 OBJECTIVE

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

RESEARCH DESIGN AND METHODS

With the use of English primary care data, average glycated hemoglobin (HbA1c) during 2008–2009 was estimated for 85,312 patients with DM ages 40–89 years. Infection rates during 2010–2015 compiled from primary care, linked hospital, and mortality records were estimated across 18 infection categories and further summarized as any requiring a prescription or hospitalization or as cause of death. Poisson regression was used to estimate adjusted incidence rate ratios (IRRs) by HbA1c categories across all DM, and type 1 and type 2 DM separately. IRRs also were compared with 153,341 age-sex-practice–matched controls without DM. Attributable fractions (AF%) among patients with DM 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 with patients without DM, those with DM and optimal control (HbA1c 6–7% [42–53 mmol/mol], IRR 1.41 [95% CI 1.36–1.47]) and poor control (≥11% [97 mmol/mol], 4.70 [4.24–5.21]) had elevated hospitalization risks for infection. In patients with type 1 DM and poor control, this risk was even greater (IRR 8.47 [5.86–12.24]). Comparisons within patients with DM confirmed the risk of hospitalization with poor control (2.70 [2.43–3.00]) after adjustment for duration and other confounders. AF% of poor control were high for serious infections, particularly bone and joint (46%), endocarditis (26%), tuberculosis (24%), sepsis (21%), infection-related hospitalization (17%), and mortality (16%).

CONCLUSIONS

Poor glycemic control is powerfully associated with serious infections and should be a high priority.

Infections are widely considered to be a source of significant health care costs and to reduce quality of life among people with diabetes mellitus (DM) (1). Nevertheless, relatively few, large, well-designed, epidemiological studies have explored relationships between poorer control of DM and infections; previous studies have important limitations (1). Most randomized controlled trials (RCTs) of DM control have not
investigated the effect of improved glycemic control on infections and are unlikely to do so at present because of the high cost and lack of good-quality supporting observational evidence. One early landmark RCT, the Diabetes Control and Complications Trial, reported infection outcomes in a very restricted population (1,441 people with type 1 DM [T1DM] ages 13–39 years) (2) and showed substantial reductions in the risk of vaginal infections in the tight control group compared with the control arm (2). The benefit from tighter control also was seen after trial end in the observational follow-up (1,3). However, data on other infections in older people with type 2 DM (T2DM), in whom infections are more burdensome and risks of tighter glycemic control higher, are urgently needed. A recent review of higher-population-based epidemiological studies found clinically important (~1.5–3.5 times higher) infection risks associated with poorer DM control in some studies (usually defined as a glycated hemoglobin [HbA1c] level >7–8% [53–64 mmol/mol]) (1). However, the studies were inconsistent, generating uncertainty about the evidence.

A key concern with previous work is that the measurement of HbA1c usually was 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 effect on glycemic control, a process known as stress hyperglycemia (4); hence, blood glucose or HbA1c measurements near the time of an infection may be elevated, rendering determination of the chronology and relationship between the two difficult. Several studies with serial HbA1c measurements have shown that the stress hyperglycemia response can be substantial (4–6). Another important issue is that studies of incident DM 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 a lack of consideration of type of DM (especially T1DM) and fewer older people with DM. The current study uses a large English primary care database with repeated HbA1c measurements wherein we can classify individuals more precisely in terms of their baseline glycemic control as well as ensure that these HbA1c measurements were made before the infection episode.

**RESEARCH DESIGN AND METHODS**

**Data Source**

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the U.K. population (7). The study is based on 361 general practices in England only, with anonymous linkage to Hospital Episodes Statistics and Office for National Statistics death registration data (8).

**Study Design**

We carried out a further analysis of a retrospective matched cohort study that we have previously reported on (8) (Supplementary Fig. 1). 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, who were aged 40–89 years, and who had a Read code for DM (nationally agreed-on codes that practices are encouraged to use) (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 matched with controls were excluded. Patient DM was classified as T1DM, T2DM, or type uncertain by using a combination of DM Read codes and prescriptions of anti-DM medications (insulin, sulphonylureas, biguanides, other) to estimate type of selective section (10) within 14 days of the diagnosis. 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 matched with controls were excluded. Patient DM was classified as T1DM, T2DM, or type uncertain by using a combination of DM Read codes and prescriptions of anti-DM medications (insulin, sulphonylureas, biguanides, other) to estimate type of selective section (10) within 14 days of the diagnosis.

