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Metformin use and long-term risk of benign prostatic hyperplasia. A population-based cohort study.

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Abstract

Objective: To assess whether metformin use affects risk of benign prostatic hyperplasia (BPH) by comparing the risk of BPH in men with type 2 diabetes who initiated first-line treatment with either metformin or sulfonylurea monotherapy between 2000 or 2006 in Northern Denmark. In this period, sulfonylurea or metformin were both frequently used as first line glucose-lowering drug treatment.

Design: A population-based cohort study

Setting: Northern Denmark

Participants: All men who filled at least 2 prescriptions for metformin or for sulfonylurea, respectively during their first 6 months of glucose-lowering drug treatment. Follow-up started 6 months after treatment start.

Primary outcome measures: Rates of subsequent BPH, identified based on community prescriptions for BPH-related treatment or hospital BPH diagnoses, and rates of transurethral resection of the prostate (TURP). Rates in metformin and sulfonylurea users were compared overall and stratified by 6-month hemoglobin A_{1c} (HbA_{1c}) using Cox regression and an intention to treat (ITT) approach and an as treated analysis.

Results In 3,953 metformin initiators with a median follow-up of 10 years, the 10-year cumulative incidence was 25.7 % (95% CI 24.2 to 27.1). Compared with 5,958 sulfonylurea users (median follow-up 8 years, 10-year cumulative incidence 27.4% (95% CI 26.2 to 28.6)), the crude hazard ratio (HR) for BPH was 0.83 (95% CI 0.77 to 0.89) and adjusted HR in the ITT analyses was 0.97 (95% CI 0.88 to 1.06). For TURP the adjusted HR was 0.96 (95% CI 0.63 to 1.46). In the as-treated analysis, adjusted HR for BPH was 0.91 (95% CI 0.81 to 1.02).

Conclusions Compared with sulfonylurea, metformin did not substantially reduce the incidence of BPH in men with diabetes.

Strengths and limitations of this study

- The study used population-based data from two well-defined Danish regions.
- Use of nationwide medical registries allowed long and virtually complete follow-up
- Initiators of glucose-lowering drugs could be identified in a calendar period in which both metformin and sulfonylurea were recommended and used as first-line treatment which minimized confounding by indication.
- Benign prostatic hyperplasia was defined both based on hospital-related diagnoses and by prescriptions for relevant medication.
- We categorized treatment based on the choice of glucose-lowering drug during the first 6 months after treatment start applying an intention to treat principle but we also included an as treated analysis.

Introduction

Benign prostatic hyperplasia (BPH) associated with lower urinary tract symptoms is a common condition estimated to affect around 20% of American men aged 30-79 years [1]. Risk factors associated with dysmetabolism and low-grade inflammation, including obesity, high blood glucose, low exercise, and poor diet, seem to contribute substantially to the development of BPH and lower urinary tract symptoms [2 3]. Moreover, prostatic inflammation is likely a key factor in the development of BPH and also prostate cancer [4]. Accordingly, it has been hypothesized that insulin resistance and increased fasting plasma insulin are promoters of both BPH and prostate cancer [5].

Among men with type 2 diabetes, some observational studies have suggested that use of metformin reduces the risk of prostate cancer, compared with use of other glucose lowering drugs (GLD) [6-8] while others found no clear association [9-11]. A recent study found that metformin inhibits the proliferation of human prostate epithelial cells [12], and thus may reduce the BPH development as well as development of prostate cancer. Yet, few studies have examined the association between use of metformin and risk of BPH in diabetic men. A cohort study including 192,457 male veterans with type 2 diabetes and 259,995 person-years of follow up found no association between use of thiazolidinediones or metformin and new medical or surgical treatment for BPH, when compared with use of sulfonylurea [13]. While, a recent cohort study from South Korea found among 211,648 men with newly diagnosed BPH that men with type 2 diabetes in metformin treatment had lower risk of progression to prostatectomy than both men without type 2 diabetes and men with type 2 diabetes with no metformin treatment [14].

Comparing the effects of different GLDs in observational studies is complicated by the fact that the underlying indications/contraindications may differ between the drugs [15]. Compared with sulfonylurea, metformin has a more favorable effect on body weight and insulin resistance and

patients receiving metformin are therefore likely to have a higher prevalence of obesity and a higher plasma insulin level than users of sulfonylurea [16]. At least since 2011, metformin has been unequivocally consensus recommended as first-choice treatment in type 2 diabetes in Denmark, based on evidence from the UK Prospective Diabetes Study 1998 [17] and its 10-year follow up in 2008 [18]. Already in the mid-2000s however, the European Association for the Study of Diabetes and the American Diabetes Association recommended use of metformin as first-line drug [19 20]. Previously - in particular during the first half of the 2000s - metformin and sulfonylurea were both widely recommended and used as first-line treatment for type 2 diabetes in Denmark [21]. We therefore conducted a large population-based cohort study to examine the long-term risk of BPH in men with type 2 diabetes who initiated pharmacotherapy with either metformin or sulfonylurea between 2000 and 2006 in Northern Denmark. Our hypothesis was that use of metformin was associated with a lower BPH rate than use of sulfonylurea in men with type 2 diabetes.

Methods

Setting

We conducted a population-based cohort study among men with type 2 diabetes living in Northern Denmark using Danish medical databases. Northern Denmark consists of two regions, the Central Denmark region and the North Denmark region with approximately 700,000 male inhabitants. All residents are provided free tax-supported access to health care. All Danish residents are, at birth or upon immigration, assigned a unique personal identifier, the CPR number, by the Danish Civil Registration system (CRS)[22]. This identifier allows unambiguous linkage of data at the individual level. The CRS additionally tracks changes in vital status, residence, and migration for the entire Danish population on a daily basis. The Danish National Patient Registry (DNPR) has recorded all admissions to all Danish hospitals since 1977 [23]. Hospital outpatient and emergency room visits

have been included in the DNPR since 1995. Diagnoses are classified according to the *International Classification of Diseases*, *Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter.

Assembly of the cohort

We included all men 30 years or older with incident type 2 diabetes, who received their first GLD treatment between 1 January 2000 and 31 December 2006, corresponding to the time period when the Danish guidelines recommended both metformin and sulfonylurea as first line treatment for type 2 diabetes [21]. We defined incident type 2 diabetes as either a first record in the Danish National Patient Registry (DNPR) of a diabetes-associated inpatient admission (data available from 1977) or outpatient clinic contact (data available from 1995) or the first record of a GLD prescription in the Aarhus University Prescription Database (data available from 1996)[24]. Thus, patients with a GLD prescription in the 1996-1999 period were excluded.

GLD treatment

We categorized patients according to their first GLD treatment, metformin or sulfonylurea. To avoid including patients who switched or augmented GLD treatment very early (potentially due to adverse reactions or insufficient early glucose control) we required the patients to receive either metformin or sulfonylurea monotherapy for at least six months by requiring two prescriptions for the same type of GLD within 6 months after treatment start. Accordingly, we did not include patients who started combination therapy or who switched type of treatment away from metformin or sulfonylurea monotherapy, respectively during the first 6 months of treatment. First, we used an intention to treat principle and ignored treatment after the first 6 months when categorizing the patients according to treatment exposure. Next, we categorized patients "as treated" so that patients

were considered exposed with a specific GLD from first prescription of this GLD until the end of the last prescription of this type of GLD (based on the estimated number of days covered by the pack size of a filled prescription) + a washout period.

Outcome

Our primary outcome was first-time BPH defined as the first of a first-time hospital-related discharge diagnosis (See supplementary data for codes) recorded in DNPR or a first time filled community pharmacy prescription for BPH–treatment (alpha-blockers or 5-alpha reductase inhibitors).

As a secondary outcome, we included information on transurethral resection of the prostate (TURP). Additionally, we examined hospital-related BPH diagnoses separately. Finally, we identified all hospital contacts with a first time diagnosis code of urinary retention since this may be a first acute manifestation of BPH but can also be caused by neuropathic bladder disease [25] and we analyzed BPH and acute urinary retention as a composite outcome. We excluded men with any of these outcomes before start of follow-up.

Diabetes severity

We assessed diabetes severity at the time of follow-up start 6 months after first GLD treatment, using diabetes duration (see below), the presence of microvascular and macrovascular diabetes complications (see supplementary data for codes), and glycemic control, i.e. the latest hemoglobin A1c (HbA_{1c}) measured in the year prior to start of follow-up. HbA_{1c} -levels were registered in the clinical laboratory information system database (LABKA) which contains results of all analyses of blood samples drawn from primary care and hospitalized patients and analyzed in hospital laboratories in the Northern and Central Denmark regions [26]. We categorized HbA_{1c} into three levels (<7% [53 mmol/mol], 7-<8% [53-<64 mmol/mol], ≥8% [64 mmol/mol]), and categorized

those with missing variables separately.

