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Rates of Community-based Antibiotic Prescriptions and Hospital-treated Infections in Individuals With and Without Type 2 Diabetes: A Danish Nationwide Cohort Study, 2004–2012

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Background. The excess risk of antibiotic use and hospital-treated infections in patients with type 2 diabetes (T2D) compared with general population is poorly understood.

Methods. In a nationwide cohort of patients with incident T2D (n = 155 158) and an age-, gender-, and residence-matched comparison cohort (n = 774 017), we used Cox regression to compute rates and confounder-adjusted rate ratios (aRRs) of community-based antibiotic prescription redemption and hospital-treated infections during 2004–2012.

Results. The rates of community-based antibiotic prescriptions in the T2D and comparison cohorts were 364 vs 275 per 1000 person-years after a median follow-up of 1.1 years (aRR = 1.24; 95% confidence interval [CI], 1.23 to 1.25). The corresponding rates for hospital-treated infection were 58 vs 39 per 1000 person-years after a median follow-up of 2.8 years (aRR = 1.49; 95% CI, 1.47 to 1.52). The aRRs were increased particularly for urinary tract infections (UTIs, 1.41; 95% CI, 1.35 to 1.45), skin infections (1.50; 95% CI, 1.45 to 1.55), septicemia (1.60; 95% CI, 1.53 to 1.67), and tuberculosis (1.61; 95% CI, 1.25 to 2.06) and of community-based antibiotics prescribed for UTIs (1.31; 95% CI, 1.29 to 1.33), *Staphylococcus aureus* infections (1.32; 95% CI, 1.30 to 1.34), and mycobacterial infections (1.69; 95% CI, 1.36 to 2.09). The 1-year aRR declined from 1.89 (95% CI, 1.75 to 2.04) in 2004 to 1.59 (95% CI, 1.45 to 1.74) in 2011 for hospital-treated infection (trend $P = .007$) and from 1.31 (95% CI, 1.27 to 1.36) in 2004 to 1.26 (95% CI, 1.22 to 1.30) in 2011 for community-based antibiotic prescriptions (trend $P = .006$).

Conclusions. Patients with T2D have rates of community-based antibiotic prescriptions and hospital-treated infections that are higher than for the general population.

Keywords. type 2 diabetes mellitus; infections; epidemiology; time trends; antibiotics.

Type 2 diabetes (T2D) is a major clinical problem in the globally increasing population [1–5] and an important cause of premature death in patients with this infection [1, 6]. The rising prevalence of diabetes may contribute to the increasing burden of infection-related hospitalizations and antibiotic overuse worldwide [3, 4]. The risks of micro- and macrovascular T2D complications have reportedly declined in the past 2 decades compared with the general population [7]. Comparative data on the excess risk of hospital-treated infection and antibiotic use in community settings are limited [1, 2, 8].

Recent data suggest that T2D may be associated with a 1.5-fold increased risk of hospitalization for respiratory tract infections [1], including pneumonia [9] and tuberculosis [10]; a 1.5-fold increased risk of surgical site infections [11]; a 2-fold increased risk of urinary tract infections (UTIs) [12]; and a 2- to 3-fold increased risk of bacteremia [13, 14]. However, the magnitude of excess risk for specific infections associated with T2D is under debate, and data from population-based settings comparing the risk with that in the general population are scarce, particularly for antibiotic use [1, 15, 16]. A study from the Netherlands reported a 60% increase in use of antibiotics between 1995 and 2003 for lower respiratory tract infections and a 15% increase in use for UTIs among T2D patients [8], but these findings were not compared with trends in the general population.

We recently observed that early glycemic control has improved in incident Danish T2D patients from 2000 to 2012 [17]. With other studies from Europe [18], the United States

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[19], and Asia [20] showing significant improvements over time for short- and long-term diabetes treatment targets, the risk of infection in T2D may have decreased compared with the general population [7]. We performed a nationwide population-based study to examine the association between T2D and antibiotic use in community settings, as well as hospital-treated infection, compared with a matched general population cohort during 2004–2012.

METHODS

Data Sources

The study was based on the Danish National Patient Registry (DNPR), which contains information on all hospitalizations in Denmark since 1977 and on all outpatient and emergency room visits since 1995 [21]. Data in the DNPR includes patients' central personal registry (CPR) number, a primary discharge diagnosis, and up to 20 secondary discharge diagnoses coded according to the *International Classification of Diseases* (ICD) (8th edition until the end of 1993 and 10th edition thereafter). We also used the Danish National Health Service Prescription Database (DNHSPD), which contains complete data on all reimbursed prescription medications dispensed from community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 [22]. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Individual-level data from Danish registries can be linked using the unique CPR number assigned by the Danish Civil Registration System (CRS) at birth or upon immigration [23]. The CRS contains electronic records on vital status (date of death or emigration), place of residence, and marital status for the entire Danish population since 1968 and is updated daily.

Identification of Patients with T2D and Matched Comparisons

We conducted this population-based cohort study among all patients with an incident diagnosis of T2D recorded between 1 July 2004 and 31 December 2012. We identified patients with T2D by searching both the DNPR for the first record of a diabetes-associated hospital inpatient or outpatient contact and the DNHSPD for the first record of a glucose-lowering drug prescription, whichever came first. We excluded participants aged <30 years at the time of their first diagnosis of any diabetes (the index date) in order to decrease the chance of including people with type 1 diabetes.

For each patient with T2D, we selected 5 individuals without diabetes from the general population and matched individually to the corresponding patient's age (birth year), sex, municipality of residence, and index date. Matched individuals who were diagnosed or treated for T2D during follow-up were censored and switched to the T2D cohort on their diabetes diagnosis date.

Assessment of Infection Outcomes

We defined the study outcome as either redemption of an antibiotic prescription in the community setting or an episode of hospital-treated infection during the study period. Community antibiotic use was defined as any redeemed first-time antibiotic prescription recorded in the DNHSPD after the index date. We investigated groups of antibiotics prescribed to treat specific infections according to the National Danish Guidelines for Primary Care [24] (see Supplementary Materials for ATC codes). Hospital-treated infection was defined as any first-time inpatient admission or hospital outpatient clinic contact with an infection after the index date. We examined a wide range of infections including certain rare infections that have been associated closely with diabetes in the literature [2] (see Supplementary Materials for ICD codes).

