**Glycaemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study**

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**Abstract**

Objective

Diabetes mellitus (DM) increases risk of infections, but the impact of better control has not been thoroughly investigated.

Research Design and Methods

Using English primary care data, average glycated haemoglobin (HbA1c) during 2008-9 was estimated for 85,312 DM patients aged 40-89. Infection rates during 2010-5, compiled from primary care, linked hospital and mortality records, were estimated across 18 infection categories and further summarised as any requiring a prescription, hospitalisation, or as cause of death. Poisson regression was used to estimate adjusted incidence rate ratios (IRRs) by HbA1c categories across all DM, and T1DM and T2DM separately. IRRs were also compared to 153,341 age-sex-practice matched controls without DM. Attributable fractions (AF%) among DM patients were estimated for an optimal control scenario (HbA1c 6-7%; 42-53 mmol/mol).

Results

Long-term Infection risk rose with increasing HbA1c for most outcomes. Compared to non-DM patients, both DM patients with optimal control (HbA1c=6-7%; 42-53 mmol/mol, IRR=1.41 95%CI 1.36-1.47) and poor control (HbA1c≥11%;97 mmol/mol, IRR=4.70, 95%CI 4.24-5.21) had elevated hospitalisation risks for infection. In patients with T1DM and poor control this risk was even greater (IRR=8.47, 95% CI 5.86-12.24). Comparisons within patients with DM confirmed the risk of hospitalisation with poor control (IRR=2.70, 95% CI 2.43-3.00) after adjustment for duration and other confounders. AF% attributed to poor control were high for serious infections particularly bone and joint infections (46%), endocarditis (26%), tuberculosis (23%), sepsis (21%), infection-related hospitalisation (17%) and mortality (16%).

Conclusions

Poor glycaemic control is powerfully associated with serious infections and should be a higher priority.

**Introduction**

Infections are widely considered to be a source of significant health care costs and reduce the quality of life among people with diabetes mellitus (DM)([1](#_ENREF_1)). Nevertheless, relatively few large well-designed epidemiological studies have explored relationships between poorer control of diabetes and infections; previous studies have important limitations([1](#_ENREF_1)). Most randomised controlled trials of DM control have not investigated the effect of improved glycaemic control on infections, and are unlikely to do so at present due to the high cost and lack of good quality supporting observational evidence. One early landmark RCT, the Diabetes Control and Complications Trial (DCCT), reported infection outcomes in a very restricted population (1441 people with type 1 [T1DM] aged 13-39)([2](#_ENREF_2)) showing substantial reductions in risk of vaginal infections in the “tight control” group compared with the control arm([2](#_ENREF_2)). The benefit from tighter control was also seen after the trial end in observational follow-up([1](#_ENREF_1), [3](#_ENREF_3)). However, data on other infections in older people with type 2 (T2DM) where infections are more burdensome, and risks of tighter glycaemic control are higher, is urgently needed. A recent review of higher quality population based epidemiological studies found clinically important (roughly 1.5 to 3.5 times higher) infection risks associated with poorer DM control in some studies (usually defined as a glycated haemoglobin [HbA1c] level greater than about 7-8% (53-64 mmol/mol) ([1](#_ENREF_1)). However, studies were inconsistent, generating uncertainty about the evidence.

A key concern with previous work is that the measurement of HbA1c was usually made at or near to the time of the infection, so any association could be explained by reverse causality. Any infectious disease episode can itself have an adverse impact on glycaemic control, a process known as “stress hyperglycaemia”([4](#_ENREF_4)); hence blood glucose or HbA1c measurements near the time of an infection may be elevated, rendering it difficult to determine the chronology and relationship between the two. Several studies with serial HbA1c measurements have shown that the stress hyperglycaemia response can be very substantial([4-6](#_ENREF_4)). Another important issue is that studies of incident diabetes often use measurements of HbA1c obtained during initial presentation, and these typically do not represent subsequent levels after initiation of treatment; use of such measurements may obscure associations between usual HbA1c level and infection risk. Other limitations of previous work include lack of consideration of type of DM (especially T1DM) and fewer older people with DM. Our study uses a large English primary care database with repeated HbA1c measurements, where we can classify individuals more precisely in terms of their baseline glycaemic control as well as ensuring that these HbA1c measurements were made before the infection.

**Methods**

*Data Source*

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the United Kingdom (UK) population([7](#_ENREF_7)). Our study is based on 361 general practices in England only with anonymous linkage to Hospital Episodes Statistics (HES) and Office for National Statistics (ONS) death registration data ([8](#_ENREF_8)).

