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ARTICLE

Elevated risk of infection in individuals with hyperinsulinaemic type 2 diabetes: a Danish 12 year cohort study

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Abstract

Aims/hypothesis A better understanding of the mechanisms underlying an elevated infection risk in individuals with type 2 diabetes is needed to guide risk stratification and prevention. We investigated the risk of infection in subgroups of individuals with type 2 diabetes according to indices of insulin sensitivity and beta cell function.

Methods We classified 7265 individuals with recently diagnosed type 2 diabetes (median duration 1.4 years, IQR 0.5–2.9 years) into hyperinsulinaemic (high beta cell function [HOMA 2-beta-cell function, HOMA2-B], low insulin sensitivity [HOMA 2-insulin sensitivity, HOMA2-S]), classical (low HOMA2-B, low HOMA2-S) and insulinopenic (low HOMA2-B, high HOMA2-S) type 2 diabetes. Individuals were followed until first hospital-treated infection or first prescription for an anti-infective agent (community-treated infection). We used Cox regression analysis to estimate HRs adjusted for age, sex, index year, diabetes duration and treatment, lifestyle behaviours and comorbidities.

Results Among study participants, 28% had hyperinsulinaemic, 63% had classical and 9% had insulinopenic type 2 diabetes. The 10 year risks of hospital-treated infections were 42.3%, 36.8% and 31.0% in the three subgroups, respectively. Compared with the insulinopenic subgroup, adjusted HRs for hospital-treated infections were elevated for hyperinsulinaemic (1.38 [95% CI 1.16, 1.65]) and classical type 2 diabetes (1.20 [95% CI 1.02, 1.42]). The 10 year risks of community-treated infections were high in all three subgroups at 91.6%, 90.1% and 88.3%, respectively, corresponding to adjusted HRs of 1.20 (95% CI 1.08, 1.33) for the hyperinsulinaemic and 1.10 (95% CI 1.00, 1.21) for the classical subgroup. Infection risk in the hyperinsulinaemic subgroup decreased substantially when further adjusted for abdominal obesity, metabolic derangements and low-grade inflammation.

Conclusions/interpretation The risk of severe infections is clearly elevated in individuals with type 2 diabetes characterised by a higher degree of insulin resistance/hyperinsulinaemia.

Keywords Clinical diabetes · Complications (all) · Epidemiology · Human · Insulin sensitivity and resistance

Abbreviations

CCI	Charlson comorbidity index
DAG	Directed acyclic graph
DD2	Danish Centre for Strategic Research in Type 2 Diabetes
DDDA	Danish Diabetes Database for Adults
GLP-1	Glucagon-like peptide-1
HOMA2-S	HOMA 2-insulin sensitivity
hsCRP	High-sensitivity C-reactive protein
IL-1RA	IL-1 receptor antagonist
SGLT-2	Sodium–glucose cotransporter 2

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Research in context

What is already known about this subject?

- The risk of infections is elevated in individuals with type 2 diabetes compared with the general population
- Hyperglycaemia and obesity are well-established risk factors for infections
- Little is known about the impact of insulin resistance and/or hyperinsulinaemia on the risk of infections in individuals with type 2 diabetes

What is the key question?

- Is infection risk elevated in type 2 diabetes subgroups according to the degree of insulin resistance or hyperinsulinaemia?

What are the new findings?

- The risk of particularly severe infections requiring hospitalisation was elevated in individuals with hyperinsulinaemic type 2 diabetes (high HOMA2-B, low HOMA2-S)
- The risk of community-treated infections was also elevated, albeit to a lesser degree
- Abdominal obesity, metabolic derangements and low-grade inflammation explained a substantial part of the association

How might this impact on clinical practice in the foreseeable future?

- Our data indicate an unmet need for targeted prevention of infections in individuals with new-onset type 2 diabetes characterised by a higher degree of insulin resistance/hyperinsulinaemia

Introduction

Infections are a leading complication of type 2 diabetes and an underestimated cause of death [1–8]. Despite strong evidence of a 1.5- to twofold elevated risk of many different infections in individuals with type 2 diabetes compared with the general population [2, 4, 5, 7, 8], the exact mechanisms underlying this association remain poorly understood. Knowledge is limited about infection predictors beyond poor glycaemic control [9–13] and increased BMI [14, 15] or abdominal obesity [16].

We recently proposed that type 2 diabetes can be classified into three pathophysiological subgroups, hyperinsulinaemic, classical and insulinopenic, based on the HOMA2 indices of fasting insulin sensitivity and beta cell function [17]. Compared with the other subgroups, individuals in the hyperinsulinaemic subgroup are characterised by low insulin sensitivity and compensatory high beta cell function with more severe metabolic derangement, including abdominal obesity, dyslipidaemia, hypertension, systemic low-grade inflammation and an elevated risk of cardiovascular diseases and mortality [18, 19]. Individuals in the classical subgroup have low insulin sensitivity and low beta cell function and an intermediate cardiovascular risk, while individuals in the insulinopenic subgroup with high insulin sensitivity and low beta cell function are generally slimmer and cardio-metabolically healthier. Still, the latter group may have relatively high HbA_{1c} and be at elevated risk of outcomes closely related to hyperglycaemia, such as retinopathy [18] and possibly also infections [9, 13], but data are scarce.