Covariates

We used the DNPR to collect information on the comorbidities included in the Charlson comorbidity index (CCI), based on each individual's entire hospital contact history for 10 years before the index date. We defined the following 3 comorbidity levels: low (CCI score 0), medium (CCI score 1–2), and high (CCI score ≥3). We also retrieved information on other conditions associated with infection risk; on presence of alcoholism-related disorders; and on use of immunosuppressive drugs, oral corticosteroids, and statins [25, 26]. In addition, we obtained data on marital status [27] (married, divorced, widowed, and never married) from the CRS.

Statistical Analyses

We followed all study participants from the index date until occurrence of the first outcome event, death, emigration, or end of the study period (31 December 2012). We computed rates separately for community-based antibiotic prescriptions and for hospital-treated infections in both cohorts by dividing the total number of incident outcome events by the total risk-time, expressed per 1000 person-years. We also computed rate differences (RDs) per 1000 person-years between the T2D and comparison cohorts.

We then applied a Cox proportional hazard regression analysis to compute rate ratios (RRs) of infection with 95% confidence intervals (CIs). We first adjusted for marital status, alcoholism-related disorders, and CCI comorbidities, except for cardiovascular and renal disease categories, as these may be regarded as possible effects of T2D (model 1). Next, we added cardiovascular and renal comorbidities (model 2). Last, we added use of statins, steroids, and immunosuppressants (model 3). To assess whether risk of infection was affected by possible glycemic deterioration or increased clinical surveillance early after T2D diagnosis, we examined infection rates separately for the first 6 months and for the first 12 months post-diagnosis. Proportionality assumptions were confirmed graphically by plotting log-log plots.

We performed stratified analyses to assess the impact of T2D on infection risk in strata of sex, age groups, comorbidity, and statin use [25, 26], dissolving the matching in our stratified analyses. To assess trends in excess infection risk over time, we

stratified the analyses according to calendar years (from July to June), comparing adjusted rate ratios (aRRs) of infection restricted to 1 year of follow-up, and used linear regression to assess linear trends across calendar time. We considered $P < .05$ to be statistically significant.

Sensitivity and Bias Analyses

First, to focus on likely community-acquired infections, we followed both cohorts until their first primary hospital diagnosis of infection, disregarding all secondary hospital diagnoses. Next, to consider the total burden of infections (ie, all infection events occurring during follow-up), we used the Wei, Lin, and Weissfeld method [28] to account for repeated events. Third, because we had data only on hospital-diagnosed obesity, we computed estimates externally adjusted for unmeasured obesity (body mass index [BMI] ≥ 30 kg/m^2) [29] using previous data on the distribution and association of BMI with, respectively, T2D [30] and infections [24]:

$$\text{caRR} = \frac{\text{aRR}}{(Pc1(\text{RRcd} - 1) + 1)/(Pc0(\text{RRcd} - 1) + 1)}$$

where caRR is the obesity-aRR, aRR is the crude RR observed in our study, P*c*0 is the estimated proportion of comparisons with obesity (0.13) [30], P*c*1 is the estimated proportion of T2D patients with obesity (0.36) [30], and RRcd is the estimated RR between obesity and infection (1.5 for hospital-treated infection and 1.23 for community-based antibiotic prescriptions [24]).

We analyzed the data using SAS software (version 9.1.3; SAS Institute, Cary, North Carolina) and Stata (version 12; StataCorp, College Station, Texas). The Danish Data Protection Agency (record 2014-54-0922) approved the study.

RESULTS

Study Cohorts

A total of 155 158 patients with T2D (mean age 66 years) were matched with 774 017 persons from the general population. Patients with T2D were more likely to have comorbidities included in the CCI (29% vs 21%), including myocardial infarction (5% vs 3%), congestive heart failure (4% vs 2%), cerebrovascular diseases (7% vs 5%), peripheral vascular diseases (4% vs 2%), and chronic pulmonary disease (6% vs 2%; Table 1). In addition, T2D was associated with higher prevalence of statin use (52% vs 19%) and with slightly more use of oral corticosteroids (5% vs 3%). A total of 9.6% (80 536) of the comparison participants were diagnosed with T2D during follow-up and shifted to the T2D cohort on their diagnosis date.

Community-based Antibiotic Prescriptions

Among patients with T2D, 92 672 (62%) received an antibiotic prescription (median follow-up, 1.1 years; interquartile range [IQR], 0.4, 2.4 years) compared with 429 175 (55%) in the matched comparisons (median follow-up, 1.4 years; IQR, 0.5, 2.9 years). This corresponded to rates of 363.6/1000 person-years in the T2D cohort and 275.3/1000 person-years in the comparison cohort (RD = 88.3; 95% CI, 85.9 to 90.7; Table 2).

The crude aRR of an antibiotic prescription with T2D was 1.30 (95% CI, 1.29 to 1.31) and decreased successively to 1.28 (95% CI, 1.27 to 1.29) in model 1, 1.26 (95% CI, 1.25 to 1.27) in model 2, and 1.24 (95% CI, 1.23 to 1.25) in model 3. The aRRs were highest shortly after diagnosis of diabetes (Table 2).

