

## Journal Pre-proofs

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PII: S0168-8227(23)00786-6  
DOI: <https://doi.org/10.1016/j.diabres.2023.111023>  
Reference: DIAB 111023

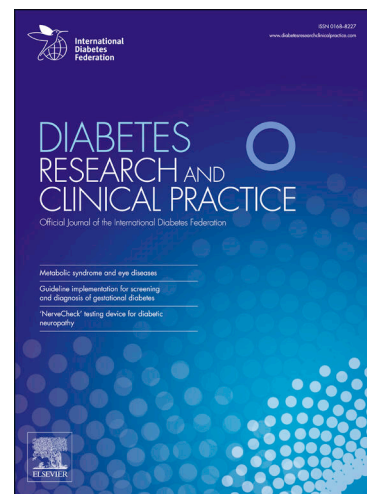
To appear in: *Diabetes Research and Clinical Practice*

Received Date: 31 August 2023  
Revised Date: 13 November 2023  
Accepted Date: 17 November 2023

Please cite this article as: U. A R Chaudhry, I.M. Carey, J.A. Critchley, S. DeWilde, E.S. Limb, L. Bowen, A. Panahloo, D.G. Cook, P.H. Whincup, T. Harris, A Matched Cohort Study Evaluating the Risks of Infections in People with Type 1 Diabetes and their Associations with Glycated Haemoglobin, *Diabetes Research and Clinical Practice* (2023), doi: <https://doi.org/10.1016/j.diabres.2023.111023>

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## **A Matched Cohort Study Evaluating the Risks of Infections in People with Type 1 Diabetes and their Associations with Glycated Haemoglobin**

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**Manuscript Word Count = 4,077**

## Highlights

- People with type 1 diabetes have higher infection risks compared to those without
- Associations are slightly stronger in ages <50 years and non-White ethnicities
- High HbA1c mean level and variability are associated with increasing infection risk
- Improved glycaemic control may reduce infection risk, particularly for more serious infections requiring hospitalisation
- Guidelines for type 1 diabetes should put a greater emphasis on infection risks

## Keywords

Type 1 diabetes

Glycated haemoglobin (HbA1c)

Infections

Ethnicity

Variability

## Tweet

People with type 1 diabetes have an increased risk of infections. Mean HbA1c and its variability are important predictors.

## Abstract

### Aims

People with type 1 diabetes (T1D) have raised infection rates compared to those without, but how these risks vary by age, sex and ethnicity, or by glycated haemoglobin (HbA1c), remain uncertain.

### Methods

33,829 patients with T1D in Clinical Practice Research Datalink on 01/01/2015 were age-sex-ethnicity matched to two non-diabetes patients. Infections were collated from primary care and linked hospitalisation records during 2015-2019, and incidence rate ratios (IRRs) were estimated versus non-diabetes. For 26,096 people with T1D, with

≥3 HbA1c measurements in 2012-2014, mean and coefficient of variation were estimated, and compared across percentiles.

### Results

People with T1D had increased risk for infections presenting in primary care (IRR=1.81, 95%CI 1.77-1.85) and hospitalisations (IRR=3.37, 3.21-3.53) compared to non-diabetes, slightly attenuated after further adjustment. Younger ages and non-White ethnicities had greater relative risks, potentially explained by higher HbA1c mean and variability amongst people with T1D within these sub-groups. Both mean HbA1c and greater variability were strongly associated with infection risks, but the greatest associations were at the highest mean levels (hospitalisations IRR=4.09, 3.64-4.59) for >97 versus ≤53mmol/mol.

### Conclusions

Infections are a significant health burden in T1D. Improved glycaemic control may reduce infection risks, while prompter infection treatments may reduce hospital admissions.

**Abstract Word Count = 199**

## 1. Introduction

Type 1 diabetes mellitus affects about 8.4 million individuals worldwide, with case numbers predicted to rise to almost 17.4 million by 2040[1]. Approximately 400,000 people, or 8% of all people with diabetes, are living with type 1 diabetes (T1D) in the UK[2]. The disease burden in T1D remains high as it impacts people's quality of life, causes serious long-term complications, and bears considerable costs for individuals and healthcare systems[1, 3, 4]. There is growing awareness that the greater susceptibility to infections amongst people living with diabetes, and especially T1D has been largely overlooked [5]. The consequences of managing infections amongst people with diabetes include substantial healthcare use, both in primary and secondary care[3, 6].

Over the past few decades, emerging evidence has confirmed the pathophysiological and clinical basis for the greater susceptibility to infections amongst people with diabetes, and the need for improved blood sugar control to prevent certain infections[7-9]. Large cohort studies have generally focussed on the higher risk of infections amongst people with type 2 diabetes (T2D) compared to people without diabetes, with hyperglycaemia being associated with greater infection risk[10-13]. Specifically for T1D, our previous analyses demonstrated that over a 5.5-year period, 15% of people with T1D had an infection requiring hospitalisation; more than trebling the risk compared to age-sex-practice matched people without diabetes[10] and that the relative risks of infections were greater amongst people living with T1D, compared to T2D[10]. Glycaemic levels and control are also known important predictors of infection risk, and our previous analyses highlighted the significantly high risk of infections in T1D patients with high glycated haemoglobin (HbA1c) levels[11].

