Risk of infection in type 1 and type 2 diabetes compared to the general population: a matched cohort study

Running title (47 chars max): Diabetes type and infection risk

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Abstract

Objective

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

Research Design and Methods

A retrospective cohort study compared 102,493 English primary care patients aged 40-89 years with a DM diagnosis by 2008 (n=5,863 T1DM, n=96,630 T2DM) to 203,518 age-sex-practice matched controls without DM. Infection rates during 2008-15, compiled from primary care and linked hospital and mortality records, were compared across 19 individual infection categories. These were further summarised as any requiring a prescription, hospitalisation, or as cause of death. Poisson regression was used to estimate incidence rate ratios (IRRs) between: (i) people with diabetes and controls; (ii) T1DM and T2DM adjusted for age, sex, smoking, BMI and deprivation.

Results

Compared to controls without diabetes, DM patients had higher rates for all infections, with the highest IRRs seen for bone and joint infections, sepsis and cellulitis. IRRs for infection-related hospitalisations 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 vs. T2DM (death from infection IRR = 2.19, 95%CI 1.75-2.74). We estimate 6% of infection-related hospitalisations and 12% of infection-related deaths were attributable to DM.

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.

Words: 249

Diabetes mellitus (DM) is one of the leading causes of morbidity and mortality across the globe and the burden of disease is projected to increase from 415 to 642 million adults between 2015 and 2040.(1) The association between diabetes (DM) and infection is well known clinically,(2; 3), and has been linked to a number of causal pathways including impaired immune responses within the hyperglycaemic environment(4), as well as potentially other abnormalities associated with diabetes such as neuropathy and altered lipid 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 hospitalisation(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 datasets have overcome some of these limitations,(7-13) but do not always separate Type 1 (T1DM) from Type 2 (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 to 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 DM patients that may be associated with infection risk such as BMI, smoking, medication use, duration of diabetes, and co-morbidities or DM 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 T1DM and T2DM patients.

Research Design and Methods

Data Source

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

Study Design

We carried out a retrospective matched cohort study. Firstly, we identified all patients (n=1,488,921) who, as of 1/1/2008, 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 1/1/2008 for DM using nationally agreed-upon codes that practices are encouraged to use(20) (Supplemental figure S1). Then from the remaining pool of patients, we randomly selected two age-sex-practice matched controls. Matching on practice accounts for broad geographical differences and practice-related differences in clinical care and recording that may exist. While controls were required to have no DM code by 1/1/2008, they could be diagnosed as such after this date. Patients with DM (n=100) not able to be matched to any controls were excluded. All patients were followed until the earliest date of: death, de-registration from practice, practice leaving CPRD or 31/12/2015.

Classification of Type

Whilst DM type is generally recorded via specific Read codes, there are noted concerns around misclassification(21). We took a pragmatic approach to resolving this, cross-classifying DM Read codes (T1DM, T2DM or non-specific) up to 1/1/2008 with prescribing of anti-DM medication in 2007 (insulin, sulphonylureas, biguanides, other antidiabetic) to estimate type at baseline. As historical prescribing of anti-DM 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 (Supplemental figure S2), 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 anti-DM medication in 2007 as their type was uncertain (n=759); or if their only insulin was prior to 2007 (n=93); if they had no insulin in their record ever we assumed the code was wrong and classed 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 anti-DM 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 non-specific codes): if they were prescribed insulin in 2007 with no other anti-DM medication in their record they were classed as T1DM (n=724) unless they had codes for gestational DM and were thus excluded (n=12); if they were prescribed insulin only prior to 2007 with no other anti-DM medication they were excluded (n=47); all remaining patients were

assumed to be T2DM (n=3,329). Overall this resulted in 5,863 T1DM patients, 96,630 T2DM patients and 2,124 excluded patients who could not be clearly classified.

Classification of Infections

Infections during 2008-15 were classified into 19 different groupings using Read codes for GP data and ICD-10 classifications for hospital admissions and cause of death (Supplemental Table S1). 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 were counted for each patient. Three summary groups were defined: (i) any infection with a prescription for antibiotic/antifungal/antiviral drug (BNF 5.1) within 14 days of the diagnosis, (ii) any infection event which resulted in a hospital admission, (iii) any infection which 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 controls, Poisson regression conditioned on the matchsets 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 co-morbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, IHD, peripheral vascular disease, stroke & 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 DM. To look for effect modification, we stratified the model by the following variables: gender, 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 DM was estimated by calculating population attributable risk fractions (PAF).(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 1/1/2008 within each age-group to calculate the prevalence of DM. An overall PAF for DM was estimated by extending the formula, assuming DM type is a polytomous exposure(23).

Results

The baseline characteristics of patients with and without diabetes are shown in Table 1. T2DM patients were on average approximately 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 approximately five-and-a-half years, with 5.0% (n=10,139) of controls subsequently receiving a DM Read code during follow-up.

During follow-up, 56.9% of T2DM patients (n=54,972) had at least one infection accompanied by a prescription compared to 46.2% of controls (n=88,568) (Supplemental Table S2). The

disparity was broadly similar between T1DM patients (55.0%, n=3,226) and their controls (41.3%, n=4,828). For hospitalisations for infection, 15.7% of T2DM patients (n=15,1951) had at least one during follow-up compared to 9.8% of controls (n=18,706). Among T1DM, the disparity between patients with diabetes (14.6%, n=856) and controls (5.4%, n=630) was greater.

Table 2 summarises infection rates between people with diabetes and controls for T1DM and T2DM separately. The resulting IRRs were overall higher for T1DM due to lower rates in their (younger) controls, 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 hospitalisation, 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 co-morbidity between people with diabetes and controls (Supplemental table S3). 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 controls who developed diabetes during the study (Supplemental table S4), did not materially alter our findings.

