients.

Results

A total of 1 629 409 treated patients with type 2 diabetes constituted the source population. After applying exclusion criteria, we identified 61 587 patients exposed to pioglitazone, 56 337 of whom we were able to match to at least one patient not exposed to pioglitazone (table 2). In total, we identified 317 109 non-pioglitazone exposed multiple matches.

Tables 3 and 4 provide descriptive summaries of the baseline variables used in the matching. The standardised differences were low, indicating that the groups exposed and not exposed to pioglitazone were well matched regarding baseline characteristics. Duration of the treated diabetes (that is, time since the initiation of the first diabetes drug) was comparable between the exposed groups, with 7805 (14%) and 7883 (14%) patients having treated diabetes for less than one year and 18 788 (33%) and 18 786 (33%) for more than six years in the exposed and non-exposed groups, respectively.

Table 5 shows the distribution of other variables at cohort entry. The mean age at the cohort entry date was

Table 2 | Patient selection from source population to matched cohorts in each dataset

	Dataset						
Cohort	Finland	Sweden	Netherlands hospital	Netherlands GP	UK GP	UK GP-hospital	Total
Diabetic patients who initiated or switched treatment							
Source population	438 229	295 001	208 962	63 284	317 632	306 301	1 629 409
Eligible patients after applying all exclusion criteria							
Exposed to pioglitazone	18 794	3712	9081	2829	12 662	14 504	61 587
Not exposed to pioglitazone	332 255	224 742	131 028	42 174	70 471	78 037	878 707
Cohort sizes after matching*							
Exposed to pioglitazone	18 794	3712	7491 (8965)	2823	11 408	12 109	56 337
Not exposed to pioglitazone							
Nearest matched cohort	18 794	3712	7491 (8965)	2823	11 408	12 109	56 337
Multiple matched cohort	157 263	31 040	42 048 (50 493)	15 775	35 799	35 184	317 109

*Numbers in parentheses are the cohort size before overlap between Netherland cohorts was removed.

Table 3 | Distribution of number of patients for exact matching variables at cohort entry date

	Pioglitazone cohort (no (%) of patients)			Standardised difference	
	Exposed to pioglitazone (n=56 337)	Not exposed to pioglitazone (nearest match cohort; n=56 337)	Not exposed to pioglitazone (multiple match cohort; n=317 109)	Nearest match cohort	Multiple match cohort
Type of treatment change at cohort entry date					
Add-on	36 237 (64.32)	36 237 (64.32)	212 245 (66.93)	0.00	0.00
Switch	20 100 (35.68)	20 100 (35.68)	104 864 (33.07)	0.00	0.00
Use of another thiazolidinedione before cohort entry date					
Never	41 847 (74.28)	41 847 (74.28)	276 452 (87.18)	0.00	0.00
Ever	14 490 (25.72)	14 490 (25.72)	40 657 (12.82)	0.00	0.00
Diabetes treatment taken immediately before cohort entry date*					
Metformin only	16 526 (29.33)	16 526 (29.33)	115 003 (36.27)	0.00	0.00
Sulphonylureas only	6110 (10.85)	6110 (10.85)	36 673 (11.56)	0.00	0.00
Metformin and sulphonylureas	14 277 (25.34)	14 277 (25.34)	61 494 (19.39)	0.00	0.00
Insulin (only or in combination)	2705 (4.80)	2705 (4.80)	16 940 (5.34)	0.00	0.00
Other drugs (one drug only or combination	10 062 (17.86)	10 062 (17.86)	31 743 (10.01)	0.00	0.00
No treatment	6657 (11.82)	6657 (11.82)	55 256 (17.42)	0.00	0.00

*Treatments initiated at cohort entry date not included.

Table 4 | Distribution of propensity score variables for matched cohorts (exposed versus not exposed to pioglitazone) at cohort entry date