However, our previous study was limited by including only people with T1D aged 40 and above, and not being able to stratify by ethnicity due to lack of reporting[10, 14]. Measuring risk by ethnicity is important, as emerging evidence has indicated that underlying HbA1c levels vary by ethnicity amongst T1D patients, with non-White ethnicity associated with higher HbA1c[15]. We could also not assess the effect of HbA1c fluctuations on infection risk; variability in HbA1c has been shown to be very strongly associated with diabetes complications, including infections, in earlier studies[5, 16].

Therefore, to comprehensively evaluate the risk of infections amongst people with T1D, a much larger dataset is required, including all adult age groups, better reporting of ethnicity and incorporating more HbA1c measurements. This current study utilises a substantially larger dataset and describes: (i) the risk of infections presenting in primary or secondary care by age, sex and ethnicity amongst people with T1D, and (ii) the impact of HbA1c, both mean levels and variability, on infection risk. We chose a follow-up period ending just prior to the COVID-19 pandemic, as the pandemic severely disrupted non-COVID-19 infection reporting.

## 2. Subjects, Materials and Methods

### 2.1 Data resource

CPRD is a UK primary care database jointly sponsored by the Medicines and Healthcare products Regulatory Agency (MHRA) and the National Institute for Health and Care Research and has been described previously[17, 18]. It provides a pseudonymised longitudinal medical record for all registered patients (over 99% of the UK population are registered with a General Practitioner), with diagnoses and other clinical information recorded using Read codes. The database recently expanded (CPRD Aurum) to include 16 million currently registered patients[18], with over 80% having their ethnicity recorded[19]. Over 90% of contributing CPRD practices in England have consented to data linkage to external sources[20], including HES (Hospital Episodes Statistics), which records every NHS hospital admission in England[21] and the Index of Multiple Deprivation (IMD), a composite small-area (approximately 1500 people) measure used in England for resource allocation[22] and provides a good proxy for individual socio-economic deprivation[23].

### 2.2 Study design and participants

We conducted a retrospective matched cohort study including all patients aged 18-90 alive on 1<sup>st</sup> January 2015, and actively registered for at least one year, from practices with HES linkage. A total of 8,722,348 patients from 1,447 practices in England were eligible (Supplemental Figure S1). Study ethical approval was granted by CPRD's Research Data Governance (protocol number 21\_000592).

Patients with Read codes for diabetes recorded up to 1<sup>st</sup> January 2015 were classified into type 1 or 2 based on an algorithm previously described[17], which combines information from these codes, recent anti-diabetes medication and age at diagnosis. To be classed as T1D, patients had to either have: (i) Read codes specific to T1D, with no other Read code mentioning T2D, be prescribed insulin in 2014 and receive no other anti-diabetes medication in 2014 (except for biguanides or dapagliflozin), or (ii) at least one specific Read code indicating T1D, be prescribed insulin in 2014 and no other anti-diabetes medication, have no history of gestational diabetes and be first diagnosed under age 30. A total of 33,851 (0.4% prevalence) were selected.

For each T1D patient, two sets of patients without prediabetes or diabetes were created, matched on: (i) age, sex, practice and (ii) age, sex, ethnicity. Ethnicity was grouped into 5 broad categories (White, South Asian, Black, Mixed/Other and missing) based on recorded Read codes[17]. 33,829 (99.9%) T1D patients were matched (Supplemental Figure S1). All patients were followed up to the earliest date of: patient death or de-registration, practice leaving CPRD, or 31<sup>st</sup> December 2019.

### 2.3 Infection outcomes and covariates

We have previously described how we classified and grouped infections using an extensive list of Read codes (primary care) and ICD-10 codes (hospital data) for all

infection diagnoses[17]. We electronically searched the data over a 5-year period (2015-2019) for the following: (i) any infection with a prescription in primary care for an antibiotic, antifungal or antiviral within +/-14 days of diagnosis; (ii) any new hospital admission with infection as the primary diagnosis, or a subsequent hospital acquired infection during an in-patient stay[21]. For each summary group, only one event was counted within a 90-day period, with multiple codes assumed to be the same event. For hospitalisations, we carried out an analysis by specific infection type for the most common types (bone/joint, gastro-intestinal, genito-urinary, lower respiratory, sepsis, skin and surgical site). Following earlier concerns around ICD-10 coding on death certification data resulting in sepsis being underestimated[24], we took a conservative approach and counted sepsis, even if it was not the primary reason for the admission episode, but if it appeared within the first 5 diagnoses.

We further investigated infection risk in relation to both (medium-term) average and variability of HbA1c measurements among T1D patients. We restricted to T1D with at least 3 measurements during 2012-4 ( $n=26,096$ , 77.1%) (Supplemental Figure S1). We then defined categories of average level based on these cut-offs ( $\leq 53$ ,  $>53-64$ ,  $>64-75$ ,  $>75-86$ ,  $>86-97$ ,  $>97$  mmol/mol) following clinical guidelines[25, 26]. For variability we used the coefficient of variation (CoV) (ratio of standard deviation to mean) and then assigned categories to match the distribution of the categories for average level, in order to directly compare the effects of average and variability in HbA1c on infection risks.