The IRRs between those with diabetes and controls for infections requiring hospitalisation were stratified by gender, age, duration of diabetes and practice region (Figure 1). Although men had higher IRRs for both T1DM (4.07 vs. 3.46) and T2DM (1.96 vs. 1.82), confidence intervals overlapped for both types. The increase in relative risk compared to those without diabetes

declined with age for both types, but while risk increased with duration of diabetes for T2DM, this trend was not seen for T1DM.

Population attributable risk fractions (PAFs) were estimated for selected infection groups from Table 2 (Supplemental table S5). The highest PAFs for DM for individual infections were observed for bone and joint infections (22.6%) and sepsis (9.3%). We estimate 6.3% of hospitalisations for infections and 12.4% of deaths from infection were attributable to DM.

Table 3 summarises risk factor IRRs for infection requiring hospitalisation *within* T1DM and T2DM individuals 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 T2DM patients. Insulin prescribing among T2DM patients was a strong predictor, and explained much of the trend with duration of diabetes seen in Figure 2. In a mutually adjusted model, T2DM patients prescribed a statin in 2007 had lower infection hospitalisation rates (IRR=0.83, 95% CI 0.80-0.87), while 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 (Supplemental table S6). 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 to T2DM. However, the higher risks of hospitalisation 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 T1DM and T2DM patients.

Discussion

In a large English primary care database, we have detailed the increased risk of infection among people with diabetes compared to the general population. Organ systems where bacterial infections predominate (pneumonia, sepsis, endocarditis, skin, bone and joint infections) as well as fungal diseases (mycoses) were associated with substantial increases in magnitude among both T1DM and T2DM patients, but risks were consistently higher for T1DM. Among people with diabetes, those at highest risk of infection events and poor outcomes (hospitalisation) were patients who were older (aged ≥70 years), morbidly obese (BMI >40), currently smoking, had a longer duration of DM (T2DM only), had serious co-morbidities and were living in more deprived areas.

Strengths and limitations

The strengths of our analyses are the large size of the dataset including many older patients, length of follow-up (up to 7 years), and comprehensiveness of the infections outcomes by utilising 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, socio-economic status, BMI, type and duration of DM, and medication use. This level of detail permits a more nuanced assessment of the characteristics of patients most at risk of 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 DM type coding in UK primary care data,(21) and more complex algorithms to classify patients have been proposed,(24) only a small proportion of DM patients by 2008 had

solely non-specific codes, or codes for both types of diabetes on their electronic record. While we cannot discount some misclassification, we required all patients coded as T1DM to be in receipt of insulin without any other anti-DM medication in the year before baseline, creating a clearly defined T1DM group, excluding patients otherwise. Any misclassification of true T1DM patients 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 UK primary care. Our finding that about 1-in-4 (25.8%) T2DM patients were not in receipt of any recent anti-DM medication in 2007 is consistent with other recent data.(24) Although our design allowed the population controls to receive diabetes diagnoses during follow-up, sensitivity analyses excluding these controls did not materially alter our findings.

Another potential limitation was that our analyses were limited to ages 40+ in 2008, thus missing a significant proportion of all T1DM patients. However, we do not expect that this would have impacted on our conclusion that 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, though risk of bacterial and fungal infections appears to be increased most substantially among DM patients. 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 DM compared to the controls without DM. However, more serious infections diagnosed in hospital would be supported by laboratory findings, and the associations with DM tended to be strongest for these infections. Most of 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 UK study.(11) Previously in the UK, a study also using CPRD data between 1990-2007 showed a 53% higher risk of 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 RRs for osteomyelitis (RR=4.2-4.4), sepsis (RR=2.5), 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 2000-2010 to report all-ages SMRs 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 (ages 40 and over only). Similarly, the Australian data reported elevated morality from septicaemia and osteomyelitis among T1DM.(9) Previously, the Dutch National Survey of General Practice compared infections during 2000-2 between T1DM and T2DM and a control population,(8) and while 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 T1DM patients (OR=1.96)(8) compares closely to IRR=1.81 in our study.

The near doubling of risk for hospitalisation for infection for T2DM patients we found, compared to patients without diabetes, is consistent with data from the US,(17) Australia(14) and Canada.(7) Among T1DM patients we estimated the relative risk to be greater (RR=3.71), higher than the RR=2.30 estimated from national data from Finland for hospitalisation for bacterial infections.(15) However, a Danish study of pneumonia related hospitalisations during 1997-2005 also found similar higher risks compared to the general population for T1DM than T2DM (RR=4.43 vs. 1.23).(16) This study also reported 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 to 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 T2DM patients on insulin at baseline were at double the risk of hospitalisation for infection compared to those patients not using insulin, which may reflect some misclassification of T1DM patients as T2DM, but more likely is a marker for severity of diabetes. A recent American study found a higher risk of hospitalisation for infection among DM patients with insulin therapy, but was unable to distinguish between T1DM and T2DM.(25) We observed that T2DM patients on statins at baseline were at lower risk of hospitalisation for infection, which builds on recent similar findings from the Netherlands which found lower antibiotic prescribing among T2DM patients who initiated statins.(26) We did not however replicate this finding among T1DM patients, 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 UK guidelines for T2DM do not currently mention infection as a possible complication, nor 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, pneumonia), hospitalisation, and infection related mortality. The associations with bone and joint infections were particularly striking. Osteomyelitis is a potentially devastating infection in any person, and among people with diabetes is associated with increased risk of limb amputation.(28)

