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Association between glycaemic control and common infections in people with Type 2 diabetes: a cohort study

J. L. Hine[1], S. de Lusignan[1], D. Burleigh[1], S. Pathirannehelage[1], A. McGovern[1], P. Gatenby[1,2], S. Jones[1], D. Jiang[3], J. Williams[1], A. J. Elliot[4], G. E. Smith[4], J. Brownrigg[5], R. Hinchcliffe[5] and N. Munro[1]

[1]Section of Clinical Medicine and Ageing, University of Surrey, Guildford, [2]Royal Surrey County Hospital, Guildford, Surrey, UK, [3]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN, USA, [4]Public Health England, Birmingham, UK and [5]St George's Vascular Institute, Division of Cardiovascular Sciences, St George's University of London, London, UK

Correspondence to: Julia Hine. E-mail: jhine@doctors.org.uk.

What's new?

- This is the first large-scale study of the impact of glycaemic control on the incidence of infection across a wide range of conditions, with adjustment for important confounders.
- Worse glycaemic control was associated with greater risk of conditions that are most commonly of bacterial, fungal or yeast origin, but not of those of viral origin (with the exception of bronchitis).

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Abstract

Aim To investigate the impact of glycaemic control on infection incidence in people with Type 2 diabetes.

Methods We compared infection rates during 2014 in people with Type 2 diabetes and people without diabetes in a large primary care cohort in the UK (the Royal College of General Practitioners Research and Surveillance Centre database). We performed multilevel logistic regression to investigate the impact of Type 2 diabetes on presentation with infection, and the effect of glycaemic control on presentation with upper respiratory tract infections, bronchitis, influenza-like illness, pneumonia, intestinal infectious diseases, herpes simplex, skin and soft tissue infections, urinary tract infections, and genital and perineal infections. People with Type 2 diabetes were stratified by good [HbA_{1c} <53 mmol/mol (<7%)], moderate [HbA_{1c} 53–69 mmol/mol (7–8.5%)] and poor [HbA_{1c} >69 mmol/mol (>8.5%)] glycaemic control using their most recent HbA_{1c} concentration. Infection incidence was adjusted for important sociodemographic factors and patient comorbidities.

Results We identified 34 278 people with Type 2 diabetes and 613 052 people without diabetes for comparison. The incidence of infections was higher in people with Type 2 diabetes for all infections except herpes simplex. Worsening glycaemic control was associated with increased incidence of bronchitis, pneumonia, skin and soft tissue infections, urinary tract infections, and genital and perineal infections, but not with upper respiratory tract infections, influenza-like illness, intestinal infectious diseases or herpes simplex.

Conclusions Almost all infections analysed were more common in people with Type 2 diabetes. Infections that are most commonly of bacterial, fungal or yeast origin were more frequent in people with worse glycaemic control.

Introduction

Diabetes is known to be associated with an increased risk of a range of infections [1]. The mechanisms are not fully understood, but hyperglycaemia has been shown to impair multiple immune pathways including neutrophil activation and antibody function [2,3]. In addition to these systemic factors, local factors such as foot ulceration can contribute to higher infection rates [4]. Specific infections in diabetes, including foot and urinary tract infections [5,6], have been studied in detail. Furthermore, several studies have confirmed excess mortality from infection in people with diabetes [7,8], and worse outcomes in people with diabetes who are hospitalized as a result of infections [9].

The relationship between glycaemic control, and rates of community-acquired infections in people with diabetes have not been well characterized. Small-scale studies suggest that there is an association between poor glycaemic control and the risk of certain infections [9,10]. A recent review identified a number of observational studies and clinical trials that showed a possible association between poor glycaemic control and rates of infection, but no single study had adequate characterization of glycaemic control before the observed infection episode, adequate control of

major confounders and adequate sample size [11]. The review authors called for higher-quality observational data on the impact of poor glycaemic control on infection rates. We aimed to provide this evidence in the present study, with measures of incident rates across a wide range of important infections in a large UK-based primary care cohort using data from the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database. This database collects data from a network of primary care centres across England with the primary purpose of infection surveillance [12,13]. Data on infectious diseases routinely collected by practitioners at these practices have been collated on a weekly basis (twice weekly during epidemics) since 1957. Clinicians receive regular feedback about data quality and therefore the network provides an extremely high standard of infection surveillance data. The information quality of infection recording from this network has previously been validated using virological data [14] and hospital episode data [15].

