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TITLE PAGE

TITLE

Risk of bladder cancer in patients with diabetes: a retrospective cohort study

RUNNING TITLE

Diabetes and the risk of bladder cancer

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ABSTRACT**Objective**

The objective of this study was to examine the association between diabetes and both urinary bladder cancer (UBC) risk and mortality.

Methods

We conducted a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) linked to the Office of National Statistics (ONS). Patients diagnosed with diabetes mellitus type 1 or 2 or using anti-diabetic drugs (ADD) were compared to matched non-diabetic controls. Cox proportional hazards models were used to estimate the risk and mortality of UBC. We adjusted for age, sex, smoking status and BMI.

Results

The cohort included 329,168 patients using ADD and 307,315 controls with 1,295 and 1,071 patients, respectively, diagnosed as having UBC during follow-up. The adjusted hazard ratios (HR) of UBC were 0.77 (95% CI 0.57-1.05) and 1.04 (95% CI 0.96-1.14) for type 1 and 2 diabetes, respectively. These results were similar if we restricted our analysis to an inception cohort. We noticed a small increased risk during the first year after diagnosis (HR = 1.26 (95% CI 1.05-1.52)), which could be explained by detection bias. There was no influence of the severity of diabetes as measured by the HbA1c. Mortality of UBC was not increased for patients with either type 1 (HR = 0.95 (95% CI 0.39-2.34)) or type 2 diabetes (HR = 1.16 (95% CI 0.91-1.46)).

Conclusion

Neither the risk of UBC, nor the mortality from UBC, was increased in type 1 and patients with type 2 diabetes in the CPRD data.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The CPRD is a large population-based cohort representative of the total UK population.
- Detailed longitudinal information on drug prescription is available within the CPRD and 95 % and 80 %, of patients with type 1 and 2 diabetes, respectively had received a formal diabetes diagnosis.
- Smoking status was available for all patients in our analysis.
- Detailed information about the cause of death is available for 44 % of the patients by linking the patients to the ONS data.
- The effect of different anti-diabetic drug medications is not considered in our analyses and this is a major limitation.

MAIN TEXT

BACKGROUND

The global 2013 estimate of diabetes mellitus prevalence among adults (aged 20–79 years) was 8,3 %, affecting 382 million adults in the world and 6,6 % in the United Kingdom (1). Between 2010 and 2030, the number of adults with diabetes in developing countries is expected to increase by 69% and by 20% developed countries (2, 3). In 2012, more than 400,000 cases of urinary bladder cancer (UBC) occurred worldwide, making it the 7th most common type of cancer (4). It is more frequent in men than in women and age is now widely accepted as the greatest single risk factor for developing UBC. Cigarette smoking, specific occupational exposures, such as

carcinogenic dyes for painters and some genetic polymorphisms, are main known other causes of UBC (5). Previous meta-analyses from cohort and case-control studies have shown an increased risk of UBC associated with type 2 diabetes with relative risks (RR) ranging from 1.11 (95% CI 1.00-1.23) to 1.32 (95% CI 1.18–1.49) (6-9). There is also evidence for a positive association between type 2 diabetes and mortality from UBC (RR = 1.33 (95% CI 1.14–1.55) (7). However, misclassification of type 1 and 2 diabetes was not excluded in these studies because diagnostic codes were lacking and details about the diabetic history (duration, metabolic control) were not considered.

Two studies on type 1 diabetes reported an increased overall cancer incidence by 20 % while the mechanisms remain unclear (10, 11). The observed number of bladder cancer cases in these studies is very small ranging from 4 to 27 cases (10-12). The objective of this study was to examine the association between diabetes mellitus and both UBC risk and mortality taking into account diabetes duration, metabolic control as expressed by haemoglobin A1c (HbA1c) and type of diabetes.

METHODS

Data sources

We conducted a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) (January 1987-October 2013) linked to the Office of National Statistics (ONS) (January 1998 – January 2012). The CPRD comprises prospectively collected computerized medical records of over 10 million patients under the care of more than 600 general practitioners (GPs) in the United Kingdom

(UK). The Read classification is used to enter medical diagnoses and procedures, and prescriptions are recorded based on the UK *Prescription Pricing Authority Dictionary*. The recorded information on diagnoses and drug use was validated and proved to be of high quality (13). The ONS provided data for the cause(s) of death and the exact date of death as recorded on death certificates by a registered medical practitioner attending to the patient during their last period.

Study population

All patients with at least one prescription of anti-diabetic drugs (ADD) (oral anti-diabetic drugs (NIAD) and/or insulin) and aged above 18 years during the period of valid CPRD data collection were included. Each ADD user was matched to one non-diabetic control by year of birth, sex and practice. The date of the first ADD prescription defined the index date and controls were assigned the same index date as their matched ADD user. All subjects with missing data for smoking status, a history of any cancer prior to the index date, except non-melanoma skin cancer, or a diagnosis of gestational diabetes or secondary diabetes ever during follow-up were excluded. All control patients who used diabetes treatment or had ever been diagnosed with type 1 or 2 diabetes ever during follow-up were excluded. All ADD users with diagnoses of both type 1 and 2 diabetes were excluded as well, as were patients aged 30 years and older without a diagnosis of diabetes, who used insulin only at baseline. All study participants were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, or the patient's death.

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Patients with type 1 diabetes were defined as those patients with a formal diagnosis of type 1 diabetes (as recorded in CPRD) or younger than 30 years and using insulin only at index date. Patients with type 2 diabetes were all patients with a formal diagnosis of type 2 diabetes (as recorded in CPRD) or using an oral ADD at index date. The total period of follow-up for each patient (patients with diabetes and unexposed controls) was divided into fixed time periods of 90 days. Age was determined at the start of each interval. The classification of type 1 and 2 diabetes, as well as sex, smoking status and BMI was determined at baseline. Diabetes duration was assessed in a time-dependent manner by estimating the time since the date of the first ADD prescription (the index date). Diabetes control was assessed in a time-dependent manner using the most recent HbA1c record before the start of each time interval and within the previous year.