*Study Design*

We carried out a further analysis of a retrospective matched cohort study that we have previously reported on ([8](#_ENREF_8)) (Supplemental Figure S1). Initially we identified all patients with DM (n=104,717) as of 1 January 2008, who were alive and actively registered for at least 1 year, aged 40-89 and who had a Read code for DM (nationally agreed-upon codes that practices are encouraged to use([9](#_ENREF_9)). Two age-sex-practice matched controls were selected from the remaining pool of similarly registered patients with no DM diagnosis by 1 January 2008. Patients with DM (n=100) not able to be matched to any controls were excluded. Patients with DM were classified as T1DM, T2DM, or “type uncertain” using a combination of DM Read codes, and prescribing of anti-DM medication (insulin, sulphonylureas, biguanides, other antidiabetic) to estimate type as of 1 January2008([8](#_ENREF_8)) – see Supplemental Figure S2.

*Ascertainment of HbA1c level*

From the original cohort, we collated all recorded HbA1c measurements on the 104,617 DM patients between 1 January 2008 and 31 December 2009 (Supplemental Figure S1), and calculated mean HbA1c for each patient. From these we subsequently excluded patients no longer active in CPRD on 1 January 2010 (n=15,416): 6636 had died during 2008-9, 5,638 had transferred out of their practice, and 3,412 were from a practice which stopped contributing data to CPRD. Among active patients, n=2,932 had no HbA1c measured during 2008-9 and n=1,496 had no remaining controls by 1 January 2010. A small number of patients (n=267) who had been classed as T1DM were not prescribed insulin during 2008-9 and re-classed as “Type uncertain”. This resulted in 85,312 patients with DM (n=78,964 T2DM, n=4,496 T1DM, n=1,852 uncertain), and 153,341 matched controls, eligible on 1 January 2010 for our analysis of subsequent infection. All patients were followed until the earliest date of: death, de-registration from practice, practice leaving CPRD or 31 December 2015. Mean follow-up time for all patients was approximately 4.2 years.

To minimise the potential for infections influencing HbA1c level among the 307,652 total HbA1c measurements, we excluded any measurements (n=5,029, 1.6%) made within +14 days of a recorded infection event occurring within the baseline HbA1c assessment period (2008-09).

*Classification of Infections*

Infections subsequent to the 2-year HbA1c assessment period, recorded between 2010-15, were classified into 18 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 recordings within 90 days were assumed to be 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 (British National Formulary section 5.1)([10](#_ENREF_10)) 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 estimate and compare incidence rate ratios (IRRs) of infection (Stata version 13), with an offset accounting for total days registered. We first carried out comparisons using non-DM patients as the reference group. We fitted a model conditioned on the matchsets to estimate differences in rates of infections between DM and non-DM patients. This model implicitly adjusts for age, sex and practice. We also adjusted for smoking, BMI and IMD (the Index of Multiple Deprivation [IMD] a composite small-area ecological measure of deprivation based on postcodes([11](#_ENREF_11))). Additional adjustment for co-morbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, ischaemic heart disease, peripheral vascular disease, stroke & transient ischaemic attack, and chronic obstructive pulmonary disease) was also performed. In (non-conditional) Poisson models we then fitted categories of mean HbA1c (<6%; [42 mmol/mol], ≥6-<7% [42-53 mmol/mol], ≥7-<8%; [53-64 mmol/mol], ≥8-<9% [64-75 mmol/mol], ≥9-<10%; [75-86 mmol/mol], ≥10-<11%; [86-97 mmol/mol], ≥11%; [97 mmol/mol], with non-DM patients firstly as the comparison group, now adjusting for age and sex. We stratified these models by age (40-64, 65-89) to describe any effect modification by age. Finally, we re-fitted these models but only on DM patients, using HbA1c between ≥6-<7% (42-53 mmol/mol) as the reference category. To account for clustering by practice, all models used a sandwich estimator to obtain robust standard errors.

Sensitivity analyses were performed using alternate summaries of glycaemic control. These included: fitting HbA1c as a continuous variable, using the median value, and incorporating a time-dependent element to the value to account for measurements taken during follow-up (a repeated measures analysis using mean HbA1c calculated every January 1 for each individual if still active based on measurements from the previous 2 year period). We also extended the exclusion period for HbA1c measurements around any infection from 14 days up to 30 or 90 days. None of these approaches changed our findings in any meaningful way, so we retained the baseline summary for the main results.

Within diabetics we calculated attributable risk fractions (AF%)([12](#_ENREF_12)) for all infections, by estimating the percentage of infections that would not have occurred if all individuals had the same infection risk as those in the optimal control group of HbA1c between 6-7% (42-53 mmol/mol). Confidence intervals (CI) were obtained by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.