Evidence from animal and clinical studies suggests that insulin resistance and/or hyperinsulinaemia may lower protection against infection by dysregulating cytokine production, altering macrophage differentiation and disrupting the balance between the immune system and adipose cells [20–22]. Previous studies focusing mainly on respiratory tract infections, such as COVID-19, influenza and pneumonia [10–12, 14–16, 21–24], have suggested that obesity is a risk factor, regardless of type 2 diabetes. Other studies suggest that there is an acute and reversible impact of hyperglycaemia or high glucose variability on infection risk in individuals with diabetes [9, 25]. There is a scarcity of data regarding the impact of insulin resistance and/or hyperinsulinaemia on the risk of infections in individuals with type 2 diabetes [1, 9].

To guide risk stratification and improve our understanding of mechanisms underlying the elevated infection risk in individuals with type 2 diabetes, we conducted a nationwide cohort study among individuals with recently

diagnosed type 2 diabetes and varying degree of insulin resistance/hyperinsulinaemia. We aimed to clarify whether indices of insulin resistance and beta cell function predict a particularly elevated risk of hospital-treated and community-treated infections in routine clinical care.

Methods

Study cohort and registry linkage We used the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort and biobank to conduct this study. DD2 is an ongoing nationwide cohort of individuals with recently diagnosed type 2 diabetes (median time from diagnosis to DD2 enrolment ~1 year) [26]. Participants have been enrolled from general practitioners' offices and hospital outpatient clinics since November 2010. At enrolment, they complete a short interview and undergo a physical examination. Urine and blood samples are also collected and stored in the DD2 biobank [26].

The unique personal identifier (CPR number) assigned to all Danish residents at birth or upon immigration enables record linkage on an individual level among Danish health and administrative registries [27]. The last digit in the CPR number further indicates the sex of the person by being odd for male and even for female individuals. Data from the DD2 cohort are linked to the nationwide Danish Diabetes Database for Adults (DDDA), the Danish Civil Registration System, the Danish National Patient Registry, the Danish National Prescription Registry and the Nationwide Register of Laboratory Results for Research. These registries provide additional detailed clinical data and complete follow-up [27]. We did not have access to information on ethnicity or race in the current dataset. A description of the registries is provided in the electronic supplementary material (ESM: Linkage with medical databases).

The DD2 project was approved by the Danish Data Protection Agency (nos 2016-051-000001/438/2514 and 2008-58-0035) and the Danish Regional Ethical Committee on Health Research for Southern Denmark (record no. S-20100082). All participants give written informed consent.

Study cohort Our study included participants enrolled in DD2 between November 2010 and March 2022 (N=10,329, ESM Fig. 1). Exclusion criteria included the following reasons: no blood sample collected in the DD2 biobank (n=316); diagnosed with other specific forms of diabetes than type 2 diabetes (n=515); lacking measurements of glucose or C-peptide to calculate HOMA2 (n=411); non-fasting at the time of blood sampling (n=1771); belonging to a type 2 diabetes subgroup characterised by normoglycaemia and normoinsulinaemia (n=35); or residing in Denmark for less than 1 year prior to DD2 enrolment (n=16) [26, 28].

HOMA2 measurements Fasting serum C-peptide and plasma glucose values were measured at time of DD2 enrolment and used in the HOMA2 computational model (University of Oxford, Oxford, UK) to calculate indices of insulin sensitivity (HOMA 2-insulin sensitivity, HOMA2-S) and beta cell function (HOMA 2-beta cell function, HOMA2-B) [29]. We classified study participants into three distinct type 2 diabetes subgroups: hyperinsulinaemic (HOMA2-S<63.5 and HOMA2-B≥115.3), classical (HOMA2-S<63.5 and HOMA2-B<115.3) and insulinopenic (HOMA2-S≥63.5 and HOMA2-B<115.3). This classification was based on cut-offs utilising the median insulin sensitivity and beta cell function values derived from a random non-diabetic population residing in the region of Southern Denmark (a detailed description of the classification is provided in ESM Fig. 2).

Infection outcomes We examined two primary outcomes: hospital-treated infections and community-treated infections, respectively [7, 9, 30]. Hospital-treated infections were defined as the first post-enrolment occurrence of a hospital contact yielding a primary or secondary discharge diagnosis of any infection recorded in the Patient Registry [9]. Community-treated infections were defined as the first post-enrolment prescription redemption at a community pharmacy for a systemic anti-infective agent prescribed by either a primary care or hospital-based physician, as recorded in the Prescription Registry.

Covariates ESM Tables 1–4 provide definitions of study covariates. Data on potentially important risk factors for infections ascertained from the literature were obtained at DD2 enrolment and from the linked registries described above. Covariates accessed at DD2 enrolment included anthropometric measures (i.e. waist circumference, height and weight), alcohol intake (i.e. above or below the Danish Health Authority's recommendation), self-reported physical activity (i.e. number of days with ≥30 min of moderate to vigorous physical activity) and biomarkers of low-grade inflammation (high-sensitivity C-reactive protein [hsCRP], TNF-α, IL-6 and IL-1 receptor antagonist [IL-1RA]). We also accessed information on smoking habits and smoking-related diseases/medication, comorbidities, history of previous infections, use of medication and routine care laboratory biomarkers from the linked registries.