Other covariates

We obtained information on age from the Civil Registration System (CRS). From the DNPR we included the 19 major comorbidities included in the Charlson comorbidity index (CCI), based on each cohort member's entire hospital contact history prior to his index date and calculated the patients CCI score (0, 1, 2+). We also included information on previous ischemic heart disease (yes/no), cerebrovascular disease (yes/no), chronic obstructive pulmonary disease (COPD) (yes/no), renal disease (yes/no) along with other covariates potentially associated with BPH or prostatic inflammation: microvascular and macrovascular diabetes complications not included in the CCI; diabetes duration (if a hospital diagnosis of diabetes was present before the GLD initiation/index date); a hospital diagnosis of obesity (yes/no); alcoholism-related disorders (yes/no); use of immunosuppressive drugs (yes/no), use of oral corticosteroids (yes/no), and use of statins (yes/no); marital status as a marker of social support (married/never married/divorced/widowed); and calendar period of GLD initiation (2000–2002/2003–2006).

Statistical analyses

Follow-up started 6 months after date of first GLD treatment. We tabulated characteristics at the start of follow-up for users of metformin and sulfonylurea, respectively.

The men were followed until the outcome of interest, death, emigration, or end of study (7 October 2016), whichever came first. The outcome of interest could be a diagnosis of BPH, a diagnosis of BPH and/ or a BPH-related prescription, and a diagnosis of BPH and/or a BPH-related prescription and/or acute urinary retention, respectively or it could be a TURP.

We computed incidence rates (IRs) for BPH (separately for the three BPH definitions and for TURP, by dividing the number of incident outcome events by total exposed patient-time during follow-up (expressed per 1,000 patient-years at risk). We used an intention to treat approach in our main analysis in which we carried the GLD treatment used at follow-up start 6 month after GLD initiation (metformin or sulfonylurea) forward. We constructed cumulative incidence curves to illustrate time to BPH and/or BPH treatment while treating death as a competing risk.

We also conducted an as treated analysis in which a patient was considered exposed to a certain GLD as long as the prescription continued, based on the estimated number of days covered by the pack size of a filled prescription + a 30 day wash-out period that accounted for overlapping prescriptions and irregular drug use. In sensitivity analyses we changed the washout period to 0 and 90 days, respectively. In this analysis, we censored the patient if another GLD was added. Additional censoring criteria were metformin or sulfonylurea treatment cessation and crossover to the other study drug.

We computed hazard ratios (HRs) of each definition of BPH (with 95% CIs) and of TURP associated with the exposure categories described above (both intention to treat and as treated), using Cox regression with sulfonylurea initiation as reference with adjustment for age, marital status, diabetes duration, comorbidity (CCI level,) presence of micro- or macro-vascular complications, HbA_{1c} level achieved at start of follow-up, obesity, alcohol-related disease, use of glucocorticoids, use of statins, and calendar period of first GLD treatment and we also stratified by HbA_{1c} level achieved at start of follow-up. We used a complete case analysis to handle missing data. As sensitivity analysis we additionally analyzed the data using the missing indicator method

Patient and public involvement

This research was done without involvement of patients.

Research ethics

The study was approved by the Danish Data Protection Agency (Record number 2014-54-0922 KEA-2015-4). Since no patient contact was involved, no separate permission from the Danish Scientific Ethical Committee was required according to Danish Legislation.

Results

In the Northern Denmark cohort, we identified 9,911 men without BPH who filled at least two prescriptions within 6 months after treatment start for either metformin or sulfonylurea in 2000-2006. Of these, 3,953 (40%) started metformin treatment and 5,987 (60%) started sulfonylurea (Table 1).

The median age was 57 years (interquartile range [IQR] 49-65) for metformin users and 63 years (IQR 54-72) for sulfonylurea users. In addition to being younger, metformin users had less micro-vascular (5.9% versus 9.0%) and macro-vascular complications (22.2% versus 28.1%). Median HbA_{1c} levels achieved at start of follow-up were similar 6.9% (52 mmol/mol) versus 6.8% (51 mmol/mol). The prevalence of hospital-recorded obesity was highest in metformin users while the prevalence of other included comorbidities was higher in sulfonylurea users (Table 1). Metformin users had highest prevalence of statin use, 38.2% versus 27.7 % in sulfonylurea users but had slightly lower prevalence of hospital-diagnosed cardiovascular disease.

In the intention to treat analyses within up to 17 years of follow-up (median 10 years), 1,061 metformin users had a hospital-related BPH diagnosis or a BPH-related prescription corresponding to an IR per 1,000 PY of 33.36 (95% CI 31.35 to 35.37) and the 10-year cumulative incidence was 25.7 % (95% CI 24.2 to 27.1) (Table 2 and Figure 1). The IR per 1,000 PY in users of sulfonylurea was 40.32 (95% CI 38.45 to 42.20) and the 10-year cumulative incidence of hospital-related BPH

was 27.4% (95% CI 26.2 to 28.6). Compared with sulfonylurea users, the crude HR for BPH (diagnosis or a BPH-related prescription) was 0.83 (95% CI 0.77 to 0.89) and after adjustment it was 0.97 (95% CI 0.88 to 1.06).

The number of metformin users with a hospital-related diagnosis of BPH was 196, yielding an IR per 1,000 PY of 5.30 (95% CI 4.56-6.04) and a 10-year cumulative incidence of 4.7% (95% CI 4.1 to 5.5). Compared with sulfonylurea users, the crude HR for hospital-related BPH was 0.63 (95% CI 6.4 to 7.7) and after adjustment it was 0.87 (95% CI 0.70 to 1.08).

When combining urinary retention and BPH (diagnosis and/or BPH-related prescriptions), the adjusted HR was 0.97 (95% CI 0.88 to 1.07). For TURP the adjusted HR was 0.96 (95% C, 0.63 to 1.46) (Table 2).

When we included GLD treatment as a time-varying exposure and assumed a 30-day washout period, metformin users had a marginally lower BPH rate (adjusted HR = 0.91 [95% CI 0.81 to 1.02]). For hospital-related BPH the adjusted HR was 0.75 (95% CI 0.58 to 0.96) and for TURP the adjusted HR was 0.83 (95% CI 0.50 to 1.35) (Table 2). Changing the washout period to 0 days and 90 days, respectively only marginally changed these estimates.

When we stratified by HbA_{1c} level in the intention to treat analyses, we observed a slightly lower risk of hospital-related BPH diagnoses or use of BPH–related prescriptions in users of metformin with HbA_{1c} below <7% (53 mmol/mol) compared with sulfonylurea user with HbA_{1c} below <7% (53 mmol/mol), adjusted HR 0.91 (95% 0.80 to 1.03), while there was no beneficial effect among those with HbA_{1c} ≥7% (53 mmol/mol) (Table 3). Similarly results were found in the as treated analyses with a 30-day washout period with use of metformin being associated with a slightly lower risk of a hospital related BPH diagnosis or use of BPH-related prescriptions compared with use of

sulfonylurea (HR =0.87 [95% CI 0.76 to 1.00]) in patients with a HbA_{1c} <7% (53 mmol/mol) (Table 3).

Using the missing indicator method instead of complete case analysis to account for missing HbA_{1c} values did not affect the estimates. In the ITT analysis, the adjusted HR of BPH (diagnosis or a BPH-related prescription) was 0.97 (95% CI 0.90 to1.06) in the missing indicator analysis and 0.97 (95% CI 0.88 to 1.06) in the complete case analysis.

Discussion

In this population based cohort study including more than 9,000 men with type 2 diabetes who started either metformin or sulfonylurea treatment as monotherapy in 2000-2006, we could not confirm our hypothesis that users of metformin had substantially lower BPH rate than users of sulfonylurea.

Accordingly, the results from our study with much longer follow-up (median 10 years) thereby largely supports the previous findings by Murff et al from the US national Veterans Health Administration database [13] of no overall association between type of GLD treatment and BPH over a mean follow-up of 1.4 years. Since we additionally took glycemic control into consideration, our findings add to the existing literature.