The higher rates of infection we consistently observed among T1DM patients, including a doubling of risk for infection related mortality compared with T2DM patients, 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. Hyperglycaemic environments have been shown to damage neutrophil function(29) and also T lymphocyte responses to infection.(30) Additionally, polymorphonuclear neutrophil (PMN) cell performance has been shown to be modified in DM patients,(31) and may predispose them to greater infection risk. Better understanding of potential mechanisms may increase 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 hospitalisation among older people with diabetes where such risks were 3-4 times higher among those aged 80-89 compared with those aged 40-49. A high proportion of infection related hospitalisation among older people was for pneumonia (35%). It is unclear at present whether improved DM 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 carers could also be trialled 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 RCTs of diabetes management, only one (DCCT) reported on a very limited range of infection related outcomes, though 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 anti-viral drug, in practice mostly an antibiotic. It seems possible that increased prescribing of antibiotics, amongst DM patients could be contributing to the development of drug resistance and serious antibiotic associated infections such as MRSA and Clostridium difficile, though 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 DM patients, where there is most concern about the development of resistance (data not shown). However, infections requiring a prescription were very common among both T1DM and T2DM patients at over 265 per 1000 DM patients per year, substantially higher than among age-sex matched controls, which may of itself 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 6.4% of all hospitalisations for infections in people aged 40-89 years in England during 2008-15 are attributable to diabetes; almost 9% among those aged 50-69 (Supplemental table S5). For severe infections, this tends to be even higher; almost 13% of infection related deaths could be attributed statistically to DM. With the UK population steadily ageing, recent estimates have suggested as much as a trebling of the prevalence in T2 diabetes between 1991-2013,(35) there is likely to be a substantial an increase

in the burden of DM associated infections.(36) Whilst T1DM is comparatively rare, it is also increasing globally(37) and is associated with a particularly high risk of infection.

Conclusions

This cohort study of over 100,000 people with diabetes and over 200,000 controls provides robust evidence that individuals with both T1DM and T2DM are at higher risk of a range of common infection including skin infections, bone and joint infection, mycoses, pneumonia, and more serious rare infections such as sepsis and endocarditis. They are also nearly twice as likely to be hospitalised with infection, and 2 to 8 times more likely to die of infection-related death, compared to age-sex and practice matched controls. T1DM patients are at roughly double the risk of T2DM patients. These data show that infectious disease among people with diabetes represent an important population burden. Future research should explore both education and management strategies with both patients and their carers to lessen this, such as whether improvements in glycaemic control can reduce the risk of developing severe infections and poor treatment outcomes.

Acknowledgments

Ethical approval

This study (protocol number 16_206R) was approved by the Independent Scientific Advisory Committee (ISAC) evaluation of protocols of research involving CPRD data in March 2017. St George's Joint Research and Enterprise Office, acting on behalf of the study sponsor, confirmed no further ethical review was required.

Conflicts of interests

We declare no competing interests.

Author contributions

JC and DC conceived the original idea for the study. TH and SdW provided clinical input regarding the coding of infections. IC and FH extracted the data from CPRD. IC carried out the statistical analysis. All authors contributed to the development of the project methodology, interpretation of the results, drafting of the paper, and approved the final version. IC 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.

Table 1: Summary of people with diabetes and matched controls on 1/1/2008

Baseline characteristic		People with T2DM (n=96,630)		T2DM Controls (n=191,822)		People with T1DM (n=5,863)		T1DM Controls (n=11.696)	
		n	%	n	%	n	%	n	%
Gender	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	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	>0 to 5 years	44,989	**46.6**	n/a	_	466	**8.0**	n/a	_
	>5 to 15 years	41,507	**43.0**	n/a	_	1,495	**25.5**	n/a	_
	>15 years	10,134	**10.5**	n/a	_	3,902	**66.6**	n/a	_
Current DM Drugs*	Insulin	13,967	**14.5**	n/a	_	5,863	**100.0**	n/a	_
	Sulphonylureas	31,846	**33.0**	n/a	_	0	**0.0**	n/a	_
	Biguanides	58,216	**60.3**	n/a	_	0	**0.0**	n/a	_
	Other	6,315	**6.5**	n/a	_	0	**0.0**	n/a	_
	None	24,898	**25.8**	n/a	_	0	**0.0**	n/a	_
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	>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**
	Not known	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 & TIA	8,457	**8.8**	9,917	**5.2**	308	**5.3**	303	**2.6**

* - Has prescription for drug class during 2007. † - Index of Multiple Deprivation (see methods)

Note - Patients can appear in multiple drugs and disease categories, so percentages may sum to >100%

Table 2: Summary of infection rates during 2008-15 and incidence rate ratios (IRRs) among people with diabetes versus matched controls

Type of Infection	People with T2DM (n=96,630)		T2DM Controls (n=191,822)	T2DM vs. Controls	People with T1DM (n=5,863)		T1DM Controls (n=11,696)	T1DM vs. Controls
	Events	Rate†	Rate†	**IRR*** (95%CI)	Events	Rate†	Rate†	**IRR*** (95%CI)
Bone & 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)
(Acute) Cholecystitis	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)
Gastro-Intestinal	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)
Mycoses - 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)
(Acute) Sinusitis	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)
Skin - 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)
TB	123	0.25	0.16	**1.64** (1.23-2.20)	9	0.28	0.09	**2.63** (0.84-8.24)
(Other) Upper Respiratory Tract Infection	25,843	51.51	40.56	**1.27** (1.24-1.30)	1,686	53.22	41.61	**1.29** (1.19-1.39)
Urinary Tract Infection	28,705	57.50	38.95	**1.53** (1.49-1.56)	1,490	47.04	27.25	**1.81** (1.63-2.01)
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 hospitalisation‡	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)

* – Incidence rate ratios estimated from Poisson model conditioned on matchsets (age-sex-practice matched), † - Rate per 1,000 per year

‡ – Leading causes: Pneumonia (35%), LRTI (15%), Cellulitis (12%), Gasto-Intestinal (8%), Sepsis (7%), Surgical Site (6%), UTI (4%), Skin-Other (3%)