We extracted information on smoking history, body mass index (BMI), and co-morbidities as of 1st January 2015. We selected 12 chronic conditions that are reliably recorded and as they are routinely collected as part of the Quality and Outcomes Framework (QOF), a UK wide system for performance management and payment of GPs in primary care[27]. These were atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, dementia, epilepsy, heart failure, hypertension, peripheral vascular disease, serious mental illness and stroke.

## 2.4 Statistical analyses

Conditional Poisson regression first compared infection incidence rate ratios (IRRs) during follow-up between people with T1D to those without diabetes, with an offset fitted for total days of follow-up time in the study (Stata version 15). Conditioning on the match-sets, implicitly controlled for matching factors (age, sex, practice/ethnicity). Models were initially fitted without any further adjustment, and then adjusted for socio-economic status (IMD quintile, with quintile 1 representing the most deprived 20% small areas in England), smoking, BMI and co-morbidity count. We explored the impact of sex, age (18-34, 35-49, 50-) and ethnicity as effect modifiers by fitting stratified models and comparing estimates. This was done in two ways: (i) directly comparing the IRRs by fitting an interaction term for the sub-group in the conditional model, (ii) fitting a Poisson model that does not condition on the matching but instead directly adjusts for age and sex. The latter model will account for any underlying age differences by ethnicity, important since people from UK ethnic minority groups are on average younger than the White population. For analyses of mean and variability of HbA1c, we first fitted stratified models by their respective categories, comparing risks



relative to people without diabetes. Then we summarised the risk amongst T1D patients only, by fitting Poisson models that adjusted for age and sex directly, using a reference category ( $\leq 53$  mmol/mol or CoV=0-3.7%), as per clinical guidelines[25, 26] as our baseline. Finally, we adjusted mean HbA1c for variability in HbA1c and vice versa, plus other potential confounders listed above. We also carried out a sensitivity analysis for HbA1c level only, where we redefined the reference category as  $>48$  to  $53$  mmol/mol to investigate whether there was an increase in hospitalisation infections associated with the lowest levels ( $\leq 48$  mmol/mol).

### 3. Results

#### 3.1 Prevalence and characteristics

Figure 1 (data in Supplemental Table S1) shows the age-specific prevalence of T1D in the adult population by sex (1a) and ethnicity (1b). Prevalence was higher overall for men (4.5 vs 3.3 per 1000 people). While prevalence for women tended to decline from age 18-30 onwards (3.8 per 1000), for men it increased in middle age, peaking between age 41 and 60 (5.4 per 1000). People of White ethnicity had a higher prevalence (4.6 per 1000); approximately twice as high as the non-White groups; this difference was most apparent at younger ages. Compared to people without diabetes, people with T1D had similar deprivation scores, a greater number of co-morbidities and were more likely to have a BMI  $\geq 30$ , though mean BMI was similar (Supplemental Table S2). The median time since diagnosis was 20 years (interquartile range 11 to 35 years).

#### 3.2 Infections

The crude rate of primary care infections was 1.8 times higher [(incidence rate ratios) IRR=1.81, 95%CI 1.77-1.85] and of hospital infections 3.4 times higher (IRR=3.37, 3.21-3.53) in people with T1D overall compared to patients without diabetes (Table 1). Adjusting for potential confounders (socio-economic status, smoking, BMI and co-morbidity count) only slightly attenuated associations (primary care=1.64, 1.61-1.68, hospitalisation=2.74, 2.60-2.88). Analyses using age-sex-practice controls were similar (Supplemental Table S3). Table 2 summaries the IRRs for both infection outcomes stratified by age, sex and ethnicity. The pattern by sex was inconsistent such that the impact of T1D on primary care infections was marginally higher in men, but for infections resulting in hospitalisation, the estimated IRRs were lower than among women. Compared to people of White ethnicity, the impact of T1D among non-White ethnicities was estimated to be higher (around 20% for primary care infections). The impact of T1D on infection risk was significantly higher in ages 18-34 compared to ages 50 and over (27% higher for primary care, 69% higher for infection risk resulting in hospitalisation). Unlike age, time since T1D diagnosis had minimal effect on the relative risk of infection rates (Supplemental Table S4).



When only infections resulting in hospital admissions were considered (Figure 2), the largest relative difference compared to people without diabetes was seen with bone and joint infections (IRR=23.02, 16.55-32.02), where such infections in the non-diabetes group were extremely rare (0.2 per 1,000 person years). Sepsis was also over five times higher in T1D patients (IRR=5.25, 4.68-5.89), with more common infections such as genitourinary infections (IRR=3.85, 3.46-4.29) and skin infections (IRR=3.83, 3.45-4.26) almost four times higher compared to people without diabetes.

