



# Prevalence of micro- and macrovascular diabetes complications at time of type 2 diabetes diagnosis and associated clinical characteristics: A cross-sectional baseline study of 6958 patients in the Danish DD2 cohort



Anne Gedebjerg<sup>a,b,\*</sup>, Thomas Peter Almdal<sup>c</sup>, Klara Berencsi<sup>a</sup>, Jørgen Rungby<sup>d</sup>, Jens Steen Nielsen<sup>e</sup>, Daniel R. Witte<sup>b,f</sup>, Søren Friberg<sup>e</sup>, Ivan Brandslund<sup>g</sup>, Allan Vaag<sup>h</sup>, Henning Beck-Nielsen<sup>e</sup>, Henrik Toft Sørensen<sup>a</sup>, Reimar Wernich Thomsen<sup>a</sup>

<sup>a</sup> Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark

<sup>b</sup> Danish Diabetes Academy, Odense University Hospital, Odense, Denmark

<sup>c</sup> Department of Endocrinology PE, Rigshospitalet, University of Copenhagen, Denmark

<sup>d</sup> Department of Endocrinology IC, Bispebjerg University Hospital, Copenhagen, Denmark

<sup>e</sup> Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark

<sup>f</sup> Department of Public Health, Aarhus University, Aarhus, Denmark

<sup>g</sup> Department of Biochemistry, Lillebaelt Hospital, Vejle, Denmark

<sup>h</sup> AstraZeneca, Mölndal, Sweden

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## ABSTRACT

**Aims:** To examine the prevalence of micro- and macrovascular complications and their associated clinical characteristics at time of type 2 diabetes (T2D) diagnosis.

**Methods:** We examined the prevalence of complications and associated clinical characteristics among 6958 newly diagnosed T2D patients enrolled in the prospective Danish Center for Strategic Research in T2D cohort during 2010–2016. We calculated age- and gender-adjusted prevalence ratios (aPRs) of complications using log-binomial and Poisson regression.

**Results:** In total, 35% (n = 2456) T2D patients had diabetic complications around diagnosis; 12% (n = 828) had microvascular complications, 17% (n = 1186) macrovascular complications, and 6% (n = 442) had both. HbA1c levels of  $\geq 7\%$  were associated with microvascular complications [HbA1c 7%–8%; aPR: 1.35, 95% confidence interval (CI): 1.12–1.62] but not macrovascular complications [aPR: 0.91, 95% CI: 0.76–1.08]. High C-peptide  $\geq 800$  pmol/L was associated with macrovascular [aPR 1.34, 95% CI: 1.00–1.80] but not microvascular [aPR 0.97, 95% CI: 0.71–1.33] complications. Macrovascular complications were associated with male sex, age > 50 years, obesity, hypertriglyceridemia, low HDL cholesterol, smoking, elevated CRP levels, and anti-hypertensive therapy. Microvascular complications were associated with high blood pressure, hypertriglyceridemia, and absence of lipid-lowering therapy.

**Conclusions:** One-third of patients with T2D had diabetes complications around time of diagnosis. Our findings suggest different pathophysiological mechanisms behind micro- and macrovascular complications.

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## 1. Introduction

It is a major clinical and public health problem that a variable proportion of individuals with T2D remains undiagnosed and untreated before developing diabetes complications.<sup>1</sup> Many patients with T2D thus

present with complications already at time of diagnosis,<sup>1</sup> as the various pathophysiological abnormalities associated with T2D, such as hyperglycemia, dyslipidemia, and hypertension may have existed for several years.<sup>2,3</sup>

Recent data on the prevalence of diabetes-related complications at time of diagnosis are scarce. Many studies that examined this issue are 10–20 years old, and generally showed high prevalences of complications,<sup>4</sup> e.g., a ~36% prevalence of retinopathy in the UKPDS study.<sup>4</sup> Diabetes case-finding has been increasing in populations-at-

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\* Corresponding author at: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Alle 43–45, DK-8200 Aarhus N, Denmark.