Statistical analyses We first described characteristics of study participants according to their underlying type 2 diabetes subgroup: hyperinsulinaemic, classical and insulinopenic. We then followed each individual from DD2 enrolment until the first occurrence of an infection, death,

emigration or study end (31 May 2023). Analyses of hospital-treated and community-treated infections were conducted separately. We computed rates of hospital-treated and community-treated infections by dividing the number of first incident infection events by the total number of person-years in each subgroup. We used the Aalen–Johansen estimator to report the 10 year cumulative risk of infections during follow-up, taking competing risk of death into consideration. We employed a Cox proportional hazard regression model to calculate crude and adjusted HRs with 95% CIs. In accordance with our research hypothesis that insulin resistance/hyperinsulinaemia predicts an elevated infection risk, we chose the insulinopenic/insulin-sensitive subgroup as the reference group.

Plausible confounding variables (i.e. that may contribute in causing the pathophysiological type 2 diabetes subgroup defined at DD2 enrolment and cause elevated infection risk) were chosen before conducting the analyses, based on prior knowledge and literature search (ESM Fig. 3 describes a directed acyclic graph [DAG] for this relation) [10–12]. Using an iterative approach, we built an adjustment model and described the strength of association for each adjustment domain of plausible confounders.

In accordance with our DAG, the main model included the following confounder domains: demographic factors (age, sex and index year), diabetes duration and intensity of glucose-lowering drug treatment, lifestyle behaviours (physical activity, alcohol intake, smoking habits and smoking-related diseases/medications) and comorbidities (any macro- or microvascular diabetes complications, eGFR as a marker of kidney function, chronic pulmonary disease, chronic liver disease, alcohol-related disorders, cancer and Charlson comorbidity index [CCI] score). The DAG also revealed important factors that could be affected by the level of insulin sensitivity and beta cell function characterising each type 2 diabetes subgroup and in turn increase the risk of infections. Thus, these factors could be potential intermediates: abdominal obesity (waist circumference), metabolic derangements (triglycerides, HDL-cholesterol, HbA_{1c} and hypertension) and markers of low-grade inflammation (hsCRP, TNF-α, IL-6 and IL-1RA). We included these factors in an extended model based on a stepwise approach to investigate any further changes in risk estimates when adjusting for them as recommended [31]. Low-grade inflammation markers were log-transformed.

While data on covariates recorded at DD2 enrolment had high completeness (>90%), covariates accessed from the DDDA and the Register of Laboratory Results for Research had an incompleteness of 17–45% (ESM Tables 1–4). To overcome potential selection bias in our complete case analysis, we imputed missing values for all covariates assuming that the values were missing at random (see the ESM: Multiple imputation of missing covariates).

We visually inspected log minus log plots and tested the assumption of proportional hazards during follow-up using Schoenfeld residuals. No deviation was found in either model.

Additional analyses To improve our understanding of potential mechanisms underlying the exposure–outcome association, we carried out additional analyses. First, to test for any heterogeneity of results, we stratified the main model on age (≤54, 55–69, ≥70 years), sex (male, female), CCI score (0, 1+), abdominal obesity (waist circumference </≥88/102 cm [female/male]), hsCRP (<1 mg/l, 1–3 mg/l, >3 mg/l), hyperglycaemia (HbA_{1c} </≥53 mmol/mol [</≥7.0%]) and prior hospital-treated infection ≤1 year (yes/no). Second, we performed analyses for the following common subtypes of hospital-treated infections: urinary tract infections, skin and subcutaneous infections, sepsis, respiratory tract infections and gastrointestinal/intra-abdominal infections. Third, we used restricted cubic spline models to represent the association of continuously measured HOMA2-S and HOMA2-B with infection outcomes, thus allowing for non-linear associations. Based on an a priori assumption that the exposure–outcome association might be complex, we chose to use a five-knot spline to characterise any dose–response association with a high degree of flexibility [32]. Knots were placed at default locations [33]. In the study cohort, the 5th percentile of the HOMA2-S distribution corresponded to 17.5% and the 95th percentile corresponded to 72.9%, while for HOMA2-B the 5th percentile corresponded to 42.3% and the 95th percentile corresponded to 169.7%. Fourth, to limit the risk of reverse causality, i.e. early/ongoing infections that possibly had affected metabolic factors, we excluded study participants with very high levels of inflammatory markers (above the 99th percentile of the hsCRP, TNF-α, IL-6 or IL-1RA distributions). Fifth, we restricted our analyses of hospital-treated infections to include only primary (first-listed) discharge diagnoses of infection, indicating that infection was community-acquired and the main reason for admission. Sixth, we reran our main model with additional adjustment for history of infections as well as use of glucagon-like peptide-1 (GLP-1) receptor agonists and sodium–glucose cotransporter 2 (SGLT-2) inhibitors prior to study enrolment. All data management, statistical analyses and graphical computation were performed using Stata version 18 (StataCorp LLC, Texas, US).

Results

Individual characteristics by type 2 diabetes subgroup Among the 7265 individuals included in the study, 28% had hyperinsulinaemic, 63% had classical and 9% had insulinopenic type 2 diabetes (Table 1, ESM Fig. 1).