### 3.3 HbA1c and infection risk

A total of 26,096 (77.1%) of T1D patients had at least 3 HbA1c measurements recorded during 2012-4 and were included in analyses of HbA1c and infection risk. Among these patients, the mean number of HbA1c measurements was 5.1 (SD=1.9), with an estimated mean HbA1c of 70.0 mmol/mol (SD=16.2). 3,004 (11.5%) had a mean HbA1c of  $\leq 53$  mmol/mol, and 1,678 (6.4%)  $>97$  mmol/mol. Both the mean and coefficient of variation (CoV) fell with age (Supplemental Figure S2), and T1D patients of Black ethnicity had higher HbA1c levels (especially at younger ages) and more variability between measurements. T1D patients of White ethnicity had the lowest HbA1c and CoV across all age groups (Supplemental Figure S2).

Figure 3 (accompanying data in Supplemental Table S5) summarises infection IRRs in people with T1D by separate categories of HbA1c mean and variability, compared to people without diabetes (Figure 3a-3b), and then simultaneously among T1D patients only using reference categories (Figure 3c-3d). Trends of increasing risk are seen for both level (3a) and variability (3b), but even T1D patients with the lowest levels or most stable measurements are still at higher risk than their non-diabetes comparison group. For example, among people with T1D with mean HbA1c  $\leq 53$  mmol/mol, the IRR=1.52 (95%CI 1.41-1.52) for infections presenting in primary care and IRR=2.08 (95%CI 1.76-2.45) for infections resulting in hospital admissions.

When HbA1c mean and variability were considered simultaneously in T1D only models (Figure 3c-3d), stronger trends were observed with mean level. People with T1D with a mean HbA1c  $>97$  mmol/mol were approximately four times more likely (IRR=4.09, 95% 3.55-4.71) to have a hospitalisation infection than those with mean HbA1c  $\leq 53$  mmol/mol, whereas people with the least stable HbA1c measurements (CoV $>21.3\%$ ) were only two times more likely (IRR=2.24, 95%CI 1.90-2.64). Accounting for potential confounders (Supplemental Table S5) attenuated these risks, but the relative risk with the highest HbA1c level was still over three times higher (IRR=3.22, 95% 2.80-3.70). Adjusting for HbA1c level and variability appear to explain the higher risks observed at the youngest ages and among the Black ethnic group (Supplemental Table S6). When specific infections resulting in hospitalisation were considered, mean level was mostly strongly associated with bone and joint infections, while variability showed the greatest trend with sepsis (Supplemental Table S7). In a sensitivity analysis for HbA1c level only, we found some evidence of a J-shape risk among all infections resulting in hospitalisation when we sub-divided our reference group to  $\leq 48$  and  $>48$  to 53 mmol/mol (Supplemental Table S8).

## 4. Discussion

### 4.1 Principal Findings

This study evaluating risk of infections amongst T1D patients demonstrated two key findings. Firstly, that T1D patients are at substantially increased risk of infections, requiring treatment both in primary care and those requiring hospitalisations, compared to people without diabetes of the same age, sex and ethnicity. The increased infection risk remained despite adjusting for potential confounders, especially those that could be influenced by ethnicity. These risks were broadly consistent across most demographic profiles, but we observed that younger age groups and non-White ethnicity had greater relative risk. This finding could be explained by higher HbA1c mean and variability amongst these sub-population groups. Our second key finding was that high mean HbA1c levels and, to a lesser extent, greater variability, were both associated with increasing infection risk; especially for infections requiring hospitalisation.

### 4.2 Strengths and weaknesses

A major strength of this study is the large T1D sample size, including almost 34,000 T1D patients followed for up to 5 years. This large dataset enabled us to provide prevalence estimates by ethnicity for T1D using a source of 8 million adults. Very few studies with large T1D cohorts have been published and previous CPRD analyses including ours, had fewer than 6,000 T1D patients[10, 28], therefore stratifying by age, sex and especially ethnicity, and assessing their impact on T1D outcomes was impossible. A long follow-up period spanning 5 years ending prior to the COVID-19 pandemic also ensured infection-related outcomes were measured accurately and not during a period when primary care data reporting was disrupted.

Our cohort therefore represents one of the largest studies of T1D patients to assess infection-related outcomes[1], and observe how ethnic-specific associations were modified by age[17]. We observed that T1D patients <50years and of non-White ethnicity had overall higher relative infection risk, for primary care infections and those requiring hospitalisations. When other factors were considered (e.g., deprivation, co-morbidity count, smoking, BMI and ethnicity), which potentially have a greater impact or are more common in people with T1D, the relative risk was attenuated. As some of these co-morbidities may be T1D associated consequences, this analysis might have over-adjusted, though the overall conclusions remained.

We also went to significant lengths to avoid misclassification of people with T2D as having T1D in our study. Generally, the quality of recording of diabetes type in QOF has improved over time[29, 30] and substantial effort was made to remove any patients who might have T2D and were incorrectly coded (e.g., removing those with prescribed anti-diabetic medication not typically associated with T1D in patient records, lack of current insulin prescribing, or any code suggesting earlier gestational diabetes in female patients) to ensure accuracy by following a consistent diabetes classification[17].