Outcomes

The primary outcome was UBC, as defined by Read codes, and was assessed in the complete CPRD study population. The secondary outcome was bladder cancer related mortality as recorded on death certificates (International Classification of Diseases (ICD-10) categories C65, C67) and was assessed in the population eligible for linkage between CPRD and ONS data (44% of the subjects). The period of follow-up was restricted to the time that ONS data were available (January 1998 – January 2012).

Risk factors

The major covariates of interest included age, sex, smoking status and BMI. Smoking status was characterized at baseline as current, former, or lifelong nonsmoker.

Statistical analysis

Analyses were conducted using Cox proportional hazards models with various sub-analyses. The first analysis compared the risk of UBC in ADD users with that in control patients to yield an estimate of the relative risk [as a hazard ratio (HR)] of UBC associated with ADD use. The calculations were adjusted for age, sex, smoking status and BMI. Results were stratified to type 1 and type 2 diabetes. In a secondary analysis, risks were estimated for an inception cohort of ADD users using a 1-year lead-in time. The risk of UBC for patients with incident type 2 diabetic was further stratified by disease duration, sex and HbA1c. The risk of UBC mortality in ADD users compared with that of controls was assessed by Cox models as well and results were stratified by type of diabetes. All data management and statistical analyses were conducted using SAS® 9.1/9.2 software.

This study was approved by the Medicines and Healthcare products Authorities' Independent Scientific Advisory Committee, protocol number 13_050R.

RESULTS

After exclusion of all patients with a diagnosis of gestational diabetes (1,983 and 154 for ADD users and controls respectively), or secondary diabetes (485 and 70 for ADD users and controls respectively), or cancer prior to index date (34,955 and 34,384 for ADD users and controls respectively) or missing data for smoking status during follow up (13,416 and 27,558 for ADD users and controls respectively), the study population consisted of 329,168 patients with diabetes of whom 30,823 (9.4 %) and 298,345 (90.6 %) with type 1 and 2 diabetes, respectively and 307,315 controls. Patients diagnosed with type 1 and 2 diabetes at baseline (7614) and patients without diagnosis, using insulin only at baseline and 30 years or older (10178) were not included in our analysis.

Table 1 shows baseline characteristics. The mean age at index date was 58 years.

Forty-six percent of the patients with diabetes had a BMI of 30 or above in contrast with 30 % of the control subjects.

During nearly six years of follow-up 1,071 patients of the control group and 1,295 of the ADD users were diagnosed with bladder cancer. Patients with type 1 diabetes had no significantly lower risk of UBC (HR = 0.77 (95% CI 0.57-1.05)) than patients with type 2 diabetes (HR = 1.04 (95% CI 0.96-1.14)) based on a Wald test (p=0,054). The results for incident ADD users were similar. (Table 2)

For patients with incident type 2 diabetes, we noticed an increased risk of UBC (HR = 1.26 (95 % CI 1.05-1.52)) during the first year after the first ADD prescription, compared to controls, disappearing in subsequent years (Table 3). There was no difference in UBC risk between males and females patients with type 2 diabetes (HR = 1.11 (95 % CI 0.98-1.25) and 1.01 (95 % CI 0.79-1.29), respectively). In patients with type 2 diabetes, there was no influence of HbA1c as an indicator of diabetes severity on UBC risk (Table 4). UBC related mortality was neither increased in patients with type 1 diabetes (HR = 0.79 (95 % CI 0.32-1.94)) nor in patients with type 2 diabetes compared to controls (HR = 1.05 (95 % CI 0.83-1.33)) (Table 5).

DISCUSSION

We could not detect a significantly increased risk of UBC nor of increased mortality due to UBC in patients with type 1 and 2 diabetes patients compared to controls even if we reduced our cohort to incident ADD users. However, we noticed an increased risk of UBC in patients with type 2 diabetes during the first year after diagnosis. Diabetes control, as expressed by HbA1c, had no influence on the UBC risk in

patients with type 2 diabetes.

Previous meta-analyses reported an increased risk (6-9). Even when these meta-analyses (6-8) were restricted to studies that adjusted for smoking, there was still an increased RR ranging from 1.32 (95% CI 1.18–1.49) to 1.48 (95% CI 1.25–1.77), comparable to our RR for type 2 diabetes.

On the other hand, in several studies diabetes ascertainment was based on self-reporting (8). Those studies had an RR of 1.34 (95 % CI 1.11-1.62). The increased risk of UBC in patients with diabetes decreased and significance disappeared when diabetes was asserted by other methods (RR = 1.11 (95 % CI 0.95-1.31)). Furthermore, not all studies distinguished between diabetes type 1 and 2. Most of the studies excluded type 1 diabetes as a diagnosis of diabetes before 30 years of age (7, 8). Subgroup analysis of studies restricted to Europe did not show an increased risk of UBC in patients with type 2 diabetes (6-8). Hence, our result is in line with those of European studies (12, 14-21). It is not clear why there is a difference between European and other regions.

We did not find an increased risk of bladder cancer in diabetes type 1, which is in line with the results found in Sweden (10, 11), and in the UK (12).

An increased risk of UBC during the first year after diabetes diagnosis was found in several other studies (20, 22-24). Likewise, for colorectal, lung, breast, liver, cervical, endometrial, ovarian, pancreatic and prostate cancers a significantly increased risk was found within the months following diabetes onset (10, 25, 26). This most likely indicates the presence of a detection bias, in the sense that the diagnosis of diabetes leads to increased medical attention, and thus to earlier detection of any present but undiagnosed cancer. This phenomenon has also been observed immediately after the

diagnosis of prostate cancer. The incidence of UBC was 18 times higher in patients with prostate cancer due to diagnostic bias (27, 28). On the other hand, in contrast with some other studies we could not confirm the hypothesis that fewer physician visits in the year before diabetes diagnosis increases the risk of bladder cancer diagnosis in contrast with some other studies (24, 26).