**Ascertainment of HbA1c Level**

From the original cohort, we collated all recorded HbA1c measurements on the 104,617 patients with DM between 1 January 2008 and 31 December 2009 (Supplementary Fig. 1) and calculated the mean HbA1c for each patient. From these we excluded patients no longer active in CPRD on 1 January 2010 (n = 15,416); 6,636 had died during 2008–2009, 5,638 had transferred out of their practice, and 3,412 were from a practice that stopped contributing data to CPRD. Among active patients, 2,932 had no HbA1c measured during 2008–2009, and 1,496 had no remaining controls by 1 January 2010. A small number of patients (n = 262) who had been classified as having T1DM were not prescribed insulin during 2008–2009 and were reclassified as type uncertain, resulting in 85,312 patients with DM (78,964 with T2DM, 4,496 with T1DM, 1,852 with type uncertain) and 153,341 matched controls who were eligible on 1 January 2010 for analysis of subsequent infection. All patients were followed until the earliest date of death, deregistration from practice, their practice leaving CPRD, or 31 December 2015. Mean follow-up time for all patients was ~4.2 years. To minimize 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 (2008–2009).

**Classification of Infections**

Infections subsequent to the 2-year HbA1c assessment period, recorded between 2010 and 2015, were classified into 18 different groupings by using Read codes for general practice data and ICD-10 classifications for hospital admissions and cause of death (Supplementary Table 1). For each group, all recordings within 90 days were assumed to be the same event, with codes >90 days apart assumed to be distinct events. The total number of infection events was counted for each patient. Three summary groups were defined: 1) any infection with a prescription for an antibiotic, antifungal, or antiviral drug (British National Formulary section 5.1) (10) within 14 days of the diagnosis; 2) any infection event that resulted in a hospital admission; and 3) any infection that resulted in death.

**Statistical Analyses**

Poisson regression was used to estimate and compare incidence rate ratios (IRRs) of infection (Stata 13 statistical software), with an offset accounting for total days registered. We first carried out comparisons using patients without DM as the reference group. We fitted a model conditioned on the match sets to estimate differences in rates of infections between patients with and without DM. This model implicitly adjusts for age, sex, and practice. We also adjusted for smoking, BMI, and Index of Multiple Deprivation, a composite small-area ecological measure of deprivation based on postal codes (11). Additional adjustment for comorbidities (chronic kidney disease, heart failure, hypertension, hypothyroidism, ischemic heart disease, peripheral vascular disease, stroke and transient ischemic attack, and chronic
obstructive pulmonary disease) also was performed. In (nonconditional) Poisson models, we then fitted categories of mean HbA1c (<6%; [42 mmol/mol], ≥6 to <7% [42–53 mmol/mol], ≥7 to <8% [53–64 mmol/mol], ≥8 to <9% [64–75 mmol/mol], ≥9 to <10% [75–86 mmol/mol], ≥10 to <11% [86–97 mmol/mol], ≥11% [97 mmol/mol]) with patients without DM first as the comparison group, now adjusting for age and sex. We stratified these models by age (40–64, 65–89 years) to describe effect modification by age. Finally, we refitted these models only on patients with DM by using HbA1c between ≥6 and <7% (42 and 53 mmol/mol) as the reference category. To account for clustering by practice, all models used a sandwich estimator to obtain robust SEs.

Sensitivity analyses were performed using alternate summaries of glycemic control, which 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 1 January for each individual if still active on the basis of the measurements from the previous 2-year period). We also extended the exclusion period for HbA1c measurements around any infection from 14 up to 30 or 90 days. None of these approaches changed the findings in a meaningful way, so we retained the baseline summary for the main results.

Within patients with DM, we calculated attributable risk fractions (AF%) (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 6–7% (42–53 mmol/mol). The CIs were obtained by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.

RESULTS

Supplementary Table 2 summarizes the distribution of mean HbA1c during 2008–2009 for all patients with DM by age, sex, duration of DM, BMI, smoking, and deprivation. The distribution of mean HbA1c during 2008–2009 also is shown in Supplementary Fig. 3 by DM type. Mean (SD) HbA1c was ~1% higher for patients with T1DM (8.3% [1.4]) versus T2DM (7.4% [1.4]), with patients with T1DM more than twice as likely to have a mean HbA1c ≥9% (26.9 vs. 11.0%). Patients whose DM was classified as type uncertain had mean HbA1c levels similar to patients with T1DM (8.3% [1.6]). The mean number of HbA1c measurements recorded during 2008–2009 was similar in both types (3.5 for T1DM, 3.6 for T2DM). Patients with T2DM were on average ~10 years older than those with T1DM (66.9 vs. 56.1 years in 2008) and far more likely to have been diagnosed in the past 5 years (47.2 vs. 7.3%). Poorer glycemic control (increasing categories of HbA1c) were associated with younger age, longer duration of DM, deprivation, and obesity (Supplementary Table 2). Low HbA1c (<6%) was unusual (1.7% of patients with DM), but more common in older age and strongly associated with BMI; one in five overweight patients (20.5%; BMI <20 kg/m²) had a mean level <6%.