Due to the shared biologic mechanisms of BPH and cancer, our results also indirectly add to the uncertainty regarding a causal role of metformin in prostate cancer. A recent meta-analysis found no association between metformin use and prostate cancer risk (RR was 0.97, 95% CI 0.80, 1.16) but had significant heterogeneity between studies [27]. Similarly, another systematic review included a comprehensive bias evaluation and concluded that the studies least likely to be affected by bias

did not support a causal effect of metformin on cancer risk [28]. A recent Taiwanese study found that treatment with metformin reduced the risk of prostate cancer in men with Type 2 diabetes and BPH (adjusted HR of 0.69 [95% CI 0.49, 0.96]) [8] but found a similar effect of traditional Chinese medicine which also points to a non-causal explanation. Thus, this issue remains unsettled.

Use of nationwide medical registries allowed us to conduct a large population-based cohort study with long and virtually complete follow-up. Patients with type 2 diabetes can be identified with at least 90% completeness using Danish registries [29] and the positive predictive value is >95%, with general practitioners registration as the gold standard. To minimize confounding by indication we identified GLD initiators in a calendar period in which both metformin and sulfonylurea were recommended and used as first-line treatment. Still, our study has some weaknesses that should be considered. We identified men with BPH partly by diagnosis codes recorded in a hospital-based setting, and these codes may not be entirely accurate. However, the positive predictive values of other diagnosis codes in the group of urogenital diseases are between 75% and 100% in DNPR [30]. We additionally included patients who were identified as having BPH based on the redemption of a prescription for BPH-related medication. Still, we may have missed men with untreated BPH and no contact to the hospital system. Since we do not expect the proportion of untreated BPH patients to vary by type of GLD treatment, we do not, however, expect this to bias our relative estimates.

Also, several methodological challenges exist when comparing the effect of different GLDs and these may affect our study. We categorized GLD treatment based on the choice of treatment during the first 6 months after treatment start applying an intention to treat principle. Since patients may switch between different GLDs, this approach likely leads to misclassification of treatment status witch may bias the results towards the Null. We did, however, find similar tendency in our results when using an as treated approach. Although metformin and sulfonylurea both were recommended as first line drugs in our study period and have similar expected A1c-reducing efficiency, physicians

may have been more likely to prescribe sulfonylurea in patients with more severe type 2 diabetes (including complications such as early signs of renal disease, or indicators of less insulin production), and metformin in obese patients where weight gain or hypoglycemia was to be avoided. Consistent with these expectations, we did observe different patient characteristics with metformin users being younger, more obese, and fewer having micro-or macro-vascular complications. Accordingly, even though we adjusted for these differences, residual confounding could still be present. Unfortunately, measures of C-peptide was not available for this study period and we could not take endogenous insulin secretion into account. We also lacked information about lifestyle factors and in a previous Danish study smoking was more prevalent in users of sulfonylurea compared with users of metformin [16]. Yet, an association between smoking and BPH is not clearly established [31]. Furthermore, unmeasured confounding due to differences in factors related to unhealthy lifestyle and less social support between users of metformin and sulfonylurea might have influenced our findings as well.

In conclusion, metformin did not seem to substantially reduce the risk of BPH in men with diabetes compared with sulfonylurea.

Contributorship statement: MN designed the study, supervised the analyses, interpreted the data, and wrote the manuscript. BD contributed to the design of the study, cleaned the data, conducted the statistical analyses, interpreted the data, and revised the manuscript critically. RWT contributed to the planning and design of the study, acquired the data, supervised the analyses, interpreted the data, and revised the manuscript critically. All authors read and approved the final manuscript.

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Competing interests: None declared.

Patient consent for publication: Not required for registry-based research

Ethics approval: Ethics approval is not needed for purely registry-based studies in Denmark. Patients were not involved in setting the research question, the outcome measures, or the design or implementation of the study. There are no plans to involve patients in dissemination of the results.

Data Sharing: No additional data available

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Table 1. Baseline characteristics of men initiating either metformin or sulfonylurea monotherapy

Characteristics	Metformin N (%)	Sulfonylurea N (%)
Total	3,953	5,958
Median age (Interquartile range)	57 (49–65)	63 (54–72)
Age group		
30 to <50 years	1,003 (25.4)	822 (13.8)
50 to <70 years	2,373 (60.0)	3,267 (54.8)
≥70 years	577 (14.6)	1,869 (31.4)
Year of study inclusion		
2000-2002	1,104 (27.9)	2,726 (45.8)
2003-2006	2,849 (72.1)	3,232 (54.2)
Marital status		
Married	2,435 (61.6)	3,890 (65.3)
Never married	681 (17.2)	765 (12.8)
Divorced	536 13.6)	657 (11.0)
Widowed	223 (5.6)	597 (10.0)
Missing	78 (2.0)	49 (0.8)
Diabetes duration		
Newly diagnosed	2,328 (58.9)	3,759 (63.1)
<1 year	1,047 (26.5)	1,367 (22.9)
1-5 years	409 (10.3)	532 (8.9)
>5 years	169 (4.3)	300 (5.0)
Diabetes complications		
Microvascular	235 (5.9)	535 (9.0)
Macrovascular	878 (22.2)	1,677 (28.1)
Hemoglobin A1c level		

< 7 % (53mmol/mol)	1,542 (39.0)	2,243 (37.6)
7-<8 % (53-<64 mmol/mol)	769 (19.5)	980 (16.4)
≥8 % (64 mmol/mol)	561 (14.2)	839 (14.1)
Missing	1,081 (27.3)	1,896 (31.8)
Comorbidities		
Myocardial infarction	304 (7.7)	624 (10.5)
Congestive heart failure	175 (4.4)	435 (7.3)
Peripheral vascular disease	132 (3.3)	342 (5.7)
Cerebrovascular disease	299 (7.6)	546 (9.2)
Chronic pulmonary disease	305 (7.7)	537 (9.0)
Cancer	138 (3.5)	365 (6.1)
Obesity	501 (12.7)	313 (5.3)
Alcoholism-related disorders	184 (4.7)	328 (5.5)
Charlson comorbidity Index score		
0	1,910 (48.3)	2,781 (46.7)
1-2	1,677 (42.4)	2,270 (38.1)
>2	366 (9.3)	907 (15.2)
Statins ever use	1,511 (38.2)	1,652 (27.7)
Immunosuppressants	25 (0.6)	51 (0.9)
Oral corticosteroids	228 (5.8)	495 (8.3)

- Treatment initiation was defined as at least 2 prescriptions for the same drug and no prescriptions for other glucose lowering drugs prescribed during the first 6 months of treatment.
- Characteristics were measured at date of treatment start except Hemoglobin A_{1c} level which was measured at start of follow-up 6 months after treatment start.

Table 2. Occurrence of benign prostatic hyperplasia in men with diabetes according to treatment initiation with metformin or sulfonylurea

	Intention to treat analysis		As treated analysis	
	Metformin	Sulfonylurea	Metformin	Sulfonylurea
BPH diagnosis or use of BPH-related drugs				
Number	1,061	1,773	774	1,299
Rate per 1,000 PY (95% CI)	33.36 (31.35-35.37)	40.32 (38.45-42.20)	31.21 (29.01-33.41)	39.98 (37.81-42.16)
Crude HR (95% CI)	0.83 (0.77 to 0.89)	(ref)	0.78 (0.71 to 0.85)	(ref)
Adjusted HR (95% CI)	0.97 (0.88 to 1.07)	(ref)	0.91 (0.81 to 1.02)	(ref)
BPH diagnosis				
Number	196	441	139	330
Rate per 1,000 PY (95% CI)	5.30 (4.56-6.04)	8.49 (7.70-9.28)	4.88 (4.07-5.69)	8.77 (7.82-9.72)
Crude HR (95% CI)	0.62 (0.53 to 0.74)	(ref)	0.56 (0.46 to 0.68)	(ref)
Adjusted HR (95% CI)	0.87 (0.70 to 1.08)	(ref)	0.75 (0.58 to 0.96)	(ref)
BPH diagnosis or use of BPH related prescriptions or urinary retention				
Number	1,124	1,885	826	1,392
Rate per 1,000 PY (95% CI)	35.59 (33.51-37.67)	43.18 (41.23-45.13)	33.53 (31.24-35.82)	43.15 (40.88-45.42)
Crude HR (95% CI)	0.83 (0.77 to 0.89)	(ref)	0.78 (0.7 to 0.85)	(ref)
Adjusted HR* (95% CI)	0.97 (0.88 to 1.07)	(ref)	0.91 (0.81 to 1.01)	(ref)
Trans-urethral resection of the prostate				
Number	63	125	42	94
Rate per 1,000 PY (95% CI)	1.67 (1.25-2.08)	2.33 (1.92-2.73)	1.45 (1.01-1.88)	2.42 (1.93-2.90)
Crude HR (95% CI)	0.72 (0.53 to 0.98)	(ref)	0.61 (0.42 to 0.87)	(ref)
Adjusted HR (95% CI)	0.96 (0.63 to 1.46)	(ref)	0.83 (0.50 to 1.35)	(ref)

- Numbers, rates per 1,000 person years (PY), and hazard ratios (HRs) of benign prostatic hyperplasia (BPH) within up to 17 years of follow-up in men with diabetes according to initial treatment with metformin or sulfonylurea (intention to treat) and analyzed in an as treated approach (i.e time-varying exposure including a 30-day wash-out period).
- HRs were adjusted for age, Charlson comorbidity index score, calendar period of diagnosis, marital status, HbA1c-level, microvascular and macro-vascular complications, obesity, and alcohol related disease, use of corticosteroids, use of statins and diabetes duration.

