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Supplementary appendix

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Increased infection risk in the elderly with reduced glycaemic control: Supplementary appendix

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Methods

We performed a retrospective analysis of infection rates in older people with diabetes. We used data from the Royal College of General Practitioners Research and Surveillance Centre (RCGP-RSC) database. This contains data from a primary care sentinel network primarily involved in infectious disease surveillance. At the time of analysis the database contained primary care records collected from 649,844 people registered with a 110 practices distributed across England.

We identified people with diabetes using clinical diagnostic codes, laboratory results (HbA1c measurement and glucose measurements), the presence of prescriptions for diabetes specific medications, and process of care codes (diabetes clinical review codes). We selected all people with diabetes (type 1 and type 2) who were 65 or older on 1st January 2014 for inclusion in the study.

We identified incident cases of pneumonia, urinary tract infections, and skin and soft tissue infections occurring during 2014, from the clinical record. We analysed the impact of HbA1c on the rates of infection using logistic regression. The HbA1c values used were the most recent prior to 1st January 2014. HbA1c values more than 3 years prior to this date were excluded. Odds ratios for annual incidence of each infection are provided after adjusting for age, gender, deprivation, smoking status, body mass index (BMI), diabetes type, and co-morbidities. Deprivation was calculated using the index of multiple deprivation score for each person based on their postcode with people categorised by quintile (compared to national quintiles). Comorbidities included in regression models were chronic obstructive pulmonary disease (COPD) and asthma, previous stroke, ischaemic heart disease and heart failure, peripheral vascular disease, and chronic kidney disease. Ischaemic heart disease was defined as previous myocardial infarction, angina, or previous revascularisation procedure. Chronic kidney disease was defined as a definitive clinical diagnostic code for renal impairment of stage 3 to stage 5.

Statistical analyses

We report the number and proportion of people within the cohort with each variable of interest with means and standard deviation for numeric measures. For each infection type we performed two logistic regression analyses; firstly using HbA1c as a continuous variable, secondly stratifying HbA1c by good (53mmol/mol, <7.0%), moderate (53-69mmol/mol, 7.0-8.5%), and poor (>69mmol/mol, >8.5%) control. The presence or absence of the infection of interest for each model was used as the binary outcome variable for each model. Each model included adjustment for the covariates listed above. Model selection was performed by backwards step-wise elimination of non-significant ($p<0.05$) variables; all the available covariates were initially included and then removed individually starting the least significant. We provide odds ratios for the presence of incident infection during the follow up year with 95% confidence intervals and p values. All statistical analyses were performed using R version 3.2.2.

Results

We identified 19,806 people with diabetes (19,534 with type 2 and 272 with type 1) aged 65 or over. The mean age of this cohort was 75.3 (SD 7.2) years. The minority (9,193, 47.1%) were female. Most people in the cohort (19,456; 98.2%) had a recent HbA1c measurement. The mean HbA1c was 54.6 (SD 14.2) mmol/mol with 10,516 (53.8%) with good control, 6,741 (34.5%) with moderate control, and 2,199 (11.2%) with poor control. Complete information on demographics and comorbidities is

demonstrated in Table S1. During the year analysed there were 113 (0.6%) people who were diagnosed with pneumonia, 1,169 (6.0%) with urinary tract infections and 1,487 (7.6%) with skin and soft tissue infections.

The crude annual incidence of pneumonia, urinary tract infections, and skin and soft tissue infections was higher in people with poor glycaemic control (Table S2). After adjusting for confounding variables (Table S3) poor glycaemic control (HbA1c >69mmol/mol; >8.5%) was significantly associated with increased risk of each infection (see Table 1 in main article). Moderate glycaemic control (HbA1c 53-69mmol/mol; 7.0-8.5%) did not appear to increase infection risk after adjustment for confounders.

