Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study

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OBJECTIVE

We describe in detail the burden of infections in adults with diabetes within a large national population cohort. We also compare infection rates between patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM).

RESEARCH DESIGN AND METHODS

A retrospective cohort study compared 102,493 English primary care patients aged 40–89 years with a diabetes diagnosis by 2008 (*n* = 5,863 T1DM and *n* = 96,630 T2DM) with 203,518 age-sex-practice–matched control subjects without diabetes. Infection rates during 2008–2015, compiled from primary care and linked hospital and mortality records, were compared across 19 individual infection categories. These were further summarized as any requiring a prescription or hospitalization or as cause of death. Poisson regression was used to estimate incidence rate ratios (IRRs) between *1*) people with diabetes and control subjects and *2*) T1DM and T2DM adjusted for age, sex, smoking, BMI, and deprivation.

RESULTS

Compared with control subjects without diabetes, patients with diabetes had higher rates for all infections, with the highest IRRs seen for bone and joint infections, sepsis, and cellulitis. IRRs for infection-related hospitalizations were 3.71 (95% CI 3.27–4.21) for T1DM and 1.88 (95% CI 1.83–1.92) for T2DM. A direct comparison of types confirmed higher adjusted risks for T1DM versus T2DM (death from infection IRR 2.19 [95% CI 1.75–2.74]). We estimate that 6% of infection-related hospitalizations and 12% of infection-related deaths were attributable to diabetes.

CONCLUSIONS

People with diabetes, particularly T1DM, are at increased risk of serious infection, representing an important population burden. Strategies that reduce the risk of developing severe infections and poor treatment outcomes are under-researched and should be explored.

Diabetes is one of the leading causes of morbidity and mortality across the globe, and the burden of disease is projected to increase from 425 to 629 million adults between 2017 and 2045 (1). The association between diabetes and infection is well known clinically (2,3) and has been linked to a number of causal pathways, including impaired immune responses within the hyperglycemic environment (4), as well as potentially other abnormalities associated with diabetes such as neuropathy and altered lipid

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metabolism. It has been described in other studies and populations (5–17); however, not all have consistently controlled for confounding factors such as smoking, which are more common in people with diabetes and associated with infection (18). Initially, studies mainly considered predominately common infections (6,8,12), with few able to include important but rare infections (7), such as endocarditis, or considered the whole range of infection outcomes from health service use (17) to hospitalization (16) and mortality (9). Also, few studies have included large numbers of older people, for whom infections may be frequent and more serious (5). Larger recent studies, primarily from higher-income countries using national data sets, have overcome some of these limitations (7–13) but do not always separate type 1 diabetes mellitus (T1DM) from type 2 diabetes mellitus (T2DM) or only consider T2DM.

In this study, we use a large primary care database in England to comprehensively describe and quantify the increased risk of infection in T1DM and T2DM compared with the general population, using a wide range of infection categories. A novel feature of our analysis is that the study is large enough to identify other characteristics of patients with diabetes that may be associated with infection risk, such as BMI, smoking, medication use, duration of diabetes, and comorbidities or diabetes complications. We consider the impact of adjustment for common confounding factors and describe how the associations vary by age, sex, region, and duration of diabetes. Finally, we make a direct comparison of infection risk between patients with T1DM and T2DM.

RESEARCH DESIGN AND METHODS

Data Source

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the population of the U.K. (19). We included 361 general (family) practices in England recording data on 1 January 2008, anonymously linked to Hospital Episode Statistics and Office for National Statistics death registration data. In the U.K., every admission to a National Health Service hospital is recorded in Hospital Episode Statistics and allows for identification of the primary reason for the admission. Similarly, the Office for National Statistics data allow the underlying cause of death to be identified.

Study Design

We performed a retrospective matched-cohort study. First, we identified all patients (n = 1,488,921) who, as of 1 January 2008, were alive, 40–89 years old, and registered for at least 1 year with their practice. We then extracted electronic records for all patients (n = 104,717) with a Read code by 1 January 2008 for diabetes using nationally agreed-upon codes that practices are encouraged to use (20) (Supplementary Fig. 1). Then from the remaining pool of patients, we randomly selected two age-sex-practice–matched control subjects. Matching on practice accounts for broad geographical differences and practice-related differences in clinical care and recording that may exist. Although control subjects were required to have no diabetes code by 1 January 2008, they could be diagnosed as such after this date. Patients with diabetes (n = 100) not able to be matched to any control subjects were excluded. All patients were followed until the earliest date of the following: death, deregistration from practice, practice leaving CPRD, or 31 December 2015.

Classification of Type

Although diabetes type is generally recorded via specific Read codes, there are noted concerns around misclassification (21). We took a pragmatic approach to resolving this by cross-classifying diabetes Read codes (T1DM, T2DM, or nonspecific) up to 1 January 2008 with prescribing of antidiabetes medication in 2007 (insulin, sulfonylureas, biguanides, or other antidiabetes) to estimate type at baseline. As historical prescribing of antidiabetes medication is not reliably available for patients with diabetes who were diagnosed many years previously, especially at time of diagnosis, we chose not to apply any more detailed prescribing criteria. We excluded patients where there was a high potential for misclassification (Supplementary Fig. 2); although sensitivity analyses including them produced similar findings (data not shown).