Glycemic Control and Infection Risk Among Patients With DM Compared With Controls Without DM

Crude infection rates during 2010–2015 estimated across 18 different categories confirmed consistently higher rates among patients with DM (Supplementary Fig. 4). For many infections (e.g., skin, cellulitis, candidiasis, bone and joint), crude rates tended to rise with increasing HbA1c. Some infections (e.g., mycosis [other fungal], sepsis) also showed elevated rates among patients with DM in the lowest HbA1c category (<6%).

Table 1 summarizes infection risk (any plus prescription, any hospitalization, and death as a result of infection) between patients with and without DM by first 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., hospitalization IRR 3.34 [95% CI 2.82–3.96]) than for those with T2DM (1.70 [1.64–1.76]). Because of the small number of deaths among patients with T1DM, comparisons for death as a result of infection were estimated for all DM combined (2.44 [2.13–2.79]). Additional adjustment for comorbidity attenuated differences but did not explain the association between DM and infection (Supplementary Table 3).

Clear trends were observed for increasing risk of infection with poorer levels of glycemic control (Table 1). However, even patients with DM with good control were at an increased risk compared with matched controls without DM. Thus, compared with patients without DM, patients with DM and good control (mean HbA1c 6–7%, IRR 1.41 [95% CI 1.36–1.47]) and those with poor control (≥11%, 4.70 [4.24–5.21]) had elevated hospitalization risks for infection. These risks were higher among patients with T1DM. For example, patients with T1DM with a mean HbA1c ≥11%, had more than eight times the risk of hospitalization than their matched controls without DM (IRR 8.47 [5.86–12.24]), whereas for T2DM, this was four times higher (4.31 [3.88–4.80]).

The trend between increasing HbA1c and infection risk was present in both younger (40–64 years) and older (65–89 years) patients with DM (Fig. 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 as a result of infection during follow-up than patients without DM and almost three times as likely to be hospitalized.

Glycemic Control and Infection Risk Within Patients With DM

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 glycemic control were confirmed. For example, patients with mean HbA1c ≥11% were almost three times as likely to be hospitalized for infection (IRR 2.95 [95% CI 2.66–3.28]). Further adjustment for comorbidity did not substantiably alter the risk estimates (Supplementary Table 3). Patients with T1DM still had higher rates of hospitalization (1.12 [1.01–1.24]) and death as a result of infection (1.42 [1.03–1.96]) than patients with T2DM, 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 patients with DM are detailed in Table 3 for the individual infection categories. The largest relative associations between the poorest level of glycemic control (HbA1c ≥11%) and optimal control (6–7%) were seen for bone
### Table 1—Adjusted IRRs for summary infection groups during 2010–2015 by mean HbA1c level during 2008–2009, with patients without DM as the reference group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-DM</th>
<th>DM vs. non-DM*</th>
<th>&lt;6%</th>
<th>≥6 to &lt;7%</th>
<th>≥7 to &lt;8%</th>
<th>≥8 to &lt;9%</th>
<th>≥9 to &lt;10%</th>
<th>≥10 to &lt;11%</th>
<th>≥11%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DM (n = 85,312)</td>
<td>1 (reference)</td>
<td>1.31 (1.30–1.33)</td>
<td>1.23 (1.18–1.29)</td>
<td>1.20 (1.18–1.22)</td>
<td>1.28 (1.25–1.30)</td>
<td>1.42 (1.39–1.46)</td>
<td>1.56 (1.50–1.62)</td>
<td>1.62 (1.53–1.72)</td>
<td>1.80 (1.70–1.90)</td>
</tr>
<tr>
<td>Any plus prescription</td>
<td>1 (reference)</td>
<td>1.78 (1.72–1.84)</td>
<td>1.65 (1.54–1.76)</td>
<td>1.41 (1.36–1.47)</td>
<td>1.58 (1.52–1.65)</td>
<td>2.02 (1.91–2.13)</td>
<td>2.44 (2.26–2.64)</td>
<td>3.43 (3.14–3.75)</td>
<td>4.70 (4.24–5.21)</td>
</tr>
<tr>
<td>Any as hospitalization</td>
<td>1 (reference)</td>
<td>2.44 (2.13–2.79)</td>
<td>2.01 (1.71–2.37)</td>
<td>1.63 (1.45–1.85)</td>
<td>1.93 (1.70–2.19)</td>
<td>2.23 (1.86–2.66)</td>
<td>2.41 (1.85–3.14)</td>
<td>5.38 (3.98–7.26)</td>
<td>5.51 (3.83–7.93)</td>
</tr>
</tbody>
</table>