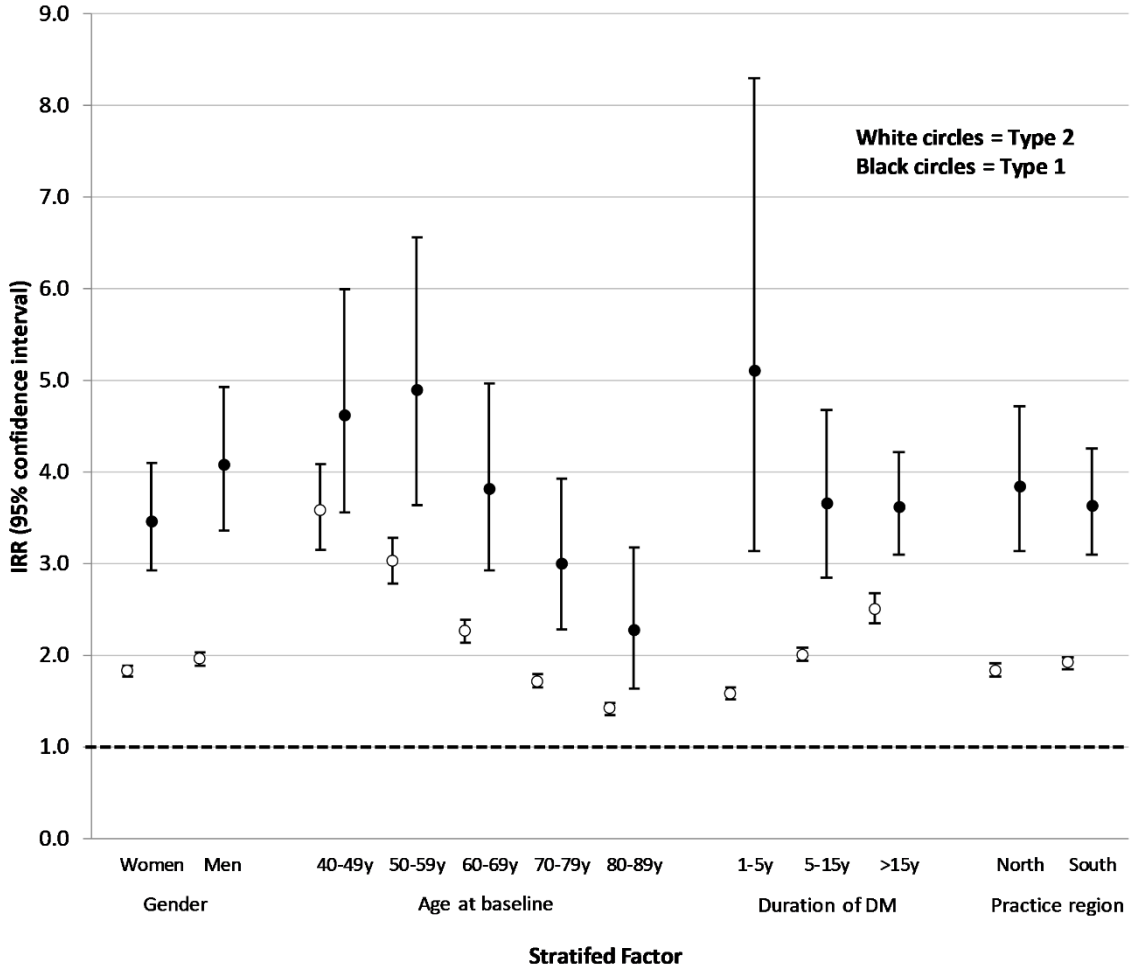
§ – Leading causes: Pneumonia (70%), Sepsis (7%), LRTI (5%), Gasto-Intestinal (5%), Endocarditis (4%), Cellulitis (3%)

Table 3: Mutually adjusted IRRs for hospitalisation for infection during 2008-15 among individuals with diabetes only

Baseline characteristic		People with T2DM (n=96,630)				People with T1DM (n=5,863)			
		IRR*	95%CI	**IRR†**	95%CI	**IRR***	95%CI	**IRR†**	95%CI
Gender	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	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	>0 to 5 years	**1**		**1**		**1**		**1**	
Diabetes	>5 to 15 years	**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 years	**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	Insulin	**2.04**	1.95-2.12	**1.68**	1.60-1.76	**n/a**		**n/a**	
DM	Sulphonylureas	**1.16**	1.12-1.20	**1.18**	1.14-1.23	**n/a**		**n/a**	
Drugs‡	Biguanides	**0.97**	0.94-1.00	**0.94**	0.91-0.97	**n/a**		**n/a**	
	Other	**1.01**	0.94-1.08	**0.94**	0.87-1.01	**n/a**		**n/a**	
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	1 – Least	**1**		**1**		**1**		**1**	
Quintile§	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	Never	**1**		**1**		**1**		**1**	
Status	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	>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	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
Disease	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 & 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

* – Incidence rate ratios estimated from Poisson model conditioned on matchsets (age-sex-practice matched), † – Additionally adjusted for all other factors listed in table, ‡ - Has prescription for drug class during 2007. § - Index of Multiple Deprivation (see methods).

Figure: Incidence rate ratios (IRRs) for hospitalisation for infection during 2008-15 between people with diabetes and matched controls stratified by sex, age, duration of diabetes and practice region. IRRs are derived from Poisson models conditioned on matchsets (age-sex-practice matched), which were fitted separately within each subgroup, for T1DM vs. controls and T2DM vs. controls individually.