Table 3. Association between metformin and sulfonylurea initiation and occurrence of benign prostatic hyperplasia stratified by hemoglobin A_{1c} level.

	HbA_{1c}					
	<7 % (53mmol/mol)		7 to <8% (53 to <64 mmol/mol)		≥ 8 % (64 mmol/mol)	
	Crude HR (95% CI)	Adj HR (95% CI)	Crude HR (95% CI)	Adj HR (95% CI)	Crude HR (95% CI)	Adj HR (95% CI)
Intention to treat						
Metformin	0.78 (0.69 to 0.88)	0.91 (0.80 to 1.03)	0.86 (0.72 to 1.02)	1.03 (0.85 to 1.25)	0.92 (0.74 to 1.15)	1.07 (0.71 to 1.63)
Sulfonylurea	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
As treated						
Metformin	0.75 (0.66 to 0.86)	0.87 (0.76 to 1.00)	0.78 (0.63 to 0.96)	0.95 (0.75 to 1.20)	0.90 (0.68 to 1.20)	0.99 (0.72 to 1.34)
Sulfonylurea	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)

- Crude and adjusted (adj) hazard ratios (HRs) of benign prostatic hyperplasia (BPH) defined as either a hospital-related BPH diagnosis or a first BHP-related prescription in men with diabetes according to initial treatment (intention to treat) and an as treated approach (including a 30 days washout period) stratified by hemoglobin A1c level (HbA_{1c}).
- HRs were adjusted for age, Charlson comorbidity index score, calendar period of diagnosis, marital status, microvascular complications, macrovascular complications, obesity, and alcohol related disease, use of corticosteroids, use of statins, and diabetes duration.

Figure legends

Figure 1 Cumulative incidence of a hospital-related diagnosis of benign prostatic hyperplasia (BPH) or a prescription for BPH-related treatment in men with type 2 diabetes according to metformin or sulfonylurea treatment. Death is regarded as a competing risk.

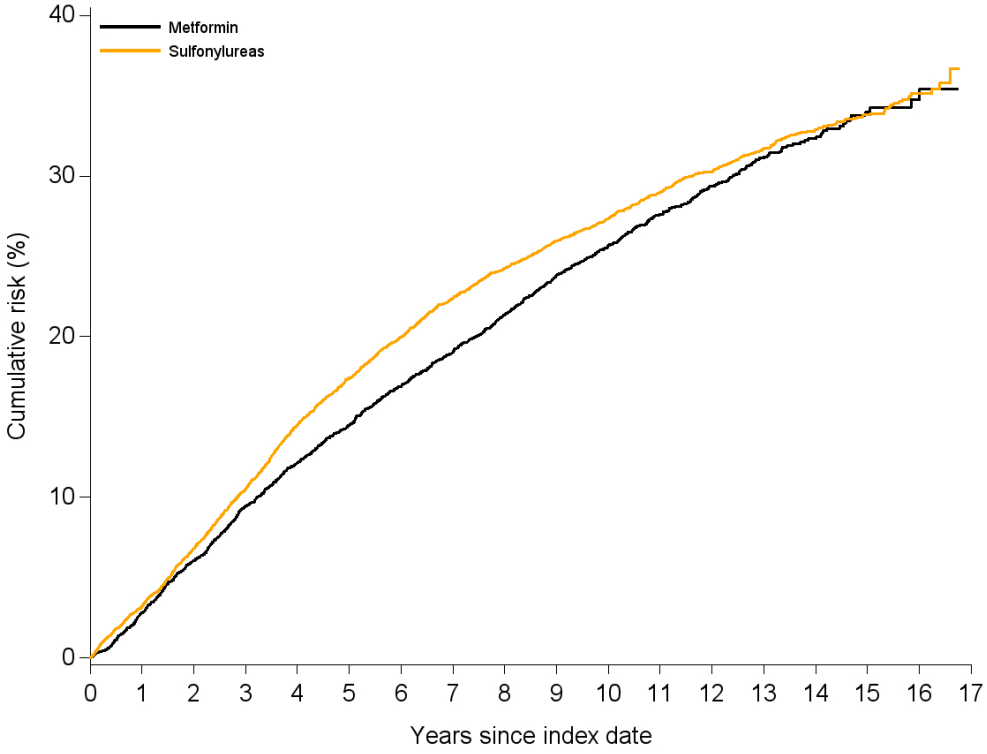

Figure 1 Cumulative incidence of a hospital-related diagnosis of benign prostatic hyperplasia (BPH) or a prescription for BPH-related treatment in men with type 2 diabetes according to metformin or sulfonylurea treatment. Death is regarded as a competing risk.

Supplementary data

Diagnosis, procedure and medication codes used in the study

Hospital contact for type 2 diabetes

ICD-8-codes: 249.x, 250.x.

ICD-10-codes: E10.x, E11.x, E14·x, G63.2.x, H36.0, N08.3

Glucose-lowering drugs ATC-codes:

Metformin: A10BAxx; Sulfonylureas: A10BBxx; Insulin and analogues: A10Axxx;

Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1

(GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02,

A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase

inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx

BPH:

ICD-8 codes: 600, ICD-10:N40

Transurethral resection of the prostate (TURP):

Procedure code (Nomesco): KKED22

BPH-related medical treatments:

alpha-blockers: ATC-codes: C02CA, G04CA

5-alpha reductase inhibitors (ATC code: G04)

Microvascular complications:

Nephropathy: ICD-8-codes: 25002, 24902

ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2

Retinopathy ICD-8-codes: 25001, 24901

ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335

Neuropathy ICD-8-codes: 25003, 24903

ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,

Macrovascular complications:

ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440

ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145

Alcoholism-related disorders:

ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714

Statin use: ATC-code: B04AB

Immunosuppressant use: ATC-codes: L01, L04

Oral corticosteroid use: ATC-code: H02AB

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
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	7+9
		(*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	8-9
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	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*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 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	10

Continued on next page

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	11
		(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	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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	11-12 + tables
		(*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	Figure 1
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	13
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	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
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	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.

BMJ Open

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Metformin use and long-term risk of benign prostatic hyperplasia. A population-based cohort study.

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Number of figures/tables: 3 tables (embedded in the text) and 1 figure

Keywords: benign prostatic hyperplasia, metformin, population-based cohort study, sulfonylurea, type 2 diabetes

Abstract

Objective: To assess whether metformin use affects risk of benign prostatic hyperplasia (BPH) by comparing the risk of BPH in men with type 2 diabetes who initiated first-line treatment with either metformin or sulfonylurea monotherapy between 2000 or 2006 in Northern Denmark. In this period, sulfonylurea or metformin were both frequently used as first line glucose-lowering drug treatment.

Design: A population-based cohort study

Setting: Northern Denmark

Participants: All men who filled at least 2 prescriptions for metformin or for sulfonylurea, respectively during their first 6 months of glucose-lowering drug treatment. Follow-up started 6 months after treatment start.

Primary outcome measures: Rates of subsequent BPH, identified based on community prescriptions for BPH-related treatment or hospital BPH diagnoses, and rates of transurethral resection of the prostate (TURP). Rates in metformin and sulfonylurea users were compared overall and stratified by 6-month hemoglobin A_{1c} ($HbA_{1c)}$ using Cox regression and an intention to treat (ITT) approach and an as treated analysis.