Table 1. Characteristics of Members of the Type 2 Diabetes Cohort and the Matched General Population Comparison Cohort, Denmark, 2004–2012

Characteristic	Type 2 Diabetes Cohort (%)	Matched Comparison Cohort (%)
Total	155 158	774 017
Gender		
Men	85 338 (55)	425 554 (55)
Women	69 820 (45)	348 463 (45)
Age (y)		
Mean (standard deviation)	65.6 (13.6)	65.7 (13.6)
Age groups (y)		
30–<40	8224 (5)	39 707 (5)
40–<50	16 923 (11)	83 725 (11)
50–<60	29 261 (19)	144 360 (19)
60–<70	45 275 (29)	225 388 (29)
70–<80	35 392 (23)	177 834 (23)
>80	20 083 (13)	103 003 (13)
Marital status		
Married	87 040 (56)	460 263 (59)
Never married	18 274 (12)	86 840 (11)
Divorced	23 020 (15)	105 718 (14)
Widowed	24 551 (16)	114 020 (15)
Missing	2239 (1)	7175 (1)
Alcoholism-related conditions	6176 (4)	20 427 (3)
Charlson comorbidities		
Myocardial infarction	7454 (5)	19 676 (3)
Congestive heart failure	6728 (4)	15 323 (2)
Peripheral vascular disease	5745 (4)	18 559 (2)
Cerebrovascular disease	10 305 (7)	38 351 (5)
Dementia	992 (1)	5712 (1)
Chronic pulmonary disease	9960 (6)	33 143 (4)
Connective tissue disease	3366 (2)	13 951 (2)
Ulcer disease	3645 (2)	13 385 (2)
Mild liver disease	2217 (1)	4724 (1)
Hemiplegia	248 (<1)	986 (<1)
Moderate to severe renal disease	2042 (1)	6342 (1)
Any tumor	10 364 (7)	44 718 (6)
Leukemia	315 (<1)	1278 (<1)
Lymphoma	605 (<1)	2690 (<1)
Moderate to severe liver disease	609 (<1)	1135 (<1)
Metastatic solid tumor	1246 (1)	3761 (<1)
AIDS	65 (<1)	490 (<1)
Charlson comorbidity index score		
Low (0)	109 524 (71)	608 567 (79)
Medium (1–2)	37 094 (24)	139 336 (18)
High (≥3)	8540 (5)	26 114 (3)
Current medication use		
Statins	81 229 (52)	147 834 (19)
Steroids	7744 (5)	23 947 (3)
Immunosuppressants	1237 (1)	4931 (1)

Table 2. Rates, Rate Differences, and Rate Ratios of Community Antibiotic Prescriptions in the Type 2 Diabetes Cohort and the Matched General Population Cohort, Denmark, 2004–2012

	Type 2 Diabetes Cohort		Matched Comparison Cohort			Rate Ratio (95% CI)	
Follow-up Period, Antibiotic Groups	No. of Prescriptions (%)	Rate/1000 person-years (95% CI)	No. of Prescriptions (%)	Rate/1000 person-years (95% CI)	Rate Difference (95% CI)	Crude	Adjusted[a]
Overall antibiotic prescriptions in community							
Six-month follow-up	35 216 (23)	548.4 (542.7–554.1)	132 963 (17)	395.1 (393.0–397.2)	153.3 (147.2–159.4)	1.39 (1.37–1.41)	1.32 (1.30–1.33)
One-year follow-up	53 811 (35)	481.4 (477.3–485.5)	215 250 (28)	358.9 (357.4–360.4)	122.5 (118.1–126.8)	1.34 (1.33–1.36)	1.28 (1.26–1.29)
Total follow-up	92 672 (62)	363.6 (361.3–365.9)	429 175 (55)	275.3 (274.5–276.2)	88.3 (85.9–90.7)	1.30 (1.29–1.31)	1.24 (1.23–1.25)
Specific antibiotic prescriptions listed by increasing rate ratios							
Azithromycin	12 790 (8)	18.9 (18.5–19.2)	58 053 (7)	17.3 (17.1–17.4)	1.6 (1.2–1.9)	1.10 (1.07–1.12)	1.05 (1.02–1.07)
Phenoxymethylpenicillin	73 206 (47)	157.7 (156.5–158.8)	336 015 (43)	139.4 (139.0–139.9)	18.3 (17.0–19.5)	1.13 (1.12–1.14)	1.09 (1.08–1.10)
Tetracycline	507 (<1)	0.7 (.7–.8)	2107 (<1)	0.6 (.6–.6)	0.1 (.0–.1)	1.17 (1.06–1.30)	1.13 (1.01–1.26)
Erythromycin, roxithromycin, clarithromycin	32 382 (21)	52.8 (52.2–53.4)	136 232 (18)	43.7 (43.5–43.9)	9.1 (8.5–9.7)	1.21 (1.20–1.23)	1.15 (1.13–1.16)
Pivampicillin, amoxicillin, amoxicillin + enzyme inhibitor	33 850 (22)	54.9 (54.3–55.5)	138 221 (18)	44.0 (43.8–44.2)	10.9 (10.2–11.5)	1.25 (1.24–1.27)	1.17 (1.15–1.18)
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim	37 798 (24)	62.7 (62.1–63.3)	147 016 (19)	47.4 (47.1–47.6)	15.4 (14.7–16.0)	1.37 (1.35–1.39)	1.31 (1.29–1.33)
Dicloxacillin, flucloxacillin	27 195 (18)	42.6 (42.1–43.1)	95 497 (13)	30.2 (30.0–30.4)	12.4 (11.8–12.9)	1.42 (1.40–1.44)	1.32 (1.30–1.34)
Ciprofloxacin	577 (<1)	0.8 (.7–.9)	1881 (<1)	0.5 (.5–.6)	0.3 (.2–.3)	1.55 (1.40–1.71)	1.41 (1.26–1.59)
Antimycobacterial	163 (<1)	0.2 (.2–.3)	514 (<1)	0.1 (.1–.2)	0.1 (.0–.1)	1.69 (1.40–2.04)	1.69 (1.36–2.09)
Cephalosporin	61 (<1)	0.1 (.1–.2)	183 (<1)	0.1 (<.1–.1)	<0.1 (.0–.1)	1.71 (1.26–2.32)	1.95 (1.32–2.86)

Abbreviation: CI, confidence interval.

[a] Adjusted for marital status, alcoholism-related conditions, Charlson comorbidity index comorbidities, statin use, steroid use, and immunosuppressant use.