	Pioglitazone cohort (no (%) of patients)			Standardised difference	
	Exposed to pioglitazone (n=56 337)	Not exposed to pioglitazone (nearest match cohort; n=56 337)	Not exposed to pioglitazone (multiple match cohort; n=317 109)	Nearest match cohort	Multiple match cohort
Duration of treated diabetes at cohort entry date (years)					
<1	7805 (13.85)	7883 (13.99)	67 091 (21.16)	0.40	0.91
1 to <2	6943 (12.32)	6679 (11.86)	37 879 (11.95)	1.44	1.40
2 to <4	11 865 (21.06)	11 578 (20.55)	58 668 (18.50)	1.26	1.69
4 to <6	10 936 (19.41)	11 411 (20.25)	60 944 (19.22)	2.11	1.77
≥6	18 788 (33.35)	18 786 (33.35)	92 527 (29.18)	0.01	0.26
Range	0.00-34.18	0.00-24.79	0.00-24.79	—	—
Mean (standard deviation)	4.72 (3.65)	4.78 (3.70)	4.16 (3.54)	—	—
Median (interquartile range)	4.12 (1.76-6.97)	4.19 (1.82-6.97)	3.59 (1.13-6.27)	—	—
Diabetes complications at cohort entry date					
Diabetic retinopathy or maculopathy	5747 (10.20)	5953 (10.57)	22 040 (6.95)	1.20	1.33
Lower limb severe complications	1308 (2.32)	1530 (2.72)	7521 (2.37)	2.52	2.88
Diabetic renal complications	4771 (8.47)	4870 (8.64)	17 526 (5.53)	0.63	1.51
Ketoacidosis	112 (0.20)	145 (0.26)	916 (0.29)	1.23	1.70
Hyperosmolar or ketoacidotic coma	822 (1.46)	1280 (2.27)	9053 (2.85)	6.01	4.04
Other comorbidities at cohort entry date					
Myocardial infarction or stroke	4676 (8.30)	6112 (10.85)	37 213 (11.74)	8.67	9.59
Congestive heart failure	1674 (2.97)	3077 (5.46)	22 181 (6.99)	12.42	14.06
Year at cohort entry date					
2000-03	3960 (7.03)	6485 (11.51)	42 671 (13.46)	15.50	15.78
2004-07	21 151 (37.54)	20 513 (36.41)	112 928 (35.61)	2.35	3.36
2008-11	31 226 (55.43)	29 339 (52.08)	161 510 (50.93)	6.72	5.93
Duration of treatment database membership before cohort entry date (years)					
1 to 2	5621 (9.98)	5770 (10.24)	30 884 (9.74)	0.88	1.18
3 to 4	6216 (11.03)	6998 (12.42)	38 421 (12.12)	4.32	4.15
5 to 6	7802 (13.85)	9962 (17.68)	58 311 (18.39)	10.54	9.18
≥7	36 698 (65.14)	33 607 (59.65)	189 493 (59.76)	11.35	10.37
Range	1.00-22.00	1.00-23.00	1.00-23.00	—	—
Mean (standard deviation)	8.39 (4.35)	8.14 (4.36)	8.06 (4.06)	—	—
Median (interquartile range)	8.00 (5.00-11.00)	8.00 (5.00-11.00)	8.00 (5.00-12.00)	—	—
No of different diabetes drug classes ever used before cohort entry date					
0	2260 (4.01)	2253 (4.00)	25 397 (8.01)	0.06	2.51
1	14 970 (26.57)	14 129 (25.08)	113 404 (35.76)	3.41	1.33
2	25 185 (44.70)	24 068 (42.72)	114 283 (36.04)	4.00	5.77
3	11 052 (19.62)	12 046 (21.38)	50 098 (15.80)	4.37	3.60
>3	2870 (5.09)	3841 (6.82)	13 927 (4.39)	7.29	6.34

Data are no (%) of patients unless stated otherwise.

63.2 years in the cohort exposed to pioglitazone, and 65.4 and 66.6 years in the nearest and multiple matches of cohorts not exposed to pioglitazone, respectively. The pioglitazone exposed cohort also had fewer patients aged over 70 years than the non-exposed cohorts.

The group of patients exposed to pioglitazone had 130 incident bladder cancers with a crude incidence of 7.97 per 10 000 person years; the nearest and multiple matched cohorts of patients not exposed to pioglitazone had 153 and 970 bladder cancers with crude incidence of 9.62 and 10.65 per 10 000 person years, respectively (table 6). Duration of follow-up was similar between cohorts, with a mean (maximum) of 2.9 (10.5) years in the exposed group, and 2.8 (10.8) and 2.9 (11.3) years in the nearest and multiple matched cohorts in the non-exposed group, respectively. In the exposed group, crude incidence ranged across populations from 4.4 to 20.7 per 10 000 person years, whereas in the non-exposed group, crude incidence ranged from 5.5 to 16.0 per 10 000 person years. No difference existed between groups in the time to bladder cancer, with about 16% occurring within the first six months and about 25% within the first 12 months (supplementary material).

Figures 1 and 2 present adjusted risk estimates of bladder cancer for the pooled data. Ever exposure to pioglitazone was not associated with risk of bladder cancer (hazard ratio 0.99 (95% confidence interval 0.75 to 1.30) and 1.00 (0.83 to 1.21) for nearest match and multiple match cohorts, respectively). We saw no evidence of increasing risk with increasing duration of pioglitazone treatment (P_{trend}=0.42 and 0.85) or with cumulative pioglitazone dose (P_{trend}=0.45 and 0.81) for nearest match and multiple match cohorts, respectively. Patients with more than 48 months of pioglitazone exposure had adjusted hazard ratios of 0.86