Another study strength is its assessment of HbA1c (mean and variability) on infection risk patterns. Our analyses identified that younger age groups and particularly those of Black ethnicity had higher HbA1c levels and more variability, which might explain some, and potentially be a consequence, of the higher infection risks; amongst these sub-population categories. Furthermore, our analyses used baseline HbA1c levels, and related them to future infection risk. As HbA1c can fluctuate over time, our design reduces the risk of reverse causality, in that some infections are known to raise HbA1c and blood glucose levels, and patients might have more measurements taken at the time of infectious illnesses. This approach has been used by other research groups and in our previous analyses[11, 16, 31].

This study is limited by the primary care recording of infections, which are often clinical and lack the confirmation of laboratory investigations. However, infections resulting in hospitalisations, where recording is supported by investigations, showed a much higher relative risk. Another limitation relates to using only HbA1c mean and variability as a measure for glycaemic control in T1D. Data from continuous capillary glucose monitoring (CGM) systems may enhance our understanding of glycaemic control on infection risk. 'Time in range', which refers to time in target on CGM is thought to be a better reflection of glycaemic control than conventional HbA1c measurements and could be used to assess infection risk in T1D in future research. Whilst CGM systems are increasingly being used as part of routine T1D care, such data are currently unavailable from UK primary care records.

#### 4.3 Comparisons with other studies

Few studies have investigated the overall risk of infections in T1D patients. Where T1D infection risks have been reported elsewhere[8, 32], our findings of increased risk are consistent with these, and use a large cohort with focus on both primary and secondary care infections. Our previous analysis using CPRD on a different, smaller T1D population, estimated IRRs of 1.7 and 3.7 for primary care infections and those resulting in hospitalization respectively, broadly in keeping with our current, more comprehensive, results[10]. In the current analysis, the infection risk in primary care is 1.8 times higher and those requiring hospitalisations is almost 3.4 times higher amongst T1D patients. We have also recently shown that amongst T2D and prediabetes patients, the relative risk of infection is increased when compared to non-diabetes patients, albeit overall lower as compared to T1D[17].

Some cohort studies in different countries have investigated the association between T1D and the risk of specific infections. A higher risk of pneumonia was seen amongst T1D in Denmark[33]; interestingly, in this Danish cohort study, diabetes duration of >10 years and higher HbA1c levels  $\geq 9\%$ , were associated with greater pneumonia risk[33]. In Netherlands, a cohort of 705 T1D patients were at increased risk of common primary care infections[8], and similarly a Finnish cohort of 4,748 T1D patients had higher incidences of bacterial infections[34]. Studies in South Korea and US have highlighted the higher incidence of infection-related hospitalizations, though did not differentiate between T1D or T2D[35, 36], and a recent Australian study demonstrated infection as a significant cause of mortality amongst T1D patients[32].

We have also shown that poor diabetes control, especially mean HbA1c levels at the highest level, had a four times higher infection risk compared to those with the lowest measured HbA1c levels, similar to our earlier work[11]. Additionally, our results here demonstrate that Black ethnicity is associated with higher HbA1c levels across different age groups, particularly adolescents and young adults, consistent with other T1D cohorts[37, 38]. Our finding of increased variability in HbA1c amongst minority ethnic groups, particularly Black ethnicity, is novel. Although people with T1D of Black ethnicity were generally younger than those of White ethnicity, they had consistently higher mean HbA1c and more HbA1c variability at all ages, which leads us to believe that the higher relative risks of infections we observed were being influenced by this. Generally, poor glycaemic control is known to cause serious adverse outcomes including mortality amongst T1D patients[16, 39].

Both hyperglycaemia and poor glycaemic control are known to drive immunosuppression, and hence a greater susceptibility to infections, fuelling a cycle whereby infectious disease then worsens glycaemic control[33, 34]. T1D patients from younger age groups and minority ethnic groups have consistently been shown to have poorer glycaemic control, supporting our findings [14, 37]. Some diabetes medications are thought to increase infection risk (e.g., SGLT-2 inhibitors and urinary tract infections)[40]. We examined this as a sensitivity analysis, but only 1% of T1D patients were prescribed SGLT-2 inhibitors, and excluding these did not affect the results. It has been shown that there is an increased risk of certain infections with suboptimal glycaemic control in T1D; these include urinary tract infections[41], perianal abscesses[42], streptococcal infections where the adjusted odds ratio amongst T1D was 14.8[43], but not necessarily for eye infections[44]. Although difficult to directly compare with our own analyses for specific infections, we have also demonstrated that serious infections presenting to secondary care (e.g., bone and joint infections, and sepsis) had significantly high risk amongst T1D. For sepsis, our finding was similar to a recent national study of 33,549 T1D patients in Sweden, which estimated a high relative risk of sepsis (4.26) in patients with a high level of HbA1c (>82 mmol/mol)[45]. They additionally observed a small increase in risk for patients with a HbA1c below 48 mmol/mol, which we also observed in a sensitivity analysis, however we think this a minor clinical issue compared to the impact of high HbA1c levels, since the increased risk is small and because so few T1D patients (5%) have levels this low.