**Results**

Supplemental Table S2 summarises the distribution of mean HbA1c during 2008-9 for all patients with DM by age, sex, duration of DM, BMI, smoking and deprivation. The distribution of mean HbA1c during 2008-9 is also shown in Supplemental Figure S3 by DM type. Mean HbA1c was approximately 1% higher for T1DM (8.3%, s.d.=1.4;) versus T2DM (7.4%, s.d.=1.4) patients, with patients with T1DM more than twice as likely to have a mean HbA1c ≥9 (26.9% vs. 11.0%). Patients whose DM type we classified as uncertain had mean HbA1c levels very similar to T1DM patients (8.3%, s.d.=1.6). The mean number of HbA1c measurements recorded during 2008-9 was similar in both types (T1DM=3.5, T2DM=3.6). T2DM patients were on average approximately 10 years older than T1DM (66.9 vs. 56.1 years in 2008) and far more likely to have been diagnosed in the last 5 years (47.2% vs. 7.3%). Poorer glycaemic control (increasing categories of HbA1c) were associated with younger age, being diagnosed with DM for longer, deprivation and obesity (Supplemental Table S2). Low HbA1c (<6%) was unusual (1.7% of DM patients), but more common at older age and strongly associated with BMI; 1-in-5 (20.5%) underweight patients (BMI<20) had a mean level below 6%.

*Glycaemic control and infection risk among DM patients compared to controls without DM*

Crude infection rates during 2010-5 estimated across 18 different categories confirmed consistently higher rates among patients with DM (Supplemental Figure S4). For many infections (e.g. skin, cellulitis, candidiasis, bone and joint), crude rates tended to rise with increasing HbA1c. Some infections (e.g. mycoses – other fungal, sepsis) also displayed elevated rates among DM patients in the lowest HbA1c category (<6%).

Table 1 summarises adjusted infection risk (any plus prescription, any hospitalisation and death from infection) between patients with and without DM, by firstly comparing the increase in risk associated with DM (“DM vs non-DM”), and then comparing HbA1c categories with non-DM retained as the reference category. Associations between infection and DM were more marked for patients with T1DM (e.g. hospitalisation IRR=3.34, 95% CI 2.82-3.96) than for T2DM (IRR=1.70, 95%CI 1.64-1.76). Due to the small number of deaths among T1DM patients, comparisons for death from infection were estimated for all DM combined (IRR=2.44, 95%CI 2.13-2.79). Additional adjustment for co-morbidity attenuated differences, but did not explain the association between DM and infection (Supplemental Table S3).

There were clear trends of increasing risk of infection with poorer levels of glycaemic control (Table 1). However, even diabetics with good control, were at raised risk compared to the matched non-diabetic controls. Thus compared to non-DM patients, both DM patients with good control (mean HbA1c=6-7%, IRR=1.41 95%CI 1.36-1.47) and those with poor control (mean HbA1c≥11%;, IRR=4.70, 95%CI 4.24-5.21) had elevated hospitalisation risks for infection. These risks were higher among patients with T1DM. For example, T1DM patients with mean HbA1c ≥11%;, had over 8 times the risk of hospitalisation than their matched non-DM patients (IRR=8.47, 95%CI 5.86-12.24), while for T2DM this was only 4 times higher (IRR=4.31, 95% CI 3.88-4.80).

The trend between increasing HbA1c and infection risk was present in both younger (40-64 years) and older patients (65-89 years) with DM (Figure 1). Associations were attenuated in the older groups, but remained clinically important. Older patients with DM and mean HbA1c ≥10%, were still approximately five times more likely to die from infection during follow-up compared to patients without DM, and almost three times as likely to be hospitalised.

*Glycaemic control and infection risk within DM patients*

When statistical models were fitted to patients with DM only, adjusting now for age and sex differences and mean HbA1c (Table 2), the higher risks of infection with poorer glycaemic control were confirmed. For example, patients with mean HbA1c ≥11% were almost 3 times as likely to be hospitalised for infection (IRR=2.95, 95%CI 2.66-3.28). Further adjustment for co-morbidity did not substantially alter the risk estimates (Supplemental Table S3). T1DM patients still had higher rates of hospitalisation (IRR=1.12, 95%CI 1.01-1.24) and death from infection (IRR=1.42, 95% 1.03-1.96) than T2DM patients, even after accounting for duration of DM. Despite the association between infection and duration of DM, mean HbA1c remained a stronger predictor for all summary outcomes.

Adjusted associations between HbA1c and infection for all DM patients are further detailed in Table 3 for the individual infection categories. The largest relative associations between the poorest of level glycaemic control (HbA1c ≥11%) and optimal control (6-7%) were seen for bone and joint infections (IRR=8.71), endocarditis (IRR=5.56) and sepsis (IRR=3.64). Five categories failed to show a trend with HbA1c: eye infections, infective otitis externa, mycoses (other fungal), (acute) sinusitis and (other) upper respiratory tract infection.

*Attributable Fraction for infections in DM patients*

Finally, we estimated AF% for the 3 summary groupings (Table 2) plus individual infection types (Table 3), across HbA1c categories for patients with DM compared to the optimal control scenario of 6-7%. The largest AF% estimate was for bone and joint infections, with 46.2% of hospitalisations being attributed to HbA1c values outside of the range 6-7%. Other large AF% estimates were observed for endocarditis (26.3%) and TB (22.7%), but CI were wide. Sepsis (20.9%), pneumonia (15.2%), skin infections (cellulitis 14.1%, other 12.0%) and candidiasis (16.4%) all produced AF% estimates of ≥10%. Overall, 15.7% of infection-related deaths, 16.5% of infection-related hospitalisations, and 6.8% of infections requiring a prescription were attributed to values of HbA1c outside the 6-7% range. These summary estimates were very similar in a sensitivity-analysis that used a time-updated HbA1c measurement (Supplemental Table S4).