Table 1 Characteristics of study participants according to type 2 diabetes subgroup

Characteristic	Insulinopenic	Classical	Hyperinsulinaemic
Number (%)	636 (9)	4607 (63)	2022 (28)
Age, years	63 (54–70)	61 (53–68)	62 (52–69)
Male	377 (59)	2800 (61)	1113 (55)
Diabetes duration, years	1.5 (0.5–3.2)	1.5 (0.5–3.1)	1.1 (0.4–2.4)
Relatives with type 2 diabetes	335 (53)	2560 (56)	998 (49)
>14/21 alcohol units/week (F/M)	36 (6)	305 (7)	93 (5)
Smoking[a]			
Never	202 (53)	1213 (48)	481 (45)
Former	118 (31)	855 (33)	387 (36)
Current	61 (16)	475 (19)	201 (19)
Smoking (proxy)	71 (11)	618 (13)	389 (19)
Physical activity, days/week			
Always	NA (32)	NA (25)	NA (22)
5–6	133 (21)	754 (16)	274 (14)
3–4	157 (25)	1120 (24)	453 (22)
1–2	91 (14)	957 (21)	430 (21)
Never	50 (8)	600 (13)	408 (20)
Waist circumference, cm	93 (86–101)	106 (98–116)	113 (103–123)
Waist circumference ≥88/102 cm (F/M)	237 (37)	3558 (77)	1819 (90)
BMI, kg/m^2	26 (23–29)	30 (28–34)	34 (30–38)
BMI≥35 kg/m^{2a}	14 (3)	656 (23)	550 (42)
LDL-cholesterol, mmol/l	2.2 (1.7–2.9)	2.2 (1.7–2.9)	2.1 (1.6–2.8)
Triglycerides, mmol/l	1.1 (0.8–1.5)	1.7 (1.2–2.5)	1.9 (1.3–2.6)
Triglycerides≥1.7 mmol/l[a]	95 (20)	1776 (54)	922 (60)
HDL-cholesterol, mmol/l	1.4 (1.1–1.6)	1.2 (1.0–1.4)	1.1 (0.9–1.3)
HbA_{1c}, mmol/mol	47 (42–52)	49 (44–56)	46 (42–50)
HbA_{1c}, %	6.5 (6.0–6.9)	6.6 (6.2–7.3)	6.4 (6.0–6.7)
Fasting C-peptide, pmol/l	552 (470–602)	1082 (878–1345)	1575 (1256–1916)
Fasting glucose, mmol/l	6.5 (5.9–7.4)	7.8 (7.0–8.9)	6.4 (5.9–7.0)
HOMA2-S, %	74.8 (68.6–87.8)	36.3 (28.5–45.9)	26.7 (21.7–34.4)
HOMA2-B, %	62.8 (48.2–78.4)	82.0 (64.8–97.0)	138.3 (125.2–161.2)
eGFR, ml/min per 1.73 m^2	92.0 (83.0–100.0)	91.0 (79.0–101.0)	87.0 (72.0–99.0)
hsCRP, mg/l	0.8 (0.4–2.0)	1.9 (0.8–4.2)	2. 6 (1.1–5.3)
IL-6, pg/ml	0.9 (0.6–1.4)	1.2 (0.8–1.8)	1.4 (1.00–2.1)
IL-1RA, pg/ml	159.6 (122.4–215.9)	245.4 (173.7–384.6)	314.6 (208.9–502.5)
TNF-α, pg/ml	0.9 (0.7–1.1)	1.00 (0.8–1.2)	1.1 (0.9–1.3)
Macrovascular disease	96 (15)	840 (18)	526 (26)
Microvascular disease	79 (12)	656 (14)	351 (17)
Alcohol-related disorders	8 (1)	47 (1)	30 (1)
Chronic pulmonary disease	NA	NA	NA
Chronic liver disease	NA	NA	NA
Cancer	40 (6)	280 (6)	132 (7)
Hypertension	435 (68)	3614 (78)	1709 (85)
CCI			
0	520 (82)	3440 (75)	1323 (65)
1–2	92 (14)	1013 (22)	576 (28)
3+	24 (4)	154 (3)	123 (6)
Hospital-treated infections within 10 years	125 (20)	983 (21)	568 (28)
Hospital-treated infections within 1 year	28 (4)	183 (4)	114 (6)

Table 1 (continued)

Characteristic	Insulinopenic	Classical	Hyperinsulinaemic
Glucose-lowering drug treatment			
No therapy	89 (14)	661 (14)	293 (14)
Monotherapy	384 (60)	2922 (63)	1398 (69)
Non-insulin polytherapy	80 (13)	799 (17)	253 (13)
Insulin therapy	83 (13)	225 (5)	78 (4)
Statins	420 (66)	3164 (69)	1436 (71)
Antihypertensives	355 (56)	3198 (69)	1601 (79)
Antidepressants	66 (10)	598 (13)	367 (18)
Corticosteroids	27 (4)	146 (3)	114 (6)

Continuous covariates are presented as medians with IQRs and categorical covariates as numbers with percentage points. Covariate definitions and information on missing data are provided in ESM Tables 1–4

NA due to fewer than five observations or high data completeness making the information personally identifiable