Our finding of no association between HbA1c and cancer risk is consistent with the results of a recent meta-analysis of major randomized controlled trials (29).

The strength of this study was that the CPRD is a large population-based cohort representative of the total UK population. Type 2 diabetes accounts for 85 % to 95 % of all diabetes in high-income countries (30). In the UK, 10 % of the people with diabetes have type 1 (31), which was confirmed in our analysis (9,4 %).

We had detailed longitudinal information on drug prescription and 95 % and 80 % of the patients with type 1 and 2 diabetes, respectively, had received a formal diabetes diagnosis. Patients with type 1 and 2 diabetes at baseline and patients without diagnosis, using insulin only at baseline and 30 years or older were excluded from our analysis.

Given that smoking is one of the major risk factors for bladder cancer, we had information on the smoking status of all patients that were included in our analysis (5). The link with the ONS data allowed us to have detailed information about the cause of death for 44 % of patients.

The fact that the effect of different anti-diabetic drug medications was not considered in our analyses is a major limitation. We are aware of the fact that metformin can have a protective effect on cancer (3, 32) and that pioglitazone could be associated

with an increased risk of bladder cancer (33-37). This was, however, beyond the scope of this study.

With this study, and against the background of all previous research, the likelihood of a clinically relevant association between diabetes and UBC risk has become very limited. The influence of anti-diabetic treatment on bladder cancer risk, however, is still contradictable and requires further study in the future.

CONCLUSION

Neither the risk of UBC, nor the mortality from UBC, was observed to be increased in patients with type 1 or type 2 diabetes in the CPRD data. Our results are in line with those of previous European studies.

List of abbreviations

UBC = urinary bladder cancer

CPRD = Clinical Practice Research Datalink

ONS = Office of National Statistics

ADD = anti-diabetic drugs

HR = hazard ratio

RR = relative risk

GP = general practitioner

NIAD = oral anti-diabetic drugs (non-insulin anti-diabetic drug)

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Contributorship statement

ME.G. wrote the manuscript and researched data. M.B. performed the statistical analysis and reviewed the manuscript. F.B. and MP.Z. reviewed/edited the manuscript. F.dV. and ML.DB. provided the data and reviewed/edited the manuscript.

Competing interests

The Department of Pharmacoepidemiology and Clinical Pharmacology employing authors Marloes Bazelier and Frank de Vries has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private–public-funded Top Institute Pharma (www.tipharma.nl; includes co-funding from universities, government and industry), the Dutch Medicines Evaluation Board and the Dutch Ministry of Health. The GPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare Products Regulatory Agency (MHRA). GPRD is funded by the MHRA, Medical Research Council, various universities, contract research organizations and pharmaceutical companies.

Marie L. De Bruin is employed by Utrecht University as a senior researcher conducting research in collaboration with the WHO Collaborating Centre for pharmaceutical policy and regulation. This Centre receives no direct funding or donations from private parties, including pharma industry. Research funding from public-private partnerships, e.g. IMI, TI Pharma (www.tipharma.nl) is accepted under the condition that no company-specific product or company related study is conducted. The Centre has received unrestricted research funding from public sources, e.g. Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), EU 7th Framework Program (FP7), Dutch Medicines Evaluation Board (MEB), and Dutch Ministry of Health.

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Data sharing statement

CPRD data is available under license with the Medicines and Healthcare products Regulatory Agency (MHRA) in London, UK. The datasets that have been used for this project have been licensed by the MHRA. Access to datasets that have been used for this study are available for audit purposes only, conditional upon permission by the MHRA.

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TABLE 1

Table 1: Baseline characteristics of anti-diabetic drugs (ADD) users and non-diabetic controls				
Characteristics	ADD users		Controls	
	N = 329,168	(%)	307,315	(%)
Follow-up time (years; mean)	5.91		5.66	
Sex				
Female	152 683	(46.4)	148 791	(48.4)
Male	176 485	(53.6)	158 524	(51.6)
Age at index date (years; mean, median)	58.6 (60.0)		58.2 (60.0)	
18-29	19 716	(6.0)	19 184	(6.2)
30-39	26 236	(8.0)	28 065	(9.1)
40-49	43 659	(13.3)	41 539	(13.5)
50-59	68 564	(20.8)	62 400	(20.3)
60-69	80 562	(24.5)	71 975	(23.4)
70-79	62 064	(18.9)	56 632	(18.4)
80 +	28 367	(8.6)	27 520	(9.0)
Smoking status				
Never smoker	168 832	(51.3)	166 190	(54.1)
Current smoker	66 903	(20.3)	70 765	(23.0)
Former smoker	93 433	(28.4)	70 360	(22.9)
Body mass index				
< 20.0 kg/m2	6 587	(2.0)	16 769	(5.5)
20.0 – 24.9 kg/m2	54 212	(16.5)	96 636	(31.4)
25.0 – 29.9 kg/m2	105 547	(32.1)	103 315	(33.6)
≥ 30.0 kg/m2	150 152	(45.6)	55 827	(18.2)
Unknown	12 670	(3.8)	34 768	(11.3)
ADD users				
Formal diabetes diagnosis				
Type 1	28 964	(8.8)		
Type 2	239 021	(72.6)		
No diabetes diagnosis				
Insulin only at index date and <30 years	1 859	(0.6)		
Others	59 324	(18.0)		
Diabetes patients				
Type 1 diabetes *	30 823	(9.4)		
Type 2 diabetes **	298 345	(90.6)		
(*) Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years				
(**) Defined as either formal diagnosis of type 2 diabetes or ADD use at index date				

TABLE 2

Table 2: Risk of bladder cancer in anti-diabetic drugs (ADD) users compared with controls, by type of diabetes and in incident ADD users