**Discussion**

Across most categories of infection we considered, infection rates rose steadily with HbA1c. This was particularly evident among those with the highest levels of HbA1c (≥11%), and for T1DM. Among people with DM, there was a more than doubling in the risk of hospitalisation or death for infection; with the risk being higher in T1DM, a difference only partially explained by the typically longer duration of diabetes among those with T1DM. In terms of the overall population impact, almost half of bone and joint infections among DM patients were attributed to poor control. “Diabetes foot” complications are clinically well known to be strongly associated with infection risk([13](#_ENREF_13)) , and almost half of infections in this broader category of bone and joint infections mentioned the foot as a focus of infection. The most novel and concerning finding is the very substantial proportion of other serious infections statistically attributable to poor control, particularly endocarditis, tuberculosis and sepsis. Between 20-30% of these infections in the UK diabetes population could be attributed to poor control, although the 95% CI are wide for TB and endocarditis, since these are less common infections. Similarly, between 10-20% of other potentially significant infections, such as pneumonia, skin infections, sepsis, candidiasis, as well as hospitalisation and mortality due to infection, were statistically attributed to poor glycaemic control. Whilst some age attenuation was present, there were still clinically important increases in infection risks associated with poor control in the oldest age groups where glycaemic control can be more difficult and infection most common. Given the high risk of infection with increasing age([8](#_ENREF_8)), the absolute number of cases attributable to poor control will be higher at older ages.

*Key strengths*

The key strengths of our analyses include the large dataset which contained many older patients (over 36,000 aged 70+), and the comprehensiveness of the infection outcomes considered. By utilising primary care data linked to hospital episodes and mortality, we have been able to consider a whole range of common and rare but serious infections, not possible with previous epidemiological studies. Importantly, our longitudinal design enabled us to firstly characterise the level of glycaemic control (repeated HbA1c measurements at baseline) well before the infectious disease episode, allowing us to be confident that the poor glycaemic control preceded (and was not a result of) the infection episode. This large sample size has also 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, such as age, socio-economic status, BMI, type and duration of DM. Only DM duration had an appreciable impact on the magnitude of our estimates of risk. We therefore used the Bradford-Hill criteria([14](#_ENREF_14)) to appraise the evidence for a causal relation between glycaemia and infection risk. Overall, this appears high (see Supplemental Table S5) given the temporality, strength, consistency, and dose-response relationship identified, as well as the ability to adjust for key confounders in our study.

*Key Limitations*

While we designed our study to ensure that glycaemic control was measured prior to the occurrence of any infections, the limitation here is that these measurements become out-of-date over the lengthy follow-up (up to 6 years). Our approach differs from previous research in this field, which has usually been based on measurements of DM control at or near the time of infection, and hence with less confidence about the temporality and direction of causation. To address this issue, we carried out a sensitivity analyses which incorporated a time-updated HbA1c value during follow-up, but it did not make any appreciable difference to our estimates (Supplemental Table S4). This may be because: (i) mean HbA1c within-patient was highly correlated during follow-up (r>0.7 between consecutive 2-year periods), (ii) the greater between-patient variation in HbA1c was more influential in determining infection risk in our population cohort.

We did not have comprehensive data on the type of infection or organism identified, since this is rarely available in primary care. Our results were robust to adjustment for key confounders but surveillance bias could be a possible explanation for some of our findings, if there is a tendency to diagnose infections, prescribe antibiotics, admit to hospital and/or code death as infection related among DM patients with higher HbA1c levels. However, more serious infections diagnosed in hospital would be supported by laboratory findings, and the associations with HbA1c were strongest for such 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. Our manuscript is based entirely on observational data so cannot consider the extent to which infection risk might be reversible if DM control improved.

*Comparison with previous studies*

Our inclusion of hospital and mortality data, as well as T1DM patients, may explain why we identified stronger associations than a similar UK primary care dataset which estimated a 35% increase in infection risk for good versus poor control among T2DM patients only([15](#_ENREF_15)). A study in Denmark found modest associations between HbA1c levels>10.5% among 69,318 patients with T2DM; up to about 1.2 times higher for community infection and 1.6 times greater for hospital infections([16](#_ENREF_16)). Unlike our study, it found stronger associations with more recent and time updated measurements of HbA1c than with earlier baseline measures. However their study included only incident T2DM, whilst ours was based on prevalent DM, potentially explaining the difference (newly diagnosed DM tend to have high levels of HbA1c at the time of diagnosis, which sometimes decline and become more stable with treatment). The Danish study also found that effects of poor glycaemic control on infections were greater when microvascular complications were present([15](#_ENREF_15)) (though still significant when absent); whilst controlling for comorbidities made little difference in our analyses (Supplemental Table S3).