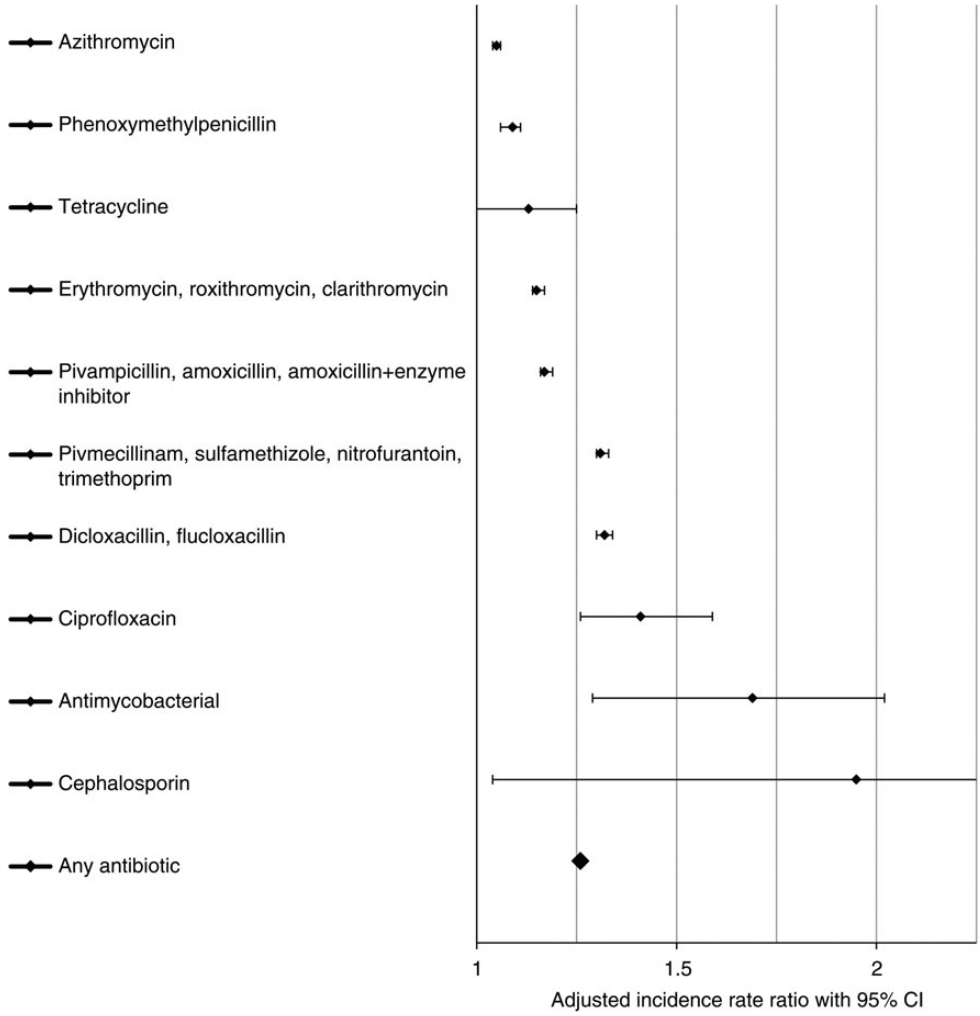

Figure 1. Adjusted rate ratios of community-based antibiotic prescriptions in the type 2 diabetes cohort compared with the matched general population cohort. Abbreviation: CI, confidence interval.

The highest aRRs were observed for cephalosporins, followed by antimycobacterial agents, quinolones, and antibiotics used for UTIs and *Staphylococcus aureus* infection (Figure 1). External adjustment for unmeasured obesity changed the crude RR from 1.30 to 1.24. When considering also repetitive antibiotic prescription episodes, we found 268 460 episodes in the T2D cohort and 1 045 191 episodes in the comparison cohort, yielding an aRR = 1.18 (95% CI, 1.17 to 1.19).

In subgroup analyses, the aRRs of community-based antibiotic prescriptions associated with T2D were highest among women, younger individuals, and those with low comorbidity (Table 3). The aRR also was substantially higher in those not using statins (aRR = 1.34; 95% CI, 1.33 to 1.35) compared with statin users (aRR = 1.10; 95% CI, 1.09 to 1.11).

Hospital-Treated Infections

In the T2D cohort, 28 938 (19%) patients had at least 1 episode of hospital-treated infection (median follow-up = 2.8 years; IQR, 1.2, 5.0 years) compared with 102 795 (13%) among comparisons (median follow-up = 3.0 years; IQR, 1.4, 5.2 years). The rate was increased in the T2D cohort, with 58.2 hospital-treated infections per 1000 person-years vs 39.0/1000 person-years in the comparison cohort (RD = 19.2; 95% CI, 18.5 to 19.9).

In the Cox model, the crude infection RR of 1.53 associated with T2D decreased to 1.46 (95% CI, 1.44 to 1.49) in model 1, decreased further to 1.42 (95% CI, 1.40 to 1.44) in model 2, and rose to 1.49 (95% CI, 1.47 to 1.52) in the fully adjusted model 3. The aRRs were particularly elevated during the first 6 months of follow-up (Table 4). The highest aRRs were observed for emphysematous cholecystitis, followed by abscesses, tuberculosis, septicemia, meningococcal infection, and skin and subcutaneous infections. The aRRs also were high for UTIs, gastrointestinal tract infection, intraabdominal infection, and pneumonia (Figure 2). External adjustment for unmeasured obesity changed the crude RR from 1.53 to 1.38. The total number of

Table 3. Rates, Rate Differences, and Rate Ratios of Community-based Antibiotic Prescriptions in the Type 2 Diabetes Cohort and the Matched General Population Cohort, Stratified by Gender, Age Group, Comorbidity Level, and Statin Use