| T1DM (n = 4,496) only | 1 (reference) | 1.56 (1.47–1.65) | 1.41 (1.08–1.85) | 1.44 (1.26–1.64) | 1.46 (1.34–1.59) | 1.74 (1.56–1.93) | 1.84 (1.59–2.13) | 2.62 (2.17–3.16) | 2.69 (2.17–3.34) |
| Any plus prescription | 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) |
| Any as hospitalization | 1 (reference) | 1.70 (1.64–1.76) | 1.62 (1.52–1.73) | 1.37 (1.23–1.43) | 1.53 (1.46–1.60) | 1.92 (1.82–2.03) | 2.40 (2.11–2.70) | 2.93 (2.55–3.35) | 4.31 (3.88–4.80) |

| T2DM (n = 78,964) only | 1 (reference) | 1.29 (1.28–1.31) | 1.23 (1.17–1.28) | 1.19 (1.17–1.22) | 1.27 (1.24–1.30) | 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 plus prescription | 1 (reference) | 1.70 (1.64–1.76) | 1.62 (1.52–1.73) | 1.37 (1.23–1.43) | 1.53 (1.46–1.60) | 1.92 (1.82–2.03) | 2.40 (2.11–2.70) | 2.93 (2.55–3.35) | 4.31 (3.88–4.80) |
| Any as hospitalization | 1 (reference) | 1.70 (1.64–1.76) | 1.62 (1.52–1.73) | 1.37 (1.23–1.43) | 1.53 (1.46–1.60) | 1.92 (1.82–2.03) | 2.40 (2.11–2.70) | 2.93 (2.55–3.35) | 4.31 (3.88–4.80) |

Data are IRR (95% CI). Number of (non-DM) age-sex-practice–matched controls: 153,519 all DM, 8,231 T1DM, 141,768 T2DM. Number of patients (%) with at least one infection event or death as a result of infection during follow-up: any infection plus prescription: 42,854 all DM (50%), 60,252 all non-DM (39%), 2,174 T1DM (48%), 2,828 non-T1DM (34%), 39,712 T2DM (50%), 56,243 non-T2DM (40%); hospitalization for infection: 11,320 all DM (13%), 10,333 all non-DM (7%), 551 T1DM (12%), 348 non-T1DM (4%), 10,769 T2DM (14%), 11,423 non-T2DM (8%); death as a result of infection: 1,106 all DM (1.3%), 1,058 all non-DM (0.7%). IRRs were adjusted for age, sex, smoking, BMI, and deprivation quintile. In the conditional model, age and sex were controlled through the matching. *Poisson model conditioned on match sets fits HbA1c categories, with non-DM as reference category.
endocarditis, tuberculosis, and sepsis. Between 20 and 30% of these infections in the English. DM population could be attributed to poor control, although the 95% CIs were wide for tuberculosis and endocarditis because these infections are less common. Similarly, between 10 and 20% of other potentially significant infections, such as pneumonia, skin infections, sepsis, and candidiasis, as well as hospitalization and mortality as a result of infection were statistically attributed to poor glyemic control. Although some age attenuation was present, there were still clinically important increases in infection risks for DM. Although some age attenuation was present, there were still clinically important increases in infection risks associated with poor control in the oldest age-groups where glyemic control was present, there were still clinically important increases in infection risks because this is rarely available.