Results During follow-up less than 5 persons were lost to follow-up due to emigration. In 3,953 metformin initiators with a median follow-up of 10 years, the 10-year cumulative incidence was 25.7 % (95% CI 24.2 to 27.1). Compared with 5,958 sulfonylurea users (median follow-up 8 years, 10-year cumulative incidence 27.4% (95% CI 26.2 to 28.6)), the crude hazard ratio (HR) for BPH was 0.83 (95% CI 0.77 to 0.89) and adjusted HR in the ITT analyses was 0.97 (95% CI 0.88 to 1.06). For TURP the adjusted HR was 0.96 (95% CI 0.63 to 1.46). In the as-treated analysis, adjusted HR for BPH was 0.91 (95% CI 0.81 to 1.02).

Conclusions Compared with sulfonylurea, metformin did not substantially reduce the incidence of BPH in men with diabetes.

Strengths and limitations of this study

- The study used population-based data from two well-defined Danish regions.
- Use of nationwide medical registries allowed long and virtually complete follow-up
- Initiators of glucose-lowering drugs could be identified in a calendar period in which both metformin and sulfonylurea were recommended and used as first-line treatment which minimized confounding by indication.
- Benign prostatic hyperplasia was defined both based on hospital-related diagnoses and by prescriptions for relevant medication.
- We categorized treatment based on the choice of glucose-lowering drug during the first 6 months after treatment start applying an intention to treat principle but we also included an as treated analysis.

Introduction

Benign prostatic hyperplasia (BPH) associated with lower urinary tract symptoms is a common condition estimated to affect around 20% of American men aged 30-79 years [1]. Risk factors associated with dysmetabolism and low-grade inflammation, including obesity, high blood glucose, low exercise, and poor diet, seem to contribute substantially to the development of BPH and lower urinary tract symptoms [2 3]. Moreover, prostatic inflammation is likely a key factor in the development of BPH and also prostate cancer [4]. Accordingly, it has been hypothesized that insulin resistance and increased fasting plasma insulin are promoters of both BPH and prostate cancer [5].

Metformin is suggested to have various beneficial therapeutic effects.[6] Among men with type 2 diabetes, some observational studies have suggested that use of metformin reduces the risk of prostate cancer, compared with use of other glucose lowering drugs (GLD) [7-9] while others found no clear association [10-12]. A recent study found that metformin inhibits the proliferation of human prostate epithelial cells [13], and thus may reduce the BPH development as well as development of prostate cancer. Yet, few studies have examined the association between use of metformin and risk of BPH in diabetic men. A cohort study including 192,457 male veterans with type 2 diabetes and 259,995 person-years of follow up found no association between use of thiazolidinediones or metformin and new medical or surgical treatment for BPH, when compared with use of sulfonylurea [14]. While, a recent cohort study from South Korea found among 211,648 men with newly diagnosed BPH that men with type 2 diabetes in metformin treatment had lower risk of progression to prostatectomy than both men without type 2 diabetes and men with type 2 diabetes with no metformin treatment [15].

Comparing the effects of different GLDs in observational studies is complicated by the fact that the underlying indications/contraindications may differ between the drugs [16]. Compared with

sulfonylurea, metformin has a more favorable effect on body weight and insulin resistance and patients receiving metformin are therefore likely to have a higher prevalence of obesity and a higher plasma insulin level than users of sulfonylurea [17]. At least since 2011, metformin has been unequivocally consensus recommended as first-choice treatment in type 2 diabetes in Denmark, based on evidence from the UK Prospective Diabetes Study 1998 [18] and its 10-year follow up in 2008 [19]. Already in the mid-2000s however, the European Association for the Study of Diabetes and the American Diabetes Association recommended use of metformin as first-line drug [20 21]. Previously - in particular during the first half of the 2000s - metformin and sulfonylurea were both widely recommended and used as first-line treatment for type 2 diabetes in Denmark [22]. We therefore conducted a large population-based cohort study to examine the long-term risk of BPH in men with type 2 diabetes who initiated pharmacotherapy with either metformin or sulfonylurea between 2000 and 2006 in Northern Denmark. Our hypothesis was that use of metformin was associated with a lower BPH rate than use of sulfonylurea in men with type 2 diabetes.

Methods

Setting

We conducted a population-based cohort study among men with type 2 diabetes living in Northern Denmark using Danish medical databases. Northern Denmark consists of two regions, the Central Denmark region and the North Denmark region with approximately 700,000 male inhabitants. All residents are provided free tax-supported access to health care. All Danish residents are, at birth or upon immigration, assigned a unique personal identifier, the CPR number, by the Danish Civil Registration system (CRS)[23]. This identifier allows unambiguous linkage of data at the individual level. The CRS additionally tracks changes in vital status, residence, and migration for the entire Danish population on a daily basis. The Danish National Patient Registry (DNPR) has recorded all

admissions to all Danish hospitals since 1977 [24]. Hospital outpatient and emergency room visits have been included in the DNPR since 1995. Diagnoses are classified according to the *International Classification of Diseases*, *Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter.

Assembly of the cohort

We included all men 30 years or older with incident type 2 diabetes, who received their first GLD treatment between 1 January 2000 and 31 December 2006, corresponding to the time period when the Danish guidelines recommended both metformin and sulfonylurea as first line treatment for type 2 diabetes [22]. We defined incident type 2 diabetes as either a first record in the Danish National Patient Registry (DNPR) of a diabetes-associated inpatient admission (data available from 1977) or outpatient clinic contact (data available from 1995) or the first record of a GLD prescription in the Aarhus University Prescription Database (data available from 1996)[25]. Thus, patients with a GLD prescription in the 1996-1999 period were excluded.

GLD treatment

We categorized patients according to their first GLD treatment, metformin or sulfonylurea. To avoid including patients who switched or augmented GLD treatment very early (potentially due to adverse reactions or insufficient early glucose control) we required the patients to receive either metformin or sulfonylurea monotherapy for at least six months by requiring two prescriptions for the same type of GLD within 6 months after treatment start. Accordingly, we did not include patients who started combination therapy or who switched type of treatment away from metformin or sulfonylurea monotherapy, respectively during the first 6 months of treatment. First, we used an intention to treat principle and ignored treatment after the first 6 months when categorizing the

patients according to treatment exposure. Next, we categorized patients "as treated" so that patients were considered exposed with a specific GLD from first prescription of this GLD until the end of the last prescription of this type of GLD (based on the estimated number of days covered by the pack size of a filled prescription) + a washout period.

Outcome

Our primary outcome was first-time BPH defined as the first of a first-time hospital-related discharge diagnosis (See supplementary data for codes) recorded in DNPR or a first time filled community pharmacy prescription for BPH–treatment (alpha-blockers or 5-alpha reductase inhibitors).

As a secondary outcome, we included information on transurethral resection of the prostate (TURP). Additionally, we examined hospital-related BPH diagnoses separately. Finally, we identified all hospital contacts with a first time diagnosis code of urinary retention since this may be a first acute manifestation of BPH but can also be caused by neuropathic bladder disease [26] and we analyzed BPH and acute urinary retention as a composite outcome. We excluded men with any of these outcomes before start of follow-up.

Diabetes severity

We assessed diabetes severity at the time of follow-up start 6 months after first GLD treatment, using diabetes duration (see below), the presence of microvascular and macrovascular diabetes complications (see supplementary data for codes), and glycemic control, i.e. the latest hemoglobin A1c (HbA_{1c}) measured in the year prior to start of follow-up. HbA_{1c} -levels were registered in the clinical laboratory information system database (LABKA) which contains results of all analyses of blood samples drawn from primary care and hospitalized patients and analyzed in hospital laboratories in the Northern and Central Denmark regions [27]. We categorized HbA_{1c} into three

levels (<7% [53 mmol/mol], 7-<8% [53-<64 mmol/mol], ≥8% [64 mmol/mol]) based on the American Diabetes Association recommended goals for HbA_{1c}[28] and we categorized those with missing variables separately.

Other covariates

We obtained information on age from the Civil Registration System (CRS). From the DNPR we included the 19 major comorbidities included in the Charlson comorbidity index (CCI), based on each cohort member's entire hospital contact history prior to his index date and calculated the patients CCI score (0, 1, 2+). We also included information on previous ischemic heart disease (yes/no), cerebrovascular disease (yes/no), chronic obstructive pulmonary disease (COPD) (yes/no), renal disease (yes/no) along with other covariates potentially associated with BPH or prostatic inflammation: microvascular and macrovascular diabetes complications not included in the CCI; diabetes duration (if a hospital diagnosis of diabetes was present before the GLD initiation/index date); a hospital diagnosis of obesity (yes/no); alcoholism-related disorders (yes/no); use of immunosuppressive drugs (yes/no), use of oral corticosteroids (yes/no), and use of statins (yes/no); marital status as a marker of social support (married/never married/divorced/widowed); and calendar period of GLD initiation (2000–2002/2003–2006).