Characteristic	Type 2 Diabetes Cohort Rate/1000 person-years (95% CI)	Matched Comparison Cohort Rate/1000 person-years (95% CI)	Rate Difference (95% CI)	Rate Ratio (95% CI)	
				Crude	Adjusted[a]
Overall	363.6 (361.3–365.9)	275.3 (274.5–276.2)	88.3 (85.9–90.7)	1.30 (1.29–1.31)	1.24 (1.23–1.25)
Gender					
Men	308.7 (306.0–311.4)	237.4 (236.4–238.4)	71.3 (68.4–74.2)	1.28 (1.26–1.29)	1.22 (1.21–1.23)
Women	446.5 (442.5–450.6)	329.3 (327.9–330.7)	117.3 (113.0–121.5)	1.31 (1.30–1.32)	1.26 (1.25–1.27)
Age groups (y)					
30–<40	436.7 (425.1–448.6)	324.6 (320.3–328.9)	112.1 (99.6–124.6)	1.31 (1.27–1.35)	1.27 (1.23–1.31)
40–<50	361.3 (354.4–368.3)	243.2 (240.9–245.5)	118.1 (110.8–125.4)	1.45 (1.42–1.48)	1.27 (1.23–1.31)
50–<60	341.9 (336.9–347.0)	238.7 (236.8–240.3)	103.3 (98.0–108.7)	1.40 (1.38–1.42)	1.28 (1.25–1.30)
60–<70	339.0 (335.0–343.1)	260.7 (259.3–262.2)	78.3 (74.0–82.6)	1.28 (1.26–1.29)	1.20 (1.18–1.21)
70–<80	357.5 (352.8–362.2)	288.0 (286.2–289.7)	69.5 (64.5–74.5)	1.22 (1.20–1.24)	1.16 (1.14–1.14)
>80	448.1 (440.7–455.5)	357.0 (354.4–359.7)	91.0 (83.1–99.0)	1.23 (1.20–1.25)	1.21 (1.19–1.23)
Charlson comorbidity index score					
Low (0)	324.1 (321.7–326.6)	248.1 (247.3–249.0)	76.0 (73.4–78.6)	1.28 (1.27–1.29)	1.25 (1.24–1.26)
Medium (1–2)	464.5 (458.8–470.3)	395.7 (393.1–398.3)	68.8 (62.5–75.2)	1.17 (1.17–1.19)	1.19 (1.18–1.21)
High (≥3)	679.3 (662.0–697.1)	566.8 (558.4–575.3)	112.5 (93.0–132.0)	1.19 (1.16–1.23)	1.19 (1.16–1.23)
Statin use					
No	392.4 (388.8–395.9)	267.2 (266.3–268.1)	125.2 (121.5–128.9)	1.42 (1.41–1.43)	1.34 (1.33–1.35)
Yes	340.4 (337.4–343.4)	312.6 (310.6–314.7)	27.8 (24.1–31.4)	1.10 (1.09–1.11)	1.10 (1.09–1.11)

Abbreviation: CI, confidence interval.

[a] Adjusted for marital status, alcoholism-related conditions, Charlson comorbidity index comorbidities, statin use, steroid use, and immunosuppressant use.

hospital-treated infections was 40 541 episodes in the T2D cohort and 122 618 episodes in the comparison cohort, yielding an aRR = 1.55 (95% CI, 1.53 to 1.57).

Results of the subgroup analyses showed a higher RR of infection associated with T2D in women than in men (Table 5), partly caused by much higher aRRs of UTIs in women (aRR = 1.41; 95% CI, 1.36 to 1.46) than in men (aRR = 1.22; 95% CI, 1.17 to 1.27). The relative impact of diabetes was highest in those aged 40–50 years (aRR = 1.77; 95% CI, 1.67 to 1.87) and then decreased to 1.29 (95% CI, 1.26 to 1.33) among those aged >80 years (Table 5). aRRs from T2D were highest in patients with low baseline comorbidity (aRR = 1.61; 95% CI, 1.58 to 1.64), decreasing to 1.22 (95% CI, 1.17 to 1.27) in those with high comorbidity. In contrast, the RD was highest for persons with a high level of comorbidity (RD = 31.7; 95% CI, 24.2 to 39.1). The aRR of infection associated with T2D was clearly higher in patients who were not using statins (aRR = 1.62; 95% CI, 1.59 to 1.65) compared with statin users (aRR = 1.21; 95% CI, 1.18 to 1.23). When primary hospital diagnoses of infection only was examined, the estimates followed a similar pattern as for any hospital-diagnosed infection (aRR = 1.39; 95% CI, 1.37 to 1.41; Supplementary Table 1).

Time Trends

No linear trends were observed in the rates of hospital-treated infection in the T2D cohort (regression coefficient = 0.12; 95% CI, −1.16 to 1.39; $P = .83$) or in the comparison cohort (regression coefficient = 0.32; 95% CI, −.18 to .84; $P = .16$). We observed decreasing linear trends in rates of community-based antibiotic prescriptions in the T2D cohort (regression coefficient = −3.85; 95% CI, −6.84 to −.86; $P = .02$) but not in the comparison cohort (regression coefficient = −0.98; 95% CI, −3.89 to 1.93; $P = .44$). The 1-year aRR for any hospital-treated infection decreased from 1.89 (95% CI, 1.75 to 2.04) in 2004–2005 to 1.59 (95% CI, 1.49 to 1.71) in 2011 to 2012 (regression coefficient = −0.05; 95% CI, −.07 to −.02; $P = .007$; Figure 3). The excess community-based antibiotic use changed less, from 1.31 (95% CI, 1.27 to 1.36) in 2004–2005 to 1.26 (95% CI, 1.22 to 1.30) in 2011–2012 (regression coefficient = −0.01; 95% CI, −.10 to −.00; $P = .006$). The observed decreases were highest in women (Supplementary Table 2).

DISCUSSION

In our study, patients with T2D experienced higher rates of both community antibiotic prescriptions and hospital-treated infections than matched members of the general population comparison cohort. The RRs were particularly high for severe infections and for hospitalizations and treatments related to UTIs and skin infections. Compared with the general population, the excess infection risk associated with T2D decreased modestly from 2004 to 2012.