The present study cohort was stratified into three HbA_{1c}-defined groups of good [53 mmol/mol (<7%)], moderate [53–69 mmol/mol (7–8.5%)] and poor [>69 mmol/mol (>8.5%)] glycaemic control.

We carried out this observational study to investigate both the impact of Type 2 diabetes on rates of presentation to primary care with infection, and, for people with Type 2 diabetes, whether infection incidence differs between HbA_{1c}-stratified groups.

Design and methods

Data source

The RCGP RSC database was receiving weekly data uploads from 110 general practices at the time of data analysis, comprising approximately 1 million people's electronic patient records. Anonymized electronic patient records from 2004 until the present were available for the present analysis; these included coded diagnostic, demographic, biochemical and prescription data at individual patient-level. UK primary care has a registration-based system whereby all citizens are entitled to free primary care through registration with a single general practice. This system results in the majority of the population being registered with a single practice, ensuring capture of people across the sociodemographic range and preventing double counting of patients.

Study population and definition of variables

The study period was defined as the 12 months between 1 January and 31 December 2014. All individuals aged >18 years on 1 January 2014 who were registered in the RCGP RSC database for the duration of the study period were eligible for inclusion. An additional 1-year period of registration in the database before the study period was required for study inclusion to enable accurate recording of baseline data. People who met the inclusion criteria were classified into those with Type 2 diabetes and those without diabetes at baseline, through an ontologically rich case-finding approach [16], consistent with consensus definitions for diabetes [17,18]. Diagnostic, biochemical and prescription data, entered before 1 January 2014, were used (see Appendix S1 for full case-definition algorithm).

The outcome measure was all recorded presentations to primary care with a new episode of infection during the study period. These were extracted from the database at patient level, using the relevant Read diagnostic codes. The codes used were taken from the validated indicators used in routine surveillance by the Research and Surveillance Centre (Appendix S2). We studied the following types of infections: upper respiratory tract infections; bronchitis; influenza-like-illness; pneumonia; intestinal infectious diseases; herpes simplex; skin and soft tissue infections; urinary tract infections; and genital and perineal infections. These were selected principally as they represent the majority of the primary care adult infectious disease burden, and include viral, bacterial and fungal infections. First or new episodes of an infection are coded accordingly in the database, enabling differentiation from chronic infections or follow-up visits for the same episode.

Demographic and baseline (most recent relevant entry before 1 January 2014) clinical data were extracted including: age; gender; socio-economic status (index of multiple deprivation [19] calculated from patient postcode); BMI; smoking status (current smoker, ex-smoker, or never smoked) and comorbidities. Comorbidities comprised chronic kidney disease, asthma or chronic obstructive pulmonary disease, previous stroke or transient ischaemic attack, peripheral vascular disease and heart failure or ischaemic heart disease. For people with Type 2 diabetes, we extracted therapeutic data, diabetes duration and their most recent HbA_{1c} value from within 3 years (including the study year). We converted all HbA_{1c} measurements to the International Federation of Clinical Chemists (IFCC) measure. Type 2 diabetes duration was calculated as the time between an individual's first record indicative of diabetes (diagnostic code, prescription, or diagnostic biochemistry), and 1 January 2014.

Data analysis

Incidence rates (per 1000 person-years) of presentation to primary care with new episodes of infection were calculated separately for the groups with Type 2 diabetes and without diabetes. Rates were calculated for each individual type of infection, and a cumulative rate for all infections. These were standardized for age and gender, using direct standardization against the 2011 England and Wales population census [20]. Multiple episodes of infection in an individual were included in these calculated rates, however, only episodes coded as first or new were counted.

We produced multilevel logistic regression models using patient-level data to assess the independent effect of Type 2 diabetes on presentation with infection. The outcome variable, presentation with infection, was converted to a binary, both for individual infection types and for the cumulative outcome of presentation with any infection. The dependent variables were Type 2 diabetes, age, gender, deprivation quintile, smoking status and comorbidities. To allow for variation between general practices, patients were nested within practices, which formed the upper level of the multilevel regression models. We report the adjusted odds ratios for the impact of Type 2 diabetes on each infection type with 95% CIs and associated *P* values.