[a]Percentage was calculated among individuals with available data

F/M, female/male; NA, not applicable

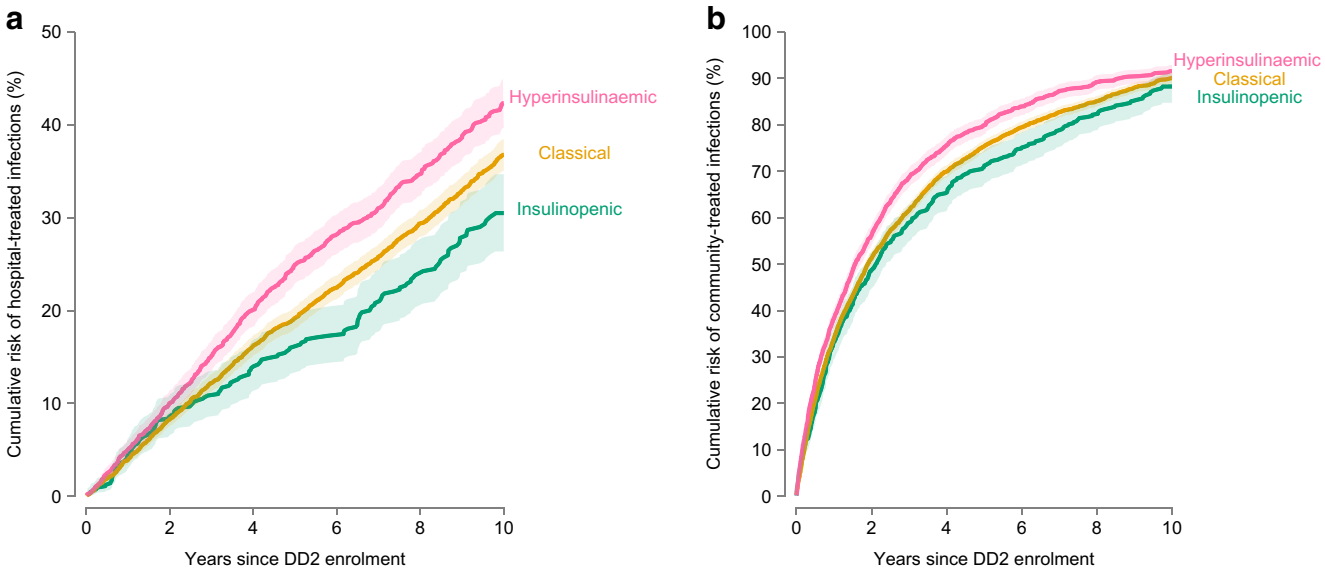

Fig. 1 Crude cumulative risk of hospital-treated (**a**) and community-treated (**b**) infections according to type 2 diabetes subgroup, treating death as a competing risk

Compared with the other two subgroups, hyperinsulinaemic individuals had shorter median diabetes duration (1.1 years for hyperinsulinaemic vs 1.5 years for classical vs 1.5 years for insulinopenic). Individuals with hyperinsulinaemic type 2 diabetes had higher prevalence of abdominal obesity (waist circumference ≥88/102 cm [female/male]: 90% vs 77% vs 37%) and more derangement of most metabolic factors (e.g. triglycerides≥1.7 mmol/l: 60% vs 54% vs 20%), except for HbA_{1c} (46 mmol/mol [6.4%] vs 49 mmol/mol [6.6%] vs 47 mmol/mol [6.5%]). They also had more comorbidity at baseline (e.g. macrovascular complications: 26% vs 18% vs 15%) and higher levels of low-grade inflammation (e.g. median IL-6 values: 1.43 pg/ml vs 1.17 pg/ml vs 0.88 pg/ml). Individuals in the hyperinsulinaemic subgroup more often had a history of previous hospital-treated infections, both within the last 10 years before enrolment (28% vs 21% vs 20%), and within 1 year prior (6% vs 4% vs 4%), as compared with individuals with classical and insulinopenic type 2 diabetes (Table 1).

Type 2 diabetes subgroups and risk of infections The entire cohort was followed for a median duration of 7.0 years (IQR 3.2–9.5 years) for hospital-treated infections. Follow-up was much shorter (1.7 years [IQR 0.6–3.7 years]) for