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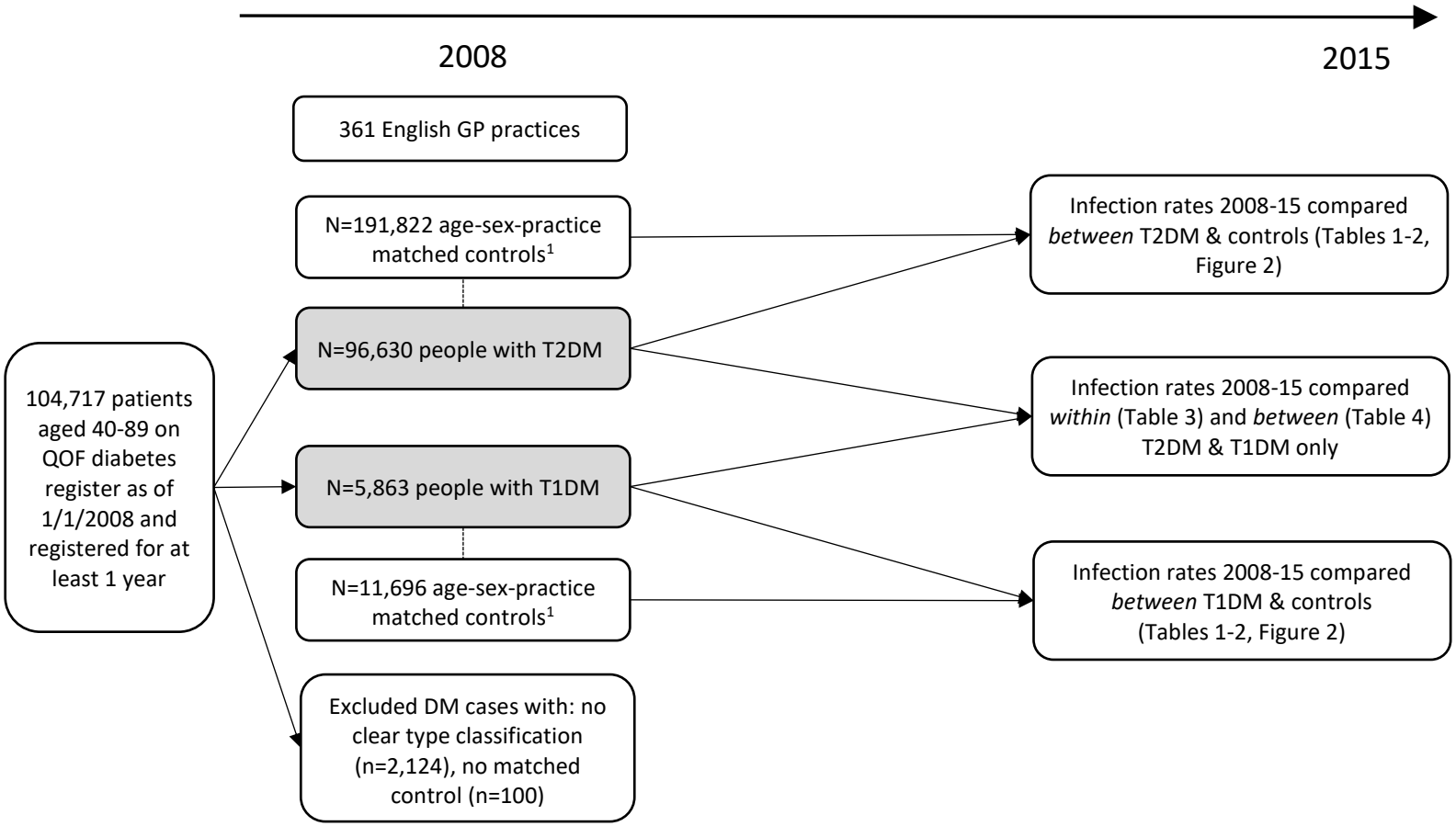
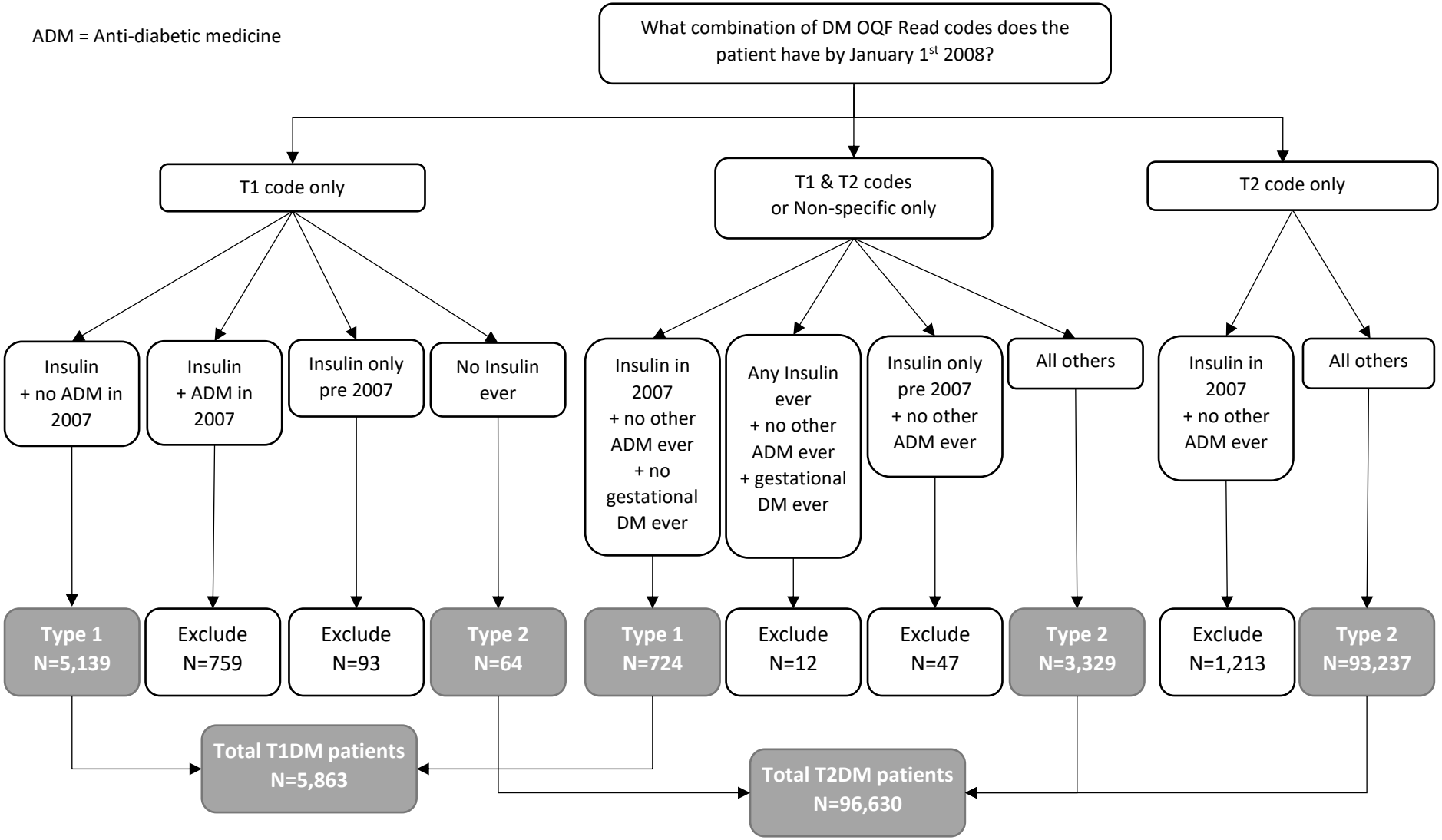
Supplemental Figure S1: Overall Study Design