Table 5 | Distribution of other non-matching variables at cohort entry date

	Pioglitazone cohort (no (%) of patients)			Standardised difference	
	Exposed to pioglitazone (n=56 337)	Not exposed to pioglitazone (nearest match cohort; n=56 337)	Not exposed to pioglitazone (multiple match cohort; n=317 109)	Nearest match cohort	Multiple match cohort
Age at cohort entry date (years)					
40-49	6728 (11.94)	5608 (9.95)	27 697 (8.73)	6.37	8.16
50-59	14 881 (26.41)	12 618 (22.40)	66 083 (20.84)	9.36	10.33
60-69	18 366 (32.60)	17 262 (30.64)	94 060 (29.66)	4.22	4.18
≥70	16 362 (29.04)	20 849 (37.01)	129 269 (40.76)	17.00	18.90
Range	40-102	40-106	40.00-107.00	—	—
Mean (standard deviation)	63.24 (10.86)	65.38 (11.56)	66.55 (11.71)	—	—
Median (interquartile range)	63.00 (55.03-71.00)	65.00 (57.00-74.00)	67.00 (58.00-75.00)	—	—
Sex					
Male	31 732 (56.33)	30 561 (54.25)	170 181 (53.67)	4.18	3.83
Female	24 605 (43.67)	25 776 (45.75)	146 928 (46.33)	4.18	3.83
No of different diabetes drug classes being used at cohort entry date					
1	6905 (12.26)	9961 (17.68)	69 336 (21.87)	15.25	15.99
2	29 216 (51.86)	29 767 (52.84)	176 356 (55.61)	1.96	1.79
3	18 446 (32.74)	15 917 (28.25)	68 964 (21.75)	9.76	10.13
>3	1770 (3.14)	692 (1.23)	2453 (0.77)	13.12	13.41
Diabetes treatment at cohort entry date*					
Metformin only	19 622 (34.83)	3496 (6.21)	34 122 (10.76)	75.80	74.90
Sulphonylureas only	7442 (13.21)	2418 (4.29)	18 768 (5.92)	31.96	31.65
Metformin and sulphonylureas	13 659 (24.25)	12 062 (21.41)	82 031 (25.87)	6.76	5.55
Insulin (only or in combination)	2595 (4.61)	20 840 (36.99)	114 382 (36.07)	87.02	86.16
Other drugs (one drug only or combination)	6114 (10.85)	17 521 (31.10)	67 806 (21.38)	51.34	50.40
No treatment	6905 (12.26)	0	0	52.86	52.86
Bladder comorbidities at cohort entry date					
Urinary incontinence	2960 (5.25)	3455 (6.13)	19 792 (6.24)	3.79	3.35
Urinary tract infection	5336 (9.47)	5774 (10.25)	22 596 (7.13)	2.61	3.12
Pyelonephritis	682 (1.21)	842 (1.49)	5650 (1.78)	2.46	2.66
Urolithiasis	1268 (2.25)	1182 (2.10)	5740 (1.81)	1.05	0.95
Haematuria	1866 (3.31)	1970 (3.50)	8368 (2.64)	1.02	1.40
Urinary retention	556 (0.99)	774 (1.37)	4324 (1.36)	3.58	3.67
Neurogenic bladder	49 (0.09)	66 (0.12)	436 (0.14)	0.95	1.20
Catheterisation	431 (0.77)	602 (1.07)	2955 (0.93)	3.19	3.41
Other comorbidities at cohort entry date					
Other urinary tract cancer (excluding bladder cancer)	114 (0.20)	122 (0.22)	869 (0.27)	0.31	0.20
Other cancer (excluding urinary tract cancer)	5663 (10.05)	6538 (11.61)	37 210 (11.73)	5.00	5.97
Chronic obstructive pulmonary disease	5406 (9.60)	6396 (11.35)	33 563 (10.58)	5.74	7.19
Use of other drug treatments before cohort entry date					
Statins	26 077 (46.29)	24 778 (43.98)	160 948 (50.75)	4.63	4.96
Angiotension receptor blocker	15 795 (28.04)	14 057 (24.95)	81 669 (25.75)	6.99	7.13
Angiotensin converting enzyme inhibitors	31 328 (55.61)	31 746 (56.35)	167 820 (52.92)	1.49	1.89
Benign prostatic hyperplasia	7401 (13.14)	7793 (13.83)	39 108 (12.33)	2.04	2.28

Data are no (%) of patients unless stated otherwise. Treatments initiated at cohort entry date are included. For the pioglitazone exposed group, listed treatments are in addition to pioglitazone.