E-mail address: [aged@clin.au.dk](mailto:aged@clin.au.dk) (A. Gedebjerg).

risk,<sup>5</sup> likely leading to earlier diabetes diagnoses and possibly a lower prevalence of complications at onset.<sup>6,7</sup> For example, Thomsen et al.<sup>6</sup> found that the median baseline hemoglobin A1c (HbA1c) measurement before initial glucose-lowering treatment in Denmark declined from 8.9% in 2000–2003 to 7.0% in 2010–2012, suggesting earlier diagnosis and therapy.

It is not well understood at present whether pathogenic processes leading to micro- and macrovascular T2D complications differ.<sup>8</sup> Hyperglycemia per se seems to be an important risk factor for microvascular outcomes but less so for macrovascular outcomes, for which traditional cardiovascular risk factors may play a greater role.<sup>4,9</sup> Moreover, several recent randomized clinical trials (RCTs)<sup>10–13</sup> have found that newer diabetes drugs exert a CVD protective effect beyond their glucose-lowering effect.<sup>9</sup> In this context, we hypothesized that clinical characteristics at baseline may differ between T2D patients presenting with micro- and macrovascular complications, with dysglycemia-related factors being more important for microvascular complications and metabolic syndrome-related factors more important for macrovascular complications. In the present study, we examined the prevalence of micro- and macrovascular complications and associated characteristics among newly diagnosed T2D patients in a large prospective Danish cohort.

## 2. Materials and methods

### 2.1. Study population

We conducted this cross-sectional study using information from the Danish Centre for Strategic Research in Type 2 Diabetes (DD2) project, which includes a nationwide cohort of newly or recently diagnosed type 2 diabetes mellitus (T2D) patients enrolled from general practitioners' (GPs) offices and hospital specialist outpatient clinics in Denmark since November 2010.<sup>14</sup> The implementation and logistics of the DD2 project, patient enrollment, and the DD2 biobank<sup>15</sup> have been described in detail previously.<sup>16</sup> In brief, GPs or hospital physicians provide detailed interview and clinical examination data for each DD2 patient at time of enrollment. This information is recorded in the DD2 database together with each patient's civil registration number (CPR number). Blood samples (fasting) and urine samples are obtained from each patient, either on the day of the interview or later.<sup>17</sup>

Our main study population consisted of all 6958 incident T2D patients currently enrolled in the DD2 cohort. The unique CPR number provided to each Danish resident, at birth or upon immigration, allowed data linkage of this cohort with other Danish registries. We could thus obtain a complete hospital contact history for each DD2 participant through linkage with the Danish National Patient Registry (DNPR), which covers all Danish hospitals and contains discharge records from all inpatient hospitalizations since 1977 and all hospital outpatient clinic and emergency department visits since 1995.<sup>18</sup> Additionally, we obtained complete data on filled medication prescriptions for each DD2 participant through linkage with the Danish National Health Service Prescription Database (DNHSPD).<sup>19</sup> Through linkage with a nationwide quality-of-care database, the Danish Diabetes Database for Adults (DDDA), we were furthermore able to extract additional clinical data for a subcohort of 5115 (75%) DD2 patients.<sup>14</sup>

### 2.2. Micro- and macrovascular complications

For each cohort member, we assessed presence or absence of diabetes complications as recorded in the DNPR between 10 years before and up till 6 months after the DD2 enrolment date. The 6 months after period was included to allow for investigation and diagnosis of prevalent diabetes complications shortly after diabetes diagnosis. We categorized diabetes complications as: (1) no

microvascular or macrovascular complications at enrolment; (2) microvascular complications; (3) macrovascular complications; and (4) both microvascular and macrovascular complications. Microvascular complications included a medical database history of the following conditions: retinopathy, including any diabetes-related eye disease, atherosclerotic eye disease, blindness or severely impaired vision, or use of retinal photocoagulation therapy; neuropathy, including any diabetes-related neurological complication; and nephropathy, including any diabetes-related kidney disease, albuminuria, chronic dialysis, or renal failure. Macrovascular complications included a medical registry history of any of the following conditions: history of ischemic heart disease including angina pectoris or coronary surgery; atherosclerotic cerebrovascular disease including thrombolysis and thrombectomy; atherosclerotic peripheral vascular disease including vascular surgery or amputation; or any operation for macroangiopathy (see Supplemental Table A1 for diagnosis and procedure codes).