[1] – Matched controls were required to have no Diabetic Read codes in their record as of 1/1/2008, but were allowed to become diabetic during follow-up

Supplemental Figure S2: Derivation of Type 1 and Type 2 Diabetes



Supplemental Table S1: ICD-10 and Read codes for Infections

	ICD-10	Read Codes
Bone & Joint Infections	M00, M86.0-M86.2	N010*, N30..-N303z, N308*, N309*, N30y.-N30zz
(Acute) Cholecystitis	K80, K80.4, K81.0, K81.9	J640*, J643*, J650*, J651z, J666.
Endocarditis	I01.1, I33, I33.0, I33.9, I38, I39, I39.8	A3642, A7422, A932*, A98y3, AB2y0, AB414, G011., G14z., G51*, G54z., G54z3, G54z4, G54zz, Gyu5E
Eye Infection	H10, H10.0, H10.2, H10.3, H10.5, H16*, H44.0,	F400*, F4A*, F4C0.-F4C05, F4C0z, F4C2*, F4C33, F4D1.-F4D13, F4D1z, F4D4., F4D5.
Gastro-Intestinal	A00-A02.0, A02.2-A09.9	A00..-A020., A022*, A02y.-A0z.., A3Ay2
Infective Otitis Externa	H60, H60.0-H60.4, H60.8-H60.9	F501*, FyuN0, FyuN1, FyuN3-FyuN7
LRTI	J20-J22	H06*, H07*
Meningitis	G00-G03.0., G03.8, G03.9	A360., A365., A366., A42*, A4z0., A4z1., A530., A54x1, A553., A721., AB2y2, AB32., Ayu8C, Ayu8D, F00*, F01*, F02.., F020., F02z., Fyu00, Fyu01, Fyu03, Fyu04
Mycoses - Candidiasis	B37*	AB2-AB2y., AB2y1-AB2z.
Mycoses - Other Fungal	B35-B36.9,B38-B49	AB…-AB1z, AB3..-ABz..
Pneumonia	A48.1, J12-J18	A3A4., H20..-H2C.., Hyu08-Hyu0H
Sepsis	A02.1, A20.7, A22.7, A26.7, A32.7, A40-A41.9, A48.3, O85	A021., A023., A202., A270100, A271100, A2706, A362., A38*, A396., A3Ay100, A3C*, A545., A98yz12, Ayu3E00- Ayu3H00, Ayu3J00, H5y0100, K190600, L090y00, L090z00, L40..11, L293*, L403*, SP25400
(Acute) Sinusitis	J01*	H01*
Skin - Cellulitis	H60.1, K12.2, L03*, N73.0-N73.2	F4D0.11, F4D14, H1y51, H1y71, J083.- J083z00, J0851, J54..11, J540.11, K2723, K2843, K403., K403100, K403z, K404., K4040, K405., K4051, K405z, M02..- M0200, M020z-M0210, M021z00, M02z.00, M03..00, M03..13, M030*, M031.00, M032-M034000, M034013- M03y000, M03z.00, M03z000, M03zz00, M08.., M080.00, M080.13- M086., M088.- M08y.
Skin - Other	A46, A49.0, J34.0, L00-L02.9, L04-L05.9, L08.1-L08.9, L30.3, L66.3, L66.4, L73.9, N73, N73.8-N73.9	A35.., A3B1*, J54..00, J54..12, J540., K403000, K403111, K4041-K404z, K4050, M0...- M01z0, M0201-M0205, M0211-M0213, M021z11, M02z.11-M02z.14, M03..11, M03..12, M031.11, M034011, M034012, M03y011, M03z100, M03zz11, M04..- M061.00, M062.- M07..00, M072.- M07y100, M07yz- M07z.13, M07z0- M07z2, M080.11, M080.12, M087., M09*, M0y*, M0z*, M244.00, M2440- M244111, M2443- M244z
Surgical Site	T79.3, T80.2, T81.4, T82.6, T82,7, T83.5, T83.6, T84.5-T84.7, T85.7, T87.4, T88.0	SP056, SP06.00, SP06.12- SP06A11, SP077, SP078, SP132, SP162, SP25.- SP253, SP255- SP25z, SP33*
TB	A15-A19.9	A1*, Ayu1.00, Ayu10, Ayu11, Ayu13- Ayu16, Ayu18, Ayu19, N304*, N305*, N306*
(Other) URTI	A37-A38, H65.0-H65.1, H66*, J02-J06.9, J36	A33*, A34*, F510.00- F5103, F5200-F520z, F526.-F528., F52z.11, H02*, H03*, H04*, H05*, H15.., Hyu01-Hyu03
UTI	N10-N12, N13.6, N15.1, N15.9, N30*	K103.12, K104.-K106., K10y.-K10z., K15*, K190*, Kyu10, Kyu1E