*Implications*

Prevalence of diagnosed T2DM has trebled in the UK over the last 20 years([17](#_ENREF_17)). Whilst some improvements in glycaemic control have also been observed over this time period, our analyses show substantial numbers still have very poor control; 16% of T2 and 41% of T1DM patients had a mean HbA1c >9 for example. The AF% of infections attributed to poor control of DM is already high and may even increase over time with rising DM prevalence and population ageing. The UK has relatively low prevalence of diabetes and good control based on international comparisons([18](#_ENREF_18)). It is therefore possible that in many low and middle-income countries the burden of infections attributable to poor glycaemic control could be substantially higher([19](#_ENREF_19)).

There are many different mechanisms that may link diabetes and hyperglycaemia with infection response([1](#_ENREF_1), [20-22](#_ENREF_20)). Immune dysfunction is associated with the development of the disease itself i.e. autoimmunity in type 1 diabetes and low-grade chronic inflammation in T2DM ([1](#_ENREF_1)). Hyperglycaemia may also have subsequent effects on immune response including reduced neutrophil degranulation([23](#_ENREF_23)) and altered cytokine and chemokine gene expression([24](#_ENREF_24)), as well as well as inhibiting effects of complement([25](#_ENREF_25)). Other important mechanisms may include peripheral diabetic neuropathy, since this results in a loss of sensation and reduced awareness of minor injuries([13](#_ENREF_13)). Alongside ischaemia, often due to related peripheral arterial disease, this can result in impaired barrier defences, skin ulcers and lesions with poor wound healing and increased risk of secondary infections([19](#_ENREF_19)). Whilst there are numerous mechanisms, they nearly all involve poor glycaemic control. It thus seems likely that improved control would reduce infections (see “Bradford-Hill” Supplemental Table S5 for further details). Achieving better control in practice is a complex issue and the failure to do so has been related to “clinical inertia” in health care([26](#_ENREF_26)), and in particular failure to prescribe additional anti-DM medications when needed, notably insulin. Tackling this complex problem is the subject of on-going research and may require a multi-faceted approach([27](#_ENREF_27)), including wider members of the health care team. Improved technology e.g. to deliver insulin([27](#_ENREF_27)) and for patient self-monitoring of blood glucose could also help; less invasive means of blood glucose testing (e.g. through saliva) might also assist with better control in the future([28](#_ENREF_28)).

Risk of infections and poor outcomes are likely to be worse in older patients; while 14% of DM patients in our study were hospitalised for infection during follow-up, this rose to 22% among patients aged 80-89 (at baseline). Recent RCT evidence has identified limited benefits in terms of reducing mortality or macrovascular risk with tighter glycaemic control among older people with DM of longer duration and at higher cardiovascular risk([29-32](#_ENREF_29)). However, these RCTs generally aimed for very tight control (HbA1c <6 or <6.5%). Such levels may not be appropriate in older frail people with comorbidities, who may be at higher risk of hypoglycaemia and falls. The functional form of the relationship between HbA1c levels and infection risk appeared to be somewhat J-shaped in this study, slightly higher for those with HbA1c <6% for some infections (Supplemental Figure S4), though after adjustment for confounders this was statistically significant only for pneumonia, sepsis, and cellulitis (Table 3). An increased risk associated with very low HbA1c has been seen in other studies of infections([16](#_ENREF_16)) and was also shown in some of these recent RCTs of cardiovascular and mortality outcomes that aimed for very tight control([29-32](#_ENREF_29)). This increased infection risk was associated with older age and low BMI in our study, so may be identifying frail older people with limited life expectancy, and very high infection risk. More modest HbA1c targets (around 8% or just below) could potentially achieve substantial population benefit, and reduce the risks associated with tighter control. Consideration of infection outcomes may potentially alter conclusions about the cost-effectiveness of better control among older people and hence treatment targets and priorities([33](#_ENREF_33)).

**Conclusion**

Overall, our analyses demonstrate a strong and likely causal association between hyperglycaemia and infection risk for both T1DM and T2DM. Diabetes duration, and other markers of severity cannot explain the increased risk; nor can the longer duration explain the increased risk for T1 compared with T2DM. This remains the case in older people, where infections are very common and often severe, and there is more uncertainty about the vascular benefits of improving diabetes control. Substantial proportions of serious infections can be attributed to poor control, even though diabetes is managed well in the UK by international standards. Interventions to reduce infection risk have been largely ignored by the diabetes community and should be a high priority for future research. Clinical trials should include patients with the poorest control, older age groups, and those with a past history of significant infectious disease.