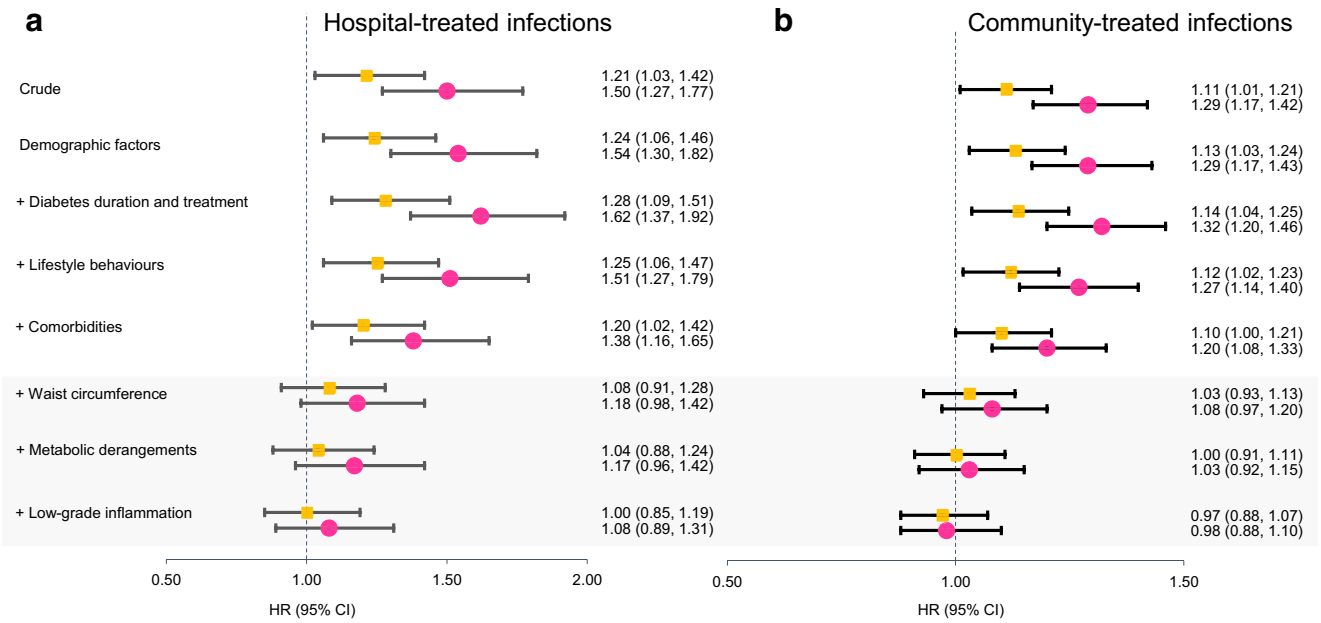

Fig. 2 HRs with additive confounder adjustment for hospital-treated (**a**) and community-treated (**b**) infections according to type 2 diabetes subgroup, with the insulinopenic subgroup used as reference. Yellow squares indicate point estimates for the classical subgroup, while pink circles indicate point estimates for the hyperinsulinaemic subgroup. The main model included the following adjustment domains: demographic factors (age, sex and index year), diabetes duration and intensity of glucose-lowering drug treatment, lifestyle behaviours (physical activity, alcohol intake, smoking habits and smoking-related diseases/medication) and comorbidities (any macrovascular or microvascular complications, eGFR, chronic pulmonary disease, chronic liver disease, alcohol abuse, cancer and CCI score). The extended adjustment model (shaded box at the bottom) further included, in addition to covariates in the main model, potential intermediate factors of the exposure–outcome association: abdominal obesity (i.e. waist circumference), metabolic derangements (i.e. triglycerides, HDL-cholesterol, HbA_{1c} and hypertension) and markers of low-grade inflammation (i.e. hsCRP, TNF-α, IL-6, IL-1RA)

community-treated infections, corresponding to systemic antibiotic treatment occurring very frequently. In total, 2234 individuals experienced a first hospital-treated infection, while 6034 experienced a first community-treated infection. The 10 year cumulative risk curves showed that, compared with the classical and insulinopenic subgroups, individuals in the hyperinsulinaemic subgroup had clearly higher risks of experiencing a hospital-treated infection (42.3% [95% CI 39.7%, 45.0%] vs 36.8% [95% CI 35.1%, 38.5%] vs 31.0% [95% CI 26.4%, 34.7%]). A similar pattern was observed for community-treated infections, which were very frequent in all subgroups, with the hyperinsulinaemic subgroup experiencing the highest risk (91.6% [95% CI 89.9%, 92.9%] vs 90.1% [95% CI 88.9%, 91.1%] vs 88.3% [95% CI 84.1%, 91.0%], respectively) (Fig. 1).

For incident hospital-treated infection, after adjustment for DAG-defined confounders (ESM Fig. 3), the adjusted HRs in the main model were markedly elevated at 1.38 (95% CI 1.16, 1.65) for hyperinsulinaemic individuals and at 1.20 (95% CI 1.02, 1.42) for the classical subgroup, compared with the insulinopenic subgroup (Fig. 2). As illustrated by the stepwise confounder adjustment, controlling only for differences in demographic factors and diabetes duration and treatment intensity led to a further increase in the infection HRs for both the hyperinsulinaemic and classical subgroups, primarily because individuals in these subgroups were younger and received more intensive glucose-lowering drug treatment compared with individuals in the insulinopenic subgroup. The HRs were attenuated again when we adjusted additionally for unhealthy lifestyle behaviours and comorbidities in the hyperinsulinaemic and classical subgroups vs the insulinopenic subgroup (Fig. 2).

A similar graduated pattern of association was observed for community-treated infections, although HRs were less markedly elevated, likely related to high baseline rates even in the reference group (Fig. 2). In the main model, adjusted HRs were 1.20 (95% CI 1.08, 1.33) for the hyperinsulinaemic and 1.10 (95% CI 1.00, 1.21) for the classical subgroup, as compared with insulinopenic individuals (Fig. 2). Again, adjusting only for demographic factors and diabetes duration and treatment intensity led the association further away from the null for both hyperinsulinaemic and classical individuals, while also adjusting for unhealthy lifestyle behaviours and comorbidities led to a decrease in HRs.

Finally, additional adjustment for potential intermediate factors (extended model), including waist circumference, triglycerides, HDL-cholesterol, hypertension, HbA_{1c}, hsCRP, TNF-α, IL-6 and IL-1RA, attenuated the association towards

the null; adjusted HRs for hospital-treated infections were thus 1.08 (95% CI 0.89, 1.31) for the hyperinsulinaemic and 1.00 (95% CI 0.85, 1.19) for the classical subgroup (Fig. 2). For community-treated infections, HRs were close to unity in the extended model, i.e. 0.98 (95% CI 0.88, 1.10) for the hyperinsulinaemic and 0.97 (95% CI 0.88, 1.07) for the classical subgroup.