Exposure category	ADD users (N = 329,168) versus controls (N = 307,315)			Incident ADD users (N = 179,598) versus controls (N = 233,505)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	1,071 (0.3)	1	1	732 (0.3)	1	1
ADD users	1,295 (0.4)	1.09 (1.00-1.18)	1.03 (0.95-1.12)	746 (0.4)	1.15 (1.04-1.27)	1.08 (0.97-1.20)
Type 1 diabetes (b)	44 (0.0)	0.76 (0.56-1.02)*	0.77 (0.57-1.05)	5 (0.0)	0.65 (0.27-1.58)	0.65 (0.27-1.57)
Type 2 diabetes (c)	1,251 (0.4)	1.10 (1.02-1.20)	1.04 (0.96-1.14)	741 (0.4)	1.15 (1.04-1.28)	1.09 (0.97-1.21)

(a) Incident = all index patients are included after one year lead-in time without anti-diabetic drugs (ADD) prescription; HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index
(b) Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years
(c) Defined as either formal diagnosis of type 2 diabetes or ADD use at index date
(*) Significant difference between type 1 DM and type 2 DM, based on Wald test

TABLE 3

Table 3: Risk of bladder cancer in incident patients with type 2 diabetes mellitus compared with controls, by duration of disease and sex			
Exposure category	Type 2 diabetes (N = 175,083) versus controls (N = 233,505)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	732 (0.3)	1	1
Type 2 diabetes	741 (0.4)	1.15 (1.04-1.28)	1.09 (0.97-1.21)
Duration of disease (b)			
< 1 year	149 (0.1)	1.34 (1.12-1.61)	1.26 (1.05-1.52)
1 to < 2 years	95 (0.1)	1.17 (0.95-1.45)	1.10 (0.88-1.37)
2 to < 5 years	201 (0.1)	1.02 (0.87-1.19)	0.95 (0.81-1.12)
5 to < 10 years	224 (0.1)	1.22 (1.05-1.41)	1.14 (0.98-1.33)
10 to < 15 years	67 (0.0)	1.19 (0.93-1.54)	1.14 (0.88-1.47)
≥ 15 years	5 (0.0)	0.43 (0.18-1.04)	0.42 (0.18-1.02)
Sex			
Male (c)	604 (0.3)	1.19 (1.06-1.33)	1.11 (0.98-1.25)
Female (d)	137 (0.1)	1.03 (0.82-1.29)	1.01 (0.79-1.29)
(a) Incident = all index patients are included after one year lead-in time without anti-diabetic drugs (ADD) prescription; HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index			
(b) As measured from first prescription			
(c) Male patients with type 2 diabetes versus male controls			
(d) Female patients with type 2 diabetes versus female controls			

TABLE 4

Table 4: Risk of urinary bladder cancer in patients with type 2 diabetes mellitus by Hemoglobin A1c level at most recent measurement

Exposure category	Patients with type 2 diabetes(N = 298,345)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Type 2 diabetes	1,251 (0.4)		
Hb A1C level*			
HbA1c < 6%	57 (0.0)	1	1
6 ≤ HbA1c < 7.0%	278 (0.1)	1.18 (0.89-1.57)	1.19 (0.90-1.58)
7 ≤ HbA1c < 8.0%	248 (0.1)	1.16 (0.87-1.55)	1.18 (0.89-1.58)
8 ≤ HbA1c < 9.0%	110 (0.0)	1.09 (0.79-1.50)	1.10 (0.80-1.52)
HbA1c ≥ 9.0%	106 (0.0)	1.17 (0.85-1.62)	1.17 (0.85-1.62)
missing	452 (0.2)	0.91 (0.68-1.20)	0.92 (0.69-1.21)

(a) HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index

*6% = 42 mmol/mol, 7% = 53 mmol/mol, 8% = 64 mmol/mol, 9% = 75 mmol/mol

TABLE 5

Table 5: Risk of urinary bladder cancer (UBC) mortality in anti-diabetic drugs (ADD) users compared with controls, by type of diabetes mellitus

Exposure category	ADD user (N = 143,566) versus controls (N = 114,994)		
	Bladder cancer mortality N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	145 (0.1)	1	1
ADD users	179 (0.1)	1.04 (0.83-1.29)	1.04 (0.83-1.31)
Type 1 diabetes	5 (0.0)	0.73 (0.30-1.79)	0.79 (0.32-1.94)
Type 2 diabetes	174 (0.1)	1.05 (0.84-1.31)	1.05 (0.83-1.33)

(a) HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index

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STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any pre-specified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed	

		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Risk of bladder cancer in patients with diabetes: a retrospective cohort study

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9 3 Risk of bladder cancer in patients with diabetes: a retrospective cohort study

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12 4 RUNNING TITLE

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Keywords

Type 1 diabetes mellitus, type 2 diabetes mellitus, bladder cancer, mortality

Word count

2541

ABSTRACT

Objective

43 The objective of this study was to examine the association between diabetes and both
44 urinary bladder cancer (UBC) risk and mortality.

45 **Methods**

46 We conducted a retrospective cohort study using data from the UK Clinical Practice
47 Research Datalink (CPRD) linked to the Office of National Statistics (ONS). Patients
48 diagnosed with diabetes mellitus type 1 or 2 or using anti-diabetic drugs (ADD) were
49 compared to matched non-diabetic controls. Cox proportional hazards models were
50 used to estimate the risk and mortality of UBC. We adjusted for age, sex, smoking
51 status and BMI.

52 **Results**

53 The cohort included 329,168 patients using ADD and 307,315 controls with 1,295
54 and 1,071 patients, respectively, diagnosed as having UBC during follow-up. The
55 adjusted hazard ratios (HR) of UBC were 0.77 (95% CI 0.57-1.05) and 1.04 (95% CI
56 0.96-1.14) for type 1 and 2 diabetes, respectively. These results were similar if we
57 restricted our analysis to an inception cohort. We noticed a small increased risk
58 during the first year after diagnosis (HR = 1.26 (95% CI 1.05-1.52)), which could be
59 explained by detection bias. There was no influence of the severity of diabetes as
60 measured by the HbA1c. Mortality of UBC was not increased for patients with either
61 type 1 (HR = 0.95 (95% CI 0.39-2.34)) or type 2 diabetes (HR = 1.16 (95% CI 0.91-
62 1.46)).