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**Author contributions:**

Conceptualization: JAC, DGC

Acquisition of Data: FJH

Clinical input: TH, SDeW

Methodology: DGC, JAC, IMC

Statistical Analysis: IMC

Interpretation of Results, drafting manuscript and approving final version: All authors

Guarantor: IMC 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

**Competing Interest**: All authors declare that no competing interests exist.

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**Figure Legends**

**Figure 1: Adjusted IRRs for summary infection groups during 2010-5 for all patients with and without DM, by mean HbA1c level during 2008-9 (DM patients only) or non-DM status, stratified by age.** Note: Dotted line represents IRR=1

**Table 1:** Adjusted IRRs for summary infection groups during 2010-5 by mean HbA1c level during 2008-9, with patients without diabetes as reference group

|  |  |  |  |
| --- | --- | --- | --- |
| Outcome | Non-DM | DM vs. non-DMa | Mean HbA1c (2008-9) in DM vs. non-DM patientsb |
|  |  |  |  **<6%** | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |
|  | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI | **IRRc,** 95% CI |
| All diabetes (n=85,312)  |  |  |  |  |  |  |  |  |  |
|  Any plus prescription | **1** (reference) | **1.31** (1.30-1.33) | **1.23** (1.18-1.29) | **1.20** (1.18-1.22) | **1.28** (1.25-1.30) | **1.42** (1.39-1.46) | **1.56** (1.50-1.62) | **1.62** (1.53-1.72) | **1.80** (1.70-1.90) |
| Any as hospitalisation | **1** (reference) | **1.78** (1.72-1.84) | **1.65** (1.54-1.76) | **1.41** (1.36-1.47) | **1.58** (1.52-1.65) | **2.02** (1.91-2.13) | **2.44** (2.26-2.64) | **3.43** (3.14-3.75) | **4.70** (4.24-5.21) |
| Death from infection | **1** (reference) | **2.44** (2.13-2.79) | **2.01** (1.71-2.37) | **1.63** (1.45-1.85) | **1.93** (1.70-2.19) | **2.23** (1.86-2.66) | **2.41** (1.85-3.14) | **5.38** (3.98-7.26) | **5.51** (3.83-7.93) |
| Type 1 diabetes (n=4,496) only |  |  |  |  |  |  |  |  |  |
| Any plus prescription | **1** (reference) | **1.56** (1.47-1.65) | **1.41** (1.08-1.85) | **1.44** (1.26-1.64) | **1.44** (1.32-1.56) | **1.46** (1.34-1.59) | **1.74** (1.56-1.93) | **1.84** (1.59-2.13) | **2.62** (2.17-3.16) |
| Any as hospitalisation | **1** (reference) | **3.34** (2.82-3.96) | **1.17** (0.52-2.63) | **2.82** (2.17-3.67) | **2.69** (2.17-3.34) | **2.79** (2.25-3.45) | **3.78** (2.96-4.83) | **5.42** (3.96-7.42) | **8.47** (5.86-12.24) |
| Type 2 diabetes (n=78,964) only |  |  |  |  |  |  |  |  |  |
| Any plus prescription | **1** (reference) | **1.29** (1.28-1.31) | **1.23** (1.17-1.28) | **1.19** (1.17-1.22) | **1.27** (1.24-1.29) | **1.42** (1.38-1.46) | **1.52** (1.46-1.58) | **1.60** (1.50-1.70) | **1.71** (1.61-1.81) |
| Any as hospitalisation | **1** (reference) | **1.70** (1.64-1.76) | **1.62** (1.52-1.73) | **1.37** (1.32-1.43) | **1.53** (1.46-1.59) | **1.92** (1.82-2.03) | **2.30** (2.11-2.50) | **3.23** (2.93-3.55) | **4.31** (3.88-4.80) |

a - Poisson model conditioned on matchsets fits a term to compare DM vs. non-DM. b - Poisson model now fits HbA1c categories, with non-DM as reference category. c -Incidence Rate Ratios adjusted for age, sex, smoking, BMI, deprivation quintile. In conditional model age and sex controlled for via the matching.
Number of (non-DM) age-sex-practice matched controls: All DM=153,341, T1DM=8,231, T2DM=141.768.
Number of patients (%) with at least infection event or died from infection during follow-up were as follows:
 - Any infection plus prescription: All DM n=42,854 (50%), All non-DM n=60,252 (39%), T1DM n=2,147 (48%), T1 non-DM n=2,828 (34%), T2DM n=39,712 (50%), T2 non-DM n=56,243 (40%)
 - Hospitalisation for infection: All DM n=11,320 (13%), All non-DM n=10,333 (7%), T1DM n=551 (12%), T1 non-DM n=348 (4%), T2DM n=10,769 (14%), T2 non-DM n=11,423 (8%)
 - Death from infection: All DM n=1,106 (1.3%), All non-DM n=1,058 (0.7%)

**Table 2:** Adjusted IRRs for summary infection groups during 2010-5 by mean HbA1c level during 2008-9 among DM patients only (n=85,312), with additional adjustment for duration of DM