For n = 6,055 patients with only T1DM codes, only those with insulin prescription(s) in 2007 were classed as T1DM (n = 5,139); we excluded patients with prescriptions for other antidiabetes medication in 2007 as their type was uncertain (n = 759) or if their only insulin was prior to 2007 (n = 93); and if they had no insulin in their record ever, we assumed the code was wrong and classified them as T2DM (n = 64). For n = 94,450 patients with only T2DM codes, we classified them as T2DM (n = 93,237) unless they had insulin prescription(s) in 2007 and no other antidiabetes medication previously in their record; in this case, they were excluded as their type was uncertain (n = 1,213). A small group (n = 4,112) of patients had both T1DM and T2DM codes (or only nonspecific codes); if they were prescribed insulin in 2007 with no other antidiabetes medication in their record, they were classed as T1DM (n = 724) unless they had codes for gestational diabetes mellitus and were thus excluded (n = 12); if they were prescribed insulin only prior to 2007 with no other antidiabetes medication, they were excluded (n = 47); and all remaining patients were assumed to be T2DM (n = 3,329). Overall, this resulted in 5,863 patients with T1DM, 96,630 patients with T2DM, and 2,124 excluded patients who could not be clearly classified.

Classification of Infections

Infections during 2008–2015 were classified into 19 different groupings using Read codes for primary care data and ICD-10 classifications for hospital admissions and cause of death (Supplementary Table 1). For each group, any repeated code within 90 days was treated as being the same event, with codes >90 days apart assumed to be distinct events. Total number of infection events was counted for each patient. Three summary groups were defined: *1*) any infection with a prescription for antibiotic/antifungal/antiviral drug (BNF 5.1) within 14 days of the diagnosis, *2*) any infection event that resulted in a hospital admission, and *3*) any infection that resulted in death.

Statistical Analyses

Poisson regression was used to compare rates of infection during follow-up (Stata version 13), with an offset accounting for total days registered. When the comparison was between people with diabetes and matched control subjects, Poisson regression conditioned on the match sets was used, which implicitly controls for age, sex, and practice. We also explored the impact of further adjustment for a range of baseline factors using information recorded up to 2008. These were smoking, BMI, and deprivation, using the Index of Multiple Deprivation (IMD), a composite small-area ecological measure of deprivation based on postcodes (22). Additionally

we adjusted for a range of comorbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, ischemic heart disease [IHD], peripheral vascular disease, stroke, and transient ischemic attack [TIA]) and whether they had been prescribed a statin or oral steroid in 2007 to see if these could explain differences between people with and without diabetes. To look for effect modification, we stratified the model by the following variables: sex, age, duration of diabetes, and practice region.

When the comparison was made within those with diabetes, we adjusted directly for age and sex, as well as all other confounding factors listed above, and additionally for diabetes medication and duration. This was done separately for T1DM and T2DM, and then in a combined model with a category for type (dropping diabetes medication from this model). To account for clustering by practice, all models used a sandwich estimator to obtain robust standard errors. Sensitivity analyses using negative binomial models to correct for overdispersion made no material difference (data not shown).

Finally, the population burden of infection attributable to diabetes was estimated by calculating population-attributable risk fractions (PAFs) (23). This was done for selected infections for T1DM and T2DM separately within 10-year age-groups using conditional Poisson regression, using the total number of patients registered in the 361 CPRD practices on 1 January 2008 within each age-group to calculate the prevalence of diabetes. An overall PAF for diabetes was estimated by extending the formula, assuming diabetes type is a polytomous exposure (23).

RESULTS

The baseline characteristics of patients with and without diabetes are shown in Table 1. Patients with T2DM were on average ~11 years older than T1DM (67.6 vs. 56.5 years) and more likely to have been diagnosed in the last 5 years (46.6 vs. 8.0%). Mean follow-up time for all patients was ~5.5 years, with 5.0% (n = 10,139) of control subjects subsequently receiving a diabetes Read code during follow-up.

During follow-up, 56.9% of patients with T2DM (n = 54,972) had at least one infection accompanied by a prescription compared with 46.2% of control subjects (n = 88,568) (Supplementary Table 2). The disparity was broadly similar between patients with T1DM (55.0%, n = 3,226) and their control subjects (41.3%, n = 4,828). For hospitalizations for infection, 15.7% of patients with T2DM (n = 15,195) had at least one during follow-up compared with 9.8% of control subjects (n = 18,706). Among T1DM, the disparity between patients with diabetes (14.6%, n = 856) and control subjects (5.4%, n = 630) was greater.

Table 2 summarizes infection rates between people with diabetes and control subjects for T1DM and T2DM separately. The resulting incidence rate ratios (IRRs) were overall higher for T1DM due to lower rates in their (younger) control subjects, with the largest disparities observed for bone and joint infections (primarily osteomyelitis) (IRR 22.34), endocarditis (IRR 6.70), and sepsis (IRR 6.10). For T2DM, the largest disparities were seen for bone and joint infections (IRR 4.93), sepsis (IRR 2.25), and cellulitis (IRR 2.03). For infections requiring hospitalization, the IRR was 3.71 (95% CI 3.27–4.21) for T1DM and 1.88 (95% CI 1.83–1.92) for T2DM. The increased risk of death from infection was also markedly higher for T1DM (IRR 7.72 [95% CI 4.47–13.33]) than for T2DM (IRR 1.92 [95% CI 1.75–2.10]). We explored the impact of adjusting for differences in smoking, BMI, deprivation, and comorbidity between people with diabetes and control subjects (Supplementary Table 3). Generally, associations were attenuated with increasing adjustment, but these could not explain the higher overall risk of infection among people with diabetes. For example, the adjusted risk of sepsis was still twice as great for people with diabetes than without (IRR 2.03 [95% CI 1.86–2.11]). Sensitivity analyses excluding control subjects who developed diabetes during the study (Supplementary Table 4) did not materially alter our findings.

The IRRs between those with diabetes and control subjects for infections requiring hospitalization were stratified by sex, age, duration of diabetes, and practice region (Fig. 1). Although men had higher IRRs for both T1DM (4.07 vs. 3.46) and T2DM (1.96 vs. 1.82), CIs overlapped for both types. The higher estimated IRRs compared with those without diabetes declined with age for both types, but whereas IRRs increased with duration of diabetes for T2DM, this trend was not seen for T1DM.