People with incomplete data for the variables used were excluded from the multilevel logistic regression models. A sensitivity analysis was performed to assess the impact of exclusion of people with incomplete data; the analysis was repeated using the complete study cohort excluding the smoking covariate from the logistic regression model. A further sensitivity analysis was performed substituting all missing variables with each of the three possible smoking statuses in turn, and repeating the analysis each time.

We produced further logistic regression models for people with Type 2 diabetes to assess the independent impact of glycaemic control on presentation with infection. Dependent variables were the same as those listed above with the addition of diabetes duration. People with Type 2 diabetes were stratified into three groups based on their most recent HbA_{1c} reading: good [<53 mmol/mol (<7%); *n*=16 321]; moderate [53–69 mmol/mol (7–8.5%); *n*=11 496]; and poor [>69 mmol/mol (>8.5%); *n*=5406) glycaemic control. We excluded people with Type 2 diabetes without an HbA_{1c} reading from within 3 years or with incomplete data for the covariates from these models. All statistical analyses were performed in R statistical package software version 3.2.1. Multilevel modelling was performed using the package lme4.

Results

Patient characteristics

A total of 647 330 adults were included in the study, 34 278 of whom had Type 2 diabetes (a crude prevalence of 5.3%). There were 317 719 (49.1%) men in the total study population. The characteristics of those with and without diabetes are shown in Table 1.

Effect of Type 2 diabetes on incidence of infections

Complete data were available for 577 291 people (89.2% of the study population); the missing data were smoking status. Only those with complete data were included in regression analysis. We found that age-standardized rates of all types of infections except herpes simplex were higher in people with Type 2 diabetes (Table 2). Adjusted odds ratios, calculated using multilevel logistic regression models, showed a significant positive association with Type 2 diabetes for all infection types except herpes simplex (Fig. 1). Genital and perineal infections were most strongly associated with prevalent Type 2 diabetes. Skin and soft tissue infections and urinary tract infections also showed strong positive associations with Type 2 diabetes. The sensitivity analysis suggested that missing data had little impact on these associations.

Effect of glycaemic control on incidence of infections in people with Type 2 diabetes

The majority (33 223; 96.9%) of people with Type 2 diabetes had an HbA_{1c} measurement from within 3 years. Of these, 92.1% were from the study year of 2014. Those with complete data were included for analysis. Adjusted odds ratios for incidence of bronchitis, pneumonia, skin and soft tissue

infections, urinary tract infections, and genital and perineal infections, increased with worsening glycaemic control (Table 3). There was no association between glycaemic control and upper respiratory tract infections, influenza-like illness, intestinal infectious diseases or herpes simplex. Sensitivity analysis showed that inclusion in the models of the 8% of people with Type 2 diabetes with an HbA_{1c} from within 3 years, but outside of the study year itself, did not significantly alter the results compared with when this 8% were excluded.

Discussion

People with Type 2 diabetes present significantly more frequently to primary care with almost all common infectious diseases than people without diabetes; only herpes simplex was as frequent in people with diabetes as those without. Other infections, most commonly of viral origin, were only slightly more common in people with Type 2 diabetes (upper respiratory tract infections and influenza-like illness).

Conditions most commonly caused by bacteria, fungi and yeasts were more common in people with worse glycaemic control (pneumonia, skin and soft tissue infections, urinary tract infections and genital and perineal infections). Conditions most commonly of viral origin showed no increased incidence in people with worsening glycaemic control (upper respiratory tract infections, influenza-like illness, intestinal infectious diseases [21,22] and herpes simplex).

Further research

The reasons for the variable association between Type 2 diabetes and different infections require further exploration. Hyperglycaemia has been shown to interfere with multiple immune mechanisms [3]; a recent study in rats has shown that hyperglycaemia inhibits humoral effector recruitment and complement-mediated opsonization and phagocytosis in response to *Staphylococcus aureus* [23]. Impaired blood supply as a result of microvascular damage can also increase local susceptibility to infection. These and other factors may exert variable influences in different infections. Possible infection-specific factors may also play a role; for example, in the case of urinary tract infections, neuropathic impairment of bladder emptying and catheter requirement, and the glycosuria caused by new sodium-glucose co-transporter-2 inhibitor drugs, may contribute to the incidence of infections [5,24].