#### 4.4 Implications of study findings and future research

Increased infection risks in T1D should be considered as a health hazard by both patients and clinicians. However, UK, European and US guidance place limited emphasis on infections in the context of managing T1D[2, 26]. Specifically, under UK guidelines, infections are referenced only in the management of diabetic ketoacidosis or common diabetic foot problems[2]; our analyses suggest that infection risks in T1D are a much broader concern. This emphasises the importance to clinicians, policymakers and other stakeholders of prompt management of infections in primary care, which has potential to reduce infections requiring hospitalisation. Only 11.5% of T1D patients had a mean HbA1c level below the recommended target ( $\leq 53$  mmol/mol)[25, 26] and since glycaemic control is a significant factor for infection and other risks, new rapid access glucose monitoring systems may have a substantial benefit, though require further study[46].

Our findings demonstrate that the infection risk in primary and secondary care in T1D is clinically important, and in fact, far higher than that observed for T2D or prediabetes. Our analyses have emphasized that people with T1D with higher mean HbA1c, which is more common amongst younger age groups and those of Black ethnicity, are at higher risk of infections, particularly those requiring hospitalisation. This is important as it identifies those T1D patients who are potentially vulnerable to developing these adverse outcomes and who particularly need to seek prompt treatment for infections. More specifically, bone and joint infections, surgical site infections and sepsis had the highest incidence rate ratios for infections resulting in hospitalisation in T1D. Earlier initiation of treatment is therefore likely to be important in preventing long-term morbidity and mortality from these illnesses, and improved glycaemic control may also be central to mitigating T1D-related infections. Therefore, it is an important priority to develop and evaluate interventions that clearly focus on these issues. There is a need for guidelines to reflect on the high risk of infections in people with T1D, to encourage earlier presentation and treatment, and therefore, reduce more serious complications.

## Acknowledgments

We thank our helpful Patient Study Advisory Group for their input, particularly to discussion and interpretation of the results.

## Data availability

The data supporting this study's findings are available from CPRD obtained under license from the UK MHRA, but restrictions apply to data availability. CPRD data governance and the data license do not allow patient data distribution, researchers must apply directly to CPRD for data access (<https://www.cprd.com>). However, code lists generated during the current study are available <https://10.24376/rd.sgul.21565557>.

## Funding

This study is funded by the National Institute for Health and Care Research (NIHR) - Research for Patient Benefit Programme (NIHR202213) and supported by the NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

### Role of the funding source

The study funder had no role in study design, collection, analysis, and interpretation of data; writing of the report or decision to submit the paper for publication. IC had full access to all the data in the study, and UC and IC had final responsibility for the decision to submit for publication.

## Authors' relationships and activities

We declare no competing interests.

## Author contributions

UC and IC wrote the first draft of the manuscript with input from all co-authors. IC led the data curation and statistical analysis. IC, UC, JC, SW, DC and TH were involved in the conception and design of the study. JC led on funding acquisition. IC, UC, JC, SW, EL, LB, AP, DC, PW and TH were involved in the interpretation of data for the work. IC, UC, JC, SW, EL, LB, AP, DC, PW, and TH approved the final version for publication. IC 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. UC and IC are the guarantors of this work.



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## Tables

Table 1 – Infection rates and incidence rate ratios in type 1 diabetes and matched patients without diabetes.

	Total Patients		Primary Care						Hospitalisations					
	T1 D	Non-D	Rates per 1,000		Incidence rate ratios for T1D vs non-D				Rates per 1,000		Incidence rate ratios for T1D vs non-D			
			T1 D	Non-D	IRR1‡	95% CI	IRR2‡	95% CI	T1 D	Non-D	IRR1‡	95% CI	IRR2‡	95% CI
All	33,829	66,789	202.7	112.7	1.81	1.77-1.85	1.64	1.61-1.68	51.3	16.4	3.37	3.21-3.53	2.74	2.60-2.88
By sex														
- Females	14,149	27,940	262.6	153.6	1.71	1.66-1.76	1.58	1.53-1.63	59.3	18.1	3.52	3.29-3.77	2.90	2.70-3.13
- Males	19,680	38,849	159.7	83.6	1.93	1.87-2.00	1.72	1.66-1.78	45.8	15.1	3.24	3.03-3.46	2.60	2.42-2.80