* - indicates a wild-card, so include all codes in hierarchy

Supplemental Table S2: Summary of infection events per patient during follow up (2008-15)

Number of Infections	People with T2DM (n=96,630)		T2DM Controls (n=191,822)		People with T1DM (n=5,863)		T1DM Controls (n=11,696)	
	n	%	n	%	n	%	n	%
Any plus prescription								
0	41,658	**43.1%**	103,254	**53.8%**	2,637	**45.0%**	6,868	**58.7%**
1	22,992	**23.8%**	42,959	**22.4%**	1,395	**23.8%**	2,484	**21.2%**
2	12,806	**13.3%**	20,738	**10.8%**	745	**12.7%**	1,083	**9.3%**
3	7,482	**7.7%**	10,702	**5.6%**	404	**6.9%**	580	**5.0%**
4	4,370	**4.5%**	5,829	**3.0%**	273	**4.7%**	304	**2.6%**
5	2,772	**2.9%**	3,445	**1.8%**	165	**2.8%**	142	**1.2%**
6+	4,550	**4.7%**	4,895	**2.6%**	244	**4.2%**	235	**2.0%**
Any as hospitalisation								
0	81,435	**84.3%**	173,116	**90.3%**	5,007	**85.4%**	11,066	**94.6%**
1	11,865	**12.3%**	15,522	**8.1%**	641	**10.9%**	524	**4.5%**
2+	3,330	**3.5%**	3,184	**1.7%**	215	**3.7%**	106	**0.9%**

Supplemental Table S3: Adjusted incidence rate ratios for Infection during 2008-15 among all patients with diabetes compared to matched controls

	IRR[1] (95%CI)	**IRR[2]** (95%CI)	**IRR[3]** (95%CI)
Bone & Joint Infections	**5.54** (4.89-6.28)	**5.19** (4.52-5.96)	**4.47** (3.78-5.29)
(Acute) Cholecystitis	**1.63** (1.49-1.78)	**1.30** (1.18-1.44)	**1.26** (1.12-1.43)
Endocarditis	**1.95** (1.42-2.68)	**1.70** (1.18-2.45)	**1.53** (0.97-2.43)
Eye Infection	**1.27** (1.23-1.30)	**1.21** (1.18-1.25)	**1.16** (1.11-1.21)
Gastro-Intestinal	**1.72** (1.65-1.80)	**1.58** (1.50-1.66)	**1.41** (1.33-1.50)
Infective Otitis Externa	**1.17** (1.12-1.22)	**1.03** (0.99-1.08)	**0.98** (0.93-1.04)
LRTI	**1.41** (1.38-1.43)	**1.24** (1.22-1.26)	**1.15** (1.12-1.17)
Meningitis	**1.82** (1.12-2.96)	**1.52** (0.88-2.62)	**1.88** (0.93-3.80)
Mycoses - Candidiasis	**2.12** (2.05-2.20)	**1.81** (1.75-1.89)	**1.70** (1.62-1.78)
Mycoses - Other Fungal	**1.26** (1.23-1.30)	**1.16** (1.12-1.19)	**1.13** (1.09-1.17)
Pneumonia	**1.62** (1.56-1.68)	**1.59** (1.53-1.66)	**1.48** (1.41-1.55)
Sepsis	**2.34** (2.19-2.50)	**2.19** (2.04-2.36)	**2.03** (1.86-2.21)
(Acute) Sinusitis	**1.09** (1.05-1.14)	**1.02** (0.97-1.07)	**0.95** (0.90-1.01)
Skin - Cellulitis	**2.05** (2.00-2.11)	**1.51** (1.46-1.56)	**1.38** (1.33-1.43)
Skin - Other	**1.75** (1.71-1.79)	**1.50** (1.47-1.54)	**1.42** (1.38-1.46)
Surgical Site	**1.71** (1.62-1.81)	**1.42** (1.33-1.51)	**1.24** (1.15-1.33)
TB	**1.68** (1.27-2.23)	**2.49** (1.79-3.46)	**2.70** (1.80-4.05)
(Other) URTI	**1.27** (1.25-1.30)	**1.16** (1.13-1.18)	**1.08** (1.06-1.11)
UTI	**1.54** (1.50-1.57)	**1.46** (1.42-1.49)	**1.37** (1.33-1.42)
Any plus prescription	**1.48** (1.46-1.50)	**1.31** (1.29-1.32)	**1.22** (1.20-1.24)
Any as hospitalisation[1]	**1.93** (1.88-1.98)	**1.74** (1.70-1.79)	**1.59** (1.54-1.64)
Death from infection[2]	**2.00** (1.83-2.20)	**2.22** (2.01-2.44)	**1.97** (1.76-2.20)

Note: Patients with Type 1 and Type 2 DM have been combined in above table (n=102,493) and compared to controls (n=203,518).

IRR[1] – Incidence rate ratios derived from Poisson models conditioned on age, sex and practice

IRR[2] – IRR[1] additionally adjusted for BMI, smoking and Index of Multiple Deprivation (IMD) quintile.

IRR[3] – IRR[2] additionally adjusted for the following co-morbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, IHD, peripheral vascular disease, stroke & TIA) and whether they had received a prescription for a statin or oral steroid in 2007.