Statistical analyses

Follow-up started 6 months after date of first GLD treatment. We tabulated characteristics at the start of follow-up for users of metformin and sulfonylurea, respectively.

The men were followed until the outcome of interest, death, emigration, or end of study (7 October 2016), whichever came first. The outcome of interest could be a diagnosis of BPH, a diagnosis of BPH and/ or a BPH-related prescription, and a diagnosis of BPH and/or a BPH-related prescription and/or acute urinary retention, respectively or it could be a TURP.

We computed incidence rates (IRs) for BPH (separately for the three BPH definitions and for TURP, by dividing the number of incident outcome events by total exposed patient-time during follow-up (expressed per 1,000 patient-years at risk). We used an intention to treat approach in our main analysis in which we carried the GLD treatment used at follow-up start 6 month after GLD initiation (metformin or sulfonylurea) forward. We constructed cumulative incidence curves to illustrate time to BPH and/or BPH treatment while treating death as a competing risk.

We also conducted an as treated analysis in which a patient was considered exposed to a certain GLD as long as the prescription continued, based on the estimated number of days covered by the pack size of a filled prescription + a 30 day wash-out period that accounted for overlapping prescriptions and irregular drug use. In sensitivity analyses we changed the washout period to 0 and 90 days, respectively. In this analysis, we censored the patient if another GLD was added. Additional censoring criteria were metformin or sulfonylurea treatment cessation and crossover to the other study drug. As alpha blockers may be used for other indications than symptomatic BPH, we also conducted a sensitivity analysis n which we defined BPH as either a recorded diagnosis of BPH or a prescription for a 5-alpha reductase inhibitor.

We computed hazard ratios (HRs) of each definition of BPH (with 95% CIs) and of TURP associated with the exposure categories described above (both intention to treat and as treated), using Cox regression with sulfonylurea initiation as reference with adjustment for age, marital status, diabetes duration, comorbidity (CCI level,) presence of micro- or macro-vascular complications, HbA_{1c} level achieved at start of follow-up, obesity, alcohol-related disease, use of glucocorticoids, use of statins, and calendar period of first GLD treatment and we also stratified by HbA_{1c} level achieved at start of follow-up. We used a complete case analysis to handle missing data. As sensitivity analysis we additionally analyzed the data using the missing indicator method

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Research ethics

The study was approved by the Danish Data Protection Agency (Record number 2014-54-0922 KEA-2015-4). Since no patient contact was involved, no separate permission from the Danish Scientific Ethical Committee was required according to Danish Legislation.

Results

In the Northern Denmark cohort, we identified 9,911 men without BPH who filled at least two prescriptions within 6 months after treatment start for either metformin or sulfonylurea in 2000-2006. Of these, 3,953 (40%) started metformin treatment and 5,987 (60%) started sulfonylurea (Table 1).

The median age was 57 years (interquartile range [IQR] 49-65) for metformin users and 63 years (IQR 54-72) for sulfonylurea users. In addition to being younger, metformin users had less micro-vascular (5.9% versus 9.0%) and macro-vascular complications (22.2% versus 28.1%). Median HbA_{1c} levels achieved at start of follow-up were similar 6.9% (52 mmol/mol) versus 6.8% (51 mmol/mol). The prevalence of hospital-recorded obesity was highest in metformin users while the prevalence of other included comorbidities was higher in sulfonylurea users (Table 1). Metformin users had highest prevalence of statin use, 38.2% versus 27.7 % in sulfonylurea users but had slightly lower prevalence of hospital-diagnosed cardiovascular disease.

In the intention to treat analyses within up to 17 years of follow-up (median 10 years) and less than 5 persons lost to follow-up due to emigration, 1,061 metformin users had a hospital-related BPH diagnosis or a BPH-related prescription corresponding to an IR per 1,000 PY of 33.36 (95% CI 31.35 to 35.37) and the 10-year cumulative incidence was 25.7 % (95% CI 24.2 to 27.1) (Table 2 and Figure 1). The IR per 1,000 PY in users of sulfonylurea was 40.32 (95% CI 38.45 to 42.20) and the 10-year cumulative incidence of hospital-related BPH was 27.4% (95% CI 26.2 to 28.6). Compared with sulfonylurea users, the crude HR for BPH (diagnosis or a BPH-related prescription) was 0.83 (95% CI 0.77 to 0.89) and after adjustment it was 0.97 (95% CI 0.88 to 1.06).

The number of metformin users with a hospital-related diagnosis of BPH was 196, yielding an IR per 1,000 PY of 5.30 (95% CI 4.56-6.04) and a 10-year cumulative incidence of 4.7% (95% CI 4.1 to 5.5). Compared with sulfonylurea users, the crude HR for hospital-related BPH was 0.62 (95% CI 0.53 to 0.74) and after adjustment it was 0.87 (95% CI 0.70 to 1.08).

When combining urinary retention and BPH (diagnosis and/or BPH-related prescriptions), the adjusted HR was 0.97 (95% CI 0.88 to 1.07). For TURP the adjusted HR was 0.96 (95% CI 0.63 to 1.46) (Table 2).

When we included GLD treatment as a time-varying exposure and assumed a 30-day washout period, metformin users had a marginally lower BPH rate (adjusted HR = 0.91 [95% CI 0.81 to 1.02]). For hospital-related BPH the adjusted HR was 0.75 (95% CI 0.58 to 0.96) and for TURP the adjusted HR was 0.83 (95% CI 0.50 to 1.35) (Table 2). Changing the washout period to 0 days and 90 days, respectively only marginally changed these estimates. Defining BPH as either a recorded BPH diagnosis or a prescription for a 5-alpha reductase inhibitor without including alpha blockers lowered the BPH rate per 1,000 PY to 8.24 (95% CI 7.31 to 9.17) for metformin and 12.42 (95% CI 11.46 to 13.39) for sulfonylurea in the intention to treat analyses and a corresponding adjusted HR

of 0.92 (95% CI 0.78 to 1.10). In the as treated analysis the adjusted HR was 0.85 (95% CI 0.70 to 1.04).

When we stratified by HbA_{1c} level in the intention to treat analyses, we observed a slightly lower risk of hospital-related BPH diagnoses or use of BPH–related prescriptions in users of metformin with HbA_{1c} below <7% (53 mmol/mol) compared with sulfonylurea user with HbA_{1c} below <7% (53 mmol/mol), adjusted HR 0.91 (95% 0.80 to 1.03), while there was no beneficial effect among those with HbA_{1c} ≥7% (53 mmol/mol) (Table 3). Similarly results were found in the as treated analyses with a 30-day washout period with use of metformin being associated with a slightly lower risk of a hospital related BPH diagnosis or use of BPH-related prescriptions compared with use of sulfonylurea (HR =0.87 [95% CI 0.76 to 1.00]) in patients with a HbA_{1c} <7% (53 mmol/mol) (Table 3).

Using the missing indicator method instead of complete case analysis to account for missing HbA_{1c} values did not affect the estimates. In the ITT analysis, the adjusted HR of BPH (diagnosis or a BPH-related prescription) was 0.97 (95% CI 0.90 to1.06) in the missing indicator analysis and 0.97 (95% CI 0.88 to 1.06) in the complete case analysis.

Discussion

In this population based cohort study including more than 9,000 men with type 2 diabetes who started either metformin or sulfonylurea treatment as monotherapy in 2000-2006, we could not confirm our hypothesis that users of metformin had substantially lower BPH rate than users of sulfonylurea.

Comparison with the exsting literature

The results from our study with much longer follow-up (median 10 years) largely supports the previous findings by Murff et al from the US national Veterans Health Administration database [14] of no overall association between type of GLD treatment and BPH over a mean follow-up of 1.4 years. Since we additionally took glycemic control into consideration, our findings add to the existing literature.

Due to the shared biologic mechanisms of BPH and cancer, our results also indirectly add to the uncertainty regarding a causal role of metformin in prostate cancer. A recent meta-analysis found no association between metformin use and prostate cancer risk (RR was 0.97, 95% CI 0.80, 1.16) but had significant heterogeneity between studies [29]. Similarly, another systematic review included a comprehensive bias evaluation and concluded that the studies least likely to be affected by bias did not support a causal effect of metformin on cancer risk [30]. A recent Taiwanese study found that treatment with metformin reduced the risk of prostate cancer in men with Type 2 diabetes and BPH (adjusted HR of 0.69 [95% CI 0.49, 0.96]) [9] but found a similar effect of traditional Chinese medicine which also points to a non-causal explanation. Thus, this issue remains unsettled.