By age														
- 18 to 34 years	9,705	19,209	214.6	109.1	1.95	1.87-2.03	1.84	1.76-1.93	44.4	11.5	3.84	3.48-4.23	3.50	3.13-3.91
- 35 to 49 years	10,407	20,594	190.2	102.7	1.86	1.78-1.93	1.68	1.61-1.75	40.5	10.3	4.04	3.69-4.45	3.23	2.91-3.59
- 50 to 90 years	13,717	26,986	204.4	122.1	1.70	1.64-1.75	1.51	1.46-1.56	64.5	23.8	2.99	2.80-3.19	2.37	2.21-2.55
By ethnicity														
- South Asian	839	1,599	234.2	109.4	2.08	1.81-2.38	1.89	1.62-2.21	51.6	12.3	4.34	3.21-5.86	3.32	2.29-4.81
- Black	594	1,145	176.9	82.0	2.03	1.68-2.45	2.08	1.70-2.55	55.6	15.1	3.71	2.55-5.40	3.51	2.29-5.39
- Mixed/Other	1,093	2,144	200.5	86.1	2.34	2.05-2.68	2.11	1.83-2.45	50.0	10.3	5.06	3.72-6.87	4.19	2.97-5.91
- White	27,315	54,064	203.2	118.4	1.73	1.69-1.77	1.59	1.55-1.63	50.6	16.8	3.24	3.08-3.41	2.68	2.53-2.83

T1 D = Type 1 diabetes. Non-D = Patients without diabetes matched on age, sex and ethnicity.

† - Annual rate per 1000 persons. 15,608 (46.1%) of T1DM patients have ≥1 primary care infection, and 5,495 (16.2%) ≥1 hospitalisation infection during follow-up compared to 30.7% and 6.0% of patients without diabetes.

‡ - Incidence rate ratio compared to matched non-diabetes. IRR1 adjusts only for matching factors. IRR2 additionally adjusts for deprivation (IMD), co-morbidity count, smoking, BMI and ethnicity.

Note: 3,988 (12%) Type 1 diabetes and 7,837 patients without diabetes had missing ethnicity.

Table 2 – Comparison of estimated infection rate ratios between type 1 diabetes and matched patients without diabetes by sex, age and ethnicity

	Primary Care						Hospitalisations					
	T1D vs non-D		T1D vs reference category				T1D vs non-D		T1D vs reference category			
	IRR2‡	95% CI	IRR3‡	95% CI	IRR4‡	95% CI	IRR2‡	95% CI	IRR3‡	95% CI	IRR4‡	95% CI
By sex												
- Females	1.58	1.53-1.63	1 (ref)	–	1 (ref)	–	2.90	2.70-3.13	1 (ref)	–	1 (ref)	–
- Males	1.72	1.66-1.78	1.09	1.04-1.14	1.08	1.04-1.13	2.60	2.42-2.80	0.89	0.81-0.99	0.90	0.82-0.98
By age												

- 18 to 34 years	1.84	1.76-1.93	1.23	1.16-1.31	1.27	1.20-1.34	3.50	3.13-3.91	1.51	1.32-1.72	1.69	1.51-1.90
- 35 to 49 years	1.68	1.61-1.75	1.13	1.07-1.19	1.15	1.09-1.21	3.23	2.91-3.59	1.44	1.28-1.63	1.57	1.41-1.76
- 50 to 90 years	1.51	1.46-1.56	1 (ref)	_	1 (ref)	_	2.37	2.21-2.55	1 (ref)	_	1 (ref)	_
By ethnicity												
- South Asian	1.89	1.62-2.21	1.18	1.03-1.37	1.21	1.06-1.40	3.32	2.29-4.81	1.21	0.87-1.67	1.26	0.94-1.68
- Black	2.08	1.70-2.55	1.14	0.93-1.39	1.19	0.98-1.44	3.51	2.29-5.39	1.16	0.76-1.77	1.11	0.76-1.62
- Mixed/Other	2.11	1.83-2.45	1.23	1.13-1.33	1.22	1.13-1.32	4.19	2.97-5.91	1.54	1.12-2.12	1.57	1.16-2.12
- White	1.59	1.55-1.63	1 (ref)	_	1 (ref)	_	2.68	2.53-2.83	1 (ref)	_	1 (ref)	_

T1 D = Type 1 diabetes (n=33,829). Non-D = Patients without diabetes matched on age, sex and ethnicity (n=66,789).

IRR2 adjusts for deprivation (IMD), co-morbidity count, smoking, BMI and ethnicity (these results are given in Table 1 in main paper)

IRR3 now tests each IRR2 between different categories and a reference category by fitting an interaction term (conditional Poisson model).

IRR4 compares between different categories and a reference category, without conditioning on the matched sets, but adjusts for age and sex as covariates in an ordinary Poisson model. This model will account for underlying age differences by ethnicity.



Journal Pre-proofs

## Legends for Figures

**Figure 1** – Estimated prevalence of type 1 diabetes in adults aged 18-90 in England

(i) By sex. Bar colours represented as follows: Female (yellow coloured bar); Male (blue coloured bar)

(ii) By ethnicity (and stratified by different age groups). Bar colours represented as follows: South Asian (green coloured bar); Black (blue coloured bar); Mixed/Other (grey coloured bar); White (orange coloured bar); Missing (white coloured bar).

**Figure 2** – Incidence rate and rate ratios for infections resulting in hospitalisation in patients with type 1 diabetes versus matched patients without diabetes

IRR = incident rate ratios (95% confidence interval) vs. patients without diabetes matched on age, sex, and ethnicity. Infection type defined as primary cause for hospital episode, except for sepsis where diagnoses within the episode ordered up to the 5<sup>th</sup> in sequence were also allowed. GIT = gastrointestinal; GUI = genitourinary; LRTI = lower urinary tract infections.