Table 6 | Number and crude incidence of bladder cancer cases in pioglitazone cohorts, according to European datasets

	Cohort					
	Exposed to pioglitazone (n=56 337)		Not exposed to pioglitazone (nearest matched cohort; n=56 337)		Not exposed to pioglitazone (multiple matched cohort; n=317 109)	
Dataset	No of cases	Crude incidence (95% CI) per 10 000 person years	No of cases	Crude incidence (95% CI) per 10 000 person years	No of cases	Crude incidence (95% CI) per 10 000 person years
Finland	24	4.42 (2.96 to 6.60)	40	7.51 (5.51 to 10.23)	423	9.34 (8.49 to 10.27)
Sweden	15	20.73 (12.50 to 34.39)	4	5.53 (2.08 to 14.73)	73	10.75 (8.55 to 13.52)
Netherlands GP	10	9.27 (4.99 to 17.24)	10	9.18 (4.94 to 17.06)	61	10.57 (8.23 to 13.59)
Netherlands hospital	27	9.97 (6.84 to 14.53)	21	8.13 (5.30 to 12.47)	161	11.53 (9.88 to 13.46)
UK GP	24	7.61 (5.10 to 11.35)	26	8.89 (6.05 to 13.06)	107	11.32 (9.36 to 13.68)
UK GP-hospital	30	9.33 (6.53 to 13.35)	52	15.99 (12.18 to 20.98)	145	14.73 (12.52 to 17.33)
Pooled dataset	130	7.97 (6.71 to 9.47)	153	9.62 (8.21 to 11.27)	970	10.65 (10.00 to 11.34)
Netherlands hospital,with overlap*	33	10.07 (7.16 to 14.16)	26	8.23 (5.61 to 12.09)	192	11.20 (9.72 to 12.90)

*Patients represented in both Netherlands datasets were removed from the Netherlands hospital dataset.

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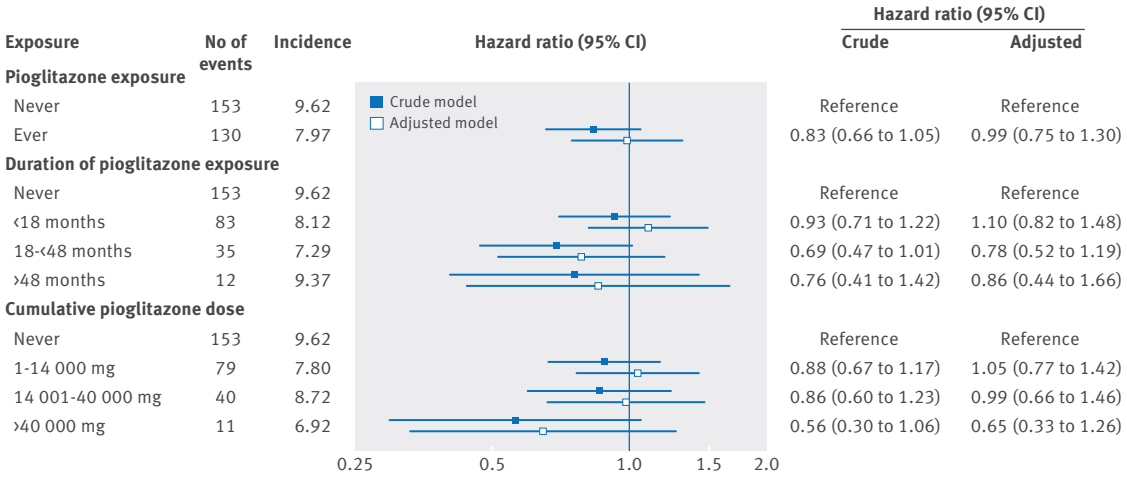

Fig 1 | Adjusted risk estimates for bladder cancer for different pioglitazone exposures using the nearest matched cohort. Crude model=pioglitazone exposure variable and a dataset identifier. Adjusted model=crude model plus age, sex, metformin use, sulphonylurea use, insulin use, use of other diabetes drugs, all exact matching variables, propensity scores (divided into five equal groups), and all propensity score variables evaluated at cohort entry date. P_{trend}=0.42 and 0.45 for increasing pioglitazone duration and dose, respectively, using the adjusted model. Incidence values measured over 10 000 person years