Additional analyses In spline models of hospital-treated infections, adjusted HRs increased with gradually lower levels of insulin sensitivity (HOMA2-S<35%), while the infection HR increased both with very low (<70%) and with increasingly high (>100%) levels of beta cell function (HOMA2-B) (ESM Fig. 4). For community-treated infections, we observed an elevated infection risk with lower levels of insulin sensitivity (HOMA2-S<50%), while observing a positive linear association between higher infection risk and higher HOMA2-B (ESM Fig. 4). When assessing subtypes of hospital-treated infection, the highest overall event rates were observed for urinary and respiratory tract infections, as expected. For all infections, we observed a consistent pattern of modestly elevated adjusted HRs in the classical subgroup and highly elevated adjusted HRs in the hyperinsulinaemic subgroup (ESM Table 5). Especially skin and subcutaneous infections were substantially elevated (HR 2.75 [95% CI 1.74, 4.33]) in the hyperinsulinaemic subgroup, but also, for sepsis and for gastrointestinal/intra-abdominal infections, HRs were about twofold elevated in this group, compared with insulinopenic individuals. In stratified analyses, the gradient of infection hazards across type 2 diabetes subgroups was similar among men and women, and across different levels of central obesity, inflammation and glucose control. However, the relative impact of the subgroups on infection risk attenuated with higher age and with number of comorbidities (CCI score=1+), i.e. adjusted HR differences were more modest among those individuals who had high baseline infection rates (ESM Tables 6, 7). Finally, the results were robust in sensitivity analyses: (1) when excluding individuals with very high inflammatory markers indicating potential ongoing infection at enrolment; (2) when restricting hospital-treated infections to primary discharge diagnoses of infection; (3) when adjusting for history of infections; and (4) when adjusting for use of GLP-1 receptor agonists and SGLT-2 inhibitors prior to enrolment (ESM Table 8).

Discussion

In a large nationwide cohort of individuals recently diagnosed with type 2 diabetes and recruited from routine clinical care settings, we found clinically important increases in infection risk in the subgroup of individuals with hyperinsulinaemia and marked insulin resistance. The relative risk in this subgroup was highest for severe infections requiring hospitalisation. Notably, increases in infection risk persisted after controlling for differences in age and sex, diabetes duration and treatment intensity, lifestyle behaviours and comorbidities. However, the associations attenuated strongly towards the null when further controlling for abdominal obesity (waist circumference), other metabolic derangements (triglycerides, HDL-cholesterol, HbA_{1c} and hypertension) and low-grade inflammation (hsCRP, TNF-α, IL-6 and IL-1RA). This suggests that these factors may account for a substantial part of the association between insulin resistance/hyperinsulinaemia and infections.

Beyond studies on COVID-19, a few prior studies in the general population have linked obesity to elevated infection risk, with HRs varying between 1.2 and 1.5 for BMI≥30 kg/m^2 [14, 15]. Studies of infection risk in individuals with diabetes have suggested mainly poor glycaemic control [9–13], type 1 vs type 2 diabetes [4, 8, 25] or presence of diabetes complications [11] as risk factors for infections. This is reflected in current risk stratification and vaccination guidelines, e.g. for COVID-19 [34]. Our study extends these findings and suggests major heterogeneity in infection risk among individuals with type 2 diabetes. A similar heterogeneity has been observed for other important clinical outcomes, e.g. cardiovascular disease, microvascular complications and all-cause mortality [18, 19].

Our results of an infection risk gradient from insulinopenic to classical to hyperinsulinaemic individuals were remarkably robust across differences in age, sex and infection subtypes. This suggests a more general effect of insulin resistance/hyperinsulinaemia on resistance to infection, as modes of transmission and infection development are rather different for the different infection subtypes examined. A similar general effect of the current level of glucose control on risk and outcomes of various infections has been reported in type 1 and type 2 diabetes cohort studies [9, 25], suggesting that both marked hyperglycaemia and marked insulin resistance/hyperinsulinaemia may independently impact immunity, and may cause both elevated risk and elevated severity of infectious diseases. In accordance, the risk of sepsis, a severe clinical manifestation of many types of infections, was particularly elevated in the hyperinsulinaemic subgroup in our study. Of interest, there was only a small attenuation of infection risk estimates when we further controlled for use of novel glucose-lowering drugs, possibly related to the rare use in our population of individuals recently diagnosed with type 2 diabetes. SGLT-2 inhibitors and GLP-1 receptor agonists (and also metformin) have been suggested to lower the risk of COVID-19-related adverse outcomes in diabetes [34]. Further studies should be made to examine in more detail whether novel glucose-lowering drugs that are known to beneficially impact insulin

resistance/hyperinsulinaemia could have an impact on reducing infection risk [35, 36].

Our findings support previous studies that have suggested insulin resistance/hyperinsulinaemia to play a role in infection susceptibility among individuals with diabetes [20–22], and extend these findings by suggesting that abdominal obesity, more severe metabolic derangement and systemic low-grade inflammation may drive a large part of the elevated infection risk in the hyperinsulinaemic subgroup. It is well known that higher BMI and abdominal obesity is linked to more severe metabolic derangements and more systemic low-grade inflammation [37]. Anatomical and mechanical factors in obesity likely play a role as well, as recently observed in individuals with severe COVID-19 [24, 38, 39]. In accordance, skin and subcutaneous infections were highly elevated in the hyperinsulinaemic subgroup, possibly because obesity may cause excessive skinfolds and increase gravitational pressure on the lower extremities, causing oedema and ulcers. Regarding inflammation, one study suggested that low-grade inflammation assessed by soluble urokinase plasminogen activator receptor (suPAR) may explain up to 84% of any effect of diabetes on the risk of COVID-19 hospitalisation [10]. In another study, C-reactive protein mediated up to 32% of the association between diabetes and COVID-19 hospitalisation [40]. We have shown previously that abdominal adiposity is tightly associated with elevated levels of IL-6, TNF-α and hsCRP in individuals recently diagnosed with type 2 diabetes, likely due to the roles of IL-6 and TNF-α that are produced in visceral adipose tissue [37]. Many individuals with type 2 diabetes and obesity are thus in a chronic low-grade inflammatory state that may predispose them to an altered inflammatory response, reduced innate immune activity, and altered distribution and function of leukocytes, which together may lead to elevated susceptibility to infections [20–22]. Individuals with type 2 diabetes also seem to have reduced cytokine release during acute viral infections [41], but more research is needed to understand the exact pathophysiological mechanisms.