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | DM Typec | Duration of Diabetes | Mean HbA1c (2008-9) in DM patients  | Attributable risk fractions |
|  | **Type 1** | **Type 2** | **0-5yrs** | **5-15yrs** | **>15yrs** |  **<6%** | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |  |
|  | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **ARd,** 95%CI |
| Any plus prescription | **1** (refer-ence) | **1.01** (0.97-1.06) | \_ | \_ | \_ | **1.03** (0.98-1.07) | **1** (refer-ence) | **1.05** (1.02-1.07) | **1.15** (1.11-1.19) | **1.24** (1.19-1.29) | **1.27** (1.20-1.36) | **1.40** (1.32-1.48) | **6.8** (5.6-8.1) |
| **1** (refer-ence) | **0.90** (0.85-0.94) | **1** (refer-ence) | **1.12** (1.10-1.15) | **1.29** (1.25-1.33) | **1.03** (0.99-1.08) | **1** (refer-ence) | **1.02** (1.00-1.05) | **1.10** (1.06-1.13) | **1.18** (1.13-1.23) | **1.21** (1.14-1.29) | **1.32** (1.25-1.40) |  |
| Any as hospitalisation | **1** (refer-ence) | **1.36** (1.24-1.50) | \_ | \_ | \_ | **1.17** (1.09-1.25) | **1** (refer-ence) | **1.09** (1.04-1.15) | **1.34** (1.26-1.42) | **1.58** (1.46-1.71) | **2.18** (1.98-2.40) | **2.95** (2.66-3.28) | **16.5** (14.1-18.8) |
| **1** (refer-ence) | **1.12** (1.01-1.24) | **1** (refer-ence) | **1.23** (1.17-1.28) | **1.54** (1.44-1.64) | **1.18** (1.11-1.27) | **1** (refer-ence) | **1.05** (0.99-1.10) | **1.23** (1.16-1.31) | **1.43** (1.32-1.56) | **1.98** (1.80-2.18) | **2.70** (2.43-3.00) |  |
| Death from infection | **1** (refer-ence) | **1.82** (1.33-2.48) | \_ | \_ | \_ | **1.25** (1.05-1.49) | **1** (refer-ence) | **1.14** (0.99-1.31) | **1.24** (1.02-1.51) | **1.31** (0.99-1.74) | **2.90** (2.13-3.94) | **3.01** (2.10-4.30) | **15.7** (8.7-22.8) |
| **1** (refer-ence) | **1.42** (1.03-1.96) | **1** (refer-ence) | **1.38** (1.20-1.59) | **1.85** (1.53-2.25) | **1.28** (1.07-1.52) | **1** (refer-ence) | **1.06** (0.92-1.23) | **1.10** (0.90-1.34) | **1.13** (0.85-1.50) | **2.51** (1.84-3.41) | **2.65** (1.86-3.77) |  |

Note - Reference category in Poisson models are patients with DM and HbA1c between 6 to 7%.
a- IRR adjusted for age, sex, smoking, BMI, deprivation quintile and type of diabetes. b - Additionally adjusted for duration of diabetes. c – Type uncertain also fitted in model (estimates not shown). d - Attributable risk fractions for infections for a baseline scenario of HbA1c=6-7% among all patients with diabetes. 95% CI calculated by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations

**Table 3:** Adjusted IRRs and attributable risk fractions for specific infections during 2010-5 by mean HbA1c level, patients with DM only (n=85,312)