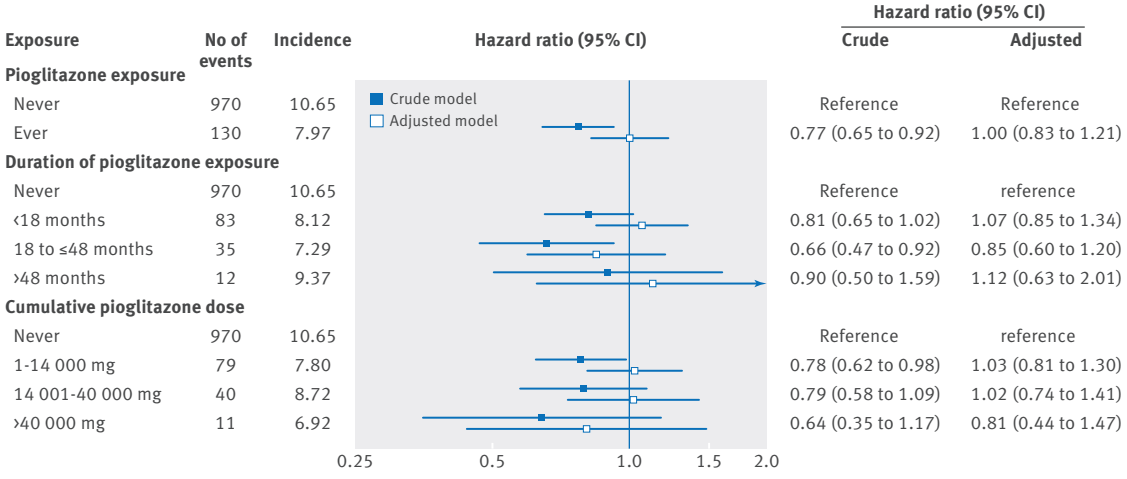

Fig 2 | Adjusted risk estimates for bladder cancer for different pioglitazone exposures using the multiple matched cohort. Crude model=pioglitazone exposure variable and a dataset identifier. Adjusted model=crude model plus age, sex, metformin use, sulphonylurea use, insulin use, use of other diabetes drugs, all exact matching variables, propensity scores (divided into five equal groups), and all propensity score variables evaluated at cohort entry date. P_{trend}=0.85 and 0.81 for increasing pioglitazone duration and dose, respectively, using the adjusted model. Incidence values measured over 10 000 person years

(0.44 to 1.66) and 1.12 (0.63 to 2.01) for nearest match and multiple match cohorts, respectively; those with a cumulative pioglitazone dose of 40 000 mg had corresponding hazard ratios of 0.65 (0.33 to 1.26) and 0.81 (0.44 to 1.47).

Figure 3 presents bladder cancer hazard ratios for patients who were ever exposed to pioglitazone for each study dataset, plus a meta-analysis of the summary hazard ratios. We saw heterogeneity between populations; the hazard ratio for ever exposed groups ranged from 0.56 (95% confidence interval 0.31 to 1.00) for the Finland dataset to 4.27 (1.26 to 14.46) for the Sweden dataset in the nearest matched cohort. However, the Sweden dataset was small and only had four bladder cancer events in the cohort not exposed to pioglitazone. The meta-analysis, with both fixed and random effect models, yielded similar results to the pooled analysis. For the multiple matched cohort, the meta-analysis results were also similar (fig 4), but had less heterogeneity between populations, with the hazard ratio in the Sweden dataset dropping to 1.52 (0.82 to 2.82).

Data on smoking, body mass index, and HbA1C were only available for the Sweden, Netherlands GP, UK GP, and UK GP-hospital datasets. In a pooled analysis of the nearest match cohort restricted to these populations, the proportion of ever (53%) and never (38%) smokers and the mean body mass index (32) did not differ between the cohort exposed to pioglitazone and

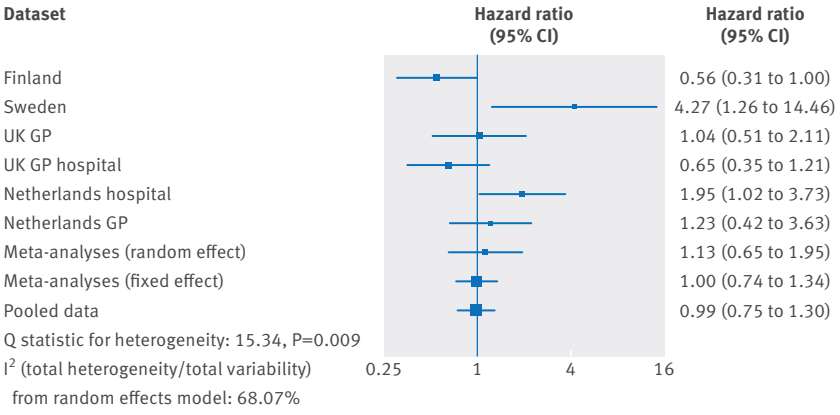

Fig 3 | Adjusted hazard ratio estimates for bladder cancer in patients ever exposed to pioglitazone in the nearest matched cohort

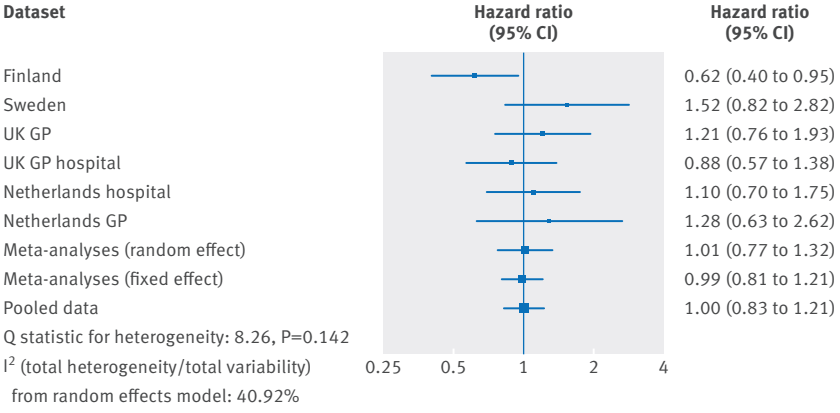

Fig 4 | Adjusted hazard ratio estimates for bladder cancer in patients ever exposed to pioglitazone in the multiple matched cohort