Our study has the advantage of accessing nationwide linked health registry data of high quality and generalisability for a population-based cohort of individuals recently diagnosed with type 2 diabetes and with complete follow-up. This minimises recall and information biases, as the infections were diagnosed and treated by medical specialists in routine care independent of our study hypotheses.

Several limitations of our study must also be noted. First, on the exposure side, use of HOMA2 provides an index of steady-state insulin sensitivity and beta cell function based on one measurement of fasting C-peptide and plasma glucose, without measuring a functional response. Although HOMA2-S and HOMA2-B are the most widely accepted surrogate measures of insulin sensitivity and beta cell function in epidemiological studies [29], our HOMA2 phenotyping has not been validated against gold standard dynamic stimulatory tests like the hyperinsulinaemic–euglycaemic clamp and the hyperglycaemic clamp in a clinical setting. Such gold standard tests are not feasible for large epidemiological studies. HOMA2 values per se should also be interpreted with caution, considering that 86% of our cohort had already started glucose-lowering medication and due to the potential time-dependent nature of HOMA2 [29]. Still, in our comparison of individuals in the insulinopenic (and insulin-sensitive) subgroup with individuals in the classical subgroup (who are also relatively insulinopenic but in addition insulin resistant), we obtain a more accurate estimation of the contribution of insulin resistance per se. Our results thus suggest an impact of insulin resistance itself on risk of severe infections. In turn, the residual high risk of infections observed in individuals with hyperinsulinaemic type 2 diabetes may be due to a further impact from high fasting insulin/C-peptide levels. Second, on the outcome side, the validity of our findings relies on the validity and completeness of diagnoses and prescriptions used for infections [7]. However, the validity of ICD-10 coding of infections in Danish registries is documented to be high [42]. Third, reverse causality may have affected our results, if previous infections (which were more frequent in hyperinsulinaemic individuals already before enrolment) had induced longer-term insulin resistance and hyperinsulinaemia [43]. However, stratification or adjustment of results by presence or absence of previous hospital-treated infections, and exclusion of participants with potentially ongoing infection at enrolment, yielded robust results. Fourth, it is difficult to determine whether covariates measured at baseline like abdominal obesity and metabolic derangements may qualify as mediators, confounders or both in our study because the exact underlying biological processes are uncertain. For example, abdominal obesity may have been a risk factor for hyperinsulinaemic type 2 diabetes and thus acts as a confounder. However, abdominal obesity may also have been influenced by high insulin levels over a prolonged period and thus acts as a mediator. In such cases, it is generally advised to conduct DAG-guided analyses both adjusting for and not adjusting for possible mediators as we have done in the present study [31]. Fifth, imperfectly measured, unmeasured, time-varying and unknown confounders may have had an impact on the risk estimates in this observational study. Finally, while the risk of infections was particularly elevated in the hyperinsulinaemic type 2 diabetes subgroup, it is important to remember that the risk of infections may still be increased in all subgroups of type 2 diabetes when compared with people without diabetes. While we in the current study could not estimate infection risk differences compared with individuals without diabetes, a previous Danish population-based cohort study of individuals with type 2 diabetes matched with a non-diabetes comparison cohort documented adjusted rate ratios

of 1.24 (95% CI 1.23, 1.25) for community-based antibiotic prescriptions and 1.49 (95% CI 1.47, 1.52) for hospital-treated infections [7].

In conclusion, presence of a higher degree of insulin resistance/hyperinsulinaemia in individuals with recently diagnosed type 2 diabetes predicted higher subsequent risk of infection, especially for severe infections requiring hospitalisation. Not only do severe infections increase mortality risk [1, 3, 8] and exacerbate insulin resistance [43], but infections might also precipitate acute metabolic complications such as diabetic ketoacidosis and hyperglycaemic hyperosmolar syndrome through direct negative effects on beta cell function in these individuals [39]. Therefore, the level of insulin resistance/hyperinsulinaemia and closely related factors (including degree of abdominal obesity, metabolic derangement and low-grade inflammation) should be considered in risk stratification efforts in clinical care, to guide appropriate preventive management of common infections. Preventive interventions may include both behavioural and pharmacological interventions, including weight loss and physical activity, good personal hygiene and vaccinations against respiratory tract infections (e.g. influenza, COVID-19 and pneumococcal disease), to reduce the excess infection risk in individuals with type 2 diabetes.

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Data availability The data that support the findings of this study are available from the authors but restrictions apply to the availability of these data, which were used under license from the Danish Health Data Authority (Copenhagen) for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission from the Danish Health Data Authority.

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Contribution statement HB-N, AV and HTS conceived the idea of and raised initial funding for establishing the DD2 cohort. RWT conceived the study idea. FPBK, SLD and RWT designed the study. FPBK did data management and statistical analysis. FPBK, SLD and RWT prepared the first draft of the manuscript. JSN is the principal manager of the DD2. HTS provided expert knowledge of clinical epidemiology, while JVS, KH, HB-N, PV, NJ, MHO, TH, CB and AV contributed with expert knowledge of type 2 diabetes and pathophysiological subgroups. All authors contributed to the interpretation of data and the drafting of the manuscript, as well as critically revising the manuscript draft. All authors approved the final version of the manuscript. FPBK and RWT are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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