The strengths of our study include the following: use of a population-based nationwide cohort; virtually no loss to follow-up; access to complete hospitalization and prescription records, which ensured inclusion of almost all infections

Table 4. Rates, Rate Differences, and Rate Ratios of Hospital-Treated Infections in the Type 2 Diabetes Cohort and the Matched General Population Cohort, Denmark, 2004–2012

	Type 2 Diabetes Cohort		Matched Comparison Cohort			Rate Ratio (95% CI)	
Follow-up Period, Infection Type	No. of Infections (%) (n = 28 938)	Rate/1000 person-years (95% CI)	No. of Infections (%) (n = 102 795)	Rate/1000 person-years (95% CI)	Rate Difference (95% CI)	Crude	Adjusted[a]
Any infection							
Six-month follow-up	6131 (4)	84.84 (82.74–86.99)	15 622 (2)	42.44 (41.77–43.11)	42.40 (40.18–44.63)	2.02 (1.96–2.08)	1.97 (1.91–2.04)
One-year follow-up	9893 (6)	72.14 (70.73–73.57)	29 226 (4)	41.52 (41.05–42.00)	30.61 (29.11–32.11)	1.76 (1.72–1.80)	1.73 (1.68–1.77)
Total follow-up	28 938 (19)	58.24 (57.57–58.92)	102 795 (13)	39.03 (38.79–39.27)	19.21 (18.50–19.92)	1.53 (1.51–1.55)	1.49 (1.47–1.52)
Specific infections listed by increasing rate ratios[b]							
Eye and ear infection	1190 (1)	1.63 (1.54–1.73)	5246 (1)	1.43 (1.39–1.47)	0.20 (.10–.30)	1.16 (1.09–1.25)	1.17 (1.09–1.26)
Upper respiratory tract infection	1631 (1)	2.24 (2.13–2.35)	6283 (1)	1.72 (1.68–1.76)	0.52 (.40–.63)	1.30 (1.23–1.38)	1.24 (1.17–1.32)
Infection of heart and blood vessels	282 (<1)	0.38 (.34–.43)	982 (<1)	0.27 (.25–.28)	0.12 (.07–.16)	1.48 (1.28–1.70)	1.25 (1.07–1.47)
Pneumonia	10 720 (7)	15.11 (14.83–15.40)	40 156 (5)	11.19 (11.08–11.30)	3.92 (3.61–4.22)	1.38 (1.35–1.41)	1.31 (1.27–1.34)
Miscellaneous bacterial infection	1308 (1)	1.79 (1.69–1.89)	4664 (1)	1.27 (1.24–1.31)	0.51 (.41–.62)	1.42 (1.33–1.52)	1.34 (1.25–1.45)
Emphysematous cystitis	610 (<1)	0.83 (.77–.90)	2236 (<1)	0.61 (.58–.63)	0.22 (.15–.30)	1.40 (1.27–1.54)	1.35 (1.22–1.50)
Gastrointestinal tract infection	2578 (2)	3.55 (3.41–3.69)	8742 (1)	2.39 (2.34–2.44)	1.15 (1.01–1.30)	1.51 (1.44–1.59)	1.39 (1.32–1.46)
Urinary tract infection	6895 (4)	9.60 (9.37–9.83)	24 374 (3)	6.74 (6.65–6.82)	2.85 (2.62–3.10)	1.47 (1.42–1.51)	1.41 (1.37–1.45)
Viral infection	1094 (1)	1.50 (1.41–1.59)	3848 (1)	1.05 (1.02–1.08)	0.45 (.35–.54)	1.46 (1.36–1.56)	1.43 (1.33–1.55)
Infection of the central nervous system	312 (<1)	0.43 (.38–.48)	1088 (<1)	0.30 (.28–.31)	0.13 (.08–.18)	1.45 (1.27–1.66)	1.44 (1.25–1.67)
Fungal infection	798 (1)	1.09 (1.02–1.17)	2733 (<1)	0.74 (.72–.77)	0.35 (.26–.43)	1.50 (1.38–1.63)	1.45 (1.32–1.59)
Perirenal abscess	78 (<1)	0.11 (.09–.13)	207 (<1)	0.06 (.05–.06)	0.05 (.03–.07)	1.79 (1.35–2.38)	1.46 (1.07–2.00)
Intraabdominal infection	4356 (3)	6.04 (5.86–6.22)	14 519 (2)	4.00 (3.93–4.06)	2.04 (1.85–2.23)	1.52 (1.47–1.58)	1.48 (1.43–1.54)
Emphysematous pyelonephritis	588 (<1)	0.80 (.74–.87)	1894 (<1)	0.52 (.49–.54)	0.29 (.22–.36)	1.54 (1.40–1.70)	1.49 (1.34–1.66)
Skin and subcutaneous infection	5637 (4)	7.86 (7.66–8.07)	18 559 (2)	5.13 (5.06–5.20)	2.73 (2.51–2.95)	1.55 (1.51–1.61)	1.50 (1.45–1.55)
Meningococcal infection	16 (<1)	0.02 (.01–.04)	44 (<1)	0.01 (.01–.02)	0.00 (.00–.02)	1.63 (0.88–3.01)	1.53 (0.72–3.24)
Septicemia	4021 (3)	5.52 (5.35–5.70)	12 270 (2)	3.35 (3.29–3.41)	2.17 (1.99–2.35)	1.67 (1.61–1.74)	1.60 (1.53–1.67)
Tuberculosis	112 (<1)	0.15 (.13–.18)	398 (<1)	0.11 (.10–1.12)	0.04 (.01–.07)	1.44 (1.16–1.80)	1.61 (1.25–2.06)
Abscess	3920 (3)	5.43 (5.26–5.60)	12 060 (2)	3.31 (3.25–3.37)	2.12 (1.94–2.30)	1.65 (1.59–1.72)	1.62 (1.55–1.69)
Emphysematous cholecystitis	597 (<1)	0.82 (.75–.88)	1721 (<1)	0.47 (.45–.49)	0.35 (.28–.41)	1.74 (1.57–1.93)	1.74 (1.56–1.94)

Abbreviation: CI, confidence interval.

[a] Adjusted for marital status, alcoholism-related conditions, Charlson comorbidity index comorbidities, statin use, steroid use, and immunosuppressant use.

[b] *International Classification of Diseases* codes for specific infections are available in the Supplementary Appendix.