Similarly, further research is needed to establish the mechanism through which poor glycaemic control results in increased incidence of infections for selected conditions. One hypothesis is that the infections that exhibit this relationship involve bacterial or fungal colonization of superficial epithelial surfaces. In individuals with a higher HbA_{1c}, there is likely to be a higher glucose concentration in these superficial tissue layers, increasing their susceptibility to colonization. Alternatively, the degree of immune inhibition caused by hyperglycaemia may show an association

with glucose concentration [3]. The possibility that infection, in turn, results in poorer glycaemic control cannot be excluded from the observed association; most importantly, we need to know if tighter glycaemic control results in reduced infection incidence. Further research into additional factors that identify people with Type 2 diabetes who are at the highest risk of infection is also required.

Comparison with the literature

Our findings support the results of previous studies that have shown increased infection rates in people with Type 2 diabetes. A smaller cohort study using primary care data found a significantly higher risk of skin, urinary and lower respiratory tract infections in people with Type 2 diabetes compared with control subjects, although rates of upper respiratory tract infections were not found to be significantly higher [25]. A larger study including a matched cohort of 400 000 patients with diabetes using both hospital and community data found increased unadjusted rates of a range of infections [26]. Population-based studies of urinary tract infections, vaginitis in females, and balanitis in males, using UK general practice data, found adjusted relative risks of these infections in people with Type 2 diabetes similar to our calculated odds ratios [5,10].

Few large-scale studies have investigated the impact of glycaemic control on infection rates. Of those that have, there has been inadequate adjustment for important confounders or limited characterization of glycaemic control [11]. Two studies of urinary tract infection, vaginitis and balanitis found an increased risk of these infections in people with poorly controlled Type 2 diabetes [HbA_{1c} >64 mmol/mol (>8%)] [5,10]. No previous large-scale study has assessed the impact of glycaemic control on the wide range of infections analysed in the present study.

Strengths and limitations

The present study was conducted in a country with a registration-based system of general practice, enabling ready extraction of patient-level demographic, diagnostic and therapeutic data. The infection data are taken from the RCCGP RSC database, one of the longest established sentinel networks, involved for nearly 60 years in disease surveillance [13,27]. Practices in the network have been coding and receiving feedback on data quality for over a decade, in particular in relation to the recording of first and new episodes of infection. This facilitates accurate and standardized recording of infections; however, even with these feedback processes, we are still unable to exclude some residual miscoding of infections in the cohort. Since 2004, UK primary care remuneration has been partially dependent on electronically recorded prevalence and management of chronic conditions; this has resulted in improved diabetes data quality [28]. The provision of almost all prescribing and Type 2 diabetes management is achieved through primary care.

The limitations of the study include the fact that it used routine data, which were not systematically collected for this purpose [29]. The data are observational and there exists the potential for residual confounding by unmeasured variables. Furthermore, comparison of the RSCGP RSC cohort with English national data to assess its representativeness reveals small differences, including slight oversampling of practices in the least deprived areas of England [30]. There may be an unequal propensity to consult with a general practitioner amongst people with and without Type 2 diabetes, which may have played a role in the observed differences between those with and without diabetes. Similarly, there may be factors that affect the willingness of general practitioners to see and treat people with Type 2 diabetes, including their higher prevalence of comorbidities. It is reassuring, however, that across viral illnesses there is minimal difference in infection incidence reported between the groups. The lack of secondary care data in this study means that the total rates in the population of some infections are likely to be underestimated. Additionally, there will be minor infections for which people do not present to their general practitioner that we have not been able to include.

Summary

Almost all infections analysed were more common in people with Type 2 diabetes, with the exception of herpes simplex. Infections most commonly of bacterial, fungal or yeast origin were more frequent in people with worse glycaemic control. People with Type 2 diabetes have higher rates of presentation to primary care with a range of common infections than those without, and rates of certain infections show a positive association with worsening glycaemic control. More research is required to understand the mechanisms underlying these findings, and to determine whether improved glycaemic control results in reduced incidence of infections.