**Key Strengths**

The key strengths of our analyses were the large data set, which contained many older patients (>36,000 age ≥70 years), and the comprehensiveness of the infection outcomes considered. By using 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. Of note, our longitudinal design enabled us to first characterize the level of glycemic control (repeated HbA1c measurements at baseline) well before the infectious disease episode, allowing us to be confident that the poor glycemic control preceded (and was not a result of) the infection episode. The large sample size 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 (e.g., age, socioeconomic status, BMI, type and duration of DM). Only DM duration had an appreciable effect on the magnitude of our estimates (Supplementary Table 4) because this is rarely available in primary care. The results were robust to adjustment for key confounders, but surveillance bias could be a possible explanation for some of the findings if a tendency exists to diagnose infections, prescribe antibiotics, admit to the hospital, and/or code death as infection related among patients with DM and higher HbA1c levels. However, more
Table 2—Adjusted IRRs for summary infection groups during 2010–2015 by mean HbA1c level during 2008–2009 among patients with DM only, with additional adjustment for duration of DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DM type</th>
<th>Duration of diabetes (years)</th>
<th>Mean HbA1c (2008–2009) in patients with DM (n = 85,312)</th>
<th>AF%b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2</td>
<td>T1</td>
<td>&lt;6%</td>
<td></td>
</tr>
<tr>
<td>Any plus prescription</td>
<td>1 (ref)</td>
<td>1.01 (0.97–1.05)</td>
<td>1.03 (0.98–1.07)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (ref)</td>
<td>0.90 (0.85–0.94)</td>
<td>1.05 (1.02–1.07)</td>
<td></td>
</tr>
<tr>
<td>Any as hospitalization</td>
<td>1 (ref)</td>
<td>1.36 (1.24–1.50)</td>
<td>1.17 (1.09–1.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (ref)</td>
<td>1.12 (1.01–1.24)</td>
<td>1.18 (1.11–1.27)</td>
<td></td>
</tr>
<tr>
<td>Death as a result of infection</td>
<td>1 (ref)</td>
<td>1.82 (1.33–2.48)</td>
<td>1.25 (1.05–1.49)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 (ref)</td>
<td>1.42 (1.03–1.96)</td>
<td>1.14 (0.99–1.31)</td>
<td></td>
</tr>
</tbody>
</table>

Data are IRR (95% CI) unless otherwise indicated. Ref category in Poisson models comprises patients with DM and HbA1c between 6 and 7%. IRR adjusted for age, sex, smoking, BMI, deprivation quintile, and DM type. AR, attributable risk; ref, reference. *Type uncertain also fitted in model (estimates not shown). AF% for infections for a baseline scenario of HbA1c of 6–7% among all patients with DM. 95% CI calculated by taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations.
By taking the 2.5th and 97.5th percentiles from 1,000 bootstrap simulations. The 95% CI was calculated –

Table 3

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean HbA1c level</th>
<th>Adjusted IRR</th>
<th>AF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>7%</td>
<td>8%</td>
<td>9%</td>
<td>10%</td>
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<tr>
<td>6%</td>
<td>7%</td>
<td>8%</td>
<td>9%</td>
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<td>8%</td>
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<td>5%</td>
<td>6%</td>
<td>5%</td>
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<tr>
<td>3%</td>
<td>4%</td>
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<td>1%</td>
</tr>
<tr>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Mean HbA1c level in patients with DM only

Other fungal

Mycosis

Tuberculosis

Surgical site

Other (Acute) sinusitis

Sepsis

Pneumonia

Skin (Acute) cholecystitis

Endocarditis

Bone and joint infections

Upper respiratory tract infections (URTIs)

Lower respiratory tract infections (LRTIs)

Table 3—Adjusted IRRs and AF% for specific infections during 2010–2015 By mean HbA1c level among patients with DM only

The risk of infections and poor outcomes are likely to be worse in older outcomes. The risk of infections in the future may require a more complex approach [28,29] to provide additional improved technology (e.g., insulin delivery, monitoring, and test strips) as well as more intensive means of monitoring DM control. The failure to control DM in the future (e.g., through saliva) also might assist a more widespread approach [27] to improve care delivery. Dx: improved technology (e.g., insulin delivery, monitoring, and test strips) can help improve care delivery for patients with diabetes. Improved insulin delivery (e.g., insulin pumps) also might assist in improving care delivery and patient self-care. Improved technology (e.g., insulin delivery, monitoring, and test strips) can help improve care delivery for patients with diabetes. Improved insulin delivery (e.g., insulin pumps) also might assist in improving care delivery and patient self-care.
limited benefits in terms of reducing mortality or macrovascular risk with tighter glycemic control among older people with DM of longer duration and at higher cardiovascular risk (29–32). However, these RCTs generally aimed for very tight control (HbA1c <6 or <6.5%). Such levels may not be appropriate in frail older people with comorbidities who may be at higher risk of hypoglycemia and falls. The functional form of the relationship between HbA1c levels and infection risk seem to be somewhat J shaped in this study, slightly higher for those with HbA1c <6% for some infections (Supplementary Fig. 4), although 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) as well as in some RCTs of cardiovascular and mortality outcomes that aimed for very tight control (29–32). This increased infection risk was associated with older age and low BMI in the current study so may be identifying frail older people with limited life expectancy and a very high infection risk. More modest HbA1c targets (~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).

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

Acknowledgments. This unfunded study is based in part on data from the CPRD obtained under license from the U.K. Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of its care and support for patients. The interpretation and conclusions contained in this article are those of the authors alone. The protocol number (16/206R) was approved by the Independent Scientific Advisory Committee evaluation of joint protocols of research involving CPRD data in March 2017.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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References