63 **Conclusion**

64 Neither the risk of UBC, nor the mortality from UBC, was increased in type 1 and
65 patients with type 2 diabetes in the CPRD data.

66

67 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 68 • The CPRD is a large population-based cohort representative of the total UK
69 population.
- 70 • Detailed longitudinal information on drug prescription is available within the
71 CPRD and 95 % and 80 %, of patients with type 1 and 2 diabetes, respectively
72 had received a formal diabetes diagnosis.
- 73 • Smoking status was available for all patients in our analysis.
- 74 • Detailed information about the cause of death is available for 44 % of the
75 patients by linking the patients to the ONS data.
- 76 • The effect of different anti-diabetic drug medications is not considered in our
77 analyses and this is a major limitation.

79 MAIN TEXT

80 BACKGROUND

81 The global 2013 estimate of diabetes mellitus prevalence among adults (aged 20–79
82 years) was 8,3 %, affecting 382 million adults in the world and 6,6 % in the United
83 Kingdom (1). Between 2010 and 2030, the number of adults with diabetes in
84 developing countries is expected to increase by 69% and by 20% developed countries
85 (2, 3). In 2012, more than 400,000 cases of urinary bladder cancer (UBC) occurred
86 worldwide, making it the 7th most common type of cancer (4). It is more frequent in
87 men than in women and age is now widely accepted as the greatest single risk factor
88 for developing UBC. Cigarette smoking, specific occupational exposures, such as

89 carcinogenic dyes for painters and some genetic polymorphisms, are main known
90 other causes of UBC (5). Previous meta-analyses from cohort and case-control studies
91 have shown an increased risk of UBC associated with type 2 diabetes with relative
92 risks (RR) ranging from 1.11 (95% CI 1.00-1.23) to 1.32 (95% CI 1.18–1.49) (6-9).
93 There is also evidence for a positive association between type 2 diabetes and mortality
94 from UBC (RR = 1.33 (95% CI 1.14–1.55) (7). However, misclassification of type 1
95 and 2 diabetes was not excluded in these studies because diagnostic codes were
96 lacking and details about the diabetic history (duration, metabolic control) were not
97 considered.

98 Two studies on type 1 diabetes reported an increased overall cancer incidence by
99 20 % while the mechanisms remain unclear (10, 11). The observed number of bladder
100 cancer cases in these studies is very small ranging from 4 to 27 cases (10-12). The
101 objective of this study was to examine the association between diabetes mellitus and
102 both UBC risk and mortality taking into account diabetes duration, metabolic control
103 as expressed by haemoglobin A1c (HbA1c) and type of diabetes.

104

105 **METHODS**

106 **Data sources**

107 We conducted a retrospective cohort study using data from the UK Clinical Practice
108 Research Datalink (CPRD) (January 1987-October 2013) linked to the Office of
109 National Statistics (ONS) (January 1998 – January 2012). The CPRD comprises
110 prospectively collected computerized medical records of over 10 million patients
111 under the care of more than 600 general practitioners (GPs) in the United Kingdom

(UK). The Read classification is used to enter medical diagnoses and procedures, and prescriptions are recorded based on the UK *Prescription Pricing Authority Dictionary*. The recorded information on diagnoses and drug use was validated and proved to be of high quality (13). The ONS provided data for the cause(s) of death and the exact date of death as recorded on death certificates by a registered medical practitioner attending to the patient during their last period.

Study population

All patients with at least one prescription of anti-diabetic drugs (ADD) (oral anti-diabetic drugs (NIAD) and/or insulin) and aged above 18 years during the period of valid CPRD data collection were included. Each ADD user was matched to one control patient by year of birth, sex and practice. Controls could have any disease as long as they were non-diabetic patients at baseline and during follow-up. The date of the first ADD prescription defined the index date and controls were assigned the same index date as their matched ADD user. All subjects with missing data for smoking status, a history of any cancer prior to the index date, except non-melanoma skin cancer, or a diagnosis of gestational diabetes or secondary diabetes ever during follow-up were excluded. All control patients who used diabetes treatment or had ever been diagnosed with type 1 or 2 diabetes ever during follow-up were excluded. All ADD users with diagnoses of both type 1 and 2 diabetes were excluded as well, as were patients aged 30 years and older without a diagnosis of diabetes, who used insulin only at baseline. All study participants were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, or the patient's death.

Exposure

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3 136 Patients with type 1 diabetes were defined as those patients with a formal diagnosis of
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5 137 type 1 diabetes (as recorded in CPRD) or younger than 30 years and using insulin
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7 138 only at index date. Patients with type 2 diabetes were all patients with a formal
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9 139 diagnosis of type 2 diabetes (as recorded in CPRD) or using an oral ADD at index
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11 140 date. The total period of follow-up for each patient (patients with diabetes and
12
13 141 unexposed controls) was divided into fixed time periods of 90 days. Age was
14
15 142 determined at the start of each interval. The classification of type 1 and 2 diabetes, as
16
17 143 well as sex, smoking status and BMI was determined at baseline. Diabetes duration
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19 144 was assessed in a time-dependent manner by estimating the time since the date of the
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21 145 first ADD prescription (the index date). Diabetes control was assessed in a time-
22
23 146 dependent manner using the most recent HbA1c record before the start of each time
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25 147 interval and within the previous year.
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31 **Outcomes**
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33 149 The primary outcome was UBC, as defined by Read codes, and was assessed in the
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35 150 complete CPRD study population (January 1987-October 2013). The secondary
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37 151 outcome was bladder cancer related mortality as recorded on death certificates
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39 152 (International Classification of Diseases (ICD-10) categories C65, C67) and was
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41 153 assessed in the population eligible for linkage between CPRD and ONS data (44% of
42
43 154 the subjects). The period of follow-up was restricted to the time that ONS data were
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45 155 available (January 1998 – January 2012).
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50 **Risk factors**
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53 157 The major covariates of interest included age, sex, smoking status and BMI. Smoking
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55 158 status was characterized at baseline as current, former, or lifelong nonsmoker.
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159 Statistical analysis