**Figure 3** – Infection rate ratios by HbA1c mean and coefficient of variation at baseline

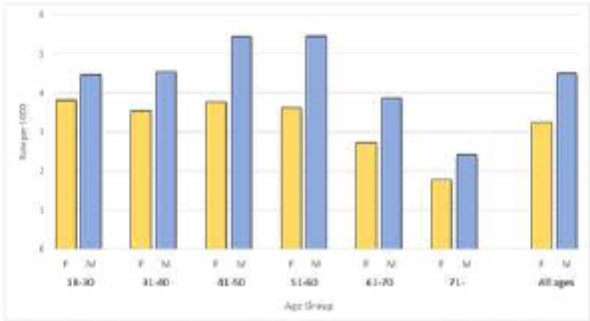
Notes: (a) and (b) are derived from fitting a conditional Poisson model that compares T1D patients to patients without diabetes matched on age, sex and ethnicity. (c) and (d) are derived from a Poisson model fitted to T1D patients only, which instead adjusts for age, sex and ethnicity. The former will not account for differences in age, sex and ethnicity between HbA1c categories, whereas the latter does. The number of T1D patients in the average HbA1c categories was:  $\leq 53$   $n=3,004$  (11.5%),  $>53$  to  $64$   $n=7,220$  (27.7%),  $>64$  to  $75$   $n=7,596$  (29.1%),  $>75$  to  $86$   $n=4,377$  (16.8%),  $>86$  to  $97$   $n=2,221$  (8.5%),  $>97$   $n=1,678$  (6.4%). The coefficient of variation categories were chose to give the same percentages.

Figure 1

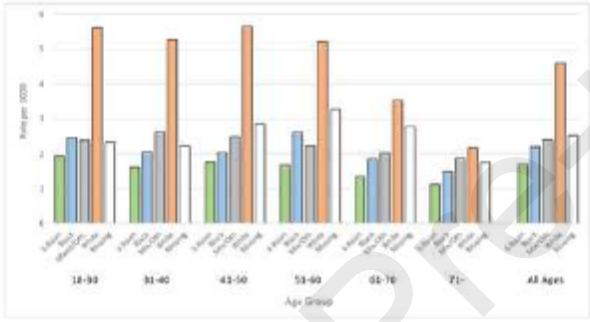
[Click here to access/download;Figure;Figure 1.jpg](#)

Figure 1

(i) By sex



(ii) By ethnicity

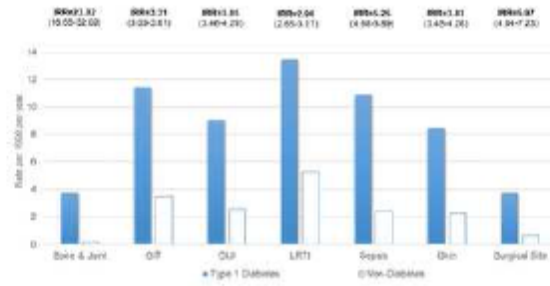


Journal Pre-proofs

Figure 2

[Click here to access/download;Figure;Figure 2.jpg](#)

Figure 2

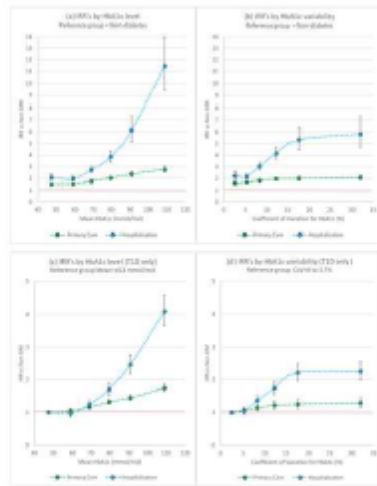


IRR = Incidence rate ratios (95% confidence interval) vs. patients without diabetes matched on age, sex and ethnicity. Infection type defined as primary cause for hospital episode, except for sepsis where diagnoses within the episode ordered up to the 5th in sequence were also allowed. GI = gastrointestinal tract; OLP = genitourinary; LRTI = lower respiratory tract infections

Figure 3

[Click here to access/download/Figure/Figure\\_3.jpg](#)

Figure 3



Notes: (a) and (b) are derived from fitting a conditional Poisson model that compares T2D patients to patients without diabetes matched on age, sex and ethnicity. (c) and (d) are derived from a Poisson model fitted to T2D patients only, which instead adjusts for age, sex and ethnicity. The former without account for differences in age, sex and ethnicity between HbA1c categories, whereas the latter does. The number of 1) 0 patients in the average HbA1c categories was: 531 n=5.094 (11.26%), 53 to 54 n=2.230 (27.7%), 64 to 75 n=1.596 (21.1%), 75 to 80 n=4.527 (30.8%), 80 to 87 n=2.211 (8.19%), 87 n=1,418 (6.4%). The coefficients of variation categories were chosen to give the same percentages.