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Competing interests

J.H., D.B., S.P., A.M.G., S.J., P.G., J.W., A.E., G.S., J.B. and R.H. have no potential conflicts of interest to disclose. S.d.L. is the Medical Director of the RCGP RSC and the chief investigator of the Eli Lilly-funded Diabetes RWE Centre, also based at the University of Surrey. S.d.L. is an investigator of a wide portfolio of other awards listed in the University and research group website (http://www.surrey.ac.uk/hcmp/people/simon_de_lusignan; clininf.eu); none have any direct

overlap with this study. D.J. is an employee and stockholder of Eli Lilly and Company. N.M. has previously received fees for serving as a speaker, a consultant, or an advisory board member for Allergan, Bristol-Myers Squibb-Astra Zeneca, GlaxoSmithKline, Eli Lilly, Lifescan, MSD, Metronic, Novartis, Novo Nordisk, Pfizer, Sankio, Sanofi, Roche, Servier & Takeda.

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FIGURE 1 Adjusted odds ratios of infection in people with Type 2 diabetes compared with people without diabetes. Covariates adjusted for: age; gender; deprivation quintile; smoking status; comorbidities; and general practice.

Table 1 Characteristics of the study cohort

	People with Type 2 diabetes: *n*= 34 278	**People without diabetes: *n*= 613 052**
Median (IQR) age, years	67.0 (57.0–76.0)	46.0 (33.0–61.0)
Men, *n* (%)	19 266 (56.2)	298 453 (48.7)
Deprivation quintile, *n* (%)		
1 (least deprived)	9351 (27.3)	194 093 (31.7)
2	7986 (23.3)	149 378 (24.4)
3	5414 (15.8)	96 134 (15.9)
4	5465 (15.9)	89 678 (14.6)
5 (most deprived)	5857 (17.1)	82 527 (13.5)
Median (IQR) BMI, kg/m^2	29.9 (26.4–34.2)	25.7 (22.8–29.3)
Smoking status*, *n* (%)		
Current smoker	4194 (12.2)	101 195 (16.5)
Ex-smoker	17492 (51.0)	179 166 (29.2)
Never smoked	12 141 (35.4)	263 103 (42.9)
Comorbidities, *n* (%)		
Asthma/chronic obstructive pulmonary disease	4953 (14.4)	58 697 (9.57)
Heart failure/ischaemic heart disease	4896 (14.3)	16 519 (2.70)
Chronic kidney disease	7272 (21.2)	22 376 (3.65)
Peripheral vascular disease	1210 (3.5)	2848 (0.46)
Stroke/ transient ischaemic attack	2122 (6.2)	9917 (1.62)
Characteristics of people with type 2 diabetes		
Mean (SD) latest HbA_{1c} value, mmol/mol †	57.0 (16.5)	N/A
No medication, *n* (%)	8317 (24.3)	N/A
Oral therapy alone, *n* (%)	20 680 (60.3)	N/A
Insulin alone, *n* (%)	1193 (3.5)	N/A
Insulin and oral therapy, *n* (%)	4088 (11.9)	N/A

IQR, interquartile range.

*Missing smoking data: people with type 2 diabetes, *n* = 451; people without diabetes, *n* = 69 588.

†From within 3 years. 92.1% from within the study year of 2014. Missing data: *n*=811.

Table 2 Age-standardized infection incidence in people with Type 2 diabetes and people without diabetes