160 Analyses were conducted using Cox proportional hazards models with various sub-
161 analyses. As time scale we used time since first ADD use. We tested the proportional
162 hazard assumption by comparing diabetes patients to non-diabetes controls. The
163 assumption was not violated. The first analysis compared the risk of UBC in ADD
164 users with that in control patients to yield an estimate of the relative risk [as a hazard
165 ratio (HR)] of UBC associated with ADD use. The calculations were adjusted for age,
166 sex, smoking status and BMI. Results were stratified to type 1 and type 2 diabetes. A
167 sensitivity analysis was performed excluding women with polycystic ovarian
168 syndrome (PCOS). In a secondary analysis, risks were estimated for an inception
169 cohort of ADD users using a 1-year lead-in time. The risk of UBC for patients with
170 incident type 2 diabetic was further stratified by disease duration, sex and HbA1c.
171 The risk of UBC mortality in ADD users compared with that of controls was assessed
172 by Cox models as well and results were stratified by type of diabetes. All data
173 management and statistical analyses were conducted using SAS® 9.1/9.2 software.
174 This study was approved by the Medicines and Healthcare products Authorities'
175 Independent Scientific Advisory Committee, protocol number 13_050R.

176 RESULTS

177 After exclusion of all patients with a diagnosis of gestational diabetes (1,983 and 154
178 for ADD users and controls respectively), or secondary diabetes (485 and 70 for ADD
179 users and controls respectively), or cancer prior to index date (34,955 and 34,384 for
180 ADD users and controls respectively) or missing data for smoking status during
181 follow up (13,416 and 27,558 for ADD users and controls respectively), the study
182 population consisted of 329,168 patients with diabetes of whom 30,823 (9.4 %) and
183 298,345 (90.6 %) with type 1 and 2 diabetes, respectively and 307,315 controls.

184 Patients diagnosed with type 1 and 2 diabetes at baseline (7,614) and patients without
185 diagnosis, using insulin only at baseline and 30 years or older (10,178) were not
186 included in our analysis.

187 Table 1 shows baseline characteristics. The mean age at index date was 58 years.

188 Forty-six percent of the patients with diabetes had a BMI of 30 or above in contrast
189 with 30 % of the control subjects.

190 During nearly six years of follow-up 1,071 patients of the control group and 1,295 of
191 the ADD users were diagnosed with bladder cancer. Patients with type 1 diabetes had
192 no significantly lower risk of UBC (HR = 0.77 (95% CI 0.57-1.05)) than patients with
193 type 2 diabetes (HR = 1.04 (95% CI 0.96-1.14)) based on a Wald test (p=0.054). The
194 results for incident ADD users were similar. (Table 2)

195 For patients with incident type 2 diabetes, we noticed an increased risk of UBC (HR =
196 1.26 (95 % CI 1.05-1.52)) during the first year after the first ADD prescription,
197 compared to controls, disappearing in subsequent years (Table 3). Sixty per cent of
198 the bladder cancers developed during the first five years after diabetes onset. There
199 was no difference in UBC risk between males and females patients with type 2
200 diabetes (HR = 1.11 (95 % CI 0.98-1.25) and 1.01 (95 % CI 0.79-1.29), respectively).

201 In patients with type 2 diabetes, there was no influence of HbA1c as an indicator of
202 diabetes severity on UBC risk (Table 4). UBC related mortality was neither increased
203 in patients with type 1 diabetes (HR = 0.79 (95 % CI 0.32-1.94)) nor in patients with
204 type 2 diabetes compared to controls (HR = 1.05 (95 % CI 0.83-1.33)) (Table 5).

205 **DISCUSSION**

206 We could not detect a significantly increased risk of UBC nor of increased mortality
207 due to UBC in patients with type 1 and 2 diabetes patients compared to controls even
208 if we reduced our cohort to incident ADD users. However, we noticed an increased

209 risk of UBC in patients with type 2 diabetes during the first year after diagnosis.

210 Diabetes control, as expressed by HbA1c, had no influence on the UBC risk in

211 patients with type 2 diabetes.

212 Previous meta-analyses reported an increased risk (6-9). Even when these meta-

213 analyses (6-8) were restricted to studies that adjusted for smoking, there was still an

214 increased RR ranging from 1.32 (95% CI 1.18–1.49) to 1.48 (95% CI 1.25–1.77),

215 comparable to our RR for type 2 diabetes. On the other hand, in several studies

216 diabetes ascertainment was based on self-reporting (8). Those studies had an RR of

217 1.34 (95 % CI 1.11-1.62). The increased risk of UBC in patients with diabetes

218 decreased and significance disappeared when diabetes was asserted by other methods

219 (RR = 1.11 (95 % CI 0.95-1.31)). Furthermore, not all studies distinguished between

220 diabetes type 1 and 2. Most of the studies excluded type 1 diabetes as a diagnosis of

221 diabetes before 30 years of age (7, 8). Subgroup analysis of studies restricted to

222 Europe did not show an increased risk of UBC in patients with type 2 diabetes (6-8).

223 Hence, our result is in line with those of European studies (12, 14-21). It is not clear

224 why there is a difference between European and other regions.

225 We did not find an increased risk of bladder cancer in diabetes type 1, which is in line

226 with the results found in Sweden (10, 11), and in the UK (12).