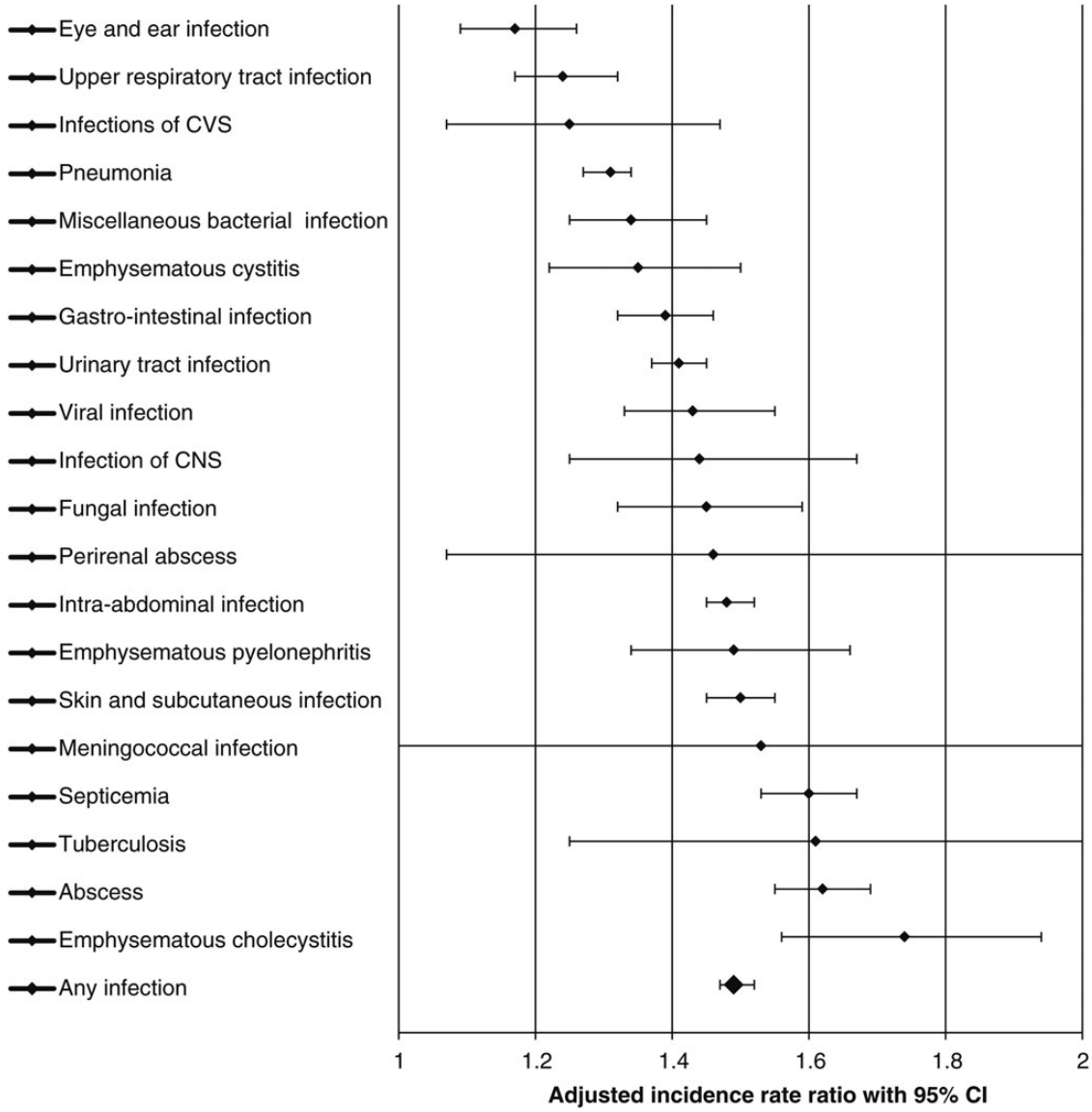

Figure 2. Adjusted rate ratios of hospital-treated specific infections in the type 2 diabetes cohort compared with the matched general population cohort. Abbreviations: CI, confidence interval; CNS, central nervous system; CVS, cardiovascular system.

requiring medical care [31]; and individual-level linkage to administrative and medical registries, which allowed adjustment for a range of potential confounders.

Our study also had limitations. We lacked clinical, socioeconomic, and lifestyle data such as detailed data on obesity, which is an important risk factor both for diabetes and infections. Still, our external adjustment for obesity suggested that only one-quarter of the observed T2D association potentially could be explained by this factor. Similarly, the lack of data on tobacco smoking might have biased our results. However, we adjusted for diseases closely related to smoking, and a recent Danish study found a lower prevalence of smoking in T2D patients compared with the general population of similar age (24% vs 29%) [30]. If the threshold for general practitioners' referral of T2D patients to hospitals is lower due to anticipated problems with glucose control and other complications, patients with T2D may have a greater likelihood of hospital treatment for a given infection compared with persons without T2D. This would lead to overestimated infection RRs [1]. Recent Danish studies found comparable disease severity and levels of inflammatory markers in individuals with and without T2D at the time of hospitalization for pneumonia [32] and higher disease severity in T2D patients than counterparts for pneumococcal bacteremia [33], arguing against selective hospitalization. Nonetheless, the higher infection estimates observed shortly after diabetes diagnosis, particularly for antibiotics, may be partly related to increased surveillance by general practitioners. Finally, our study relied on the validity of routine care diagnostic

Table 5. Rates, Rate Differences, and Rate Ratios of Hospital-Treated Infections in the Type 2 Diabetes Cohort and the Matched General Population Cohort, Stratified by Gender, Age Group, Comorbidity Level, and Statin Use