the cohort not exposed. The proportion of patients with HbA1C over 9.0% and the mean HbA1C value were lower in the exposed group than the non-exposed group (21.9% *v* 29.6% and 8.5% *v* 8.8%, respectively). Inclusion of these three covariates into the adjusted model reduced the adjusted hazard ratio by 18.7%, from 1.02 (95% confidence interval 0.70 to 1.49) to 0.83 (0.54 to 1.28). Separate introduction of smoking, HbA1C, and body mass index into the model reduced the adjusted hazard ratio by 10.5%, 11.3%, and 6.3%, respectively.

Figure 5 shows stratification of the risk estimates of bladder cancer in patients ever exposed to pioglitazone for the nearest match cohort baseline variable. We observed a non-significant sex effect. Female patients ever exposed to pioglitazone had a hazard ratio of 0.55 (95% confidence interval 0.27 to 1.10), whereas male patients had a hazard ratio of 1.11 (0.82 to 1.50). Effect modification also occurred with respect to the source of bladder cancer data. For populations where bladder cancer was ascertained from cancer registries (Finland, Sweden, UK GP-hospital datasets), the hazard ratio for patients ever exposed to pioglitazone was below unity (0.75 (0.52 to 1.08)). Conversely, for populations where cancers were not ascertained from cancer registries (Netherlands hospital, Netherlands GP, and UK GP datasets), the hazard ratio was above unity (1.51 (0.99 to 2.30)). Other covariates showed no effect modification.

Some tumours diagnosed soon after cohort entry were possibly pre-existing and unlikely related to pioglitazone treatment. Exclusion of all bladder cancer diagnoses within three months of cohort entry (hazard ratio 1.01 (95% confidence interval 0.76 to 1.35)) and within 12 months of cohort entry (0.97 (0.69 to 1.35)) had little effect.

The study included a mixture of patients with incident and prevalent diabetes. Among those with incident diabetes (that is, with at least 12 months' membership before first diabetes prescription), the adjusted hazard ratio for bladder cancer in patients ever exposed to pioglitazone was 0.72 (95% confidence interval 0.45 to 1.14). However, the corresponding hazard ratio for patients with prevalent diabetes (that is, with treatment prescriptions for diabetes within 12 months of joining database) was 1.24 (0.88 to 1.75).

Our definition of patients ever exposed to pioglitazone was at least one prescription, whereas some previous studies used more stringent criteria of at least two prescriptions within six months. In a sensitivity analysis using this more stringent definition, the adjusted hazard ratio for patients ever exposed to pioglitazone was 0.92 (95% confidence interval 0.66 to 1.29).

We also did a sensitivity analysis to assess the effect of broadening the bladder cancer definition. The above results were based on inclusion of malignancy neoplasm and carcinoma in situ of the bladder. Expansion of the definition to include bladder neoplasms of uncertain and unknown behaviour resulted in 17 more events in the group ever exposed to pioglitazone, and 14 more events in the never exposed nearest match group. The adjusted hazard ratio was similar to the corresponding value using the primary definition for bladder cancer. Finally, we assessed whether morbidity record source affected the results. In a sensitivity analysis limited to datasets with only hospital based morbidity data (Finland, Sweden, and Netherlands hospital datasets), which typically contain more severe morbidity than seen in GP records, the adjusted hazard ratio was similar to that seen in the primary analysis (0.94, 95% confidence interval 0.69 to 1.28).

Discussion

In this study, we found no association between patients ever exposed to pioglitazone treatment and risk of bladder cancer. Additionally, no evidence emerged of any dose-response relation with duration or cumulative dose of pioglitazone. Examination of pioglitazone related risk with the subgroups of selected relevant covariates did not identify any subgroups at increased risk. Multiple sensitivity analyses also found no association between exposure to pioglitazone and risk of bladder cancer.