Supplemental Table S4: IRR's for models excluding controls who become diabetic during the study

	T2DM (n=96,267) vs. Controls with no DM throughout (n=182,161)	**T1DM (n=5,854) vs. Controls with no DM throughout (n=11,218)**
	IRR (95%CI)	**IRR** (95%CI)
Any plus prescription	**1.50** (1.48-1.51)	**1.71** (1.63-1.79)
Any as hospitalisation[1]	**1.91** (1.86-1.96)	**3.76** (3.31-4.28)
Death from infection[2]	**1.89** (1.72-2.08)	**7.04** (4.10-12.11)

IRR – Incidence rate ratios estimated from conditional Poisson model (age-sex-practice matchsets)

Supplemental Table S5: Population attributable risk fractions calculations for selected infection groups

Category	Age Group					All Ages
	40-49	50-59	60-69	70-79	80-89	40-89
Total study population[1]	542,581	432,542	385,903	277,577	182,087	1,820,690
Prevalence of T2DM[2]	1.40%	3.86%	6.98%	10.53%	8.89%	5.31%
Prevalence of T1DM[2]	0.40%	0.36%	0.29%	0.26%	0.17%	0.32%
Bone & Joint Infections						
- T2DM IRR[3]	10.34	7.40	4.87	5.20	2.38	
- T2DM PAF[4]	**11.53%**	**19.80%**	**21.26%**	**30.64%**	**10.92%**	**19.03%[5]**
- T1DM IRR[3]	14.57	39.65	36.77	28.89	5.77	
- T1DM PAF[4]	**5.10%**	**12.16%**	**9.40%**	**6.88%**	**0.81%**	**5.82%[5]**
- Combined PAF[6]	**15.55%**	**27.82%**	**27.21%**	**34.02%**	**11.56%**	**22.64%[5]**
Sepsis						
- T2DM IRR[3]	3.68	3.36	2.45	2.19	1.81	
- T2DM PAF[4]	**3.60%**	**8.35%**	**9.22%**	**11.15%**	**6.73%**	**8.14%[5]**
- T1DM IRR[3]	9.24	6.06	6.51	5.95	3.45	
- T1DM PAF[4]	**3.16%**	**1.78%**	**1.57%**	**1.29%**	**0.42%**	**1.34%[5]**
- Combined PAF[6]	**6.54%**	**9.85%**	**10.52%**	**12.17%**	**7.09%**	**9.29%[5]**
Hospitalisations for Infection						
- T2DM IRR[3]	3.58	3.02	2.26	1.71	1.42	
- T2DM PAF[4]	**3.48%**	**7.23%**	**8.08%**	**6.99%**	**3.57%**	**5.71%[5]**
- T1DM IRR[3]	4.61	4.89	3.81	2.99	2.28	
- T1DM PAF[4]	**1.41%**	**1.37%**	**0.81%**	**0.52%**	**0.22%**	**0.69%[5]**
- Combined PAF[6]	**4.79%**	**8.41%**	**8.76%**	**7.45%**	**3.77%**	**6.31%[5]**
Death from Infection						
- T2DM IRR[3]	8.37	5.75	3.68	1.87	1.60	
- T2DM PAF[4]	**9.32%**	**15.50%**	**16.20%**	**8.42%**	**5.09%**	**9.75%[5]**
- T1DM IRR[3]	15.34	47.11	10.40	9.76	2.90	
- T1DM PAF[4]	**5.37%**	**14.18%**	**2.65%**	**2.28%**	**0.32%**	**3.51%[5]**
- Combined PAF[6]	**13.76%**	**25.85%**	**18.07%**	**10.32%**	**5.38%**	**12.44%[5]**

[1] - Total number of patients aged 40-89 actively registered on January 1st 2008 from 361 practices in study

[2] - Estimated from total number of patients with DM type (Table 1) divided by total study population in each age group

[3] - IRR from conditional Poisson regression stratified by age group (as shown in Figure 2)

[4] - Within each age group, PAF estimated using formula = [Proportion with DM type * (IRR-1)] / [1+ Proportion with DM type * (IRR-1)]

[5] - For all-ages PAF, the individual age-group PAF's are weighted by an estimate of the number of infections in the general population in each age-group and summed. Since we do not have access to the records of non-controls without DM, to estimate the distribution of each infection group by age-group we have had to assume that the distribution of infections is equivalent between matched controls and non-controls without DM.

[6] - The PAF estimates for all DM combined were calculated by extending the formula PAF to a scenario where the exposure is polytomous. In this case, it is assuming that T1DM and T2DM are non-overlapping exposures (see Hanley, *J Epidemiol Community Health* 2001;55:508–514)

Supplemental Table S6: IRR's for infection during 2008-15 for T1DM vs. T2DM in combined model

	Type 1 vs Type 2 (n=102,493)		
	IRR[1]	**IRR[2]**	**IRR[3]**
Selected Infections			
- Bone & Joint Infections	**2.49** (2.00-3.08)	**2.86** (2.31-3.54)	**2.54** (2.05-3.14)
- Pneumonia	**1.30** (1.15-1.47)	**1.47** (1.30-1.66)	**1.40** (1.24-1.58)
- Sepsis	**1.48** (1.23-1.79)	**1.72** (1.43-2.08)	**1.59** (1.32-1.92)
Grouped Infections			
- Any plus prescription	**0.95** (0.92-0.99)	**1.09** (1.05-1.13)	**1.06** (1.02-1.10)
- Any as hospitalisation[1]	**1.30** (1.20-1.40)	**1.63** (1.50-1.76)	**1.52** (1.40-1.64)
- Death from infection[2]	**1.93** (1.53-2.44)	**2.19** (1.75-2.74)	**2.05** (1.64-2.56)

Note: Patients with Type 1 DM (n=5,863) and Type 2 DM (n=96,630) have been directly compared with in above table.
IRR[1] – Incidence rate ratios derived from a Poisson model adjusted for age and sex.
IRR[2] – IRR[1] additionally adjusted for BMI, smoking and Index of Multiple Deprivation (IMD) quintile.
IRR[3] – IRR[2] additionally adjusted for the following co-morbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, IHD, peripheral vascular disease, stroke & TIA) and whether they had received a prescription for a statin or oral steroid in 2007.