PAFs were estimated for selected infection groups from Table 2 (Supplementary Table 5). The highest PAFs for diabetes for individual infections were observed for bone and joint infections (22.6%) and sepsis (9.3%). We estimate that 6.3% of hospitalizations for infections and 12.4% of deaths from infection were attributable to diabetes.

Table 3 summarizes risk factor IRRs for infection requiring hospitalization within individuals with T1DM and T2DM separately. For both types, there were trends of higher risk with increasing age, obesity, and deprivation. Higher risks among men and with increasing time since diagnosis were only observed for patients with T2DM. Insulin prescribing among patients with T2DM was a strong predictor and explained much of the trend with duration of diabetes seen in Fig. 1. In a mutually adjusted model, patients with T2DM prescribed a statin in 2007 had lower infection hospitalization rates (IRR 0.83 [95% CI 0.80–0.87]), whereas those prescribed an oral steroid had a doubling of a future risk (IRR 1.96 [95% CI 1.85–2.07]).

Finally, we fitted Poisson models only on people with diabetes, with a term for diabetes type (Supplementary Table 6). After adjusting for age, sex, BMI, smoking, and deprivation, the increased adjusted risk of any infection plus a prescription was small, but still statistically significant, for T1DM (IRR 1.09 [95% CI 1.05–1.13]) directly compared with T2DM. The higher risks of hospitalization for infection (IRR 1.63 [95% CI 1.50–1.76]) and death from infection (IRR 2.19 [95% CI 1.75–2.74]) were not explained by adjusting for the different baseline characteristics between patients with T1DM and T2DM.

CONCLUSIONS

In a large English primary care database, we have detailed the increased risk of infection among people with diabetes compared with the general population. Organ systems where bacterial infections predominate (pneumonia, sepsis, endocarditis, skin, and bone and joint infections) as well as fungal diseases (mycoses) were associated with substantial increases in magnitude among patients with both T1DM and T2DM, but risks were consistently higher for T1DM. Among people with diabetes, those at highest risk of infection events and poor outcomes (hospitalization) were patients who were older (aged ≥70 years), were morbidly obese (BMI >40 kg/m^2), were currently

Table 1—Summary of people with diabetes and matched control subjects on 1 January 2008

	People with T2DM (*n* = 96,630)		Control subjects with T2DM (*n* = 191,822)		People with T1DM (*n* = 5,863)		Control subjects with T1DM (*n* = 11,696)	
Baseline characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Sex								
Women	43,230	44.7	86,022	44.8	2,431	41.5	4,856	41.5
Men	53,400	55.3	105,800	55.2	3,432	58.5	6,840	58.5
Age (years)								
40–49	7,571	7.8	15,140	7.9	2,148	36.6	4,295	36.7
50–59	16,696	17.3	33,379	17.4	1,550	26.4	3,100	26.5
60–69	26,949	27.9	53,779	28.0	1,119	19.1	2,234	19.1
70–79	29,223	30.2	57,994	30.1	735	12.5	1,457	12.5
80–89	16,191	16.8	31,730	16.5	311	5.3	610	5.2
Time since diagnosis (years)								
>0 to 5	44,989	46.6	NA	—	466	8.0	NA	—
>5 to 15	41,507	43.0	NA	—	1,495	25.5	NA	—
>15	10,134	10.5	NA	—	3,902	66.6	NA	—
Current diabetes drugs*								
Insulin	13,967	14.5	NA	—	5,863	100.0	NA	—
Sulfonylureas	31,846	33.0	NA	—	0	0.0	NA	—
Biguanides	58,216	60.3	NA	—	0	0.0	NA	—
Other	6,315	6.5	NA	—	0	0.0	NA	—
None	24,898	25.8	NA	—	0	0.0	NA	—
Other drugs*								
Statins	74,735	77.3	48,721	25.4	3,876	66.1	1,607	13.7
Oral steroids	6,205	6.4	10,540	5.5	277	4.7	460	3.9
Deprivation quintile†								
1 (least)	18,138	18.8	41,926	21.9	1,361	23.2	2,922	25.0
2	22,071	22.8	46,639	24.3	1,444	24.6	2,969	25.4
3	20,025	20.7	39,915	20.8	1,194	20.4	2,417	20.7
4	20,860	21.6	37,461	19.5	1,155	19.7	2,061	17.6
5 (most)	15,458	16.0	25,735	13.4	706	12.0	1,319	11.3
Not assigned	78	0.1	146	0.1	3	0.1	8	0.1
Smoking status								
Never	35,906	37.2	85,814	44.7	2,516	42.9	5,533	47.3
Ex	47,699	49.4	71,064	37.1	2,184	37.3	3,333	28.5
Current	12,984	13.4	30,870	16.1	1,161	19.8	2,511	21.5
Unknown	41	0.1	4,074	2.1	0	—	319	2.7
BMI (kg/m^2)								
>10 to 20	1,535	1.6	8,964	4.7	234	4.0	505	4.3
>20 to 25	14,564	15.1	59,765	31.2	1,944	33.2	3,638	31.1
>25 to 30	34,213	35.4	70,329	36.7	2,318	39.5	3,997	34.2
>30 to 40	38,193	39.5	33,811	17.6	1,225	20.9	2,033	17.4
>40	7,553	7.8	2,554	1.3	106	1.8	213	1.8
Unknown	572	0.6	16,399	8.6	36	0.6	1,310	11.2
Chronic disease								
Chronic kidney	19,161	19.8	16,606	8.7	839	14.3	441	3.8
Heart failure	5,035	5.2	4,222	2.2	161	2.8	98	0.8
Hypertension	62,216	64.4	67,156	35.0	2,423	41.3	2,346	20.1
Hypothyroidism	8,981	9.3	11,947	6.2	882	15.0	533	4.6
IHD	21,336	22.1	22,192	11.6	731	12.5	655	5.6
Peripheral vascular	5,665	5.9	4,394	2.3	374	6.4	124	1.1
Stroke and TIA	8,457	8.8	9,917	5.2	308	5.3	303	2.6

Note that patients can appear in multiple drug and disease categories, so percentages may sum to >100%. NA, not applicable. *Has prescription for drug class during 2007. †IMD (see RESEARCH DESIGN AND METHODS).

smoking, had a longer duration of diabetes (T2DM only), had serious comorbidities, and were living in more deprived areas.