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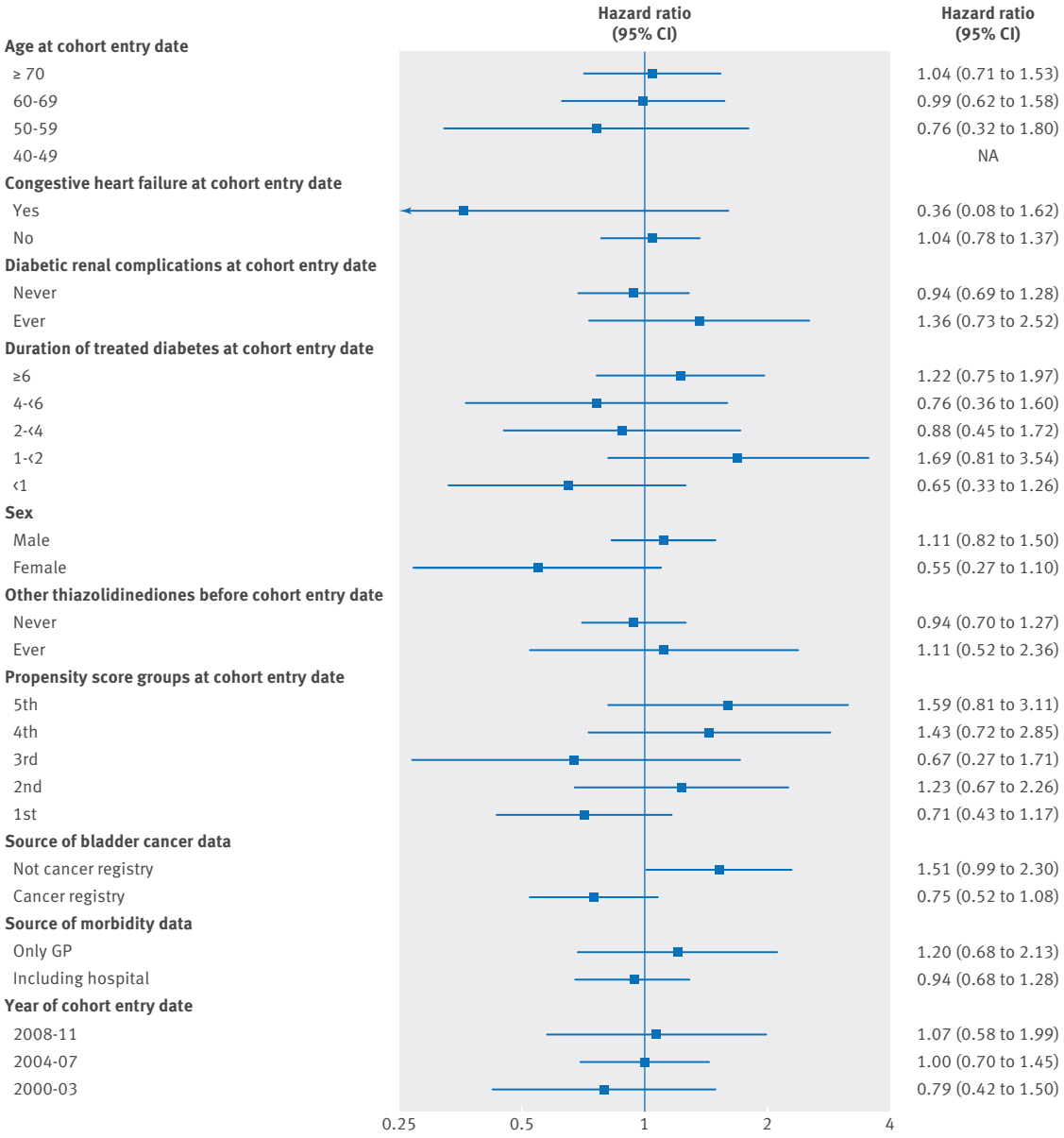

Fig 5 | **Adjusted hazard ratios in pioglitazone exposure groups (ever versus never) for stratified analysis of bladder cancer incidence, based on pooled dataset for the nearest matched cohort. NA=not available**

Comparison with previous studies

Our findings agree with several other large studies with multiple years of follow-up. The KPNC prospective cohort study of 193 000 patients with diabetes—one of the largest, most informative studies so far—recently reported their 10 year follow-up analysis,[10] indicating that exposure to pioglitazone was not associated with bladder cancer risk. A subgroup analysis limited to newly diagnosed diabetes in the KPNC cohort, for whom complete diabetic medication data was available, similarly found no association with ever exposure to pioglitazone and no evidence of a dose-response relation. Two other recent large studies also reported no association with pioglitazone exposure. An international study of 1 006 000 patients and mean follow-up of five years reported no excess risk.[12] A retrospective cohort analysis of 207 000 treated patients with diabetes in the UK with up to 10 years of follow-up also reported no association.[11]

Conversely, many earlier epidemiological studies reported an increased bladder cancer risk in patients with diabetes using pioglitazone.[6] However, an expert working group at the International Agency for Research on Cancer, believed that the observed association could not consistently rule out confounding, selection bias, detection bias, and bias related to indication or severity of disease.[8] A recent cohort study in the UK reported an increased bladder cancer risk in patients treated with pioglitazone compared with patients with type 2 diabetes treated with another diabetes drug.[13] But several of the early studies had limitations, such as little control over treatment allocation bias, or no information on known bladder cancer risk factors (such as cigarette smoking). Reference group choice might also have

introduced bias. Some studies compared patients with diabetes using pioglitazone with the general population, whereas other studies compared these patients with all other treated patients with diabetes, or patients with diabetes on specific drug treatments.