Strengths and weaknesses

Use of nationwide medical registries allowed us to conduct a large population-based cohort study with long and virtually complete follow-up. Patients with type 2 diabetes can be identified with at least 90% completeness using Danish registries [31] and the positive predictive value is >95%, with general practitioners registration as the gold standard. To minimize confounding by indication we identified GLD initiators in a calendar period in which both metformin and sulfonylurea were recommended and used as first-line treatment. Still, our study has some weaknesses that should be considered. We identified men with BPH partly by diagnosis codes recorded in a hospital-based setting, and these codes may not be entirely accurate. However, the positive predictive values of

other diagnosis codes in the group of urogenital diseases are between 75% and 100% in DNPR [32]. We additionally included patients who were identified as having BPH based on the redemption of a prescription for BPH-related medication. Still, we may have missed men with untreated BPH and no contact to the hospital system. Since we do not expect the proportion of untreated BPH patients to vary by type of GLD treatment, we do not, however, expect this to bias our relative estimates.

Since we only included men who remained on metformin or sulphonylurea monotherapy for the first 6 months of follow-up, our results does not address men with more advanced diabetes. Yet, we had a median follow-up of 10 years and were able to follow some men for up to 17 years so we did not only include information on early stage diabetes and when we stratified by achieved HbA1c we did not see any BPH protective effect of metformin in those with poor glycemic control.

We included BPH medication as part of our outcome definition but even though alpha-blockers are first line treatment for symptomatic BPH they are not used exclusively for this indication and we may therefore have included men without BPH but with other indications for alpha blockers. However, although we may have overestimated the rate of BPH when including alpha-blockers in our definition we found similar relative estimates and our conclusion was not altered.

Methodological challenges

Also, several methodological challenges exist when comparing the effect of different GLDs and these may affect our study. We categorized GLD treatment based on the choice of treatment during the first 6 months after treatment start applying an intention to treat principle. Since patients may switch between different GLDs, this approach likely leads to misclassification of treatment status witch may bias the results towards the Null. We did, however, find similar tendency in our results when using an as treated approach. Although metformin and sulfonylurea both were recommended as first line drugs in our study period and have similar expected A1c-reducing efficiency, physicians

may have been more likely to prescribe sulfonylurea in patients with more severe type 2 diabetes (including complications such as early signs of renal disease, or indicators of less insulin production), and metformin in obese patients where weight gain or hypoglycemia was to be avoided. Metformin is in more recent year even used off-label for weight reduction.[33] Consistent with these expectations, we did observe different patient characteristics with metformin users being younger, more obese, and fewer having micro-or macro-vascular complications. We based our information on obesity on registered ICD-codes and we know these are likely substantially underreported.[34 35] Accordingly, even though we adjusted for these differences, residual confounding could still be present and could potentially mask a beneficial effect of metformin. Still, registered obesity was only weakly associated with BPH in our study.

Unfortunately, measures of C-peptide was not available for this study period and we could not take endogenous insulin secretion into account. We also lacked information about lifestyle factors and in a previous Danish study smoking was more prevalent in users of sulfonylurea compared with users of metformin [17]. Yet, an association between smoking and BPH is not clearly established [36]. Furthermore, unmeasured confounding due to differences in factors related to unhealthy lifestyle and less social support between users of metformin and sulfonylurea might have influenced our findings as well.

In conclusion, metformin did not seem to substantially reduce the risk of BPH in men with diabetes compared with sulfonylurea.

Contributorship statement: MN designed the study, supervised the analyses, interpreted the data, and wrote the manuscript. BD contributed to the design of the study, cleaned the data, conducted the statistical analyses, interpreted the data, and revised the manuscript critically. RWT contributed to the planning and design of the study, acquired the data, supervised the analyses, interpreted the data, and revised the manuscript critically. All authors read and approved the final manuscript.

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Ethics approval: Ethics approval is not needed for purely registry-based studies in Denmark. Patients were not involved in setting the research question, the outcome measures, or the design or implementation of the study. There are no plans to involve patients in dissemination of the results.

Data Availability: The Danish nationwide registries used for this study are kept at and data were analyzed at a secured server at the Danish Health Data Authority. Data may be obtained from a third party and are not publicly available. Data are available upon reasonable request

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Table 1. Baseline characteristics of men initiating either metformin or sulfonylurea monotherapy

Characteristics	Metformin N (%)	Sulfonylurea N (%)
Total	3,953	5,958
Median age (Interquartile range)	57 (49–65)	63 (54–72)
Age group		
30 to <50 years	1,003 (25.4)	822 (13.8)
50 to <70 years	2,373 (60.0)	3,267 (54.8)
≥70 years	577 (14.6)	1,869 (31.4)
Year of study inclusion		
2000-2002	1,104 (27.9)	2,726 (45.8)
2003-2006	2,849 (72.1)	3,232 (54.2)
Marital status		
Married	2,435 (61.6)	3,890 (65.3)
Never married	681 (17.2)	765 (12.8)
Divorced	536 13.6)	657 (11.0)
Widowed	223 (5.6)	597 (10.0)
Missing	78 (2.0)	49 (0.8)
Diabetes duration		
Newly diagnosed	2,328 (58.9)	3,759 (63.1)
<1 year	1,047 (26.5)	1,367 (22.9)
1-5 years	409 (10.3)	532 (8.9)
>5 years	169 (4.3)	300 (5.0)
Diabetes complications		
Microvascular	235 (5.9)	535 (9.0)
Macrovascular	878 (22.2)	1,677 (28.1)
Hemoglobin A1c level		

< 7 % (53mmol/mol)	1,542 (39.0)	2,243 (37.6)
7-<8 % (53-<64 mmol/mol)	769 (19.5)	980 (16.4)
≥8 % (64 mmol/mol)	561 (14.2)	839 (14.1)
Missing	1,081 (27.3)	1,896 (31.8)
Comorbidities		
Myocardial infarction	304 (7.7)	624 (10.5)
Congestive heart failure	175 (4.4)	435 (7.3)
Peripheral vascular disease	132 (3.3)	342 (5.7)
Cerebrovascular disease	299 (7.6)	546 (9.2)
Chronic pulmonary disease	305 (7.7)	537 (9.0)
Cancer	138 (3.5)	365 (6.1)
Obesity	501 (12.7)	313 (5.3)
Alcoholism-related disorders	184 (4.7)	328 (5.5)
Charlson comorbidity Index score		
0	1,910 (48.3)	2,781 (46.7)
1-2	1,677 (42.4)	2,270 (38.1)
>2	366 (9.3)	907 (15.2)
Statins ever use	1,511 (38.2)	1,652 (27.7)
Immunosuppressants	25 (0.6)	51 (0.9)
Oral corticosteroids	228 (5.8)	495 (8.3)

- Treatment initiation was defined as at least 2 prescriptions for the same drug and no prescriptions for other glucose lowering drugs prescribed during the first 6 months of treatment.
- Characteristics were measured at date of treatment start except Hemoglobin A_{1c} level which was measured at start of follow-up 6 months after treatment start.