227 An increased risk of UBC during the first year after diabetes diagnosis was found in

228 several other studies (20, 22-24). Likewise, for colorectal, lung, breast, liver, cervical,

229 endometrial, ovarian, pancreatic and prostate cancers a significantly increased risk

230 was found within the months following diabetes onset (10, 25, 26). This most likely

231 indicates the presence of a detection bias, in the sense that the diagnosis of diabetes

232 leads to increased medical attention, and thus to earlier detection of any present but

undiagnosed cancer. This phenomenon has also been observed immediately after the diagnosis of prostate cancer. The incidence of UBC was 18 times higher in patients with prostate cancer due to diagnostic bias (27, 28). On the other hand, in contrast with some other studies we could not confirm the hypothesis that fewer physician visits in the year before diabetes diagnosis increases the risk of bladder cancer diagnosis in contrast with some other studies (24, 26). Apart from the increased risk of UBC during the first year of diabetes diagnosis possibly due to detection bias, we did not find an association between diabetes duration and developing bladder cancer. Seen that nearly 50 % of the patients had a follow-up of more than five years and only 40 % of the bladder cancers were diagnosed after these five years, while only 10 % was diagnosed after 10 years, we can conclude that having diabetes for more than five years did not alter the risk of UBC.

Our finding of no association between HbA1c and cancer risk is consistent with the results of a recent meta-analysis of major randomized controlled trials (29).

The strength of this study was that the CPRD is a large population-based cohort representative of the total UK population. Type 2 diabetes accounts for 85 % to 95 % of all diabetes in high-income countries (30). In the UK, 10 % of the people with diabetes have type 1 (31), which was confirmed in our analysis (9,4 %). We had detailed longitudinal information on drug prescription and 95 % and 80 % of the patients with type 1 and 2 diabetes, respectively, had received a formal diabetes diagnosis. Patients with type 1 and 2 diabetes at baseline and patients without diagnosis, using insulin only at baseline and 30 years or older were excluded from our analysis. Consulting rates for diabetes in the CPRD have been compared with equivalent data from the 4th National Morbidity Survey in General Practice

confirming the validity of the morbidity data in the CPRD (32). Furthermore, since 2004, GPs are stimulated to provide “quality care” by the Quality and Outcomes Framework (QOF). The UK has a National Service Framework for Diabetes (NSF) (33). Guidelines to be followed by the GPs are outlined in the guideline for type 1 (34) and 2 diabetes (35) of the National Institute for Health and Care Excellence (NICE). For diagnosis the NICE guideline refers to the International Diabetes Federation (IDF) Diabetes Atlas (30). Diagnosis of diabetes is directly linked with prescription of ADD whereas Impaired Glucose Tolerance (IGT) is referred to as people whose blood glucose levels are high but not as high as those in people with diabetes. Our cohort was restricted to those patients receiving ADD. Furthermore, we had HbA1c values for 1,251 of the 1,295 bladder cancer patients. So, 96 % of the patients have additional prove to be diabetic.

Metformin can also be used to treat obesity or PCOS. We have no means to test the possible effect of Metformin prescribed for obesity although the clinical impression exist that such treatments tend to be relatively short. In our cohort, 12,841 women were diagnosed with PCOS. None of them developed UBC. A sensitivity analysis, excluding those PCOS women showed exactly the same HRs. Additionally, we have information on the smoking status of all patients that were included in our analysis, which is essential given that smoking is one of the major risk factors for bladder cancer (5). The link with the ONS data allowed us to have detailed information about the cause of death for 44 % of patients.

The fact that the effect of different anti-diabetic drug medications was not considered in our analyses is a major limitation. We are aware of the fact that metformin can have a protective effect on cancer (3, 36) and that pioglitazone could be associated

281 with an increased risk of bladder cancer (37-41). This was, however, beyond the
282 scope of this study.

283 With this study, and against the background of all previous research, the likelihood of
284 a clinically relevant association between diabetes and UBC risk has become very
285 limited. The influence of anti-diabetic treatment on bladder cancer risk, however, is
286 still contradictable and requires further study in the future.

288 **CONCLUSION**

289 Neither the risk of UBC, nor the mortality from UBC, was observed to be increased in
290 patients with type 1 or type 2 diabetes in the CPRD data. Our results are in line with
291 those of previous European studies.

292 **List of abbreviations**

- 293 UBC = urinary bladder cancer
294 CPRD = Clinical Practice Research Datalink
295 ONS = Office of National Statistics
296 ADD = anti-diabetic drugs
297 HR = hazard ratio
298 RR = relative risk
299 GP = general practitioner
300 NIAD = oral anti-diabetic drugs (non-insulin anti-diabetic drug)
301 PCOS = Polycystic Ovarian Syndrome
302 QOF = Quality and Outcomes Framework
303 NSF = National Service Framework for Diabetes
304 NICE = National Institute for Health and Care Excellence
305 IDF = International Diabetes Federation

IGT = Impaired Glucose Tolerance

Contributorship statement

ME.G. wrote the manuscript and researched data. M.B. performed the statistical analysis and reviewed the manuscript. F.B. and MP.Z. reviewed/edited the manuscript. F.dV. and ML.DB. provided the data and reviewed/edited the manuscript.

Competing interests

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332

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338 **Data sharing statement**

339 CPRD data is available under license with the Medicines and Healthcare products
340 Regulatory Agency (MHRA) in London, UK. The datasets that have been used for
341 this project have been licensed by the MHRA. Access to datasets that have been used
342 for this study are available for audit purposes only, conditional upon permission by
343 the MHRA.

344

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TABLE 1

Table 1: Baseline characteristics of anti-diabetic drugs (ADD) users and non-diabetic controls

Characteristics	ADD users		Controls	
	N = 329,168	(%)	307,315	(%)
Follow-up time (years; mean)	5.91		5.66	
Sex				
Female	152 683	(46.4)	148 791	(48.4)
Male	176 485	(53.6)	158 524	(51.6)
Age at index date (years; mean, median)	58.6 (60.0)		58.2 (60.0)	
18-29	19 716	(6.0)	19 184	(6.2)
30-39	26 236	(8.0)	28 065	(9.1)
40-49	43 659	(13.3)	41 539	(13.5)
50-59	68 564	(20.8)	62 400	(20.3)
60-69	80 562	(24.5)	71 975	(23.4)
70-79	62 064	(18.9)	56 632	(18.4)
80 +	28 367	(8.6)	27 520	(9.0)
Smoking status				
Never smoker	168 832	(51.3)	166 190	(54.1)
Current smoker	66 903	(20.3)	70 765	(23.0)
Former smoker	93 433	(28.4)	70 360	(22.9)
Body mass index				
< 20.0 kg/m ²	6 587	(2.0)	16 769	(5.5)
20.0 – 24.9 kg/m ²	54 212	(16.5)	96 636	(31.4)
25.0 – 29.9 kg/m ²	105 547	(32.1)	103 315	(33.6)
≥ 30.0 kg/m ²	150 152	(45.6)	55 827	(18.2)
Unknown	12 670	(3.8)	34 768	(11.3)
ADD users				
Formal diabetes diagnosis				
Type 1	28 964	(8.8)		
Type 2	239 021	(72.6)		
No diabetes diagnosis				
Insulin only at index date and <30 years	1 859	(0.6)		
Others	59 324	(18.0)		
Diabetes patients				
Type 1 diabetes *	30 823	(9.4)		
Type 2 diabetes **	298 345	(90.6)		