Strengths and Limitations

The strengths of our analyses are the large size of the data set, including many older patients, length of follow-up (up to 7 years), and comprehensiveness of the infection outcomes by utilizing linkage of data from primary care, hospital episodes, and mortality. This large sample size has enabled us to consider the importance of several factors rarely considered in previous research, including key effect modifiers of the possible risk of infectious disease and more serious outcomes, including age, socioeconomic status, BMI, type and duration of diabetes, and medication use. This level of detail permits a more nuanced assessment of the characteristics of patients most

Table 2—Summary of infection rates during 2008–2015 and IRRs among people with diabetes versus matched control subjects

	People with T2DM (*n* = 96,630)		Control subjects (*n* = 191,822)	T2DM vs. control subjects	People with T1DM (*n* = 5,863)		Control subjects (*n* = 11,696)	T1DM vs. control subjects
Type of infection	Events	Rate†	Rate†	IRR* (95% CI)	Events	Rate†	Rate†	IRR* (95% CI)
Bone and joint infections	1,071	2.26	0.50	4.93 (4.34–5.61)	182	5.75	0.30	22.34 (12.12–41.20)
Cholecystitis (acute)	1,035	2.01	1.35	1.62 (1.48–1.77)	51	1.61	0.85	1.92 (1.22–3.03)
Endocarditis	100	0.20	0.13	1.84 (1.33–2.53)	8	0.25	0.08	6.70 (1.35–33.39)
Eye infection	10,986	21.92	17.42	1.26 (1.22–1.30)	638	20.14	14.58	1.38 (1.22–1.56)
Gastrointestinal	3,930	7.90	4.75	1.70 (1.63–1.78)	242	7.64	3.84	2.04 (1.69–2.46)
Infective otitis externa	7,091	14.18	12.11	1.16 (1.11–1.21)	493	15.56	11.08	1.39 (1.18–1.63)
Lower respiratory tract infection	50,609	101.11	73.36	1.40 (1.38–1.43)	2,554	80.63	54.91	1.50 (1.39–1.62)
Meningitis	37	0.07	0.05	1.64 (1.02–2.65)	5	0.16	0.03	6.34 (0.67–59.91)
Mycoses								
Candidiasis	11,025	22.20	10.78	2.11 (2.04–2.19)	721	22.76	10.15	2.39 (2.06–2.77)
Other fungal	11,954	23.80	18.99	1.25 (1.22–1.29)	783	24.72	17.87	1.40 (1.25–1.57)
Pneumonia	7,935	15.97	10.68	1.58 (1.53–1.64)	355	11.21	4.54	2.98 (2.40–3.69)
Sepsis	2,612	5.29	2.58	2.25 (2.10–2.40)	163	5.15	1.15	6.10 (4.28–8.69)
Sinusitis (acute)	6,605	13.21	12.06	1.09 (1.04–1.14)	525	16.57	14.15	1.14 (0.98–1.34)
Skin								
Cellulitis	18,974	38.35	19.75	2.03 (1.97–2.08)	995	31.41	11.76	2.84 (2.48–3.25)
Other	24,338	48.95	28.83	1.72 (1.69–1.76)	1,858	58.67	27.81	2.15 (1.98–2.35)
Surgical site	2,793	5.64	3.50	1.66 (1.57–1.76)	226	7.13	2.92	2.70 (2.14–3.40)
Tuberculosis	123	0.25	0.16	1.64 (1.23–2.20)	9	0.28	0.09	2.63 (0.84–8.24)
Upper respiratory tract infection (other)	25,843	51.51	40.56	1.27 (1.24–1.30)	1,686	53.22	41.61	1.29 (1.19–1.39)
UTI	28,705	57.50	38.95	1.53 (1.49–1.56)	1,490	47.04	27.25	1.81 (1.63–2.01)
Summary groups								
Any plus prescription	132,661	265.62	183.60	1.47 (1.46–1.49)	7,842	247.57	152.09	1.66 (1.59–1.74)
Any as hospitalization‡	19,097	38.72	21.89	1.88 (1.83–1.92)	1,178	37.19	11.67	3.71 (3.27–4.21)
Death from infection§	1,470	2.99	1.85	1.92 (1.75–2.10)	80	2.53	0.60	7.72 (4.47–13.33)

*IRRs estimated from Poisson model conditioned on match sets (age-sex-practice matched). †Rate per 1,000 per year. ‡Leading causes included pneumonia (35%), lower respiratory tract infection (15%), cellulitis (12%), gastrointestinal (8%), sepsis (7%), surgical site (6%), UTI (4%), and skin (other) (3%). §Leading causes included pneumonia (70%), sepsis (7%), lower respiratory tract infection (5%), gastrointestinal (5%), endocarditis (4%), and cellulitis (3%).

at risk for infectious diseases and poor infection outcomes who may benefit from more targeted education and monitoring strategies.