Unlike most previous studies and the recent cohort study in the UK,[13] we used exact matching as well as propensity score matching to minimise treatment allocation bias. We included duration of treated diabetes, type and number of previous treatments, and history of diabetic complications as part of the matching algorithm with the aim of having a reference group that was as similar as possible.

We observed that the risk estimate for patients ever exposed to pioglitazone was below unity for datasets where bladder cancer events were ascertained from cancer registries, but above unity for datasets without cancer registry information, although both results were non-significant. The reason for this difference is unclear, but could be related to incomplete recording or misclassification of bladder cancers in primary care records.

Strength and limitations

Strengths of our study included the propensity score matched study design, inclusion of data from multiple populations rather than one population, the large size of the pooled dataset, and several years of follow-up. Our base population of over 1.6 million patients with diabetes with up to 10 years of follow-up makes this one of the largest pioglitazone studies so far. One protocol covering six different European populations and single data analysis plans used across them ensured that the same approach was used by all investigators in matching selection and creation of analytical variables. We included variables fixed at baseline and time dependent variables, in addition to many stratified analyses to identify potential effect modification and various sensitivity analyses to assess robustness.

Our study had several limitations, including our primary analysis not being adjusted for smoking, body mass index, or HbA1C because not all datasets contained the necessary information. However, we performed analyses restricted to populations with this information.

Another limitation was left truncation of prescribing information in the Sweden dataset. Pioglitazone has been available since 2001, but the Swedish medication database did not start until July 2005 and contained no prior prescription information. Information on pioglitazone use before July 2005 was therefore missing, resulting in misclassification of exposure to the drug. Moreover, left truncation of medication information could also have caused misclassification of the matching variables, resulting in residual treatment allocation bias in the Sweden dataset. Left truncation of prescription information is an inherent limitation of database studies that include prevalent diabetics. This effect was not present in our subgroup analysis of patients with incident diabetes, for whom full prescribing information was available.

A further potential limitation of this study (and other published studies) was the unavailability of data on the incidence of bladder cancer among pioglitazone users beyond 10 years after initiation of treatment. Finally, we planned to examine cancer tumour stage and grade, but the information was not available for most of the tumours.

Tim Williams and Susan Eaton (Clinical Practice Research Datalink (CPRD)) were involved in the study design. Irene Bezemer (PHARMO Institute) participated in analytical discussions, and Eline Houben (PHARMO Institute) contributed to construction of the analysis file. Shannon Kuismanen assisted in preparing this manuscript. The Swedish National Diabetes Register provided detailed data for this study. We thank all patients and participating staff who have contributed to the register.

Contributors: All authors planned and designed the study. SC, MM, ML, EMH, LK-H, RW, and HS performed the data management and data analysis, and all authors interpreted the data. All authors drafted the manuscript, revised the paper critically for important intellectual content, and approved the final version of the manuscript. PK supervised the study and is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from Takeda Development Centre Europe for the submitted work; PK, FH, SC, and MM are employed by EPID Research, EMH is and LK-H was employed by PHARMO Institute, RW and HS are employed by CPRD, and ML and SB are employed by the Karolinska Institute; EPID Research, PHARMO Institute, CPRD and Karolinska Institute perform commissioned pharmacoepidemiological studies and thus their employees have been and currently are working in collaboration with several pharmaceutical companies (including Takeda); PD is employed by Takeda.

Ethical approval: This register based study used anonymous data and had no patient contact. In Finland, the study protocol was approved by the ethical review board of the Hjelt Institute, University of Helsinki Medical Faculty (Dnro 96/13/00/2013). The research permission numbers to use the data were obtained from Statistics Finland (Dnro TK/53-373-13), National Institute for Health and Welfare (Dnro THL/388/5.05.00/2013), Social Insurance Institute (Dnro Kela 25/522/2013), Population Register Centre (Dnro 726/410/13). In Sweden, the study was approved by the regional ethical review board at the Karolinska Institute in Stockholm, Sweden (DNR 2011/82-31/3, 2011/752-323, and 2013/347-32). The participants did not give informed written consent because this was a register study and it is prohibited by Swedish law to backtrack registered individuals. In the UK, the study protocol was reviewed and approved by the Independent Scientific Advisory Committee (ISAC), which considers and provides advice to the Medicines and Healthcare products Regulatory Agency on research projects that propose the use of data obtained from the CPRD (ISAC protocol no 13_044 and 14_065). In the Netherlands, the PHARMO compliance committee approved use of the PHARMO Database Network for the study and confirmed no ethics approval was needed.

Data sharing: Criteria and process for sharing the analytical country specific datasets and meta-analysis dataset for third parties is defined in the study protocol, available at the ENCePP E-Register of Studies.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Web appendix: Supplementary material