Characteristic	Type 2 Diabetes Cohort Rate/1000 person-years (95% CI)	Matched Comparison Cohort Rate/1000 person-years (95% CI)	Rate Difference (95% CI)	Rate Ratio (95% CI)	
				Crude	Adjusted[a]
Overall	58.24 (57.57–58.92)	39.03 (38.79–39.27)	19.2 (18.5–19.9)	1.53 (1.51–1.55)	1.49 (1.47–1.52)
Gender					
Men	57.3 (56.4–58.2)	39.4 (39.1–39.7)	17.9 (17.0–18.9)	1.47 (1.44–1.49)	1.40 (1.37–1.42)
Women	59.4 (58.4–60.4)	38.6 (38.3–39.0)	20.7 (19.7–21.8)	1.55 (1.52–1.58)	1.50 (1.47–1.53)
Age groups (y)					
30–<40	69.9 (66.6–73.4)	37.5 (36.4–38.6)	32.5 (28.9–36.0)	1.86 (1.75–1.97)	1.55 (1.48–1.62)
40–<50	43.2 (41.5–44.9)	21.4 (20.9–22.0)	21.7 (19.9–23.5)	2.00 (1.91–2.10)	1.77 (1.67–1.87)
50–<60	45.2 (43.8–46.6)	25.1 (24.7–25.6)	20.1 (18.6–21.5)	1.79 (1.73–1.86)	1.58 (1.52–1.64)
60–<70	47.9 (46.8–49.1)	31.3 (30.9–31.7)	16.6 (15.4–17.8)	1.53 (1.49–1.57)	1.41 (1.37–1.45)
70–<80	64.5 (63.0–66.0)	46.1 (45.6–46.7)	18.4 (16.8–19.9)	1.40 (1.36–1.43)	1.33 (1.30–1.37)
>80	100.8 (98.3–103.3)	78.7 (77.8–79.6)	22.1 (19.4–24.8)	1.28 (1.25–1.32)	1.29 (1.26–1.33)
Charlson comorbidity index score					
Low (0)	42.9 (42.2–43.5)	28.7 (28.5–28.9)	14.2 (13.5–14.9)	1.51 (1.48–1.54)	1.61 (1.58–1.64)
Medium (1–2)	91.2 (89.4–93.0)	76.6 (75.8–77.5)	14.6 (12.5–16.6)	1.24 (1.21–1.26)	1.29 (1.26–1.32)
High (≥3)	194.7 (188.1–201.5)	163.0 (159.7–166.4)	31.7 (24.2–39.1)	1.20 (1.15–1.25)	1.22 (1.17–1.27)
Statin use					
No	70.8 (69.7–72.0)	38.0 (37.8–38.3)	32.8 (31.7–33.9)	1.90 (1.87–1.93)	1.62 (1.59–1.65)
Yes	47.9 (47.1–48.7)	43.2 (42.7–43.8)	4.7 (3.7–5.7)	1.22 (1.20–1.25)	1.21 (1.18–1.23)

Abbreviation: CI, confidence interval.

[a] Adjusted for marital status, alcoholism-related conditions, Charlson comorbidity index comorbidities, statin use, steroid use, and immunosuppressant use.

codes. However, a recent validation study has confirmed high validity of ICD-10 codes for identifying hospital-treated infections in Danish registries [34].

Our study corroborates and extends a few previous studies [5, 6, 13, 14, 35, 36]. Muller et al [5] found an increased adjusted odds ratio of community-treated UTIs of 1.21 (95% CI, 1.07 to 1.38) but no difference in the odds of upper respiratory tract infection (1.02; 95% CI, .91 to 1.14) among 6712 patients with T2D compared with 18 911 hypertensive controls without diabetes [5]. Hirji et al [37] used the UK General Practice Research Database to estimate the incidence of UTIs in 135 920 T2D patients compared with age- and sex-matched persons without diabetes and found an aRR of 1.53 (95% CI, 1.46 to 1.59), supporting our findings of a higher excess risk for infections requiring hospitalization than for those treated in the community. A Canadian cohort study of 513 749 patients with prevalent T2D and a matched comparison cohort [14] reported a crude RR of 2.01 (99% CI, 1.96 to 2.06) for any infection leading to a hospitalization, whereas the risk ratio for all infections (including claims from community-based physicians) was 1.21 (99% CI, 1.20 to 1.22) after a 1-year follow-up. We corroborate these findings of a higher excess risk for hospitalized than community-treated infections associated with T2D and extend them by showing declining excess risks over time in community antibiotic use in T2D. These findings may be driven by earlier detection and treatment of milder T2D cases over time; by improved therapy of hyperglycemia and other risk factors; or, alternatively, by an increasing threshold of antibiotic prescribing or hospital admission in T2D (ie, declining surveillance bias over time).

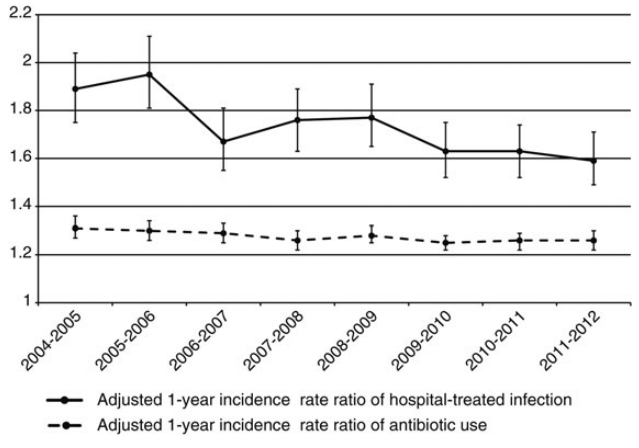

Figure 3. Time trends in adjusted rate ratios of infection among individuals with type 2 diabetes compared with members of the matched general population cohort, Denmark, 2004–2012.

The stronger relative association with infections in younger T2D patients observed in our study could be due to either increased severity of diabetes, with more obesity, physical inactivity, and higher HbA_{1c} levels and inflammation seen with T2D onset early in life, as previously observed [38], or to a lower prevalence of other competing risk factors for infection in

younger vs older people. A similar pattern by age group was observed in the Canadian study [14]. We observed a strong modification of the T2D effect on infections among statin users, possibly due to infection-protective or antiinflammatory effects of statin therapy in T2D patients [39]. Previous metaanalyses have indicated a protective effect of statin use against infections (pooled adjusted effect estimate = 0.55; 95% CI, .36 to .83) [40].

Our study provides strong evidence that T2D is associated with increased risk of antibiotic use in the community setting and hospital-treated infections.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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