Table 2. Occurrence of benign prostatic hyperplasia in men with diabetes according to treatment initiation with metformin or sulfonylurea

	Intention to treat analysis		As treated analysis	
	Metformin	Sulfonylurea	Metformin	Sulfonylurea
BPH diagnosis or use of BPH-related drugs				
Number	1,061	1,773	774	1,299
Rate per 1,000 PY (95% CI)	33.36 (31.35-35.37)	40.32 (38.45-42.20)	31.21 (29.01-33.41)	39.98 (37.81-42.16)
Crude HR (95% CI)	0.83 (0.77 to 0.89)	(ref)	0.78 (0.71 to 0.85)	(ref)
Adjusted HR (95% CI)	0.97 (0.88 to 1.07)	(ref)	0.91 (0.81 to 1.02)	(ref)
BPH diagnosis				
Number	196	441	139	330
Rate per 1,000 PY (95% CI)	5.30 (4.56-6.04)	8.49 (7.70-9.28)	4.88 (4.07-5.69)	8.77 (7.82-9.72)
Crude HR (95% CI)	0.62 (0.53 to 0.74)	(ref)	0.56 (0.46 to 0.68)	(ref)
Adjusted HR (95% CI)	0.87 (0.70 to 1.08)	(ref)	0.75 (0.58 to 0.96)	(ref)
BPH diagnosis or use of BPH related prescriptions or urinary retention				
Number	1,124	1,885	826	1,392
Rate per 1,000 PY (95% CI)	35.59 (33.51-37.67)	43.18 (41.23-45.13)	33.53 (31.24-35.82)	43.15 (40.88-45.42)
Crude HR (95% CI)	0.83 (0.77 to 0.89)	(ref)	0.78 (0.7 to 0.85)	(ref)
Adjusted HR* (95% CI)	0.97 (0.88 to 1.07)	(ref)	0.91 (0.81 to 1.01)	(ref)
Trans-urethral resection of the prostate				
Number	63	125	42	94
Rate per 1,000 PY (95% CI)	1.67 (1.25-2.08)	2.33 (1.92-2.73)	1.45 (1.01-1.88)	2.42 (1.93-2.90)
Crude HR (95% CI)	0.72 (0.53 to 0.98)	(ref)	0.61 (0.42 to 0.87)	(ref)
Adjusted HR (95% CI)	0.96 (0.63 to 1.46)	(ref)	0.83 (0.50 to 1.35)	(ref)

- Numbers, rates per 1,000 person years (PY), and hazard ratios (HRs) of benign prostatic hyperplasia (BPH) within up to 17 years of follow-up in men with diabetes according to initial treatment with metformin or sulfonylurea (intention to treat) and analyzed in an as treated approach (i.e time-varying exposure including a 30-day wash-out period).
- HRs were adjusted for age, Charlson comorbidity index score, calendar period of diagnosis, marital status, HbA1c-level, microvascular and macro-vascular complications, obesity, and alcohol related disease, use of corticosteroids, use of statins and diabetes duration.

Table 3. Association between metformin and sulfonylurea initiation and occurrence of benign prostatic hyperplasia stratified by hemoglobin A_{1c} level.

	HbA_{1c}					
	<7 % (53mmol/mol)		7 to <8% (53 to <64 mmol/mol)		≥ 8 % (64 mmol/mol)	
	Crude HR (95% CI)	Adj HR (95% CI)	Crude HR (95% CI)	Adj HR (95% CI)	Crude HR (95% CI)	Adj HR (95% CI)
Intention to treat						
Metformin	0.78 (0.69 to 0.88)	0.91 (0.80 to 1.03)	0.86 (0.72 to 1.02)	1.03 (0.85 to 1.25)	0.92 (0.74 to 1.15)	1.07 (0.71 to 1.63)
Sulfonylurea	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
As treated						
Metformin	0.75 (0.66 to 0.86)	0.87 (0.76 to 1.00)	0.78 (0.63 to 0.96)	0.95 (0.75 to 1.20)	0.90 (0.68 to 1.20)	0.99 (0.72 to 1.34)
Sulfonylurea	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)

- Crude and adjusted (adj) hazard ratios (HRs) of benign prostatic hyperplasia (BPH) defined as either a hospital-related BPH diagnosis or a first BHP-related prescription in men with diabetes according to initial treatment (intention to treat) and an as treated approach (including a 30 days washout period) stratified by hemoglobin A1c level (HbA_{1c}).
- HRs were adjusted for age, Charlson comorbidity index score, calendar period of diagnosis, marital status, microvascular complications, macrovascular complications, obesity, and alcohol related disease, use of corticosteroids, use of statins, and diabetes duration.

Figure legends

Figure 1 Cumulative incidence of a hospital-related diagnosis of benign prostatic hyperplasia (BPH) or a prescription for BPH-related treatment in men with type 2 diabetes according to metformin or sulfonylurea treatment. Death is regarded as a competing risk.

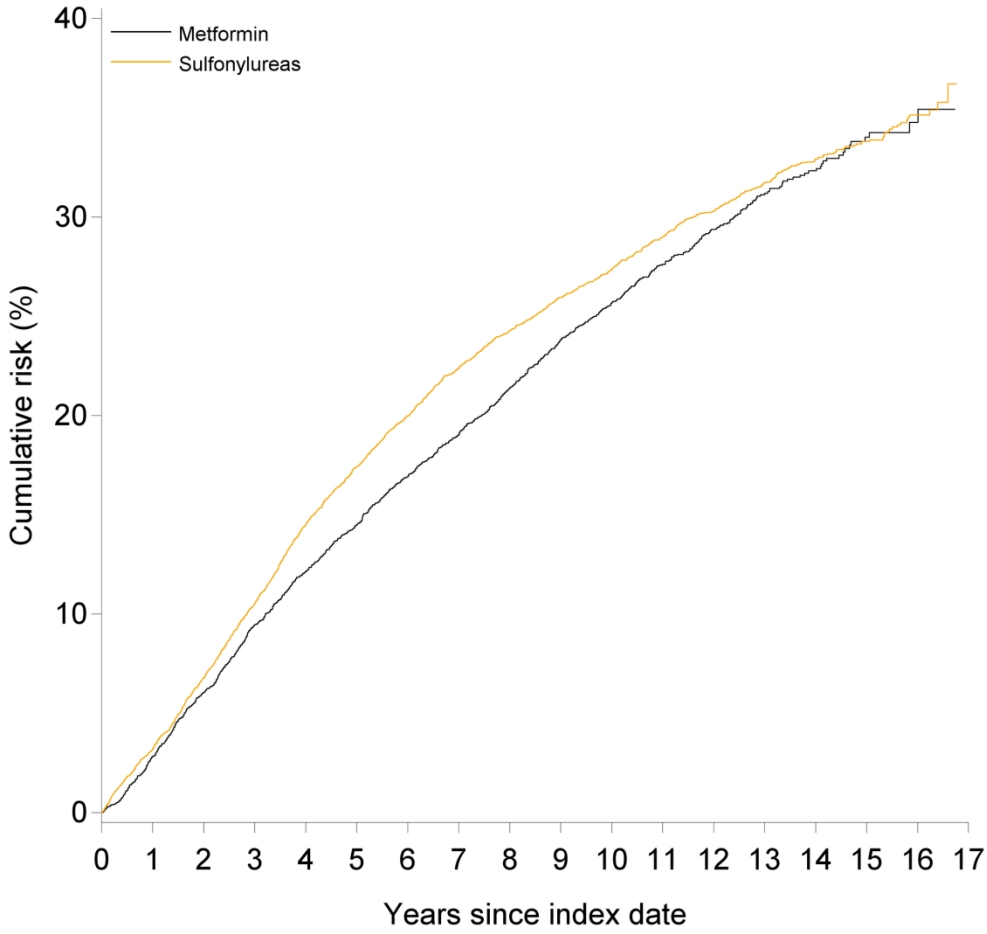

Figure 1 Cumulative incidence of a hospital-related diagnosis of benign prostatic hyperplasia (BPH) or a prescription for BPH-related treatment in men with type 2 diabetes according to metformin or sulfonylurea treatment. Death is regarded as a competing risk.

89x89mm (600 x 600 DPI)

Supplementary data

Diagnosis, procedure and medication codes used in the study

Hospital contact for type 2 diabetes

ICD-8-codes: 249.x, 250.x.

ICD-10-codes: E10.x, E11.x, E14·x, G63.2.x, H36.0, N08.3

Glucose-lowering drugs ATC-codes:

Metformin: A10BAxx; Sulfonylureas: A10BBxx; Insulin and analogues: A10Axxx;

Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1

(GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02,

A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase

inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx

BPH:

ICD-8 codes: 600, ICD-10:N40

Transurethral resection of the prostate (TURP):

Procedure code (Nomesco): KKED22

BPH-related medical treatments:

alpha-blockers: ATC-codes: C02CA, G04CA

5-alpha reductase inhibitors (ATC code: G04)

Microvascular complications:

Nephropathy: ICD-8-codes: 25002, 24902

ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2

Retinopathy ICD-8-codes: 25001, 24901

ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335

Neuropathy ICD-8-codes: 25003, 24903

ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,

Macrovascular complications:

ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440

ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145

Alcoholism-related disorders:

ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714

Statin use: ATC-code: B04AB

Immunosuppressant use: ATC-codes: L01, L04

Oral corticosteroid use: ATC-code: H02AB

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
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	7+9
		(*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	8-9
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	7-9
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*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 *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	10

Continued on next page

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	11
		(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	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Table 2
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—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	11-12 + tables
		(*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	Figure 1
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	13
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	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-15
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	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.