	Age-standardized infection rate per 1000 person-years (95% CI)					
	People with Type 2 diabetes			**People without diabetes**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
All infections	336.0 (289.8–605.8)	660.6 (609.0–737.7)	502.0 (466.9–633.5)	174.9 (173.3–176.5)	352.7 (350.4–355.0)	267.3 (265.9–268.8)
Upper respiratory tract infections	87.1 (64.0–370.9)	188.7 (152.3–255.4)	139.0 (116.9–271.8)	59.4 (58.5–60.5)	124.6 (123.3–126.1)	92.7 (91.9–93.6)
Bronchitis	71.8 (63.9–356.1)	102.0 (92.0–150.9)	87.2 (80.8–219.6)	42.5 (41.7–43.3)	64.7 (63.7–65.6)	54.4 (53.8–55.1)
Influenza-like illness	4.4 (2.8–309.6)	8.4 (4.9–61.9)	6.4 (4.4–153.8)	4.3 (4.0–4.5)	6.6 (6.3–6.9)	5.4 (5.2–5.6)
Pneumonia	2.3 (1.8– 308.5)	2.2 (1.6–57.5)	2.2 (1.9–151.4)	1.6 (1.4–1.7)	2.2 (2.0–2.4)	1.9 (1.8–2.0)
All respiratory tract infections	165.6 (140.4–439.5)	301.4 (262.8–368.4)	235.0 (211.5–365.1)	108.0 (106.8–109.3)	198.3 (196.6–200.0)	154.8 (153.7–155.8)
Intestinal infectious diseases	7.3 (4.9–311.2)	17.0 (8.6–70.5)	12.3 (7.6–157.6)	4.7 (4.5–5.0)	6.8 (6.5–7.1)	5.8 (5.6–6.0)
Herpes simplex	1.3 (0.6–308.0)	6.2 (3.8–60.2)	3.8 (2.5–152.3)	2.1 (1.9–2.2)	6.2 (5.9–6.5)	4.2 (4.0–4.4)
Skin and soft tissue infections	112.4 (88.3–392.3)	178.7 (154.4–235.0)	146.3 (128.9–277.2)	44.5 (43.7–45.3)	57.0 (56.1–57.9)	51.5 (50.9–52.2)
Urinary tract infections	39.1 (14.7–335.7)	87.4 (74.5–137.8)	63.8 (48.4–200.3)	9.0 (8.6–9.3)	51.8 (50.9–52.6)	31.1 (30.7–31.6)

Genital and perineal infections	10.5 (8.1–313.0)	69.9 (54.7–122.3)	40.8 (32.9–179.2)	6.1 (5.8–6.4)	30.5 (29.8–31.2)	18.6 (18.3–19.0)

Table 3 Adjusted odds ratios of infection in people with Type 2 diabetes with moderate [HbA_{1c} 53--69 mmol/mol (7--8.5%)] and poor [HbA_{1c} >69 mmol/mol (>8.5%)] glycaemic control, compared with people with good glycaemic control [HbA_{1c} <53mmol/mol (<7%)]

	Moderate glycaemic control			**Poor glycaemic control**		
	Adjusted odds ratio of infection	**95% CI**	***P***	**Adjusted odds ratio of infection**	**95% CI**	***P***
All infections	1.11	1.05–1.18	<0.001	1.35	1.25–1.45	<0.001
Upper respiratory tract infections	1.05	0.96-1.16	0.30	1.06	0.93–1.19	0.39
Bronchitis	1.22	1.12–1.33	<0.001	1.38	1.23–1.55	<0.001
Influenza-like illness	0.86	0.6–1.22	0.40	0.87	0.57–1.35	0.54
Pneumonia	0.88	0.58–1.33	0.56	1.73	1.07–2.79	0.03
All respiratory tract infections	1.12	1.05–1.20	<0.01	1.25	1.14–1.37	<0.001
Intestinal infectious diseases	1.07	0.81–1.41	0.62	0.88	0.60–1.29	0.51
Herpes simplex	1.58	0.94–2.65	0.08	1.39	0.73–2.66	0.32
Skin and soft tissue infections	1.05	0.96–1.16	0.28	1.35	1.20–1.52	<0.001
Urinary tract infections	1.12	1.00–1.26	0.06	1.18	1.01–1.38	0.04
Genital and perineal infections	1.53	1.24–1.90	<0.001	3.02	2.41–3.77	<0.001

Covariates adjusted for: age, gender, deprivation quintile, smoking status, comorbidities, general practice and diabetes duration

Infection category	Odds ratio	(95% C.I.)	p−value
All infections	1.50	(1.46 − 1.54)	<0.001
Upper respiratory tract infections	1.25	(1.19 − 1.30)	<0.001
Bronchitis	1.38	(1.32 − 1.44)	<0.001
Influenza−like illness	1.21	(1.02 − 1.42)	0.03
Pneumonia	1.43	(1.18 − 1.74)	<0.001
All respiratory tract infections	1.30	(1.26 − 1.34)	<0.001
Intestinal infectious diseases	1.37	(1.19 − 1.57)	<0.01
Herpes simplex	1.01	(0.80 − 1.29)	0.92
Skin and soft tissue infections	1.78	(1.69 − 1.86)	<0.001
Urinary tract infections	1.59	(1.50 − 1.69)	<0.001
Genital and perineal infections	2.14	(1.95 − 2.35)	<0.001