|  |  |  |
| --- | --- | --- |
| Infection Category | Mean HbA1c level (2008-9) in DM Patients (n=85,312) | Attributable risk fractions |
|  |  **<6%** | **≥6 to <7%** | **≥7 to <8%** | **≥8 to <9%** | **≥9 to <10%** | **≥10 to <11%** | **≥11%** |  |
|  | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **IRRa**, 95% CI | **ARb,** 95%CI |
| Bone & Joint Infections | **1.12** (0.81-1.53) | **1** (reference) | **1.55** (1.26-1.91) | **2.49** (1.95-3.17) | **3.45** (2.62-4.55) | **5.39** (3.95-7.34) | **8.71** (6.64-11.41) | **46.0** (37.5-54.0) |
| (Acute) Cholecystitis | **1.03** (0.77-1.38) | **1** (reference) | **0.98** (0.81-1.20) | **1.15** (0.90-1.47) | **0.92** (0.64-1.32) | **1.52** (1.05-2.19) | **2.28** (1.53-3.39) | **4.5** (-5.9-14.8) |
| Endocarditis | **1.16** (0.43-3.12) | **1** (reference) | **1.38** (0.74-2.56) | **1.17** (0.44-3.10) | **1.72** (0.62-4.74) | **5.01** (1.98-12.71) | **5.56** (2.09-14.78) | **26.2** (-5.3-56.3) |
| Eye Infection | **0.97** (0.87-1.08) | **1** (reference) | **0.95** (0.87-1.03) | **1.01** (0.93-1.11) | **1.13** (1.01-1.26) | **1.02** (0.86-1.19) | **1.16** (0.95-1.41) | **-0.3** (-4.2-3.6) |
| Gastro-Intestinal | **1.06** (0.92-1.21) | **1** (reference) | **1.05** (0.95-1.15) | **1.16** (1.04-1.30) | **1.23** (1.05-1.44) | **1.51** (1.22-1.86) | **1.84** (1.50-2.26) | **8.0** (2.6-12.8) |
| Infective Otitis Externa | **0.83** (0.69-1.01) | **1** (reference) | **0.99** (0.90-1.10) | **1.06** (0.95-1.19) | **1.05** (0.90-1.23) | **1.01** (0.82-1.25) | **0.98** (0.76-1.26) | **-0.4** (-5.8-5.2) |
| LRTI | **1.03** (0.97-1.10) | **1** (reference) | **1.06** (1.02-1.10) | **1.16** (1.10-1.23) | **1.26** (1.17-1.34) | **1.27** (1.15-1.40) | **1.25** (1.14-1.37) | **6.7** (4.9-8.7) |
| Mycoses - Candidiasis | **0.93** (0.82-1.05) | **1** (reference) | **1.15** (1.07-1.25) | **1.47** (1.35-1.59) | **1.50** (1.36-1.67) | **1.62** (1.41-1.86) | **1.92** (1.66-2.22) | **16.5** (12.5-20.1) |
| Mycoses - Other Fungal | **0.96** (0.86-1.06) | **1** (reference) | **1.04** (0.98-1.10) | **1.05** (0.97-1.14) | **0.95** (0.85-1.07) | **0.93** (0.79-1.09) | **0.88** (0.74-1.05) | **0.7** (-3.1-4.6) |
| Pneumonia | **1.23** (1.12-1.36) | **1** (reference) | **1.10** (1.03-1.17) | **1.40** (1.28-1.52) | **1.71** (1.51-1.94) | **2.00** (1.69-2.38) | **2.68** (2.26-3.17) | **15.3** (11.9-18.5) |
| Sepsis | **1.25** (1.06-1.47) | **1** (reference) | **1.20** (1.07-1.35) | **1.53** (1.32-1.76) | **1.69** (1.39-2.05) | **2.36** (1.85-3.00) | **3.64** (2.82-4.70) | **20.8** (15.2-26.2) |
| (Acute) Sinusitis  | **1.07** (0.93-1.23) | **1** (reference) | **1.06** (0.97-1.16) | **1.14** (1.02-1.27) | **0.98** (0.83-1.15) | **0.91** (0.72-1.14) | **0.86** (0.67-1.11) | **3.5** (-2.1-9.6) |
| Skin - Cellulitis | **1.22** (1.13-1.32) | **1** (reference) | **1.07** (1.01-1.13) | **1.28** (1.19-1.38) | **1.63** (1.49-1.79) | **1.74** (1.53-1.99) | **2.29** (2.04-2.57) | **14.0** (11.3-17.0) |
| Skin - Other | **1.06** (0.98-1.14) | **1** (reference) | **1.06** (1.01-1.12) | **1.23** (1.16-1.31) | **1.45** (1.35-1.55) | **1.52** (1.39-1.68) | **2.04** (1.83-2.27) | **12.1** (9.5-14.4) |
| Surgical Site | **0.98** (0.83-1.17) | **1** (reference) | **0.96** (0.84-1.09) | **0.93** (0.79-1.10) | **1.26** (1.04-1.53) | **1.43** (1.10-1.85) | **2.01** (1.56-2.60) | **3.0** (-3.7-10.0) |
| Tuberculosis (TB) | **0.27** (0.03-2.10) | **1** (reference) | **1.47** (0.75-2.87) | **1.13** (0.50-2.53) | **1.40** (0.55-3.59) | **3.78** (1.39-10.26) | **3.04** (1.21-7.64) | **23.7** (-11.1-54.0) |
| (Other) URTI | **0.95** (0.88-1.03) | **1** (reference) | **1.11** (1.06-1.16) | **1.09 (**1.03-1.16) | **1.10** (1.02-1.19) | **1.08** (0.97-1.20) | **0.98** (0.88-1.10) | **4.8** (2.2-7.5) |
| Urinary Tract Infection  | **1.01** (0.93-1.09) | **1** (reference) | **1.06** (1.00-1.11) | **1.18** (1.10-1.27) | **1.21** (1.10-1.34) | **1.26** (1.11-1.42) | **1.44** (1.24-1.67) | **6.3** (3.6-8.6) |

LRTI = Lower Respiratory Tract Infection; URTI = Upper Respiratory Tract Infection.
a - Incidence Ratio Ratios adjusted for age, sex, smoking, BMI, deprivation quintile. Reference category in Poisson models are patients with DM and HbA1c between 6 to 7%.

b - Attributable risk fractions for infections for a baseline scenario of HbA1c=6-7% among all patients with diabetes. 95% CI calculated by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations