Type 2 Diabetes and Risk of Infections

PhD dissertation

Anil Mor

Health
Aarhus University
Department of Clinical Epidemiology, Aarhus University Hospital
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Dedication

I dedicate this work to my mother for all her love and support and for teaching me the mantras of life that has carved me and made me the person that I am today. I wouldn't have been able to get this far without her sacrifices and efforts of putting me through the best education possible.

Supervisors

Reimar Wernich Thomsen, MD, PhD, Associate Professor (main supervisor)
Department of Clinical Epidemiology
Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Henrik Toft Sørensen, MD, PhD, DMSc, Professor (co-supervisor)
Department of Clinical Epidemiology
Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

The assessment committee

Carsten Schade Larsen, MD, DMSc, Associate professor (chairman)
Department of Infectious Diseases
Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Irwin Nazareth, MD, PhD, Professor
Department of Primary care and Population Health
University College London, London, United Kingdom

Marit Eika Jørgensen, MD, PhD, Professor
Clinical Epidemiology Research
Steno Diabetes Center, Gentofte, Denmark

Collaborators

Irene Petersen, MSc, PhD, Professor

Research Department of Primary Care and Population Health, University College London, London, UK &
Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Olaf M. Dekkers, MD, MSc, MA, PhD, Professor

Department of Endocrinology and Metabolic Diseases C4-R, Leiden University Medical Center, Leiden, The Netherlands &
Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark &

Henning Beck-Nielsen, MD, PhD, DMSc, Professor

Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark

Jens S. Nielsen, MSc, PhD, Project leader

Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark

Jørgen Rungby, MD, PhD, DMSc, Professor

Center for Diabetes Research, Gentofte University Hospital, Copenhagen, and Institute for Biomedicine, Aarhus University, Aarhus, Denmark

Søren Friborg, MD, PhD, Project coordinator

Department of Endocrinology, Odense University Hospital, Odense, Denmark

Ivan Brandslund, MD, PhD, DMSc, Professor

Department of Biochemistry, Lillebaelt Hospital, Vejle, Denmark

Jens S. Christiansen†, MD, PhD, DMSc, Professor

Department of Internal Medicine and Endocrinology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

Allan Vaag, MD, PhD, DMSc, Professor

Department of Endocrinology, Diabetes and Metabolism, Rigshospitalet and Copenhagen University, Denmark

Klára Berencsi, MD, MSc, Biostatistician

Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

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Dissertation papers

This PhD dissertation is based on three cohort studies assessing the risk of infectious complications in patients with type 2 diabetes in the Danish population. The studies will be referred by the roman numerals used below in the entire text

Study I

Mor A, Berencsi K, Nielsen JS, Rungby J, Friborg S, Brandslund I, Christiansen† JS, Vaag A, Beck-Nielsen H, Sørensen HT, Thomsen RW. Rates of community-based antibiotic prescriptions and hospital-treated infections in individuals with and without type 2 diabetes: A Danish nationwide cohort study, 2004-2012. *Clinical Infectious Diseases*, in press.

Study II

Mor A, Petersen I, Sørensen HT, Thomsen RW. Metformin and other glucose-lowering drug initiation and rates of community-based antibiotic use and hospital-treated infections in patients with type 2 diabetes: A Danish nationwide population-based cohort study. *BMJ Open*, provisionally accepted.

Study III

Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of Glycemic Control on Risk of Infections in Patients with Type 2 Diabetes: A population-based cohort study. *American Journal of Epidemiology*, provisionally accepted.

Abbreviations

ATC	Anatomical Therapeutic Chemical
AUPD	Aarhus University Prescription Database
BCE	Before the Common Era
BMI	Body mass index
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPR	Central personal registry
CRS	The Danish Civil Registration System
DNHSPD	The Danish National Health Services Prescription Database
DNPR	The Danish National Patient Registry
DPP-4	Dipeptidyl peptidase-4
GDM	Gestational Diabetes Mellitus
GLD	Glucose-lowering drug
GLP-1	Glucagon-like peptide-1
GPRD	General Practice Research Database
HbA_{1c}	Glycated haemoglobin
HR	Hazard ratio
ICD	International Classification of Diseases
LRTI	Lower respiratory tract infection
OR	Odds Ratio
PCOD	Polycystic ovarian disease
PYAR	Patient-years at risk
RR	Rate ratio
TB	Tuberculosis
T2D	Type 2 diabetes mellitus
UK	United Kingdom
URTI	Upper respiratory tract infection
US	United States
UTI	Urinary tract infection

Table of content

1. Introduction

Diabetes is one of the oldest known diseases, dating as far back as 1000 BCE as recorded in the Egyptian and Indian literature [1]. Even after centuries of advancements, diabetes is still a major public health and clinical concern [2]. Due to the complex nature of the disease, its classification and allocating a type of diabetes to patients are not always easy. However, the American Diabetes Association classify diabetes into four major types [3] – type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes (GDM), and other diabetes – in this dissertation we will focus on T2D.

Today T2D claims one death every 7 seconds and affects every 12th person on the planet [2, 4, 5]. The prevalence of T2D is increasing due to the ageing of the population, adaptation of a sedentary lifestyle, increasing urbanisation, increasing obesity, and the interaction of these with a genetic predisposition to T2D. Approximately 387 million people are now living with diagnosed T2D worldwide, and by the year 2035 this number is expected to reach 592 million [5]. In Europe alone, the prevalence of T2D will increase from the present 8.5% to 10.3% by the year 2035 [5]. Denmark is following similar trends, with an addition of 29,000 new patients with T2D every year [6-8], which may eventually result in a doubled T2D prevalence in the next 10 years. [7-9]. In Denmark, T2D is the single most frequent diagnosis among patients visiting an outpatient clinic, and the 4th most common diagnosis in general practice, [8] leading to the utilisation of a major proportion of the total health care budget [8, 10]. In 2011, the total cost attributable to diabetes was estimated to be € 4.27 billion [11].

T2D contributes to 8.5% of the total population mortality [12, 13] and reduces life expectancy by 5–10 years [14]. A multicentre prospective study found that in only 13% of mortality cases T2D was the primary cause of death, whereas diabetes-related complications – including infections – contributed to the rest 87% [15]. Premature mortality due to infections [16] is a major clinical and public health problem in people with T2D. [17]. However, compared with cardiovascular diseases and other “classic” diabetes-related complications [18], infectious complications in T2D have been a rather neglected research topic until recently [19].

During the last decade evidence has emerged linking T2D to an increased risk of several important infections [17, 19-21]. As reviewed by us in 2012 [17] and suggested by newer studies from Denmark and elsewhere, T2D appears to be associated with a 1.5-fold increased risk of hospital-treated respiratory tract infections [17] including tuberculosis (TB) [22] and pneumonia [23], a 1.5-fold increased risk of surgical site infections [24], a 2-fold increased risk of urinary tract infections (UTIs) [25], and a 2- to 3-fold increased risk of bacteraemia [26, 27]. However, limited knowledge exists on other hospitalized infections, and on infections that are treated with antibiotics in general practices [28]. With advancing diabetes care over the years [29] and the detection of milder cases at an earlier stage [30], any excess risk of infections in T2D patients may have changed [29, 31]. Moreover, the impact of hyperglycaemia and glucose-lowering therapy on infection risk has not been well studied.

Therefore, we aimed to examine the association between T2D and infections in more detail. In Study I of this dissertation, we did a comprehensive examination of the risk of any infection in T2D patients as compared with that in the general population. In Study II, we examined the association between glucose-lowering drug (GLD) use and risk of infection in first pharmacologically treated patients with T2D. And in Study III, we focussed on the association between short- and longer-term glucose control and risk of infections in patients with T2D.

2. Background

Diabetes mellitus is a multisystem metabolic disease in which the pancreas does not produce enough insulin or the body cannot effectively use the available insulin. Within this group, T2D is characterised by the onset in adult life of either a resistance to the action of insulin at the tissue level or a relative insulin deficiency or both; whereas T1D is a consequence of an autoimmune-mediated destruction of the beta cells of the pancreas, with absolute insulin deficiency and onset in early life [3, 32]. However, it can be difficult to clinically classify patients as having T1D or T2D because patients can display a mixture of phenotypes. This dissertation focuses on T2D. A detailed comprehensive review of its pathogenesis, treatment, and complications is beyond the scope of this dissertation; however, a short overview is provided below.

2.1 Risk factors and diagnosis of type 2 diabetes

The main risk factors for the development of T2D are overweight, obesity, and physical inactivity along with genetic predisposition [33]. The risk of T2D is greater in people with a family history of diabetes; those over 55 years old (the risk increases with age), those who are overweight; and in people who live a sedentary life [34]. Other risk factors include prediabetes, gestational diabetes, polycystic ovarian disease (PCOD), and certain races including Africans, Hispanics and south Asians [34]. According to the World Health Organisation T2D diagnosis is ascertained if: 1) fasting plasma glucose is above 7.0 mmol/l (126 mg/dl) or 2) plasma glucose measured 2 hours after a 75 g oral glucose load is above 11.1 mmol/l (200 mg/dl) or 3) HbA_{1c} ≥6.5% [35, 36].

2.2 Pathophysiology

The main pathophysiologic defects in T2D are characterised by peripheral resistance to insulin, dysregulation of hepatic glucose production, and decreasing beta-cell function, gradually leading to beta-cell failure [37, 38]. However, as the science is progressing, more pathophysiologic defects associated with T2D have been recognised. For example, altered

adipocyte metabolism and topography may lead to elevated free fatty acid, which can stimulate gluconeogenesis, induce insulin resistance, and impair insulin secretion due to its lipotoxic activity [39]. Furthermore, gastrointestinal tract and the alpha cells of the pancreas are major endocrine organs contributing to the pathogenesis of T2D through hepatic glucose regulation. Other than that, the kidney plays a pivotal role, and instead of secreting glucose in response to hyperglycaemia, it conserves glucose as an adaptive response to meet energy demands. And finally the brain may have impaired appetite regulation due to the reduced magnitude of the inhibitory response to hyperglycaemia in insulin-resistant individuals. All these pathophysiologic defects identified in T2D patients are together termed "the ominous octet" [39]. Due to multisystem involvement, T2D results in long-term complications affecting the cardiovascular system, eyes, kidneys, and peripheral and autonomic nervous systems [40]. Additionally, T2D has been associated with an increased risk of malignancies of the pancreas, liver, colon, endometrium, and breast [41], and with increased risk of mental and neuropsychiatric diseases including dementia [42]. These complications contribute to a large proportion of the total costs [43].

2.3 Diabetes and immunity

2.3.1 Type 2 diabetes and immune function

It is well-established that T2D is associated with a chronic pro-inflammatory state [44, 45] induced by circulating glucose and free fatty acids [46]. This inflammatory stage characterised by immune cell infiltration is also responsible for a decreased mass and a decreased secretory function of beta cells, which contribute to the pathophysiology of T2D [47]. It is found that T2D also increases circulating inflammatory markers such as C-reactive protein and interleukin-6 [48]. In contrast, diabetes patients are found to have a diminished cytokine response to acute infections [49]. In women, diabetes has been found to be associated with a reduced capacity to secrete interleukin-6; additionally, in one study, their monocytes secreted less proinflammatory cytokines in response to in vitro stimulation with lipopolysaccharide [50]. In another study, Andreasen *et al.* demonstrate that T2D is associated with attenuated

secretions of tissue necrosis factor and other cytokines in response to intravenous lipopolysaccharides [51].

Furthermore, defects in natural killer cell-activating receptors lead to innate immune system dysfunction, which may make people with T2D more susceptible to infections [52]. Additionally, decreased mannose-binding lectin capacity associated with T2D causes decreased ability to sense and buffer infectious agents and may lead to increased risk of infection [53, 54].

2.3.2 Hyperglycaemia and immune function

Some evidence [55-57] suggests that short-term hyperglycaemia acutely and reversibly compromises the innate and adaptive immune systems thereby increasing infection risk, and some [17, 58, 59] claim that long-term hyperglycaemia increases infection risk via tissue inflammation. Yet, the exact mechanism linking diabetes and infections is not well understood.

As reviewed by us [17], in vitro studies have demonstrated that acute hyperglycaemia may impair the innate immune system by several mechanisms. Hyperglycaemia appears to weaken innate immunity via its negative influence on polymorphonuclear neutrophil function and intracellular bactericidal and opsonic activity [55, 60]. Hyperglycaemia inhibits adaptive immunity by directly affecting T cells, antigen-presenting cells, and antibodies and also interferes with the complement cascade through glycosylation of immune proteins [55, 56, 61, 62]. Hyperglycaemia may also impair the production of oxygen free radicals in leukocytes required for intracellular killing of pathogens [63, 64]. Recently, Martinez *et al.* reported altered cell-mediated immunity in T2D patients compared with people without T2D and demonstrated a negative association between hyperglycaemia and memory CD4+ cells and Th17 response to infection [65, 66]. Furthermore, an increased risk of infection also may be mediated by chronic hyperglycaemia via chronic tissue inflammation or the development of other complications, which in turn increases the risk of infection [55, 56]. Rayfield *et al.* demonstrated a weak association between mean fasting plasma glucose levels and subsequent risk of infections in 241 patients with T2D more than 30 years ago [67]. Randomised trials in

patients undergoing surgery made headlines 15 years ago, showing a beneficial impact of tight glycaemic control by intensive insulin treatment in reducing the risk of surgical site infections and septicaemia in T2D patients [68, 69]. However, it is still debated if the observed beneficial effects were primarily related to the anti-inflammatory effects of insulin or reduced hyperglycaemia per se [60, 70].

2.3.3 Glucose-lowering drugs and immune function

As discussed above, hyperglycaemia may increase the risk of infections in patients with T2D [71-75]. Insulin is more effective in reducing blood glucose than most non-insulin GLDs [30], and GLDs may thus have a variable influence on the risk of infections via their different glucose-lowering effects. In addition, non-glycaemic effects of GLDs on the immune system may also play a role [60, 76-79]. For instance, metformin activates 5' adenosine monophosphate-activated protein kinase and induces the neutrophil-dependent bacterial uptake and killing associated with neutrophil activation and chemotaxis [78, 79]. It has been reported that metformin – independent of its glycaemic effect – has a beneficial effect on *Staphylococcus aureus*-induced respiratory tract infections by limiting bacterial growth via regulation of glucose flux across the airway epithelium [80]. Similarly, insulin may enhance both innate and cell-mediated immunity by suppressing the expression of toll-like receptors and by upregulating the capacity for phagocytosis and oxidative burst in monocytes [77]. Additionally, insulin regulates dyslipidaemia and promotes immunologic effects, suppresses excessive inflammation, and improves macrophage function [60, 70]. For sulfonylurea, evidence is sparse on possible effects on immune regulation, apart from its inhibitory effect on inflammasome assembly [76]. Hence the association of GLDs with immunity and infection remains unclear [81].

2.4 Infections

Infections continue to exert substantial challenges to health and health-care resources globally, despite major advances in treatment and prevention. In 2012, 5.5% of global deaths were due to respiratory infections and 11.5% were due to other infections and infestations, making infections one of the top killers on the planet [82]. In the US in 2011, 8–12% of T2D

patients were hospitalized for infection management costing over $48 billion in aggregate hospital costs [83]. The high occurrence of infections is related to many factors, including emerging chronic diseases worldwide, socio-economic, environmental and ecological factors, long-distance trade, technological developments, land clearance, climate change, and globalisation that may help in spreading infectious agents [19]. Based on the place of acquisition, infections can be divided into two major groups: community-acquired infections and hospital-acquired infections.

2.5 Narrative review of selected relevant literature on T2D and infection

To review what is known of the topic of type 2 diabetes/diabetes therapy/hyperglycemia, and risk of infection in humans, I first did a broad literature search. The purpose was to identify major important studies within this area relevant to this dissertation. I excluded studies published in languages other than English and studies published before 2000.

I searched MEDLINE using the following query: ("Diabetes Mellitus[MeSH Major Topic]" AND ("Infection[MeSH Major Topic]" OR "Antibiotic[MeSH Major Topic]")). I restricted my search to meta-analyses, clinical trials, cohort, case-control, and cross-sectional studies, and literature reviews. I excluded studies not conducted in humans.

Figure 1 illustrates the flow diagram of studies retrieval that are included in the narrative review. Briefly, the electronic database search resulted in 1555 studies. The titles and abstracts of these studies were further examined for relevance according to appropriate study population (diabetes mellitus), intervention/exposure (diabetes mellitus, glucose-lowering drugs, or HbA_{1c}), comparison, and outcome (infections or antibiotic prescriptions). This led to inclusion of 42 relevant and important studies for further description. I then reviewed the reference lists of these publications and found eight more studies [22, 24, 84-89] relevant to this dissertation. Of the 50 studies examining risk of infections in T2D patients that I deemed most relevant and important to the topic of my thesis, 2 were systematic reviews of clinical trials with meta-analysis, 3 were randomised controlled trials, 5 were systematic reviews with pooled data from several observational studies with meta-analysis, 23 were cohort studies, 14 were case-control studies, and 3 were cross-sectional studies. We described these studies in

Table 1 and arranged according to the levels of evidence adapted from the Centre for Evidence-Based Medicine at the University of Oxford (CEBM, Source: http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf).

Figure 1. Flow diagram of studies retrieval for the narrative review.

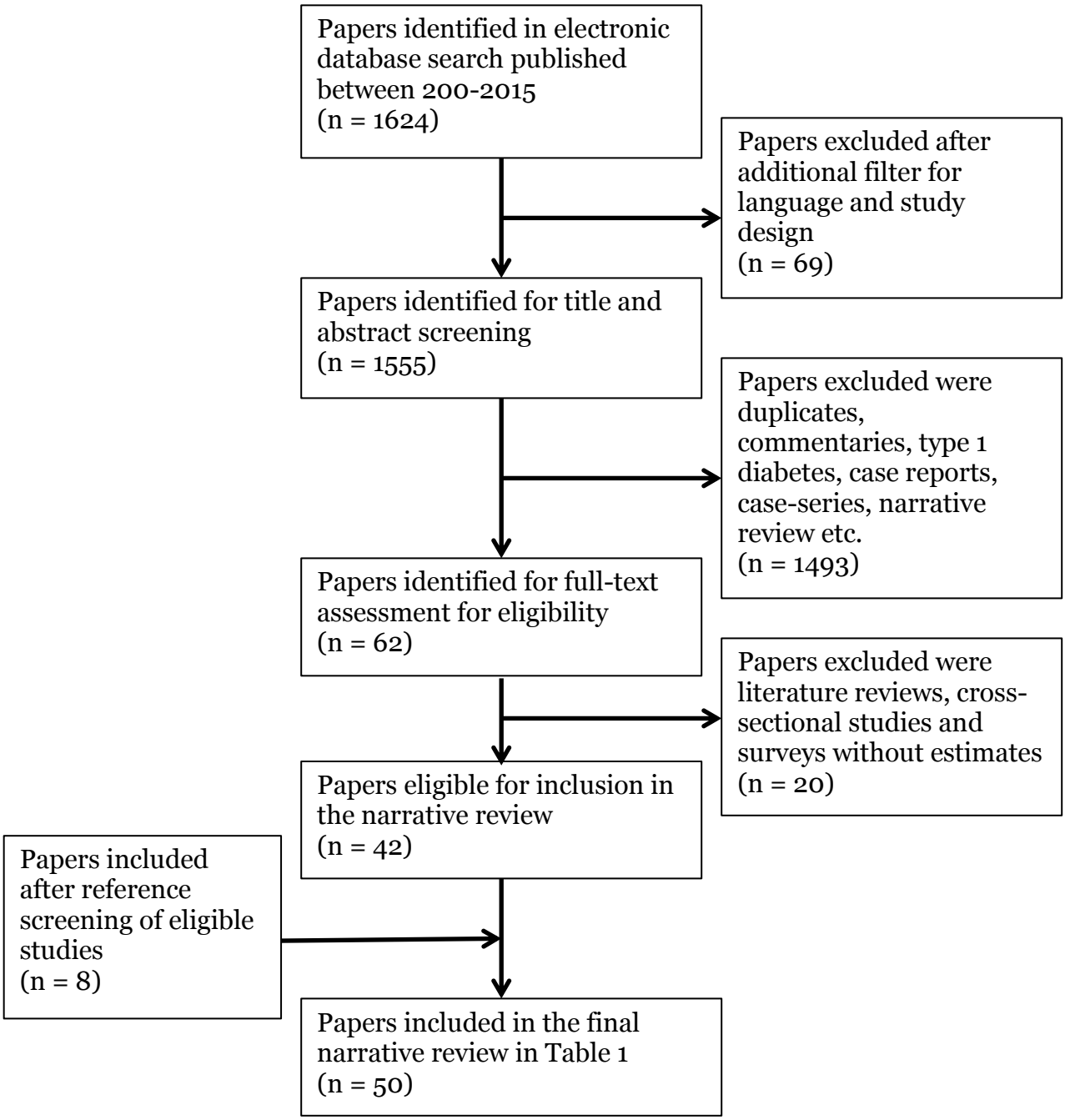


Table 1. Summary of selected important studies examining the risk of infections in patients with type 2 diabetes.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Karagiannis T *et al*. 2012 [86]	Systematic review and meta-analysis/ Worldwide	Various randomised controlled trials / A total of 27 reports with 7136 patients randomised to a DPP-4 inhibitor and 6745 patients randomised to another GLD	DPP-4 inhibitors	1980–2011/ various/ mortality, other adverse events including infections	Compared with any GLD, DPP-4 inhibitors were not associated with nasopharyngitis (HR 1.06, 95% CI 0.95–1.19), URTI (HR 1.0, 95% CI 0.83–1.22), or UTI (HR 0.86, 95% CI 0.51–1.45).	Strength of evidence was not assessed; many trials were not designed to assess infectious outcome.
Johnsson KM *et al.* 2013 [90]	Pooled analyses/ NA	Randomised controlled trials/ 3152 patients with treatment and 1393 with placebo in 12 randomized controlled trials	Dapagliflozin	Various/ 24 weeks/ UTI	UTIs were reported in 3.6%, 5.7%, 4.3%, and 3.7% in patients received dapagliflozin 2.5mg, 5mg, 10mg, and placebo, respectively.	
Nicolle LE *et al*. 2012 [91]	Randomised, double-blind, placebo-controlled, multicenter, dose-ranging study with seven arms / Canada	Multicenter trial/ 215 women and 236 men with T2D and inadequate glycaemic control while receiving a stable dose of metformin (≥1500 mg/day for at least 3 months) who were 18 to 65 years of age with HbA_{1c} levels ≥7% and ≤10.5%	Canagliflozin doses 50 mg, 100 mg, 200 mg, 300 mg daily, or 300 mg twice daily	2010/ 12 weeks/ UTI	Asymptomatic bacteriuria was present in 7.7% of canagliflozin and 6.3% of placebo/sitagliptin (control) subjects at 12 weeks (OR 1.23, 95% CI 0.45–3.89). For subjects with initially negative urine cultures at baseline, 3 out of 82 (3.7%) who received controls and 10 out of 207 (4.8%) who received canagliflozin developed bacteriuria ($P = 0.76$) at week 12. There were 21 adverse event reports of UTI; 16 (5.0%) in canagliflozin subjects and 5 (3.8%) in control subjects (OR 1.31, 95% CI, 0.45–4.68).	Small sample size; low study power; only one drug was studied.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Umpierrez G *et al.* 2014 [87]	Clinical trial /US	Multicentre trial/ 807 T2D patients	Subcutaneous dulaglutide 1.5 mg, dulaglutide 0.75 mg, or metformin	2010–2012/52 weeks/ HbA_{1c} levels, weight and other adverse events	Nasopharyngitis in dulaglutide 1.5 mg was 5.2%, in dulaglutide 0.75 mg was 3.0%, and in metformin users was 10.4%; upper respiratory tract infection (URTI) in dulaglutide 1.5 mg was 5.9%, in dulaglutide 0.75 mg was 5.6%, and in metformin users was 3.0%	
Zinman B *et al.* 2015 [92]	Randomized clinical trial/worldwide	Multicenter trial/ 7,020 T2D patients	Empagliflozin doses 10 mg, 25 mg or placebo daily	-/median observation time 3.1 years/death from cardiovascular cause	Genital infections were more common in pooled empagliflozin group (6.4%) vs. placebo (1.8%). No imbalance in complicated UTI (1.7% in empagliflozin and 1.8% in placebo)	
Hammar N *et al.* 2010 [93]	Pooled analyses/ Sweden	Pooled analyses from 10 clinical trials from Sweden/ 6016 T2D patients	T2D	2004–2007/ mean follow-up of 145 days (SD 50)/ UTI	142 patients experienced UTI (IR 59.5/1000 PYAR; 91.5/1000 in women, 28.2/1000 in men) and a cumulative incidence of 2% during 6 months.	
Martin ET *et al.* 2015 [24]	Systematic review and meta-analysis/US	Surgically operated patients in different settings /94 studies with 866,427 participants	Diabetes	1985–2015/ varied/ surgical site infections	Random effect meta-analysis gave OR of 1.53 (95% predictive interval 1.11–2.12) for surgical site infections associated with diabetes.	Mixed population of T1D & T2D; different study designs; different follow-up period.
Jeon CY *et al.* 2008 [22]	Systematic review with meta-analysis/worldwide	13 observational studies with 1,786,212 participants	Diabetes	1965–2007/ varied/ TB	Random effect meta-analysis of cohort studies provided RR of TB of 3.11 (95% CI 2.27–4.26)	Mixed population of T1D & T2D; different study designs; different follow-up period.
Stevenson CR *et al.* 2007 [94]	Systematic review/ worldwide	9 studies (1 prospective cohort study, 4 caase-control studies, 4 registry based observational studies)	Diabetes	1995-2007/varied/ TB	Odds ratios of TB varied between 1.5-7.8 associated with diabetes mellitus. Higher risk in younger patients than older.	Narrative review, no meta-analysis was done. Studies involved did not consider potential confounders.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Seshasai SR *et al.* 2011 [95]	Data from 97 cohort studies/ Worldwide	Data from Emerging Risk Factors Collaboration center/820,900 patients with diabetes without vascular complication at the time of enrolment	Diabetes	Not specified/median follow-up of 14 years/cause specific mortality	HR of mortality due to infection (excluding pneumonia) was 2.39 (95% CI 1.95–2.93); HR of mortality due to pneumonia was 1.67 (95% CI 1.45–1.92).	Mixed population of T1D & T2D; selected population; studies included in different time periods; residual bias.
Maradit Kremers H *et al.* 2015 [96]	Cohort study/ US	Mayo clinic Minnesota/ 20,171 total knee and hip arthroplasty	Diabetes, hyperglycaemia and medication use	2002–2009/one year/ prosthetic joint infection	Higher risk of prosthetic joint infections in patients with a diagnosis of diabetes (HR 1.55, 95% CI 1.11–2.16), patients using diabetes medications (HR 1.56, 95% CI 1.08–2.25) and patients with perioperative hyperglycaemia (HR 1.59, 95% CI 1.07–2.35).	Subjects enrolled from a single hospital; data for HbA_{1c} were available for a quarter of patients; misclassification of exposure.
McDonald HI *et al.* 2014 [97]	Cohort study/ UK	Primary care records from GPRD/ 218,805 T2D patients ≥65 years	T2D	1997–2011/ up to 14 years/acute community acquired infections	IRs were: 152.7/1000 PYAR for LRTI; 10.3/1000 PYAR for pneumonia; 2.51/1000 PYAR for septicaemia; and 51.4 and 147.9/1000 PYAR for UTI in men and women, respectively.	Prevalent cases of diabetes were included; hospital acquired infections were excluded.
Shah BR *et al.* 2003 [27]	Cohort study/ Canada	All patients with diabetes diagnosed in Ontario before 1999/513,749 patients with diabetes and equal number of age- sex- region- and income quitiles-matched people without diabetes	Diabetes	1999–2000/up to one year/hospital admission or physician claim of common infections	RR of overall infections was 1.21 (99% CI 1.20–1.22); RR of infection related hospitalisation was 2.17 (99% CI 2.10 – 2.23); RR of death attributable to infection was 1.92 (99% CI 1.79 –2.05).	Mixed population of T1D & T2D; short follow-up.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
McKane CK *et al.* 2014 [75]	Observational study/ US	2 teaching hospitals in Boston/ 2551 critically ill patients >18 years old with available blood culture	Diabetes	1998–2007/ NA/ community acquired blood stream infection	Compared with patients without diabetes, diabetes patients had higher risk of bloodstream infections (aOR 1.42, 95% CI 1.10–1.8) and also sepsis (aOR 1.26, 95% CI 1.04–1.54); Compared with patients with HbA_{1c} < 6.5%, risk of bloodstream infection was increased in patients with HbA_{1c} of 6.5% or higher (aOR 1.31, 95% CI 1.04–1.65)	Selected population; mixed T1D & T2D population; strict criteria to determine outcome.
Yu S *et al.* 2014 [98]	Cohort study/ US	Market scan dataset of US/ 73,151 T2D patients	T2D	2008–2011/ one year/ UTI	8.2% (6014/73,151) of subjects had ≥1 UTI	Unmeasured confounding; coding errors; incompleteness of codes.
Hirji I *et al.* 2012 [99]	Cohort study/UK	Primary care data from GPRD/125,237 female patients and 146,603 males	T2D	1990-2007/one year/balanitis & vaginitis	IR of vaginitis was 21.0/1000 PYAR (95% CI 19.8–22.1) in T2D patients and RR was 1.81 (95% CI 1.64–2.00) compared with patients without T2D. IR of balanitis in T2D patients was 8.4/1000 PYAR (95% CI 7.8–9.1) with RR= 2.85 (95% CI 2.39–3.39) compared to patients without T2D.	Misclassification of exposure; hospital infections were not included; missing data.
Hirji I *et al.* 2012 [100]	Cohort study/UK	Primary care data from GPRD/ 135,920 patients with T2D and equal number matched controls using propensity score based on age, sex, and index year	T2D	1990–2006/two years/ UTI	IRs of UTI was 46.9/1000 PYAR (95% CI 45.8–48.1) in T2D patients and 29.9/1000 PYAR (95% CI 28.9–30.8) in people without T2D with corresponding RR of 1.53 (95% CI 1.46–1.59) for all T2D patients, and 2.08 (95% CI 1.93–2.24) for patients with previously diagnosed diabetes.	Misclassification of exposure; hospital infections were not included; missing data.
Ekstrom N *et al.* 2012 [88]	Cohort study/ Sweden	Swedish primary care and hospital outpatient clinics/51,675 patients with T2D on GLD treatment	GLDs	2004–2010/up to 6 years mean follow-up 3.9 years/ cardiovascular, all-cause mortality, and serious infections	Risk of serious infections was associated with metformin use compared with any other GLD use (aHR 0.85, 95% CI 0.74–0.97).	A composite end point was chosen because of less event in case of serious infections; confounding by indication; intention to treat approach.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Ko MC *et al.* 2011 [101]	Cohort study/ Taiwan	Taiwan/ 500,522 patients with diabetes and 500,365 controls without diabetes	Diabetes	1997–2007/ up to 11 years/ perinephric abscess	The incidence density for diabetes and control subjects was 4.6 and 1.1/10,000 PYAR, respectively (aHR 3.81, 95% CI 3.44–4.23).	
Venmans LM *et al.* 2009 [28]	Cohort study/ The Netherlands	University Medical Center Utrecht General Practitioners Research Network/All patients ≥45 years with a diagnosis of diabetes, study population varied with calendar year of cohort	Diabetes	1995–2003/Up to 1 year/incidence and antibiotic usage for LRTI and UTI	IR of LRTI was 78/1000 PYAR in 1995 & 88/1000 PYAR in 2003; IR of UTI was 72/1000 PYAR in 1995 & 101/1000 PYAR in 2003. Antibiotics prescribed for LRTI was 42/100 episodes in 1995 and 67/100 episodes in 2003. Antibiotics prescribed for UTI was 78/100 episodes in 1995 & 90/100 episodes in 2003.	Mixed population of T1D & T2D; multiple episodes of infections were counted; only GP data were explored; missing data.
Schneeberger C *et al.* 2008 [102]	Cohort study/ The Netherlands	Primary care/ 10,366 women with diabetes and 200,258 women without diabetes	Diabetes	1999–2006/ 30 days/ recurrence of UTI	Premenopausal women with diabetes had higher recurrence rate of UTI than women without diabetes (16.1 versus 12.2%; $P = 0.003$); postmenopausal women with diabetes had higher recurrence rate than women without diabetes (19.1 versus 16.4%; $P < 0.001$).	Both T1D & T2D cases were included; short follow-up; only primary care data was used.
Adams AL *et al.* 2013 [103]	Cohort study/ US	Kaiser Permanente total joint replacement registry/40,491 T2D patients who underwent total joint replacement surgery	Diabetes and HbA1c	2001-2009/1 year/deep infection	18.7% had diabetes, Compared with patients without diabetes, no association between controlled diabetes (HbA1c < 7%) and the risk of deep infection (OR, 1.31; 95% CI, 0.92–1.86), Similarly, compared with patients without diabetes, no association between uncontrolled diabetes (HbA1c ≥ 7%) and the risk of deep infection (OR, 0.55; 95% CI 0.29–1.06).	Only deep infections were considered, selection bias, important confounders such as GLDs were not considered.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Benfield T *et al*. 2007 [73]	Cohort study, Denmark	All people who were enrolled in the Copenhagen City Heart Study between 1991 and 1994/ 353 with diabetes and 9710 without diabetes among those enrolled for Copenhagen heart study	Diabetes and hyperglycaemia	1991–2001/ 7 years/ infectious disease hospitalisation	1194 individuals were hospitalised due to infections. People with diabetes had higher risk of pneumonia (aHR 1.75, 95% CI 1.23–2.48), UTI (aHR 3.03, 95% CI 2.04–4.49) and skin infection (aHR 2.43, 95% CI 1.49–3.95). Each 1 mol/l increase in plasma glucose at baseline was associated with a 6–10% increased relative risk of pneumonia, UTI and skin infections.	Selected population; mixed T1D & T2D population; possible misclassification of exposure.
Boyko EJ *et al*. 2005 [104]	Cohort study/ US	Group Health Cooperative of Puget Sound in Washington state/ 218 women with diabetes and 799 women without diabetes between 55–75 years of age (post-menopausal)	Diabetes	1998–2002/ 2 years/ UTI and asymptomatic bacteriuria	IR of UTI was 12.2/100 PYAR for women with diabetes and 6.7/100 PYAR for women without diabetes (aRR 1.8, 95% CI 1.2–2.7). IR of asymptomatic bacteriuria was 6.7/100 PYAR for women with diabetes and 3.0/100 PYAR for women without diabetes (aRR 2.3, 95% CI 1.3–3.9). UTI risk was higher in women taking insulin (RR 3.7, 95% CI 1.8–7.3) and women with longer diabetes duration (≥10 years; RR 2.6, 95% CI 1.3–5.1) compared with women without diabetes.	Prevalent cases of diabetes were enrolled; selected study population.
Muller LM *et al*. 2005 [105]	Cohort study/The Netherland	Second Dutch National Survey of General Practice/705 patients with T1D and 6712 patients with T2D and 18911 control with hypertension	T1D & T2D	2000–2002/12 months/LRTI, UTI, and infections of skin and mucous membranes	LRTI: aOR 1.32 (95% CI 1.13–1.53); UTI: aOR 1.24 (95% CI 1.10–1.39); bacterial skin & mucous membrane infections: aOR 1.33 (95% CI 1.15–1.54); mycotic skin & mucous membrane infections: aOR 1.44 (95% CI 1.27–1.63).	Short follow-up; misclassification of exposure; patients with specific need for infection management were excluded.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Jackson ML et al. 2004 [106]	Cohort study/ USA	Members of Group Health Cooperative (GHC) in Washington State / 46,237 individuals aged ⩾65 years	Diabetes	1998–2001 /until death, disenrollment from GHC, outcome event, or the study end date/ community-acquired pneumonia	HR of hospitalization for pneumonia was 1.52 (95% CI 1.29 –1.78), HR of outpatient visit for pneumonia was 0.90 (95% CI 0.77—1.06), HR for any pneumonia was 1.13 (95% CI 1.13—1.27).	Selected population, lost to follow-up, false negative cases of pneumonia, low external validity
O'Meara ES et al. 2005 [107]	Cohort study/ USA	US communities: California, Pennsylvania, Maryland, North Carolina (the Cardiovascular Health Study)/ 5888 Medicare eligible people aged >= 65 years	Diabetes	1989–2001/ median follow-up 10.7 years/ pneumonia hospitalization	16% of patients who were not hospitalized with pneumonia had diabetes versus 18% of those who were hospitalized with pneumonia. Diabetes was risk factor for pneumonia hospitalization (aRR 1.34, 95% CI 1.05–1.70).	Selected population, lost to follow-up, false negative cases of pneumonia, low external validity
Gorter KJ *et al.* 2010 [108]	Cohort study/ The Netherlands	Primary care health center in The Netherlands/ 7063 women ≥ 30 years (340 with diabetes)	Primary episode of UTI	2000–2004/ 6 weeks/ relapse and reinfection	Women with diabetes had higher risk of recurrent UTI compared with women without diabetes (OR 2.0, 95% CI 1.4–2.9). The risk was high in women taking oral GLDs (OR 2.1, 95% CI 1.2–3.5) or insulin (OR 3.0, 95% CI 1.7–5.1) or who had had diabetes for ≥5 years (OR 2.9, 95% CI 1.9–4.4) or who had retinopathy (OR 4.1, 95% CI 1.9–9.1).	
Sanden AK *et al.* 2010 [109]	Change in GLD and risk of UTI	North Jutland county/ Cohort study/ Denmark	Change in therapy in T2D patients	1997–2005/425 days/ UTI	UTI occurred in 446 (16.3%) T2D patients in the insulin period and 437 (16.0%) in the oral GLD period (aRR 1.04, 95% CI 0.86–1.26).	Bias due to unknown compliance; confounding by indication; unmeasured risk factor for UTI.
Leth RA *et al.* 2011 [110]	Cohort study/ Denmark	Obstetrics department at 3 hospitals in Denmark/ 2492 women who had caesarean section	T1D, T2D and gestational diabetes	2007–2008/ 30 days/ post caesarean infections	T2D was weak predictor of infection risk (OR 1.18, 95%CI 0.72–1.93).	Selected population; small sample size; short follow-up; prevalent diabetes cases were enrolled.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Humphers JM *et al.* 2014 [111]	Cohort study/ US	Tertiary care hospital in Texas/222 T2D patients who underwent foot and ankle surgeries	HbA1c	2012-2013/ postoperative infection	OR of infection 1.25 (95% CI 1.02–1.53) associated with every 1% increase in HbA1c	Small sample size, selected population, short follow-up.
Hamilton EJ *et al.* 2013 [71]	Cohort study/ Australia	Fremantle Diabetes Study cohort/1294 T2D patients enrolled in the Fremantle Diabetes Study phase 1 and 5156 age-, sex- and area matched controls	T2D	1993–2010/12 ±5.4 years/incident hospitalisation for bacterial infections as primary diagnosis	IR of infection 23.7/1000 PYAR; RR of infection was 2.13 (95% CI 1.88–2.42); RRs for pneumonia, cellulitis, & septicaemia were 1.86 (95% CI 1.55–2.21), 2.45 (95% CI 1.92–3.12), and 2.08 (95% CI 1.41–3.04), respectively.	Detailed data unavailable for controls; only hospitalisations with primary diagnosis were considered.
Davis TM *et al.* 2005 [72]	Matched pair cohort study/ Australia	Fremantle Diabetes Study cohort/68 patients with DM from community based cohort and their partners	Diabetes	Not specified/one year/infections	33.3% patients with diabetes and 18.3% of the partners got more than 1 infections (P = 0.02).	Small sample size; short follow-up; unmeasured confounding.
Willemen MJ *et al.* 2011 [112]	Nested case control study/ worldwide	VigiBase dataset of World Health Organisation from 98 countries /106,469 case reports of adverse reaction from GLDs	GLDs	1999–2009/ NA/ infections	Reporting of infections was higher for patients using DPP-4 inhibitors compared with users of biguanides (OR 2.3, 95% CI 1.9–2.7). Reporting of URTIs (OR 12.3, 95% CI 8.6–17.5) was significantly associated with use of DPP-4 inhibitors.	
Leegaard A *et al.* 2011 [85]	Case-control study/Denmark	Northern Denmark/2950 patients with TB and 14,274 age-sex-residence matched controls without TB	Diabetes	1980–2008/until data was available/TB	aOR of TB = 1.18 (95% CI 0.96–1.45). Compared with people without diabetes, diabetes patients with an HbA_{1c} <7.0, 7–7.9, and ≥8.0% had ORs of TB 0.91 (95% CI 0.51–1.63), 1.05 (95% CI 0.41–2.66), and 1.19 (95% CI 0.61–2.30), respectively.	Mixed T1D & T2D; older data; case control design.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Boyko EJ *et al.* 2002 [113]	Case-control study/ US	Group Health Cooperative of Puget Sound in Washington state/ 901 women with acute symptomatic UTI and 913 control women without UTI between 55–75 years of age (post-menopausal)	Diabetes	1998–2002/ 2 years/ UTI and asymptomatic bacteriuria	Diabetes was reported in 13.1% cases and 6.8% controls, yielding an adjusted OR of 2.2 (95% CI 1.6 – 3.0).	Case-control design; selected study population.
Scholes D *et al.* 2005 [114]	Case-control study/ US	Group Health Cooperative of Puget Sound in Washington state/ 788 non-pregnant women 18-49 years old, 242 with pyelonephritis and 546 without.	Diabetes	200–2001/ NA/ pyelonephritis	Diabetes was reported in 6.6% cases and 1.6% controls, yielding an OR of 4.1 (95% CI 1.6 – 10.9).	Case-control design; selected study population.
Thomsen RW *et al.* 2011 [74]	Case control study/ Denmark	Northern Denmark/397 patients >15 years with first time hospitalisation for haemolytic streptococcal bacteraemia and 3970 age- and sex-matched controls	Diabetes and hyperglycaemia	1992–2006/ until the data is available for diabetes and latest HbA1c measurement for hyperglycaemia/ bacteraemia	Compared with people without diabetes, risk of bacteraemia was associated with presence of diabetes (aOR 2.1, 95% CI 1.5–2.9), HbA_{1c} <7% (aOR 1.5, 95% CI 0.8–3.0) and HbA_{1c} ≥9% (aOR 3.6, 95% CI 1.6–8.1).	Small sample size with diabetes; misclassification of exposure possible; inclusion of T1D as well.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Factor SH *et al.* 2003 [115]	Case-control study/ US-Canada	Atlanta, Georgia, Baltimore, Toronto/ 48 cases with invasive group A streptococcal disease and 115 control without (18-44 years)	Diabetes	1997–1999/ever diagnosed/ invasive group A streptococcal disease	Diabetes was reported in 13% cases and 4% controls, yielding an adjusted OR of 2.1 (95% CI 0.6 – 7.1).	Small sample size, case-control design; selected study population.
Bishara J *et al.* 2009 [116]	Case control study/ Israel	1 Medical center in Israel/ 89 patients with and 555 patients without anaerobic bacteraemia	Diabetes	1988–2004/ until data available/ anaerobic bacteraemia	Diabetes increased the risk of anaerobic bacteraemia when the source of the bacteraemia was unknown, OR 2.29 (95% CI 1.22–4.29).	Selected population from a single medical center; misclassification of exposure.
Thomsen RW *et al.* 2007 [117]	Case control study/ Denmark	Denmark/ 1448 patients with pyogenic liver abscess and 1:50 age- and sex-matched population controls per case	Diabetes	1977–2002/ until data was available/ pyogenic liver abscess	Patients with diabetes were at increased risk of pyogenic liver abscess compared with population controls (aRR 3.6, 95% CI 2.9–4.5).	Older data; case control design; prevalent diabetes cases; misclassification of exposure.
Kornum JB *et al.* 2008 [23]	Case control study/ Denmark	Northern Denmark/34,239 pneumonia-related admissions and 342,390 sex and age-matched controls	T1D & T2D	1997–2005/until data was available/ pneumonia hospitalisation	aRR of pneumonia hospitalisation was 4.43 (95% CI 3.40 –5.77) in T1D and 1.23 (95% CI 1.19 –1.28) in T2D patients	Mixed population of T1D & T2D; misclassification due to different follow-up time and unavailability of very old data; only severe hospitalised cases were enrolled.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Movahed MR *et al.* 2007 [118]	Case control study/ USA	Veteran health administration hospitals in USA/ 293,124 patients with diabetes and 552,623 patients with hypertension and without diabetes	Diabetes	1990–2000/ from 1969 or since the earliest data available/ infectious endocarditis	Infectious endocarditis was present in 1340 (0.5%) diabetes patients versus 1412 (0.3%) patients from the control group (aOR 1.9, 95% CI 1.8–2.1)	Misclassification of exposure; mixed population of typ1 & 2 diabetes.
Thomsen RW *et al.* 2005 [26]	Case control study/ Denmark	Patients hospitalised with bacteraemia in Northern Denmark/ 1317 patients >15 years with and 13,170 sex- age- and residence-matched controls without enterobacterial bacteraemia	Diabetes	1992–2001/ until data was available/ Enterobacterial bacteraemia	aOR bacteraemia was 2.9 (95% CI 2.4–3.4).	Mixed population of T1D & T2D; misclassification due to different follow-up time and unavailability of very old data.
Thomsen RW *et al.* 2004 [119]	Case control study/ Denmark	Northern Denmark/ 598 patients with pneumococcal bacteraemia and 5980 age, sex and residence matched controls	Diabetes	1992–2001/ all available data before index admission/ pneumococcal bacteraemia	Patients with diabetes had higher risk of pneumococcal bacteraemia compared with people without diabetes (aOR 1.5, 95% CI 1.1–2.0). The impact as most pronounced in adults ≤ 40 years (aOR 4.2, 95% CI 1.1–16.7) and in people without comorbidity (aOR 2.3, 95% CI 1.3–3.9).	Mix of patients with T1D & T2D; prevalent cases were enrolled.
Lipsky BA et al. 1986 [84]	Case-control study/ USA	The SVAMC general medical clinic, Washington/ 63 patients (all men) with pneumococcal pneumonia and 130 controls without	Diabetes	1977–1982/ until the records are available in the practice/ pneumococcal pneumonia	21% of both cases and controls had a history of diabetes, yielding an adjusted OR of 0.99 (95% CI 0.45–2.09).	Small sample size, selected population.

Author/ year	Design/ country	Setting/Study population	Exposure	Study period/follow-up/outcome	Results	Comments
Jackson LA et al. 1995 [89]	Case-control study/ USA	Metropolitan areas of California, Georgia and Baltimore/ 219 adult patients with group B streptococcal pneumonia and 645 hospital-matched controls	Diabetes	1991–1992/all available data in records before index admission/ group B streptococcal infection	37% cases and 17% controls had diabetes yielding an OR of 3.0 (95% CI 1.9–4.7).	Selected study sample, small study population, misclassification of exposure.
Walker C *et al.* 2010 [120]	Cross sectional study/ UK	UK / 3461 TB patients	Diabetes	2005/ NA/ TB	Of 3461 new cases of pulmonary TB in England in 2005, 384 (95% CI 202–780) were estimated to be attributable to diabetes.	
Bomberg H *et al.* 2015 [121]	Cross-sectional study/ Germany	Patients undergoing continuous regional anaesthesia from 25 clinical centres in Germany/ 3990 patients with diabetes and 32,891 patients without diabetes	Diabetes	2007–2012/ until the day after catheter is removed/ catheter associated infection	Diabetes patients had higher risk of catheter-related infections (no diabetes 3.0% versus any diabetes 4.2%; $P < 0.001$; aOR 1.26, 95% CI 1.02–1.55). The risk of infection was higher in the lower limb catheters only (aOR 2.42, 95% CI 1.05–5.57).	BothT1D & T2D were included; selected population; important confounders were not available.
Michalia M *et al.* 2009 [122]	Cross sectional study/ Greece	Intensive care unit of tertiary care hospital/ 63 patients with diabetes and 280 without diabetes, all admitted in intensive care unit for > 48 hours	Diabetes	2004–2007/ NA/ blood stream infection	Diabetes patients had an increased risk getting at least one blood stream infection episode compared with nondiabetes patients (aHR 1.66, 95% CI 1.04–2.64).	Single center study; small sample size; cross sectional design; selected population.

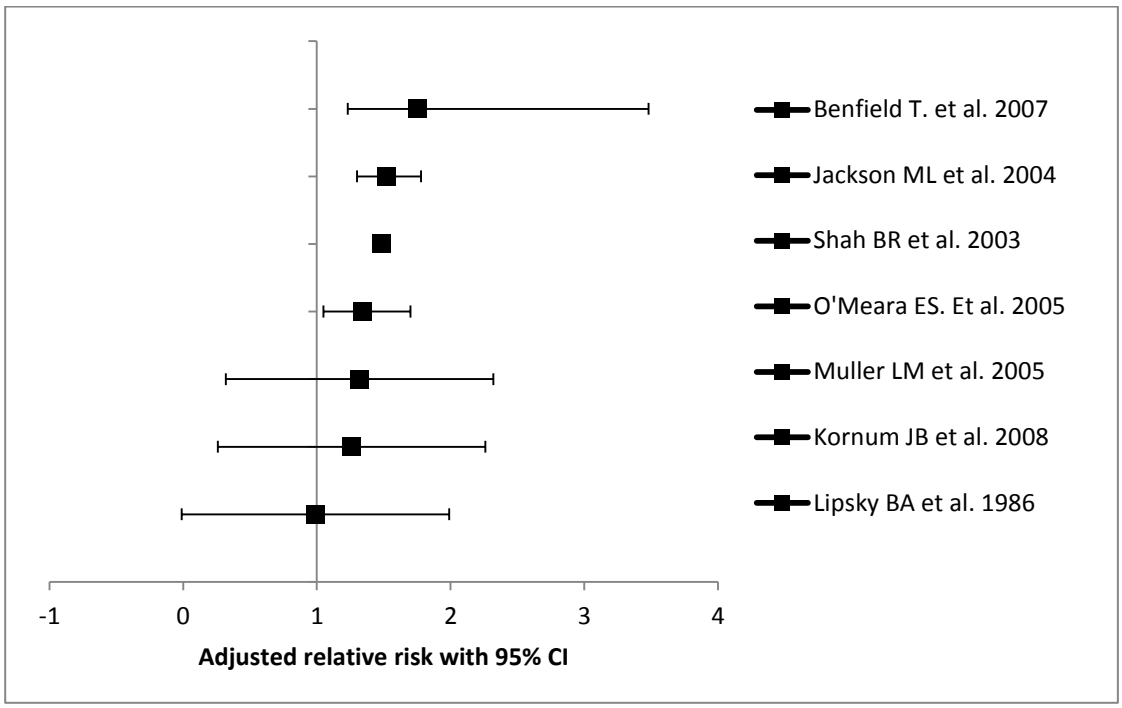
2.6 Type 2 diabetes and risk of specific infections

Infections are an emerging clinical problem in the globally increasing population of T2D [17, 21, 97, 105, 123], and may lead to many premature deaths in this patient group [17, 95]. Although rates of micro- and macrovascular complications in patients with T2D have declined lately [29], data on time-trends in the risk of community-based antibiotic use and hospital-treated infections are limited [17, 28]. As the literature review showed, T2D seems to increase the risk of selected important community-acquired infections by 1.5- to 3-fold [17, 22-27, 95, 105], although the exact magnitude is debated [72]. Additionally, certain infections such as invasive otitis externa, rhinocerebral mucormycosis, and emphysematous infections seem to occur almost exclusively in diabetes patients, as reported in case reports [19]. Yet, the excess risk for many important infections associated with T2D is debated, and population-based evidence comparing infection risk with that in the general population after adjustment for potential confounders is scarce, particularly for community-treated infections and antibiotic use [17, 72, 85]. In the following, I discuss the risk of specific infections in more detail.

2.6.1 Risk of respiratory tract infections

Respiratory tract infections are commonly classified into upper respiratory tract infection (URTI) that includes any infection of nose, sinuses, and throat, and LRTI that includes any infection of the airways and lungs. As seen from Table 1 and illustrated in Figure 1 five cohort studies and 1 case-control study [23, 27, 73, 105-107] have reported that T2D increases the risk of pneumonia by 1.26- to 1.75-fold, while one another case-control study did not find any association [84] (Figure 2). Besides, the relative risk of TB associated with T2D is reported to be between 1.5 and 7.8 in a systematic review of nine cohort and case-control studies [94]. A meta-analysis of 13 population-based studies with 1,786,212 participants reported a 3-fold increased risk of TB (adjusted RR 3.1, 95% CI 2.3 – 4.3) in patients with T2D based on random-effect meta-analyses of three cohort studies, and the remaining ten case-control/cross-sectional studies were heterogeneous, with OR ranging between 1.16 and 7.83 [22].

Figure 2. Forest plot of studies with estimates for risk of pneumonia in patients with diabetes.



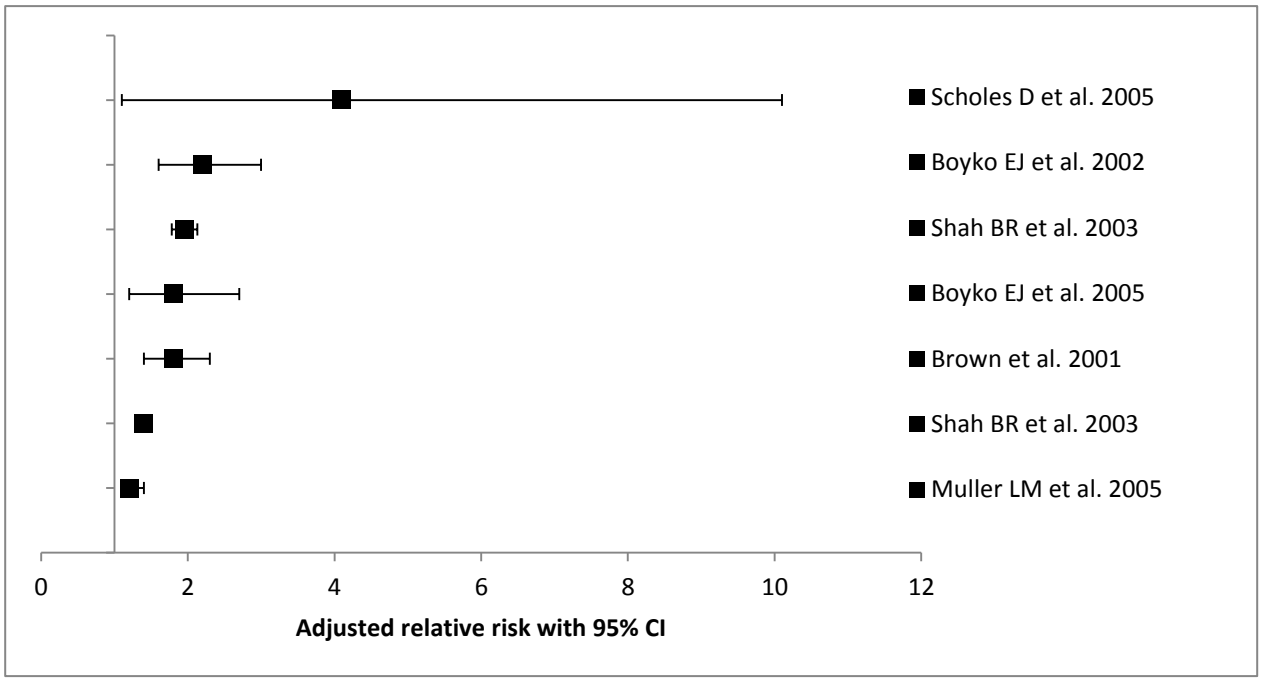
A Danish case-control study found a lower diabetes-TB RR of only 1.18 (95% CI 0.96 – 1.45) [85], perhaps due to more well-controlled diabetes. Additionally, T2D also has been associated with an increased risk of multi-drug resistant TB [124-126]. In conclusion, the existing literature suggests that T2D is associated with a 25-50% increased risk of respiratory tract infections with a probably higher RR for TB.

2.6.2 Risk of urinary tract infections

UTIs are common clinical complications in patients with T2D [127-130]. Figure 3 illustrates a forest plot of 4 follow-up studies and 3 case-control studies showing risk of UTI in patients with T2D. In a follow-up study, Boyko *et al.* found a 2.3-fold (95% CI 1.3 – 3.9) increased risk of asymptomatic bacteriuria in women with T2D compared with women without T2D [113]. Concerning symptomatic UTI, a case-control study from the US reported an adjusted OR of

2.2 (95% CI 1.6 – 3.0) associated with T2D in 901 women with acute symptomatic UTI and 913 controls [113]. These findings have later been confirmed in studies based on postmenopausal women, e.g., by Boyko *et al.* (RR 1.8, 95% CI 1.2 – 2.7) [104]. In a Canadian cohort, the RR of a community- or hospital-treated UTI associated with T2D was found to be 1.39 (95% CI 1.36 – 1.42) for cystitis and 1.95 (95% CI 1.78 – 2.13) for pyelonephritis [27]. Another study based on data from general practices in the Netherlands found an OR of 1.2 (95% CI 1.1 – 1.4) for UTI associated with T2D [105]. These results were corroborated by a population-based case-control study from the US that reported adjusted OR of 4.1 (95% CI 1.6 – 10.9) for the risk of pyelonephritis associated with T2D among people younger than 50 years [114]. In conclusion, the above studies show a 1.2-4.1-fold association between T2D and risk of UTI (Figure 3).

Figure 3. Forest plot of studies with estimates for risk of urinary tract infections in patients with diabetes.

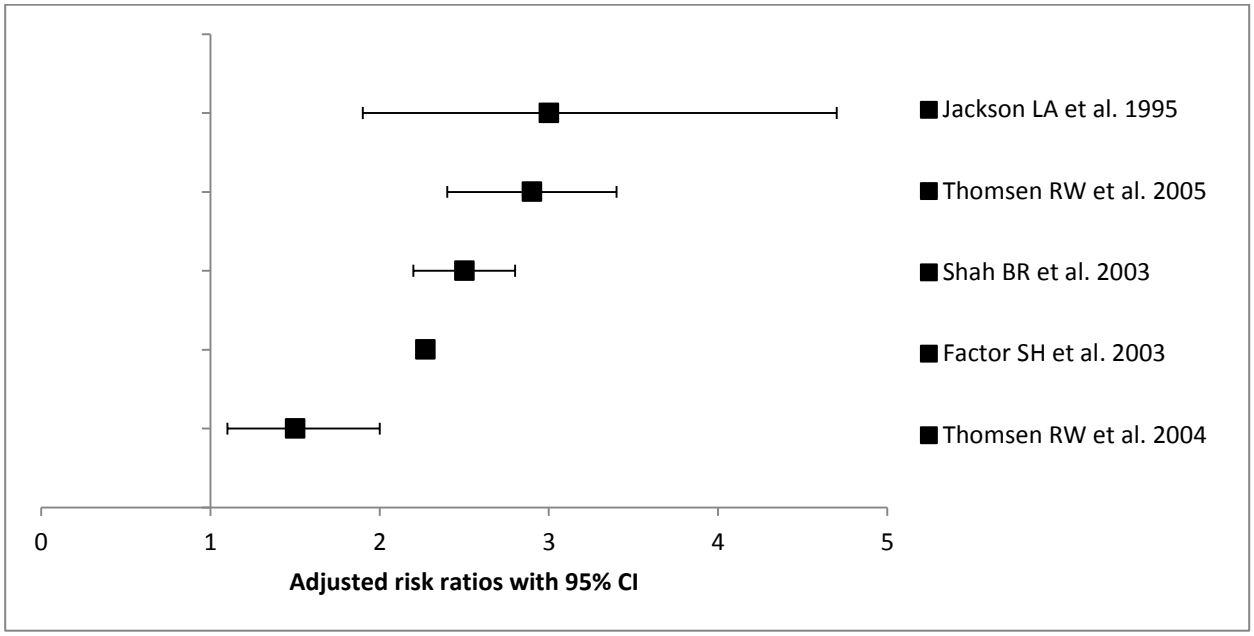


2.6.3 Risk of bacteraemia

Presence of bacteria in the blood is called bacteraemia. In some individuals these bacteria lead to clinical symptoms and potentially life-threatening infection called septicaemia, which

requires prompt treatment with antibiotics. A Canadian population-based cohort study of 513,749 patients with T2D and an equal number of matched comparisons reported a RR of 2.5 (95% CI 2.2 – 2.7) for hospitalisation with septicaemia associated with T2D [27]. A Danish population-based case-control study of 598 patients with pneumococcal bacteraemia and ten matched controls per case reported an adjusted OR of 1.5 (95% CI 1.1 – 2.0) for pneumococcal bacteraemia in patients with T2D [119]. A population-based case-control study from Denmark, based on 1,317 patients with bacteraemia and ten population controls per case, found that T2D substantially increased the risk of bacteraemia caused by *Escherichia coli* (adjusted OR 2.9, 95% CI 2.4 – 3.4) [26]. Additionally, epidemiological evidence suggests that the presence of T2D increases the risk of bacteraemia due to *Haemolytic streptococci* by 2- to 3-fold [89, 115]. This evidence suggests an association of T2D with a 1.5-3-fold increased risk of septicaemia (Figure 4).

Figure 4. Forest plot of studies with estimates for risk of bacteraemia in patients with diabetes.



2.7 Type 2 diabetes and risk of community-based antibiotic use

Antibiotic use in the community and the global prevalence of T2D are increasing in parallel [2, 131, 132]. Antimicrobial resistance has become a global health crisis that demands new multidisciplinary approaches [133]. High use, and potential overuse, of antibiotics in patients with T2D has clinical importance because antibiotic use may increase microbial resistance and worsen subsequent infection outcomes [134]. Some antibiotics may interfere with glycaemic regulation [135] and insulin production in T2D patients [136]. Moreover, high use of antibiotics may have adverse long-term effects on e.g. colorectal cancer risk which is increased in T2D [17, 137]. Therefore, up-to-date knowledge about any excess risk of community antibiotic treated infections with T2D is important [138].

As seen from Table 1 a study from the Netherlands reported a 60% increase in use of antibiotics between 1995 and 2003 for LRTIs and a 15% increase in the use for UTIs among patients with T2D [28], whereas comparative data for persons with no T2D were not provided. Furthermore, three other follow-up studies [72, 100, 105] used claims or self-reported data to examine the risk of infections reported in primary care that are likely to be treated with an antibiotics and observed that patients with T2D were at 53% increased risk of UTI [100], 30% increased risk of LRTI [105], and 79% increased risk of any self-reported community-acquired infection [72] compared with people without T2D. These evidence suggest that T2D may increase use of antibiotic in primary care by 15% to 79% compared to people without diabetes.

2.8 Glucose-lowering drug use and risk of infection

T2D treatment guidelines recommend early start of pharmacotherapy with GLDs already at T2D diagnosis [139, 140] to delay development of diabetes-related complications. Consequently, three-quarters of patients now start pharmacotherapy with GLD within 1 year of T2D diagnosis [141]. Limited evidence exists on the influence of GLDs on the risk of infections [60, 76-79, 81, 88]. As reviewed in Table, a Swedish study of different T2D treatment outcomes found that compared with metformin, the risk of hospital-treated infection was higher in insulin only users (HR 1.37, 95% CI 1.26 – 1.50) and other oral GLDs

users (80% of these were sulfonylurea users, HR 1.16, 95% CI 1.04 – 1.28) in 51,675 pharmacologically treated patients with T2D [88]. In a double-blind randomised study of 807 patients with T2D, the risk of URTI was higher in patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitors than in those treated with metformin (5.9% versus 3%) after a follow-up of 52 weeks, although the difference was not statistically significant ($P > 0.05$) [87]. Thus, evidence points towards a beneficial impact of metformin on the risk of infection.

2.9 Hyperglycaemia and risk of infection

The effect of glycaemic control *per se* on the risk of infections in T2D has not been focussed on in randomised trials, and the evidence from observational studies is sparse and inconsistent [71-75, 104]. Boyko *et al.* [104] reported that UTI risk increased with worsening glycaemic control (adjusted HR for baseline HbA_{1c} values of ≤7.5%, 7.6–8.5% and >8.5% were 1.3 (95% CI 0.7 – 2.3), 1.8 (95% CI 0.9 – 3.3) and 1.9 (95% CI 0.7 – 4.8), respectively). Population-based case-control studies based in Denmark have found that compared to people without diabetes the increased risk of certain infections in patients with T2D was associated with poor glycaemic control (HbA_{1c} ≥9%), for example, bacteraemia caused by *Haemolytic streptococci* (adjusted OR 3.6, 95% CI 1.6 – 8.1) [74], pneumonia (adjusted OR 1.60, 95% CI 1.44 – 1.76) [23], and TB (adjusted OR 1.19, 95% CI 0.61 – 2.30) [85]. In another Danish study based on the Copenhagen City Heart Study cohort, a 6%–10% increase in the risk of subsequent pneumonia, UTI, or skin infection was reported with every 1 mmol/l increase in plasma glucose at baseline [73]. Two other studies based on the UK GPRD reported a 3.5-fold greater risk of genital infections [99] and a 2-fold greater risk of UTI in patients with poorly controlled diabetes (at least one HbA_{1c} measurement ≥8%) versus better-controlled diabetes [100]. Whereas the Australian Fremantle Diabetes Study did not demonstrate a significant difference in baseline HbA_{1c} levels among T2D patients with and without infections in the subsequent 12 years [71, 72]. A population-based study from Denmark based on 2737 T2D patients reported that the annual risk of community-treated UTI was high in patients treated with oral GLDs (16.0%) and similarly high when treated with insulin (16.3%); no evidence was found that tightened glycaemic control decreased the risk of UTI [109]. Furthermore, in another study each 1% increase in pre-operative HbA_{1c} levels was associated with an increased

risk of post-operative infections (OR 1.25, 95% CI 1.02 – 1.53) after foot and ankle surgery [111]. In contrast, Adams *et al.* did not find any increased risk of post total knee replacement surgical infections in diabetes patients with HbA_{1c} >= 7% compared with patients without diabetes (OR 0.55, 95% CI 0.29 – 1.06) [103]. Larger studies are required to provide robust result on the association between hyperglycaemia and a comprehensive range of infections in T2D patients.

2.10 Limitations of the review and of the existing literature

In conclusion, considerable gaps exist in the available knowledge on the risk of infections associated with T2D, GLD therapy, and hyperglycaemia. The space limitations of a PhD-dissertation in mind, the above narrative review focussed on selected important English-language studies performed during the last 15 years. Systematic review and meta-analyses of all available evidence for the individual research questions in this dissertation may have identified additional studies of relevance.

There are clear limitations to the identified studies. Only few randomized clinical trials exist on the research questions in this dissertation. Clinical trials are obviously not a feasible study design for investigating diabetes as a risk factor for infections. In glucose control and GLD therapy trials, infections have been rarely studied as an outcome. Second, previous studies often focused on selected infections only, such as pneumonia, UTI, and surgical infections, with varying results related to different definitions of these infection outcomes, including patient-reported infections. Third, evidence of rare diabetes-related infections such as malignant external otitis, emphysematous infections, etc. comes from case series only. Fourth, studies examining community-based antibiotic use as an outcome in T2D or GLD exposed patients are very limited. Fifth, many studies were based on single centre or other selected clinical settings and T2D populations, making it difficult to compare the results and to generalize them to the population-based routine clinical care setting. Sixth, many studies did not distinguish between T1D and T2D, and many have included a mixture of prevalent, not incident T2D cases. Seventh, previous observational studies had limitations due to risk of selection and information bias, related to short and incomplete follow-up in cohort studies, inappropriate selection of cases and controls in case-control studies, and selected reporting of

outcomes. Finally, an important drawback of studies examining risk of infection associated with glucose control was that HbA_{1c} or blood glucose was usually measured on a single occasion, hampering our understanding of the importance of short- versus long-term hyperglycaemia over time. Therefore, stronger and more tangible evidence is needed from large population-based studies.

3. Aims of the dissertation

We undertook three population-based studies to examine the association between T2D and community-based antibiotic use and hospital-treated infections. Hypotheses and specific aims of each study are described below.

Study I

Research hypothesis: Patients with T2D are at increased risk of infections compared with the general population without diabetes.

Aim: To examine the excess risk of community-based antibiotic use and hospital-treated infections in patients with T2D compared with matched comparisons from the general population.

Study II

Research hypothesis: GLDs differentially influence risk of infectious complications in patients with T2D.

Aim: To determine the association between pharmacotherapy initiation with GLDs and subsequent risk of community-based antibiotic use and hospital-treated infections in patients with T2D.

Study III

Research hypothesis: Current (short-term) glycaemic control – via immune function regulation – has greater influence on the risk of infections than early or long-term glycaemic control in patients with T2D.

Aim: To assess the association between long- and short-term glycaemic control and community-treated infections and hospital-treated infection risk in patients with T2D.

4. Material and methods

4.1 Setting

We conducted Study I and Study II within the entire Danish population of approximately 5.5 million inhabitants [142] and Study III within the North and the Central Regions of Denmark, which have approximately 2 million inhabitants [143]. The Danish National Health Service provides tax-funded universal access to health care, including access to primary care, hospitals, outpatient speciality clinics, and a partial reimbursement of costs of prescription medications, including GLDs [144]. Denmark collects and stores administrative and medical data in national databases, and the tradition of collecting data goes back to 1645 [145]. This Danish setting, with available data in these databases, is ideal for conducting epidemiological studies [142].

4.2 Data sources

All included studies are based on prospectively collected data recorded in various medical and administrative databases. Individual-level data from Danish registries can be linked using the unique 10-digit personal identifier – the central personal registry (CPR) number – assigned at birth or upon immigration [146, 147].

4.2.1 The Danish Civil Registration System

The Danish Civil Registration System (CRS) was established in 1968 with the purpose of collecting personal information for administrative purposes [146]. It registers every Danish resident and provides a CPR number at birth to all those born in Denmark and on immigration to those who live in Denmark legally for more than 3 months. It contains information on date of birth and death, place of residence, marital status, information on parents and children, and date of emigration and immigration. The database is updated daily [146]. Additionally, we used the registry to obtain complete follow-up data on mortality or emigration and to ascertain that the participants were residents of the study area, particularly in Study III. We used this dataset in all three studies.

4.2.2 The Danish National Patient Registry

The Danish National Patient Registry (DNPR) contains information on all non-psychiatric hospitalisations in Denmark since 1977, and all outpatient and emergency room visits are included since 1995 [148]. Data from private hospitals were added to the registry from 2003 [149]. Danish private hospitals account for 2% of the total hospital activity in the country [149]. It is mandatory to report to the DNPR because it is used to monitor, measure, and reimburse healthcare cost. The DNPR includes information on patients' CPR number, admission date, discharge date, type and date of surgery, major treatment/interventions and procedures, a primary discharge diagnosis, and up to 19 secondary discharge diagnoses. These diagnoses are assigned by the discharging physician and are coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993 and *Tenth Revision* (ICD-10) thereafter) [148]. We used this dataset in all three studies.

4.2.3 The Danish National Health Service Prescription Database

The Danish National Health Service Prescription Database (DNHSPD) collects data from all community pharmacies and hospital-based outpatient pharmacies [150]. It archives information on patients' CPR number, drugs dispensed, place and date of dispensing, size of packet, strength of the medications contained in the packet, defined daily dose of the drug, and prescriber-related information for all prescription medications dispensed in Denmark since 2004 [150]. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system [151]. In Denmark, GLDs and antibiotics are available only by prescription [152]. We used this dataset in studies I & II.

4.2.4 The Aarhus University Prescription Database

The Aarhus University Prescription Database (AUPD) gathers information on reimbursed drugs retrieved at public pharmacies and hospital-based outpatient pharmacies located in the North and the Central Denmark Regions [153]. It contains complete data on all prescription medications dispensed since 1998, and additionally has including data from Danish counties of North Jutland since 1992, Aarhus since 1996, and Ringkøbing and Viborg since 1998 [153]. It collects data on patients' CPR number, drug- and prescriber-related information for

all redeemed medications coded according to the ATC classification system. We used this dataset in Study III.

4.2.5 The Clinical Laboratory Information System

The Clinical Laboratory Information System (LABKA) is used to order biochemical tests and to provide the results online for clinicians in general practice and at hospitals. It includes data on virtually all specimens analysed in clinical laboratories and general practices in the North and the Central Denmark Regions since 2000 [154]. It collects data on CPR number, name and code of test performed, unit of measurements, the result, and the date of test. The tests are coded according to the International Union for Pure and Applied Chemistry [155, 156]. We used the LABKA database to collect information on all HbA_{1c} measurements available for the cohort in Study III.

4.3 Study design

All three studies included in this dissertation are population-based follow-up studies based on the databases described above (Table 2). Study I is a nationwide population-based matched-cohort study. Study II is a nationwide population-based pharmacoepidemiological cohort study, and Study III is population-based cohort study conducted in the North Denmark Region because laboratory data on HbA_{1c} was available only for this region.

Table 2. Study design overview.

	Study I	Study II	Study III
Aim	Examine the risk of community-based antibiotic use and hospital-treated infections in patients with T2D compared with matched comparisons from the general population	Examine the association between pharmacotherapy initiation with GLDs and risk of community-treated infections (defined by antibiotics) and hospital-treated infections in pharmacologically treated patients with T2D	To assess the association between long- and short-term glycaemic control and risk of community-treated infections (defined by all antiinfectives) and hospital-treated infections in patients with T2D
Design	Population-based matched cohort study	Population-based cohort study	Population-based cohort study
Data sources	CRS, DNPR, DNHSPD	CRS, DNPR, DNHSPD	CRS, DNPR, AUPD, LABKA
Study setting and period	Nationwide, 2004–2012	Nationwide, 2005–2012	The Central and North Denmark Regions, 2000–2012
Study population	155,158 patients with T2D and 774,017 age-gender-residence matched comparisons	131,949 pharmacologically treated T2D patients	69,318 T2D patients with available HbA_{1c} information
Exposure	T2D	GLDs	Glucose control
Major outcome	Community-based antibiotic use and hospital-treated infections	Community-based antibiotic use and hospital-treated infections	Community-treated infection and hospital-treated infections
Covariates	Age, sex, marital status, alcoholism-related conditions, CCI score, statin use, steroid use, and immunosuppressant use	Age, sex, CCI score, hospital-diagnosed obesity, previous hospitalization, previous infection, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/ immunosuppressive drugs, and calendar period of study inclusion	Age, gender, CCI score, micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date
Statistical analyses	Computed IR and used Cox regression to compute HRs; used linear regression to assess time-trends of HRs	Computed IR and cumulative risk using Kaplan–Meier; and Cox proportional hazard analysis to compute HRs	Computed IR and used Cox proportional hazard analysis to compute HRs
Confounder control	Matching, stratification, multivariate adjustment	Stratification, multivariable adjustment	Stratification, multivariate adjustment
Sensitivity analyses	External adjustment for unmeasured BMI	External adjustment for unmeasured BMI and smoking, and subgroup analyses adjusting additionally for baseline HbA1c	Analysis restricted to newly diagnosed T2D patients; separate analyses for primary and secondary diagnosis of hospital-treated infection

4.4 Study populations

For all three studies, we identified patients with T2D by searching the DNPR for their any inpatient and outpatient clinic contact with a diagnosis of diabetes, and the DNHSPD (studies I & II) or AUPD (Study III) for any GLD prescription redemption record. Incident diabetes was defined as either the first record in the DNPR of a diabetes-associated inpatient admission (data available from 1977) or outpatient clinic contact (data available from 1995) or the first record of a GLD prescription in the DNHSPD (data available from January 2004) for Studies I and II or in the AUPD (data available from January 1992) for Study III, whichever came first [157]. This date of the first healthcare contact with diabetes thus identified is called the date of incident diabetes diagnosis in the rest of this dissertation. In all three studies, we excluded subjects under 30 years of age at the date of incident diabetes diagnosis to decrease the chance of including people with T1D in our T2D cohort [158].

We conducted Study I among all patients with an incident diagnosis of T2D recorded in the healthcare system between 1 July 2004 and 31 December 2012. We excluded subjects if they had a record of T2D prior to the study period and created a final cohort of patients with T2D for this study. We defined the index date as the date of incident T2D diagnosis. To create a 1:5 matched comparison cohort for each patient in the T2D cohort, we selected five individuals from the general population who did not have diabetes as of the index date. We matched them individually to the corresponding T2D patient with regard to year of birth, sex, and municipality. If a matched individual was diagnosed with T2D during follow-up, that person was censored and switched to the T2D cohort on their diabetes diagnosis date. The index date of patients in the T2D cohort was assigned as the index date for corresponding matched individuals in the matched cohort. Finally, we included 155,158 patients with T2D in the T2D cohort and included 774,017 persons without diabetes from the general population in the matched comparison cohort.

We conducted Study II in a Danish nationwide cohort of patients who had an incident T2D diagnosis between 1 January 2005 and 31 December 2012. During this study period, we identified 147,396 patients who were 30 years or older at the first record of T2D. Then we excluded patients who had no records of GLD prescription available during the study period

(n = 14,120). We also excluded 1327 female patients who were diagnosed with PCOD recorded in the DNPR and were using metformin monotherapy recorded in the DNHSPD. This left a final study cohort of 131,949 patients with incident pharmacotherapy for T2D. The index date was defined as the first record of GLD prescription redemption available in the DNHSPD during the study period after the record of incident T2D (as defined above).

We conducted Study III among patients with T2D in the Northern Denmark Region. We identified 70,299 patients with an incident T2D diagnosis between 1 January 2000 and 31 December 2012 who were older than 30 years and had at least one HbA_{1c} measurement record available in the LABKA database. We excluded female patients who had a PCOD diagnosis recorded in the DNPR and used metformin monotherapy (n = 981). The final study cohort consisted of 69,318 patients with T2D. The index date for this study was defined as the date of first HbA_{1c} measurement on or after the date of the diabetes diagnosis.

4.5 Main exposures

In Study I, the exposure was the diagnosis of T2D.

In Study II, we defined exposure as the first record of a GLD prescription redemption available in the DNHSPD after the first record of diabetes diagnosis. We retrieved information from the DNHSPD on all GLD prescriptions and divided them into seven categories: metformin (biguanides), sulfonylurea, insulin, any fixed drug combinations, DPP-4 inhibitors, glucagon like peptidase-1 (GLP-1) analogues, meglitinides, and other (includes thiazolidenidiones and alpha glucosidase inhibitors). Please see the Appendix for ATC codes.

In Study III, the exposure was ascertained from the available HbA_{1c} measurements in the LABKA database during the study period. The laboratories in the Northern Denmark Region analyse HbA_{1c} in venous blood using laboratory methods standardised according to the Diabetes Control and Complications Trial assay and provide measurement as percentages [159]. We also converted HbA_{1c} values from the Diabetes Control and Complications Trial to International Federation of Clinical Chemistry standards and reported the HbA_{1c} value in

mmol/mol in Study III [159]. To convert the values, we used the following formula: HbA_{1c} in mmol/mol = [0.9148 × HbA1c %] + 2.152 [160]. To assess the importance of time-varying HbA_{1c} exposure, we categorised four HbA_{1c} exposure groups [161, 162]:

1. Early baseline HbA_{1c}: defined as the first HbA_{1c} value recorded on the index date.

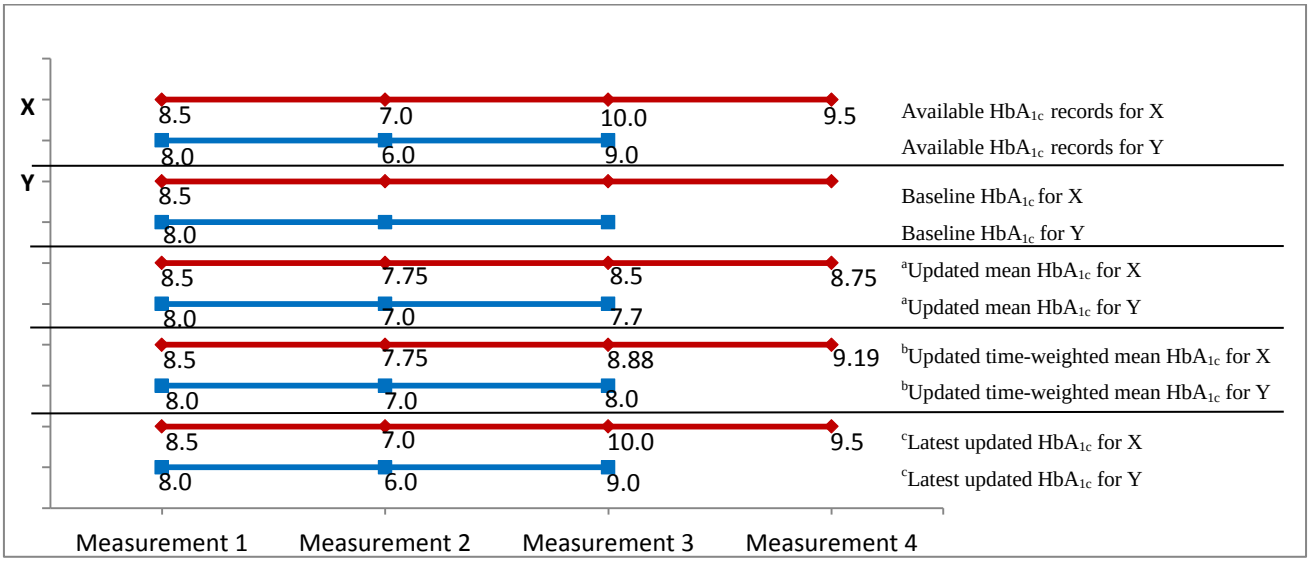
2. Updated mean HbA_{1c}: defined as the time-varying mean of all available HbA_{1c} values at the time of each new measurement.

3. Updated time-weighted mean HbA_{1c}: calculated as a time-weighted mean at the time of each new HbA_{1c} measurement. For example, the time-weighted mean at the third measurement was the mean of the third HbA_{1c} value and the mean of the first two HbA_{1c} values; the fourth time-weighted mean HbA_{1c} was the mean of the fourth HbA_{1c} value and the third time-weighted mean HbA_{1c} value, and so forth.

4. Latest updated HbA_{1c}: defined as the time varying actual HbA_{1c} value.

Within each exposure definitions, we divided the resulting HbA_{1c} values into seven categories (<5.5%, 5.5% to <6.5%, 6.5% to <7.5%, 7.5% to <8.5%, 8.5% to <9.5%, 9.5% to <10.5%, and ≥10.5%). Figure 5 illustrates these exposure definitions with examples.

Figure 5. HbA_{1c} exposure categorisation with examples of two study participants, X and Y.



[a]Updated mean HbA_{1c} was updated at each new measurement, which contributed to risk-time until the next measurement. For example, for participant Y, the HbA_{1c} value of 8.0% contributed from date of measurement 1 to date of measurement 2; then the mean at measurement 2 [(8.0% + 6.0%)/2 = 7.0%] contributed from date of measurement 2 to date of measurement 3, and the mean at measurement 3 [(8.0% + 6.0% +9.0%)/3 = 7.7%] contributed to the risk-time from date of measurement 3 until the next measurement or until the outcome or end of follow-up.

[b]Updated time-weighted mean HbA_{1c} was calculated as the mean of the current HbA_{1c} measurement and the mean of the previous measurements and was updated at each new measurement, which contributed to risk-time until next measurement. For example, for participant X, the HbA_{1c} value of 8.5% contributed to risk-time from date of measurement 1 to date of measurement 2; then the updated mean at measurement 2 [(8.5% + 7.0%)/2 = 7.75%] contributed from the date of measurement 2 to the date of measurement 3, and the updated mean at measurement 3 [(7.75% +10.0%)/2 = 8.875%] contributed to the risk time from date of measurement 3 to date of measurement 4, and the updated mean at measurement 4 [(8.875% +9.5%)/2 = 9.1875%] contributed until the next measurement or until the outcome or end of follow-up.

[c]Latest updated HbA_{1c} value: each HbA_{1c} measurement contributed to risk-time extending from the date of the measurement until the next measurement. For example, for X the first measurement (i.e., 8.5%) contributed from the date of measurement 1 to the next measurement 2, and the next measurement (i.e., 7.0%) contributed from the date of measurement 2 to the subsequent measurement 3.

4.6 Outcomes

In studies I and II, the main outcome measures were community-treated infections (defined by antibiotic use) and hospital-treated infections. In Study III, the main outcome measures were community-treated infections (defined by any antiinfective use) and hospital-treated infections.

Community-based antibiotic use was defined as any first-time redeemed antibiotic prescription recorded in the DNHSPD (in studies I & II) or in the AUPD (in Study III) after the index date. We investigated groups of antibiotics prescribed to treat specific infections according to the National Danish guidelines for primary care [163, 164]. Antibiotics were combined in the following ten groups: 1) phenoxymethylpenicillin (first line drug against community-acquired respiratory tract infections); 2) pivampicillin, amoxicillin, and amoxicillin with enzyme inhibitor (broad-spectrum beta-lactams used mainly for respiratory tract infections in selected patients); 3) azithromycin (used mainly to treat genital infections); 4) erythromycin, roxithromycin, and clarithromycin (used for respiratory tract infections in the presence of penicillin allergy or for *Mycoplasma pneumonia*); 5) pivmecillinam, sulfamethizole, nitrofurantoin, and trimethoprim, (drugs almost exclusively used to treat UTIs in Denmark); 6) dicloxacillin and flucloxacillin (used mainly to treat skin infections / *S. aureus*); 7) antitmycobacterials (used to treat TB); 8) ciprofloxacin (used to treat UTIs and gastrointestinal infections in selected cases); 9) tetracycline; and 10) cephalosporins (see the Appendix for ATC codes). In Study III, after experience from the first studies, we added systemic antifungal and systemic antiviral prescriptions ("any antiinfectives") to the list to define community-treated infections more completely.

Hospital-treated infection was defined as any first-time inpatient admission or hospital outpatient clinic contact with a primary or secondary diagnosis of an infection after the index date. We examined a wide range of hospital-treated infections by searching the DNPR. We divided hospital-treated infections into the following 16 categories: 1) eye and ear infections, 2) URTIs, 3) pneumonia, 4) infections of the heart and blood vessels, 5) gastrointestinal tract infections, 6) intra-abdominal infections, 7) UTIs, 8) infections of the central nervous system, 9) meningococcal infections, 10) skin and subcutaneous infections, 11) abscesses, 12)

septicaemia, 13) TB, 14) miscellaneous bacterial infections, 15) viral infections, and 16) fungal infections (see the Appendix for ICD codes). We specifically investigated certain rare infections that have been closely associated with diabetes in the literature [123], *i.e.*; malignant external otitis, emphysematous cholecystitis, perirenal abscess, emphysematous pyelonephritis, and emphysematous cystitis.

4.7 Covariates

We obtained data on various variables to describe the study population, examine subgroup effects, and to adjust for potential confounders. We considered potential confounders those variables that are associated with exposure and outcome of interest are unequally distributed between the exposed and unexposed populations and are not intermediate between the exposure and the outcome [165].

4.7.1 Demographic variables

We used the CRS to collect information on age, gender, marital status, and date of emigration and death. We used the registry to follow study participants throughout the study period.

4.7.2 Coexisting morbidities

We used the DNPR to collect data on inpatient and outpatient discharge diagnoses recorded on or within 10 years of the index date to compute a Charlson Comorbidity Index (CCI) score for each study participant [166]. We chose 10 years before the index date because older diagnoses would not likely affect the outcome occurrence. The CCI score includes major diabetes-related complications, e.g., myocardial infarction, peripheral vascular disease, stroke, chronic heart failure, and renal disease [167]. Overall comorbidity levels were defined as low (CCI score of 0), medium (CCI score of 1 to 2), and high (CCI score of ≥ 3). Furthermore, for Study II and Study III, we retrieved information on the presence of diabetes-related micro- and macrovascular complication as of index date not included in the CCI score, e.g., angina pectoris, atherosclerotic heart diseases, various neuropathies and retinopathies, etc (see the Appendix for ICD codes). Additionally, we retrieved information on the presence of other conditions such as alcoholism-related disorders and hospital-diagnosed obesity from

the DNPR, and retrieved information on concurrent use of statins, oral corticosteroids, and immunosuppressive drugs from the DNHSPD or AUPD [168, 169]. Additionally, in Study II we retrieved information on presence of any acute inpatient hospitalization or emergency room visit within 6 month before the index date of first GLD prescription, including any acute hospitalization or emergency room visit with an infection diagnosis.

4.8 Statistical methods

We described demographic and clinical characteristics of study populations in each study using frequency tables with summary statistics [170]. In all studies, we presented a distribution of variables according to exposure status – presence or absence of T2D in Study I, different GLDs in Study II, and baseline HbA_{1c} category in Study III.

4.8.1 Follow-up and risk-time contribution

In Study I, we followed both cohorts from the index date until the occurrence of the first outcome event, emigration, death, or end of study period. i.e., 31 December 2012, whichever came first. For both cohorts, risk-time was calculated from the index date until the end of follow-up. Matched individuals who were diagnosed or treated for T2D during follow-up were censored and switched to the T2D cohort on their diabetes diagnosis date.

In Study II, we followed up the patient cohort from the index date until the occurrence of the first outcome event, emigration, death, or end of study period, i.e., 31 December 2012, whichever came first. We primarily followed the intention-to-treat approach where the exposure was assigned at the index date and was fixed [171], and risk-time was calculated for each initial GLD category separately from the index date until the end of follow-up disregarding any future alteration of therapy.

In Study III, we followed the patient cohort from the index date until the occurrence of the first outcome event, emigration, death, or end of study period, i.e., 31 December 2012, whichever came first. The risk-time for different HbA_{1c} exposures was calculated separately according to the categories of HbA_{1c}:

1. Early baseline HbA_{1c}: contributed to exposure risk-time from the index date to the end of follow-up.
2. Updated mean HbA_{1c}: each updated mean HbA_{1c} value contributed to the exposure risk-time until the consecutive measurement.
3. Updated time-weighted mean HbA_{1c}: each updated time-weighted mean HbA_{1c} contributed to the exposure risk-time until the consecutive measurement.
4. Latest updated HbA_{1c}: each latest updated HbA_{1c} value contributed to the exposure risk-time until a new measurement was taken.

4.8.2 Rates of outcome events

For each study, we followed all study participants from the index date, and reported incidence rates (IRs) of community-based antibiotic use/community-treated infections and hospital-treated infections per 1000 patient-years at risk (PYAR), calculated as the number of patients who developed an outcome divided by the number of patient-years of follow-up in each exposure category.

4.8.3 Cox proportional hazard regression analysis

We used Cox proportional hazards regression analysis in all three studies to compute HRs of community-based antibiotic use/community-treated infections and hospital-treated infections with 95% CIs according to the exposure categories. The HRs were used as a measure of rate ratios (RRs). Multivariate Cox regression was used to adjust for confounders. Proportionality assumptions were assessed graphically by plotting log-log plots and were found to be valid.

In Study I, we computed RRs and created three models to adjust for confounders in the multivariate Cox regression analysis. In Model 1, we adjusted for age, sex, marital status, CCI comorbidities except for cardiovascular and renal disease categories (as these may be consequences of having T2D), and alcoholism-related disorders; in Model 2, we additionally adjusted for cardiovascular and renal comorbidities; and in fully adjusted Model 3, we added use of statins, steroids, and immunosuppressants.

In Study II, we computed HRs associated with the categories of initial GLDs, with metformin as reference category. We first adjusted for age and sex (Model 1), and then added all available confounders (Model 2). We mainly focussed our results on the three largest GLD categories, i.e., metformin, sulfonylurea, and insulin. We did not run the analyses for ≤ 4 outcome events [172].

In Study III, we computed HRs for every 1% increase in HbA_{1c} level and for the HbA_{1c} categories, with the HbA_{1c} level of 5.5% to <6.5% as the referent. We computed HRs for all four exposure definitions. We included age, sex, marital status, diabetes duration, calendar period of enrolment, CCI score, micro- and macrovascular diabetes complications (not covered in the CCI), alcoholism-related conditions, concurrent use of statins, corticosteroids, and immunosuppressive drugs, and type of GLD use at index date.

In all three studies, we repeated all the analyses separately for specific infections and specific antibiotic groups, as described in sub-section 4.6.

4.8.4 Stratified analysis

We performed sub-group analyses to assess the impact of exposure on outcome in the strata of different variables. In Study I and Study III, we included stratified analyses by age groups, sex, CCI score, and statin use [168, 169]. In Study I, because the 1:5 technique of matching T2D patients with comparisons could not be retained for these analyses, we used ordinary Cox regression adjusted for age, sex, and the potential confounders listed previously.

4.8.5 Trends analysis

We assessed trends over time in infection risk among the T2D cohort and the comparison cohort in Study I. For each calendar year (from July to June), we computed adjusted RRs of community-based antibiotic use and hospital-treated infections restricted to 1-year of follow-up. We used linear regression to assess linear trends across calendar-time. We considered $P < 0.05$ to be statistically significant.

4.8.6 Sensitivity analysis

In Study I, we repeated the regression analyses to examine 6-month and 12-month risk of infection to assess whether rates of outcome were higher early after T2D diagnosis, due to increased clinical surveillance or deteriorated glucose control. We divided hospital-treated infections into primary and secondary diagnoses and repeated the analyses.

In Study II, we performed five additional sensitivity analyses:

1) To examine confounding by baseline HbA_{1c} which may be related both to choice of GLD and to subsequent risk of infections, we investigated a subcohort of our study population (n = 33 795), for which we had additional information on latest HbA_{1c} level before GLD initiation (baseline HbA_{1c}). We repeated the analyses for this subcohort including baseline HbA_{1c} categories (reference category: 5.5%-6.5%) as an additional confounder in the fully adjusted model.

2) To examine any residual confounding by comorbidity caused by using the original CCI score instead of newer versions (e.g., the CCI score was recently updated and validated using new scores by Quan et al. [173]), we collected new information from the registries and computed the CCI score as suggested by Quan et al. We repeated the analysis by replacing the traditional CCI score with the updated CCI score and compared the results.

3) To reduce any misclassification caused by mixture of type 1 and type 2 diabetes patients, we excluded all patients who used insulin as their first single GLD for pharmacotherapy after their diabetes diagnosis and were younger than 40 years old (n = 1430) at GLD start. We repeated the analysis within the restricted T2D patient cohort.

4) As an alternative to our intention-to-treat approach, we repeated the multivariable analysis by censoring the patients at the first change in GLD therapy from the initial therapy.

5) Finally, as intention-to-treat analysis may lead to conservative bias due to increasing exposure misclassification during follow-up, we performed an additional as-treated analysis considering time-varying drug exposure with the individual GLD regimen contributing to risk-time until the consecutive prescription redemption record. For this analysis, to explore

association of different important combinations of GLDs with infection outcomes, we categorized four main groups: metformin + sulfonylurea, metformin + insulin, sulfonylurea + insulin, and any other combinations, in addition to initiation therapy.

In Study III, we performed sensitivity analyses to see the effect in newly diagnosed T2D. We repeated regression analyses restricted to newly diagnosed T2D patients defined as those who had their first HbA_{1c} measurement recorded less than 3 months after their incident T2D diagnosis.

4.8.7 Bias analysis

Obesity is closely associated with T2D and smoking with the GLDs and both may increase infection risk, but we lacked detailed data on these factors. Therefore we used Schneeweiss' method [174] to compute externally adjusted estimates to assess the proportion of observed association explained by unmeasured obesity and smoking. To compute unmeasured confounder-adjusted rate ratio (caRR), we used the formula:

$$\text{caRR} = \frac{\text{aRR}}{\frac{Pc1(RRcd-1)+1}{Pc0(RRcd-1)+1}}$$

In Study I, we externally adjusted for obesity (body mass index [BMI] ≥30 kg/m²). In the formula, aRR is the crude rate ratio, P*c*0 and P*c*1 are the estimated proportion of obesity among the comparison cohort (0.13) and the T2D cohort (0.36), respectively [175], and *RRcd* is the estimated rate ratio between obesity and infection (1.23 for community-based antibiotic use and 1.5 for hospital-treated infections [164]).

In Study II, we used the same formula to compute externally adjusted estimates for obesity and tobacco smoking. In the formula, to compute caRR for obesity, we used the crude rate ratio observed between exposure and outcome in our study (aRR in the formula), Pc0 (for metformin) = 0.49, Pc1 for insulin = 0.19, Pc1 for sulfonylurea = 0.26; and RRcd for community-based antibiotic use = 1.23 and RRcd for hospital-treated infection=1.5 [164, 175]. Similarly, we computed caRR for smoking (Pc0 for metformin = 0.22, Pc1 for insulin = 0.26, Pc1 for sulfonylurea = 0.30, and RRcd for community-based antibiotic use = 1.17 and RRcd for hospital-treated infection = 4.1) [175-177].

We used SAS software (Version 9.1.3; SAS Institute, Cary, NC, USA) and STATA version 12 (StataCorp. 2011, Stata Statistical Software Release 12. College Station, TX, USA: StataCorp LP) for data management and analyses.

5. Ethics

Since none of the registry-based studies involved any patient contact or any sort of intervention, approval and involvement of the Danish Scientific Ethical Committee was not required according to Danish legislation. As we used sensitive data from administrative and healthcare databases, permission from Danish Data Protection Agency was required. Hence, the following approvals were obtained:

Study I: Approved by the Danish Data Protection Agency, record number: 2014-54-0922.

Study II: Approved by the Danish Data Protection Agency, record numbers: 2012-41-0793 and 2013-41-1924.

Study III: Approved by the Danish Data Protection Agency, record number: 2013-41-1924.

6. Results

In this section, we will present the main results of each of the three studies. For detailed results, please see the section 'Dissertation papers'.

6.1 Study I

6.1.1 Study cohort characteristics

We identified 155,158 patients with T2D and 774,017 matched comparisons without diabetes from the general population. Compared with the matched comparisons, patients with T2D were more likely to have myocardial infarction (5% versus 3%), congestive heart failure (4% versus 2%), cerebrovascular diseases (7% versus 5%), peripheral vascular diseases (4% versus 2%), chronic pulmonary disease (6% versus 2%), statin use (52% versus 19%), and oral corticosteroids use (5% versus 3%) (Table 3).

6.1.2 Community-based antibiotic use

We found that 92,672 (62%) patients with T2D and 429,175 (55%) individuals from the comparison cohort redeemed at least one antibiotic prescription from a community pharmacy after a median follow-up of 1.1 years (interquartile range [IQR], 0.4, 2.4 years) and 1.4 years (IQR, 0.5, 2.9 years), respectively. The rates of antibiotic use were 363.6 per 1000 PYAR in the T2D cohort and 275.3 per 1000 PYAR in the comparison cohort (Dissertation paper I).

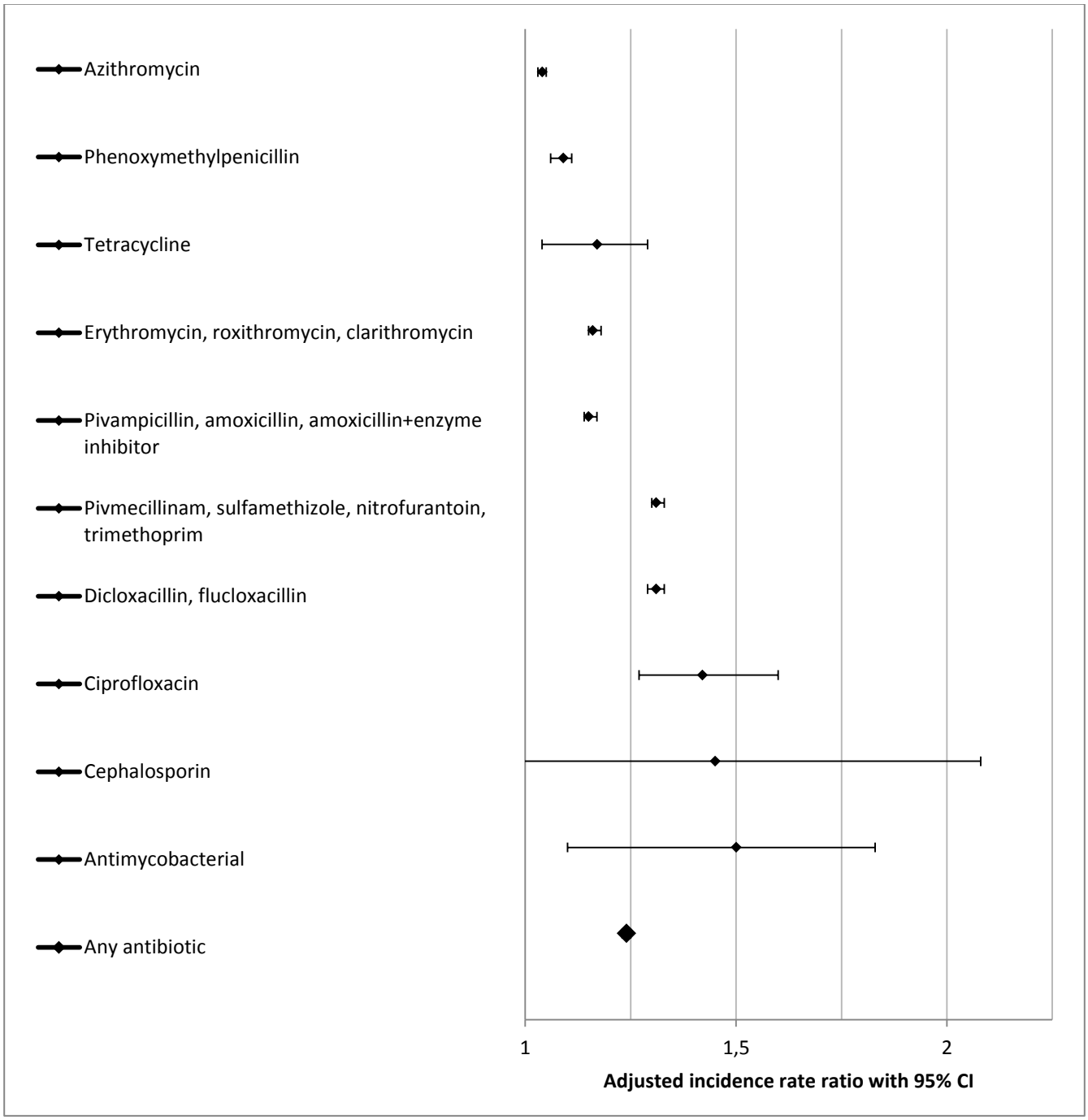
Table 3. Demographic and clinical characteristics of members of the T2D cohort and the matched comparison cohort, Denmark, 2004-2012.

	Type 2 diabetes cohort (%)	Matched comparison cohort (%)
Total	155,158	774,017
Men	85,338 (55)	425,554 (55)
Mean age (years) (standard deviation)	65.6 (13.6)	65.7 (13.6)
Age groups (in years)		
30 – <40	8,224 (5)	39,707 (5)
40 – <50	16,923 (11)	83,725 (11)
50 – < 60	29,261 (19)	144,360 (19)
60 – <70	45,275 (29)	225,388 (29)
70 – <80	35,392 (23)	177,834 (23)
>80	20,083 (13)	103,003 (13)
Marital status		
Married	87,040 (56)	460,263 (59)
Never married	18,274 (12)	86,840 (11)
Divorced	23,020 (15)	105,718 (14)
Widowed	24,551 (16)	114,020 (15)
Missing	2239 (1)	7175 (1)
Alcoholism-related conditions	6176 (4)	20,427 (3)
Charlson comorbidities		
Myocardial infarction	7454 (5)	19,676 (3)
Congestive heart failure	6728 (4)	15,323 (2)
Peripheral vascular disease	5745 (4)	18,559 (2)
Cerebrovascular disease	10,305 (7)	38,351 (5)
Dementia	992 (1)	5712 (1)
Chronic pulmonary disease	9960 (6)	33,143 (4)
Connective tissue disease	3366 (2)	13,951 (2)
Ulcer disease	3645 (2)	13,385 (2)
Mild liver disease	2217 (1)	4724 (1)
Hemiplegia	248 (<1)	986 (<1)
Moderate to severe renal disease	2042 (1)	6342 (1)
Any tumour	10,364 (7)	44,718 (6)
Leukaemia	315 (<1)	1278 (<1)
Lymphoma	605 (<1)	2690 (<1)
Moderate to severe liver disease	609 (<1)	1135 (<1)
Metastatic solid tumour	1246 (1)	3761 (<1)
AIDS	65 (<1)	490 (<1)
Charlson Comorbidity Index score		
Low (score of 0)	109,524 (71)	608,567 (79)
Medium (score of 1-2)	37,094 (24)	139,336 (18)
High (score of ≥3)	8540 (5)	26,114 (3)
Statin use	81,229 (52)	147,834 (19)
Corticosteroid use	7744 (5)	23,947 (3)
Immunosuppressant use	1237 (1)	4931 (1)

T2D was associated with community-based antibiotic use (crude RR 1.29, 95% CI 1.28 – 1.30), and the association persisted even after controlling for all available confounders (adjusted RR 1.24, 95% CI 1.23 – 1.25). When using individual comorbidities instead of CCI scores in the model, the adjusted RRs essentially remained the same (adjusted HR 1.24, 95% CI 1.23 – 1.25). Furthermore, after censoring the matched comparisons that developed diabetes during the follow-up the aRRs did not change. The crude RR decreased from 1.29 to 1.23 after external adjustment for obesity. The adjusted RR increased after restricting the follow-up to 6 months (adjusted RR 1.32, 95% CI 1.30 – 1.33) (Dissertation paper I). The RRs were increased for all individual antibiotic groups, in particular for use of cephalosporins, antimycobacterial agents, quinolones, and antibiotics used to treat UTIs and *S. aureus* infection (Figure 6).

In stratified analyses, we found stronger association of T2D with community-based antibiotic use in women than in men, in younger individuals than in older individuals, in people with low comorbidity than in people with high comorbidity, and in those not using statins than in those using statins on index date (Dissertation paper I).

Figure 6. Adjusted[a] rate ratios of community-based antibiotic use in the T2D cohort compared with the matched comparison cohort.



[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Cormorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

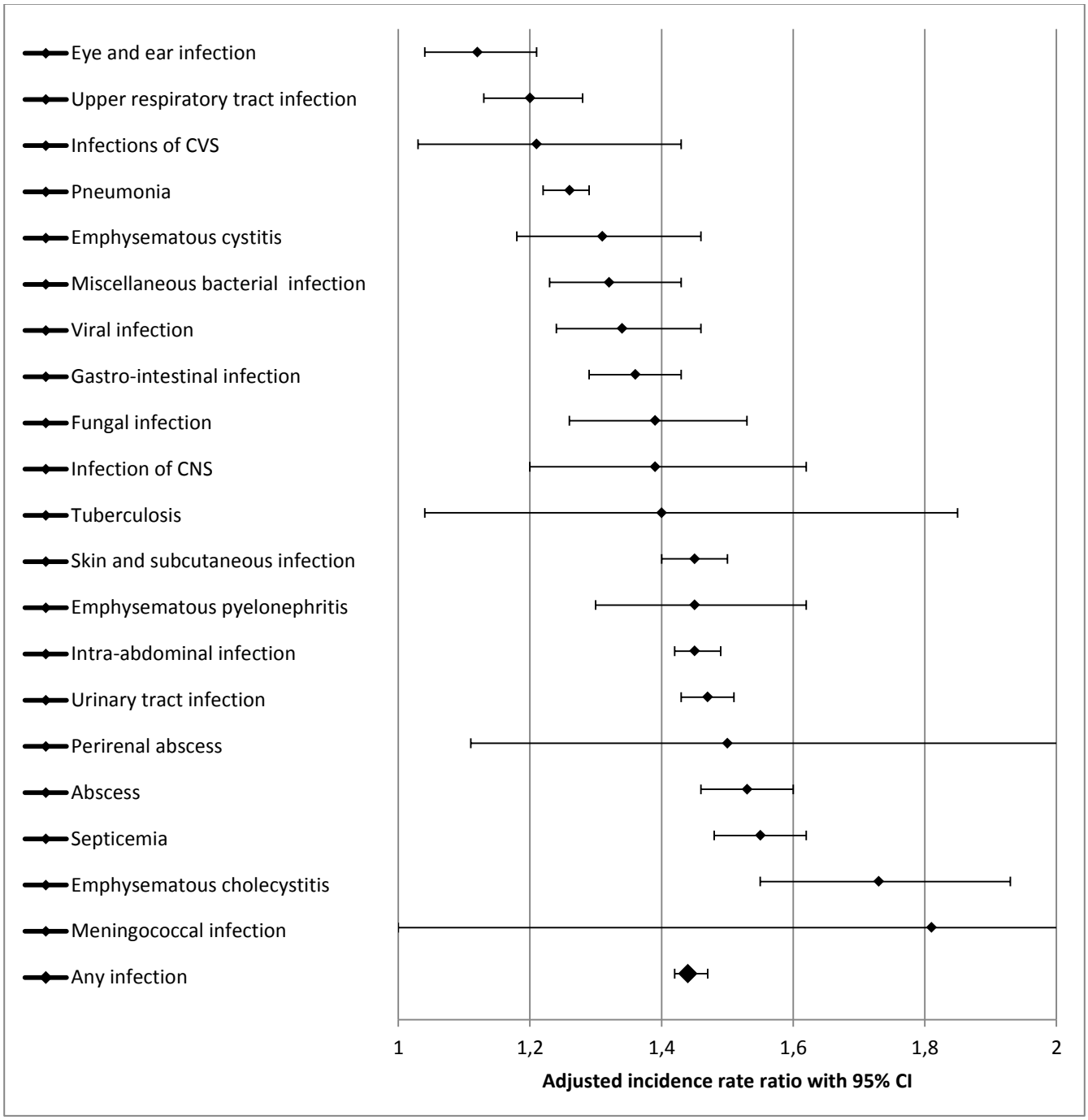
6.1.3 Hospital-treated infections

We identified 28,938 (19%) patients with T2D and 102,795 (13%) people from the comparisons with at least one episode of hospital-treated infection after a median follow-up of 2.8 years (IQR, 1.2, 5.0 years) and 3.0 years (IQR, 1.4, 5.2 years), respectively. The rates of hospital-treated infections were 58.2 per 1000 PYAR in patients with T2D compared to 39.0 per 1000 PYAR in the comparison cohort (Dissertation paper I).

In the Cox model, the crude RR of hospital-treated infections was 1.49 (95% CI 1.47 – 1.51), which reduced to 1.44 (95% CI 1.42 – 1.46) after adjusting for available confounders. After replacing CCI score with individual comorbidities in the multivariate model the adjusted RRs did not change. Furthermore, after censoring the matched comparisons that developed diabetes during follow-up the aRRs reduced to 1.41 (95% CI 1.39 – 1.43). In bias analysis, adjustment for unmeasured obesity changed the crude RR from 1.49 to 1.34. The adjusted RRs were particularly elevated during the first 6 months of follow-up after a T2D diagnosis (adjusted RR 1.92, 95% CI 1.86 – 1.98) (Dissertation paper I). The RRs were increased for all infection types, and the highest adjusted RRs were observed for emphysematous cholecystitis, followed by abscesses, TB, septicaemia, meningococcemia, and skin and subcutaneous infections (Figure 7).

In stratified analyses, we found a stronger association of T2D with hospital-treated infections in women than in men, in younger individuals than in older individuals, in people with low comorbidity than in people with high comorbidity, and in those not using statins than in those using statins at the index date (Dissertation paper I).

Figure 7. Adjusted[a] rate ratios of specific hospital-treated infections in the T2D cohort compared with the matched comparison cohort.

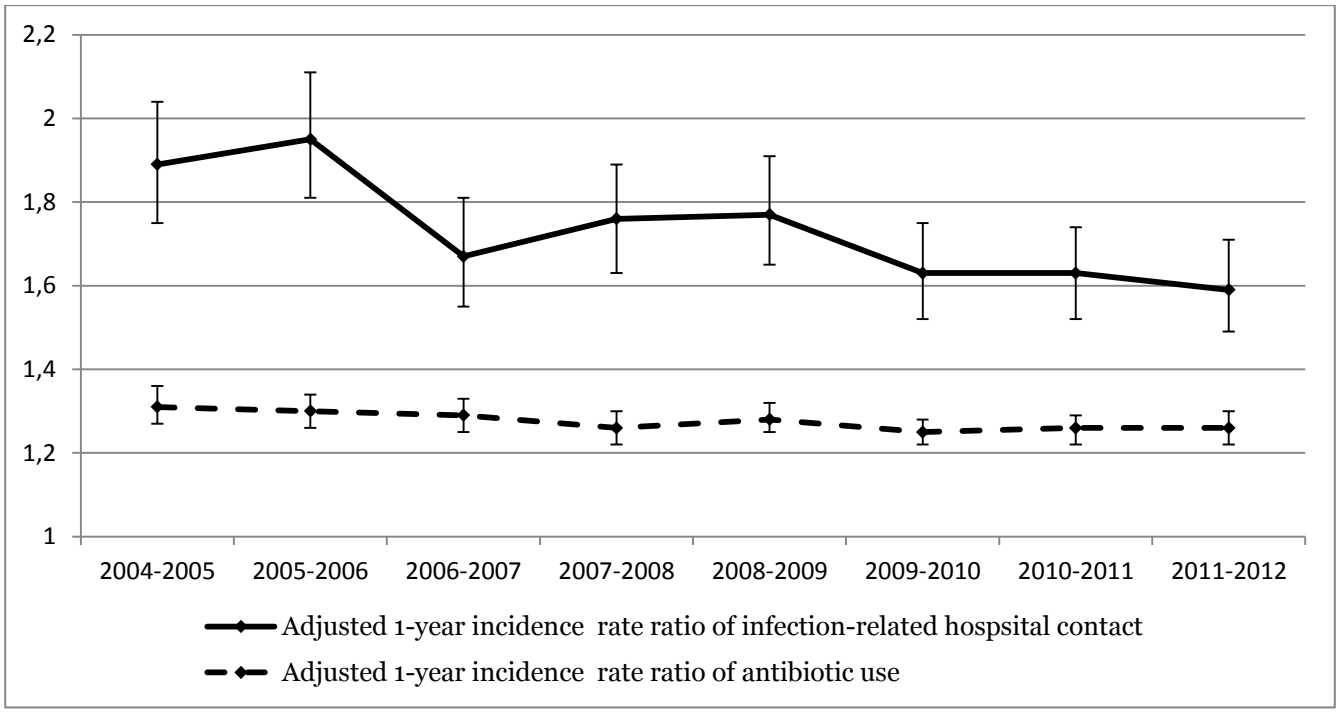


[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Cormorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

6.1.4 Time trends

Rates of community-based antibiotic use decreased in the T2D cohort but not in the comparison cohort; however, no linear trends were observed in the rates of hospital-treated infections in either of the cohorts (Dissertation paper I). We observed only a 4% change in community-based antibiotic use over the years, from 1.31 (95% CI, 1.27 – 1.36) in 2004-2005 to 1.26 (95% CI, 1.22 – 1.30) in 2011-2012 (regression coefficient -0.01, 95% CI, -0.10 – -0.00, P = 0.006); and a 19% reduction in the one-year adjusted RR for any hospital-treated infections from 1.89 (95% CI, 1.75 – 2.04) in 2004-2005 to 1.59 (95% CI, 1.49 – 1.71) in 2011-2012 (regression coefficient -0.05, 95% CI, -0.07 – -0.02, P = 0.007) (Figure 8). The observed decreases were higher in women than in men, although the difference was not statistically significant (Dissertation paper I).

Figure 8. Time trends in adjusted rate ratios of infection among individuals with T2D compared with the matched comparisons, Denmark, 2004-2012.



6.2 Study II

6.2.1 Study cohort characteristics

We identified 131,949 patients with T2D who initiated pharmacotherapy with any GLDs between 2005 and 2012. Of all, 106,424 (81%) initiated metformin, 16,703 (13%) initiated sulfonylurea, 7293 (6%) initiated insulin, and the rest 1529 (<1%) initiated other GLDs. The majority of the study cohort were men (74,391, 56%), and the median age at enrolment was 62 years (IQR, 52, 70 years). In Table 4, we illustrate the characteristics of the study cohort according to the first GLD used at the start of pharmacotherapy after T2D diagnosis.

Table 4. Demographic and clinical characteristics of 131,949 patients with T2D, according to incident pharmacotherapy with glucose-lowering drugs (2005-2012).

Characteristics	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other	Total
n (%)[a]	106,424 (81)	16,703 (13)	7293 (6)	553 (<1)	358 (<1)	295(<1)	231(<1)	92(<1)	131,949 (100)
Sex									
Men	59,213 (56)	9879 (59)	4421 (61)	355 (64)	212 (59)	126 (43)	128 (55)	57 (62)	74,391 (56)
Women	47,211 (44)	6824 (41)	3872 (39)	198 (36)	146 (41)	169 (57)	103 (45)	35 (38)	57,558 (44)
Median age (IQR)	62 (52, 70)	67 (57, 76)	56 (43, 68)	62 (52, 70)	67 (56, 76)	52 (44, 61)	62 (53, 72)	58 (46, 69)	62 (52, 70)
Age-groups (years)									
30 – <50	22,611 (21)	2026 (12)	2728 (37)	124 (22)	41 (11)	128 (43)	49 (21)	28 (30)	27,735 (21)
50 – <70	58,184 (55)	7835 (47)	3050 (42)	291 (53)	182 (51)	143 (48)	116 (50)	43 (47)	69,844 (53)
>70	25,629 (24)	6842 (41)	1515 (21)	138 (25)	135 (38)	24 (8)	66 (29)	21 (23)	34,370 (26)
Year of study inclusion									
2005 – 2008	37,692 (35)	13,,433 (80)	3702 (51)	181 (33)	123 (34)	5 (2)	174 (75)	53 (58)	55,363 (42)
2009 – 2012	68,732 (65)	3270 (20)	3591 (49)	372 (67)	235 (66)	290 (98)	57 (25)	39 (42)	76,586 (58)
Marital status									
Married	64,123 (61)	9630 (59)	4062 (58)	322 (59)	214 (60)	196 (66)	157 (69)	59 (64)	78,763 (60)
Never married	13,404 (13)	1271 (8)	1211 (17)	85 (16)	34 (10)	55 (19)	13 (6)	10 (11)	16,083 (12)
Divorced	15,457 (15)	2150 (13)	1080 (15)	85 (16)	46 (13)	32 (11)	22 (10)	17 (18)	18,889 (14)
Widowed	12,561 (12)	3269 (20)	701 (10)	55 (10)	60 (17)	12 (4)	36 (16)	6 (7)	16,700 (13)
CCI score									
Low (score of 0)	75 550 (71)	10 224 (61)	3953 (54)	385 (70)	202 (56)	207 (70)	154 (67)	54 (59)	90 729 (69)
Medium (scores of 1-2)	25 957 (24)	5035 (30)	2076 (28)	134 (24)	110 (31)	72 (24)	59 (26)	28 (30)	33 471 (25)
High (score ≥3)	4917 (5)	1444 (9)	1264 (17)	34 (6)	46 (13)	16 (5)	18 (8)	10 (11)	7749 (6)
Diabetes complications									
No complications	77,981 (73)	10,968 (66)	5024 (69)	417 (75)	204 (57)	237 (80)	168 (73)	71 (77)	95,070 (72)
Microvascular	6422 (6)	1423 (9)	729 (10)	33 (6)	31 (9)	16 (5)	22 (10)	6 (7)	8682 (7)
Macrovascular	22,021 (21)	4312 (26)	1540 (21)	103 (19)	123 (34)	42 (14)	41 (18)	15 (16)	28,197 (21)

Characteristics	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other	Total
Alcoholism-related conditions	2651 (2)	595 (4)	742 (10)	12 (2)	17 (5)	4 (2)	10 (4)	3 (3)	4034 (3)
Hospital-diagnosed obesity	9566 (9)	602 (4)	528 (7)	46 (8)	28 (8)	79 (27)	7 (3)	17 (18)	10,873 (8)
Hospital outpatient follow-up in 1st year after study inclusion	16,463 (15)	3502 (21)	1695 (23)	86 (16)	62 (17)	18 (6)	33 (14)	11 (12)	21,870 (17)
Therapy change during follow-up	30,845 (29)	9977 (60)	2353 (32)	259 (47)	173 (48)	48 (16)	135 (58)	41 (45)	43,831 (33)
Therapy change within 1 year	16,530 (16)	3618 (22)	1752 (24)	140 (25)	122 (34)	31 (11)	62 (27)	23 (25)	22,278 (17)
Therapy change within 2 years	21,877 (21)	5581 (33)	1970 (27)	184 (33)	147 (41)	45 (15)	86 (37)	33 (36)	29,923 (23)
Acute hospitalization within 6 months	9,486 (9)	2616 (16)	4993 (68)	33 (6)	53 (15)	15 (5)	16 (7)	11 (12)	17,223 (13)
Infection-hospitalization within 6-months	1265 (1)	401 (2)	443 (6)	8 (1)	16 (4)	4 (1)	8 (3)	5 (5)	2150 (2)
No. of patients with HbA_{1c} measurement in subcohort	27,200 (56)	4576 (59)	1649 (61)	164 (64)	115 (59)	35 (43)	34 (55)	22 (62)	33,795 (56)
Median % HbA_{1c} (IQR)	7.1 (6.5, 8.3)	7.6 (6.9, 9.2)	10.1 (7.5, 12.1)	8.3 (7.0, 10.6)	7.0 (6.5, 7.7)	6.4 (6.0, 7.3)	7.1 (6.1, 7.9)	7.0 (5.9, 7.8)	7.2 (6.6, 8.7)
Other medication use									
Statins	50,817 (48)	6230 (37)	1522 (21)	230 (42)	167 (47)	80 (27)	63 (27)	24 (26)	59,163 (45)
Immunosuppressants	669 (1)	134 (1)	85 (1)	2 (<1)	3 (1)	4 (1)	2 (1)	5 (5)	904 (1)
Corticosteroids	3825 (4)	1163 (7)	1044 (14)	20 (4)	21 (6)	11 (4)	15 (6)	6 (7)	6105 (5)

6.2.2 Community-based antibiotic use

A total of 78,847 (60%) patients redeemed at least one antibiotic prescription from community pharmacies after a follow-up of 218,032 PYAR (IR 361.8 per 1000 PYAR, 95% CI 359.2 – 364.3). The rates of community-based antibiotic use were higher in patients who initiated pharmacotherapy with insulin or sulfonylurea compared with those who initiated treatment with metformin (Dissertation paper II). Pharmacotherapy initiation with sulfonylurea was not associated with an increased risk of community-based antibiotic use when compared with metformin initiators (adjusted HR 1.01, 95% CI 0.99 – 1.03). External adjustment for unmeasured obesity and smoking changed the crude HR from 1.06 to 1.11 and to 1.05, respectively. However, sulfonylurea initiation was associated with increased use of azithromycin (adjusted HR 1.10, 95% CI 1.03 – 1.17), quinolones (adjusted HR 1.36, 95% CI 1.06 – 1.75), and other broad-spectrum antibiotics (adjusted HR 1.06, 95% CI 1.02 – 1.10) (Figure 9).

Similarly, insulin initiators were not at greater risk of community antibiotic use than metformin initiators (adjusted HR 0.99, 95% CI 0.96 – 1.03). External adjustment for unmeasured obesity and smoking changed the crude HR from 1.13 to 1.20 and to 1.12, respectively. For specific antibiotic groups, insulin initiators had an increased risk of treatment with quinolones (adjusted HR 3.27, 95% CI 2.43 – 4.39), cephalosporins (adjusted HR 4.23, 95% CI 1.75 – 10.24), and with antibiotics used to treat UTI (adjusted HR 1.08, 95% CI 1.02 – 1.15) (Figure 9).

Moreover, compared with metformin initiators, the risk of community-based antibiotic use associated with other less frequently used GLDs was not raised except for GLP-1 analogue initiators (adjusted HR 1.20, 95% 1.02 – 1.41) (Table 5). The HRs (if no. of events > 4) and number of infections treated with specific antibiotic groups are provided in Dissertation paper II.

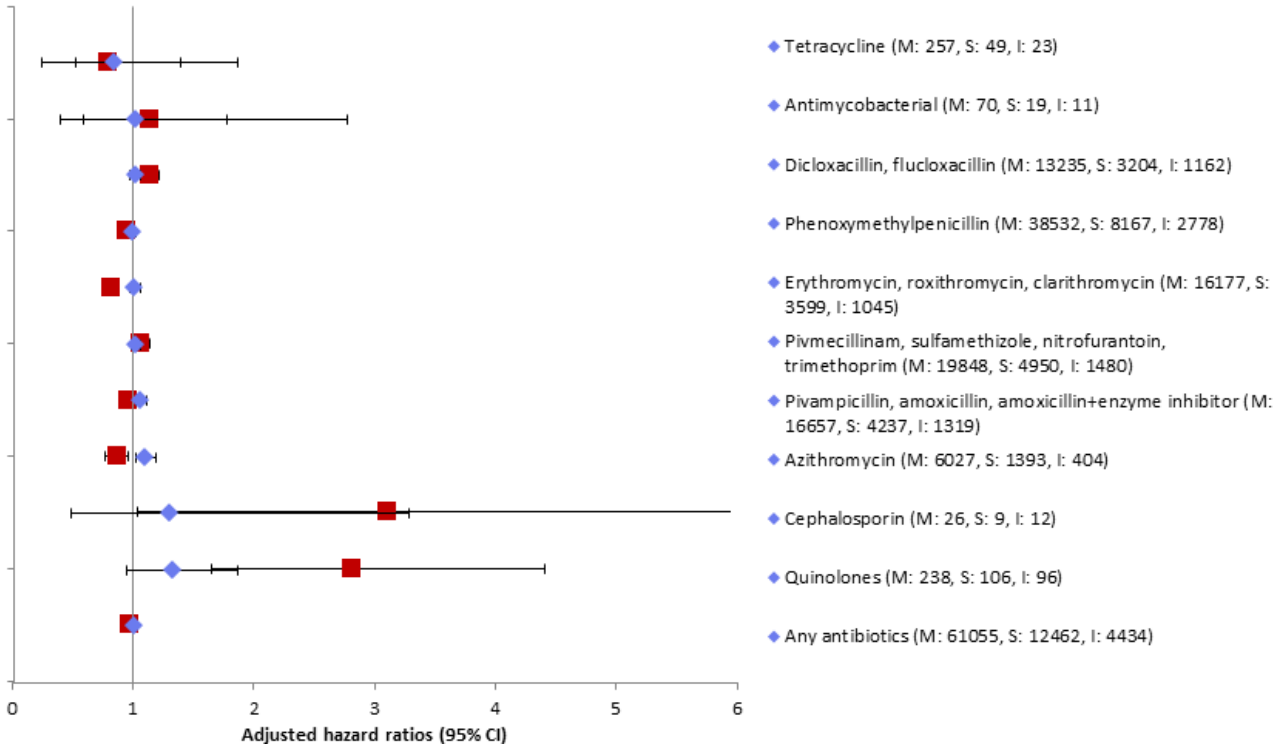
Table 5. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes, according to drug category.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	61,055	12,462	4434	317	213	146	183	64
Crude HR (95% CI)	1.00 (referent)	1.06 (1.04 – 1.08)	1.13 (1.09 – 1.16)	1.03 (0.92 – 1.15)	1.16 (1.01 – 1.32)	1.31 (1.12 – 1.55)	1.07 (0.92 – 1.24)	1.17 (0.92 – 1.50)
Model 1[a] HR (95% CI)	1.00 (referent)	1.05 (1.03 – 1.07)	1.18 (1.15 – 1.22)	1.06 (0.95 – 1.18)	1.16 (1.01 – 1.32)	1.29 (1.09 – 1.51)	1.06 (0.92 –1.23)	1.17 (0.92 – 1.50)
Model 2[b] HR (95% CI)	1.00 (referent)	1.02 (1.00 – 1.04)	1.04 (1.01 – 1.07)	1.04 (0.93 – 1.16)	1.11 (0.97 – 1.27)	1.20 (1.02 – 1.41)	1.01 (0.87 – 1.17)	1.07 (0.84 – 1.36)
Model 3[c] HR (95% CI)	1.00 (referent)	1.01 (0.99 – 1.03)	0.99 (0.96 – 1.03)	1.05 (0.94 – 1.17)	1.10 (0.96 – 1.26)	1.20 (1.02 – 1.41)	1.00 (0.87 – 1.16)	1.06 (0.83 – 1.36)
Hospital-treated infections								
No. of events	13,949	4350	1785	74	53	18	61	18
Crude HR (95% CI)	1.00 (referent)	1.41 (1.36 – 1.46)	1.96 (1.87 – 2.06)	1.06 (0.85 – 1.34)	1.28 (0.98 – 1.68)	0.85 (0.54 – 1.36)	1.40 (1.09 – 1.79)	1.29 (0.81 – 2.05)
Model 1[a] HR (95% CI)	1.00 (referent)	1.20 (1.16 – 1.24)	2.28 (2.17 – 2.39)	1.05 (0.84 – 1.33)	1.14 (0.87 – 1.49)	1.05 (0.66 – 1.66)	1.34 (1.04 – 1.72)	1.28 (0.81 – 2.03)
Model 2[b] HR (95% CI)	1.00 (referent)	1.12 (1.08 – 1.16)	1.63 (1.54 – 1.72)	1.03 (0.82 – 1.30)	1.05 (0.80 – 1.38)	0.93 (0.58 – 1.47)	1.27 (0.98 – 1.64)	1.04 (0.66 – 1.65)
Model 3[c] HR (95% CI)	1.00 (referent)	1.09 (1.05 – 1.13)	1.32 (1.25 – 1.40)	1.04 (0.82 – 1.31)	1.03 (0.79 – 1.35)	0.95 (0.60 – 1.51)	1.30 (1.00 – 1.67)	0.99 (0.62 – 1.57)

[a]Model 1 adjusted for age and sex.
[b]Model 2 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs
[c]Model 3 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Figure 9. Adjusted hazard ratios of specific antibiotics associated with pharmacotherapy initiation with sulfonylureas (shown as blue diamonds) and insulin (shown as red squares), compared with metformin, in patients with T2D.

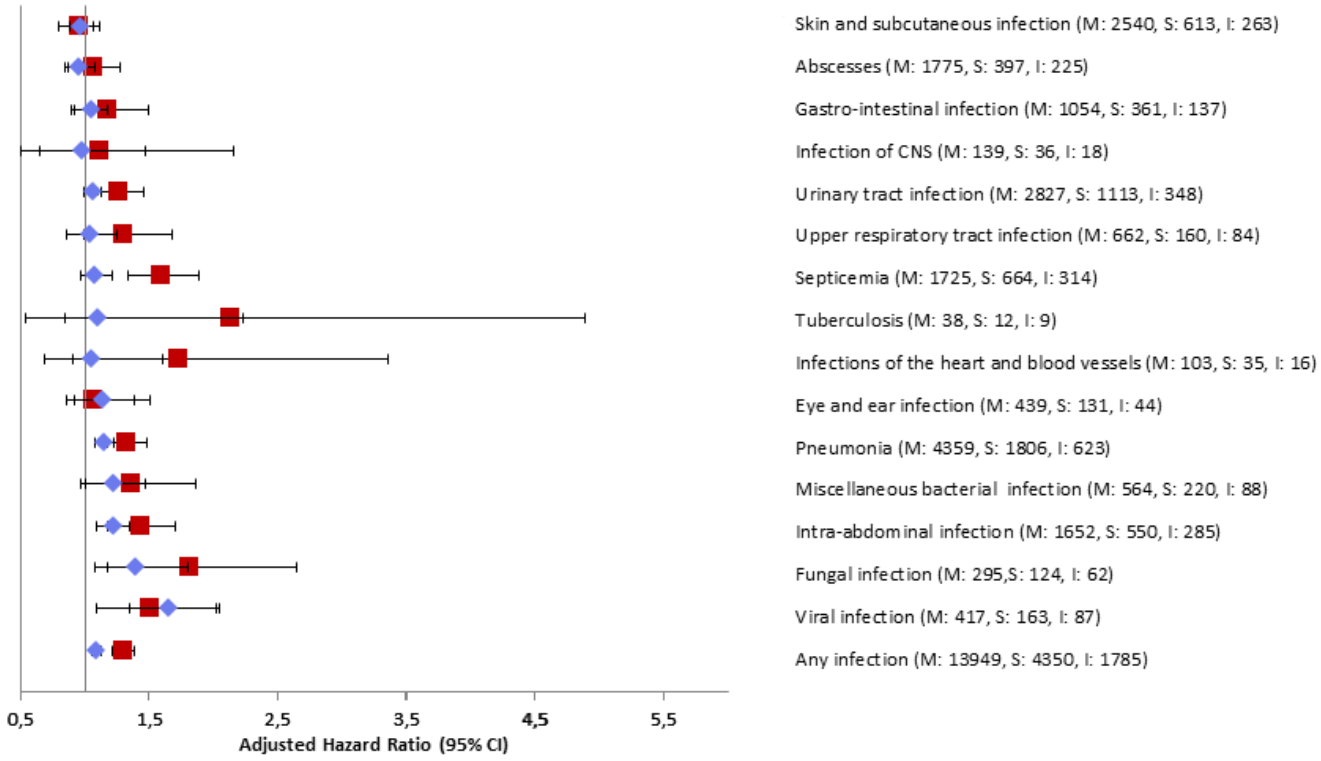


6.2.3 Hospital-treated infection

A total of 20,308 (15%) patients were admitted with a diagnosis of infection after a follow-up of 395,171 PYAR (IR 51.4 per 1000 PYAR, 95% CI 50.7 – 52.1). The rates of hospital-treated infections were highest in insulin initiators, followed by patients who initiated sulfonylurea and metformin (Dissertation paper II). Sulfonylurea initiation was associated with higher risk of hospital-treated infections (adjusted HR 1.09, 95% CI 1.05 – 1.13) compared with metformin initiation. The crude HR changed from 1.41 to 1.55 and to 1.23 after external adjustment for obesity and smoking, respectively. Furthermore, sulfonylurea initiation was associated with increased risk of hospitalisation for viral infections (adjusted HR 1.66, 95% CI 1.37 – 2.03), fungal infections (adjusted HR 1.39, 95% CI 1.11 – 1.76), bacterial infections (adjusted HR 1.23, 95% CI 1.04 – 1.46), intra-abdominal infections (adjusted HR 1.22, 95% CI 1.10 – 1.36), and pneumonia (adjusted HR 1.15, 95% CI 1.08 – 1.22), compared with treatment initiation with metformin (Figure 10).

The risk of hospital-treated infection was higher in insulin initiators than in metformin initiators (adjusted HR 1.32, 95% CI 1.25 – 1.40). The crude HR changed from 1.96 to 2.23 and to 1.83 after external adjustment for obesity and smoking, respectively. Insulin initiators were at increased risk of hospitalisation for nearly all examined infections, in particular fungal infections (adjusted HR 1.86, 95% CI 1.34 – 2.58), viral infections (adjusted HR 1.61, 95% CI 1.21 – 2.13), bacterial infections (adjusted HR 1.44, 95% CI 1.10 – 1.88), UTI (adjusted HR 1.25, 95% CI 1.10 – 1.42), pneumonia (adjusted HR 1.36, 95% CI 1.23 – 1.50), and septicaemia (adjusted HR 1.63, 95% CI 1.41 – 1.89), compared with metformin initiators (Figure 6). For GLD categories other than insulin and sulfonylurea, we did not detect any difference in the risk of infection-related hospital contacts compared with metformin (Table 5). For GLDs other than sulfonylurea and insulin, the HRs (if no. of events > 4) and number of outcome events are provided in Dissertation paper II.

Figure 10. Adjusted hazard ratios of specific hospital-treated infections associated with pharmacotherapy initiation with sulfonylureas (shown as blue diamonds) and insulin (shown as red squares), compared with metformin, in patients with T2D.



6.2.4 Sensitivity analyses

Community-based antibiotic use

We performed analyses on the subcohort of patients with baseline HbA_{1c} information. Compared with metformin initiators, sulfonylurea and insulin initiators had adjusted HRs of community-based antibiotic use of 1.04 (95% CI 1.00 – 1.08) and 0.98 (95% CI 0.91 – 1.06), respectively (versus 1.01, 95% CI 0.99 – 1.03, and 0.99, 95% CI 0.96 – 1.03 in the full cohort). After additional adjustment for baseline HbA_{1c}, the HRs did not change for sulfonylurea initiators, but increased slightly for insulin initiators (adjusted HR 1.02, 95% CI 0.95 – 1.10) (Dissertation paper II, Supplementary Table S3). After replacing traditional CCI score with

updated CCI score in the multivariate model, the fully adjusted HRs of any community-based antibiotic use did not change (Dissertation paper II, Supplementary Table S4). After excluding insulin initiators who were younger than 40 years (reducing type 2 diabetes misclassification), the adjusted HRs did not change (Dissertation paper II, Supplementary Table S5). Furthermore, in sensitivity analysis where we censored drug initiators at the first change in therapy, we found that adjusted HRs of community-based antibiotic use did not change substantially for sulfonylurea initiators (adjusted HR 1.02 [95% CI 1.01 – 1.04] versus 1.01 [95% CI 0.99 – 1.03] in the original analysis) as well as for insulin initiators (adjusted HR 0.99 [95% CI 0.55 – 1.03] versus 0.99 [95% CI 0.96 – 1.03] in the original analysis) (Table 6). Finally, in sensitivity analysis where we considered time-varying drug exposure (as-treated approach) the adjusted estimates for sulfonylurea monotherapy users at any time were slightly higher than for sulfonylurea initiators (adjusted HR 1.04 [95% CI 1.02 – 1.07] versus1.01 [95% CI 0.99 – 1.03] in the original intention-to-treat analytic approach) and also were slightly higher for insulin monotherapy users at any time versus insulin initiators (adjusted HR 1.03 [95% CI 1.00 – 1.07] versus 0.99 [95% CI 0.96 – 1.03] in the original intention-to-treat analytic approach) (Table 7). Furthermore, we found that for individuals exposed to combination therapies, any drug combination that included insulin was strongly associated with risk of community-based antibiotic use compared to metformin monotherapy (e.g. for metformin+insulin adjusted HR was 1.10 [95% CI 1.04 – 1.17], and for insulin+sulfonylurea adjusted HR was 1.49 [95% CI 1.28 – 1.73] versus single metformin use, but for metformin+sulfonylurea the adjusted HR versus metformin was 1.01 [95% CI 0.98 – 1.04]) (Table 8).

Table 6. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes who were censored at the first change in the initial therapy, according to drug category.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	50,220	9163	3376	1054	158	127	122	43
Crude HR (95% CI)	1.00 (referent)	1.09 (1.06 – 1.11)	1.16 (1.12 – 1.20)	1.10 (1.03 – 1.17)	1.27 (1.08 – 1.48)	1.24 (1.04 – 1.48)	1.04 (0.87 – 1.24)	1.15 (0.86 – 1.56)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.02 (1.00 – 1.04)	0.99 (0.55 – 1.03)	1.09 (1.03 – 1.16)	1.20 (1.03 – 1.41)	1.13 (0.95 – 1.34)	0.96 (0.82 – 1.17)	1.01 (0.75 – 1.36)
Hospital-treated infections								
No. of events	10,109	2860	1402	209	33	14	44	10
Crude HR (95% CI)	1.00 (referent)	1.60 (1.53 – 1.67)	2.29 (2.16 – 2.42)	1.37 (1.19 – 1.57)	1.34 (0.95 – 1.89)	0.80 (0.48 –0.36)	1.85 (1.38 – 2.49)	1.30 (0.70 – 2.41)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.17 (1.11 – 1.22)	1.50 (1.40 – 1.60)	1.20 (1.04 – 1.38)	1.06 (0.76 – 1.50)	0.88 (0.52 – 1.49)	1.71 (1.27 – 2.31)	0.98 (0.53 – 1.82)

[a]Adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Table 7. As-treated approach: Hazard ratios (HRs) of infection associated with use of single glucose-lowering drugs in patients with type 2 diabetes, according to drug category.

	Metformin	Sulfonylurea	Insulin	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use							
No. of events	52,996	11,001	4333	384	250	184	81
Crude HR (95% CI)	1.00 (referent)	1.10 (1.08 – 1.12)	1.15 (1.11 – 1.18)	1.17 (1.06 – 1.30)	1.27 (1.12 – 1.44)	1.18 (1.02 – 1.36)	1.13 (0.91 – 1.40)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.04 (1.02 – 1.07)	1.03 (1.00 – 1.07)	1.11 (1.01 – 1.23)	1.20 (1.06 – 1.35)	1.11 (0.96 – 1.29)	1.04 (0.83 – 1.29)
Hospital-treated infections							
No. of events	11,253	36,265	1973	132	71	71	21
Crude HR (95% CI)	1.00 (referent)	1.58 (1.53 – 1.64)	2.17 (2.07 – 2.27)	1.50 (1.26 – 1.78)	1.18 (0.93 – 1.50)	1.87 (1.48 – 2.37)	1.18 (0.77 – 1.81)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.20 (1.15 – 1.24)	1.63 (1.55 – 1.72)	1.26 (1.06 – 1.50)	1.26 (1.00 – 1.60)	1.71 (1.35 – 2.16)	0.98 (0.64 – 1.51)

[a]Adjusted for age, sex, comorbidity (CCI score), microvascular and macrovascular diabetes complications not covered in the CCI, diabetes duration, hospital-diagnosed obesity, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Table 8. As-treated approach: Hazard ratios (HRs) of infection associated with use of combination glucose-lowering drugs in patients with type 2 diabetes, according to various combination drug categories.

	Metformin	Metformin+Sulfonylurea	Metformin+Insulin	Insulin+Sulfonylurea	Other combinations
Community-based antibiotic use					
No. of events	52,996	4681	1326	175	3458
Crude HR (95% CI)	1.00 (referent)	0.99 (0.96 – 1.02)	1.13 (1.07 – 1.19)	1.71 (1.47 – 1.98)	0.99 (0.96 – 1.03)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.01 (0.98 – 1.04)	1.10 (1.04 – 1.17)	1.49 (1.28 – 1.73)	1.02 (0.99 – 1.06)
Hospital-treated infections					
No. of events	11,253	1383	504	84	1191
Crude HR (95% CI)	1.00 (referent)	1.06 (1.00 – 1.12)	1.46 (1.33 – 1.59)	3.03 (2.45 – 3.76)	1.01 (0.95 – 1.08)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.04 (0.98 – 1.10)	1.33 (1.21 – 1.46)	2.02 (1.62 – 2.52)	1.07 (1.01 – 1.14)

[a]Adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Hospital-treated infections

We again performed analyses on the subcohort of patients with baseline HbA_{1c} information. With metformin as the comparator, adjusted HRs of hospital-treated infection associated with sulfonylurea and insulin initiation in the subcohort were 1.14 (95% CI 1.06 – 1.23) and 1.61 (95% CI 1.43 – 1.82), respectively (versus 1.09 and 1.30 in the full cohort). Additional adjustment for baseline HbA_{1c} did not change the adjusted HR for sulfonylurea initiators (adjusted HR 1.14, 95% CI 1.05 – 1.23), and increased it slightly for insulin initiators (adjusted HR 1.67, 95% CI 1.47 – 1.89). After replacing traditional CCI score with updated CCI score in the multivariate model, the fully adjusted HRs for sulfonylurea initiators did not change; however, adjusted HRs reduced for insulin initiators (adjusted HR 1.30 [95% CI 1.23 – 1.38] versus 1.32 [95% CI 1.25 – 1.40] in the original analysis). Similarly, after excluding insulin initiators who were younger than 40 years, the adjusted HRs did not change for sulfonylurea initiators but reduced for insulin initiators (adjusted HR 1.26 [95% CI 1.19 – 1.34] versus 1.32 [95% CI 1.25 – 1.40] in the original analysis) (Dissertation paper II, Supplementary Table S5). Furthermore, in sensitivity analyses where we censored patients at the first change in therapy, we found that adjusted HRs of hospital-treated infection for sulfonylurea monotherapy users at any time were slightly higher than for sulfonylurea initiators (adjusted HR 1.17 [95% CI 1.11 – 1.22] versus 1.09 [95% CI 1.05 – 1.13] in the original analysis) and also for insulin monotherapy users at any time were slightly higher than for insulin initiators (adjusted HR 1.50 [95% CI 1.40 – 1.60] versus 1.32 [95% CI 1.25 – 1.40] in the original analysis) (Table S6). In sensitivity analyses with time-varying exposure (as-treated approach) the adjusted HRs were much higher compared with HRs from intention-to-treat approach for sulfonylurea monotherapy (adjusted HR 1.20 [95% CI 1.15 – 1.24] versus 1.09 [95% CI 1.05 – 1.13] in the original intention-to-treat analytic approach) and for insulin monotherapy (adjusted HR 1.63 [95% CI 1.55 – 1.72] versus 1.32 [95% CI 1.25 – 1.40] in the original intention-to-treat analytic approach) (Table 7). Furthermore, we observed that any insulin combination therapies were strongly associated with risk of hospital-treated infections compared to metformin monotherapy (e.g. for metformin+insulin adjusted HR was 1.33 [95% CI 1.21 – 1.46] and for insulin+sulfonylurea adjusted HR was 2.02 [95% CI 1.62 – 2.52] but for metformin+sulfonylurea the adjusted HR was 1.04 [95% CI 0.98 – 1.10]) (Table 8).

6.3 Study III

6.3.1 Study cohort characteristics

We identified 69,318 patients with T2D who had at least one HbA_{1c} measurement available in the North and the Central Denmark Regions. The majority of this cohort were men, the median age at the first HbA_{1c} measurement was 63.3 years (IQR 53.5, 72.6 years), and the median duration of diabetes before the first HbA_{1c} measurement was 2.1 months (IQR 0.6, 5.8 months), 73% were taking GLDs at the time of their first HbA_{1c} measurement, and the mean HbA_{1c} was 7.5% (standard deviation 1.9) at baseline (Table 9). Compared with patients having baseline HbA_{1c} value 5.5%–6.5%, patients with higher HbA1c values were younger, more likely to be men, had less comorbidity, more likely to use GLDs, and less likely to use statins (Table 9).

After a follow-up of 123,113 PYAR, 48,442 patients (70%) were treated with systemic antiinfectives in the community, yielding an IR of 393.5 (95% CI 390.0 – 397.0) per 1000 PYAR. And after a follow-up of 259,524 PYAR, 16,227 patients (23%) were hospitalised with a diagnosis of an infection, yielding an IR of 62.5 (95% CI 61.6 – 63.5) hospital-treated infections per 1000 PYAR.

Table 9. Characteristics of 69,318 patients with T2D according to baseline HbA_{1c} level at study inclusion. Northern Denmark, 2000-2012.

		Baseline HbA_{1c} (%) (mmol/mol)							
Patient characteristics	Total	<5.5% (<37 mmol/mol)	5.5% - <6.5% (37 - <48 mmol/mol)	6.5% - <7.5% (48 - <59 mmol/mol)	7.5% - <8.5% (59 - <69 mmol/mol)	8.5% - <9.5% (69 - <80 mmol/mol)	9.5% - <10.5% (80 - <91 mmol/mol)	≥10.5% (≥91 mmol/mol)	
Total (%)[a]	69,318 (100)	2697 (4)	21,361 (31)	21,081 (30)	8970 (13)	5007 (7)	3455 (5)	6747 (10)	
Mean HbA_{1c} (SD) (%)	7.5 (1.9)	5.1 (0.4)	6.1 (0.3)	6.9 (0.3)	7.9 (0.3)	8.9 (0.3)	9.9 (0.3)	12.0 (1.1)	
Mean HbA_{1c} (mmol/mol)[b]	58.5	32.2	43.2	51.9	62.8	73.8	84.7	107.7	
Gender									
Male	38,456 (55)	1130 (42)	10,868 (51)	11,517 (55)	5234 (58)	3148 (63)	2242 (65)	4317 (64)	
Female	30,862 (45)	1567 (58)	10,493 (49)	9564 (45)	3736 (42)	1859 (37)	1213 (35)	2430 (36)	
Median age (IQR)	63.3 (53.5 – 72.6)	57.8 (40.2 – 69.0)	64.9 (55.7 – 73.6)	65.0 (56.0 – 73.6)	62.6 (52.8 – 72.1)	60.4 (50.7 – 70.7)	59.2 (49.4 – 68.5)	58.6 (48.7 – 68.5)	
Age-groups (y)									
30 – <40	4281 (6)	668 (25)	1100 (5)	726 (3)	484 (5)	350 (7)	287 (8)	666 (10)	
40 – <50	8512 (12)	345 (13)	2154 (10)	2110 (10)	1266 (14)	830 (17)	623 (18)	1184 (18)	
50 – <60	15,267 (22)	471 (17)	4306 (20)	4498 (21)	2051 (23)	1263 (25)	897 (26)	1781 (26)	
60 – <70	19,661 (28)	581 (22)	6452 (30)	6361 (30)	2526 (28)	1238 (25)	876 (25)	1627 (24)	
70 – <80	14,006 (20)	378 (14)	4838 (23)	4851 (23)	1697 (19)	828 (17)	476 (14)	938 (14)	
>80	7591 (11)	254 (9)	2511 (12)	2535 (12)	946 (11)	498 (10)	296 (9)	551 (8)	
Median diabetes duration (m) (IQR)	2.1 (0.6–5.8)	4.5 (1.3–23.7)	3.0 (1.4–7.1)	2.5 (1.0–5.9)	1.8 (0.6–6.6)	1.1 (0.2–3.9)	0.5 (0.0–1.8)	0.0 (0.0–0.5)	
Marital status									
Married	40,328 (58)	1529 (57)	12,684 (59)	12,448 (59)	5172 (58)	2841 (57)	1937 (56)	3717 (55)	
Never married	7745 (11)	373 (14)	2084 (10)	1856 (9)	1010 (11)	694 (14)	56 (16)	1172 (17)	
Divorced	8944 (13)	394 (15)	2643 (12)	2710 (13)	1207 (13)	656 (13)	470 (14)	864 (13)	
Widowed	10,974 (16)	351 (13)	3632 (17)	3715 (18)	1386 (15)	679 (14)	412 (12)	799 (12)	
Missing	1327 (2)	50 (2)	318 (1)	352 (2)	195 (2)	137 (3)	80 (2)	195 (3)	
CCI score									
Low (score of 0)	44,528 (64)	1733 (64)	13,388 (63)	13,253 (63)	5718 (64)	3281 (66)	2370 (69)	4785 (71)	
Medium (score of 1-2)	19,856 (29)	695 (26)	6442 (30)	6319 (30)	2595 (29)	1389 (28)	849 (25)	1567 (23)	
High (score ≥3)	4934 (7)	269 (10)	1531 (7)	1,509 (7)	657 (7)	337 (7)	236 (7)	395 (6)	
Diabetes-related complications[c]									
No complications	49,202 (71)	1975 (68)	14,511 (68)	14,537 (69)	6451 (72)	3707 (74)	2708 (78)	5313 (79)	
Macrovascular	18,071 (26)	605 (22)	6117 (29)	6021 (29)	2280 (25)	1137 (23)	654 (19)	1257 (19)	
Microvascular Nephropathy	524 (1)	26 (1)	138 (1)	159 (1)	70 (1)	57 (1)	23 (1)	51 (1)	

Retinopathy	1859 (3)	117 (4)	764 (4)	477 (2)	198 (2)	121(2)	65 (2)	117 (2)
Neuropathy	665 (1)	19 (1)	168 (1)	204 (1)	98 (1)	63 (1)	37 (1)	76 (1)
Alcoholism-related conditions[d]	2141 (3)	206 (8)	642 (3)	485 (2)	269 (3)	180 (4)	117 (3)	242 (4)
Statin	27,728 (40)	609 (23)	9926 (47)	10,212 (48)	3373 (38)	1545 (31)	831 (24)	1232 (18)
Immunosuppressant	543 (1)	30 (1)	189 (1)	167 (1)	65 (1)	37 (1)	19(1)	36 (1)
Oral corticosteroid	3946 (6)	92 (4)	923 (4)	1221 (6)	686 (8)	412 (8)	222 (6)	390 (6)
Glucose-lowering drugs								
No glucose-lowering drugs	18,455 (27)	1432 (53)	6513 (30)	4187 (20)	1729 (19)	1062 (21)	909 (26)	2623 (39)
Insulin only	2043 (3)	77 (3)	388 (2)	521 (2)	427 (5)	279 (6)	150 (4)	201 (3)
Oral glucose-lowering drugs only	47,761 (69)	1165 (43)	14,319 (67)	16,103 (76)	6556 (73)	3497 (70)	2138 (67)	3803 (56)
Insulin ± oral glucose-lowering drugs	1059 (2)	23 (1)	141 (1)	270 (1)	258 (3)	169 (3)	78 (2)	120 (2)
Calendar year of diagnosis								
2000-2002	7293 (11)	224 (8)	1359 (6)	1837 (9)	1248 (14)	801 (16)	579 (17)	1245 (18)
2003-2005	11,876 (17)	410 (15)	3000 (14)	3364 (16)	1833 (20)	1089 (22)	761 (22)	1419 (21)
2006-2008	19,041 (27)	619 (23)	5283 (25)	6038 (29)	2764 (31)	1485 (30)	957 (28)	1895 (28)
2009-2012	31,108 (45)	1442 (54)	11,703 (55)	9858 (47)	3116 (35)	1655 (33)	1147 (33)	2187 (32)

[a]Parentheses contain percentages unless specified otherwise.
[b]Mean HbA_{1c} in mmol/mol was calculated using the following formula: HbA_{1c} in mmol/mol = [0.9148 * HbA_{1c}%] + 2.152.
[c]Not mutually exclusive.
[d]Defined as hospitalisation history due to diagnoses related to alcoholism; ICD codes used to identify these conditions are provided in the Appendix.

Abbreviations: CCI, Charlson Comorbidity Index score; SD, standard deviation; IQR, inter-quartile range

6.3.2 Risk of community-treated and hospital-treated infection

We observed no association between early baseline HbA_{1c} and risk of community-treated infections and hospital-treated infections (adjusted HR per 1% increase in baseline HbA_{1c} 0.99, 95% CI 0.99 – 1.00 and 1.01, 95% CI 1.00 – 1.02, respectively). Compared with a HbA_{1c} value 5.5%–<6.5%, a baseline HbA_{1c} value <5.5% was associated with an increased risk of community-treated infection (adjusted HR 1.06, 95% CI 1.01 – 1.12) and hospital-treated infection (adjusted HR 1.29, 95% CI 1.19 – 1.40), whereas a HbA_{1c} value >6.5% was not associated with increased risk (Table 10). For updated mean HbA_{1c}, the risk of community-treated and hospital treated infection increased by 1% and 6% with every 1% increase in updated mean HbA_{1c} values (adjusted HR 1.01, 95% CI 1.01 – 1.02, and 1.06, 95% CI 1.04 – 1.07), respectively. Furthermore, updated mean HbA_{1c} values <5.5% and ≥10.5% had the highest risk of community-treated infections and hospital-treated infections compared with updated mean HbA_{1c} values of 5.5%–<6.5% (Table 10). Similarly, for updated time-weighted mean HbA_{1c} values, rates of community-treated and hospital-treated infection increased by 2% and 6% with every 1% increase in HbA_{1c} value (adjusted HR 1.02, 95% CI 1.01 – 1.03, and 1.06, 95% CI 1.05 – 1.07), with the greatest increase seen for HbA_{1c} values ≥10.5% (Table 6). Finally, for latest updated HbA_{1c}, the risk of community-treated and hospital-treated infection increased by 3% and 6% with each 1% increase in HbA_{1c} (adjusted HR 1.03, 95% CI 1.02 – 1.04, and 1.06, 95% CI 1.05 – 1.07). An increased risk was seen for the latest updated HbA_{1c} values of <5.5% and ≥8.5%, with highest risk for a latest updated HbA_{1c} value ≥10.5% (adjusted HR 1.20, 95% CI 1.14 – 1.26) compared with HbA_{1c} values of 5.5% – 6.5% (Table 11).

Table 10. Community-treated Infections: Rates and Hazard Ratios Associated With Every Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

		HbA_{1c} category % (mmol/mol)						
	Every 1% increase	<5.5% (<37 mmol/mol)	5.5% - <6.5% (37 - <48 mmol/mol)	6.5% - <7.5% (48 - <59 mmol/mol)	7.5% - <8.5% (59 - <69 mmol/mol)	8.5% - <9.5% (69 - <80 mmol/mol)	9.5% - <10.5% (80 - <91 mmol/mol)	≥10.5% (≥91 mmol/mol)
Baseline HbA_{1c} value								
Events/ p-y	48,442/123,113	1,811/3,913	14,040/34,328	14,765/36,419	6,673/17,204	3,688/9,808	2,546/6,985	4,919/14,456
IR/1000 p-y (95% CI)	393 (390 – 397)	463 (442 – 485)	409 (402 – 416)	405 (366 – 412)	388 (379 – 397)	376 (364 – 388)	365 (351 – 379)	340 (331 – 350)
Crude (95% CI)	0.98 (0.98– 0.99)	1.11 (1.06 – 1.17)	1.00 (Referent)	1.01 (0.99 – 1.04)	1.01 (0.99 – 1.04)	0.98 (0.95– 1.02)	0.96 (0.92 – 1.00)	0.91 (0.88–0.94)
Adjusted[a] HR (95% CI)	0.99 (0.99 – 1.00)	1.06 (1.01 – 1.12)	1.00 (Referent)	1.03 (1.01 – 1.06)	1.03 (1.00 – 1.06)	1.03 (1.01 – 1.07)	1.03 (0.99 – 1.08)	0.97 (0.94–1.00)
Updated mean HbA_{1c} value								
Events/ p-y	48,442/123,113	1,785/3,827	15,800/40,225	16,758/44,047	7,415720,130	3,304/8,364	1,623/3,507	1,757/3,011
IR/1000 p-y (95% CI)	393 (390 – 397)	466 (445 – 489)	393 (387 – 399)	380 (374 – 386)	368 (360 – 377)	395 (382 – 409)	463 (441 – 486)	583 (557 – 611)
Crude (95% CI)	1.00 (0.99 – 1.00)	1.12 (1.07 – 1.17)	1.00 (Referent)	1.01 (0.99 – 1.03)	1.00 (0.97 – 1.02)	0.99 (0.95 – 1.02)	1.01 (0.96 – 1.07)	1.02 (0.97 – 1.07)
Adjusted[a] HR (95% CI)	1.01 (1.01 – 1.02)	1.07 (1.02 – 1.13)	1.00 (Referent)	1.04 (1.01 – 1.06)	1.04 (1.01 – 1.07)	1.03 (1.00 – 1.08)	1.08 (1.03 – 1.14)	1.09 (1.03 – 1.14)
Updated time-weighted mean HbA_{1c} value								
Events/ p-y	48,442/123,113	1,930/4,437	16,913/44,158	16,615/43,665	6,698/17,147	2,978/7,281	1,531/3,390	1,777/3,034
IR/1000 p-y (95% CI)	393 (390 – 397)	435 (416 – 455)	383 (377 – 389)	381 (375 – 386)	391 (381 – 400)	409 (395 – 424)	452 (430 – 475)	586 (559 – 614)
Crude (95% CI)	1.01 (1.00 – 1.01)	1.10 (1.05 – 1.15)	1.00 (Referent)	1.01 (0.99 – 1.03)	1.03 (1.01 – 1.05)	1.01 (0.98 – 1.05)	1.03 (0.97 – 1.08)	1.06 (1.01 – 1.11)
Adjusted[a] HR (95% CI)	1.02 (1.01 – 1.03)	1.06 (1.01 – 1.11)	1.00 (Referent)	1.03 (1.01 – 1.06)	1.07 (1.04 – 1.10)	1.07 (1.03 – 1.11)	1.10 (1.04 – 1.16)	1.13 (1.08 – 1.19)
Latest updated HbA_{1c} value								
Events/ p-y	48,442/123,113	2,197/5,298	17,769/46,767	16,483/42,935	6,076/15,367	2,666/6,401	1,444/3,160	1,807/3,184
IR/1000 p-y (95% CI)	393 (390 – 397)	415 (398 – 432)	380 (374 – 386)	384 (378 – 390)	395 (386 – 405)	416 (401 – 433)	457 (434 – 481)	567 (542 – 594)
Crude (95% CI)	1.02 (1.01 – 1.02)	1.07 (1.03 – 1.12)	1.00 (Referent)	1.02 (1.00 – 1.05)	1.05 (1.02 – 1.08)	1.07 (1.03 – 1.11)	1.08 (1.02 – 1.14)	1.12 (1.07 – 1.18)
Adjusted[a] HR (95% CI)	1.03 (1.02 – 1.04)	1.04 (1.01 – 1.09)	1.00 (Referent)	1.04 (1.02 – 1.07)	1.09 (1.05 – 1.12)	1.11 (1.07 – 1.16)	1.15 (1.08 – 1.21)	1.19 (1.14 – 1.26)

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

Table 11. Hospital-Treated Infections: Rates and Hazard Ratios Associated With Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000–2012

		HbA_{1c} category % (mmol/mol)						
	Every 1% increase	**<5.5% (<37 mmol/mol)**	**5.5% - <6.5% (37 - <48 mmol/mol)**	**6.5% - <7.5% (48 - <59 mmol/mol)**	**7.5% - <8.5% (59 - <69 mmol/mol)**	**8.5% - <9.5% (69 - <80 mmol/mol)**	**9.5% - <10.5% (80 - <91 mmol/mol)**	**≥10.5% (≥91 mmol/mol)**
Events/ p-y	16,227/259,524	675/8,187	4,391/69,570	4,807/77,431	2,388/37,800	1,304/21,544	910/15,205	1,752/29,787
IR/1000 p-y (95% CI)	63 (62 – 64)	82 (76 – 89)	63 (61 – 65)	62 (60 – 64)	63 (61 – 66)	61 (57 – 64)	60 (56 – 64)	59 (56 – 62)
Crude (95% CI)	0.99 (0.98 – 1.00)	1.30 (1.20 – 1.41)	1.00 (Referent)	1.00 (0.96 – 1.04)	1.03 (0.98 – 1.09)	0.99 (0.93 – 1.06)	0.98 (0.92 – 1.06)	0.97 (0.91 – 1.02)
Adjusted[a] HR (95% CI)	1.01 (1.00 – 1.02)	1.29 (1.19 – 1.40)	1.00 (Referent)	1.04 (1.00 – 1.08)	1.10 (1.05 – 1.16)	1.09 (1.02 – 1.16)	1.10 (1.02 – 1.18)	1.08 (1.02 – 1.14)
Events/ p-y	16,227/259,524	628/7,370	4,986/81,157	5,725/97,270	2,726/45,192	1,160/17,392	482/6,645	520/4,497
IR/1000 p-y (95% CI)	63 (62 – 64)	85 (79 – 92)	61 (60 – 63)	59 (57 – 60)	60 (58 – 63)	67 (63 – 71)	73 (66 – 79)	116 (106 – 126)
Crude (95% CI)	1.02 (1.01 – 1.04)	1.34 (1.23 – 1.45)	1.00 (Referent)	0.98 (0.94 – 1.02)	1.01 (0.96 – 1.06)	1.07 (1.01 – 1.14)	1.08 (0.98 – 1.19)	1.37 (1.25 – 1.50)
Adjusted[a] HR (95% CI)	1.06 (1.04 – 1.07)	1.39 (1.28 – 1.51)	1.00 (Referent)	1.03 (1.01 – 1.07)	1.12 (1.06 – 1.17)	1.23 (1.15 – 1.31)	1.26 (1.15 – 1.38)	1.55 (1.42 – 1.71)
Events/ p-y	16,227/259,524	788/8,854	5,497/90,299	5,425/94,126	2,348/38,292	1,074/15,749	522/6,961	573/5,243
IR/1000 p-y (95% CI)	63 (62 – 64)	89 (83 – 95)	61 (59 – 63)	58 (56 – 59)	61 (59 – 64)	68 (64 – 72)	75 (69 – 82)	109 (101 – 119)
Crude (95% CI)	1.02 (1.00 – 1.04)	1.43 (1.33 – 1.54)	1.00 (Referent)	0.95 (0.92 – 0.99)	1.01 (0.96 – 1.06)	1.09 (1.02 – 1.17)	1.14 (1.04 – 1.24)	1.37 (1.26 – 1.50)
Adjusted[a] HR (95% CI)	1.06 (1.05 – 1.07)	1.48 (1.37 – 1.60)	1.00 (Referent)	1.01 (0.97 – 1.05)	1.13 (1.07– 1.18)	1.25 (1.17 – 1.34)	1.35 (1.23 – 1.48)	1.58 (1.44 – 1.72)
Events/ p-y	16,227/259,524	915/10,491	5,650/93,627	5,378/92,852	2,134/34,959	962/14,373	531/6,923	657/6,298
IR/1000 p-y (95% CI)	63 (62 – 64)	87 (82 –93)	60 (59 – 62)	58 (56 – 59)	61 (59 – 64)	67 (63 – 71)	77 (70 – 84)	104 (97 –113)
Crude (95% CI)	1.03 (1.02 – 1.04)	1.43 (1.34 – 1.54)	1.00 (Referent)	0.97 (0.93 – 1.00)	1.02 (0.97 – 1.07)	1.09 (1.01 – 1.16)	1.19 (1.09 – 1.31)	1.43 (1.32 – 1.55)
Adjusted[a] HR (95% CI)	1.06 (1.05 – 1.07)	1.45 (1.35 – 1.55)	1.00 (Referent)	1.02 (0.98 – 1.06)	1.12 (1.07 – 1.18)	1.24 (1.16 – 1.33)	1.41 (1.29 – 1.54)	1.64 (1.51 – 1.79)

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

6.3.3 Risk of specific community-treated and hospital-treated infections

Each 1% increase in latest updated HbA_{1c} was associated with greater risk of community prescription redemption of broad-spectrum antibiotics cephalosporins (adjusted HR 1.27, 95% CI 1.08 – 1.50) and for dicloxacillin/flucloxacillin (adjusted HR 1.09, 95% CI 1.08 – 1.10) used to treat *S. aureus* infections, and for antifungal (adjusted HR 1.12, 95% CI 1.10 – 1.13) (Dissertation paper III). Furthermore, each 1% increase in latest updated HbA_{1c} was particularly associated with increased risks of hospitalisation for abscesses (adjusted HR 1.15, 95% CI 1.12 – 1.18), skin infections (adjusted HR 1.14, 95% CI 1.11 – 1.17), and infections of the central nervous system (adjusted HR 1.12, 95% CI 1.01 – 1.25), but also for fungal infections (adjusted HR 1.12, 95% CI 1-05 – 1.19), viral infections (adjusted HR 1.14, 95% CI 1.08 – 1.20), septicaemia (adjusted 1.08, 95% CI 1.05 – 1.12), UTI (adjusted HR 1.07, 95% CI 1.05 – 1.09), and eye and ear infections (adjusted HR 1.10, 95% CI 1.03 – 1.17) (Dissertation paper III).

6.3.4 Subgroup and sensitivity analyses

The relation between increased risk of infections and higher HbA_{1c} levels was found consistently in all subgroups (shown for latest updated HbA_{1c} levels in Dissertation paper III). Of note, the association of a high HbA_{1c} level with infection risk seemed to be strongest in patients with microvascular complications at baseline. In contrast, the hazard of infection associated with poor glucose control was similar in patients with and without comorbidity, in all age groups, and in patients with and without GLD use at baseline. In a sensitivity analysis including only the 42,499 patients (61%) who had their first HbA_{1c} measurement recorded within 3 months of their first documented diabetes diagnosis, the adjusted HRs for community-treated infections followed a pattern similar to that seen in the complete cohort; however, for hospital-treated infection, HRs were reduced for baseline, updated mean, and updated weighted mean HbA_{1c}, but remained approximately the same for the latest updated HbA_{1c} (Dissertation paper III).

7. Discussion

7.1 Main conclusions from studies I-III

We observed that patients with T2D had increased rates of community-treated and hospital-treated infections versus matched comparisons without T2D (Study I). Relative risks were particularly high for severe infections including septicaemia and for UTIs and skin infection. T2D patients treated with any GLD for the first time had high overall rates of hospital-treated infections, and pharmacotherapy initiation with metformin was associated with lower risk of hospital-treated infections in particular when compared with insulin and to a lesser extent when compared with sulfonylurea (Study II). In contrast, there was no substantial difference in the rates of community-based antibiotic use between initiators of any GLDs. In patients with T2D from the Northern Denmark, who had HbA_{1c} information, we found that current glycaemic control – assessed as the latest updated HbA_{1c} level – is more important for the risk of infections in patients with T2D compared to mean longer-term glycaemic control; and we found no association with baseline HbA_{1c} levels (Study III).

7.2 Comparison with existing literature

7.2.1 Study I

Previous studies [19, 26, 27, 95, 105, 178] corroborate or results that patients with T2D are at higher risk of some infections compared with people without T2D. Muller *et al.* [105] demonstrated an increased risk of community-treated UTI (adjusted OR 1.21, 95% CI, 1.07 – 1.38) but no difference in the risk of URTI (adjusted OR 1.02, 95% CI, 0.91 – 1.14) among 6712 patients with T2D compared with 18,911 controls with hypertension and without T2D [105]. Hirji *et al.* [100] used the UK GPRD and found an adjusted RR of 1.53 (95% CI, 1.46 – 1.59) for UTI in 135,920 patients with T2D compared with equal number of age- and sex-matched people without T2D. Our findings of a stronger association of T2D with increased risk for hospital-treated infections than for community-based antibiotic treatment are in line with a Canadian cohort study [27] of 513,749 patients with T2D and a matched comparison cohort reported an RR of 2.01 (99% CI, 1.96 – 2.06) for hospital-treated infections after one year

follow-up, whereas the RR reduced to 1.21 (99% CI, 1.20 – 1.22) after including claims from community-based treatment for infections. We corroborate these findings of a higher excess risk for hospitalized than community-treated infections associated with T2D, and extend them by showing declining excess risks over time in community antibiotic use in T2D. These findings may be driven by earlier detection and treatment of milder T2D cases over time; by improved therapy of hyperglycaemia and other risk factors; or, alternatively, by an increasing threshold of antibiotic prescribing or hospital admission in T2D (i.e., declining surveillance bias over time). The effect of T2D on infections was diminished in statin users, may be due to anti-inflammatory or infection-protective effects of statin treatment in patients with T2D [179], as indicated by previous Danish studies [180] and a meta-analyses that showed a protective effect of statin use against infections (pooled adjusted effect estimate 0.55, 95% CI, 0.36 – 0.83) [181]. Furthermore, we found stronger relative association of T2D with infections in younger patients, which is in line with the Canadian study that observed similar estimate pattern for age groups [27]. These differences might be due to either increased severity of early-onset diabetes [141] or to a lower frequency of other competing risk factors for infections in younger versus older people.

7.2.2 Study II

Our findings support results from the Swedish study [119] that found a higher risk of hospital-treated infections in T2D patients who started their treatment with insulin alone (HR 1.37, 95% CI 1.26 – 1.50) or with oral GLDs other than metformin (HR 1.16, 95% CI 1.04 – 1.28), compared with those who initiated treatment with metformin [88]. Furthermore, our results corroborates the findings from a study of 43,015 cases with septicaemia and control subjects nested in a cohort of incident T2D patients from Taiwan, which found that metformin use was associated with reduced risk of developing septicaemia (OR 0.80, 95% CI 0.77 – 0.83) compared with metformin never users and increased risk in sulfonylurea users versus sulfonylurea never users (OR 1.06, 95% CI 1.03 – 1.10) [182]. There are few effectiveness studies that looked into infection risk associated with newer second-line GLDs [86, 87]. Our results are in line with results from a double-blind randomised study of 807 patients with T2D where 3% of patients treated with metformin and 6% of patients treated with DPP-4

inhibitors suffered from at least one episode URTI during a follow-up of 52 weeks ($p > 0.05$) [87]. Our results support findings from a recent systematic review and meta-analysis of 19 randomised controlled trials that observed no difference in the risk of URTI (RR 1.00, 95% CI 0.83 – 1.22) and UTI (RR 0.86, 95% CI 0.51 – 1.45) between patients receiving DPP-4 inhibitors and those receiving metformin pharmacotherapy [86].

7.2.3 Study III

In Study III, we found that current hyperglycaemia measured by the updated latest HbA_{1c} level is important for infectious complications, supporting the hypothesis of an acute and reversible effect of hyperglycaemia on infections. Evidence from population-based studies of the association of glucose control over time with risk of infection in patients with T2D is sparse [23, 73, 74, 183, 184]. Our results corroborate findings from a Dutch study based on general practice data that reported no difference in mean HbA_{1c} in T2D patients with and without infection, whereas patients who presented with an infection at some point during follow-up showed higher HbA_{1c} levels in that period compared to periods without any infection [184]. Other studies have focussed on selected infections and assessed single-point HbA_{1c} exposure. These studies found an increased risk associated with poor glucose control for septicaemia [74, 183], pneumonia [23], TB [85], genital tract infection [99], and UTI [100]. Furthermore, in line with our results, the Copenhagen City Heart Study of the general population found that baseline hyperglycaemia is associated with increased risk of UTI and skin infections [73].

7.3 Methodological considerations

The aim of the studies included in this dissertation was to produce valid and precise estimates of the association between exposure and outcome, as well as to produce reproducible estimates that can be generalised to relevant target population [185]. In all three studies we largely have statistically precise estimates with narrow 95% CIs for most associations examined, because of a large cohort of participants along with large number of outcome events; therefore, we argue that type 1 error due to chance has played only a minor role. Furthermore, we expect high generalisability (external validity) of our results as we used

population-based nationwide data. Below we will discuss the factors affecting internal validity i.e. biases in more detail. We can classify biases into three major types: selection bias, information bias and confounding.

7.3.1 Selection bias

Selection bias can lead to estimates observed in the study participants different than the estimates in non-participants [165]. In all three cohort studies we included nearly all cases with the exposure as recorded in a well-defined region and we had complete follow-up of all participants ensured by the CRS as described earlier [142, 146]. The use of Danish medical registries that prospectively collected data on all patients irrespective of underlying conditions reduced the risk of selection bias in our studies [157]. However, we acknowledge that the inclusion in the medical registries in the first place requires some selection. For example, we may have excluded mild T2D cases with lifestyle interventions that were not treated with GLDs or hospitalized, and over-sampled severe T2D patients, which could have led to overestimation of the association with infection. However, a recent study found that 74% of patients with T2D start pharmacotherapy within a year of diagnosis [141]. In study III, we may have over-sampled T2D patients with more severe glycaemic derangement since we could include only patients who had HbA_{1c} measurements done, but there was still enough exposure contrast for internal comparisons in our cohort.

7.3.2 Information bias

Information bias is another kind of systematic error that may arise due to incorrectly classifying exposure or outcome [165].

Misclassification of exposure

In Study I, misclassification of T2D exposure may have arisen due to incorrectly coding T2D in healthcare registries. However, previous validation studies have reported high positive predictive value for diabetes when a GLD prescription or hospital diagnosis is present [188]. Thus, previous studies have found a sensitivity of at least 85% and positive predictive value of 95% for identifying diabetes when combining prescription and hospital data [157, 187]. Using

the age < 30 years and insulin criterion, we may have misclassified in particular some late presenting T1D patients as T2D, and we may have misclassified some early presenting T2D or "T1.5D" [189] as T1D. This is unavoidable when using routine care registries, but may be improved by adding information from clinical quality databases in the future such as the Danish Diabetes Database for Adults [190].

In Study II, we had to rely on redeemed prescriptions from the public pharmacy as a measure of drug exposure. We lacked information on drug compliance. However, patients have to pay a certain proportion of the cost; therefore misclassification due to compliance is less likely [191]. Second, our primary intention-to-treat approach – ignoring future shifts and add-ons in medication – has the advantage of less bias by informative censoring or indication for treatment change, but on the other hand may lead to conservative bias due to increasing exposure misclassification during follow-up [192]. We therefore used alternative as-treated approaches as well, and found that the adjusted HRs associated with GLDs other than metformin further increased, in particular for insulin use, not changing our overall conclusions that metformin exposure predicted lower infection risk than sulfonylurea and in particular insulin use. Overall, we observed that 20% and 33% patients altered the initiated therapy to another regimen during the entire follow-up for community-based antibiotic prescription outcome and hospital-treated infection outcome, respectively. These were more like to be insulin or sulfonylurea initiators. Third, we had no access to in-hospital drug use, which may have impacted our estimates.

In Study III, misclassification of exposure category was possible due to incorrect registration of an HbA_{1c} results. However, this this is unlikely to happen frequently and would probably cause non-differential misclassification leading to underestimation of our results. Additionally, LABKA system is used in daily practice and the data is based on immediate direct entry of results after approval [154]. Factors like blood transfusion and enteral or parenteral nutrition were not available and they may have affected HbA_{1c} measurements. Another limitation was that we relied on everyday clinical care data to define real-time HbA1c exposure. Our study may be considered a hybrid between a clinical cohort study (collecting information at the time of health-care contact associated with clinical evolution of the

condition) and interval cohort study (where the information on exposure is collected at fixed interval, e.g. in Denmark every diabetes patient should preferably be seen at a general practice every six months) [193]. Beside this it was not feasible to collect more information on exposure. Therefore we used all the available HbA_{1c} measurements to mimic as closely as possible the real time-varying exposure.

Misclassification of outcome

With respect to community-based antibiotic use, low-dose topically administered antibiotics are available over the counter in limited supply, while systematically acting antibiotics are available only on prescription. We may have missed some of the mild cases of infections that either did not require antibiotics or have used only local antibiotics. Alternatively, some patients might have used previously unused antibiotics leading to false negative outcome. Furthermore, some of the patients might have got the prescription for prophylactic purposes e.g. before travel to tropical countries. In such cases we may have misclassified outcome; however, we do not expect this misclassification was differential. For hospital-treated infections, there are chances of misclassification of infection outcome (misdiagnosis) in all our studies. However, a recent validation study has confirmed high validity of ICD-10 codes for infection recorded in Danish registries [194].

Surveillance bias arises when the probability of identifying an outcome is conditional on the presence of exposure/risk factor [195]. In Study I, the cohort with T2D may have been more closely followed for outcome compared with the comparison cohort. In studies II & III, T2D patients with poorly controlled blood glucose or insulin therapy may have been more closely followed to detect occurrence of infections compared to patients with well-regulated blood glucose, leading us to overestimate associations with infection. Patients in the insulin and sulfonylurea treated exposure groups also had higher comorbidity and were apparently frailer compared to patients treated with metformin and may thus have had lower threshold to get hospitalised for similar infection severity. However, our results were consistent for hospitalisation for severe infections such as septicaemia; thus we argue that our results cannot be completely explained by surveillance bias.

7.3.3 Confounding

Bias due to confounding arises when an apparent effect of exposure on outcome is due to the presence of other factors. To qualify as a confounder a factor should be an independent risk factor of outcome, should be differentially distributed in exposed and un-exposed groups, and should not be an intermediate in the causal pathway between exposure and outcome [165]. Bias due to confounding can be countered in study design e.g. matching, restrictions, and randomisation, and also in statistical analysis by adjustment, stratification, and standardisations. Of all these methods, only randomisation can prevent confounding due to unknown confounders, whereas other methods can only prevent bias due to known and well-measured confounders. Thus, in all our studies, incomplete measurement of some variables – e.g. comorbidity – might have led to residual confounding. Another confounder in all our studies could be ethnicity, which might be related to both severe diabetes/glucose derangement and infection risk. However, non-Caucasian ethnicity is rare in Denmark during our study period (~5%) and we thus believe ethnic differences are not able to explain the observed associations.

In Study I, we controlled for confounding at two levels. At study design level we matched our exposed and unexposed cohort on age, sex, and municipality to prevent confounding due to these factors. At analysis level we used adjustment and stratification to remove confounding due to measured confounders. Nevertheless, we cannot rule out the possibility of confounding due to unmeasured factors such as lifestyle, alcohol, smoking, BMI, and recreational drug use. However, we performed sensitivity analyses by externally adjusting for some of the factor and we argue that it is unlikely that unmeasured confounding can entirely explain the observed association. Furthermore, stratified analysis has limitation due to its inability to control for multiple confounders simultaneously especially in presence of many confounding variables.

In Study II, we measured potential confounders at baseline and controlled for confounding at analysis level. We adjusted for variables which can potentially confound our results and included age, sex, comorbidity (CCI score), hospital diagnosed obesity, alcoholism-related conditions, marital status, micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive

drugs, previous hospitalization, previous diagnosis of infection, and calendar period of enrolment in our multivariate model. One of the major limitations in this study was likely confounding by indication due to treatment choice based on severity of diabetes and other difficult-to-measure characteristics [196]. A propensity score matched analysis would bring no much improvement in efficiency compared with a fully adjusted regression model with the same available variables used to predict the propensity score [197, 198]. Furthermore, in this study both the exposed group and the comparators were new first-time initiators of pharmacological GLD treatment, increasing comparability to some degree [199]. Thus, we argue against that confounding by indication can entirely explain the observed associations in this study. We were not able to include non-GLD-using lifestyle-treated T2D in primary care from our data sources, and we chose not to include hospital-diagnosed T2D patients with no GLD treatment as these are likely to constitute a special group of individuals [199].

In Study III, although we adjusted for several potential confounders, our results – as in the others studies – may still be biased by confounding due to time varying variables. We defined exposure in four different ways and three of them were time-varying; but, we measured confounder information at the index date. This might have led to confounded estimates; however, we had a short median follow-up time and major confounders such as comorbidity, gender etc. are constant over time. Furthermore, a more complex and advanced analytic model such as trajectory analysis could potentially have improved our study. Such analysis is based on the trajectory of variables over time and takes into account the effect of other variables on the shape of trajectories [200]. Finally, there was a possibility of reverse causality in some cases in Study III, i.e., latent infection may have led to higher HbA_{1c}.

7.4 Clinical implications and future perspectives

Through this dissertation we add to the existing knowledge of the complex relation between T2D and infections. We found robust evidence that T2D patients are at 1.24-fold increased risk of community-based antibiotic use and 1.49-fold increased risk of hospital-treated infections than general population. This risk depends on short-term hyperglycaemia and treatment initiation with insulin and sulfonylureas. We provide evidence that the increased risk is consistent with all specific infections groups. Our results underline present guidelines for HbA_{1c} targets and support metformin as first line treatment from an infectious point of view.

These results may help to answer some of the infection risk related questions raised by newly diagnosed T2D patients. Awareness of the increased risk of infections in T2D patients may help to prevent infections by lifestyle changes and home remedies to decrease risk of getting infections. The knowledge about increased infection risk with acute hyperglycaemia may act as an extra motivation for patients and physicians to keep HbA_{1c} levels within the normal range at all times. Knowledge about infection risk variation with GLD use may help physicians to be extra vigilant in certain group of high risk T2D patients.

Nonetheless, several questions remain unanswered, such as: what is the exact biological mechanism behind the increased risk of infection in these patients? What are the predictors of infections in this patient population? Are there non-glycaemic effects of GLDs contributing to the differential risk of infections associated with GLDs? What are the best preventive measures that can reduce the risk of infection in these patients? For safety of GLDs with respect to infectious outcome, future randomised control studies should report infection outcome as well. Future observational studies within detailed prospective cohorts of T2D patients with rich clinical data, lifestyle data, and biobank data may add to our understanding. In future studies we should also further examine predictors of prognosis of T2D patients suffering from infections.

8. Summary

Type 2 diabetes (T2D) affects every 12th person globally and claims one death every 7 seconds leading to tremendous burden on health care system of any country. Increased mortality associated with infections in T2D patients is a major clinical and public health problem. However, this issue has been rather neglected in research compared with cardiovascular diseases and other "classic" diabetes-related complications.

To improve our understanding of infection risk in T2D patients, we initiated this PhD project. We started with the aim to examine the rates of community-based antibiotic use and hospital treated infections in T2D patients compared with the rates in general population in a nationwide matched cohort study (Study I). We then investigate if first GLDs used to treat incident T2D patients have variable influence in relation to infection risk (Study II). And finally, we wanted to explore whether it is short- or long-term glycaemic control that plays major role in relation to infection risk in patients with T2D and to what extent increasing HbA_{1c} contributes to this risk (Study III).

In Study I (2004-2012), we included a nationwide cohort of 155,158 patients with incident T2D and 774,017 matched comparisons from general population. The rates of community-treated infections (defined by antibiotic use) and hospital-treated infections were substantially higher in the T2D cohort than in the comparison cohort. And presence of T2D accounted for 24% increased risk of community-based antibiotic use and 44% increased risk of hospital-treated infections compared to people without diabetes.

In Study II (2005-2012), we used nationwide population-based cohort of 131,949 patients with T2D who initiated pharmacotherapy with a glucose-lowering drug (GLD) between 2005 and 2012. We found that the rates of community-treated infections and hospital-treated infections were high in this cohort. Compared to metformin, sulfonylurea initiators and insulin initiators were at 9% and 32% increased risk of hospital-treated infection, respectively. However, virtually no difference was observed for overall community-treated infections.

In Study III (2000-2012), we included 69,318 patients with T2D to examine the association of short- and long-term glycaemic control with risk of infections. For the first recorded HbA_{1c} after T2D diagnosis (baseline HbA_{1c}), we observed no change in the risk of either community-treated infection or hospital treated infections. However, the risk of community-treated infections increased by 3% and the risk of hospital-treated infections increased by 6% for every 1% increase in latest updated HbA_{1c}. Additionally, compared to patients with a latest updated HbA_{1c} value of 5.5%–6.5%, patients with HbA_{1c} value of ≥10.5% were at 64% increased risk of hospital-treated infections and 19% increased risk of community-treated infection. These findings suggest that short-term hyperglycaemia is of more importance than long-term hyperglycaemia with respect to infection risk.

In conclusion, we found that T2D patients are at increased risk of infections. As this risk is influenced by modifiable factors such as glycaemic control, infections in T2D patients may be reduced.

9. Dansk resume

Type-2 diabetes (T2D) rammer hver 12. person globalt og forårsager et dødsfald hvert 7. sekund og er dermed en enorm byrde på sundhedssystemerne. Infektioner er forbundet med øget dødelighed hos patienter med T2D og udgør derved et stort klinisk og samfundsmæssigt problem. Eksisterende diabetesforskning har fokuseret på klassiske komplikationer som eksempelvis hjerte-kar-sygdomme, mens problematikken omkring infektioner er sparsomt belyst.

For at forbedre vores forståelse af sammenhængen mellem infektioner og T2D har vi lavet dette ph.d.-projekt. Vi begyndte med at undersøge raterne af antibiotikaforbrug udenfor hospitalerne og raterne af infektioner behandlet under indlæggelse hos T2D patienter og sammenlignede med baggrundsraterne hos den danske befolkning i et landsdækkende matchet kohortestudie (Studie I). Derefter undersøgte vi, om GLD-medicin ("glucose-lowering drugs") anvendt som førstebehandling af T2D patienter har indflydelse på risikoen for infektioner (Studie II). Endeligt ønskede vi at undersøge, om det er glykæmisk kontrol på kort eller lang sigt, der er vigtigt for infektionsrisikoen hos patienter med T2D, og i hvilket omfang stigende HbA_{1c} bidrager til denne risiko (Studie III).

I Studie I (2004–2012) inkluderede vi en landsdækkende kohorte af 155.158 patienter med T2D og 774.017 matchede personer fra baggrundsbefolkningen. Raterne af infektioner behandlet udenfor hospitalet (defineret som antibiotikaforbrug) og raterne af infektioner behandlet under indlæggelse var væsentligt højere hos T2D-patietnerne sammenlignet med baggrundsbefolkningen. Patienter med T2D havde en 24% øget risiko for at have været behandlet med antibiotika udenfor hospitalet samt en 44% øget risiko for at have været behandlet for infektioner under indlæggelse sammenlignet med mennesker uden diabetes.

I Studie II (2005–2012) inkluderede vi en landsdækkende populationsbaseret kohorte bestående af 131.949 patienter med T2D, som blev opstartet i behandling med GLD-medicin mellem 2005 og 2012. Vi fandt, at risikoen for at have været behandlet for infektioner udenfor

hospitalet samt risikoen for at have været behandlet for infektion under indlæggelse var høj blandt disse patienter. Sammenlignet med patienter behandlet med metformin, sulfonylurea og insulin var risikoen for indlæggelseskrævende infektion øget med 9% og 32%. Vi fandt dog næsten ingen forskel for den samlede risiko for behandling med antibiotika udenfor hospitalet.

I Studie III (2000–2012) inkluderede vi 69.318 patienter diagnosticeret med T2D for at undersøge sammenhængen mellem glykæmisk kontrol på kort- og lang sigte og risikoen for infektioner. Vi fandt ikke nogen øget risiko for infektioner behandlet udenfor hospitalet eller for indlæggelseskrævende infektioner i forhold til den første målte HbA_{1c} (baseline værdien). Derimod fandt vi en 3% øget risiko for infektioner behandlet udenfor hospitalet og en 6% øget risiko for indlæggelseskrævende infektioner for hver 1% stigning i HbA_{1c} målt som nyeste opdaterede værdi. Vi fandt også, at patienter med en HbA_{1c} værdi på ≥10.5% målt som den nyeste opdaterede værdi havde en 64% øget risiko for indlæggelseskrævende infektioner og 19% øget risiko for infektioner behandlet udenfor hospitalet sammenlignet med patienter med HbA_{1c} værdi på 5,5% -6,5%. Disse resultater tyder på, at nylig hyperglykæmi har den størst betydning for udvikling af infektioner for T2D patienter.

Vores konklusion er, at T2D patienter har øget risiko for infektioner. Denne risiko er påvirkelig af modificerbare faktorer såsom glykæmisk kontrol, hvilket tyder på at infektioner hos T2D patienter kan reduceres.

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1. Appendix

World Health Organization *International Classification of Diseases, Eighth Revision* (ICD-8) and *Tenth Revision* (ICD-10) codes and Anatomical Therapeutical Chemical classification system (ATC) codes used in this study.

Codes used to identify type 2 diabetes	
Hospital contact for type 2 diabetes	ICD-8-codes: 249.x, 250.x. ICD-10-codes: E10.x, E11.x, E14.x, G63.2.x, H36.0, N08.3
Glucose-lowering drugs	ATC-codes:- Insulin and analogues: A10Axxx; Metformin: A10BAxx; Sulfonylureas: A10BBxx; Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1 (GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02, A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx
Codes used to identify diabetes complications	
Microvascular complications	
Nephropathy	ICD-8-codes: 25002, 24902 ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2
Retinopathy	ICD-8-codes: 25001, 24901 ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335
Neuropathy	ICD-8-codes: 25003, 24903 ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,

Macrovascular complications	ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440 ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145

Codes used to identify any infection	
Hospital-treated (inpatient or outpatient) infection	ICD-10-codes: A00-B99, D73.3, E06.0, E06.9, E32.1, G00-G02, G04-07, H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0, I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1, J00-J06, J09-J18, J20-22, J34.0, J36, J38.3D, J38.7G, J39.0-1, J39.8A, J44.0, J85.1-3, J86, K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1, L00-03, L05-08, L88, M00-01, M46.1-5, M49.0-3, M60.0, M60.8, M63.0-2, M65.0-1, M68.0, M71.0-1, M86.0-2, M86.9, M90.0-2, N10, N12, N13.6, N15.1, N16.0, N20.0I, N29.1, N30.0, N33.0, N34.0-1, N39.0, N41, N43.1, N45.0, N45.9, N48.1-2, N49, N61, N70-77, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98, T80.2, T81.4, T82.6-7, T83.5-6, T84.5-7, T85.7, T88.0, and T89.9
Community-treated infections	ATC-codes: J01xx, J02xx, J04AB, J05xx, and A07AA

ICD-10 codes used to identify specific hospital-treated (inpatient or outpatient) infections	
Eye and ear infections	H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0
Upper respiratory tract infections	K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, J00, J01, J02, J03, J04, J05, J06, J36, J38, J39
Pneumonia	J12, J13, J14, J15, J16, J17, J18
Infections of heart and blood vessels	I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1
Gastrointestinal tract infections	A00-A09
Intra-abdominal infections	K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1
Urinary tract infections	N10, N12, N15.1, N30.0, N33.0, N34.0-1, N39.0

Infection of central nervous system	G00-G02, G04-07, A80-A89
Meningococcal infections	A39
Skin and subcutaneous infections	A46, J34, L000-L08
Abscess	A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P
Septicaemia	A40, A41
Tuberculosis	A15-A19
Miscellaneous bacterial infections	A20-A38, A42-A44, A48, A49, A65-A79
Viral infections	B00-B09, B15-B19, B25-B34, A90-A99
Fungal infections	B35-B49
Malignant external otitis	H60.2
Emphysematous cholecystitis	K81.0
Emphysematous cystitis	N30.8
Emphysematous pyelonephritis	N10
Perirenal abscess	N15.9

ATC-codes used to identify specific subgroups of antiinfectives	
Phenoxymethylpenicillin	J01CE02
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor	J01CA02, J01CA04, J01CR02
Macrolides	J01FA
Azithromycin	J01FA10
Erythromycin, roxithromycin, clarithromycin	J01FA01, J01FA06, J01FA09
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim	J01CA08, J01EB02, J01XE01, J01EA01,
Dicloxacillin, flucloxacillin	J01CF01, J01CF05
Antimycobacterial	J04A

Quinolones	J01M
Tetracycline	J01A
Cephalosporin	J01D
Antifungal	J02xx
Antiviral	J05xx
Codes used to identify covariates	
Alcoholism-related disorders	ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714
Statins	ATC-codes: B04AB
Immunosuppresants	ATC-codes: L01, L04
Oral corticosteroids	ATC-codes: H02AB

12. Dissertation papers

This section contains the full manuscripts for Study I, Study I, and Study III, including supplementary material.

Study I

- Dissertation paper I

Study II

- Dissertation paper II

Study III

- Dissertation paper III

Study I

- Dissertation paper I

Rates of Community-based Antibiotic Prescriptions and Hospital-treated Infections in Individuals with and without Type 2 Diabetes: A Danish nationwide cohort study, 2004–2012

Anil Mor[1], Klara Berencsi[1], Jens S. Nielsen[2], Jørgen Rungby[3], Søren Friborg[2], Ivan Brandslund[2], Jens S. Christiansen[4†], Allan Vaag[5], Henning Beck-Nielsen[2], Henrik T. Sørensen[1], Reimar W. Thomsen[1]

[1]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

[2]Danish Centre for Strategic Research in Type 2 Diabetes (DD2), Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark

[3]Center for Diabetes Research, Gentofte University Hospital, Copenhagen, and Institute for Biomedicine, Aarhus University, Aarhus, Denmark

[4]Department of Internal Medicine and Endocrinology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

[5]Department of Endocrinology, Diabetes and Metabolism, Rigshospitalet, and Copenhagen University, Denmark

[†]Deceased

Keywords: Type 2 diabetes mellitus, infections, epidemiology, time-trends, antibiotics

Running title: Rates of Infection in Type 2 Diabetes

Summary: Patients with type 2 diabetes had a 1.49-fold increased rate of hospital-treated infections and a 1.24-fold increased rate of community-based antibiotic prescriptions compared with the general population. Relative rates of infection declined only modestly over the last decade.

ABSTRACT

Background: The excess risk of antibiotic use and hospital-treated infections in patients with type 2 diabetes (T2D) compared with the general population is poorly understood.

Methods: In a nationwide cohort of Danish patients with incident T2D (*n* = 155 158) and an age- gender- and residence- matched general-population comparison cohort (*n* = 774 017), we used Cox regression to compute rates and confounder-adjusted rate ratios (aRRs) of community-based antibiotic prescription redemption and hospital-treated infections during 2004-2012.

Results: The rates of community-based antibiotic prescriptions in the T2D and comparison cohorts were 364 *vs.* 275 per 1000 person-years after a median follow-up of 1.1 years (aRR = 1.24 [95% confidence interval (CI), 1.23 – 1.25]). The corresponding rates for hospital-treated infection were 58 *vs.* 39 per 1000 person-years after a median follow-up of 2.8 years (aRR = 1.44 [95% CI, 1.42 – 1.46]). T2D patients had increased rates of all hospital-treated infection types, particularly urinary tract infections (UTIs) (aRR =1.47 [95% CI, 1.43 – 1.50]), skin infections (aRR =1.45 [95% CI, 1.41 – 1.50]), septicemia (aRR =1.55 [95% CI, 1.49 – 1.61]), and tuberculosis (aRR =1.40 [95% CI, 1.13 – 1.75]); and of community-based antibiotics prescribed for UTIs (aRR =1.31 [95% CI, 1.29 – 1.32]), *S. aureus* infections (aRR =1.31 [95% CI, 1.29 – 1.33]), and mycobacterial infections (aRR =1.50 [95% CI, 1.24 –1.80]). The aRR for infection in the year following the T2D diagnosis declined from 1.89 (95% CI, 1.75 – 2.04) in 2004 to 1.59 (95% CI, 1.45 – 1.74) in 2011 for hospital-treated infection (trend *P*= .007); and from 1.31 (95% CI, 1.27 – 1.36) in 2004 to 1.26 (95% CI, 1.22 – 1.30) in 2011 for community-based antibiotic prescriptions (trend *P*= .006).

Conclusion: Patients with T2D have higher than the general population rates of community-based antibiotic prescriptions and hospital-treated infections.

INTRODUCTION

Infections are a major clinical problem in the globally increasing population with type 2 diabetes (T2D) [1-5] and an important cause of premature death in this patient group [1,6]. The rising prevalence of diabetes may contribute to the increasing burden of infection-related hospitalizations and antibiotic overuse worldwide [3,4]. The risks of micro- and macrovascular T2D complications have reportedly declined in the past two decades, compared with the general population [7]. Comparative data on the excess risk of hospital-treated infection and antibiotic use in community settings are limited [1,2,8].

Recent data suggest that T2D may be associated with a 1.5-fold increased risk of hospitalization for respiratory tract infections, [1] including pneumonia [9] and tuberculosis [10], a 1.5-fold increased risk of surgical site infections [11], a 2-fold increased risk of urinary tract infections (UTIs) [12], and a 2- to 3-fold increased risk of bacteremia [13,14]. However, the magnitude of excess risk for specific infections associated with T2D is debated and data from population-based settings comparing the risk with that in the general population are scarce, particularly for antibiotic use [1,15,16]. A study from The Netherlands reported a 60% increase in use of antibiotics between 1995 and 2003 for lower respiratory tract infections and a 15% increase in use for UTIs among T2D patients [8], but these findings were not compared with trends in general population.

We have recently observed that early glycemic control has improved in incident Danish T2D patients from 2000-2012 [17]. With other studies from Europe [18], the US [19] and Asia [20] showing significant improvements over time for short- and long-term diabetes treatment targets, the risk of infection in T2D may have decreased compared with the general population [7]. We thus undertook a nationwide population-based study to examine the association between T2D and antibiotic use in community settings, as well as hospital-treated infection, compared with a matched general population cohort during 2004-2012.

METHODS

Data sources

This study was based on the Danish National Patient Registry (DNPR), which contains information on all hospitalizations in Denmark since 1977 and on all outpatient and emergency room visits since 1995 [21]. Data in the DNPR includes patients' central personal registry (CPR) number, a primary discharge diagnosis, and up to 20 secondary discharge diagnoses coded according to the *International Classification of Diseases* (ICD). We also used the Danish National Health Service Prescription Database (DNHSPD), which contains complete data on all reimbursed prescription medications dispensed from community pharmacies and hospital-based outpatient pharmacies in Denmark since 2004 [22]. The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Individual-level data from Danish registries can be linked using the unique CPR number assigned by the Danish Civil Registration System (CRS) at birth or upon immigration [23]. The CRS contains electronic records on vital status (date of death or emigration); place of residence; and marital status for the entire Danish population since 1968, and is updated daily.

Identification of patients with T2D and matched comparisons

We conducted this population-based cohort study among all patients with an incident diagnosis of T2D recorded between July 1, 2004 and December 31, 2012. We identified patients with T2D by searching both the DNPR for the first record of a diabetes-associated hospital inpatient or outpatient contact and the DNHSPD for the first record of a glucose-lowering drug prescription, whichever came first. We excluded subjects under 30 years old at the time of their first diagnosis of any diabetes (the index date), to decrease the chance of including people with type 1 diabetes.

For each patient with T2D, we selected five individuals without diabetes from the general population and matched individually to the corresponding patient's age (birth year), sex, municipality of residence, and index date. Matched individuals who were diagnosed or treated

for T2D during follow-up were censored and switched to the T2D cohort on their diabetes diagnosis date.

Assessment of infection outcomes

We defined the study outcome as either redemption of an antibiotic prescription in the community setting or an episode of hospital-treated infection during the study period. Community antibiotic use was defined as any redeemed first-time antibiotic prescription recorded in the DNHSPD after the index date. We investigated groups of antibiotics prescribed to treat specific infections according to the National Danish Guidelines for Primary Care [24] (see Appendix for ATC codes). Hospital-treated infection was defined as any first-time inpatient admission or hospital outpatient clinic contact with an infection after the index date. We examined a wide range of infections including certain rare infections that have been associated closely with diabetes in the literature [2] (see Appendix for ICD codes).

Covariates

We used the DNPR to collect information on the comorbidities included in the Charlson Comorbidity Index (CCI), based on each individual's entire hospital contact history for 10 years before the index date. We defined three comorbidity levels: low (CCI score 0), medium (CCI score 1-2), and high (CCI score ≥ 3). We also retrieved information on other conditions associated with infection risk, on presence of alcoholism-related disorders, and on use of immunosuppressive drugs, oral corticosteroids, and statins [25,26]. In addition, we obtained data on marital status [27] (married, divorced, widowed, and never married) from the CRS.

Statistical analysis

We followed all study participants from the index date until occurrence of the first outcome event, death, emigration, or end of the study period (31 December 2012). We computed rates separately for community-based antibiotic prescriptions and for hospital-treated infections in both cohorts by dividing the total number of incident outcome events by total risk-time, expressed per 1000 person-years. We also computed rate differences (RDs) per 1000 person-years between the T2D and comparison cohorts.

We then applied a Cox proportional hazard regression analysis to compute rate ratios (RRs) of infection with 95% confidence intervals (CIs). We first adjusted for age, sex, marital status, alcoholism-related disorders, and CCI comorbidities except for cardiovascular and renal disease categories, as these may be regarded as possible effects of T2D (Model 1); next we added cardiovascular and renal comorbidities (Model 2); finally, we added use of statins, steroids, and immunosuppressants (Model 3). To assess whether risk of infection was affected by possible glycemic deterioration or increased clinical surveillance early after T2D diagnosis, we examined infection rates separately for the first 6 months and for the first 12 months post-diagnosis. Proportionality assumptions were confirmed graphically by plotting log-log plots. We performed stratified analyses to assess the impact of T2D on infection risk in strata of sex, age groups, comorbidity, and statin use [25,26]. To assess trends in excess infection risk over time, we stratified the analyses according to calendar years (from July to June), comparing aRRs of infection restricted to one-year of follow-up, and used linear regression to assess linear trends across calendar-time. We considered $P < .05$ to be statistically significant.

Sensitivity and bias analysis

First, to focus on likely community-acquired infections, we followed both cohorts until their first primary hospital diagnosis of infection, disregarding all secondary hospital diagnoses. Next, to consider the total burden of infections (i.e., all infection events occurring during follow-up), we used the Wei, Lin, and Weissfeld (WLW) method [28] to account for repeated events. Third, because we had data only on hospital-diagnosed obesity, we computed estimates externally adjusted for unmeasured obesity (BMI ≥30 kg/m2) [29], using previous data on the distribution and association of BMI with, respectively, T2D [30] and infections [24]:

$$\text{caRR} = \frac{\text{aRR}}{\frac{Pc1(RRcd-1)+1}{Pc0(RRcd-1)+1}}$$

where caRR is the obesity-adjusted rate ratio, aRR is the crude rate ratio observed in our study, Pc0 is the estimated proportion of comparisons with obesity (0.13) [30], Pc1 is the estimated proportion of T2D patients with obesity (0.36) [30], and *RRcd* is the estimated rate

ratio between obesity and infection (1.5 for hospital-treated infection and 1.23 for community-based antibiotic prescriptions [24]).

We analyzed the data using SAS software (Version 9.1.3; SAS Institute, Cary, NC) and STATA version 12 (StataCorp. 2011, Stata Statistical Software Release 12. College Station, TX: StataCorp LP). The Danish Data Protection Agency (Record number 2014-54-0922) approved the study.

RESULTS

Study cohorts

A total of 155 158 patients with T2D (mean age 66 years) were matched with 774 017 persons from the general population. Patients with T2D were more likely to have comorbidities included in the CCI (29% *vs.* 21%), including myocardial infarction (5% *vs.* 3%), congestive heart failure (4% *vs.* 2%), cerebrovascular diseases (7% *vs.* 5%), peripheral vascular diseases (4% *vs.* 2%), and chronic pulmonary disease (6% *vs.* 2%) (Table 1). In addition, T2D was associated with higher prevalence of statin use (52% *vs.* 19%) and with slightly more use of oral corticosteroids (5% *vs.* 3%). A total of 9.6% (80 536) of the comparison subjects were diagnosed with T2D during follow-up and shifted to the T2D cohort on their diagnosis date.

Community-based antibiotic prescriptions

Among patients with T2D, 92 672 (62%) received an antibiotic prescription (median follow-up 1.1 years (interquartile range [IQR], 0.4, 2.4 years)) compared with 429 175 (55%) in the matched comparisons (median follow-up 1.4 years [IQR, 0.5, 2.9 years]). This corresponded to rates of 363.6/1000 person-years in the T2D cohort and 275.3/1000 person-years in the comparison cohort (RD=88.3 [95% CI, 85.9 – 90.7]) (Table 2).

The crude aRR of an antibiotic prescription with T2D was 1.29 (95% CI, 1.28 – 1.30) and decreased successively to 1.28 (95% CI, 1.26 – 1.29) in Model 1, 1.25 (95% CI, 1.23 – 1.27) in Model 2, and 1.24 (95% CI, 1.23 – 1.25) in Model 3. The aRRs were highest shortly after

diagnosis of diabetes (Table 2). The highest aRRs were observed for cephalosporins, followed by antimycobacterial agents, quinolones, and antibiotics used for UTIs and *S. aureus* infection (Figure 1). External adjustment for unmeasured obesity changed the crude RR from 1.29 to 1.23. When considering also repetitive antibiotic prescription episodes, we found a total of 268 460 episodes in the T2D cohort and 1 045 191 episodes in the comparison cohort, yielding an aRR=1.18 (95% CI, 1.17 – 1.19).

In subgroup analyses, the aRRs of community-based antibiotic prescriptions associated with T2D were highest among women, younger individuals, and those with low comorbidity (Table 3). The aRR also was substantially higher in those not using statins (aRR=1.34 [95% CI, 1.33 – 1.35]) compared with statin users (aRR=1.10 [95% CI, 1.09 – 1.11]).

Hospital-treated infections

In the T2D cohort, 28 938 (19%) patients had at least one episode of hospital-treated infection (median follow-up=2.8 years [IQR, 1.2, 5.0 years]), compared with 102 795 (13%) among comparisons (median follow-up=3.0 years [IQR, 1.4, 5.2 years]). The rate was increased in the T2D cohort, with 58.2 hospital-treated infections per 1000 person-years *vs.* 39.0/1000 person-years in the comparison cohort (RD=19.2 [95% CI, 18.5 – 19.9]).

In the Cox model, the crude infection RR of 1.49 associated with T2D decreased to 1.45 (95% CI, 1.43 – 1.49) in Model 1, decreased further to 1.42 (95% CI, 1.40 – 1.45) in Model 2, and rose to 1.44 (95% CI, 1.42 – 1.546) in the fully adjusted Model 3. The aRRs were particularly elevated during the first six months of follow-up (Table 4). The highest aRRs were observed for emphysematous cholecystitis, followed by abscesses, tuberculosis, septicemia, meningococcal infection, and skin and subcutaneous infections. The aRRs also were high for UTI, gastrointestinal tract infection, intra-abdominal infection, and pneumonia (Figure 2). External adjustment for unmeasured obesity changed the crude RR from 1.49 to 1.34. The total number of hospital-treated infections was 40 541 episodes in the T2D cohort and 122 618 episodes in the comparison cohort, yielding an aRR=1.55 (95% CI, 1.53 – 1.57).

Results of the subgroup analyses showed a higher RR of infection associated with T2D in women than in men (Table 5), partly caused by much higher aRRs of UTI in women

(aRR=1.41 [95% CI, 1.36 – 1.46]) than in men (aRR=1.22 [95% CI, 1.17 – 1.27]). The relative impact of diabetes was highest between 40 and 50 years of age (aRR=1.77 [95% CI, 1.67 – 1.87]) and then decreased to 1.29 (95% CI, 1.26 – 1.33) among those over 80 years old (Table 5). aRRs from T2D were highest in patients with low baseline comorbidity (aRR=1.61 [95% CI, 1.58 – 1.64]), decreasing to 1.22 (95% CI, 1.17 – 1.27) in those with high comorbidity. In contrast, the RD was highest for persons with a high level of comorbidity (RD=31.7 [95% CI, 24.2 – 39.1]). The aRR of infection associated with T2D was clearly higher in patients who were not using statins (aRR=1.62 [95% CI, 1.59 – 1.65]) compared with statin users (aRR=1.21 [95% CI, 1.18 – 1.23]). When examining primary hospital diagnoses of infection only, the estimates followed a similar pattern as for any hospital-diagnosed infection (aRR=1.39 [95% CI, 1.37 – 1.41]) (Supplementary table 1).

Time trends

No linear trends were observed in the rates of hospital-treated infection in the T2D cohort (regression coefficient=0.12 [95% CI, -1.16 – 1.39] P = .83) or in the comparison cohort (regression coefficient=0.32 [95% CI, -0.18 – 0.84] P = .16). We observed decreasing linear trends in rates of community-based antibiotic prescriptions in the T2D cohort (regression coefficient=-3.85 [95% CI, -6.84 – -0.86] P = .02) but not in the comparison cohort (regression coefficient=-0.98 [95% CI, -3.89 – 1.93] P = .44). The one-year aRR for any hospital-treated infection decreased from 1.89 (95% CI, 1.75 – 2.04) in 2004-2005 to 1.59 (95% CI, 1.49 – 1.71) in 2011-2012 (regression coefficient=-0.05 [95% CI, -0.07 – -0.02] P = .007) (Figure 3). The excess community-based antibiotic use changed less, from 1.31 (95% CI, 1.27 – 1.36) in 2004-2005 to 1.26 (95% CI, 1.22 – 1.30) in 2011-2012 (regression coefficient=-0.01 [95% CI, -0.10 – -0.00] P = .006). The observed decreases were highest in women (Supplementary table 2).

DISCUSSION

In our study, patients with T2D experienced higher rates of both community antibiotic prescriptions and hospital-treated infections than matched members of the general population comparison cohort. The rate ratios were particularly high for severe infections and

for hospitalizations and treatments related to UTIs and skin infection. Compared with the general population, the excess infection risk associated with T2D decreased modestly from 2004 to 2012.

The strengths of our study include: use of a population-based nationwide cohort, virtually no loss to follow-up, access to complete hospitalization and prescription records, which ensured inclusion of almost all infections requiring medical care [31], and individual-level linkage to administrative and medical registries, which allow adjustment for a range of potential confounders.

Our study also had limitations. We lacked clinical, socioeconomic, and lifestyle data such as detailed data on obesity, which is an important risk factor both for diabetes and infections. Still, our external adjustment for obesity suggested that only one-quarter of the observed T2D association potentially could be explained by this factor. Similarly, the lack of data on tobacco smoking might have biased our results. However, we adjusted for diseases closely related to smoking, and a recent Danish study in the 2000s found a lower prevalence of smoking in T2D patients compared to the general population of similar age (24% *vs.* 29%) [30]. Patients with T2D may have a greater likelihood of hospital treatment for a given infection compared with persons without T2D, if the threshold for general practitioners' referral of T2D patients to hospitals is lower due to anticipated problems with glucose control and other complications. This would lead to overestimated infection rate ratios [1]. Recent Danish studies found comparable disease severity and levels of inflammatory markers individuals with and without T2D at the time of hospitalization for pneumonia [32] and higher disease severity in T2D patients than counterparts for pneumococcal bacteremia [33], arguing against selective hospitalization. Nonetheless, the higher infection estimates observed shortly after diabetes diagnosis, particularly for antibiotics, may be partly related to increased surveillance by GPs. Finally, our study relied on the validity of routine care diagnostic codes. However, a recent validation study has confirmed high validity of ICD-10 codes for identifying hospital-treated infections in Danish registries [34].

Our study corroborates and extends a few previous studies [5,6,13,14,35,36]. Muller *et al.* [5] found an increased adjusted odds ratio of community-treated UTI of 1.21 (95% CI, 1.07 – 1.38) but no difference in the odds of upper respiratory tract infection (1.02 [95% CI, 0.91 – 1.14]) among 6712 patients with T2D compared with 18 911 hypertensive controls without diabetes [5]. Hirji *et al.* [37] used the UK General Practice Research Database to estimate the incidence of UTI in 135 920 T2D patients compared with age- and sex-matched persons without diabetes and found an aRR of 1.53 (95% CI, 1.46 – 1.59). Supporting our findings of a higher excess risk for infections requiring hospitalization than for those treated in the community, a Canadian cohort study of 513 749 patients with prevalent T2D and a matched comparison cohort [14] reported a crude RR of 2.01 (99% CI, 1.96 – 2.06) for any infection leading to a hospitalization, whereas the risk ratio for all infections (including claims from community-based physicians), was 1.21 (99% CI, 1.20 – 1.22) after a follow-up period of one year. We corroborate these findings of a higher excess risk for hospitalized than community-treated infections associated with T2D, and extend them by showing declining excess risks over time in community antibiotic use in T2D. These findings may be driven by earlier detection and treatment of milder T2D cases over time; by improved therapy of hyperglycemia and other risk factors; or, alternatively, by an increasing threshold of antibiotic prescribing or hospital admission in T2D (i.e., declining surveillance bias over time).
The stronger relative association with infections in younger T2D patients observed in our study could be due to either increased severity of diabetes – with more obesity, physical inactivity, and higher HbA_{1c} levels and inflammation seen with T2D onset early in life, as previously observed [38] – or to a lower prevalence of other competing risk factors for infection in younger *vs.* older people. A similar pattern by age-group was observed in the Canadian study [14]. We observed a strong modification of the T2D effect on infections among statin users, possibly due to infection-protective or anti-inflammatory effects of statin therapy in T2D patients [39]. Previous meta-analyses have indicated a protective effect of statin use against infections (pooled adjusted effect estimate=0.55 [95% CI, 0.36 – 0.83]) [40].

CONCLUSIONS

Our study provides strong evidence that T2D is associated with increased risk of antibiotic use in the community setting and hospital-treated infections.

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Table 1. Characteristics of members of the type 2 diabetes cohort and the matched general population comparison cohort, Denmark, 2004-2012.

	Type 2 diabetes cohort (%)	Matched comparison cohort (%)
Total	155 158	774 017
Gender		
Men	85 338 (55)	425 554 (55)
Women	69 820 (45)	348 463 (45)
Age (in years)		
Mean (standard deviation)	65.6 (13.6)	65.7 (13.6)
Age groups (in years)		
30 – <40	8 224 (5)	39 707 (5)
40 – <50	16 923 (11)	83 725 (11)
50 – < 60	29 261 (19)	144 360 (19)
60 – <70	45 275 (29)	225 388 (29)
70 – <80	35 392 (23)	177 834 (23)
>80	20 083 (13)	103 003 (13)
Marital status		
Married	87 040 (56)	460 263 (59)
Never married	18 274 (12)	86 840 (11)
Divorced	23 020 (15)	105 718 (14)
Widowed	24 551 (16)	114 020 (15)
Missing	2 239 (1)	7 175 (1)
Alcoholism-related conditions	6 176 (4)	20 427 (3)
Charlson comorbidities		
Myocardial infarction	7 454 (5)	19 676 (3)
Congestive heart failure	6 728 (4)	15 323 (2)
Peripheral vascular disease	5 745 (4)	18 559 (2)
Cerebrovascular disease	10 305 (7)	38 351 (5)
Dementia	992 (1)	5 712 (1)
Chronic pulmonary disease	9 960 (6)	33 143 (4)
Connective tissue disease	3 366 (2)	13 951 (2)
Ulcer disease	3 645 (2)	13 385 (2)
Mild liver disease	2 217 (1)	4 724 (1)
Hemiplegia	248 (<1)	986 (<1)
Moderate to severe renal disease	2 042 (1)	6 342 (1)
Any tumor	10 364 (7)	44 718 (6)
Leukemia	315 (<1)	1 278 (<1)
Lymphoma	605 (<1)	2 690 (<1)
Moderate to severe liver disease	609 (<1)	1 135 (<1)
Metastatic solid tumor	1 246 (1)	3 761 (<1)

	Type 2 diabetes cohort (%)	Matched comparison cohort (%)
AIDS	65 (<1)	490 (<1)
Charlson Comorbidity Index score		
Low (score of 0)	109 524 (71)	608 567 (79)
Medium (score of 1-2)	37 094 (24)	139 336 (18)
High (score of ≥3)	8 540 (5)	26 114 (3)
Current medication use		
Statins	81 229 (52)	147 834 (19)
Steroids	7 744 (5)	23 947 (3)
Immunosuppressants	1 237 (1)	4 931 (1)

Table 2. Rates, rate differences, and rate ratios of community antibiotic prescriptions in the type 2 diabetes cohort and the matched general population cohort, Denmark, 2004-2012.

	Type 2 diabetes cohort		Matched comparison cohort			Rate ratio (95% CI)	
	No. of prescriptions (%)	Rate /1000 p-y (95% CI)	No. of prescriptions (%)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Overall antibiotic prescriptions in community							
Six-month follow-up	35 216 (23)	548.4 (542.7 – 554.1)	132 963 (17)	395.1 (393.0 – 397.2)	153.3 (147.2 – 159.4)	1.38 (1.37 – 1.40)	1.32 (1.30 – 1.33)
One-year follow-up	53 811 (35)	481.4 (477.3 – 485.5)	215 250 (28)	358.9 (357.4 – 360.4)	122.5 (118.1 – 126.8)	1.33 (1.32 – 1.35)	1.28 (1.26 – 1.29)
Total follow-up	92 672 (62)	363.6 (361.3 – 365.9)	429 175 (55)	275.3 (274.5 – 276.2)	88.3 (85.9 – 90.7)	1.29 (1.28 – 1.30)	1.24 (1.23 – 1.25)
Specific antibiotic prescriptions listed by increasing rate ratios							
Azithromycin	12 790 (8)	18.9 (18.5 – 19.2)	58 053 (7)	17.3 (17.1 – 17.4)	1.6 (1.2 – 1.9)	1.09 (1.07 – 1.12)	1.04 (1.02 – 1.07)
Phenoxymethylpenicillin	73 206 (47)	157.7 (156.5 – 158.8)	336 015 (43)	139.4 (139.0 – 139.9)	18.3 (17.0 – 19.5)	1.13 (1.12 – 1.14)	1.09 (1.08 – 1.10)
Tetracycline	507 (<1)	0.7 (0.7 – 0.8)	2 107 (<1)	0.6 (0.6 – 0.6)	0.1 (0.0 – 0.1)	1.19 (1.08 – 1.31)	1.17 (1.05 – 1.29)
Erythromycin, roxithromycin, clarithromycin	32 382 (21)	52.8 (52.2 – 53.4)	136 232 (18)	43.7 (43.5 – 43.9)	9.1 (8.5 – 9.7)	1.21 (1.19 – 1.22)	1.16 (1.14 – 1.17)
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor	33 850 (22)	54.9 (54.3 – 55.5)	138 221 (18)	44.0 (43.8 – 44.2)	10.9 (10.2 – 11.5)	1.25 (1.23 – 1.26)	1.15 (1.14 – 1.17)
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim	37 798 (24)	62.7 (62.1 – 63.3)	147 016 (19)	47.4 (47.1 – 47.6)	15.4 (14.7 – 16.0)	1.32 (1.30 – 1.33)	1.31 (1.29 – 1.32)
Dicloxacillin, flucloxacillin	27 195 (18)	42.6 (42.1 – 43.1)	95 497 (13)	30.2 (30.0 – 30.4)	12.4 (11.8 – 12.9)	1.41 (1.39 – 1.43)	1.31 (1.29 – 1.33)
Ciprofloxacin	577 (<1)	0.8 (0.7 – 0.9)	1 881 (<1)	0.5 (0.5 – 0.6)	0.3 (0.2 – 0.3)	1.52 (1.38 – 1.66)	1.42 (1.29 – 1.57)
Antimycobacterial	163 (<1)	0.2 (0.2 – 0.3)	514 (<1)	0.1 (0.1 – 0.2)	0.1 (0.0 – 0.1)	1.56 (1.31 – 1.87)	1.50 (1.24 – 1.80)
Cephalosporin	61 (<1)	0.1 (0.1 – 0.2)	183 (<1)	0.1 (<0.1 – 0.1)	<0.1 (0.0 – 0.1)	1.64 (1.23 – 2.20)	1.45 (1.08 – 1.97)

Abbreviations: p-y, person-years; CI, confidence interval

[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Comorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

Table 3. Rates, rate differences and rate ratios of community-based antibiotic prescriptions in the type 2 diabetes cohort and the matched general population cohort, stratified by gender, age group, comorbidity level, and statin use.

	Type 2 diabetes cohort	Matched comparison cohort		Rate ratio (95% CI)	
	Rate /1000 p-y (95% CI)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Overall	363.6 (361.3 – 365.9)	275.3 (274.5 – 276.2)	88.3 (85.9 – 90.7)	1.29 (1.28 – 1.30)	1.24 (1.23 – 1.25)
Gender					
Men	308.7 (306.0 – 311.4)	237.4 (236.4 – 238.4)	71.3 (68.4 – 74.2)	1.28 (1.26 – 1.29)	1.22 (1.21 – 1.23)
Women	446.5 (442.5 – 450.6)	329.3 (327.9 – 330.7)	117.3 (113.0 – 121.5)	1.31 (1.30 – 1.32)	1.26 (1.25 – 1.27)
Age groups (years)					
30 – <40	436.7 (425.1 – 448.6)	324.6 (320.3 – 328.9)	112.1 (99.6 – 124.6)	1.31 (1.27 – 1.35)	1.27 (1.23 – 1.31)
40 – <50	361.3 (354.4 – 368.3)	243.2 (240.9 – 245.5)	118.1 (110.8 – 125.4)	1.45 (1.42 – 1.48)	1.27 (1.23 – 1.31)
50 – < 60	341.9 (336.9 – 347.0)	238.7 (236.8 – 240.3)	103.3 (98.0 – 108.7)	1.40 (1.38 – 1.42)	1.28 (1.25 – 1.30)
60 – <70	339.0 (335.0 – 343.1)	260.7 (259.3 – 262.2)	78.3 (74.0 – 82.6)	1.28 (1.26 – 1.29)	1.20 (1.18 – 1.21)
70 – <80	357.5 (352.8 – 362.2)	288.0 (286.2 – 289.7)	69.5 (64.5 – 74.5)	1.22 (1.20 – 1.24)	1.16 (1.14 – 1.14)
>80	448.1 (440.7 – 455.5)	357.0 (354.4 – 359.7)	91.0 (83.1 – 99.0)	1.23 (1.20 – 1.25)	1.21 (1.19 – 1.23)
CCI score					
Low (score of 0)	324.1 (321.7 – 326.6)	248.1 (247.3 – 249.0)	76.0 (73.4 – 78.6)	1.28 (1.27 – 1.29)	1.25 (1.24 – 1.26)
Medium (score of 1-2)	464.5 (458.8 – 470.3)	395.7 (393.1 – 398.3)	68.8 (62.5 – 75.2)	1.17 (1.17 – 1.19)	1.19 (1.18 – 1.21)
High (score of ≥3)	679.3 (662.0 – 697.1)	566.8 (558.4 – 575.3)	112.5 (93.0 – 132.0)	1.19 (1.16 – 1.23)	1.19 (1.16 – 1.23)
Statin use					
No	392.4 (388.8 – 395.9)	267.2 (266.3 – 268.1)	125.2 (121.5 – 128.9)	1.42 (1.41 – 1.43)	1.34 (1.33 – 1.35)
Yes	340.4 (337.4 – 343.4)	312.6 (310.6 – 314.7)	27.8 (24.1 – 31.4)	1.10 (1.09 – 1.11)	1.10 (1.09 – 1.11)

Abbreviations: CCI, Charlson Comorbidity Index; p-y, person-years; CI, confidence interval

[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Comorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

Table 4. Rates, rate differences, and rate ratios of hospital-treated infections in the type 2 diabetes cohort and the matched general population cohort, Denmark, 2004-2012.

	Type 2 diabetes cohort		Matched comparison cohort			Rate ratio (95% CI)	
	No. of infections (%) (n=28 938)	Rate /1000 p-y (95% CI)	No. of infections (%) (n=102 795)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Any infection							
Six-month follow-up	6 131 (4)	84.84 (82.74 – 86.99)	15 622 (2)	42.44 (41.77 – 43.11)	42.40 (40.18 – 44.63)	2.00 (1.94 – 2.06)	1.92 (1.86 – 1.98)
One-year follow-up	9 893 (6)	72.14 (70.73 – 73.57)	29 226 (4)	41.52 (41.05 – 42.00)	30.61 (29.11 – 32.11)	1.74 (1.70 – 1.78)	1.68 (1.64 – 1.72)
Total follow-up	28 938 (19)	58.24 (57.57 – 58.92)	102 795 (13)	39.03 (38.79 – 39.27)	19.21 (18.50 – 19.92)	1.49 (1.47 – 1.51)	1.44 (1.42 – 1.46)
Specific infections listed by increasing rate ratios[b]							
Eye and ear infection	1 190 (1)	1.63 (1.54 – 1.73)	5 246 (1)	1.43 (1.39 – 1.47)	0.20 (0.10 – 0.30)	1.14 (1.07 – 1.21)	1.12 (1.05 – 1.20)
Upper respiratory tract infection	1 631 (1)	2.24 (2.13 – 2.35)	6 283 (1)	1.72 (1.68 – 1.76)	0.52 (0.40 – 0.63)	1.30 (1.23 – 1.37)	1.20 (1.13 – 1.27)
Infection of heart and blood vessels	282 (<1)	0.38 (0.34 – 0.43)	982 (<1)	0.27 (0.25 – 0.28)	0.12 (0.07 – 0.16)	1.43 (1.26 – 1.64)	1.21 (1.05 – 1.38)
Pneumonia	10 720 (7)	15.11 (14.83 – 15.40)	40 156 (5)	11.19 (11.08 – 11.30)	3.92 (3.61 – 4.22)	1.35 (1.32 – 1.38)	1.26 (1.24 – 1.29)
Miscellaneous bacterial infection	1 308 (1)	1.79 (1.69 – 1.89)	4 664 (1)	1.27 (1.24 – 1.31)	0.51 (0.41 – 0.62)	1.41 (1.32 – 1.50)	1.32 (1.23 – 1.40)
Emphysematous cystitis	610 (<1)	0.83 (0.77 – 0.90)	2 236 (<1)	0.61 (0.58 – 0.63)	0.22 (0.15 – 0.30)	1.37 (1.25 – 1.49)	1.31 (1.19 – 1.44)
Gastrointestinal tract infection	2 578 (2)	3.55 (3.41 – 3.69)	8 742 (1)	2.39 (2.34 – 2.44)	1.15 (1.01 – 1.30)	1.48 (1.42 – 1.55)	1.36 (1.30 – 1.42)
Urinary tract infection	6 895 (4)	9.60 (9.37 – 9.83)	24 374 (3)	6.74 (6.65 – 6.82)	2.85 (2.62 – 3.10)	1.44 (1.40 – 1.47)	1.47 (1.43 – 1.50)
Viral infection	1 094 (1)	1.50 (1.41 – 1.59)	3 848 (1)	1.05 (1.02 – 1.08)	0.45 (0.35 – 0.54)	1.42 (1.33 – 1.52)	1.34 (1.25 – 1.44)
Infection of the central nervous system	312 (<1)	0.43 (0.38 – 0.48)	1 088 (<1)	0.30 (0.28 – 0.31)	0.13 (0.08 – 0.18)	1.44 (1.27 – 1.63)	1.39 (1.22 – 1.59)
Fungal infection	798 (1)	1.09 (1.02 – 1.17)	2 733 (<1)	0.74 (0.72 – 0.77)	0.35 (0.26 – 0.43)	1.47 (1.35 – 1.59)	1.39 (1.28 – 1.50)
Perirenal abscess	78 (<1)	0.11 (0.09 – 0.13)	207 (<1)	0.06 (0.05 – 0.06)	0.05 (0.03 – 0.07)	1.84 (1.41 – 2.39)	1.50 (1.14 – 1.98)
Intra-abdominal infection	4 356 (3)	6.04 (5.86 – 6.22)	14 519 (2)	4.00 (3.93 – 4.06)	2.04 (1.85 – 2.23)	1.51 (1.46 – 1.56)	1.45 (1.40 – 1.51)
Emphysematous pyelonephritis	588 (<1)	0.80 (0.74 – 0.87)	1 894 (<1)	0.52 (0.49 – 0.54)	0.29 (0.22 – 0.36)	1.56 (1.42 – 1.71)	1.45 (1.32 – 1.60)
Skin and subcutaneous infection	5 637 (4)	7.86 (7.66 – 8.07)	18 559 (2)	5.13 (5.06 – 5.20)	2.73 (2.51 – 2.95)	1.53 (1.49 – 1.58)	1.45 (1.41 – 1.50)
Meningococcal infection	16 (<1)	0.02 (0.01 – 0.04)	44 (<1)	0.01 (0.01 – 0.02)	0.00 (0.00 – 0.02)	1.82 (1.03 – 3.22)	1.81 (0.99 – 3.31)
Septicemia	4 021 (3)	5.52 (5.35 – 5.70)	12 270 (2)	3.35 (3.29 – 3.41)	2.17 (1.99 – 2.35)	1.65 (1.59 – 1.71)	1.55 (1.49 – 1.61)

	Type 2 diabetes cohort		Matched comparison cohort			Rate ratio (95% CI)	
	No. of infections (%) (n=28 938)	Rate /1000 p-y (95% CI)	No. of infections (%) (n=102 795)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Tuberculosis	112 (<1)	0.15 (0.13 – 0.18)	398 (<1)	0.11 (0.10 – 1.12)	0.04 (0.01 – 0.07)	1.41 (1.14 – 1.74)	1.40 (1.13 – 1.75)
Abscess	3 920 (3)	5.43 (5.26 – 5.60)	12 060 (2)	3.31 (3.25 – 3.37)	2.12 (1.94 – 2.30)	1.63 (1.58 – 1.69)	1.53 (1.48 – 1.59)
Emphysematous cholecystitis	597 (<1)	0.82 (0.75 – 0.88)	1 721 (<1)	0.47 (0.45 – 0.49)	0.35 (0.28 – 0.41)	1.74 (1.58 – 1.91)	1.73 (1.56 – 1.90)

Abbreviations: p-y, person-years; CI, confidence interval

[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Cormorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

[b]ICD codes for specific infections are available in the Appendix.

Table 5. Rates, rate differences, and rate ratios of hospital-treated infections in the type 2 diabetes cohort and the matched general population cohort, stratified by gender, age group, comorbidity level, and statin use.

	Type 2 diabetes cohort	Matched comparison cohort		Rate ratio (95% CI)	
	Rate /1000 p-y (95% CI)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Overall	58.24 (57.57 – 58.92)	39.03 (38.79 – 39.27)	19.2 (18.5 – 19.9)	1.49 (1.47 – 1.51)	1.44 (1.42 – 1.46)
Gender					
Men	57.3 (56.4 – 58.2)	39.4 (39.1 – 39.7)	17.9 (17.0 – 18.9)	1.47 (1.44 – 1.49)	1.40 (1.37 – 1.42)
Women	59.4 (58.4 – 60.4)	38.6 (38.3 – 39.0)	20.7 (19.7 – 21.8)	1.55 (1.52 – 1.58)	1.50 (1.47 – 1.53)
Age groups (years)					
30 – <40	69.9 (66.6 – 73.4)	37.5 (36.4 – 38.6)	32.5 (28.9 – 36.0)	1.86 (1.75 – 1.97)	1.55 (1.48 – 1.62)
40 – <50	43.2 (41.5 – 44.9)	21.4 (20.9 – 22.0)	21.7 (19.9 – 23.5)	2.00 (1.91 – 2.10)	1.77 (1.67 – 1.87)
50 – < 60	45.2 (43.8 – 46.6)	25.1 (24.7 – 25.6)	20.1 (18.6 – 21.5)	1.79 (1.73 – 1.86)	1.58 (1.52 – 1.64)
60 – <70	47.9 (46.8 – 49.1)	31.3 (30.9 – 31.7)	16.6 (15.4 – 17.8)	1.53 (1.49 – 1.57)	1.41 (1.37 – 1.45)
70 – <80	64.5 (63.0 – 66.0)	46.1 (45.6 – 46.7)	18.4 (16.8 – 19.9)	1.40 (1.36 – 1.43)	1.33 (1.30 – 1.37)
>80	100.8 (98.3 – 103.3)	78.7 (77.8 – 79.6)	22.1 (19.4 – 24.8)	1.28 (1.25 – 1.32)	1.29 (1.26 – 1.33)
CCI score					
Low (score of 0)	42.9 (42.2 – 43.5)	28.7 (28.5 – 28.9)	14.2 (13.5 – 14.9)	1.51 (1.48 – 1.54)	1.61 (1.58 – 1.64)
Medium (score of 1-2)	91.2 (89.4 – 93.0)	76.6 (75.8 – 77.5)	14.6 (12.5 – 16.6)	1.24 (1.21 – 1.26)	1.29 (1.26 – 1.32)
High (score of ≥3)	194.7 (188.1 – 201.5)	163.0 (159.7 – 166.4)	31.7 (24.2 – 39.1)	1.20 (1.15 – 1.25)	1.22 (1.17 – 1.27)
Statin use					
No	70.8 (69.7 – 72.0)	38.0 (37.8 – 38.3)	32.8 (31.7 – 33.9)	1.90 (1.87 – 1.93)	1.62 (1.59 – 1.65)
Yes	47.9 (47.1 – 48.7)	43.2 (42.7 – 43.8)	4.7 (3.7 – 5.7)	1.22 (1.20 – 1.25)	1.21 (1.18 – 1.23)

Abbreviations: CCI, Charlson Comorbidity Index; p-y, person-years; CI, confidence interval

[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Comorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

Supplementary table 1. Rates, rate differences, and rate ratios of primary diagnosis of hospital-treated infection in the type 2 diabetes cohort and the matched general population cohort, Denmark, 2004-2012.

	Type 2 diabetes cohort		Matched comparison cohort			Rate ratio (95% CI)	
	No. of infections (%) (n=28 938)	Rate /1000 p-y (95% CI)	No. of infections (%) (n=102 795)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Any admission with primary diagnosis of infection							
Six-month follow-up	4 764 (3)	64.73 (62.91 – 66.59)	12 474 (2)	33.83 (33.24 – 34.43)	30.90 (28.97 – 32.83)	1.92 (1.86 – 1.99)	1.87 (1.80 – 1.94)
One-year follow-up	7 858 (5)	55.43 (54.22 – 56.67)	23 524 (3)	33.01 (32.59 – 33.43)	22.42 (21.13 – 23.72)	1.69 (1.64 – 1.73)	1.65 (1.60 – 1.70)
Total follow-up	25 886 (17)	39.29 (38.81 – 39.77)	94 360 (12)	27.77 (27.60 – 27.95)	11.52 (11.01 – 12.03)	1.44 (1.41 – 1.46)	1.39 (1.37 – 1.41)
Admission with primary diagnosis of specific infections listed by increasing rate ratios[b]							
Meningococcal infection	10 (<1)	0.01 (0.01 – 0.03)	38 (<1)	0.01 (0.01 – 0.01)	0.00 (0.00 – 0.02)	1.17 (0.56 – 1.45)	0.98 (0.40 – 2.42)
Perirenal abscess	18 (<1)	0.02 (0.02 – 0.02)	70 (<1)	0.02 (0.02 – 0.02)	0.00 (0.00 – 0.00)	1.25 (0.72 – 2.17)	0.99 (1.52 – 1.86)
Eye and ear infection	929 (1)	1.27 (1.19 – 1.36)	4 142 (1)	1.13 (1.10 – 1.17)	0.14 (0.05 – 0.23)	1.16 (1.07 – 1.25)	1.18 (1.08 – 1.27)
Infection of heart and blood vessels	210 (<1)	0.29 (0.25 – 0.33)	774 (<1)	0.21 (0.20 – 0.23)	0.08 (0.03 – 0.12)	1.38 (1.17 – 1.63)	1.21 (1.01 – 1.45)
Upper respiratory tract infection	1 389 (1)	1.90 (1.80 – 2.00)	5 325 (1)	1.45 (1.42 – 1.49)	0.45 (0.34 – 0.55)	1.28 (1.20 – 1.36)	1.23 (1.15 – 1.31)
Pneumonia	7 770 (5)	10.84 (10.61 – 11.09)	29 567 (4)	8.19 (8.10 – 8.29)	2.65 (2.39 – 2.91)	1.35 (1.32 – 1.39)	1.29 (1.25 – 1.32)
Miscellaneous bacterial infection	937 (1)	1.28 (1.20 – 1.36)	3 478 (1)	0.95 (0.92 – 0.98)	0.33 (0.24 – 0.42)	1.37 (1.27 – 1.48)	1.31 (1.21 – 1.43)
Emphysematous cystitis	485 (<1)	0.66 (0.60 – 0.72)	1 761 (<1)	0.48 (0.46 – 0.50)	0.18 (0.12 – 0.24)	1.41 (1.27 – 1.57)	1.35 (1.21 – 1.52)
Gastrointestinal tract infection	1 854 (1)	2.54 (2.43 – 2.66)	6 359 (1)	1.74 (1.69 – 1.78)	0.81 (0.68 – 0.93)	1.50 (1.42 – 1.59)	1.38 (1.30 – 1.47)
Viral infection	785 (1)	1.07 (1.00 – 1.15)	2 959 (<1)	0.81 (0.78 – 0.84)	0.27 (0.19 – 0.35)	1.38 (1.27 – 1.50)	1.38 (1.26 – 1.51)
Urinary tract infection	3 838 (2)	5.29 (5.13 – 5.46)	13 303 (2)	3.65 (3.59 – 3.71)	1.64 (1.46 – 1.82)	1.48 (1.42 – 1.54)	1.42 (1.36 – 1.48)
Intra-abdominal infection	3 722 (2)	5.15 (4.99 – 5.32)	12 590 (2)	3.46 (3.40 – 3.52)	1.69 (1.52 – 1.87)	1.49 (1.43 – 1.55)	1.46 (1.40 – 1.53)
Emphysematous pyelonephritis	482 (<1)	0.66 (0.60 – 0.72)	1 583 (<1)	0.43 (0.41 – 0.45)	0.23 (0.16 – 0.29)	1.54 (1.38 – 1.71)	1.46 (1.29 – 1.64)
Skin and subcutaneous infection	4 942 (3)	6.88 (6.69 – 7.07)	16 242 (2)	4.48 (4.41 – 4.20)	2.40 (2.19 – 2.60)	1.54 (1.49 – 1.59)	1.49 (1.43 – 1.55)
Fungal infection	290 (<1)	0.40 (0.35 – 0.44)	1 003 (<1)	0.27 (0.26 – 0.29)	0.12 (0.07 – 0.17)	1.52 (1.32 – 1.75)	1.50 (1.28 – 1.75)
Tuberculosis	84 (<1)	0.11 (0.09 – 0.14)	311 (<1)	0.08 (0.08 – 0.09)	0.03 (0.00 – 0.06)	1.36 (1.05 – 1.76)	1.51 (1.13 – 2.02)
Infection of the central nervous system	268 (<1)	0.36 (0.32 – 0.41)	912 (<1)	0.25 (0.23 – 0.26)	0.12 (0.07 – 0.16)	1.52 (1.31 – 1.76)	1.55 (1.32 – 1.81)

	Type 2 diabetes cohort		Matched comparison cohort			Rate ratio (95% CI)	
	No. of infections (%) (n=28 938)	Rate /1000 p-y (95% CI)	No. of infections (%) (n=102 795)	Rate /1000 p-y (95% CI)	Rate difference (95% CI)	Crude	Adjusted[a]
Abscess	3 546 (2)	4.90 (4.74 – 5.06)	10 992 (1)	3.02 (2.96 – 3.07)	1.88 (1.71 – 2.06)	1.64 (1.57 – 1.71)	1.60 (1.53 – 1.67)
Septicemia	3 075 (2)	4.22 (4.07 – 4.37)	9 328 (1)	2.55 (2.50 – 2.60)	1.67 (1.52 – 1.83)	1.71 (1.63 – 1.78)	1.64 (1.56 – 1.72)
Emphysematous cholecystitis	524 (<1)	0.71 (0.66 – 0.78)	1 517 (<1)	0.41 (0.39 – 0.43)	0.30 (0.24 – 0.37)	1.74 (1.56 – 1.94)	1.75 (1.56 – 1.97)

Abbreviations: p-y, person-years; CI, confidence interval

[a]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Cormorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

[b]ICD codes for specific infections are available in the Appendix.

Supplementary table 2. Time trend of one-year rates and rate ratios of community antibiotic prescriptions and hospital-treated infections in the type 2 diabetes cohort and in the matched general population comparison cohort, Denmark, 2004-2012.

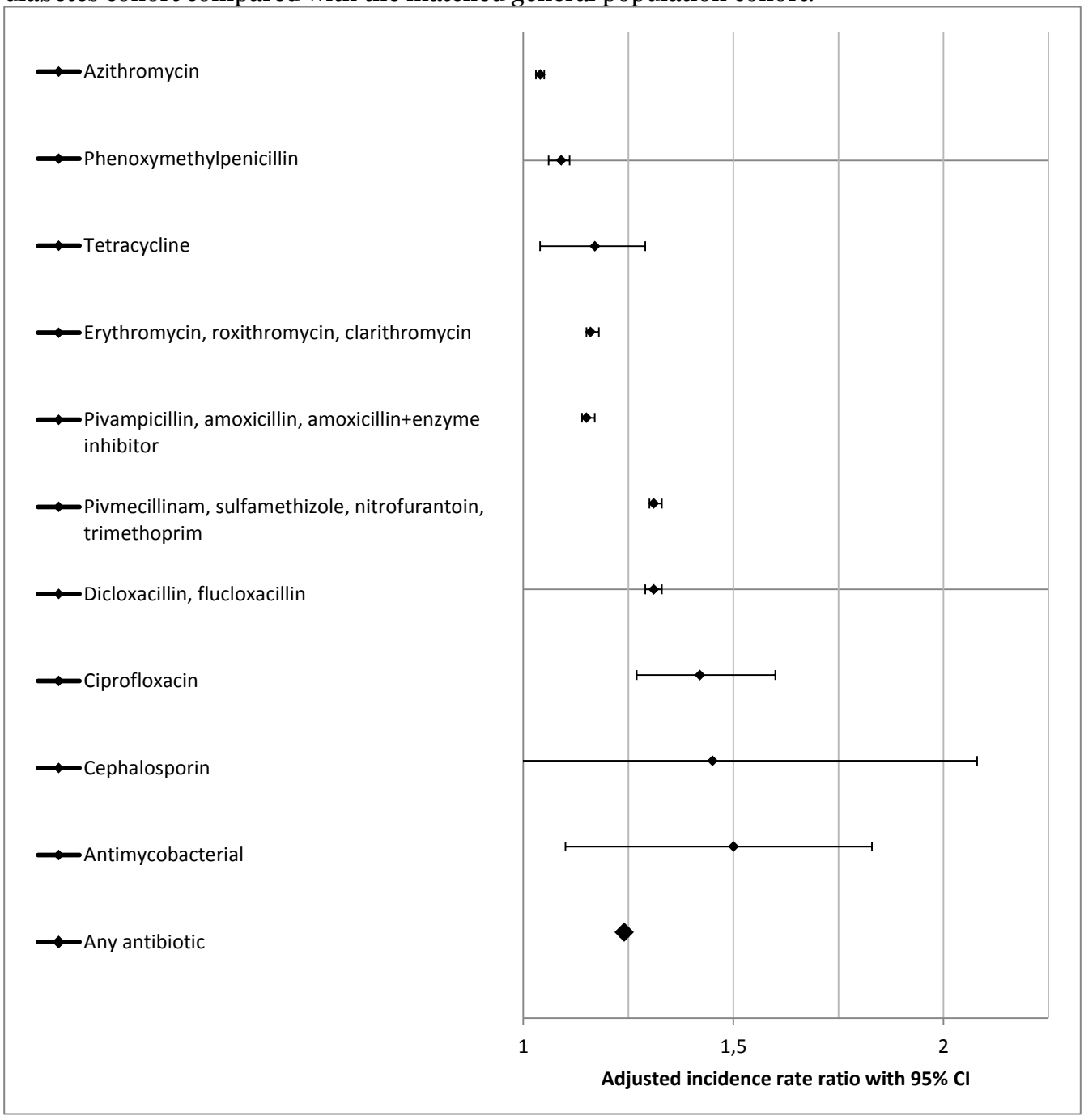
Year of enrollment[a]	2004-2005	2005-2006	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012	Regression coefficient	*P* for trend
Community antibiotic prescriptions										
1-year rates per 1000 p-y										
T2D cohort	491.2	482.7	498.0	483.6	476.1	475.7	479.8	457.7	-3.85 (-6.84 – -0.86)	.020
Comparison cohort	358.1	356.6	365.4	364.4	350.1	360.4	365.0	344.5	-0.98 (-3.89–1.93)	.441
Crude 1-year RR[b]	1.37	1.36	1.36	1.33	1.36	1.33	1.32	1.33	-0.0	
95% CI	(1.33–1.41)	(1.32–1.41)	(1.32 –1.40)	(1.29–1.37)	(1.32–1.40)	(1.29–1.37)	(1.28–1.35)	(1.29–1.37)	(-0.01 –-0.00)	.013
Adjusted 1-year RR[b]	1.31	1.30	1.29	1.26	1.28	1.25	1.26	1.26	-0.01	
(95% CI)	(1.27–1.36)	(1.26–1.34)	(1.25– 1.33)	(1.22–1.30)	(1.25–1.32)	(1.22–1.29)	(1.22–1.29)	(1.22–1.30)	(-0.10–-0.00)	.006
Adjusted 1-year RR[b]	1.27	1.31	1.25	1.28	1.34	1.25	1.22	1.22	-0.01	
(95% CI) in men	(1.22–1.33)	(1.25–1.37)	(1.19– 1.31)	(1.22–1.33)	(1.29–1.40)	(1.20–1.30)	(1.18–1.27)	(1.17–1.28)	(-0.02–0.01)	.193
Adjusted 1-year RR[b]	1.35	1.29	1.32	1.25	1.24	1.26	1.29	1.29	-0.01	
(95% CI) in women	(1.30–1.41)	(1.23–1.34)	(1.27–1.38)	(1.20–1.30)	(1.18–1.29)	(1.21–1.31)	(1.25–1.35)	(1.24–1.35)	(-0.2–0.01)	.222
Hospital-treated infections										
1-year rates per 1000 p-y										
T2D cohort	72.34	72.20	65.65	71.73	71.05	67.66	68.60	75.55	0.12 (-1.16–1.39)	.830
Comparison cohort	41.55	38.77	39.98	40.31	40.17	40.52	40.79	43.85	0.32 (-0.18–0.84)	.162
Crude 1-year RR[b]	1.79	1.87	1.68	1.80	1.79	1.69	1.69	1.71	-0.02	
(95% CI)	(1.67–1.92)	(1.74–2.01)	(1.56–1.80)	(1.68 –1.93)	(1.68–1.92)	(1.58–1.80)	(1.59–1.80)	(1.61–1.82)	(-0.04–0.01)	.112
Adjusted 1-year RR[b]	1.89	1.95	1.67	1.76	1.77	1.63	1.63	1.59	-0.05	
(95% CI)	(1.75–2.04)	(1.81–2.11)	(1.55–1.81)	(1.63–1.89)	(1.65–1.91)	(1.52–1.75)	(1.52–1.74)	(1.49–1.71)	(-0.07–-0.02)	.007
Adjusted 1-year RR[b]	1.91	1.94	1.62	1.71	1.82	1.63	1.54	1.59	-0.05	
(95% CI) in men	(1.81–2.02)	(1.75–2.16)	(1.45–1.80)	(1.54–1.90)	(1.65–2.00)	(1.47–1.79)	(1.41–1.69)	(1.45–1.74)	(-0.09–-0.01)	.021
Adjusted 1-year RR[b]	1.99	1.96	1.73	1.82	1.73	1.64	1.73	1.60	-0.05	
(95% CI) in women	(1.78–2.22)	(1.75–2.19)	(1.55–1.94)	(1.63–2.02)	(1.55–1.93)	(1.47–1.82)	(1.57–1.91)	(1.44–1.77)	(-0.08–-0.02)	.004

Abbreviations: T2D, type 2 diabetes; p-y, person-years; CI, confidence interval; RR, rate ratio

[a]Enrollment was counted from 1 July to 30 June.

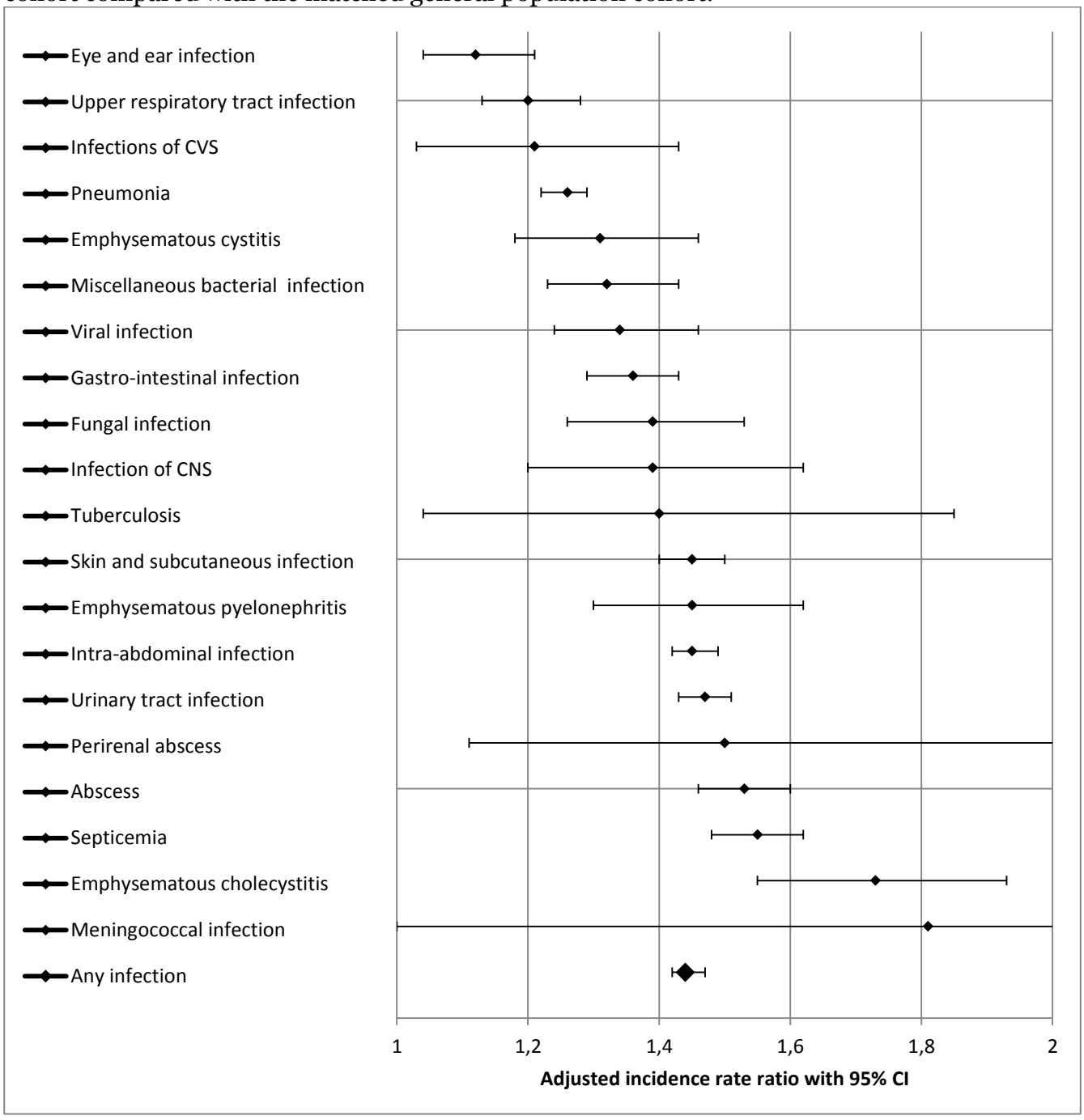
[b]Adjusted for age, sex, marital status, alcoholism-related conditions, Charlson Comorbidity Index comorbidities, statin use, steroid use, and immunosuppressant use.

Figure 1. Adjusted rate ratios of community-based antibiotic prescriptions in the type 2 diabetes cohort compared with the matched general population cohort.



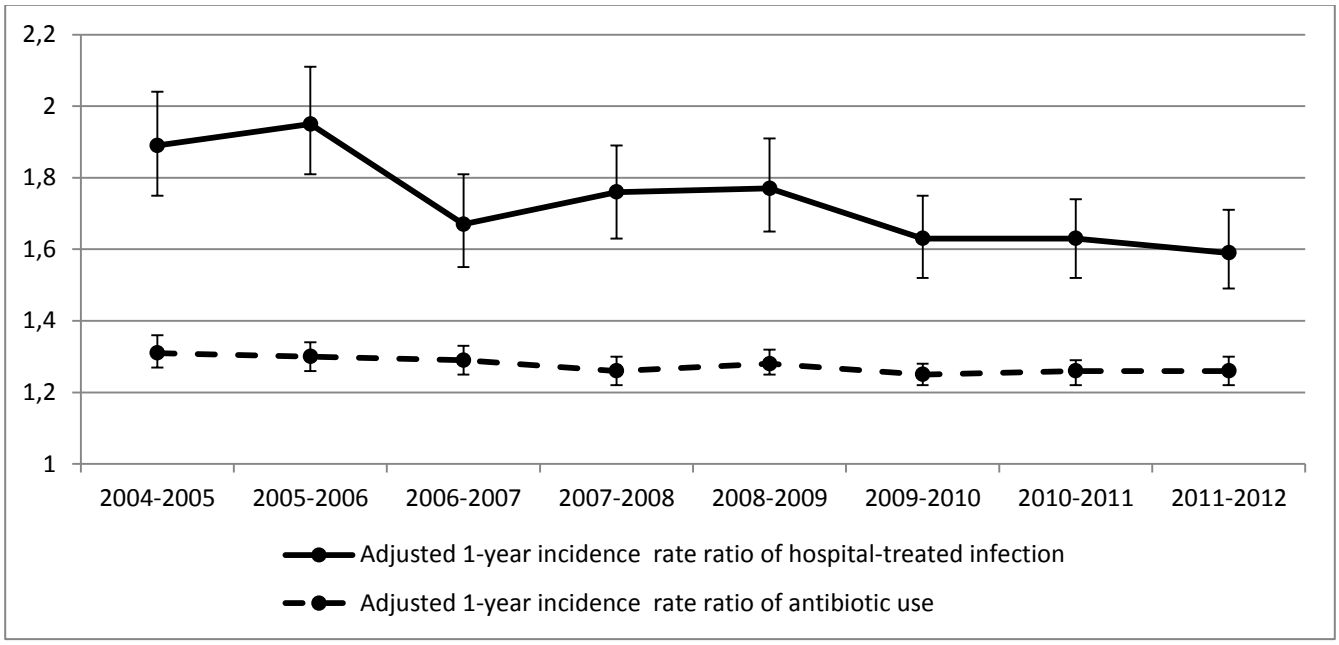
Abbreviation: CI, confidence interval

Figure 2. Adjusted rate ratios of hospital-treated specific infections in the type 2 diabetes cohort compared with the matched general population cohort.



Abbreviations: CVS, cardiovascular system; CNS, central nervous system, CI, confidence interval

Figure 3. Time trends in adjusted rate ratios of infection among individuals with type 2 diabetes compared with members of the matched general population cohort, Denmark, 2004-2012.



Appendix

World Health Organization *International Classification of Diseases, Eighth Revision* (ICD-8) and *Tenth Revision* (ICD-10) codes and Anatomical Therapeutical Chemical classification system (ATC) codes used in this study.

Codes used to identify type 2 diabetes	
Hospital contact for type 2 diabetes	ICD-8-codes: 249.x, 250.x. ICD-10-codes: E10.x, E11.x, E14·x, G63.2.x, H36.0, N08.3
Glucose-lowering drugs	ATC-codes:- Insulin and analogues: A10Axxx; Metformin: A10BAxx; Sulfonylureas: A10BBxx; Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1 (GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02, A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx
Codes used to identify diabetes complications	
Microvascular complications	
Nephropathy	ICD-8-codes: 25002, 24902 ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2
Retinopathy	ICD-8-codes: 25001, 24901 ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335
Neuropathy	ICD-8-codes: 25003, 24903 ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,

Macrovascular complications	ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440 ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145

Codes used to identify any infection

Hospital-treated (inpatient and outpatient) infections	ICD-10-codes: A00-B99, D73.3, E06.0, E06.9, E32.1, G00-G02, G04-07, H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0, I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1, J00-J06, J09-J18, J20-22, J34.0, J36, J38.3D, J38.7G, J39.0-1, J39.8A, J44.0, J85.1-3, J86, K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1, L00-03, L05-08, L88, M00-01, M46.1-5, M49.0-3, M60.0, M60.8, M63.0-2, M65.0-1, M68.0, M71.0-1, M86.0-2, M86.9, M90.0-2, N10, N12, N13.6, N15.1, N16.0, N20.0I, N29.1, N30.0, N33.0, N34.0-1, N39.0, N41, N43.1, N45.0, N45.9, N48.1-2, N49, N61, N70-77, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98, T80.2, T81.4, T82.6-7, T83.5-6, T84.5-7, T85.7, T88.0, and T89.9
Antibiotics dispensed by community pharmacies	ATC-codes: J01xx, J02AA, J04AB, and A07AA

ICD-10 codes used to identify specific hospital-treated infections

Eye and ear infections	H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0
Upper respiratory tract infections	K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, J00, J01, J02, J03, J04, J05, J06, J36, J38, J39
Pneumonia	J12, J13, J14, J15, J16, J17, J18

Infections of heart and blood vessels	I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1
Gastrointestinal tract infections	A00-A09
Intra-abdominal infections	K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1
Urinary tract infections	N10, N12, N15.1, N30.0, N33.0, N34.0-1, N39.0
Infection of central nervous system	G00-G02, G04-07, A80-A89
Meningococcal infections	A39
Skin and subcutaneous infections	A46, J34, L000-L08
Abscesses	A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P
Septicemia	A40, A41
Tuberculosis	A15-A19
Miscellaneous bacterial infections	A20-A38, A42-A44, A48, A49, A65-A79
Viral infections	B00-B09, B15-B19, B25-B34, A90-A99
Fungal infections	B35-B49

Malignant external otitis	H60.2
Emphysematous cholecystitis	K81.0
Emphysematous cystitis	N30.8
Emphysematous pyelonephritis	N10
Perirenal abscess	N15.9

ATC codes used to identify specific subgroups of antibiotics	
Phenoxymethylpenicillin (first-line drug for community-acquired respiratory tract infections in Denmark)	J01CE02
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor (broad-spectrum beta-lactams used mainly for respiratory tract infections in selected patients)	J01CA02, J01CA04, J01CR02
Azithromycin (used mainly to treat genital infections)	J01FA10
Erythromycin, roxithromycin, clarithromycin (used for respiratory tract infections in the presence of a penicillin allergy or for *Mycoplasma pneumonia*)	J01FA01, J01FA06, J01FA09

Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim (drugs almost exclusively used to treat UTI in Denmark)	J01CA08, J01EB02, J01XE01, J01EA01,
Dicloxacillin, flucloxacillin (used mainly to treat skin infections / *S. aureus*)	J01CF01, J01CF05
Antimycobacterial	J04A
Quinolones (used to treat UTI and gastrointestinal infections in selected cases)	J01M
Tetracycline	J01A
Cephalosporin	J01D

Codes used to identify covariates	
Alcoholism-related disorders	ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714
Statin use	ATC-codes: B04AB
Immunosuppressant use	ATC-codes: L01, L04
Oral corticosteroid use	ATC-codes: H02AB

Study II

- Dissertation paper II

Metformin and other glucose-lowering drug initiation and rates of community-based antibiotic use and hospital-treated infections in patients with type 2 diabetes: A Danish nationwide population-based cohort study

Anil Mor[1], Irene Petersen[1,2], Henrik T. Sørensen[1], Reimar W. Thomsen[1]

[1]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

[2]Research Department of Primary Care and Population Health, University College London, London, UK

Corresponding author: Anil Mor, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, DK-8200 Aarhus N, Denmark (E-mail: anil.mor@clin.au.dk; phone: +45 8716 8486, fax: +45 8716 7215)

Key words: hypoglycaemic agents, type 2 diabetes mellitus, pharmacoepidemiology, infections, antibiotics

ABSTRACT

Objective: Data on early risk of infection in patients receiving their first treatment for type 2 diabetes are limited. We examined rates of community-based antibiotic use and hospital-treated infection in initiators of metformin and other glucose-lowering drugs (GLDs).

Design: Population-based cohort study using medical databases.

Setting: General practice and hospitals in Denmark.

Participants: 131 949 patients with type 2 diabetes who initiated pharmacotherapy with a GLD between 2005 and 2012.

Exposure: Initial GLD used for pharmacotherapy.

Main outcome measures: We computed rates and adjusted hazard ratios (HRs) of community-based antibiotic use and hospital-treated infection associated with choice of initial GLD with reference to metformin initiation, using an intention-to-treat approach.

Results: The rate of community-based antibiotic use was 362 per 1000 patient-years at risk [PYAR] and that for hospital-treated infection was 51/1000 PYAR. Compared to metformin, the risk of hospital-treated infection was slightly higher in sulfonylurea initiators (HR 1.09, 95% confidence interval [CI] 1.05 to 1.13) and substantially higher in insulin initiators (HR 1.32, 95% CI 1.25 to 1.40) initiators after adjustment for comorbid conditions, co-medications, and other confounding factors. In contrast, virtually no difference was observed for overall community-based antibiotic use (HR 1.01, 95% CI 0.99 to 1.03, for sulfonylurea initiators; and 0.99, 95% CI 0.96 to 1.03, for insulin initiators).

Conclusions: Rates of community-based antibiotic treatment and hospitalization for infection were high in patients receiving their first treatment for type 2 diabetes and differed with the choice of initial GLD used for pharmacotherapy.

ARTICLE SUMMARY

Strengths and limitations of this study

- Large nationwide population-based study based on prospectively collected data from hospitals and general practices
- Comprehensive list of infections and antibiotics studied in people receiving their first treatment for type 2 diabetes
- Main limitation was possible residual confounding by differences in diabetes severity

INTRODUCTION

Glucose-lowering drugs (GLDs) are prescribed increasingly in patients with type 2 diabetes,[1] with the aim of reducing macrovascular and microvascular complications. Three out of 4 patients diagnosed with diabetes initiate pharmacotherapy within the following year.[2] Although infections are a major clinical problem and an important cause of death in patients with type 2 diabetes,[3,4] population-based data are scarce on early infection risk in patients initiating GLD pharmacotherapy.

It has been observed recently that metformin use is associated with reduced risk of infections after surgery[5] and reduced risk of septicaemia,[6] with improved prognosis following septicaemia and other critical illness,[7] and with a beneficial effect on prevention and treatment of respiratory tract infections due to *Staphylococcus aureus*.[8] Limited epidemiological data are available comparing the association of different GLDs with risk of infections.[6,9] In a Swedish study based on 51 675 patients with type 2 diabetes treated with GLDs between 2004 and 2007, the hazard ratio (HR) of hospitalization for infection with co-occurrence of acidosis was greater for insulin monotherapy users (HR 1.37, 95% confidence interval [CI] 1.26 to 1.50) and other oral GLDs users (80% sulfonylurea) (HR 1.16, 95% CI 1.04 to 1.28) compared to metformin users.[9] Another study of 43 015 cases with septicaemia and control subjects nested in a cohort of newly diagnosed type 2 diabetes patients from Taiwan found that metformin use was associated with reduced risk of developing septicaemia (odds ratio [OR] 0.80, 95% CI 0.77 to 0.83) compared with metformin non-users.[6] For other infections including those treated by general practitioners, comprehensive data on the risk among users of different GLDs is lacking.

Therefore, we undertook a large cohort study using nationwide Danish population data to investigate rates of community-based antibiotic use and hospital-treated infection associated with initiation of different GLDs in type 2 diabetes patients.

METHODS

Data sources

We used the Danish National Patient Registry (DNPR),[10] the Danish National Health Service Prescription Database (DNHSPD),[11] and the Danish Civil Registration System (CRS)[12] to conduct this study. The Danish National Health Service provides Danish residents with universal access to general practice and hospitals and reimburses most of the cost of prescription drugs, including glucose-lowering drugs.[11] We used the unique central personal registry (CPR) number to link individual-level data among registries. The CRS began to assign a CPR number to all residents at birth or upon immigration in 1968.[12] Since then the CRS has maintained daily updated records of date of death or emigration, previous and current place of residence, marital status, and CPR number for all Danish residents. The DNPR contains nationwide information on all hospitalizations since 1977 and on all outpatient and emergency room visits since 1995.[10] It records patients' CPR number, a primary discharge diagnosis and up to 19 secondary discharge diagnoses coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) until the end of 1993, and *Tenth Revision* (ICD-10) thereafter. The DNHSPD collects data from all community pharmacies and hospital-based outpatient pharmacies. It has archived patient-, drug-, and prescriber-related information on all prescription medications dispensed in Denmark since 2004.[11] The drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification system.

Study design and population

We conducted this population-based cohort study in a Danish nationwide cohort of patients with an incident type 2 diabetes diagnosis recorded between January 1, 2005 and December 31, 2012. Incident type 2 diabetes was defined as either the first record in the DNPR of a diabetes-associated inpatient admission (data available from 1977) or outpatient clinic contact (data available from 1995) or the first record of a GLD prescription in the DNHSPD (data available from January 2004), whichever came first.[13] To decrease the chance of including patients with type 1 diabetes, we restricted our cohort to patients who were 30 years or older when first diagnosed with diabetes (n = 147 396).[14] We also excluded patients with a diabetes diagnosis but no recorded GLD prescription during the 2005-2012 study period (n = 14 120). Women with a recorded diagnosis of polycystic ovarian disease who were using metformin monotherapy, identified from the DNPR and the DNHSPD, were excluded as well (n = 1327). This left a final study cohort of 131 949 patients with incident pharmacotherapy for type 2 diabetes.

We defined exposure as the first record of a redeemed GLD prescription in the DNHSPD (the index date) between 2005 and 2012. We disregarded any change or addition of other GLD afterwards. We established seven mutually exclusive categories of exposure according to type of first-prescribed GLD: metformin (biguanides); sulfonylurea; insulin; any fixed drug combinations; dipeptidyl peptidase-4 (DPP-4) inhibitors; glucagon-like peptidase-1 (GLP-1) analogue; meglitinides; other (including thiazolidinediones; and alpha glucosidase inhibitors) (see Appendix 1 for ATC codes). We followed the study cohort from the index date until death, emigration, or end of the study period (December 31, 2012), whichever came first.

Assessment of outcomes

Our outcomes were hospital-treated infections and community-based antibiotic use. Hospital-treated infection was defined as any first inpatient admission or outpatient hospital clinic contact associated with a primary or secondary discharge diagnosis of infection after the index date. We further divided hospital-treated infections into subcategories (see Appendix 1 for categories and associated ICD codes).

Community-based antibiotic use was defined as any first record of an antibiotic prescription in the DNHSPD that was redeemed during the study period after the index date. We investigated 10 groups of antibiotics prescribed to treat specific infections according to national Danish guidelines for general practitioners (see Appendix 1 for ATC codes).[15,16]

Assessment of covariates

We searched the DNPR for information on 19 major comorbidities included in the Charlson Comorbidity Index (CCI),[17] based on each cohort member's entire hospital contact history during the 10 years prior to his/her index date. We defined three comorbidity levels: low (CCI score of 0), medium (CCI scores of 1 or 2), and high (CCI score ≥ 3).[18] We also collected information on other covariates associated with risk of infection: microvascular and macrovascular diabetes complications not included in the CCI (see Appendix 1); diabetes duration (if a hospital diagnosis was present before the GLD initiation/index date); presence of alcoholism-related disorders (yes/no); a hospital diagnosis of obesity (yes/no); use of immunosuppressive drugs (yes/no), oral corticosteroids (yes/no), or statins (yes/no); marital status as a marker of social support (married/never married/divorced/widowed); and

calendar period of inclusion (2005-2008/2009-2012). Additionally, we retrieved information on presence of any acute inpatient hospitalization or emergency room visit within 6 month before the index date of first GLD prescription, including any acute hospitalization or emergency room visit with an infection diagnosis.

Statistical analysis

We described cohort characteristics at the time the first GLD was redeemed according to GLD categories (Table 1). We defined the exposure status at the index date and used an intention-to-treat approach[19] and computed incidence rates (IRs) separately for community-based antibiotic use and for hospital-treated infections, by dividing the number of incident outcome events by total exposed patient-time during follow-up (expressed per 1000 patient-years at risk [PYAR]). We then used Cox regression to compute HRs of community-based antibiotic use and hospital-treated infections (with 95% CIs) associated with the exposure categories described above, using metformin initiation as reference. We computed estimates adjusted for age and sex (Model 1), then we added comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs (Model 2) and finally we added presence of any hospitalization or emergency room visit within 6 months with either infection or with any other diagnosis in the fully adjusted Model 3. We repeated the analyses for specific infections and antibiotic groups, except for those associated with four or fewer events during complete follow-up.

Bias analyses

Increased body mass index (BMI) and tobacco smoking may both be associated with type 2 diabetes, choice of diabetes therapy, and infection risk. As we had data only on hospital-diagnosed obesity and tobacco-related diseases, and no detailed data on smoking or BMI, we computed externally adjusted estimates of unmeasured obesity (BMI ≥30 kg/m^2) and smoking, respectively, and compared them to our crude estimates, to assess the proportion of effect possibly explained by obesity or smoking alone, using the array approach as presented by Schneeweiss[20]:

$$\text{caHR} = \frac{\text{aHR}}{\frac{Pc1(HRcd-1)+1}{Pc0(HRcd-1)+1}}$$

where caHR is the obesity-adjusted HR, aHR is the crude rate ratio observed in our study, Pc0 is the proportion of patients with obesity in the reference (metformin) group (estimated at 0.49 in the study period based on the study by Ulrichsen *et al.* [21]), Pc1 is the proportion of patients with obesity in the exposed group (for insulin, 0.19; for sulfonylurea, 0.26)[21], and HRcd is the expected rate ratio of infection related to obesity (1.5 for hospital-treated infections and 1.23 for community-based antibiotic use)[16]. Similarly, we computed externally adjusted estimates for tobacco smoking (Pc0=0.22, Pc1 for insulin =0.26, Pc1 for sulfonylurea=0.30, HRcd for hospital-treated infection=4.1, and HRcd for antibiotic use=1.17).[21–23] Additionally, using a rule-out approach[20] we estimated how strongly a single unmeasured binary confounder (e.g. BMI, smoking) would need to be associated with choice of GLD and infection to fully explain our adjusted results. We repeated this sensitivity analysis

for the observed lower limit of the 95% CI of the adjusted HR. We describe the details of the methods and the choice of parameter in Appendix 2.

Sensitivity analyses

We performed 5 additional sensitivity analyses:

1) To examine confounding by baseline HbA_{1c} which may be related both to choice of GLD and to subsequent risk of infections, we investigated a subcohort of our study population (n = 33 795), for which we had additional information on latest HbA_{1c} level before GLD initiation (baseline HbA_{1c}). We repeated the analyses for this subcohort including baseline HbA_{1c} categories (reference category: 5.5%-6.5%) as an additional confounder in the fully adjusted model.

2) To examine any residual confounding by comorbidity caused by using the original CCI score instead of newer versions (e.g., the CCI score was recently updated and validated using new scores by Quan et al.[24]), we collected new information from the registries and computed the CCI score as suggested by Quan et al. We repeated the analysis by replacing the traditional CCI score with the updated CCI score and compared the results.

3) To reduce any misclassification caused by mixture of type 1 and type 2 diabetes patients, we excluded all patients who used insulin as their first single GLD for pharmacotherapy after their diabetes diagnosis and were younger than 40 years old (n = 1430) at GLD start. We repeated the analysis within the restricted T2D patient cohort.

4) As an alternative to our intention-to-treat approach, we repeated the multivariable analysis censoring patients at the first change in GLD therapy from the initial therapy.

5) Finally, as intention-to-treat analysis has inherent limitations due to potential change in therapy during the follow-up, we performed as-treated analysis where we considered time-varying exposure and the individual GLD contributed to the risk-time until the consecutive prescription redemption record. In this analysis, to explore association of different combinations of GLDs with our outcomes we divided the combination GLD category into four groups: metformin + sulfonylurea, metformin + insulin, sulfonylurea + insulin, and any other combinations.

We used SAS software (Version 9.1.3; SAS Institute, Cary, NC) for data management. Analyses were carried out using STATA version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). The study was approved by the Danish Data Protection Agency (records no. 2012-41-0793 and 2013-41-1924).

RESULTS

Cohort characteristics

Of the 131 949 type 2 diabetes patients receiving their first anti-diabetic medication, 106 424 (81%) started with metformin, 16 703 (13%) started with sulfonylurea, and 7293 (6%) started with insulin. Only 1529 (<1%) individuals used one of the other GLDs as their initial drug (Table 1). In our study cohort, 56% (74 391) were men and the median age at inclusion was 62 years (interquartile range [IQR] 52 to 70 years). Compared with type 2 diabetes patients who used metformin as their first drug, sulfonylurea initiators were older (median age 67 years

versus 62 years), more likely to be enrolled before 2008 (80% versus 35%), more likely to change therapy within one or two years (22% and 33% versus 16% and 21%, respectively), more likely to have hospitalization 6 months before the index date (16% versus 9%), and more likely to have comorbidities (39% versus 29%), diabetes-related macrovascular complications (26% versus 21%), or alcoholism-related conditions (4% versus 2%) (Table 1). Patients who initiated their therapy with sulfonylurea also had less hospital-diagnosed obesity (4% versus 9%), and were less likely to be using statins at the time of GLD initiation (37% versus 48%).

Insulin initiators were younger (median age 56 years versus 62 years); more likely to have been included in the study before 2008 (51% versus 35%); more likely to have comorbidities (45% versus 29%), microvascular complications (10% versus 6%), and alcoholism-related conditions (10% versus 2%); less likely to be using statins (21% versus 48%); more likely to be hospitalized 6 six months before the index date (68% versus 9%); more likely to have infection in past 6 months (6% versus 1%); and more likely to have changed their therapy within one or two years (24% and 27% versus 16% and 21%, respectively) than metformin initiators (Table 1).

Rates of community-based antibiotic use and hospital-treated infections

During 218 032 PYAR, we identified 78 847 events (60% of all patients), yielding an IR of 361.8 per 1000 PYAR (95% CI 359.2 to 364.3). The IRs of community-based antibiotic use were higher in patients who initiated their treatment with insulin compared with those who initiated with sulfonylurea or metformin (Supplementary Table S1). We identified 20 308 (15%) initial-onset hospital-treated infection events during 395 171 PYAR, yielding an overall

IR of 51.4 per 1000 PYAR (95% CI 50.7 to 52.1). Incidence rates of hospital-treated infections were highest in patients who initiated their treatment with insulin, followed by patients who initiated with sulfonylurea and metformin (Supplementary Table S1). Cumulative rates of community-based antibiotic prescriptions and hospital-treated infections within the first four years in patients who initiated their treatment with metformin, sulfonylurea, or insulin are illustrated in Figure 1. The Figure shows that infection rates increased most sharply shortly after GLD treatment initiation. The unadjusted curves for the three treatment modalities diverged early during follow-up, with insulin initiators experiencing more infections than sulfonylurea initiators throughout follow-up, and sulfonylurea initiators experiencing more infections than metformin initiators (log-rank test for equality of survival function between the 3 exposure groups, P <0.00001 for both outcomes) (Figure 1).

Community-based antibiotic use

Compared with patients who initiated their treatment with metformin, the crude risk of subsequent community-based antibiotic prescriptions was increased in patients who initiated treatment with sulfonylurea (crude HR 1.06, 95% CI 1.04 to 1.08). The HR remained stable after adjusting for age and sex (HR 1.05, 95% CI 1.03 to 1.07), but reduced to 1.01 (95% CI 0.99 to 1.03) in the fully adjusted model (Table 2). For specific antibiotic groups, patients who initiated anti-diabetic treatment with sulfonylurea were at increased risk of treatment for infection with azithromycin (adjusted HR 1.10, 95% CI 1.03 to 1.17), quinolones (adjusted HR 1.36, 95% CI 1.06 to 1.75), and other broad-spectrum antibiotics (adjusted HR 1.06, 95% CI 1.02 to 1.10) (Figure 2 and Supplementary Table S2).

Similarly, the risk of community-based antibiotic use in patients who initiated their treatment with insulin decreased from 1.13 (95% CI 1.09 to 1.16) to 0.99 (95% CI 0.96 to 1.03) in the fully adjusted model (Table 2). For specific antibiotic groups, insulin initiators had increased risks of subsequent treatment of infections with quinolones (adjusted HR 3.27, 95% CI 2.43 to 4.39), cephalosporins (adjusted HR 4.23, 95% CI 1.75 to 10.24), dicloxacillin/flucloxacillin (adjusted HR 1.21, 95% CI 0.55 to 1.67), and with antibiotics used to treat UTI (adjusted HR 1.08, 95% CI 1.02 to 1.15) (Figure 2 and Supplementary Table S2).

The HRs were not increased for the rest of the rarer GLD categories except for GLP-1 analogue initiators (Table 2). The HRs and number of infections treated with specific antibiotic groups are provided in Supplementary Table S2 for all GLDs.

Bias analysis

In bias analyses for sulfonylurea vs. metformin, external adjustment for unmeasured obesity (lower with sulfonylurea) changed the crude HR from 1.06 to 1.11 and for smoking (higher with sulfonylurea) changed the crude HR from 1.06 to 1.05, respectively. For insulin vs. metformin, external adjustment for unmeasured obesity changed the crude HR from 1.13 to 1.20 and for smoking changed the crude HR from 1.13 to 1.12, respectively. The rule-out sensitivity analysis suggested that had we been able to account for obesity, we would likely have observed an association of antibiotic use with sulfonylurea or insulin compared with metformin that was stronger than we observed, as obesity is more prevalent among metformin users than the other treatment (see Appendix 2 for details). In contrast had we been able to account for more smoking in sulfonylurea or insulin compared with metformin

users, this might have nullified our weakly increased antibiotic HRs. For example, if smoking were 1.3-fold more prevalent among sulfonylurea than metformin users the relatively likelihood of being prescribed antibiotics would have to be about 50% greater in those who smoke for the HR to be equal or less than 1, which is plausible from findings in the literature[21] (Figure 1.4 in Appendix 2).

Sensitivity analyses

We performed further analyses on the subcohort of patients with baseline HbA_{1c} information. Compared with those who initiated their treatment with metformin, patients who initiated their treatment with sulfonylurea and insulin had adjusted HRs of community-based antibiotic use of 1.04 (95% CI 1.00 to 1.08) and 0.98 (95% CI 0.91 to 1.06), respectively (versus 1.01, 95% CI 0.99 to 1.03, and 0.99, 95% CI 0.96 to 1.03 in the full cohort). After additional adjustment for baseline HbA_{1c}, the HRs did not change for sulfonylurea initiators (adjusted HR 1.04, 95% CI 1.01 to 1.09), but increased slightly for insulin initiators (adjusted HR 1.02, 95% CI 0.95 to 1.10) (Supplementary Table S3). After replacing traditional CCI score with updated CCI score in the multivariate model, the fully adjusted HRs of any community-based antibiotic use did not change (Supplementary Table S4). After excluding insulin initiators who were younger than 40 years (reducing type 2 diabetes misclassification), the adjusted HRs did not change (Supplementary Table S5). Furthermore, in sensitivity analysis where we censored patients at the first change in therapy, we found that adjusted HRs of community-based antibiotic use did not change substantially for sulfonylurea (adjusted HR 1.02 [95% CI 1.01 to 1.04] versus 1.01 [95% CI 0.99 to 1.03] in the original ITT analysis) as well as insulin initiators (adjusted HR 0.99 [95% CI 0.55 to 1.03] versus 0.99 [95% CI 0.96 to

1.03] in the original ITT analysis) (Supplementary Table S6). Finally, in sensitivity analysis where we considered time-varying exposure (as-treated approach) the adjusted estimates increased for sulfonylurea (adjusted HR 1.04 [95% CI 1.02 to 1.07] versus1.01 [95% CI 0.99 to 1.03] in the original ITT analysis) and insulin initiators (adjusted HR 1.03 [95% CI 1.00 to 1.07] versus 0.99 [95% CI 0.96 to 1.03] in the original ITT analysis) (Supplementary Table S7). Furthermore, we found that any combination that includes insulin was strongly associated with risk of community-based antibiotic use compared to metformin monotherapy (e.g. for metformin+insulin adjusted HR was 1.10 [95% CI 1.04 to 1.17], and for insulin+sulfonylurea adjusted HR was 1.49 [95% CI 1.28 to 1.73] but for metformin+sulfonylurea adjusted HR was 1.01 [95% CI 0.98 to 1.04]) (Supplementary Table S7).

Hospital-treated infections

Compared to patients who initiated treatment with metformin, the risk of hospital-treated infections was higher in patients who initiated treatment with sulfonylurea (HR 1.41, 95% CI 1.36 to 1.46). The HR was reduced to 1.20 (95% CI 1.16 to 1.24) in Model 1 and further reduced to 1.09 (95% CI 1.05 to 1.13) in fully adjusted Model 3 (Table 2). Patients who initiated their treatment with sulfonylurea had increased risk of hospitalization for viral infections (adjusted HR 1.66, 95% CI 1.37 to 2.03), fungal infections (adjusted HR 1.39, 95% CI 1.11 to 1.76), intra-abdominal infections (adjusted HR 1.22, 95% CI 1.10 to 1.36), bacterial infections (adjusted HR 1.23, 95% CI 1.04 to 1.46), and pneumonia (adjusted HR 1.15, 95% CI 1.08 to 1.22) compared with those who initiated treatment with metformin (Figure 3 and Supplementary Table S8).

The risk of hospital-treated infections was twice as high in patients initiating treatment with insulin compared with metformin initiators (HR 1.96, 95% CI 1.87 to 2.07), and the association strengthened after adjusting for age and sex (HR 2.28 95% CI 2.17 to 2.39). After inclusion of other confounders, the HR decreased to 1.32 (95% CI 1.25 to 1.40) in the full model (Table 2). Type 2 diabetes patients who initiated treatment with insulin had a greater risk of hospitalization for nearly all examined infections in particular fungal infections (adjusted HR 1.86, 95% CI 1.34 to 2.58), viral infections (adjusted HR 1.61, 95% CI 1.21 to 2.13), bacterial infections (adjusted HR 1.44, 95% CI 1.10 to 1.88), UTI (adjusted HR 1.25, 95% CI 1.10 to 1.42), infections of the heart and blood vessels (adjusted HR 2.14, 95% CI 1.14 to 4.02), and septicaemia (adjusted HR 1.63, 95% CI 1.41 to 189), compared with patients who initiated treatment with metformin (Figure 3 and Supplementary Table S8).

Few episodes of infection occurred in patients taking medication in the remaining small GLD categories, and we did not detect a clear difference compared with metformin (Table 2). For GLDs other than sulfonylurea and insulin, the HRs and number of hospital contacts (if ≤ 4) for specific infections are provided in Supplementary Table S8.

Bias analysis

In bias analysis for sulfonylurea vs. metformin, external adjustment for unmeasured obesity changed the crude HR from 1.41 to 1.55, while external adjustment for smoking decreased the HR to 1.23, respectively. For insulin vs. metformin, external adjustment for unmeasured obesity (lower with insulin) increased the crude HR from 1.96 to 2.23 and decreased to 1.83 after external adjustment for smoking (more with insulin). The rule-out approach of

sensitivity analyses illustrated that for hospital-treated infections neither obesity nor smoking could completely explain the observed association in our study (see Appendix 2 for details). For example, if obesity were 1.6-fold more frequent among sulfonylurea users than metformin users the relative likelihood of hospital-treated infections would have to be increased by a factor of 3 or more to explain our findings fully, if no increased risk actually existed, which is unlikely based on available literature[21] (Figure 2.2 in Appendix 2).

Sensitivity analyses

When using treatment initiation with metformin as the comparator, adjusted HRs of hospital-treated infection associated with sulfonylurea and insulin initiation in the subcohort were 1.14 (95% CI 1.06 to 1.23) and 1.61 (95% CI 1.43 to 1.82), respectively (versus 1.09 and 1.30 in the full cohort) (Supplementary Table S5). Additional adjustment for baseline HbA_{1c} did not change the adjusted HR for sulfonylurea initiators (adjusted HR 1.14, 95% CI 1.05 to 1.23), and increased it slightly for insulin initiators (adjusted HR 1.67, 95% CI 1.47 to 1.89) (Supplementary Table S3). After replacing traditional CCI score with updated CCI score in the multivariate model, the fully adjusted HRs for sulfonylurea initiators did not change; however, adjusted HRs reduced for insulin initiators (adjusted HR 1.30 [95% CI 1.23 to 1.38] versus 1.32 [95% CI 1.25 to 1.40] in the original analysis) (Supplementary Table S4). Similarly, after excluding insulin initiators who were younger than 40 years, the adjusted HRs did not change for sulfonylurea initiators but reduced for insulin initiators (adjusted HR 1.26 [95% CI 1.19 to 1.34] versus 1.32 [95% CI 1.25 to 1.40] in the original analysis) (Supplementary Table S5). Furthermore, in sensitivity analysis where we censored patients at the first change in therapy, we found that adjusted HRs of hospital-treated infection increased for sulfonylurea

initators (adjusted HR 1.17 [95% CI 1.11 to 1.22] versus 1.09 [95% CI 1.05 to 1.13] in the original analysis) and for insulin initiators (adjusted HR 1.50 [95% CI 1.40 to 1.60] versus 1.32 [95% CI 1.25 to 1.40] in the original analysis) (Supplementary Table S6). In sensitivity analysis where we considered time-varying exposure (as-treated approach) the adjusted HRs were much higher compared with HRs from intention-to-treat approach for sulfonylurea (adjusted HR 1.20 [95% CI 1.15 to 1.24] versus 1.09 [95% CI 1.05 to 1.13] in the original IIT analytic approach) and for insulin initiators (adjusted HR 1.63 [95% CI 1.55 to 1.72] versus 1.32 [95% CI 1.25 to 1.40] in the original ITT analytic approach) (Supplementary Table S7). Furthermore, we observed that any insulin combination therapies were strongly associated with risk of hospital-treated infections compared to metformin monotherapy (e.g. for metformin+insulin adjusted HR was 1.33 [95% CI 1.21 to 1.46], and for insulin+sulfonylurea adjusted HR was 2.02 [95% CI 1.62 to 2.52] but for metformin+sulfonylurea adjusted HR was 1.04 [95% CI 0.98 to 1.10]) (Supplementary Table S7).

DISCUSSION

In this study of patients with type 2 diabetes treated pharmacologically for the first time, we found high rates of community-based antibiotic treatment and hospitalizations for infection during follow-up. We also found that patients who initiated pharmacotherapy with insulin, and to less extent those who initiated sulfonylurea, were at increased risk of hospital-treated infection compared with those who initiated pharmacotherapy with metformin. In contrast, there was little difference in rates of community-based antibiotic use between initiators of different GLDs.

Our results corroborate findings from the Swedish study that reported an increased risk of hospitalization for infection among patients who initiated their pharmacotherapy with insulin alone (HR 1.37, 95% CI 1.26 to 1.50) or with other oral GLDs (other than metformin) (HR 1.16, 95% CI 1.04 to 1.28), compared with metformin.[9] Furthermore, our results are in line with the observed reduced odds of septicaemia in metformin users versus metformin never users (OR 0.80, 95% CI 0.77 to 0.83) and increased odds in sulfonylurea users versus sulfonylurea never users (OR 1.06, 95% CI 1.03 to 1.10) in the nationwide cohort of GLD-treated type 2 diabetes patients from Taiwan.[6] Few comparative studies have examined newer second-line GLDs.[25,26] Although statistically imprecise, our results are in line with those from a double-blind randomized study of 807 type 2 diabetes patients, in which 3% of patients treated with metformin and 6% of patients treated with DPP-4 inhibitors experienced an upper respiratory tract infection (URTI) event during a follow-up period of 52 weeks ($p > 0.05$).[26] Our results support a recent systematic review and meta-analysis of 19 randomized controlled trials that found no difference in risk of UTI (RR 0.86, 95% CI 0.51 to 1.45) between patients receiving DPP-4 inhibitors and those receiving metformin.[25]

Hyperglycaemia may be a risk factor for infections in patients with type 2 diabetes.[27–31] Therefore GLDs in theory might influence risk of infections via their different glucose-lowering mechanisms and effectiveness. Hyperglycaemia seems to weaken innate immunity via its negative influence on polymorphonuclear neutrophil function and intracellular bactericidal and opsonic activity.[32] Insulin is more effective in reducing blood glucose than sulfonylureas and metformin;[33] and insulin has been suggested to enhance innate and cell-mediated immunity[34] and promote macrophage function,[32,35]. This contrasts with our

observation that insulin initiators had the highest risk of infections. Other non-glycaemic effects of GLDs on the immune system might be at play.[32,34,36–37] It has been suggested that the 5' adenosine monophosphate-activated protein kinase activation property of metformin facilitates neutrophil-dependent bacterial uptake and killing associated with inhibition of neutrophil activation and chemotaxis.[36,37] This mechanism might contribute to the lower risk of infections in patients taking metformin versus insulin or sulfonylureas.[9] Apart from the inhibitory effect of sulfonylureas on inflammasome assembly, evidence is sparse on their association with immune regulation.[35] Thus, while the mechanisms underlying the association of different GLDs with infection remain unclear,[38] our results support metformin as the preferred first-line drug in treatment algorithms from the point of view of infections.

The main strengths of our study are its population-based design, the large nationwide cohort of patients with type 2 diabetes, and virtually no loss to follow-up (<1%). Use of high-quality medical databases to identify infections treated in the community and in the hospital setting ensured inclusion of nearly all diagnosed infections.

Nonetheless, observational studies of the comparative effects of diabetes drugs have several major methodological challenges.[39] Therefore; our results for different therapies should be interpreted with caution, bearing in mind the limitations of this routine registry-based study. A main limitation was lack of accurate data on clinical severity of diabetes, which might have led to residual confounding by indication.[40] Nevertheless, increased clinical severity of type 2 diabetes (including complications such as early signs of renal disease, or indicators of less insulin production), other contraindications to metformin, and/or anticipated worse glucose derangement may have led physicians to initiate treatment with sulfonylurea and particularly

insulin instead of metformin. This may be supported by our observation that sulfonylurea and insulin initiators had more subsequent therapy shifts than metformin initiators, possibly related to glycaemic control problems. However, our regional subcohort analysis suggested that differences in pre-treatment HbA_{1c} (highest with insulin initiation) did not explain observed drug differences. It is also possible that a pre-existing predisposition to infections may have led physicians to choose insulin versus other drugs as initial pharmacotherapy. Furthermore, unmeasured confounding due to combination of other factors such as those related to unhealthy lifestyle and less social support might have influenced the risk of infections. Our sensitivity analyses suggested that the observed weak associations between non-metformin GLDs and increased antibiotic use may have been explained by differences in smoking, although on the other hand, differences in BMI and baseline HbA_{1c} may have led to an underestimation of the associations. Finally, we chose intention-to-treat approach as the primary analysis instead of as-treated approach, which is the approach of choice for pharmacoepidemiological studies. The intention-to-treat approach has the advantage of less bias by informative censoring or indication for treatment change, but it leads to conservative bias due to increasing exposure misclassification during follow-up. We therefore used alternative as-treated approaches as well, and found that the adjusted HRs associated with GLDs compared with metformin further increased, not changing our overall conclusions. Overall, we observed that 20% and 33% patients altered the initiated therapy to another regimen during the entire follow-up for community-based antibiotic prescription outcome and hospital-treated infection outcome, respectively. These were more like to be insulin or sulfonylurea initiators.

Our results for infections treated in the hospital suggest either increased severity of infections associated with specific GLDs, or a lower threshold for hospitalizing a patient with a given infection, *e.g.,* due to anticipated problems with glycaemic control or more comorbidity/frailty among patients in these treatment groups (surveillance bias). However, since we observed consistent results for hospitalizations for severe infections, such as septicaemia, for which all patients are likely to receive inpatient care, it is unlikely that our results can be explained by increased surveillance alone. As well, the initial GLD therapy choice may be altered, which may lead to increasing exposure misclassification with longer follow-up periods. However, we observed that less than one quarter of our patients changed therapy within the first year of commencing treatment with an anti-diabetic drug. Changes were most likely for patients treated with insulin and sulfonylurea and thus unlikely to explain their increased infection risk compared with metformin users.

In conclusion, the present study provides evidence that rates of infection are high in type 2 diabetes patients during early treatment, and that pharmacotherapy initiation with metformin may be associated with reduced risk of hospital-treated infections, compared with other GLDs.

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revised the manuscript for intellectual content and approved the final version for submission. AM is the guarantor of this work and, as such, had full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical approval: The Danish Data Protection Agency approved the study (records no. 2012-41-0793 and 2013-41-1924). As this registry-based study did not include human biological material, approval by the Danish Scientific Ethical Committee was not needed, according to Danish legislation.

Transparency declaration: AM affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data are available.

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Table 1. Baseline characteristics of 131 949 patients with type 2 diabetes, according to initial pharmacotherapy with glucose-lowering drugs (2005-2012).

Characteristics	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other	Total
***n* (%)[a]**	106 424 (81)	16 703 (13)	7293 (6)	553 (<1)	358 (<1)	295(<1)	231(<1)	92(<1)	131 949 (100)
Sex									
Men	59 213 (56)	9879 (59)	4421 (61)	355 (64)	212 (59)	126 (43)	128 (55)	57 (62)	74 391 (56)
Women	47 211 (44)	6824 (41)	3872 (39)	198 (36)	146 (41)	169 (57)	103 (45)	35 (38)	57 558 (44)
Age in years									
Median age (IQR)	62 (52, 70)	67 (57, 76)	56 (43, 68)	62 (52, 70)	67 (56, 76)	52 (44, 61)	62 (53, 72)	58 (46, 69)	62 (52, 70)
Age-groups (years)									
30 – <50	22 611 (21)	2026 (12)	2728 (37)	124 (22)	41 (11)	128 (43)	49 (21)	28 (30)	27 735 (21)
50 – <70	58 184 (55)	7835 (47)	3050 (42)	291 (53)	182 (51)	143 (48)	116 (50)	43 (47)	69 844 (53)
>70	25 629 (24)	6842 (41)	1515 (21)	138 (25)	135 (38)	24 (8)	66 (29)	21 (23)	34 370 (26)
Year of study inclusion									
2005 – 2008	37 692 (35)	13 433 (80)	3702 (51)	181 (33)	123 (34)	5 (2)	174 (75)	53 (58)	55 363 (42)
2009 – 2012	68 732 (65)	3270 (20)	3591 (49)	372 (67)	235 (66)	290 (98)	57 (25)	39 (42)	76 586 (58)
Marital status									
Married	64 123 (61)	9630 (59)	4062 (58)	322 (59)	214 (60)	196 (66)	157 (69)	59 (64)	78 763 (60)
Never married	13 404 (13)	1271 (8)	1211 (17)	85 (16)	34 (10)	55 (19)	13 (6)	10 (11)	16 083 (12)
Divorced	15 457 (15)	2150 (13)	1080 (15)	85 (16)	46 (13)	32 (11)	22 (10)	17 (18)	18 889 (14)
Widowed	12 561 (12)	3269 (20)	701 (10)	55 (10)	60 (17)	12 (4)	36 (16)	6 (7)	16 700 (13)
CCI score									
Low (score of 0)	75 550 (71)	10 224 (61)	3953 (54)	385 (70)	202 (56)	207 (70)	154 (67)	54 (59)	90 729 (69)
Medium (scores of 1-2)	25 957 (24)	5035 (30)	2076 (28)	134 (24)	110 (31)	72 (24)	59 (26)	28 (30)	33 471 (25)
High (score ≥3)	4917 (5)	1444 (9)	1264 (17)	34 (6)	46 (13)	16 (5)	18 (8)	10 (11)	7749 (6)
Diabetes complications									
No complications	77 981 (73)	10 968 (66)	5024 (69)	417 (75)	204 (57)	237 (80)	168 (73)	71 (77)	95 070 (72)
Microvascular	6422 (6)	1423 (9)	729 (10)	33 (6)	31 (9)	16 (5)	22 (10)	6 (7)	8682 (7)
Macrovascular	22 021 (21)	4312 (26)	1540 (21)	103 (19)	123 (34)	42 (14)	41 (18)	15 (16)	28 197 (21)
Alcoholism-related conditions	2651 (2)	595 (4)	742 (10)	12 (2)	17 (5)	4 (2)	10 (4)	3 (3)	4034 (3)
Hospital-diagnosed obesity	9566 (9)	602 (4)	528 (7)	46 (8)	28 (8)	79 (27)	7 (3)	17 (18)	10 873 (8)

Characteristics	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other	Total
Hospital outpatient follow-up in 1st year after study inclusion	16 463 (15)	3502 (21)	1695 (23)	86 (16)	62 (17)	18 (6)	33 (14)	11 (12)	21 870 (17)
Therapy change during follow-up	30 845 (29)	9977 (60)	2353 (32)	259 (47)	173 (48)	48 (16)	135 (58)	41 (45)	43 831 (33)
Therapy change within 1 year	16 530 (16)	3618 (22)	1752 (24)	140 (25)	122 (34)	31 (11)	62 (27)	23 (25)	22 278 (17)
Therapy change within 2 years	21 877 (21)	5581 (33)	1970 (27)	184 (33)	147 (41)	45 (15)	86 (37)	33 (36)	29 923 (23)
Acute hospitalization within 6 months	9 486 (9)	2 616 (16)	4 993 (68)	33 (6)	53 (15)	15 (5)	16 (7)	11 (12)	17 223 (13)
Infection-hospitalization within 6-months	1 265 (1)	401 (2)	443 (6)	8 (1)	16 (4)	4 (1)	8 (3)	5 (5)	2 150 (2)
No. of patients with HbA_{1c} measurement	27 200 (56)	4576 (59)	1649 (61)	164 (64)	115 (59)	35 (43)	34 (55)	22 (62)	33 795 (56)
Median % HbA_{1c} (IQR)	7.1 (6.5, 8.3)	7.6 (6.9, 9.2)	10.1 (7.5, 12.1)	8.3 (7.0, 10.6)	7.0 (6.5, 7.7)	6.4 (6.0, 7.3)	7.1 (6.1, 7.9)	7.0 (5.9, 7.8)	7.2 (6.6, 8.7)
Other medication use									
Statins	50 817 (48)	6230 (37)	1522 (21)	230 (42)	167 (47)	80 (27)	63 (27)	24 (26)	59 163 (45)
Immunosuppressants	669 (1)	134 (1)	85 (1)	2 (<1)	3 (1)	4 (1)	2 (1)	5 (5)	904 (1)
Corticosteroids	3825 (4)	1163 (7)	1044 (14)	20 (4)	21 (6)	11 (4)	15 (6)	6 (7)	6105 (5)

Abbreviations: CCI, Charlson Comorbidity Index; IQR, inter-quartile range; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

[a]Parentheses contain percentages unless otherwise specified.

Table 2. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes, according to drug category.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	61 055	12 462	4434	317	213	146	183	64
Crude HR (95% CI)	1.00 (referent)	1.06 (1.04 to 1.08)	1.13 (1.09 to 1.16)	1.03 (0.92 to 1.15)	1.16 (1.01 to 1.32)	1.31 (1.12 to 1.55)	1.07 (0.92 to 1.24)	1.17 (0.92 to 1.50)
Model 1[a] HR (95% CI)	1.00 (referent)	1.05 (1.03 to 1.07)	1.18 (1.15 to 1.22)	1.06 (0.95 to 1.18)	1.16 (1.01 to 1.32)	1.29 (1.09 to 1.51)	1.06 (0.92 to 1.23)	1.17 (0.92 to 1.50)
Model 2[b] HR (95% CI)	1.00 (referent)	1.02 (1.00 to 1.04)	1.04 (1.01 to 1.07)	1.04 (0.93 to 1.16)	1.11 (0.97 to 1.27)	1.20 (1.02 to 1.41)	1.01 (0.87 to 1.17)	1.07 (0.84 to 1.36)
Model 3[c] HR (95% CI)	1.00 (referent)	1.01 (0.99 to 1.03)	0.99 (0.96 to 1.03)	1.05 (0.94 to 1.17)	1.10 (0.96 to 1.26)	1.20 (1.02 to 1.41)	1.00 (0.87 to 1.16)	1.06 (0.83 to 1.36)
Hospital-treated infections								
No. of events	13 949	4350	1785	74	53	18	61	18
Crude HR (95% CI)	1.00 (referent)	1.41 (1.36 to 1.46)	1.96 (1.87 to 2.06)	1.06 (0.85 to 1.34)	1.28 (0.98 to 1.68)	0.85 (0.54 to 1.36)	1.40 (1.09 to 1.79)	1.29 (0.81 to 2.05)
Model 1[a] HR (95% CI)	1.00 (referent)	1.20 (1.16 to 1.24)	2.28 (2.17 to 2.39)	1.05 (0.84 to 1.33)	1.14 (0.87 to 1.49)	1.05 (0.66 to 1.66)	1.34 (1.04 to 1.72)	1.28 (0.81 to 2.03)
Model 2[b] HR (95% CI)	1.00 (referent)	1.12 (1.08 to 1.16)	1.63 (1.54 to 1.72)	1.03 (0.82 to 1.30)	1.05 (0.80 to 1.38)	0.93 (0.58 to 1.47)	1.27 (0.98 to 1.64)	1.04 (0.66 to 1.65)
Model 3[c] HR (95% CI)	1.00 (referent)	1.09 (1.05 to 1.13)	1.32 (1.25 to 1.40)	1.04 (0.82 to 1.31)	1.03 (0.79 to 1.35)	0.95 (0.60 to 1.51)	1.30 (1.00 to 1.67)	0.99 (0.62 to 1.57)

[a]Model 1 adjusted for age and sex.
[b]Model 2 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs
[c]Model 3 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Figure 1. Kaplan–Meier curves showing cumulative rates of community-based antibiotic prescriptions and hospital-treated infections as percentages within the first 4 years following treatment initiation with metformin, sulfonylurea, or insulin.

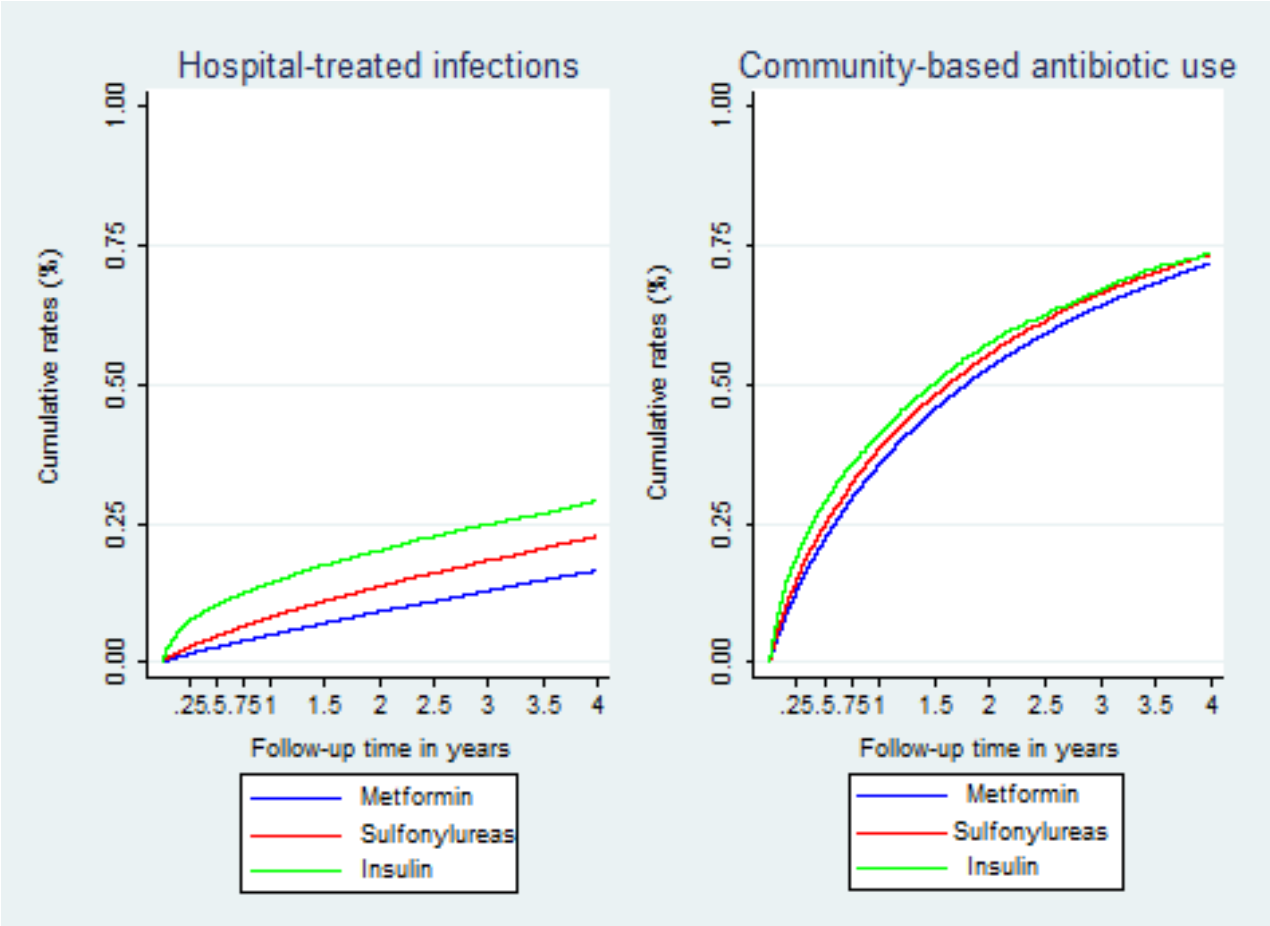
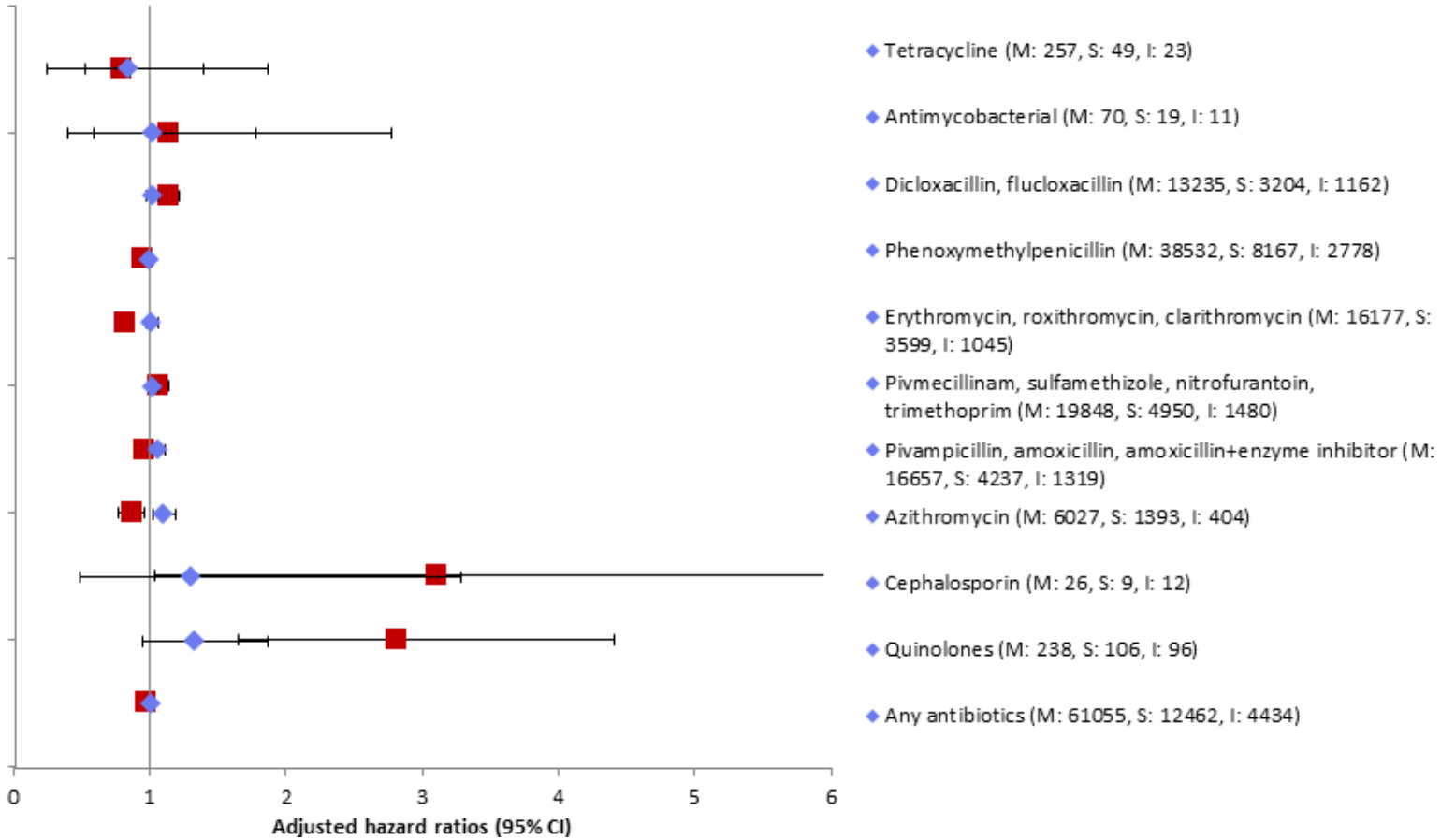
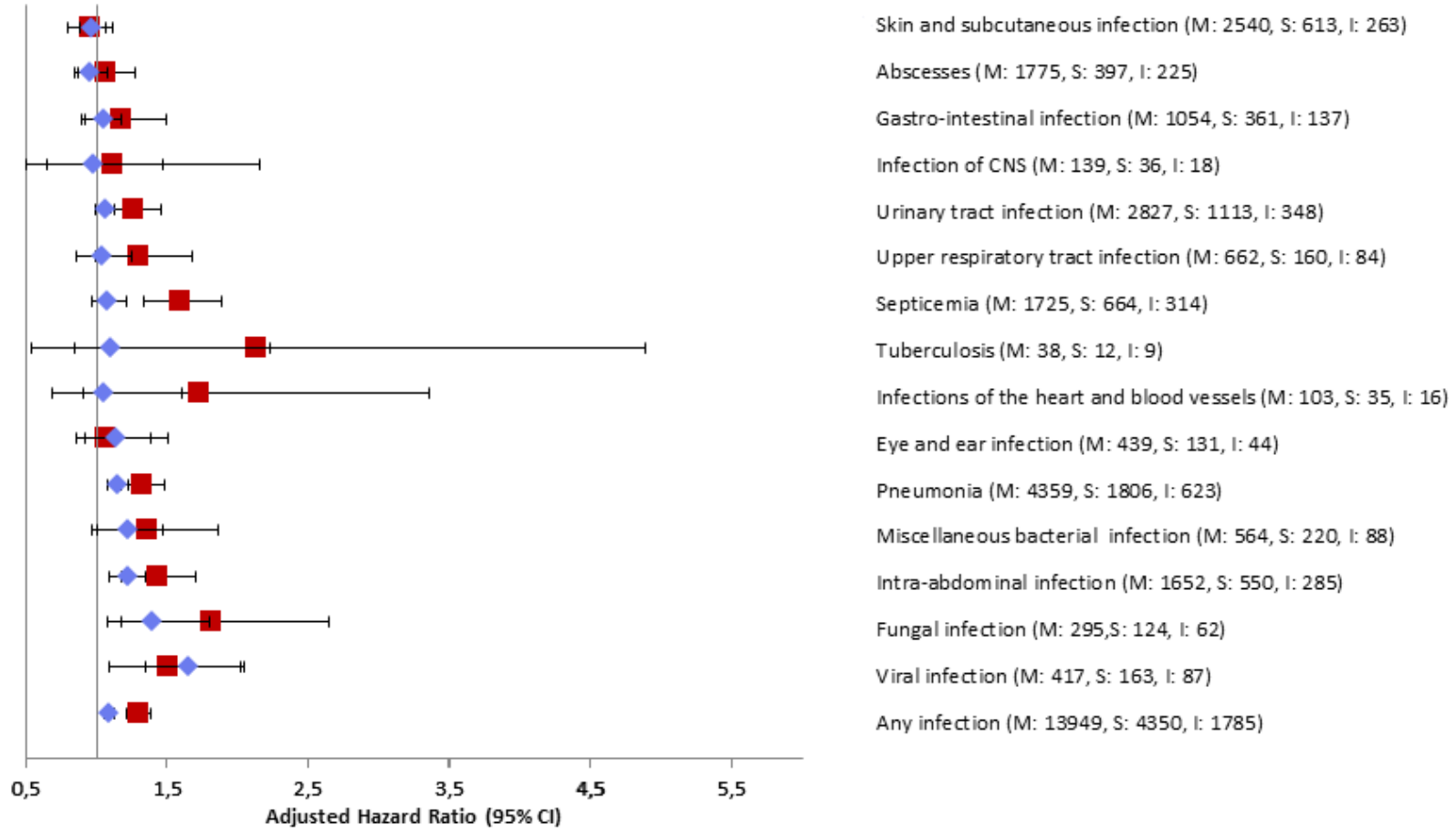


Figure 2. Adjusted hazard ratios of specific antibiotic therapies associated with pharmacotherapy initiation with sulfonylureas vs. metformin (shown as blue diamonds) and insulin vs. metformin (shown as red squares), in patients with type 2 diabetes.



M, S, and I denote total number or hospital-treated infections in Metformin, Sulfonylurea, and Insulin initiators, respectively.

Figure 3. Adjusted hazard ratios of specific hospital-treated infections associated with pharmacotherapy initiation with sulfonylureas vs. metformin (shown as blue diamonds) and insulin vs. metformin (shown as red squares), in patients with type 2 diabetes.



M, S, and I denote total number or hospital-treated infections in Metformin, Sulfonylurea, and Insulin initiators, respectively.

Supplementary Table S1. Incidence rates of infections per 1000 patient-years at risk (PYAR) by categories of glucose-lowering drugs.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other	Total
n	106 424	16 703	7293	553	358	295	231	92	131 949
Antibiotic use in the community									
Number of infections (%)	61 055 (57)	12 462 (75)	4434 (61)	317 (57)	213 (60)	146 (49)	183 (79)	64 (70)	78 874 (60)
PYAR	169 337	35 320	11 192	837	497	262	522	155	218 032
Median follow-up in years (IQR)	1.1 (0.4 to 2.3)	1.4 (0.4 to 3.3)	0.8 (0.2 to 2.3)	1.1 (0.4 to 2.2)	1.0 (0.3 to 2.1)	0.7 (0.3 to 1.3)	1.6 (0.5 to 3.5)	1.0 (0.4 to 2.5)	1.1 (0.4 to 2.4)
IR /1000 PYAR (95% CI)	360.6 (357.7 to 363.4)	353.7 (347.6 to 360.0)	396.2 (384.7 to 408.0)	378.8 (339.3 to 422.9)	428.4 (374.6 to 490.0)	558.2 (474.6 to 656.5)	350.4 (303.1 to 405.0)	411.8 (322.3 to 526.2)	361.8 (359.2 to 364.3)
Hospital-treated infections									
Number of infections (%)	13 949 (13)	4350 (26)	1785 (24)	74 (13)	53 (15)	18 (6)	61 (26)	18 (20)	20 308 (15)
PYAR	301 895	69 378	19 818	1494	881	412	984	307	395 171
Median follow-up in yrs (IQR)	2.4 (1.1 to 4.3)	4.4 (2.1 to 6.2)	2.2 (0.5 to 4.5)	2.4 (1.2 to 4.0)	2.2 (0.9 to 4.1)	1.3 (0.6 to 2.0)	4.4 (2.1 to 6.7)	2.9 (1.5 to 5.5)	2.6 (1.1 to 4.6)
IR /1000 PYAR (95% CI)	46.2 (45.4 to 7.0)	62.7 (60.9 to 64.6)	90.1 (86.0 to 94.4)	49.5 (39.4 to 62.2)	60.1 (45.9 to 78.7)	43.7 (27.5 to 69.3)	62.0 (48.2 to 79.6)	58.5 (36.9 to 92.9)	51.4 (50.7 to 52.1)

Abbreviations: IR, incidence rates; CI, confidence interval; PYAR, patient-years at risk; IQR, inter-quartile range; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1

Supplementary Table S2. Hazard ratios (HRs) of antibiotic use in the community associated with pharmacotherapy initiation with specific glucose-lowering drugs in patients with type 2 diabetes.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Overall								
No. of events	61 055	12 462	4434	317	213	146	183	64
Crude HR (95% CI)	1.00 (referent)	1.06 (1.04 to 1.08)	1.13 (1.09 to 1.16)	1.03 (0.92 to 1.15)	1.16 (1.01 to 1.32)	1.31 (1.12 to 1.55)	1.07 (0.92 to 1.24)	1.17 (0.92 to 1.50)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.01 (0.99 to 1.03)	0.99 (0.96 to 1.03)	1.05 (0.94 to 1.17)	1.10 (0.96 to 1.26)	1.20 (1.02 to 1.41)	1.00 (0.87 to 1.16)	1.06 (0.83 to 1.36)
Phenoxymethylpenicillin								
No. of events	38 532	8 167	2778	182	128	76	123	41
Crude HR (95% CI)	1.00 (referent)	1.00 (0.98 to 1.03)	1.09 (1.05 to 1.13)	0.89 (0.77 to 1.03)	1.09 (0.92 to 1.30)	1.18 (0.94 to 1.48)	1.05 (0.88 to 1.25)	1.12 (0.82 to 1.52)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.00 (0.98 to 1.03)	0.96 (0.91 to 1.00)	0.90 (0.77 to 1.04)	1.09 (0.92 to 1.30)	1.10 (0.88 to 1.38)	1.01 (0.84 to 1.21)	1.03 (0.76 to 1.40
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor								
No. of events	16 657	4237	1319	91	62	30	46	28
Crude HR (95% CI)	1.00 (referent)	1.15 (1.12 to 1.19)	1.16 (1.10 to 1.23)	1.10 (0.90 to 1.36)	1.25 (0.97 to 1.61)	1.18 (0.82 to 1.69)	0.85 (0.64 to 1.14)	1.79 (1.24 to 2.60)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.06 (1.02 to 1.10)	0.99 (0.93 to 1.05)	1.10 (0.89 to 1.35)	1.09 (0.85 to 1.40)	1.10 (0.77 to 1.57)	0.81 (0.60 to 1.08)	1.63 (1.12 to 2.36)
Macrolides								
Azithromycin								
No. of events	6027	1393	404	42	28	18	26	7
Crude HR (95% CI)	1.00 (referent)	1.02 (0.97 to 1.09)	0.97 (0.88 to 1.07)	1.40 (1.04 to 1.90)	1.57 (1.08 to 2.27)	2.06 (1.30 to 3.28)	1.37 (0.93 to 2.01)	1.12 (0.53 to 2.35)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.10 (1.03 to 1.17)	0.90 (0.80 to 1.00)	1.43 (1.05 to 1.94)	1.61 (1.11 to 2.32)	1.76 (1.10 to 2.79)	1.34 (0.91 to 1.97)	1.04 (0.50 to 2.19)
Erythromycin, roxithromycin, clarithromycin								
No. of events	16 177	3599	1045	83	68	33	54	22
Crude HR (95% CI)	1.00 (referent)	1.00 (0.96 to 1.03)	0.93 (0.87 to 0.98)	1.02 (0.82 to 1.27)	1.46 (1.15 to 1.85)	1.36 (0.97 to 1.92)	1.04 (0.80 to 1.36)	1.40 (0.92 to 2.13)

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Adjusted[a] HR (95% CI)	1.00 (referent)	1.00 (0.97 to 1.04)	0.83 (0.78 to 0.89)	1.07 (0.86 to 1.32)	1.41 (1.11 to 1.79)	1.17 (0.83 to 1.65)	1.01 (0.77 to 1.32)	1.29 (0.85 to 1.96)
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim								
No. of events	19 848	4950	1480	105	72	40	78	15
Crude HR (95% CI)	1.00 (referent)	1.19 (1.15 to 1.23)	1.10 (1.04 to 1.16)	1.03 (0.85 to 1.25)	1.19 (0.95 to 1.51)	1.18 (0.86 to 1.61)	1.36 (1.09 to 1.70)	0.73 (0.44 to 1.21)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.02 (0.99 to 1.06)	1.08 (1.02 to 1.15)	1.11 (0.91 to 1.34)	1.02 (0.80 to 1.28)	1.14 (0.84 to 1.55)	1.26 (1.01 to 1.58)	0.66 (0.40 to 1.09)
Dicloxacillin, flucloxacillin								
No. of events	13 235	3204	1162	82	48	17	39	15
Crude HR (95% CI)	1.00 (referent)	1.06 (1.02 to 1.11)	1.30 (1.23 to 1.39)	1.27 (1.02 to 1.58)	1.20 (0.90 to 1.59)	0.87 (0.54 to 1.40)	0.89 (0.65 to 1.22)	1.11 (0.67 to 1.83)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.03 (0.60 to 1.76)	1.21 (0.55 to 1.67)	-	-	-	-	-
Antimycobacterial								
No. of events	70	19	11	0	0	2	1	0
Crude HR (95% CI)	1.00 (referent)	1.14 (0.69 to 1.91)	2.24 (1.19 to 4.23)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.03 (0.60 to 1.76)	1.21 (0.55 to 2.66)	-	-	-	-	-
Quinolones								
No. of events	238	106	96	2	1	0	2	1
Crude HR (95% CI)	1.00 (referent)	1.98 (1.57 to 2.49)	5.83 (4.59 to 7.38)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.36 (1.06 to 1.75)	3.27 (2.43 to 4.39)	-	-	-	-	-
Tetracycline								
No. of events	257	49	23	0	0	4	0	0
Crude HR (95% CI)	1.00 (referent)	0.82 (0.60 to 1.11)	1.28 (0.83 to 1.96)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	0.85 (0.62 to 1.18)	0.77 (0.48 to 1.25)	-	-	-	-	-
Cephalosporin								
No. of events	26	9	12	0	0	0	0	0

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Crude HR (95% CI)	1.00 (referent)	1.49 (0.69 to 3.19)	6.64 (3.35 to 13.17)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.38 (0.59 to 3.21)	4.23 (1.75 to 10.24)	-	-	-	-	-

[a]Adjusted for age, sex, comorbidity (CCI score), microvascular and macrovascular diabetes complications not covered in the CCI, diabetes duration, hospital-diagnosed obesity, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S3. Patient subcohort (n = 33 795) with information on HbA_{1c}. Hazard ratios (HRs) of infection associated with initial glucose-lowering drug use in patients with type 2 diabetes, according to drug categories.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	14 757	3393	972	101	72	16	25	12
Crude HR (95% CI)	1.00 (referent)	1.12 (1.08 to 1.16)	1.13 (1.06 to 1.21)	1.11 (0.91 to 1.35)	1.30 (1.03 to 1.64)	1.44 (0.88 to 2.36)	1.12 (0.76 to 1.66)	0.95 (0.54 to 1.68)
Model 1[a] HR (95% CI)	1.00 (referent)	1.09 (1.05 to 1.13)	1.20 (1.13 to 1.29)	1.16 (0.95 to 1.41)	1.26 (1.00 to 1.59)	1.42 (0.87 to 2.32)	1.14 (0.77 to 1.68)	0.89 (0.50 to 1.56)
Model 2[b] HR (95% CI)	1.00 (referent)	1.04 (1.00 to 1.08)	0.98 (0.91 to 1.06)	1.18 (0.97 to 1.44)	1.19 (0.94 to 1.50)	1.30 (0.80 to 2.12)	1.04 (0.70 to 1.54)	0.82 (0.46 to 1.44)
Model 3[c] HR (95% CI)	1.00 (referent)	1.04 (1.00 to 1.09)	1.02 (0.95 to 1.10)	1.21 (0.99 to 1.47)	1.19 (0.94 to 1.50)	1.31 (0.80 to 2.14)	1.04 (0.70 to 1.54)	0.79 (0.45 to 1.40)
Hospital-treated infections								
No. of events	3019	1100	409	22	16	5	6	3
Crude HR (95% CI)	1.00 (referent)	1.47 (1.37 to 1.58)	2.27 (2.04 to 2.52)	1.14 (0.75 to 1.74)	1.30 (0.80 to 2.13)	2.25 (0.94 to 5.41)	1.30 (0.58 to 2.89)	1.25 (0.40 to 3.87)
Model 1[a] HR (95% CI)	1.00 (referent)	1.25 (1.16 to 1.34)	2.68 (2.41 to 2.97)	1.18 (0.77 to 1.79)	1.12 (0.68 to 1.83)	2.68 (1.11 to 6.44)	1.25 (0.56 to 2.79)	1.06 (0.34 to 3.30)
Model 2[b] HR (95% CI)	1.00 (referent)	1.14 (1.06 to 1.23)	1.61 (1.43 to 1.82)	1.21 (0.78 to 1.86)	0.94 (0.56 to 1.56)	2.45 (1.02 to 5.91)	1.12 (0.50 to 2.50)	0.88 (0.28 to 2.74)
Model 3[c] HR (95% CI)	1.00 (referent)	1.14 (1.05 to 1.23)	1.67 (1.47 to 1.89)	1.22 (0.80 to 1.88)	0.94 (0.56 to 1.56)	2.49 (1.03 to 6.00)	1.02 (0.46 to 2.29)	0.86 (0.28 to 2.66)

[a]Model 1 adjusted for age and sex.

[b]Model 2 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

[c]Model 3 adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, calendar period of study inclusion, and HbA_{1c} categories (with 5.5%-6.5% as reference).

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table 4. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes, according to drug category using updated CCI instead of original CCI in multivariate model.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	61 055	12 462	4434	317	213	146	183	64
Crude HR (95% CI)	1.00 (referent)	1.06 (1.04 to 1.08)	1.13 (1.09 to 1.16)	1.03 (0.92 to 1.15)	1.16 (1.01 to 1.32)	1.31 (1.12 to 1.55)	1.07 (0.92 to 1.24)	1.17 (0.92 to 1.50)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.01 (0.99 to 1.03)	0.98 (0.95 to 1.02)	1.06 (0.95 to 1.19)	1.09 (0.95 to 1.24)	1.23 (1.04 to 1.44)	1.01 (0.87 to 1.16)	1.10 (0.86 to 1.40)
Hospital-treated infections								
No. of events	13 949	4350	1785	74	53	18	61	18
Crude HR (95% CI)	1.00 (referent)	1.41 (1.36 to 1.46)	1.96 (1.87 to 2.06)	1.06 (0.85 to 1.34)	1.28 (0.98 to 1.68)	0.85 (0.54 to 1.36)	1.40 (1.09 to 1.79)	1.29 (0.81 to 2.05)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.09 (1.05 to 1.14)	1.30 (1.23 to 1.38)	1.07 (0.85 to 1.35)	1.01 (0.77 to 1.33)	0.98 (0.62 to 1.56)	1.35 (1.04 to 1.73)	1.10 (0.69 to 1.74)

[a]Adjusted for age, sex, comorbidity (CCI score), microvascular and macrovascular diabetes complications not covered in the CCI, diabetes duration, hospital-diagnosed obesity, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S5. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes excluding insulin users younger than 40 years, according to drug category.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	61 055	12 462	3517	317	213	146	183	64
Crude HR (95% CI)	1.00 (referent)	1.06 (1.04 to 1.08)	1.18 (1.14 to 1.22)	1.03 (0.92 to 1.15)	1.16 (1.01 to 1.32)	1.31 (1.12 to 1.55)	1.07 (0.92 to 1.24)	1.17 (0.92 to 1.50)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.01 (0.99 to 1.03)	0.99 (0.95 to 1.03)	1.05 (0.94 to 1.17)	1.10 (0.96 to 1.26)	1.20 (1.02 to 1.42)	1.00 (0.87 to 1.16)	1.06 (0.83 to 1.36)
Hospital-treated infections								
No. of events	13 949	4350	1542	74	53	18	61	18
Crude HR (95% CI)	1.00 (referent)	1.40 (1.36 to 1.46)	2.24 (2.13 to 2.37)	1.07 (0.85 to 1.34)	1.29 (0.98 to 1.68)	0.86 (0.54 to 1.36)	1.39 (1.08 to 1.79)	1.29 (0.81 to 2.05)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.09 (1.05 to 1.13)	1.26 (1.19 to 1.34)	1.04 (0.82 to 1.31)	1.03 (0.78 to 1.35)	0.96 (0.61 to 1.53)	1.29 (1.00 to 1.67)	0.99 (0.62 to 1.57)

[a]Adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S6. Hazard ratios (HRs) of infection associated with initial use of glucose-lowering drugs in patients with type 2 diabetes who were censored at the first change in the initial therapy, according to drug category.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use								
No. of events	50 220	9163	3376	1054	158	127	122	43
Crude HR (95% CI)	1.00 (referent)	1.09 (1.06 to 1.11)	1.16 (1.12 to 1.20)	1.10 (1.03 to 1.17)	1.27 (1.08 to 1.48)	1.24 (1.04 to 1.48)	1.04 (0.87 to 1.24)	1.15 (0.86 to 1.56)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.02 (1.00 to 1.04)	0.99 (0.55 to 1.03)	1.09 (1.03 to 1.16)	1.20 (1.03 to 1.41)	1.13 (0.95 to 1.34)	0.96 (0.82 to 1.17)	1.01 (0.75 to 1.36)
Hospital-treated infections								
No. of events	10 109	2860	1402	209	33	14	44	10
Crude HR (95% CI)	1.00 (referent)	1.60 (1.53 to 1.67)	2.29 (2.16 to 2.42)	1.37 (1.19 to 1.57)	1.34 (0.95 to 1.89)	0.80 (0.48 to 0.36)	1.85 (1.38 to 2.49)	1.30 (0.70 to 2.41)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.17 (1.11 to 1.22)	1.50 (1.40 to 1.60)	1.20 (1.04 to 1.38)	1.06 (0.76 to 1.50)	0.88 (0.52 to 1.49)	1.71 (1.27 to 2.31)	0.98 (0.53 to 1.82)

[a]Model adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S7. As-treated approach: Hazard ratios (HRs) of infection associated with use of single glucose-lowering drugs in patients with type 2 diabetes, according to drug category.

	Metformin	Sulfonylurea	Insulin	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Community-based antibiotic use							
No. of events	52 996	11 001	4333	384	250	184	81
Crude HR (95% CI)	1.00 (referent)	1.10 (1.08 to 1.12)	1.15 (1.11 to 1.18)	1.17 (1.06 to 1.30)	1.27 (1.12 to 1.44)	1.18 (1.02 to 1.36)	1.13 (0.91 to 1.40)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.04 (1.02 to 1.07)	1.03 (1.00 to 1.07)	1.11 (1.01 to 1.23)	1.20 (1.06 to 1.35)	1.11 (0.96 to 1.29)	1.04 (0.83 to 1.29)
Hospital-treated infections							
No. of events	11 253	36265	1973	132	71	71	21
Crude HR (95% CI)	1.00 (referent)	1.58 (1.53 to 1.64)	2.17 (2.07 to 2.27)	1.50 (1.26 to 1.78)	1.18 (0.93 to 1.50)	1.87 (1.48 to 2.37)	1.18 (0.77 to 1.81)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.20 (1.15 to 1.24)	1.63 (1.55 to 1.72)	1.26 (1.06 to 1.50)	1.26 (1.00 to 1.60)	1.71 (1.35 to 2.16)	0.98 (0.64 to 1.51)

[a]Adjusted for age, sex, comorbidity (CCI score), microvascular and macrovascular diabetes complications not covered in the CCI, diabetes duration, hospital-diagnosed obesity, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S7 continued. As-treated approach: Hazard ratios (HRs) of infection associated with use of combination glucose-lowering drugs in patients with type 2 diabetes, according to various combination drug categories.

	Metformin	Metformin+Sulfonylurea	Metformin+Insulin	Insulin+Sulfonylurea	Other combinations
Community-based antibiotic use					
No. of events	52 996	4681	1326	175	3458
Crude HR (95% CI)	1.00 (referent)	0.99 (0.96 to 1.02)	1.13 (1.07 to 1.19)	1.71 (1.47 to 1.98)	0.99 (0.96 to 1.03)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.01 (0.98 to 1.04)	1.10 (1.04 to 1.17)	1.49 (1.28 to 1.73)	1.02 (0.99 to 1.06)
Hospital-treated infections					
No. of events	11 253	1383	504	84	1191
Crude HR (95% CI)	1.00 (referent)	1.06 (1.00 to 1.12)	1.46 (1.33 to 1.59)	3.03 (2.45 to 3.76)	1.01 (0.95 to 1.08)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.04 (0.98 to 1.10)	1.33 (1.21 to 1.46)	2.02 (1.62 to 2.52)	1.07 (1.01 to 1.14)

[a]Adjusted for age, sex, comorbidity (CCI score), hospital-diagnosed obesity, alcoholism-related conditions, marital status, microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.

Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Supplementary Table S8. Hazard ratios (HRs) of hospital-treated infection associated with pharmacotherapy initiation with specific glucose-lowering drugs in patients with type 2 diabetes.

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Overall								
No. of events	13 949	4350	1785	74	53	18	61	18
Crude HR (95% CI)	1.00 (referent)	1.41 (1.36 to 1.46)	1.96 (1.87 to 2.06)	1.06 (0.85 to 1.34)	1.28 (0.98 to 1.68)	0.85 (0.54 to 1.36)	1.40 (1.09 to 1.79)	1.29 (0.81 to 2.05)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.09 (1.05 to 1.13)	1.32 (1.25 to 1.40)	1.04 (0.82 to 1.31)	1.03 (0.79 to 1.35)	0.95 (0.60 to 1.51)	1.30 (1.00 to 1.67)	0.99 (0.62 to 1.57)
Eye and ear infections								
No. of events	439	131	44	0	1	1	3	0
Crude HR (95% CI)	1.00 (referent)	1.31 (1.08 to 1.60)	1.46 (1.07 to 1.99)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.14 (0.92 to 1.40)	1.09 (0.76 to 1.55)	-	-	-	-	-
Upper respiratory tract infections								
No. of events	662	160	84	4	3	2	1	1
Crude HR (95% CI)	1.00 (referent)	1.00 (0.84 to 1.19)	1.80 (1.44 to 2.26)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.04 (0.86 to 1.25)	1.31 (1.00 to 1.70)	-	-	-	-	-
Pneumonia								
No. of events	4359	1806	623	23	19	3	26	5
Crude HR (95% CI)	1.00 (referent)	1.78 (1.68 to 1.88)	2.06 (1.90 to 2.24)	1.06 (0.70 to 1.60)	1.49 (0.95 to 2.33)	-	1.80 (1.23 to 2.65)	1.10 (0.46 to 2.66)
Adjusted[a] HR (95% CI)	1.00 (referent)	1.15 (1.08 to 1.22)	1.36 (1.23 to 1.50)	1.05 (0.70 to 1.58)	1.04 (0.66 to 1.62)	-	1.63 (1.10 to 2.41)	0.78 (0.33 to 1.88)
Infections of the heart and blood vessels								
No. of events	103	35	16	0	1	0	2	1
Crude HR (95% CI)	1.00 (referent)	1.43 (0.97 to 2.10)	2.21 (1.30 to 3.74)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.07 (0.71 to 1.62)	2.14 (1.14 to 4.02)	-	-	-	-	-
Gastrointestinal tract infections								

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
No. of events	1054	361	137	6	10	1	5	1
Crude HR (95% CI)	1.00 (referent)	1.41 (1.25 to 1.59)	1.85 (1.54 to 2.21)	1.16 (0.52 to 2.59)	3.31 (1.78 to 6.17)	-	1.37 (0.57 to 3.29)	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.05 (0.92 to 1.20)	1.21 (0.98 to 1.48)	1.19 (0.53 to 2.65)	2.39 (1.24 to 4.61)	-	1.29 (0.53 to 3.10)	-
Intra-abdominal infections								
No. of events	1652	550	285	7	3	1	6	1
Crude HR (95% CI)	1.00 (referent)	1.46 (1.33 to 1.61)	2.52 (2.22 to 2.86)	0.84 (0.40 to 1.77)	-	-	1.12 (0.50 to 2.49)	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.22 (1.10 to 1.36)	1.45 (1.25 to 1.68)	0.86 (0.41 to 1.80)	-	-	1.01 (0.45 to 2.25)	-
Urinary tract infections								
No. of events	2827	1113	348	21	12	4	11	3
Crude HR (95% CI)	1.00 (referent)	1.68 (1.56 to 1.80)	1.77 (1.58 to 1.98)	1.50 (0.98 to 2.31)	1.44 (0.82 to 2.54)	-	1.15 (0.63 to 2.07)	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.05 (0.97 to 1.13)	1.25 (1.10 to 1.42)	1.47 (0.95 to 2.29)	0.94 (0.52 to 1.69)	-	1.04 (0.57 to 1.88)	-
Infections of the central nervous system								
No. of events	139	36	18	1	0	1	2	0
Crude HR (95% CI)	1.00 (referent)	1.08 (0.74 to 1.56)	1.83 (1.12 to 3.00)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	0.98 (0.66 to 1.45)	1.14 (0.64 to 2.03)	-	-	-	-	-
Meningococcal infection								
No. of events	9	1	2	0	0	0	0	0
Crude HR (95% CI)	1.00 (referent)	-	-	-	-	-	-	
Adjusted[a] HR (95% CI)	1.00 (referent)	-	-	-	-	-	-	-
Skin and subcutaneous infections								
No. of events	2540	613	263	8	7	5	10	5
Crude HR (95% CI)	1.00 (referent)	1.02 (0.93 to 1.11)	1.48 (1.31 to 1.69)	0.63 (0.31 to 1.25)	0.94 (0.45 to 1.96)	1.46 (0.61 to 3.51)	1.16 (0.62 to 2.15)	1.83 (0.76 to 4.41)

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Adjusted[a] HR (95% CI)	1.00 (referent)	0.96 (0.87 to 1.05)	0.96 (0.83 to 1.11)	0.61 (0.31 to 1.22)	0.73 (0.33 to 1.62)	1.32 (0.55 to 3.18)	1.14 (0.61 to 2.12)	1.55 (0.65 to 3.74)
Abscesses								
No. of events	1775	397	225	6	4	3	7	1
Crude HR (95% CI)	1.00 (referent)	0.95 (0.85 to 1.06)	1.83 (1.59 to 2.10)	0.67 (0.30 to 1.50)	-	-	1.18 (0.56 to 2.47)	-
Adjusted[a] HR (95% CI)	1.00 (referent)	0.96 (0.86 to 1.08)	1.08 (0.92 to 1.27)	0.57 (0.24 to 1.37)	-	-	1.15 (0.54 to 2.41)	-
Septicaemia								
No. of events	1725	664	314	7	8	3	6	2
Crude HR (95% CI)	1.00 (referent)	1.59 (1.46 to 1.75)	2.59 (2.30 to 2.92)	0.82 (0.39 to 1.72)	1.61 (0.80 to 3.22)		-1.00 (0.45 to 2.34)	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.08 (0.98 to 1.19)	1.63 (1.41 to 1.89)	0.80 (0.39 to 1.69)	1.03 (0.56 to 2.26)	-	0.93 (0.42 to 2.08)	-
Tuberculosis								
No. of events	38	12	9	0	2	0	1	0
Crude HR (95% CI)	1.00 (referent)	1.37 (0.71 to 2.65)	3.40 (1.64 to 7.04)	-	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.08 (0.53 to 2.19)	2.13 (0.89 to 5.09)	-	-	-	-	-
Miscellaneous bacterial infections								
No. of events	564	220	88	5	2	1	0	1
Crude HR (95% CI)	1.00 (referent)	1.62 (1.38 to 1.89)	2.21 (1.77 to 2.77)	1.80 (0.75 to 4.34)	-	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.23 (1.04 to 1.46)	1.44 (1.10 to 1.88)	1.70 (0.71 to 4.11)	-	-	-	-
Viral infections								
No. of events	417	163	87	3	5	0	4	0
Crude HR (95% CI)	1.00 (referent)	1.76 (1.47 to 2.11)	3.05 (2.42 to 3.84)	-	3.96 (1.64 to 9.56)	-	-	-
Adjusted[a] HR (95% CI)	1.00 (referent)	1.66 (1.37 to 2.03)	1.61 (1.21 to 2.13)	-	2.74 (1.02 to 7.35)	-	-	-
Fungal infections								
No. of events	295	124	62	1	2	0	0	0
Crude HR (95% CI)	1.00 (referent)	1.78 (1.44 to 2.20)	3.00 (2.28 to 3.94)	-	-	-	-	-

	Metformin	Sulfonylurea	Insulin	Fixed drug combinations	DPP-4 inhibitors	GLP-1 analogues	Meglitinides	Other
Adjusted[a] HR (95% CI)	1.00 (referent)	1.39 (1.11 to 1.76)	1.86 (1.34 to 2.58)	-	-	-	-	-

[a]Adjusted for age, sex, comorbidity (CCI score), microvascular and macrovascular diabetes complications not included in the CCI, diabetes duration, hospital-diagnosed obesity, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, any hospitalization within 6 months, any infection within 6 months, and calendar period of study inclusion.
Abbreviations: CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1

Appendix 1

World Health Organization *International Classification of Diseases, Eighth Revision* (ICD-8) and *Tenth Revision* (ICD-10) codes and Anatomical Therapeutical Chemical classification system (ATC) codes used in this study.

Codes used to identify type 2 diabetes	
Hospital contact for type 2 diabetes	ICD-8-codes: 249.x, 250.x. ICD-10-codes: E10.x, E11.x, E14·x, G63.2.x, H36.0, N08.3
Glucose-lowering drugs	ATC-codes:- Insulin and analogues: A10Axxx; Metformin: A10BAxx; Sulfonylureas: A10BBxx; Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1 (GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02, A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx
Codes used to identify diabetes complications	
Microvascular complications	
Nephropathy	ICD-8-codes: 25002, 24902 ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2
Retinopathy	ICD-8-codes: 25001, 24901 ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335
Neuropathy	ICD-8-codes: 25003, 24903 ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,
Macrovascular complications	ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440 ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145
Codes used to identify infections	

Hospital-treated (inpatient and outpatient) infection	ICD-10-codes: A00-B99, D73.3, E06.0, E06.9, E32.1, G00-G02, G04-07, H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0, I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1, J00-J06, J09-J18, J20-22, J34.0, J36, J38.3D, J38.7G, J39.0-1, J39.8A, J44.0, J85.1-3, J86, K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1, L00-03, L05-08, L88, M00-01, M46.1-5, M49.0-3, M60.0, M60.8, M63.0-2, M65.0-1, M68.0, M71.0-1, M86.0-2, M86.9, M90.0-2, N10, N12, N13.6, N15.1, N16.0, N20.0I, N29.1, N30.0, N33.0, N34.0-1, N39.0, N41, N43.1, N45.0, N45.9, N48.1-2, N49, N61, N70-77, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98, T80.2, T81.4, T82.6-7, T83.5-6, T84.5-7, T85.7, T88.0, and T89.9
Community-based antibiotics	ATC-codes: J01xx, J02AA, J04AB, and A07AA
ICD-10 codes used to identify specific hospital-treated infections	
Eye and ear infections	H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0
Upper respiratory tract infections	K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, J00, J01, J02, J03, J04, J05, J06, J36, J38, J39
Pneumonia	J12, J13, J14, J15, J16, J17, J18
Infections of heart and blood vessels	I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1
Gastrointestinal tract infections	A00-A09
Intra-abdominal infections	K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1
Urinary tract infections	N10, N12, N15.1, N30.0, N33.0, N34.0-1, N39.0
Infection of central nervous system	G00-G02, G04-07, A80-A89
Meningococcal infections	A39
Skin and subcutaneous infections	A46, J34, L000-L08

Abscesses	A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P
Septicemia	A40, A41
Tuberculosis	A15-A19
Miscellaneous bacterial infections	A20-A38, A42-A44, A48, A49, A65-A79
Viral infections	B00-B09, B15-B19, B25-B34, A90-A99
Fungal infections	B35-B49
Malignant external otitis	H60.2
Emphysematous cholecystitis	K81.0
Emphysematous cystitis	N30.8
Emphysematous pyelonephritis	N10
Perirenal abscess	N15.9

ATC codes used to identify specific subgroups of antibiotics

Phenoxymethylpenicillin (first-line drug for community-acquired respiratory tract infections in Denmark)	J01CE02
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor (broad-spectrum beta-lactams used mainly for respiratory tract infections in selected patients)	J01CA02, J01CA04, J01CR02
Azithromycin (used mainly to treat genital infections)	J01FA10
Erythromycin, roxithromycin, clarithromycin (used for respiratory tract infections in the presence of a penicillin allergy or for *Mycoplasma pneumonia*)	J01FA01, J01FA06, J01FA09

Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim (drugs used almost exclusively to treat UTI in Denmark)	J01CA08, J01EB02, J01XE01, J01EA01,
Dicloxacillin, flucloxacillin (used mainly to treat skin infections / *S. aureus*)	J01CF01, J01CF05
Antimycobacterial	J04A
Quinolones (used to treat UTI and gastrointestinal infections in selected cases)	J01M
Tetracycline	J01A
Cephalosporin	J01D
Codes used to identify covariates	
Alcoholism-related disorders	ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714
Statin use	ATC-codes: B04AB
Immunosuppressant use	ATC-codes: L01, L04
Oral corticosteroid use	ATC-codes: H02AB

Study III

- Dissertation paper III

Impact of Glycemic Control on Risk of Infections in Patients with Type 2 Diabetes: A population-based cohort study

Anil Mor, Olaf M. Dekkers, Jens S. Nielsen, Henning Beck-Nielsen, Henrik T. Sørensen, Reimar W. Thomsen

Corresponding author and contact for reprints request: Anil Mor, Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43-45, DK-8200 Aarhus N, Denmark (E-mail: anil.mor@clin.au.dk; phone: +45 8716 8257, fax: +45 8716 7215)

ABSTRACT

Infections are a major clinical challenge for type 2 diabetes patients, but little is known about the impact of glycemic control. We used Cox regression analyses to examine the association between baseline and time-varying updated HbA_{1c} values and development of community-treated and hospital-treated infections in 69,318 patients with type 2 diabetes diagnosed between 2000 and 2012. The incidence rates were 394/1000 patient-years for community-treated infections and 63/1000 patient-years for hospital-treated infections. The adjusted hazard ratios (HRs) for community-treated infection associated with a high HbA_{1c} value of ≥10.5% were 0.97 (95% confidence interval [CI]: 0.94, 1.00) for HbA_{1c} measured at early baseline, 1.09 (95% CI: 1.03, 1.14) for updated mean HbA_{1c}, 1.13 (95% CI: 1.08, 1.19) for updated time-weighted mean HbA_{1c}, and 1.19 (95% CI: 1.14, 1.26) for the latest updated HbA_{1c} (reference HbA1c 5.5%-<6.5%). Corresponding estimates for hospital-treated infections were 1.08 (95% CI: 1.02, 1.14) for early baseline HbA_{1c}, 1.55 (95% CI: 1.42, 1.71) for updated mean HbA_{1c}, 1.58 (95% CI: 1.44, 1.72) for updated time-weighted mean HbA_{1c}, and 1.64 (95% CI: 1.51, 1.79) for the latest updated HbA_{1c}. Our findings provide evidence for an association of current hyperglycemia with infection risk in type 2 diabetes patients.

KEY WORDS: Type 2 diabetes mellitus, infections, HbA1c, epidemiology

Infections are a major clinical challenge for patients with type 2 diabetes and a common cause of death (1, 2). Type 2 diabetes patients have a 1.5- to 3-fold increased risk of primary care treated and in particular of hospital-treated infections compared with the general population (1-5), but the exact mechanisms linking diabetes and infections are not well understood (6, 7).

Risk of infection may depend on glycemic control. Although randomized trials and observational studies consistently have shown that early intensive glycemic control reduces the risk of diabetic microvascular complications by 10%–25% (8-12), the effect on infections has not been examined in randomized trials (13-21). Attempts to use observational data to clarify these issues have been hampered by inconsistent results. As well, HbA_{1c} usually has been measured on a single occasion in patients with prevalent diabetes, preventing clarification of the importance of acute versus longer-term hyperglycemia (22). Whether poor glucose control in type 2 diabetes is associated with an increase in community prescriptions for antiinfective agents has not been examined to date.

Such data are needed to understand and potentially prevent infections. We therefore undertook a large, population-based study to assess in detail the impact of glycemic control on risk of infectious complications in persons with type 2 diabetes.

METHODS

Study design and data sources

We conducted this population-based cohort study among individuals with type 2 diabetes in Northern Denmark. The region has 2 million inhabitants of which ~95% are Caucasian. We used the Danish National Patient Registry (DNPR) (23), the Aarhus University Prescription

Database (AUPD) (24), and the clinical laboratory information system (LABKA) research database (25) to carry out our study. The DNPR contains information on all hospitalizations in Denmark since 1977 and on all outpatient and emergency room visits since 1995 (23). The AUPD gathers patient-, drug-, and prescriber-related information. It contains complete data on all prescription medications dispensed from community pharmacies and hospital-based outpatient pharmacies in Northern Denmark since 1998 (24). The LABKA database has recorded data on virtually all specimens analyzed in clinical laboratories and general practices in Northern Denmark since 2000 (25). We used the Danish central personal registry (CPR) number to link individual-level data among these registries, and used the registry to collect data on age, gender, marital status, and death (24).

Identification of patients with type 2 diabetes

We defined incident diagnosis of diabetes as a first glucose-lowering drug prescription or a first inpatient or outpatient hospital contact for type 2 diabetes. We identified 70,299 patients with first ever record of an incident type 2 diabetes diagnosis between January 1, 2000 and December 31, 2012, who also had at least one HbA_{1c} measurement available in the LABKA database. We excluded patients under age 30 years at the time of their diabetes diagnosis to decrease the probability of including persons with type 1 diabetes (19). We also excluded 981 females who used metformin monotherapy and had polycystic ovarian disease, as recorded in the DNPR. After these exclusions, 69,318 patients remained in the study cohort.

Data on HbA_{1c}

We collected all HbA_{1c} measurements available during the study period. HbA_{1c} was analysed in venous blood at each laboratory in Northern Denmark using laboratory methods standardized according to the Diabetes Control and Complications Trial (DCCT) assay (26). We also recorded HbA_{1c} values using International Federation of Clinical Chemistry (IFCC) standards (26). The start date of follow-up (the index date) was defined as the date of study subjects' first HbA_{1c} measurement following their first incident diabetes diagnosis.

Data on infection endpoints

Community-treated infection was defined as the first redemption after the index date of a prescription from a primary care physician for an antiinfective agent for systemic use. Hospital-treated infection was defined as the first occurrence after the index date of a hospital inpatient or outpatient clinic contact associated with a primary or secondary discharge diagnosis of infection. We used Anatomical Therapeutic Chemical (ATC) codes to identify prescriptions for antiinfectives recorded in the AUPD, and ICD-10 codes to identify relevant hospital contacts recorded in the DNPR (see Appendix for codes). We further categorized prescriptions into specific groups of antiinfectives and diagnoses into specific types of infection (see Appendix for groups and codes). We followed all patients from their index date until occurrence of infection, death, emigration, or end of the study period *i.e.,* December 31, 2012, whichever came first.

Data on covariates

We obtained data for potential confounders, selected a priori from the data sources. These variables included age, gender, marital status, comorbidities, alcoholism-related disorders, and concurrent use of immunosuppressive drugs, oral corticosteroids, statins, and prescriptions for glucose-lowering drugs by type before or on the index date. We used all discharge diagnoses recorded in the DNPR on or before the index date to compute a Charlson Comorbidity Index (CCI) score for each patient. This score includes major diabetes complications, such as previous myocardial infarction, stroke, peripheral vascular disease, chronic heart failure, and renal disease (27). Overall comorbidity levels were defined as low (CCI score of 0), medium (CCI score of 1-2), and high (CCI score of ≥ 3). Duration of known diabetes before follow-up start was defined as the difference between the first incident diabetes diagnosis (*i.e.,* first prescription for a glucose-lowering drug or first diabetes-related hospital contact) and the index date (first HbA_{1c} measurement following diagnosis).

Statistical analysis

To assess the importance of different HbA_{1c} values over time for development of infection, we created four HbA_{1c} exposure groups (22):

1. *Early baseline HbA_{1c}*: The first baseline HbA_{1c} value, recorded on the index date.

2. *Updated mean HbA_{1c}*: The mean of all available HbA_{1c} values, calculated at the time of each new HbA_{1c} measurement, contributing to the exposure risk window until the next measurement.

3. *Updated time-weighted mean HbA_{1c}*: This was calculated as a time-weighted mean at the time of each new HbA_{1c} measurement. For instance, the time-weighted mean at the third measurement was the mean of the third HbA_{1c} value and the mean of the first two HbA_{1c} values; the fourth time-weighted mean HbA_{1c} was the mean of the fourth HbA_{1c} value and the third time-weighted mean HbA_{1c} value, and so forth.

4. *Latest updated HbA_{1c}*: The most recent HbA_{1c} value, which contributed to the exposure risk window until a new measurement was taken. *Figure 1* illustrates these exposure definitions with examples.

Within each exposure group, we separated the resulting HbA_{1c} values into seven categories (<5.5%, 5.5% to <6.5%, 6.5% to <7.5%, 7.5% to <8.5%, 8.5% to <9.5%, 9.5% to <10.5%, and ≥10.5%), and described patient characteristics as of the index date according to the early baseline HbA_{1c} exposure definition (*Table 1*).

We followed all patients from the index date, and reported incidence rates (IRs) of community-treated infection and hospital-treated infection per 1000 patient-years (p-y), calculated as the number of patients who contacted an infection divided by the number of patient-years of follow-up.

We used Cox proportional hazards regression analysis to compute HRs with 95% CIs of community-treated infection and hospital-treated infection according to the different HbA_{1c} exposure groups described above. HRs were computed both for every 1% increase in HbA_{1c} level, and for the seven HbA_{1c} categories, using the HbA_{1c} level of 5.5% to <6.5% as the reference category. We adjusted for age, gender, comorbidity (CCI score), micro- and

macrovascular diabetes complications not covered by the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date. We also performed stratified analyses to assess the impact of type 2 diabetes on infection risk in strata of gender, age, comorbidity, and glucose-lowering drug categories. We repeated all the analyses separately for specific infections and specific antiinfective agents for the HbA1c exposure group with strongest association.

Sensitivity analyses

We repeated the analyses restricted to newly diagnosed type 2 diabetes patients who had HbA1c measurements recorded within 3 months of the diabetes diagnosis date. Furthermore, we repeated the analyses for primary diagnosis and secondary diagnosis of overall and specific hospital-treated infection groups to explore the differences in the risk associated with every 1% increase in HbA_{1c} level and by HbA_{1c} categories.

All analyses were performed using STATA version 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP). The study did not involve any contact with patients or interventions, it was therefore not necessary to obtain consent. Permission to use health registry data was obtained from the Danish Data Protection Agency (Record number 2013-41-1924).

RESULTS

Among the 69,318 patients with type 2 diabetes, more than half (55%) were male; median age was 63.3 years (interquartile range [IQR]: 53.5, 72.6 years); median duration of recorded diabetes before the first HbA_{1c} measurement was 2.1 months (IQR: 0.6, 5.8 months); and 73% were taking glucose-lowering drugs at the time of their first HbA_{1c} measurement (Table 1). Mean HbA_{1c} value at baseline was 7.5% (SD 1.9); 35% of patients had an HbA_{1c} value of 7.5% or more; and a small proportion (4%) had an HbA_{1c} value <5.5%. Compared to patients with a reference HbA_{1c} value 5.5%–6.5%, patients with higher HbA_{1c} values at baseline were more likely to be male, were younger, had less comorbidity and less statin use, and were more likely to use glucose-lowering drugs at onset (except those with HbA_{1c} values >10.5%) (Table 1).

The risk of community-treated infection was high; 48,442 patients (70%) received systemic antiinfectives in the community during a follow-up of 123,113 p-y at risk, yielding an overall IR = 393.5 (95% CI: 390.0, 397.0) per 1000 p-y (Table 1). 16,227 patients (23%) experienced hospital-treated infection over a follow-up of 259,524 p-y at risk, yielding an IR = 62.5 (95% CI: 61.6, 63.5) per 1000 p-y (Table 2).

Early baseline HbA_{1c}

The IRs of community-treated infections and hospital-treated infections appeared to decrease with increasing baseline HbA_{1c} values (Table 2 & Table 3). After adjustment for variables associated with a high baseline HbA_{1c} (including younger age and less comorbidity), we observed no increase in the rate of community-treated infections and hospital-treated

infections per 1% increase in baseline HbA_{1c} (adjusted HR 0.99 [95% CI: 0.99, 1.00] and 1.01 [95% CI: 1.00, 1.02], respectively). Compared with the reference HbA_{1c} value of 5.5%–<6.5%, a baseline HbA_{1c} value <5.5% was associated with an increased rate of community-treated infection (adjusted HR 1.06 [95% CI: 1.01, 1.12]) and hospital-treated infection (adjusted HR 1.29 [95% CI: 1.19, 1.40]), while adjusted HRs were close to or slightly above one in categories of increasing baseline HbA_{1c} values (Figure 2 & Figure 3).

Updated mean and updated time-weighted mean HbA_{1c}

For measures of updated mean HbA_{1c}, there was a more clear association between increasing HbA1c values and community-treated and hospital-treated infection IRs (Table 2 & Table 3). For every 1% increase in updated mean HbA_{1c} values the adjusted HR for community-treated infection was 1.01 (95% CI: 1.01, 1.02) and for hospital-treated infection was 1.06 (95% CI: 1.04, 1.07). Compared with an updated mean HbA_{1c} 5.5%–<6.5%, rates of community-treated infection were increased both for updated mean HbA_{1c} values of <5.5% and for increasing values ≥6.5% (Table 2, Figure 2). For hospital-treated infection, the association was stronger and an updated mean HbA1c of ≥10.5% was associated with an adjusted HR of 1.55 (95% CI: 1.42, 1.71). For updated time-weighted mean HbA_{1c} values, rates of community-treated infection increased by 2% (adjusted HR 1.02 [95% CI: 1.01, 1.03]) with each 1% increase, and rates of hospital-treated infection increased by 6% (adjusted HR 1.06 [95% CI: 1.05, 1.07]). Infection rates for updated time-weighted mean HbA_{1c} followed a similar gradient as for updated mean HbA_{1c}, with the highest rate observed in patients with HbA_{1c} values ≥10.5% for both community-treated and hospital-treated infections (Table 2, Figure 2).

Latest updated HbA_{1c}

The IR of community-treated infection was lowest at 380 per 1000 p-y in patients with a latest updated HbA1c value 5.5%–<6.5% and increased monotonically with increasing HbA1c levels (Table 2). The IR of hospital-treated infection was lowest at 58 per 1000 p-y in patients with a latest updated HbA1c value 6.5%–7.5% and increased with increasing or decreasing HbA1c levels (Table 3). For every 1% increase in the latest updated HbA_{1c} value, the rate of community-treated infection increased by 3% (adjusted HR 1.03 [95% CI: 1.02, 1.04) and the rate of hospital-treated infection increased by 6% (adjusted HR 1.06 [95% CI: 1.05, 1.07). An association with risk of infection was observed particularly for latest updated HbA1c values of ≥8.5%, reaching adjusted HRs of 1.19 (95% CI: 1.14, 1.26) for community-treated infection and 1.64 (95% CI: 1.51, 1.79) for hospital-treated infection in patients with HbA_{1c} value ≥10.5% compared to HbA_{1c} values of 5.5%–6.5% (Figure 2 & Figure 3).

Association of latest updated HbA_{1c} with specific community-treated and hospital-treated infections

Table 4 provides adjusted HRs of specific community-treated and hospital-treated infection groups associated with every 1% increase and by different HbA1c categories of latest updated HbA1c. For community-treated infections, the strongest associations with each 1% increase in the latest updated HbA_{1c} value were observed for broad-spectrum antibiotics cephalosporins (adjusted HR 1.38), for dicloxacillin/flucloxacillin normally used to treat *S. aureus* infections (adjusted HR 1.07), for quinolones (adjusted HR 1.13),and for antifungal therapy (adjusted HR 1.13). Adjusted HRs per 1% increase in latest updated HbA_{1c} values were increased particularly for abscesses (1.17), skin infections (1.14), and infections of the central nervous

system (1.10), but also for fungal infections (1.11), viral infections (1.07), septicaemia (1.08), upper respiratory tract infection (1.07), urinary tract infections (1.04), and eye and ear infections (1.09) (Table 4).

Subgroup and sensitivity analyses

The relation between increased risk of infections and higher HbA_{1c} levels was found consistently in all subgroups (shown for latest updated HbA_{1c} levels in Table 5). Of note, the impact of a high HbA_{1c} level seemed to be strongest in patients with microvascular complications. Otherwise, the hazard of infection associated with poor glucose control was similar in patients with and without comorbidity, in all age groups, and in patients with and without glucose-lowering drug use at baseline (Table 5).

In a sensitivity analysis including only the 42,499 patients (61%) who had their first HbA_{1c} measurement recorded within 3 months of their first documented diabetes diagnosis, adjusted HRs for community-treated infections and hospital-treated infections followed a pattern similar to that seen in the complete cohort (Supplementary Table S1).

When examining primary and secondary hospital diagnoses of infection as separate outcomes, the HR estimates followed a similar pattern as the overall hospital infection estimates (Supplementary Tables S2 to S4).

DISCUSSION

This population-based study of patients with type 2 diabetes suggests that average glycemic control, and in particular current glycemic control – assessed as the latest updated HbA_{1c} level – is important for the risk of infection in type 2 diabetes, particularly for hospital-treated infections. In contrast, there seemed to be no strong association between baseline HbA_{1c} levels obtained soon after start of therapy and later infections.

Our findings underscore the importance of present guidelines for HbA_{1c} targets (28). Our results indicate that for infectious complications, current hyperglycemia measured by the single latest HbA_{1c} level is important, supporting the hypothesis of an acute and reversible impact of hyperglycemia on infections. There may be differences in the mechanisms at play for infection and micro- and macrovascular complications. For vascular diabetes complications, Lind *et al.* (22) suggested that mean or updated mean HbA_{1c} values in general are more important compared with single HbA_{1c} measurements.

Evidence from similar cohort studies on the association between glycemic control over time and risk of infection in type 2 diabetes is limited (15-18, 29). Our study corroborate findings from a smaller Dutch study from general practice that reported no overall difference in mean HbA_{1c} in type 2 diabetes patients with and without infection, whereas patients who presented with an infection at some point during follow-up showed higher HbA_{1c} levels in that period compared to periods without any infection (29). Other studies have assessed single-point HbA_{1c} values, focusing on specific selected infections. They reported an increased risk associated with poor glycemic control for bloodstream infections (16, 17), for pneumonia requiring hospitalization (18), for tuberculosis (19), for vaginitis and balanitis (20), and for

urinary tract infection (UTI) (21). The Copenhagen City Heart Study of the general population assessed plasma glucose at baseline and found a particularly increased risk of UTI and skin infections with increased glucose levels (15). This is in line with our results. In patients undergoing surgical cardiac procedures, acute hyperglycemia is a known predictor of wound infections (3, 30), and randomized trials have shown that intensive insulin treatment may reduce the risk of subsequent sepsis (31) or wound infections (30).

In our study we found increased risk of infections at HbA_{1c} levels below 5.5%. A similar J-shaped association has been observed between HbA_{1c} levels and mortality (32) and cardiovascular disease (33). We observed that patients with a very low HbA1c tended to be younger and at the same time had more comorbidity and alcohol abuse than other type 2 diabetes patients. Fewer were treated with glucose-lowering drugs, i.e., more may have their (possibly mild) diabetes diagnosed during hospital work-up and treatment for other severe diseases. We thus speculate that the apparently higher infection risk associated with very low levels of HbA_{1c} might be explained by unmeasured comorbidity and lifestyle factors in these patients

In our study, the setting of the Danish healthcare system permitted a population-based design with inclusion of all patients with hospital- or drug-treated type 2 diabetes in a well-defined region with homogenous population, complete follow-up, and availability of laboratory data to assess glycemic control. These features largely eliminated the selection problems prevalent in smaller follow-up studies based on limited participants. By using both prescription and hospital-based data, we were able to identify all infections requiring medical attention, unlike previous studies, which often focused exclusively on infections treated in the hospital. Our

study also has limitations. First, we relied on HbA_{1c} measurements as ordered by general practitioners, and our findings apply to patients defined by glucose-lowering drug initiation or hospital treatment, not all incident type 2 diabetes. Second, patients with poor glycemic control may have a lower threshold of antiinfective or hospital treatment when infection is suspected (surveillance bias), leading to an overestimation of the association. Third, we cannot exclude the possibility of reverse causality in some patients in clinical practice, i.e., latent infection leading to increasing HbA_{1c}. Fourth, most of our confounders were measured at the index date, and some of them may have changed during follow-up. However, follow-up was short due to early outcome events in many patients, and factors that may be affected by exposure to high HbA_{1c} levels should not be adjusted for. Fifth, we did not have information on certain prognostic factors that may have affected HbA1c values, such as blood transfusions or enteral or parenteral nutrition, which could have led to HbA1c misclassification in some patients. Finally, as in any observational study, imperfectly measured, unmeasured, or unknown factors may have affected the observed associations, including high body mass index, smoking, low physical activity, and other adverse lifestyle and socioeconomic measures. Nonetheless, we were able to adjust for a wide range of medical conditions closely associated with these adverse factors, likely reducing their confounding effect.

It has been hypothesized that increased risk of infection may be mediated primarily by long-term chronic hyperglycemia via chronic tissue inflammation or development of other complications, which in turn increase risk of infection (3, 6, 7). As reviewed elsewhere (3), numerous in vitro studies have demonstrated that hyperglycemia may impair the innate immune system by acutely and reversibly impairing polymorphonuclear neutrophil cell

function and cytokine production, by inhibiting adaptive immunity through directly affecting T-cell, antigen-presenting cells and antibodies, or by interfering with complement cascade through glycosylation of immune proteins (6, 7). Such processes may underlie our finding of increased risk of infection associated with current hyperglycemia. Alternatively, unmeasured factors associated with high HbA_{1c} levels, such as high body mass index and lower socioeconomic status, both of which are documented risk factors for infection (34, 35), may explain our findings in part. A large proportion of patients with very high HbA_{1c} levels (≥10.5%) used neither glucose-lowering nor statin treatments. Such poor glucose control may be a marker of decreased compliance with preventive therapies in general, including other cardiovascular drugs and possibly vaccinations.

In summary, our population-based cohort study provides evidence that among patients with type 2 diabetes current hyperglycemia is associated with increased risk of community-treated infections and hospital-treated infections. The findings from this study suggest that infections in type 2 diabetes may be prevented with appropriate and consistent glycemic control.

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1) Author affiliations: Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark (Anil Mor, Olaf M. Dekkers, Henrik T. Sørensen, Reimar W. Thomsen); Department of Endocrinology and Metabolic Diseases C4-R, Leiden University Medical Center, Leiden, The Netherlands (Olaf M. Dekkers); The Danish Centre for Strategic Research in Type 2 Diabetes (DD2), Diabetes Research Centre,

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Table 1. Baseline Characteristics of 69,318 Patients With Type 2 Diabetes According to Baseline HbA_{1c} Level at Study Inclusion, Northern Denmark, 2000-2012

Patient characteristics	Total		Baseline HbA_{1c} (%) (mmol/mol)													
			<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Total (%)[a]	69,318	100	2,697	4	21,361	31	21,081	30	8,970	13	5,007	7	3,455	5	6,747	10
Mean HbA_{1c} % (SD)	7.5	1.9	5.1	0.4	6.1	0.4	6.9	0.3	7.9	0.3	8.9	0.3	9.9	0.3	12.0	1.1
Mean HbA_{1c} (mmol/mol)[b]	58.5		32.2		43.2		51.9		62.8		73.8		84.7		107.7	
Gender																
Male	38,456	55	1,130	42	10,868	51	11,517	55	5,234	58	3,148	63	2,242	65	4,317	64
Female	30,862	45	1,567	58	10,493	49	9,564	45	3,736	42	1,859	37	1,213	35	2,430	36
Age in years																
Median age (IQR)	63.3	53.5, 72.6	57.8	40.2, 69.0	64.9	55.7, 73.6	65.0	56.0, 73.6	62.6	52.8, 72.1	60.4	50.7, 70.7	59.2	49.4, 68.5	58.6	48.7, 68.5
Age-groups in years																
30 – <40	4,281	6	668	25	1,100	5	726	3	484	5	350	7	287	8	666	10
40 – <50	8,512	12	345	13	2,154	10	2,110	10	1,266	14	830	7	623	18	1,184	18
50 – <60	15,267	22	471	17	4,306	20	4,498	21	2,051	23	1,263	25	897	26	1,781	26
60 – <70	19,661	28	581	22	6,452	30	6,361	30	2,526	28	1,238	25	876	25	1,627	24
70 – <80	14,006	20	378	14	4,838	23	4,851	23	1,697	19	828	17	476	14	938	14
>80	7,591	11	254	9	2,511	12	2,535	12	9,46	11	498	10	296	9	551	8
Diabetes duration in months																
Median (IQR)	2.1	0.6, 5.8	4.5	1.3, 23.7	3.0	1.4, 7.1	2.5	1.0, 5.9	1.8	0.6, 6.6	1.1	0.2, 3.9	0.5	0.0, 1.8	0.0	0.0, 0.5
Marital status																
Married	40,328	58	1,529	57	12,684	59	12,448	59	5,172	58	2,841	57	1,937	57	3,717	55
Never married	7,745	11	373	14	2,084	10	1,856	9	1,010	11	694	14	56	16	1,172	17
Divorced	8,944	13	394	15	2,643	12	2,710	13	1,207	13	656	13	470	14	864	13
Widowed	10,974	16	351	13	3,632	17	3,715	18	1,386	15	679	14	412	12	799	12
Missing	1,327	2	50	2	318	3	352	2	195	2	137	3	80	2	195	3
CCI score																
Low (score of 0)	44,528	64	1,733	64	13,388	63	13,253	63	5,718	64	3,281	66	2,370	69	4,785	71
Medium (score of 1-2)	19,856	29	695	26	6,442	30	6,319	30	2,595	29	1,389	28	849	25	1,567	23
High (score ≥3)	4,934	7	269	10	1,531	7	1,509	7	657	7	337	7	236	7	395	6
Diabetes complications[c]																
No complications	49,202	71	1,975	68	14,511	68	14,537	69	6,451	72	3,707	74	2,708	78	5,313	79
Macrovascular	18,071	26	605	22	6,117	29	6,021	29	2,280	25	1,137	23	654	19	1,257	19

Microvascular														
Nephropathy	524	1	26	1	138	1	159	1	70	1	57	1	23	1	51	1
Retinopathy	1,859	3	117	4	764	4	477	2	198	2	121	2	65	2	117	2
Neuropathy	665	1	19	1	168	1	204	1	98	1	63	1	37	1	76	1
Alcoholism-related conditions[d]	2,141	3	206	8	642	3	485	2	269	3	180	4	117	3	242	4
Other medication use														
Statins	27,728	40	609	23	9,926	47	10,212	48	3,373	38	1,545	31	831	24	1,232	18
Immunosuppressant	543	1	30	1	189	1	167	1	65	1	37	1	19	1	36	1
Oral corticosteroid	3,946	6	92	4	923	4	1,221	6	686	8	412	8	222	6	390	6
Glucose-lowering drugs														
No glucose-lowering drugs	18,455	27	1,432	53	6,513	30	4,187	20	1,729	19	1,062	21	909	26	2,623	39
Insulin only	2,043	3	77	3	388	2	521	2	427	5	279	6	150	4	201	3
Oral glucose-lowering drugs only	47,761	69	1,165	43	14,319	67	16,103	76	6,556	73	3,497	70	2,138	67	3,803	56
Insulin ± oral glucose-lowering drugs	1,059	2	23	1	141	1	270	1	258	3	169	3	78	2	120	2
Calendar year of diagnosis														
2000-2002	7,293	11	224	8	1,359	6	1,837	9	1,248	14	801	16	579	17	1,245	18
2003-2005	11,876	17	410	15	3,000	14	3,364	16	1,833	20	1,089	22	761	22	1,419	21
2006-2008	19,041	27	619	23	5,283	25	6,038	29	2,764	31	1,485	30	957	28	1,895	28
2009-2012	31,108	45	1,442	54	11,703	55	9,858	47	3,116	35	1,655	35	1,147	33	2,187	32

Abbreviations: CCI, Charlson Comorbidity Index; IQR, inter-quartile range

[a]Parentheses contain percentages unless specified otherwise.

[b]Mean HbA_{1c} in mmol/mol was calculated using the following formula: HbA_{1c} in mmol/mol = [0.9148 * HbA_{1c}%] + 2.152.

[c]Not mutually exclusive.

[d]Defined as hospitalization history due to diagnoses related to alcoholism; ICD codes used to identify these conditions are provided in the Appendix.

Table 2. Community-Treated Infections: Rates and Hazard Ratios Associated With Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

			HbA_{1c} category % (mmol/mol)													
	Every 1% increase		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI
Baseline HbA_{1c} value																
Events	48,442	123,113	1,811	3,913	14,040	34,328	14,765	36,419	6,673	17,204	3,688	9,808	2,546	6,985	4,919	14,456
IR/1000 p-y	393	390, 397	463	442, 485	409	402, 416	405	366, 412	388	379, 397	376	364, 388	365	351, 379	340	331, 350
HR Crude	0.98	0.98, 0.99	1.11	1.06, 1.17	1.00	Referent	1.01	0.99, 1.04	1.01	0.99, 1.04	0.98	0.95, 1.02	0.96	0.92, 1.00	0.91	0.88, 0.94
HR Adjusted[a]	0.99	0.99, 1.00	1.06	1.01, 1.12	1.00	Referent	1.03	1.01, 1.06	1.03	1.00, 1.06	1.03	1.01, 1.07	1.03	0.99, 1.08	0.97	0.94, 1.00
Updated mean HbA_{1c} value																
Events	48,442	123,113	1,785	3,827	15,800	40,225	16,758	44,047	7,415	20,130	3,304	8,364	1,623	3,507	1,757	3,011
IR/1000 p-y	393	390, 397	466	445, 489	393	387, 399	380	374, 386	368	360, 377	395	382, 409	463	441, 486	583	557, 611
HR Crude	1.00	0.99, 1.00	1.12	1.07, 1.17	1.00	Referent	1.01	0.99, 1.03	1.00	0.97, 1.02	0.99	0.95, 1.02	1.01	0.96, 1.07	1.02	0.97, 1.07
HR Adjusted[a]	1.01	1.01, 1.02	1.07	1.02, 1.13	1.00	Referent	1.04	1.01, 1.06	1.04	1.01, 1.07	1.03	1.00, 1.08	1.08	1.03, 1.14	1.09	1.03, 1.14
Updated time-weighted mean HbA_{1c} value																
Events	48,442	123,113	1,930	4,437	16,913	44,158	16,615	43,665	6,698	17,147	2,978	7,281	1,531	3,390	1,777	3,034
IR/1000 p-y	393	390, 397	435	416, 455	383	377, 389	381	375, 386	391	381, 400	409	395, 424	452	430, 475	586	559, 614
HR Crude	1.01	1.00, 1.01	1.10	1.05, 1.15	1.00	Referent	1.01	0.99, 1.03	1.03	1.01, 1.05	1.01	0.98, 1.05	1.03	0.97, 1.08	1.06	1.01, 1.11
HR Adjusted[a]	1.02	1.01, 1.03	1.06	1.01, 1.11	1.00	Referent	1.03	1.01, 1.06	1.07	1.04, 1.10	1.07	1.03, 1.11	1.10	1.04, 1.16	1.13	1.08, 1.19
Latest updated HbA_{1c} value																
Events	48,442	123,113	2,197	5,298	17,769	46,767	16,483	42,935	6,076	15,367	2,666	6,401	1,444	3,160	1,807	3,184
IR/1000 p-y	393	390, 397	415	398, 432	380	374, 386	384	378, 390	395	386, 405	416	401, 433	457	434, 481	567	542, 594
HR Crude	1.02	1.01, 1.02	1.07	1.03, 1.12	1.00	Referent	1.02	1.00, 1.05	1.05	1.02, 1.08	1.07	1.03, 1.11	1.08	1.02, 1.14	1.12	1.07, 1.18
HR Adjusted[a]	1.03	1.02, 1.04	1.04	1.01, 1.09	1.00	Referent	1.04	1.02, 1.07	1.09	1.05, 1.12	1.11	1.07, 1.16	1.15	1.08, 1.21	1.19	1.14, 1.26

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Table 3. Hospital-Treated Infections: Rates and Hazard Ratios Associated With Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

			HbA_{1c} category % (mmol/mol)													
	Every 1% increase		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI
Baseline HbA_{1c} value																
Events	16,227	259,524	675	8,187	4,391	69,570	4,807	77,431	2,388	37,800	1,304	21,544	910	15,205	1,752	29,787
IR/1000 p-y	63	62, 64	82	76, 89	63	61, 65	62	60, 64	63	61, 66	61	57, 64	60	56, 64	59	56, 62
HR Crude	0.99	0.98, 1.00	1.30	1.20, 1.41	1.00	Referent	1.00	0.96, 1.04	1.03	0.98, 1.09	0.99	0.93, 1.06	0.98	0.92, 1.06	0.97	0.91, 1.02
HR Adjusted[a]	1.01	1.00, 1.02	1.29	1.19, 1.40	1.00	Referent	1.04	1.00, 1.08	1.10	1.05, 1.16	1.09	1.02, 1.16	1.10	1.02, 1.18	1.08	1.02, 1.14
Updated mean HbA_{1c} value																
Events	16,227	259,524	628	7,370	4,986	81,157	5,725	97,270	2,726	45,192	1,160	17,392	482	6,645	520	4,497
IR/1000 p-y	63	62, 64	85	79, 92	61	60, 63	59	57, 60	60	58, 63	67	63, 71	73	66, 79	116	106, 126
HR Crude	1.02	1.01, 1.04	1.34	1.23, 1.45	1.00	Referent	0.98	0.94, 1.02	1.01	0.96, 1.06	1.07	1.01, 1.14	1.08	0.98, 1.19	1.37	1.25, 1.50
HR Adjusted[a]	1.06	1.04, 1.07	1.39	1.28, 1.51	1.00	Referent	1.03	1.01, 1.07	1.12	1.06, 1.17	1.23	1.15, 1.31	1.26	1.15, 1.38	1.55	1.42, 1.71
Updated time-weighted mean HbA_{1c} value																
Events	16,227	259,524	788	8,854	5,497	90,299	5,425	94,126	2,348	38,292	1,074	15,749	522	6,961	573	5,243
IR/1000 p-y	63	62, 64	89	83, 95	61	59, 63	58	56, 59	61	59, 64	68	64, 72	75	69, 82	109	101, 119
HR Crude	1.02	1.00, 1.04	1.43	1.33, 1.54	1.00	Referent	0.95	0.92, 0.99	1.01	0.96, 1.06	1.09	1.02, 1.17	1.14	1.04, 1.24	1.37	1.26, 1.50
HR Adjusted[a]	1.06	1.05, 1.07	1.48	1.37, 1.60	1.00	Referent	1.01	0.97, 1.05	1.13	1.07, 1.18	1.25	1.17, 1.34	1.35	1.23, 1.48	1.58	1.44, 1.72
Latest updated HbA_{1c} value																
Events	16,227	259,524	915	10,491	5,650	93,627	5,378	92,852	2,134	34,959	962	14,373	531	6,923	657	6,298
IR/1000 p-y	63	62, 64	87	82,93	60	59, 62	58	56, 59	61	59, 64	67	63,71	77	70,84	104	97,113
HR Crude	1.03	1.02, 1.04	1.43	1.34, 1.54	1.00	Referent	0.97	0.93, 1.00	1.02	0.97, 1.07	1.09	1.01, 1.16	1.19	1.09, 1.31	1.43	1.32, 1.55
HR Adjusted[a]	1.06	1.05, 1.07	1.45	1.35, 1.55	1.00	Referent	1.02	0.98, 1.06	1.12	1.07, 1.18	1.24	1.16, 1.33	1.41	1.29, 1.54	1.64	1.51, 1.79

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Table 4. Adjusted[a] Hazard Ratios of Specific Community-treated Infections and of Specific Hospital-treated Infections Associated With Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

		Latest updated HbA_{1c} % (mmol/mol)																	
		Per 1% increase in HbA_{1c} value		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 -<48 mmol/mol)		6.5% - <7.5% (48 -<59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Community-treated infections																			
Overall	48,442	1.03	1.02, 1.04	1.04	1.00, 1.09	1.00	Referent	1.04	1.02, 1.07	1.09	1.05, 1.12	1.11	1.07, 1.16	1.15	1.08, 1.21	1.19	1.14, 1.26		
Phenoxymethylpenicillin	30,475	1.03	1.02, 1.04	1.00	0.95, 1.06	1.00	Referent	1.06	1.03, 1.08	1.10	1.06, 1.15	1.11	1.05, 1.17	1.20	1.12, 1.28	1.13	1.06, 1.21		
Pivampicillin, amoxicillin, or amoxicillin+enzyme inhibitor	16,400	1.01	0.99, 1.02	1.17	1.09, 1.26	1.00	Referent	1.03	0.99, 1.07	1.05	1.00, 1.10	1.06	0.99, 1.14	1.08	0.98, 1.19	1.03	0.93, 1.14		
Macrolides																			
Azithromycin	4,797	1.00	0.97, 1.02	0.96	0.83, 1.10	1.00	Referent	1.05	0.98, 1.12	1.03	0.94, 1.13	1.07	0.94, 1.21	0.82	0.68, 1.00	0.99	0.83, 1.19		
Erythromycin, roxithromycin, clarithromycin	13,051	1.01	1.00, 1.02	0.95	0.87, 1.04	1.00	Referent	1.01	0.97, 1.05	1.04	0.99, 1.10	1.01	0.93, 1.09	1.02	0.91, 1.14	1.04	0.93, 1.16		
Pivmecillinam, sulfamethizole, nitrofurantoin, or trimethoprim	19,202	1.00	0.99, 1.01	1.17	1.09, 1.25	1.00	Referent	0.97	0.94, 1.01	0.98	0.94, 1.03	1.05	0.98, 1.13	1.06	0.97, 1.16	1.11	1.02, 1.20		
Dicloxacillin, flucloxacillin	13,726	1.07	1.05, 1.08	1.08	0.99, 1.18	1.00	Referent	1.06	1.02, 1.10	1.10	1.04, 1.17	1.21	1.12, 1.30	1.37	1.25, 1.51	1.54	1.41, 1.69		
Antimycobacterials	95	1.07	0.93, 1.23	1.29	0.49, 3.37	1.00	Referent	1.34	0.81, 2.21	1.24	0.64, 2.43	0.88	0.30, 2.53	1.30	0.39, 4.32	2.81	1.19, 6.64		
Quinolones	466	1.13	1.06, 1.20	1.76	1.17, 2.64	1.00	Referent	1.15	0.91, 1.45	1.49	1.12, 1.98	1.55	1.05, 2.29	1.80	1.10, 2.96	2.34	1.49, 3.68		
Tetracycline	180	0.91	0.81, 1.03	1.39	0.76, 2.55	1.00	Referent	0.72	0.50, 1.04	0.94	0.59, 1.50	1.05	0.58, 1.93	0.92	0.40, 2.15	0.59	0.21, 1.64		
Cephalosporin	46	1.38	1.18, 1.63	NA		1.00	Referent	NA		NA		NA		NA		NA			
Antifungal	6,493	1.13	1.12, 1.15	1.23	1.10, 1.38	1.00	Referent	1.05	0.98, 1.11	1.27	1.17, 1.37	1.52	1.37, 1.68	1.93	1.70, 2.19	2.13	1.89, 2.40		
Antiviral	2,641	1.00	0.97, 1.03	0.91	0.74, 1.11	1.00	Referent	1.02	0.93, 1.12	1.01	0.89, 1.14	0.94	0.78, 1.12	0.82	0.63, 1.07	1.15	0.91, 1.45		
Hospital-treated infections																			
Overall	16,227	1.06	1.05, 1.07	1.45	1.35, 1.55	1.00	Referent	1.02	0.98, 1.06	1.12	1.07, 1.18	1.24	1.16, 1.33	1.41	1.29, 1.54	1.64	1.51, 1.79		
Eye and ear infections	421	1.09	1.02, 1.17	1.35	0.85,	1.00	Referent	1.24	0.98,	1.42	1.04,	2.13	1.48,	2.18	1.35, 3.53	1.17	0.63,		

					2.16			1.58		1.94		3.08				2.19
Upper respiratory tract infections	730	1.07	1.02, 1.13	1.23	0.87, 1.73	1.00	Referent	1.00	0.83, 1.20	1.11	0.88, 1.40	1.09	0.78, 1.52	1.93	1.36, 2.73	1.45	0.97, 2.16
Pneumonia	5,528	1.03	1.01, 1.05	1.49	1.33, 1.68	1.00	Referent	1.05	0.99, 1.12	1.11	1.02, 1.21	1.20	1.07, 1.26	1.20	1.01, 1.42	1.37	1.17, 1.60
Infections of heart and blood vessels	158	0.98	0.86, 1.11	1.70	0.91, 3.17	1.00	Referent	0.74	0.50, 1.08	0.73	0.43, 1.26	1.06	0.54, 2.08	1.09	0.43, 2.73	1.48	0.66, 3.29
Gastrointestinal tract infections	1,184	1.05	1.00, 1.10	1.70	1.34, 2.16	1.00	Referent	0.96	0.84, 1.11	1.09	0.90, 1.31	1.27	0.98, 1.63	1.14	0.78, 1.65	1.89	1.39, 2.57
Intra-abdominal infections	2,000	1.05	1.02, 1.09	1.37	1.12, 1.66	1.00	Referent	1.08	0.97, 1.20	1.15	0.99, 1.32	1.47	1.23, 1.76	1.37	1.07, 1.76	1.35	1.06, 1.72
Urinary tract infections	4,003	1.04	1.02, 1.07	1.45	1.26, 1.67	1.00	Referent	0.97	0.90, 1.04	1.11	1.00, 1.22	1.13	0.98, 1.31	1.36	1.13, 1.64	1.50	1.25, 1.79
Infections of the central nervous system	145	1.10	0.98, 1.23	1.53	0.71, 3.31	1.00	Referent	1.57	1.05, 2.35	1.29	0.73, 2.27	1.35	0.62, 2.91	1.34	0.48, 3.79	2.22	0.97, 5.05
Skin and subcutaneous infections	2,625	1.14	1.11, 1.17	1.30	1.09, 1.55	1.00	Referent	1.03	0.93, 1.13	1.18	1.04, 1.34	1.47	1.25, 1.72	1.76	1.45, 2.13	2.44	2.05, 2.90
Abscess	2,034	1.17	1.13, 1.20	1.24	1.01, 1.52	1.00	Referent	1.04	0.93, 1.16	1.34	1.16, 1.54	1.72	1.45, 2.05	2.01	1.63, 2.49	2.42	1.99, 2.93
Septicaemia	1,961	1.08	1.05, 1.12	1.63	1.34, 1.98	1.00	Referent	0.98	0.88, 1.10	1.31	1.14, 1.51	1.27	1.04, 1.55	1.37	1.05, 1.79	2.04	1.62, 2.57
Tuberculosis	44	1.08	0.90, 1.29	0.93	0.21, 4.18	1.00	Referent	0.87	0.39, 1.96	1.60	0.68, 3.80	0.75	0.17, 3.37	4.01	1.48, 10.91	0.51	0.07, 4.02
Viral infections	472	1.07	1.01, 1.14	1.60	1.09, 2.23	1.00	Referent	1.02	0.80, 1.29	1.80	1.37, 2.34	1.27	0.85, 1.91	2.00	1.29, 3.11	1.39	0.85, 2.26
Fungal infections	418	1.11	1.04, 1.18	1.06	0.67, 1.67	1.00	Referent	0.83	0.65, 1.05	1.02	0.75, 1.40	1.11	0.73, 1.70	1.36	0.81, 2.30	1.89	1.21, 2.95
Rare infections associated with diabetes																	
Emphysematous cystitis	348	0.91	0.83, 1.01	0.82	0.47, 1.46	1.00	Referent	0.78	0.61, 0.99	0.66	0.45, 0.97	0.94	0.57, 1.55	0.56	0.23, 1.37	0.76	0.33, 1.73
Perirenal abscess	37	0.69	0.48, 1.00	1.94	0.65, 5.79	1.00	Referent	0.36	0.15, 0.86	0.43	0.12, 1.47	0.72	0.16, 3.18	NA		0.77	0.10, 6.01
Emphysematous pyelonephritis	336	1.04	0.96, 1.13	1.41	0.88, 2.25	1.00	Referent	0.97	0.74, 1.26	1.19	0.85, 1.66	0.91	0.53, 1.54	1.40	0.77, 2.56	1.42	0.78, 2.61
Emphysematous cholecystitis	232	1.06	0.96, 1.16	1.40	0.60, 2.28	1.00	Referent	1.32	0.97, 1.81	1.29	0.85, 1.97	1.63	0.95, 2.79	1.01	0.40, 2.51	1.03	0.41, 2.58

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable because of too few events to calculate HR

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

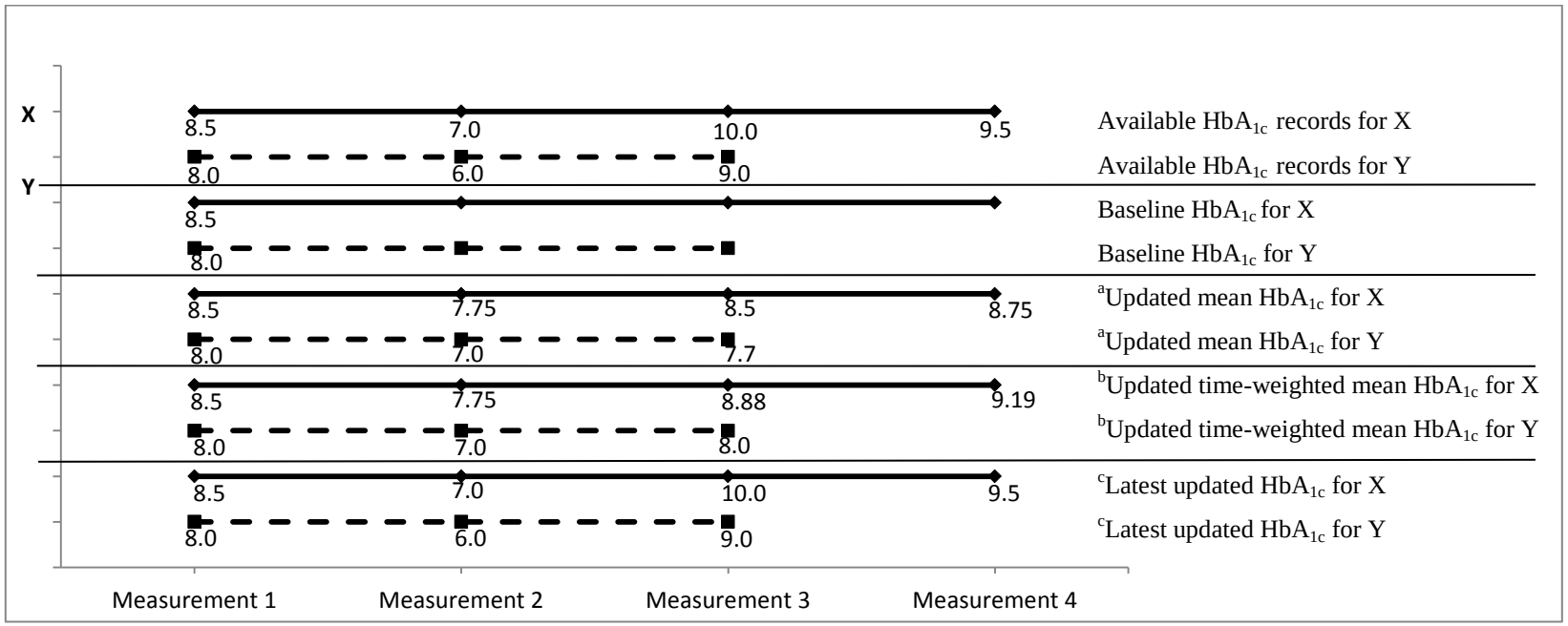
Table 5. Adjusted[a] Hazard Ratios of Community-treated and Hospital-treated Infection Associated With Every 1% Increase in Latest Updated HbA_{1c} Value by Subgroups of Patients With Type 2 Diabetes, Northern Denmark, 2000-2012

	Community-treated infection		Hospital-treated infection	
	HR	95% CI	HR	95% CI
Latest updated HbA_{1c} value (every 1% increase)	1.03	1.02, 1.04	1.06	1.05, 1.07
Gender				
Male	1.04	1.03, 1.05	1.06	1.04, 1.08
Female	1.03	1.02, 1.04	1.07	1.05, 1.09
Age groups in years				
30 , <40	1.05	1.02, 1.07	1.06	1.02, 1.10
40 , <50	1.03	1.01, 1.05	1.07	1.03, 1.10
50 , < 60	1.03	1.02, 1.04	1.05	1.03, 1.08
60 , <70	1.05	1.03, 1.06	1.08	1.05, 1.10
70 , <80	1.03	1.01, 1.04	1.08	1.05, 1.10
>80	1.02	1.00, 1.04	1.06	1.03, 1.09
CCI score				
Low (score of 0)	1.04	1.03, 1.04	1.07	1.06, 1.09
Medium (score of 1-2)	1.03	1.01, 1.04	1.05	1.03, 1.07
High (score ≥3)	1.02	1.00, 1.04	1.03	1.00, 1.07
Presence of diabetes complications				
No complications	1.03	1.02, 1.04	1.06	1.05, 1.08
Microvascular	1.07	1.05, 1.10	1.08	1.04, 1.12
Macrovascular	1.02	1.01, 1.04	1.04	1.02, 1.07
Glucose-lowering drugs				
No glucose-lowering drugs	1.02	1.01, 1.03	1.05	1.04, 1.07
Oral glucose-lowering drugs only	1.03	1.02, 1.04	1.05	1.04, 1.07
Insulin only	1.06	1.02, 1.09	1.04	0.99, 1.09
Insulin + oral glucose-lowering drugs	1.03	0.98, 1.08	1.05	0.96, 1.13

Abbreviations: CCI, Charlson Comorbidity Index score; CI, confidence interval; HR, hazard ratio

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Figure 1. HbA_{1c} Exposure Definition With Examples of two Study Participants, X and Y

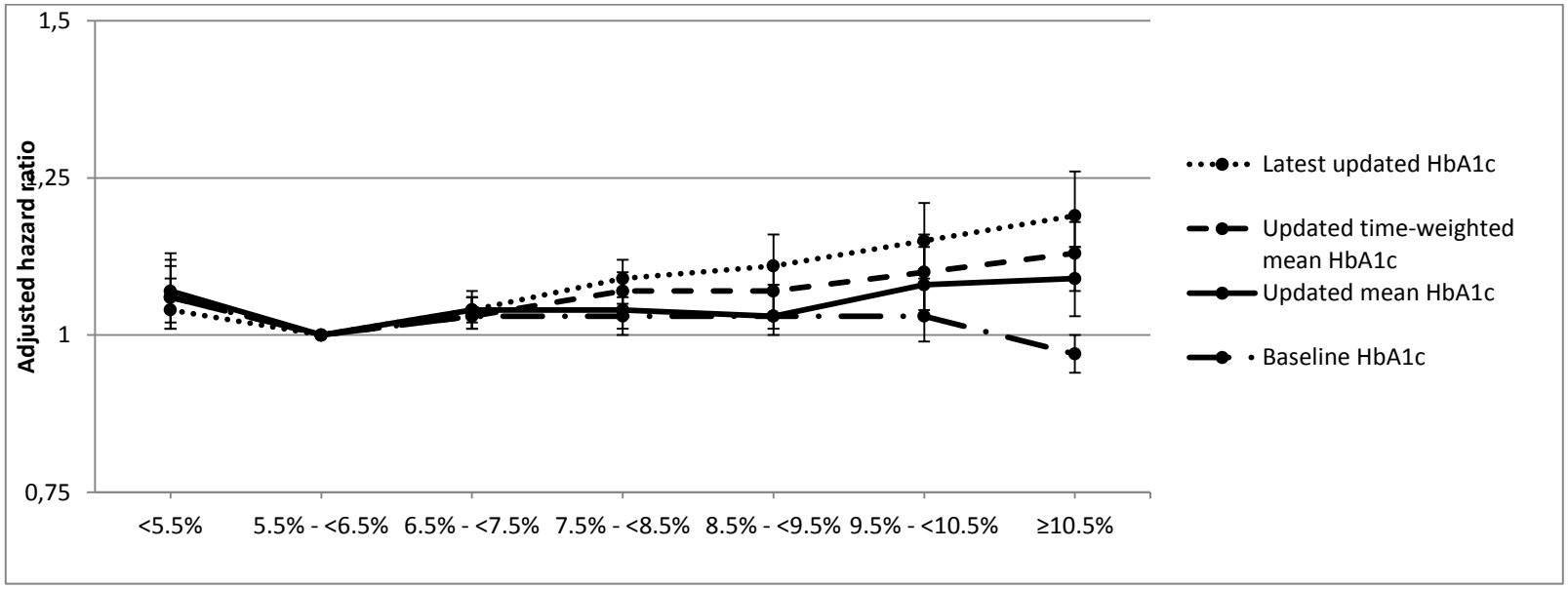


[a]Updated mean HbA_{1c} was updated at each new measurement, which contributed to risk-time until the next measurement. For example, for participant Y, the HbA_{1c} value of 8.0% contributed from date of measurement 1 to date of measurement 2; then the mean at measurement 2 [(8.0% + 6.0%)/2 = 7.0%] contributed from date of measurement 2 to date of measurement 3, and the mean at measurement 3 [(8.0% + 6.0% +9.0%)/3 = 7.7%] contributed to the risk-time from date of measurement 3 until the next measurement or until the outcome or end of follow-up.

[b]Updated time-weighted mean HbA_{1c} was calculated as the mean of the current HbA_{1c} measurement and the mean of the previous measurements and was updated at each new measurement, which contributed to risk-time until next measurement. For example, for participant X, the HbA_{1c} value of 8.5% contributed to risk-time from date of measurement 1 to date of measurement 2; then the updated mean at measurement 2 [(8.5% + 7.0%)/2 = 7.75%] contributed from the date of measurement 2 to the date of measurement 3, and the updated mean at measurement 3 [(7.75% +10.0%)/2 = 8.875%] contributed to the risk time from date of measurement 3 to date of measurement 4, and the updated mean at measurement 4 [(8.875% +9.5%)/2 = 9.1875%] contributed until the next measurement or until the outcome or end of follow-up.

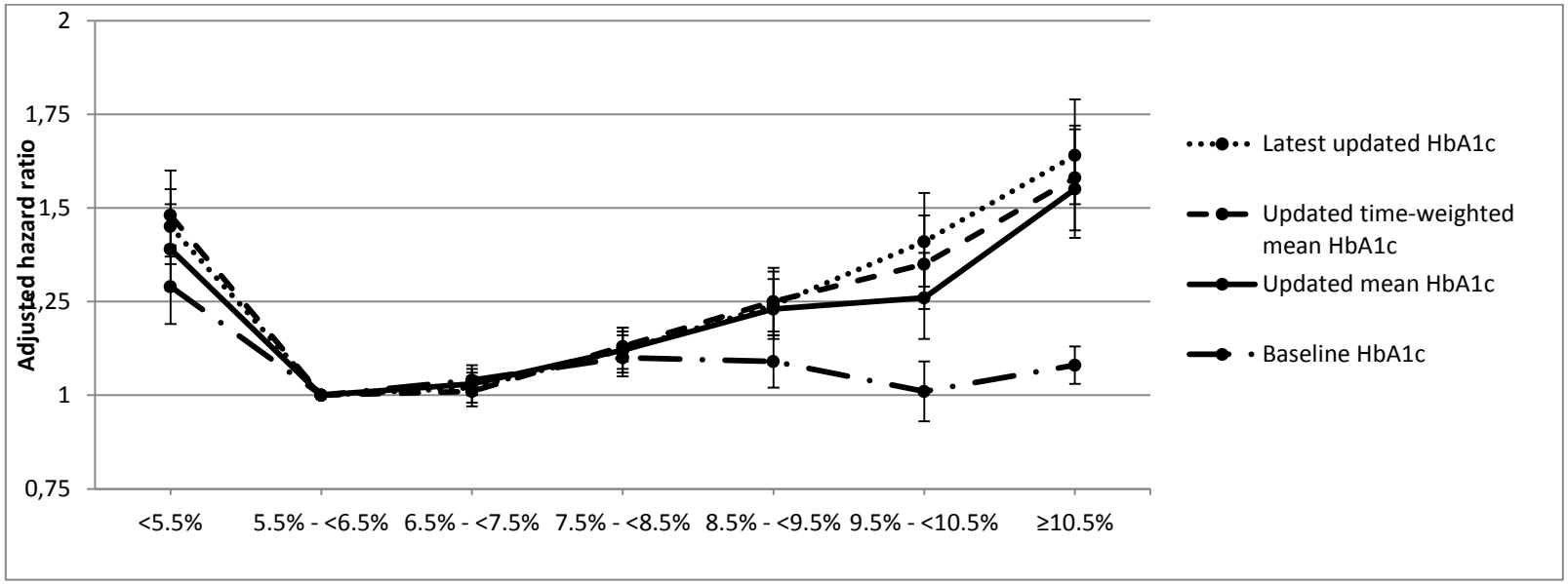
[c] Latest updated HbA_{1c} value: each HbA_{1c} measurement contributed to risk-time extending from the date of the measurement until the next measurement. For example, for X the first measurement (*i.e,* 8.5%) contributed from the date of measurement 1 to the next measurement 2, and the next measurement (*i.e.*, 7.0%) contributed from the date of measurement 2 to the subsequent measurement 3.

Figure 2. Community-treated Infection: Adjusted[a] Hazard Ratios by Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012



[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date.
Vertical error bars illustrate 95% confidence intervals.

Figure 3. Hospital-treated Infection: Adjusted[a] Hazard Ratios by Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c} Categories, Northern Denmark, 2000-2012



[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date.
Vertical error bars illustrate 95% confidence intervals.

Supplementary Table S1. Incidence Rates and Hazard Ratios of Community-treated Infection and Hospital-treated Infection Associated With the Latest Updated HbA_{1c} Value in Newly Diagnosed Type 2 Diabetes Patients, Northern Denmark, 2000-2012

			Latest updated HbA_{1c} % (mmol/mol)															
	Every 1% increase		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI
Community-treated infection																		
Events	29,648	77,873	1,115	3,034	10,694	29,796	10,126	27,304	3,736	9,525	1,663	3,918	953	2,006	1,361	2,288		
IR/1000 p-y	381	376, 385	367	346, 390	359	352, 366	371	364, 378	392	380, 405	424	405, 445	475	446, 506	595	564, 627		
HR Crude	1.02	1.01, 1.03	1.03	0.97, 1.09	1.00	Referent	1.04	1.01, 1.06	1.07	1.03, 1.11	1.08	1.03, 1.14	1.09	1.02, 1.16	1.12	1.05, 1.18		
HR Adjusted[a]	1.03	1.02, 1.04	1.02	0.96, 1.08	1.00	Referent	1.05	1.02, 1.08	1.11	1.07, 1.15	1.14	1.08, 1.20	1.15	1.08, 1.23	1.17	1.10, 1.24		
Hospital-treated infection																		
Events	10,179	163,970	551	5,834	3,418	59,792	3,445	59,322	1,354	21,708	598	8,848	337	4,275	476	4,189		
IR/1000 p-y	62	61, 63	94	87, 102	57	55, 59	58	56, 60	62	59, 66	68	62, 73	79	71, 88	114	104, 124		
HR Crude	1.03	1.01, 1.04	1.65	1.51, 1.81	1.00	Referent	1.01	0.97, 1.06	1.07	1.00, 1.14	1.10	1.01, 1.20	1.19	1.06, 1.33	1.41	1.27, 1.55		
HR Adjusted[a]	1.05	1.03, 1.06	1.59	1.45, 1.74	1.00	Referent	1.06	1.01, 1.11	1.15	1.08, 1.23	1.22	1.12, 1.34	1.36	1.21, 1.52	1.52	1.37, 1.68		

Abbreviations: CI, confidence interval; IR, incidence rates; HR, hazard ratio; p-y, patient-years.

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date.

Supplementary Table S2. Hospital-treated Infection, Primary Diagnosis: Rates and Hazard Ratios Associated With Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

			HbA_{1c} category % (mmol/mol)													
	Every 1% increase		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI
Baseline HbA_{1c} value																
Events	13,313	266,873	526	8539	3,588	71,414	4,023	79,224	1,971	38,784	1,057	22,276	748	15,708	1,400	30,927
IR/1000 p-y	50	49, 51	62	57, 67	50	49, 52	51	49, 52	51	49, 53	47	45, 50	48	44, 51	45	43, 48
HR Crude	0.98	0.98, 0.99	1.22	1.11, 1.34	1.00	Referent	1.02	0.98, 1.07	1.03	0.98, 1.09	0.97	0.90, 1.04	0.97	0.90, 1.05	0.92	0.87, 0.98
HR Adjusted[a]	1.00	0.99, 1.01	1.21	1.10, 1.33	1.00	Referent	1.06	1.01, 1.11	1.10	1.04, 1.16	1.05	0.98, 1.13	1.08	0.99, 1.17	1.02	0.96, 1.09
Updated mean HbA_{1c} value																
Events	13,313	266,873	490	7700	4,086	83,250	4,744	100,004	2,291	46,579	936	17,874	402	6,819	364	4,646
IR/1000 p-y	50	49, 51	64	58, 70	49	48, 51	47	46, 49	49	47, 51	52	49, 56	59	53, 65	78	71, 87
HR Crude	1.02	1.01, 1.03	1.26	1.15, 1.39	1.00	Referent	0.98	0.94, 1.02	1.02	0.97, 1.08	1.06	0.97, 1.13	1.12	1.01, 1.24	1.25	1.12, 1.39
HR Adjusted[a]	1.05	1.03, 1.06	1.30	1.19, 1.43	1.00	Referent	1.03	0.99, 1.08	1.12	1.06, 1.18	1.19	1.11, 1.28	1.28	1.15, 1.42	1.40	1.25, 1.56
Updated time-weighted mean HbA_{1c} value																
Events	13,313	266,873	626	9259	4,495	92,847	4,477	96,547	1,980	39,419	872	16,181	443	7,190	420	5,428
IR/1000 p-y	50	49, 51	68	63, 73	48	47, 50	46	45, 48	50	48, 52	54	50, 58	62	56, 68	77	70, 85
HR Crude	1.02	1.01, 1.04	1.38	1.26, 1.50	1.00	Referent	0.96	0.92, 1.00	1.04	0.99, 1.10	1.09	1.01, 1.17	1.20	1.08, 1.32	1.30	1.18, 1.44
HR Adjusted[a]	1.06	1.04, 1.07	1.42	1.30, 1.54	1.00	Referent	1.02	0.98, 1.06	1.15	1.09, 1.21	1.24	1.15, 1.33	1.40	1.27, 1.54	1.48	1.33, 1.64
Latest updated HbA_{1c} value																
Events	13,313	266,873	747	10,994	4,639	96,281	4,401	95,197	1,775	35,953	801	14,775	443	7,150	507	6,523
IR/1000 p-y	50	49, 51	68	63, 73	48	47, 50	46	45, 48	49	47, 52	54	51, 58	62	56, 68	78	71, 85
HR Crude	1.03	1.02, 1.04	1.40	1.30, 1.52	1.00	Referent	0.96	0.93, 1.01	1.03	0.97, 1.08	1.11	1.03, 1.19	1.23	1.11, 1.35	1.40	1.27, 1.53
HR Adjusted[a]	1.06	1.05, 1.07	1.41	1.30, 1.52	1.00	Referent	1.02	0.97, 1.06	1.13	1.07, 1.19	1.25	1.16, 1.35	1.42	1.29, 1.57	1.59	1.45, 1.75

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Supplementary Table S3. Hospital-treated Infection, Secondary Diagnosis: Rates and Hazard Ratios Associated With Baseline, Updated Mean, Updated Time-weighted Mean, and Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

			HbA_{1c} category % (mmol/mol)													
	Every 1% increase		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 - <48 mmol/mol)		6.5% - <7.5% (48 - <59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI	No., IR, or HR	p-y or 95% CI
Baseline HbA_{1c} value																
Events	15,290	260,315	648	8,214	4,097	69,765	4,501	77,662	2,260	37,937	1,240	21,634	870	15,225	1,674	29,880
IR/1000 p-y	59	58, 60	62	57, 67	50	49, 52	51	49, 52	51	49, 53	47	45, 50	48	44, 51	45	43, 48
HR Crude	1.00	0.99, 1.00	1.34	1.23, 1.45	1.00	Referent	1.00	0.96, 1.05	1.05	1.00, 1.11	1.02	0.95, 1.08	1.02	0.94, 1.09	1.00	0.94, 1.05
HR Adjusted[a]	1.01	1.00, 1.02	1.31	1.20, 1.42	1.00	Referent	1.04	1.00, 1.08	1.11	1.05, 1.17	1.09	1.03, 1.17	1.11	1.03, 1.20	1.09	1.03, 1.15
Updated mean HbA_{1c} value																
Events	15,290	260,315	596	7,415	4,655	83,250	5,373	100,004	2,601	46,579	1,104	17,874	459	6,819	502	4,646
IR/1000 p-y	59	58, 60	64	58, 70	49	48, 51	47	46, 49	49	47, 51	52	49, 56	59	53, 65	78	71, 87
HR Crude	1.03	1.02, 1.04	1.35	1.24, 1.47	1.00	Referent	0.99	0.95, 1.03	1.04	0.99, 1.09	1.10	1.03, 1.17	1.10	1.00, 1.21	1.40	1.28, 1.54
HR Adjusted[a]	1.06	1.04, 1.07	1.38	1.27, 1.51	1.00	Referent	1.04	1.00, 1.08	1.13	1.08, 1.19	1.23	1.15, 1.19	1.25	1.13, 1.38	1.54	1.40, 1.70
Updated time-weighted mean HbA_{1c} value																
Events	15,290	260,315	744	8,914	5,134	90,606	5,107	94,384	2,229	38,400	1,033	15,783	490	6,975	553	5,251
IR/1000 p-y	59	58, 60	83	78, 90	57	55, 58	54	53, 56	58	57, 61	65	62, 70	70	64, 77	105	97, 114
HR Crude	1.03	1.02, 1.04	1.44	1.33, 1.55	1.00	Referent	0.97	0.93, 1.00	1.03	0.98, 1.09	1.13	1.06, 1.21	1.14	1.04, 1.26	1.41	1.29, 1.54
HR Adjusted[a]	1.06	1.05, 1.07	1.47	1.36, 1.59	1.00	Referent	1.02	0.98, 1.06	1.14	1.09, 1.19	1.27	1.19, 1.36	1.33	1.21, 1.46	1.58	1.44, 1.73
Latest updated HbA_{1c} value																
Events	15,290	260,315	860	10,552	5,304	93,976	5,050	93,071	2,023	35,071	915	14,404	510	6,920	628	6,319
IR/1000 p-y	59	58, 60	68	63, 73	48	47, 50	46	45, 48	49	47, 52	54	51, 58	62	56, 68	78	71, 85
HR Crude	1.03	1.02, 1.05	1.43	1.33, 1.54	1.00	Referent	0.97	0.94, 1.01	1.03	0.98, 1.09	1.11	1.03, 1.19	1.23	1.12, 1.35	1.45	1.33, 1.58
HR Adjusted[a]	1.06	1.05, 1.07	1.43	1.32, 1.53	1.00	Referent	1.02	0.99, 1.06	1.12	1.07, 1.18	1.24	1.16, 1.34	1.42	1.30, 1.56	1.63	1.50, 1.78

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; p-y, person-years

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Supplementary Table S4. Specific Hospital-treated Infections, Primary and Secondary Diagnoses: Adjusted[a] Hazard Ratios Associated With Latest Updated HbA_{1c}, Northern Denmark, 2000-2012

		HbA_{1c} category % (mmol/mol)																	
		Per 1% increase in HbA_{1c} value		<5.5% (<37 mmol/mol)		5.5% - <6.5% (37 -<48 mmol/mol)		6.5% - <7.5% (48 -<59 mmol/mol)		7.5% - <8.5% (59 - <69 mmol/mol)		8.5% - <9.5% (69 - <80 mmol/mol)		9.5% - <10.5% (80 - <91 mmol/mol)		≥10.5% (≥91 mmol/mol)	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		
Admissions with primary diagnosis of infection																			
Overall	13,313	1.06	1.05, 1.07	1.41	1.30, 1.52	1.00	Referent	1.02	0.97, 1.06	1.13	1.07, 1.19	1.25	1.16, 1.35	1.42	1.29, 1.57	1.59	1.45, 1.75		
Eye and ear infections	287	1.12	1.04, 1.21	1.17	0.65, 2.11	1.00	Referent	1.23	0.92, 1.66	1.24	0.83, 1.83	2.36	1.54, 3.61	3.10	1.88, 5.11	0.92	0.40, 2.14		
Upper respiratory tract infections	586	1.07	1.01, 1.14	1.12	0.75, 1.66	1.00	Referent	1.08	0.88, 1.32	1.00	0.76, 1.32	1.00	0.69, 1.47	1.87	1.26, 2.77	1.53	0.99, 2.36		
Pneumonia	3,869	1.03	1.00, 1.05	1.50	1.30, 1.74	1.00	Referent	1.08	1.00, 1.17	1.12	1.01, 1.24	1.20	1.04, 1.39	1.24	1.01, 1.51	1.29	1.06, 1.58		
Infections of heart and blood vessels	114	0.98	0.85, 1.14	2.42	1.23, 4.76	1.00	Referent	0.85	0.54, 1.34	0.84	0.44, 1.58	0.93	0.39, 2.22	1.59	0.62, 4.07	1.57	0.61, 4.07		
Gastrointestinal tract infections	849	1.06	1.01, 1.12	1.70	1.29, 2.25	1.00	Referent	0.91	0.77, 1.08	1.14	0.92, 1.42	1.31	0.97, 1.75	1.17	0.76, 1.80	1.91	1.34, 2.72		
Intra-abdominal infections	1,716	1.04	1.01, 1.08	1.22	0.98, 1.52	1.00	Referent	1.04	0.92, 1.17	1.15	0.99, 1.34	1.38	1.13, 1.68	1.35	1.03, 1.76	1.10	0.83, 1.47		
Urinary tract infections	2,107	1.04	1.00, 1.07	1.29	1.05, 1.58	1.00	Referent	0.94	0.85, 1.04	1.08	0.94, 1.24	1.20	0.99, 1.46	1.42	1.10, 1.82	1.13	0.84, 1.51		
Infections of the central nervous system	114	1.13	0.99, 1.28	1.52	0.63, 3.67	1.00	Referent	1.64	1.04, 2.58	1.48	0.79, 2.76	1.43	0.59, 3.47	0.96	0.23, 4.03	2.71	1.11, 6.66		
Skin and subcutaneous infections	2,291	1.14	1.11, 1.17	1.23	1.01, 1.49	1.00	Referent	1.02	0.92, 1.14	1.19	1.04, 1.36	1.49	1.26, 1.76	1.77	1.44, 2.18	2.40	1.99, 2.89		
Abscess	1,827	1.18	1.14, 1.21	1.17	0.94, 1.46	1.00	Referent	1.06	0.94, 1.19	1.34	1.15, 1.55	1.70	1.42, 2.04	2.10	1.69, 2.61	2.54	2.08, 3.11		
Septicaemia	1,557	1.08	1.04, 1.12	1.57	1.25, 1.96	1.00	Referent	0.96	0.85, 1.08	1.26	1.08, 1.47	1.23	0.98, 1.54	1.42	1.06, 1.90	1.93	1.48, 2.52		
Tuberculosis	33	1.09	0.89, 1.34	0.58	0.07, 4.58	1.00	Referent	0.85	0.33, 2.16	1.69	0.63, 4.51	1.03	0.22, 4.78	4.55	1.49, 13.87				
Viral infections	326	1.07	0.99, 1.15	1.32	0.81, 2.14	1.00	Referent	0.89	0.67, 1.20	1.81	1.32, 2.84	1.52	0.97, 2.37	1.87	1.09, 3.19	1.06	0.55, 2.06		
Fungal infections	136	1.07	0.95, 1.21	0.67	0.27, 1.70	1.00	Referent	0.84	0.56, 1.27	1.03	0.61, 1.74	0.82	0.37, 1.82	1.94	0.34, 2.64	1.72	0.76, 3.86		
Admissions with secondary diagnosis of infection																			

Overall	15,290	1.06	1.05, 1.07	1.43	1.32, 1.53	1.00	Referent	1.02	0.99, 1.06	1.12	1.07, 1.18	1.24	1.16, 1.34	1.42	1.30, 1.56	1.63	1.50, 1.78
Eye and ear infections	149	1.03	0.91, 1.16	1.71	0.83, 3.52	1.00	Referent	1.18	0.79, 1.77	1.63	1.00, 2.67	1.37	0.67, 2.84	0.63	0.15, 2.60	1.78	0.74, 4.24
Upper respiratory tract infections	199	1.15	1.05, 1.26	1.24	0.63, 2.44	1.00	Referent	0.87	0.60, 1.26	1.74	1.16, 2.61	1.63	0.94, 2.85	2.26	1.18, 4.34	1.43	0.65, 3.18
Pneumonia	2,615	1.04	1.01, 1.08	1.40	1.17, 1.67	1.00	Referent	1.05	0.96, 1.15	1.15	1.02, 1.31	1.32	1.12, 1.56	1.25	0.99, 1.59	1.39	1.11, 1.74
Infections of heart and blood vessels	58	0.88	0.70, 1.11	0.98	0.29, 3.26	1.00	Referent	0.59	0.32, 1.10	0.38	0.13, 1.11	1.16	0.44, 3.08	0.48	0.06, 3.60	0.94	0.22, 4.09
Gastrointestinal tract infections	416	1.02	0.94, 1.11	1.75	1.16, 2.63	1.00	Referent	1.08	0.85, 1.36	1.03	0.74, 1.43	1.20	0.76, 1.88	1.06	0.54, 2.09	1.81	1.04, 3.16
Intra-abdominal infections	515	1.08	1.02, 1.14	2.03	1.44, 2.86	1.00	Referent	1.20	0.96, 1.50	1.22	0.91, 1.63	1.56	1.08, 2.25	1.62	1.01, 2.60	2.11	1.41, 3.16
Urinary tract infections	2,435	1.04	1.01, 1.08	1.59	1.34, 1.88	1.00	Referent	0.98	0.89, 1.08	1.07	0.93, 1.21	1.05	0.87, 1.28	1.44	1.14, 1.82	1.74	1.40, 2.16
Infections of the central nervous system	45	1.10	0.90, 1.34	3.23	0.99, 10.47	1.00	Referent	1.82	0.84, 3.97	0.73	0.20, 2.69	2.74	0.91, 8.26	3.28	0.88, 12.29	2.20	0.47, 10.39
Skin and subcutaneous infections	627	1.15	1.09, 1.21	1.56	1.11, 2.18	1.00	Referent	0.97	0.79, 1.19	1.13	0.88, 1.46	1.15	0.81, 1.64	1.91	1.31, 2.79	2.61	1.87, 3.64
Abscess	408	1.20	1.13, 1.27	1.81	1.19, 2.76	1.00	Referent	1.10	0.84, 1.43	1.55	1.13, 2.11	2.07	1.42, 3.02	1.99	1.21, 3.27	3.18	2.13, 4.74
Septicaemia	588	1.10	1.04, 1.16	1.53	1.06, 2.19	1.00	Referent	1.04	0.85, 1.28	1.37	1.06, 1.77	1.47	1.04, 2.08	1.51	0.95, 2.41	2.21	1.48, 3.30
Tuberculosis	23	1.06	0.82, 1.37	1.05	0.12, 8.87	1.00	Referent	1.20	0.40, 3.59	2.36	0.75, 7.46			3.15	0.62, 16.13	1.25	0.14, 10.91
Viral infections	228	1.07	0.98, 1.16	2.65	1.67, 4.21	1.00	Referent	1.19	0.84, 1.70	1.73	1.15, 2.61	1.19	0.63, 2.22	2.36	1.28, 4.35	2.01	1.08, 3.72
Fungal infections	311	1.12	1.04, 1.21	1.28	0.78, 2.09	1.00	Referent	0.83	0.62, 1.10	1.04	0.72, 1.49	1.35	0.85, 2.15	1.58	0.88, 2.83	1.93	1.16, 3.22

Abbreviations: CI, confidence interval; HR, hazard ratio

[a]Adjusted for age, gender, comorbidity (CCI score), micro- and macrovascular diabetes complications not covered in the CCI, diabetes duration, alcoholism-related conditions, marital status, concurrent use of statins/corticosteroids/immunosuppressive drugs, calendar period of diabetes diagnosis, and type of glucose-lowering drug regimen as of the index date

Appendix

World Health Organization *International Classification of Diseases, Eighth Revision* (ICD-8) and *Tenth Revision* (ICD-10) codes and Anatomical Therapeutical Chemical classification system (ATC) codes used in this study.

Codes used to identify type 2 diabetes	
Hospital contact for type 2 diabetes	ICD-8-codes: 249.x, 250.x. ICD-10-codes: E10.x, E11.x, E14.x, G63.2.x, H36.0, N08.3
Glucose-lowering drugs	ATC-codes:- Insulin and analogues: A10Axxx; Metformin: A10BAxx; Sulfonylureas: A10BBxx; Dipeptidyl peptidase 4 (DPP 4) inhibitors: A10BHxx; Glucagon-like peptide 1 (GLP-1) analogue: A10BX04, A10BX05, A10BX07, A10BX10; Maglitinides: A10BX02, A10BX03, A10BX08; Other glucose-lowering drugs: A10BFxx (alpha glucosidase inhibitor), A10BGxx (Thiazolidinedione); Combination tablets: A10BDxx
Codes used to identify diabetes complications	

Microvascular complications

Nephropathy	ICD-8-codes: 25002, 24902 ICD-10-codes: E102, E112, E142, I120, N083, N06, N17, N18, N19, R809, BJFD2
Retinopathy	ICD-8-codes: 25001, 24901 ICD-10-codes: E103, E113, E123, E133, E143, H340, H341, H342, H280, H334, H450, H360, H540, H541, H544, H25, H268, H269, H430, H431, H438C, H439, H334A, H330, H335
Neuropathy	ICD-8-codes: 25003, 24903 ICD-10-codes: E104, E114, E124, E134, E144, G590, G632, G603, G609, G618, G619, G620, G621, G622, G628, G629, G630, G631, G634, G635, G636, G638, G730, G990,

Macrovascular complications	ICD-8-codes: 410, 411, 412, 413, 414, 432, 433, 434, 435, 436, 437, 440 ICD-10-codes: I20, I21, I22, I23, I24, I25, I61, I63, I64, I65, I66, I672, I678, I679, I691, I693, I698, I702, I742, I745, I739, I792, E105, E115, E125, E135, E145

Codes used to identify any infection	
Hospital-treated (inpatient or outpatient) infection	ICD-10-codes: A00-B99, D73.3, E06.0, E06.9, E32.1, G00-G02, G04-07, H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0, I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1, J00-J06, J09-J18, J20-22, J34.0, J36, J38.3D, J38.7G, J39.0-1, J39.8A, J44.0, J85.1-3, J86, K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1, L00-03, L05-08, L88, M00-01, M46.1-5, M49.0-3, M60.0, M60.8, M63.0-2, M65.0-1, M68.0, M71.0-1, M86.0-2, M86.9, M90.0-2, N10, N12, N13.6, N15.1, N16.0, N20.0I, N29.1, N30.0, N33.0, N34.0-1, N39.0, N41, N43.1, N45.0, N45.9, N48.1-2, N49, N61, N70-77, O23, O26.4, O41.1, O75.3, O85, O86, O88.3, O91, O98, T80.2, T81.4, T82.6-7, T83.5-6, T84.5-7, T85.7, T88.0, and T89.9
Community-treated infections	ATC-codes: J01xx, J02xx, J04AB, and A07AA, J05xx

ICD-10 codes used to identify specific hospital-treated (inpatient or outpatient) infections	
Eye and ear infections	H00, H01.0, H03.0-1, H04.0, H04.3, H05.0, H06.1, H10, H13.0-1, H15.0, H19.1-2, H22.0, H32.0, H44.0-1, H60.0-1, H60.3, H62.0-3, H65.0-1, H66.0-4, H66.9, H67.1, H67.8, H68.0 H70.2, H73.0, H75.0, H94.0
Upper respiratory tract infections	K04.0, K04.6-7, K05.2, K11.2-3, K12.2, K13.0A, K14.0A, J00, J01, J02, J03, J04, J05, J06, J36, J38, J39
Pneumonia	J12, J13, J14, J15, J16, J17, J18
Infections of heart and blood vessels	I00-02, I30.1, I32.0-1, I33.0, I38, I39.8 I40.0, I41, I43.0, I52.0-1, I68.1, I98.1
Gastrointestinal tract infections	A00-A09
Intra-abdominal infections	K20.9A, K23.0-1, K35, K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.8I, K67, K75.0-1, K77.0, K80.0, K80.3-4, K81.0, K83.0, K85.9, K93.0-1
Urinary tract infections	N10, N12, N15.1, N30.0, N33.0, N34.0-1, N39.0

Infection of central nervous system	G00-G02, G04-07, A80-A89, A39
Skin and subcutaneous infections	A46, J34, L000-L08
Abscess	A06.5, A54.1, B43, D73.3, E06.0A, E23.6A, E32.1, G06, G07, H00.0A, H05.0A, H44.0A, H60.0, J34.0A, J36, J38.3D, J38.7G, J39.0, J39.1, J39.8A, J85.1, J85.2, J85.3, K04.6, K04.7, K11.3, K12.2, K13.0A, K14.0A, K20.9A, K35.3A, K35.3B, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K75.0, K81.0A, K85.8A, L02, L05.0, L05.9, M60.8A, M86.8A, M86.9A, N15.1, N34.0, N41.2, N45.0, N48.2, N49.2A, N61.9A, N61.9B, N70.0A, N70.0B, N71.0A, N73.0A, N73.0B, N73.2A, N73.2B, N73.3A, N73.5A, N73.8A, N73.8C, N75.1, N76.4, N76.8A, Except: A54.1B, B43.0, B43.8, B43.9, K57.0B, K57.0C, K57.2B, K57.2C, K57.4A, K65.0M, K65.0N, K65.0O, K65.0P
Septicaemia	A40, A41
Tuberculosis	A15-A19
Viral infections	B00-B09, B15-B19, B25-B34, A90-A99
Fungal infections	B35-B49
Malignant external otitis	H60.2
Emphysematous cholecystitis	K81.0
Emphysematous cystitis	N30.8
Emphysematous pyelonephritis	N10
Perirenal abscess	N15.9

ATC-codes used to identify specific subgroups of antibiotics

Phenoxymethylpenicillin	J01CE02
Pivampicillin, amoxicillin, amoxicillin+enzyme inhibitor	J01CA02, J01CA04, J01CR02
Macrolides	J01FA
Azithromycin	J01FA10
Erythromycin, roxithromycin, clarithromycin	J01FA01, J01FA06, J01FA09
Pivmecillinam, sulfamethizole, nitrofurantoin, trimethoprim	J01CA08, J01EB02, J01XE01, J01EA01,
Dicloxacillin, flucloxacillin	J01CF01, J01CF05
Antimycobacterial	J04A
Quinolones	J01M

Tetracycline	J01A
Cephalosporin	J01D
Antifungal	J02xx
Antiviral	J04xx
Codes used to identify covariates	
Alcoholism-related disorders	ICD-10-codes: K70, K852, K860, E244, F101, F102, F103, F104, F105, F106, F107, F108, F109, G621, G721, G312, I426, K292, Z721, T500A, E529A, Z502, Z714
Statins	ATC-codes: B04AB
Immunosuppresants	ATC-codes: L01, L04
Oral corticosteroids	ATC-codes: H02AB

Reports/PhD theses from Department of Clinical Epidemiology

1. Ane Marie Thulstrup: Mortality, infections and operative risk in patients with liver cirrhosis in Denmark. Clinical epidemiological studies. PhD thesis. *2000*.

2. Nana Thrane: Prescription of systemic antibiotics for Danish children. PhD thesis. *2000*.

3. Charlotte Søndergaard. Follow-up studies of prenatal, perinatal and postnatal risk factors in infantile colic. PhD thesis. *2001*.

4. Charlotte Olesen: Use of the North Jutland Prescription Database in epidemiological studies of drug use and drug safety during pregnancy. PhD thesis. *2001*.

5. Yuan Wei: The impact of fetal growth on the subsequent risk of infectious disease and asthma in childhood. PhD thesis. *2001*.

6. Gitte Pedersen. Bacteremia: treatment and prognosis. PhD thesis. *2001*.

7. Henrik Gregersen: The prognosis of Danish patients with monoclonal gammopathy of undertermined significance: register-based studies. PhD thesis. *2002*.

8. Bente Nørgård: Colitis ulcerosa, coeliaki og graviditet; en oversigt med speciel reference til forløb og sikkerhed af medicinsk behandling. PhD thesis. *2002*.

9. Søren Paaske Johnsen: Risk factors for stroke with special reference to diet, Chlamydia pneumoniae, infection, and use of non-steroidal anti-inflammatory drugs. PhD thesis. *2002*.

10. Elise Snitker Jensen: Seasonal variation of meningococcal disease and factors associated with its outcome. PhD thesis. *2003*.

11. Andrea Floyd: Drug-associated acute pancreatitis. Clinical epidemiological studies of selected drugs. PhD thesis. *2004*.

12. Pia Wogelius: Aspects of dental health in children with asthma. Epidemiological studies of dental anxiety and caries among children in North Jutland County, Denmark. PhD thesis. *2004*.

13. Kort-og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg og Århus amter 1985-2003. *2004*.

14. Reimar W. Thomsen: Diabetes mellitus and community-acquired bacteremia: risk and prognosis. PhD thesis. *2004*.

15. Kronisk obstruktiv lungesygdom i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

16. Lungebetændelse i Nordjyllands, Viborg og Århus amter 1994-2004. Forekomst og prognose. Et pilotprojekt. *2005*.

17. Kort- og langtidsoverlevelse efter indlæggelse for nyre-, bugspytkirtel- og leverkræft i Nordjyllands, Viborg, Ringkøbing og Århus amter 1985-2004. *2005*.

18. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Nordjyllands, Viborg, Ringkøbing og Århus amter 1995-2005. *2005*.

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20. Alma Becic Pedersen: Studies based on the Danish Hip Arthroplastry Registry. PhD thesis. *2006*.

    Særtryk: Klinisk Epidemiologisk Afdeling - De første 5 år. *2006*.

21. Blindtarmsbetændelse i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

22. Andre sygdommes betydning for overlevelse efter indlæggelse for seks kræftsygdomme i Nordjyllands, Viborg, Ringkjøbing og Århus amter 1995-2005. *2006*.

23. Ambulante besøg og indlæggelser for udvalgte kroniske sygdomme på somatiske hospitaler i Århus, Ringkjøbing, Viborg, og Nordjyllands amter. *2006*.

24. Ellen M Mikkelsen: Impact of genetic counseling for hereditary breast and ovarian cancer disposition on psychosocial outcomes and risk perception: A population-based follow-up study. PhD thesis. *2006*.

25. Forbruget af lægemidler mod kroniske sygdomme i Århus, Viborg og Nordjyllands amter 2004-2005. *2006*.

26. Tilbagelægning af kolostomi og ileostomi i Vejle, Ringkjøbing, Viborg, Nordjyllands og Århus Amter. *2006*.

27. Rune Erichsen: Time trend in incidence and prognosis of primary liver cancer and liver cancer of unknown origin in a Danish region, 1985-2004. Research year report. *2007*.

28. Vivian Langagergaard: Birth outcome in Danish women with breast cancer, cutaneous malignant melanoma, and Hodgkin's disease. PhD thesis. *2007*.

29. Cynthia de Luise: The relationship between chronic obstructive pulmonary disease, comorbidity and mortality following hip fracture. PhD thesis. *2007*.

30. Kirstine Kobberøe Søgaard: Risk of venous thromboembolism in patients with liver disease: A nationwide population-based case-control study. Research year report. *2007*.

31. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1995-2006. *2007*.

32. Mette Skytte Tetsche: Prognosis for ovarian cancer in Denmark 1980-2005: Studies of use of hospital discharge data to monitor and study prognosis and impact of comorbidity and venous thromboembolism on survival. PhD thesis. *2007*.

33. Estrid Muff Munk: Clinical epidemiological studies in patients with unexplained chest and/or epigastric pain. PhD thesis. *2007*.

34. Sygehuskontakter og lægemiddelforbrug for udvalgte kroniske sygdomme i Region Nordjylland. *2007*.

35. Vera Ehrenstein: Association of Apgar score and postterm delivery with neurologic morbidity: Cohort studies using data from Danish population registries. PhD thesis. *2007*.

36. Annette Østergaard Jensen: Chronic diseases and non-melanoma skin cancer. The impact on risk and prognosis. PhD thesis. *2008*.

37. Use of medical databases in clinical epidemiology. *2008*.

38. Majken Karoline Jensen: Genetic variation related to high-density lipoprotein metabolism and risk of coronary heart disease. PhD thesis. *2008*.

39. Blodprop i hjertet - forekomst og prognose. En undersøgelse af førstegangsindlæggelser i Region Nordjylland og Region Midtjylland. *2008*.

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41. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme i Region Midtjylland og Region Nordjylland 1996-2007. *2008*.

    Sandra Kruchov Thygesen. Atrial fibrillation in patients with ischemic stroke: A population-based study. Research year report. *2008*.

42. Akutte indlæggelsesforløb og skadestuebesøg på hospiter i Region Midtjylland og Region Nordjylland 2003-2007. Et pilotprojekt. *Not published*.

43. Peter Jepsen: Prognosis for Danish patients with liver cirrhosis. PhD thesis. *2009*.

44. Lars Pedersen: Use of Danish health registries to study drug-induced birth defects – A review with special reference to methodological issues and maternal use of non-steroidal anti-inflammatory drugs and Loratadine. PhD thesis. *2009*.

45. Steffen Christensen: Prognosis of Danish patients in intensive care. Clinical epidemiological studies on the impact of preadmission cardiovascular drug use on mortality. PhD thesis. *2009*.

46. Morten Schmidt: Use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs and risk of cardiovascular events and death after intracoronary stenting. Research year report. *2009*.

47. Jette Bromman Kornum: Obesity, diabetes and hospitalization with pneumonia. PhD thesis. *2009*.

48. Theis Thilemann: Medication use and risk of revision after primary total hip arthroplasty. PhD thesis. *2009*.

49. Operativ fjernelse af galdeblæren. Region Midtjylland & Region Nordjylland. 1998-2008. *2009*.

50. Mette Søgaard: Diagnosis and prognosis of patients with community-acquired bacteremia. PhD thesis. *2009*.

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53. Kort- og langtidsoverlevelse efter indlæggelse for udvalgte kræftsygdomme. Region Midtjylland og Region Nordjylland 1997-2008. *2010*.

54. Prognosen efter akut indlæggelse på Medicinsk Visitationsafsnit på Nørrebrogade, Århus Sygehus. *2010*.

55. Kaare Haurvig Palnum: Implementation of clinical guidelines regarding acute treatment and secondary medical prophylaxis among patients with acute stroke in Denmark. PhD thesis. *2010*.

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58. Knoglemetastaser og skeletrelaterede hændelser blandt patienter med prostatakræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

59. Morten Olsen: Prognosis for Danish patients with congenital heart defects - Mortality, psychiatric morbidity, and educational achievement. PhD thesis. *2010*.

60. Knoglemetastaser og skeletrelaterede hændelser blandt kvinder med brystkræft i Danmark. Forekomst og prognose 1999-2007. *2010*.

61. Kort- og langtidsoverlevelse efter hospitalsbehandlet kræft. Region Midtjylland og Region Nordjylland 1998-2009. *2010*.

62. Anna Lei Lamberg: The use of new and existing data sources in non-melanoma skin cancer research. PhD thesis. *2011*.

63. Sigrún Alba Jóhannesdóttir: Mortality in cancer patients following a history of squamous cell skin cancer – A nationwide population-based cohort study. Research year report. *2011*.

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66. Anne-Mette Bay Bjørn: Use of corticosteroids in pregnancy. With special focus on the relation to congenital malformations in offspring and miscarriage. PhD thesis. *2012*.

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68. Christian Fynbo Christiansen: Diabetes, preadmission morbidity, and intensive care: population-based Danish studies of prognosis. PhD thesis. *2012*.

69. Jennie Maria Christin Strid: Hospitalization rate and 30-day mortality of patients with status asthmaticus in Denmark – A 16-year nationwide population-based cohort study. Research year report. *2012*.

70. Alkoholisk leversygdom i Region Midtjylland og Region Nordjylland. 2007-2011. *2012*.

71. Lars Jakobsen: Treatment and prognosis after the implementation of primary percutaneous coronary intervention as the standard treatment for ST-elevation myocardial infarction. PhD thesis. *2012*.

72. Anna Maria Platon: The impact of chronic obstructive pulmonary disease on intensive care unit admission and 30-day mortality in patients undergoing colorectal cancer surgery: a Danish population-based cohort study. Research year report. *2012*.

73. Rune Erichsen: Prognosis after Colorectal Cancer - A review of the specific impact of comorbidity, interval cancer, and colonic stent treatment. PhD thesis. *2013*.

74. Anna Byrjalsen: Use of Corticosteroids during Pregnancy and in the Postnatal Period and Risk of Asthma in Offspring - A Nationwide Danish Cohort Study. Research year report. *2013*.

75. Kristina Laugesen: In utero exposure to antidepressant drugs and risk of attention deficit hyperactivity disorder (ADHD). Research year report. *2013*.

76. Malene Kærslund Hansen: Post-operative acute kidney injury and five-year risk of death, myocardial infarction, and stroke among elective cardiac surgical patients: A cohort study. Research year report. *2013*.

77. Astrid Blicher Schelde: Impact of comorbidity on the prediction of first-time myocardial infarction, stroke, or death from single-photon emission computed tomography myocardial perfusion imaging: A Danish cohort study. Research year report. *2013*.

78. Risiko for kræft blandt patienter med kronisk obstruktiv lungesygdom (KOL) i Danmark. (Online publication only). *2013*.

79. Kirurgisk fjernelse af milten og risikoen for efterfølgende infektioner, blodpropper og død. Danmark 1996-2005. (Online publication only). *2013*.

    Jens Georg Hansen: Akut rhinosinuitis (ARS) – diagnostik og behandling af voksne i almen praksis. *2013*.

80. Henrik Gammelager: Prognosis after acute kidney injury among intensive care patients. PhD thesis. *2014*.

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90. Marie Dam Lauridsen: Impact of dialysis-requiring acute kidney injury on 5-year mortality after myocardial infarction-related cardiogenic shock - A population-based nationwide cohort study. Research year report. *2014*.

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    Mikkel S. Andersen: Danish Criteria-based Emergency Medical Dispatch – Ensuring 112 callers the right help in due time? PhD thesis. *2014*.

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99. Malene Schou Nielsson: Elderly patients, bacteremia, and intensive care: Risk and prognosis. PhD thesis. *2015*.

100. Jens Tilma: Treatment Injuries in Danish Public Hospitals 2006-2012. Research year report. *2015*.

101. Thomas Lyngaa: Intensive care at the end-of-life in patients dying of cancer and non-cancer chronic diseases: A nationwide study. Research year report. *2015*.

102. Lone Winther Lietzen: Markers of immune competence and the clinical course of breast cancer. PhD thesis. *2015*.

103. Anne Høy Seemann Vestergaard: Geographical Variation in Use of Intensive Care in Denmark: A Nationwide Study. Research year report. *2015*.

104. Cathrine Wildenschild Nielsen: Fecundability among Danish pregnancy planners. Studies on birth weight, gestational age and history of miscarriage. PhD thesis. *2015*.

105. Kathrine Dyhr Lycke: Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study. Research year report. *2015*.

106. Louise Bill: Hyponatremia in acute internal medicine patients: prevalence and prognosis. PhD thesis. *2015*.

107. Kirstine Kobberøe Søgaard: Risk and prognosis of venous thromboembolism in patients with liver disease. PhD thesis. *2015*.

108. Rikke Nørgaard Pedersen: Reoperation due to surgical bleeding in breast cancer patients and breast cancer recurrence: A Danish population-based cohort study. Research year report. *2015*.

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111. Sandra Kruchov Thygesen: Respiratory distress syndrome in moderately late and late preterm infants and selected long-term neurodevelopmental outcomes. PhD thesis. *2016*.

112. Alma Bečić Pedersen: Total hip replacement surgery - occurrence and prognosis. Doctoral dissertation. *2016*.