The large sample size allowed for a detailed and novel investigation of T1DM, overcoming the lack of statistical power in other smaller studies. Although some have expressed concerns about the quality of diabetes type coding in U.K. primary care data (21), and more complex algorithms to classify patients have been proposed (24), only a small proportion of patients with diabetes by 2008 had solely nonspecific codes, or codes for both types of diabetes on their electronic record. Although we cannot discount some misclassification, we required all patients coded as T1DM to be in receipt of insulin without any other antidiabetes medication in the year before baseline, creating a clearly defined group with T1DM, excluding patients otherwise. Any misclassification of true patients with T1DM being incorrectly coded as T2DM would be a small contribution to the larger overall group of T2DM. Regardless of misclassification, we have still produced striking findings between those coded as T1DM and T2DM in U.K. primary care. Our finding that about one in four (25.8%) patients with T2DM was not in receipt of any recent antidiabetes medication in 2007 is consistent with other recent data (24). Although our design allowed the population control subjects to receive diabetes diagnoses during follow-up, sensitivity analyses excluding these control subjects did not materially alter our findings.

Another potential limitation was that our analyses were limited to ages 40+ years in 2008, thus missing a significant proportion of all patients with T1DM. However, we do not expect that this would have impacted on our conclusion that patients with T1DM have greater risk. Indeed, it seems likely that the inclusion of younger adults would, if anything, enlarge differences in risk as baseline risks in the younger control populations would be extremely low.

We did not have comprehensive data on the type of infection or organism identified, as this is rarely available in primary care, although risk of bacterial and fungal infections appears to be increased most substantially among patients with diabetes. Our results were robust to adjustment for key confounding factors, but diagnostic bias could be a possible explanation for some of our findings, if there is a greater tendency to diagnose infections, prescribe antibiotics, admit to hospital, and/or code a death as infection related among patients with diabetes compared with the control subjects without diabetes. However, more serious infections diagnosed in the hospital would be supported by laboratory findings, and the associations with diabetes tended to be strongest for these infections. Most of

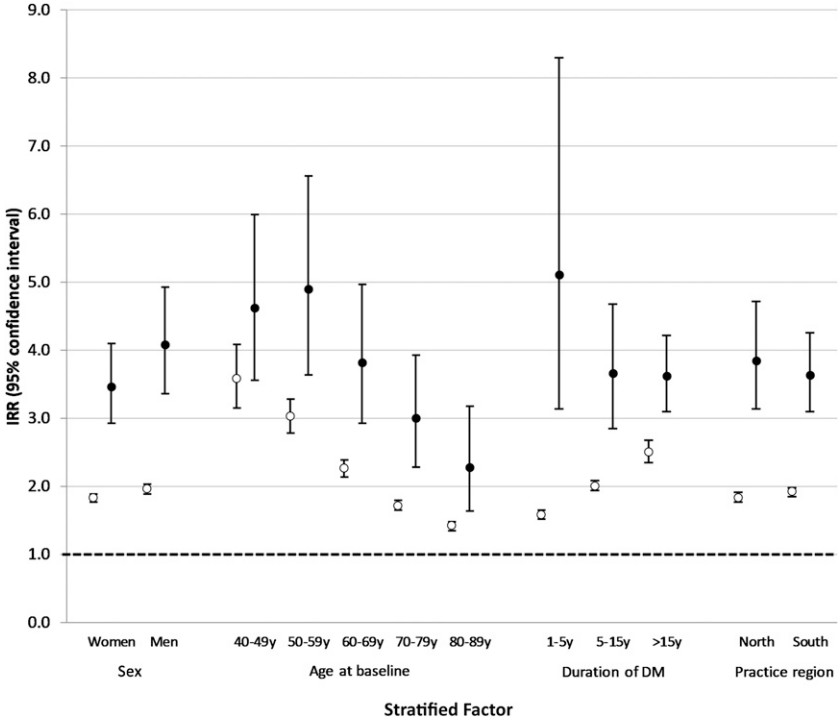

Figure 1—IRRs for hospitalization for infection during 2008–2015 between people with diabetes and matched control subjects stratified by sex, age, duration of diabetes, and practice region. IRRs were derived from Poisson models conditioned on match sets (age-sex-practice matched), which were fitted separately within each subgroup for T2DM vs. control subjects (white circles) and T1DM vs. control subjects (black circles). DM, diabetes mellitus; y, years.

our covariates are likely to be relatively stable over the period of the study, but medication use may vary, and therefore reported associations based on baseline usage may be attenuated.

Comparisons With Literature

Our finding of a 47% higher infection rate (accompanied by an antibiotic/antifungal/antiviral prescription) for T2DM relative to the general population compares very closely to a 50% higher rate of infection in a recent U.K. study (11). Previously in the U.K., a study also using CPRD data between 1990 and 2007 showed a 53% higher risk of urinary tract infection (UTI) for T2DM (12), identical to our finding (IRR 1.53). Few population studies have looked in detail at a range of specific infections; however, a large Canadian study of administrative data found elevated risks for people with diabetes in two separate cohorts (7). For example, their relative risks (RRs) for osteomyelitis (RR 4.2–4.4), sepsis (RR 2.5), and cellulitis (RR 1.8–1.9) are consistent with our IRRs of 4.9 (bone and joint infections, where 80% of diagnoses were for osteomyelitis), 2.3, and 2.0, respectively.

There have been fewer studies reporting on infection outcomes among people with T1DM. The largest study used the Australian diabetes register linked to mortality data between 2000 and 2010 to report all-ages standardized mortality ratios of 4.42 for T1DM and 1.47 for T2DM (9), which compares with IRRs of 7.72 and 1.92, respectively, in our study (age 40 years and over only). Similarly, the Australian data reported elevated mortality from septicemia and osteomyelitis among individuals with T1DM (9). Previously, the Dutch National Survey of General Practice compared infections during 2000–2002 between T1DM and T2DM and a control population (8), and whereas both types were associated with an increased overall risk, the differences between T1DM and T2DM were not consistent. The Dutch finding of a doubling of risk for UTI among patients with T1DM (odds ratio 1.96) (8) compares closely with IRR 1.81 in our study.

The near doubling of risk for hospitalization for infection for patients with T2DM that we found, compared with patients without diabetes, is consistent with data from the U.S. (17), Australia (14), and Canada (7). Among patients with T1DM, we estimated the RR to be greater (RR 3.71), higher than the RR 2.30 estimated from national data from Finland for hospitalization for bacterial infections (15). However, a Danish study of pneumonia-related hospitalizations during 1997–2005 also found similar higher risks compared with the general population for T1DM than T2DM (RR 4.43 vs. 1.23) (16). This study also reported that their risk estimates increased with duration of diabetes (16), a finding we replicated for T2DM. However, there was still an elevated risk (58%) among those diagnosed in the last 5 years, compared with people without diabetes, which compares closely with a 49% increase in hospital-treated infections in a large Danish study of incident T2DM (10).

We found that patients with T2DM on insulin at baseline were at double the risk of hospitalization for infection compared with those patients not using insulin, which may reflect some misclassification of patients with T1DM as T2DM, but more likely is a marker for severity of diabetes. A recent American study found a higher risk of hospitalization for infection among patients with diabetes with insulin therapy but was unable to distinguish between T1DM and T2DM (25). We observed that patients with T2DM on statins at baseline were at lower risk of hospitalization for infection, which builds on recent similar findings from the Netherlands, which found lower antibiotic prescribing among patients with T2DM who initiated statins (26). We did not however replicate this finding among patients with T1DM, and this warrants further exploration.

Implications

In higher-income countries, it is often thought that the risk of serious infections among people with diabetes is now reduced due to improved control of the disease and antibiotic therapy. This may be why current U.K. guidelines for T2DM do not currently mention infection as a possible complication or offer any specific guidelines for its management and prevention (27). However, our findings show substantially increased risks of infections requiring antibiotics and poor infection outcomes, particularly increases in incidence of potentially severe infections (e.g., endocarditis, sepsis, and pneumonia), hospitalization, and infection-related mortality. The associations with bone and joint infections were particularly striking.

Table 3—Mutually adjusted IRRs for hospitalization for infection during 2008–2015 among individuals with diabetes only

	People with T2DM (n = 96,630)				People with T1DM (n = 5,863)			
Baseline characteristic	IRR*	95% CI	IRR†	95% CI	IRR*	95% CI	IRR†	95% CI
Sex								
Women	1		1		1		1	
Men	1.09	1.05–1.12	1.12	1.08–1.16	0.95	0.81–1.11	1.00	0.85–1.17
Age (years)								
40–49	1		1		1		1	
50–59	0.99	0.90–1.10	1.02	0.92–1.12	1.14	0.90–1.44	1.01	0.80–1.27
60–69	1.26	1.14–1.39	1.25	1.13–1.38	1.70	1.38–2.09	1.25	1.00–1.56
70–79	1.90	1.73–2.09	1.82	1.65–2.01	2.42	1.93–3.04	1.53	1.18–1.98
80–89	3.14	2.84–3.47	2.85	2.57–3.16	4.25	3.37–5.36	2.38	1.79–3.16
Duration of diabetes (years)								
>0 to 5	1		1		1		1	
>5 to 15	1.30	1.25–1.35	1.12	1.08–1.17	0.86	0.64–1.16	0.83	0.61–1.13
>15	1.75	1.66–1.84	1.24	1.16–1.32	0.87	0.65–1.16	0.85	0.64–1.14
Current diabetes drugs‡								
Insulin	2.04	1.95–2.12	1.68	1.60–1.76	NA		NA	
Sulfonylureas	1.16	1.12–1.20	1.18	1.14–1.23	NA		NA	
Biguanides	0.97	0.94–1.00	0.94	0.91–0.97	NA		NA	
Other	1.01	0.94–1.08	0.94	0.87–1.01	NA		NA	
Other drugs‡								
Statins	0.93	0.89–0.97	0.83	0.80–0.87	1.13	0.96–1.33	0.94	0.79–1.12
Oral steroids	2.22	2.10–2.35	1.96	1.85–2.07	3.00	2.38–3.78	2.65	2.08–3.37
Deprivation quintile§								
1 (least)	1		1		1		1	
2	1.15	1.08–1.21	1.09	1.03–1.16	1.12	0.90–1.40	1.06	0.86–1.31
3	1.23	1.16–1.31	1.14	1.07–1.21	1.18	0.93–1.49	1.05	0.84–1.33
4	1.37	1.29–1.45	1.23	1.16–1.31	1.64	1.32–2.05	1.46	1.18–1.81
5 (most)	1.64	1.54–1.74	1.40	1.31–1.49	1.68	1.32–2.12	1.39	1.08–1.78
Smoking status								
Never	1		1		1		1	
Ex	1.27	1.22–1.32	1.17	1.12–1.21	1.13	0.95–1.36	1.00	0.84–1.19
Current	1.69	1.60–1.79	1.58	1.49–1.67	1.49	1.24–1.79	1.42	1.18–1.70
BMI (kg/m^2)								
>10 to 20	1.34	1.18–1.53	1.27	1.12–1.45	1.47	1.07–2.01	1.43	1.04–1.97
>20 to 25	1		1		1		1	
>25 to 30	0.93	0.88–0.97	0.93	0.89–0.98	0.96	0.81–1.14	0.95	0.80–1.12
>30 to 40	1.18	1.12–1.24	1.13	1.07–1.19	1.16	0.95–1.42	0.99	0.80–1.21
>40	2.09	1.94–2.26	1.86	1.73–2.01	1.91	1.18–3.08	1.32	0.83–2.09
Chronic disease								
Chronic kidney	1.49	1.43–1.56	1.26	1.21–1.31	2.35	1.96–2.82	1.94	1.63–2.32
Heart failure	2.18	2.07–2.30	1.56	1.47–1.64	2.46	1.81–3.35	1.52	1.08–2.16
Hypertension	1.00	0.96–1.04	0.96	0.92–0.99	1.43	1.20–1.70	1.27	1.07–1.51
Hypothyroidism	1.14	1.08–1.21	1.03	0.97–1.09	0.97	0.80–1.19	0.93	0.77–1.13
IHD	1.40	1.35–1.45	1.15	1.11–1.20	1.90	1.59–2.28	1.48	1.23–1.78
Peripheral vascular	1.74	1.64–1.84	1.30	1.23–1.38	1.95	1.58–2.40	1.31	1.05–1.62
Stroke and TIA	1.56	1.49–1.64	1.39	1.32–1.45	1.84	1.43–2.36	1.49	1.14–1.95

*IRRs estimated from Poisson model conditioned on match sets (age-sex-practice matched). NA, not applicable. †Additionally adjusted for all other factors listed in table. ‡Has prescription for drug class during 2007. §IMD (see RESEARCH DESIGN AND METHODS).

Osteomyelitis is a potentially devastating infection in any person, and among people with diabetes, it is associated with increased risk of limb amputation (28).

The higher rates of infection that we consistently observed among patients with T1DM, including a doubling of risk for infection-related mortality compared with patients with T2DM, may represent a greater underlying susceptibility. Diabetes seems to have many effects on infection risk (4), which include both an abnormal immune response and possibly increased susceptibility resulting from common complications of diabetes, such as neuropathy and vascular insufficiency. Hyperglycemic environments have been shown to damage neutrophil function (29) and also T-lymphocyte responses to infection (30). Additionally, polymorphonuclear neutrophil cell performance has been shown to be modified in patients with diabetes (31) and may predispose them to greater infection risk. Better understanding of potential mechanisms may increase the prospects for host- or pathogen-directed therapies to reduce risk (32), such as the use of metformin in tuberculosis patients (33).

Our study was able to report on the increased risk in hospitalization among older people with diabetes where such risks were three to four times higher among those aged 80–89 years compared with those aged 40–49 years. A high proportion of infection-related hospitalization

among older people was for pneumonia (35%). It is unclear at present whether improved diabetes management or earlier diagnosis of infectious disease might reduce these risks, and further studies of the prevention and management of infections among patients in primary care are required. Targeted education strategies among people with diabetes and their caregivers could also be trialed to reduce the risks of the most serious infection outcomes. These could potentially be highly effective in reducing risk and improving quality of life; of the large randomized controlled trials of diabetes management, only one (Diabetes Control and Complications Trial [DCCT]) reported on a very limited range of infection-related outcomes, although this showed both short- and long-term reductions in risk of infections in the intervention group (5).

Our definition of infectious disease in primary care was highly specific, requiring prescription of a relevant antibiotic, antifungal, or antiviral drug, in practice mostly an antibiotic. It seems possible that increased prescribing of antibiotics, among patients with diabetes could be contributing to the development of drug resistance and serious antibiotic-associated infections such as methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*, although there is limited direct evidence to assess this (34). Reassuringly, unlike a previous study from Denmark (10), we did not find evidence of differential prescribing of broader spectrum antibiotics among patients with diabetes, where there is most concern about the development of resistance (data not shown). However, infections requiring a prescription were very common among patients with both T1DM and T2DM at over 265 per 1,000 patients with diabetes per year, substantially higher than among age-sex–matched control subjects, which may help drive the development of antibiotic resistance.

The estimated population-attributable risk of infection associated with diabetes represents a considerable burden. For example, we estimate that 6.3% of all hospitalizations for infections in people aged 40–89 years in England during 2008–2015 are attributable to diabetes, almost 9% among those aged 50–69 years (Supplementary Table 5). For severe infections, this tends to be even higher; 12.4% of infection-related deaths could be attributed statistically to diabetes. With the U.K. population steadily aging, recent estimates have suggested that the prevalence of T2DM may have tripled between 1991 and 2013 (35), and there is likely to be a substantial an increase in the burden of diabetes-associated infections (36). Although T1DM is comparatively rare, it is also increasing globally (37) and is associated with a particularly high risk of infection.

Conclusion

This cohort study of over 100,000 people with diabetes and over 200,000 control subjects provides robust evidence that individuals with both T1DM and T2DM are at higher risk of a range of common infections, including skin infections, mycoses, pneumonia, and more serious rare infections such as sepsis, bone and joint infection, and endocarditis. They are also nearly twice as likely to be hospitalized with infection and to die of infection-related death, compared with age-sex-practice–matched control subjects. Patients with T1DM are at approximately double the risk of patients with T2DM for infection-related death. These data show that infectious disease among people with diabetes represents an important population burden. Future research should explore both education and management strategies with both patients and their caregivers to lessen this, such as whether improvements in glycemic control can reduce the risk of developing severe infections and poor treatment outcomes.

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The interpretation and conclusions contained in this report are those of the authors alone.

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Author Contributions. I.M.C. extracted the data from CPRD and performed the statistical analysis. J.A.C. and D.G.C. conceived the original idea for the study. S.D. and T.H. provided clinical input regarding the coding of infections. F.J.H. extracted the data from CPRD. All authors contributed to the development of the project methodology, interpretation of the results, and drafting of the manuscript and approved the final version. I.M.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium, International Diabetes Federation, 2017
2. Cockram CS, Lee N. Diabetes and infections. In *Textbook of Diabetes*. Oxford, Wiley-Blackwell, 2010, p. 835–855
3. Knapp S. Diabetes and infection: is there a link?–A mini-review. Gerontology 2013;59:99–104
4. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab 2012; 16(Suppl. 1):S27–S36
5. Pearson-Stuttard J, Blundell S, Harris T, Cook DG, Critchley J. Diabetes and infection: assessing the association with glycaemic control in population-based studies. Lancet Diabetes Endocrinol 2016;4: 148–158
6. Peleg AY, Weerarathna T, McCarthy JS, Davis TME. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev 2007;23:3–13
7. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26:510–513
8. Muller LM, Gorter KJ, Hak E, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis 2005; 41:281–288
9. Magliano DJ, Harding JL, Cohen K, Huxley RR, Davis WA, Shaw JE. Excess risk of dying from infectious causes in those with type 1 and type 2 diabetes. Diabetes Care 2015;38:1274–1280
10. Mor A, Berencsi K, Nielsen JS, et al. 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. Clin Infect Dis 2016;63: 501–511
11. Hine JL, de Lusignan S, Burleigh D, et al. Association between glycaemic control and common infections in people with type 2 diabetes: a cohort study. Diabet Med 2017;34:551–557
12. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). J Diabetes Complications 2012;26:513–516
13. Wilke T, Boettger B, Berg B, et al. Epidemiology of urinary tract infections in type 2 diabetes mellitus patients: an analysis based on a large sample of 456,586 German T2DM patients. J Diabetes Complications 2015;29:1015–1023
14. Hamilton EJ, Martin N, Makepeace A, Sillars BA, Davis WA, Davis TM. Incidence and predictors of hospitalization for bacterial infection in community-based patients with type 2 diabetes: the Fremantle Diabetes Study. PLoS One 2013;8:e60502
15. Simonsen JR, Harjutsalo V, Jarvinen A, et al.; FinnDiane Study Group. Bacterial infections in patients with type 1 diabetes: a 14-year follow-up study. BMJ Open Diabetes Res Care 2015;3: e000067
16. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. 2008; 31:1541–1545

17. Korbel L, Spencer JD. Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States. J Diabetes Complications 2015;29:192–195
18. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax 2013;68:1057–1065
19. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;44:827–836
20. NHS Digital. Quality and outcomes framework – prevalence, achievements and exceptions report–technical annex [article online], 2017. Available from https://digital.nhs.uk/media/33573/QOF-2016-17-Annex-2-Technical-annex/default/qof-1617-anx2-tech-anx. Accessed 1 January 2018
21. Tate AR, Dungey S, Glew S, Beloff N, Williams R, Williams T. Quality of recording of diabetes in the UK: how does the GP's method of coding clinical data affect incidence estimates? Cross-sectional study using the CPRD database. BMJ Open 2017;7:e012905
22. Department for Communities and Local Government. *English Indices of Deprivation 2010*. London, Department for Communities and Local Government, 2011
23. Hanley JA. A heuristic approach to the formulas for population attributable fraction. J Epidemiol Community Health 2001;55:508–514
24. Sharma M, Petersen I, Nazareth I, Coton SJ. An algorithm for identification and classification of individuals with type 1 and type 2 diabetes mellitus in a large primary care database. Clin Epidemiol 2016;8:373–380
25. Donnelly JP, Nair S, Griffin R, et al. Association of diabetes and insulin therapy with risk of hospitalization for infection and 28-day mortality risk. Clin Infect Dis 2017;64:435–442
26. Pouwels KB, Widyakusuma NN, Bos JHJ, Hak E. Association between statins and infections among patients with diabetes: a cohort and prescription sequence symmetry analysis. Pharmacoepidemiol Drug Saf 2016;25:1124–1130
27. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. NICE Guideline [NG28]. Available from https://www.nice.org.uk/guidance/ng28. Accessed 1 January 2018
28. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. Diabetes Care 1999;22:382–387
29. Stegenga ME, van der Crabben SN, Blümer RM, et al. Hyperglycemia enhances coagulation and reduces neutrophil degranulation, whereas hyperinsulinemia inhibits fibrinolysis during human endotoxemia. Blood 2008;112:82–89
30. Kumar M, Roe K, Nerurkar PV, et al. Reduced immune cell infiltration and increased pro-inflammatory mediators in the brain of type 2 diabetic mouse model infected with West Nile virus. J Neuroinflammation 2014;11:80
31. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med 1997;14:29–34
32. Ronacher K, van Crevel R, Critchley JA, et al. Defining a research agenda to address the converging epidemics of tuberculosis and diabetes: Part 2: underlying biologic mechanisms. Chest 2017;152:174–180
33. Restrepo BI. Metformin: dandidate host-directed therapy for tuberculosis in diabetes and non-diabetes patients. Tuberculosis (Edinb) 2016;101S:S69–S72
34. Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D.; Participants of the 3rd World Healthcare-Associated Infections Forum. Ready for a world without antibiotics? The Pensieres Antibiotic Resistance Call to Action. Antimicrob Resist Infect Control 2012;1:11
35. Holden SE, Jenkins-Jones S, Morgan CL, Peters JR, Schernthaner G, Currie CJ. Prevalence, glucose control and relative survival of people with type 2 diabetes in the UK from 1991 to 2013. Diabet Med 2017;34:770–780
36. McDonald HI, Nitsch D, Millett ERC, Sinclair A, Thomas SL. New estimates of the burden of acute community-acquired infections among older people with diabetes mellitus: a retrospective cohort study using linked electronic health records. Diabet Med 2014;31:606–614
37. DIAMOND Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006;23:857–866