Supplementary tables

Clinical characteristic	n (%) or mean (SD)	Clinical characteristic	n (%) or mean (SD)
Age (years)	75.3 (7.2)	**Type 1 diabetes**	272 (1.4)
Gender (female)	9,193 (46.4)	**Type 2 diabetes**	19,534 (98.6)
Deprivation status available	19,806 (100.0)	**HbA1c measured**	19,456 (98.2)
Highest quintile (least deprived)	2,569 (13.0)	**HbA1c (mmol/mol)**	54.6 (14.2)
Second quintile	2,921 (14.7)	**BMI measured**	19,198 (96.9)
Third quintile	3,281 (16.6)	**BMI (kg/m^2)**	29.6 (5.7)
Forth quintile	5,131 (25.9)	**COPD/asthma**	3,100 (15.7)
Fifth quintile (most deprived)	5,904 (29.8)	**Stroke**	1,744 (8.8)
Smoking status recorded	19,584 (98.9)	**IHD/CCF**	3,811 (19.2)
None smoker	6,385 (32.2)	**Peripheral vascular disease**	1,005 (5.1)
Current smoker	1,580 (8.0)	**Chronic kidney disease**	6,360 (32.1)
Ex-smoker	11,619 (58.7)		

Table S1. Demographic and comorbidity information for the cohort analysed (n=19,806 older people with diabetes). IMD = index of multiple deprivation, BMI = body mass index, COPD = chronic obstructive pulmonary disease, IHD = ischaemic heart disease, CCF = congestive cardiac failure.

Glycaemic control	n (%)	Pneumonia (n=113)	Urinary tract infections (n=1,169)	Skin and soft tissue infections (n=1,487)
HbA1c <53mmol/mol (<7.0%)	10,516 (53.1)	51 (0.5%)	596 (5.7%)	741 (7.0%)
HbA1c 53-69mmol/mol (7.0-8.5%)	6,741 (34.0)	32 (0.5%)	407 (6.0%)	522 (7.7%)
HbA1c >69mmol/mol (>8.5%)	2,199 (11.1)	23 (1.0%)	157 (7.1%)	210 (9.5%)

Table S2. Crude incidence rates of infections during a one year follow-up period (2014) in older people stratified by glycaemic control. Percentage values for each infection column represent the proportion of people diagnosed with that infection within each band of glycaemic control.

	Pneumonia		Urinary tract infections		Skin and soft tissue infections	
Clinical characteristic	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age (years)	1.07 (1.04-1.09)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.02-1.03)	<0.001
Female	1.00 [reference]	-	1.00 [reference]	-	1.00 [reference]	-
Male	1.62 (1.09-2.43)	0.018	0.39 (0.34-0.45)	<0.001	0.87 (0.78-0.97)	0.014
Deprivation status (IMD)						
Highest quintile (least deprived)	1.00 [reference]	-	-	-	1.00 [reference]	-
Second quintile	1.80 (0.81-3.99)	0.149	-	-	1.00 (0.81-1.24)	0.983
Third quintile	2.64 (1.25-5.60)	0.011	-	-	1.11 (0.90-1.36)	0.333
Forth quintile	1.38 (0.64-3.01)	0.414	-	-	1.21 (1.00-1.46)	0.050
Fifth quintile (most deprived)	1.30 (0.60-2.81)	0.503	-	-	1.22 (1.02-1.47)	0.034
BMI (kg/m^2)	-	-	1.01 (1.00-1.02)	0.021	-	-
COPD/asthma	3.24 (2.18-4.83)	<0.001	-	-	-	-
Stroke	-	-	1.36 (1.12-1.66)	0.002	1.40 (1.18-1.67)	<0.001
IHD/CCF	-	-	1.33 (1.14-1.54)	<0.001	1.20 (1.05-1.38)	0.007
Peripheral vascular disease	2.50 (1.43-4.36)	0.001	1.41 (1.10-1.81)	0.006	1.35 (1.08-1.69)	0.007
Chronic kidney disease	-	-	1.15 (1.01-1.31)	0.039	1.17 (1.04-1.32)	0.008

Table S3. Adjusted odds ratios for pneumonia, urinary tract infection, and skin and soft tissue infections in 19,806 older people with diabetes. Diabetes type and smoking status was not significantly associated with any infection type and has therefore been removed from all models. Other variables have been removed by backwards stepwise elimination if non-significant and therefore have no values shown in the table. HbA1c stratified by good, moderate, and poor control (see text) is also included in all three of these models (see table 1 in main article). OR = odds ratio, IMD = index of multiple deprivation, BMI = body mass index, COPD = chronic obstructive pulmonary disease, IHD = ischaemic heart disease, CCF = congestive cardiac failure.