(*) Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years

(**) Defined as either formal diagnosis of type 2 diabetes or ADD use at index date

TABLE 2

Table 2: Risk of bladder cancer in anti-diabetic drugs (ADD) users compared with controls, by type of diabetes and in incident ADD users

Exposure category	ADD users (N = 329,168) versus controls (N = 307,315)			Incident ADD users (N = 179,598) versus controls (N = 233,505)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	1,071 (0.3)	1	1	732 (0.3)	1	1
ADD users	1,295 (0.4)	1.09 (1.00-1.18)	1.03 (0.95-1.12)	746 (0.4)	1.15 (1.04-1.27)	1.08 (0.97-1.20)
Type 1 diabetes (b)	44 (0.0)	0.76 (0.56-1.02)*	0.77 (0.57-1.05)	5 (0.0)	0.65 (0.27-1.58)	0.65 (0.27-1.57)
Type 2 diabetes (c)	1,251 (0.4)	1.10 (1.02-1.20)	1.04 (0.96-1.14)	741 (0.4)	1.15 (1.04-1.28)	1.09 (0.97-1.21)

(a) Incident = all index patients are included after one year lead-in time without anti-diabetic drugs (ADD) prescription; HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index
(b) Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years
(c) Defined as either formal diagnosis of type 2 diabetes or ADD use at index date
(*) Significant difference between type 1 DM and type 2 DM, based on Wald test

TABLE 3

Table 3: Risk of bladder cancer in incident patients with type 2 diabetes mellitus compared with controls, by duration of disease and sex

Exposure category	Type 2 diabetes (N = 175,083) versus controls (N = 233,505)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	732 (0.3)	1	1
Type 2 diabetes	741 (0.4)	1.15 (1.04-1.28)	1.09 (0.97-1.21)
Duration of disease (b)			
< 1 year	149 (0.1)	1.34 (1.12-1.61)	1.26 (1.05-1.52)
1 to < 2 years	95 (0.1)	1.17 (0.95-1.45)	1.10 (0.88-1.37)
2 to < 5 years	201 (0.1)	1.02 (0.87-1.19)	0.95 (0.81-1.12)
5 to < 10 years	224 (0.1)	1.22 (1.05-1.41)	1.14 (0.98-1.33)
10 to < 15 years	67 (0.0)	1.19 (0.93-1.54)	1.14 (0.88-1.47)
≥ 15 years	5 (0.0)	0.43 (0.18-1.04)	0.42 (0.18-1.02)
Sex			
Male (c)	604 (0.3)	1.19 (1.06-1.33)	1.11 (0.98-1.25)
Female (d)	137 (0.1)	1.03 (0.82-1.29)	1.01 (0.79-1.29)

(a) Incident = all index patients are included after one year lead-in time without anti-diabetic drugs (ADD) prescription; HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index

(b) As measured from first prescription

(c) Male patients with type 2 diabetes versus male controls

(d) Female patients with type 2 diabetes versus female controls

TABLE 4

Table 4: Risk of urinary bladder cancer in patients with type 2 diabetes mellitus by Hemoglobin A1c level at most recent measurement

Exposure category	Patients with type 2 diabetes(N = 298,345)		
	Bladder cancer N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Type 2 diabetes	1,251 (0.4)		
Hb A1C level*			
HbA1c < 6%	57 (0.0)	1	1
6 ≤ HbA1c < 7.0%	278 (0.1)	1.18 (0.89-1.57)	1.19 (0.90-1.58)
7 ≤ HbA1c < 8.0%	248 (0.1)	1.16 (0.87-1.55)	1.18 (0.89-1.58)
8 ≤ HbA1c < 9.0%	110 (0.0)	1.09 (0.79-1.50)	1.10 (0.80-1.52)
HbA1c ≥ 9.0%	106 (0.0)	1.17 (0.85-1.62)	1.17 (0.85-1.62)
missing	452 (0.2)	0.91 (0.68-1.20)	0.92 (0.69-1.21)

(a) HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index
*6% = 42 mmol/mol, 7% = 53 mmol/mol, 8% = 64 mmol/mol, 9% = 75 mmol/mol

TABLE 5

Table 5: Risk of urinary bladder cancer (UBC) mortality in anti-diabetic drugs (ADD) users compared with controls, by type of diabetes mellitus

Exposure category	ADD user (N = 143,566) versus controls (N = 114,994)		
	Bladder cancer mortality N (%)	Age-sex adj HR (95 % CI)	Fully adj HR (a) (95 % CI)
Controls	145 (0.1)	1	1
ADD users	179 (0.1)	1.04 (0.83-1.29)	1.04 (0.83-1.31)
Type 1 diabetes	5 (0.0)	0.73 (0.30-1.79)	0.79 (0.32-1.94)
Type 2 diabetes	174 (0.1)	1.05 (0.84-1.31)	1.05 (0.83-1.33)

(a) HR = hazard ratio; CI = confidence interval; fully adjusted for age, sex, smoking and body mass index

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	3
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	8
		(d) If applicable, explain how loss to follow-up was addressed	8
		(e) Describe any sensitivity analyses	8
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8-9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.