### 2.3. Associated patient characteristics

From the DD2 cohort questionnaire and the linked medical databases, we extracted data on patient characteristics present at the time of DD2 enrollment. Patient characteristics of particular interest included age, sex, body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>, central obesity (defined as waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women), high waist-hip ratio (WHR) (defined as  $>1.0$  in men and  $>0.85$  in women), tobacco smoking, blood pressure (mm Hg), fasting blood-glucose level (mmol/L), C-peptide level (pmol/L), plasma lipid level (mmol/L), C-reactive protein (CRP) level (mg/L), and use of anti-hypertensive and lipid-lowering drugs. Data on age, sex, central obesity, WHR, physical activity, and use of lipid-lowering and anti-hypertensive drugs were available for the entire DD2 cohort, and data on HbA1c, blood pressure, BMI, tobacco smoking, and plasma lipids were available for the subcohort of 5115 patients (75%) currently linkable to the DDDA.<sup>14</sup> Concerning specific biomarkers, fasting blood glucose, C-peptide and CRP have currently been analyzed for the first 5563 (80%), 5800 (83%) and 1030 (15%) DD2 cohort patients in the DD2 biobank.

The DD2 project, including patient registration and sample collection, has been approved by The Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035). After receiving detailed oral and written information approved by The Regional Committees on Health Research Ethics for Southern Denmark, patients volunteer to participate in the DD2 project. Their willingness to participate is documented by a signed written informed consent document.

### 2.4. Statistical analysis

We characterized patients according to factors as described above. Prevalence of microvascular, macrovascular, and both micro- and macrovascular complications at baseline was calculated as proportions (percentages) of all DD2 cohort members. We calculated prevalence ratios (PRs) with 95% confidence intervals (CIs) of the different complications associated with presence of each factor using log-binomial and Poisson regression.<sup>20</sup> The exact pathophysiological pathways between the different dysglycemia-related and metabolic syndrome-related factors are incompletely understood and several factors may act as clusters in the same causal pathway.<sup>21</sup> We therefore only adjusted our estimates for age and gender in the main analysis (aPRs) to assess whether associations were independent of these two factors.<sup>20</sup> Because obesity and in particular abdominal obesity is thought to be a fundamental factor preceding a number of other metabolic risk factors in many individuals; we did a supplementary analysis in which

we also adjusted all associations for WHR category as a marker of abdominal obesity.

Although the DD2 project aims to enroll newly or recently diagnosed T2D patients, we conducted a sensitivity analysis to maximize the probability of T2D being a newly detected diagnosis: in this analysis, we included only T2D patients who had no earlier glucose-lowering treatment, hospital diagnosis of T2D, or registration in the DDDA quality-of-care database recorded >1 year prior to DD2 enrollment.

In addition, we calculated aPRs separately for individual complications, i.e. retinopathy, neuropathy, nephropathy, ischemic heart disease, atherosclerotic cerebrovascular disease, and atherosclerotic peripheral vascular disease.

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

### 3. Results

#### 3.1. Prevalence data

Among the 6958 patients with T2D, 35% (n = 2456) had diabetes complications around enrolment in the DD2 cohort. Of these patients, 12% (n = 828) had microvascular complications only, 17% (n = 1186) had macrovascular complications only, and 6% (n = 442) had both micro- and macrovascular complications (Table 1). Among all newly diagnosed T2D patients with any microvascular complications, 13% (n = 887) had retinopathy, 4% (n = 264) had neuropathy, and 3% (n = 234) had nephropathy (Supplementary Table A.8). Among all newly diagnosed T2D patients with any macrovascular complications, 15% (n = 1059) had ischemic heart disease, 5% (n = 365) had atherosclerotic cerebrovascular disease, and 2% (n = 151) had atherosclerotic peripheral vascular disease (Supplementary Table A.10).

#### 3.2. Characteristics associated with micro- and macrovascular complications

Tables 1 and 2 present clinical and lifestyle characteristics according to diabetes complications around time of diagnosis, with corresponding aPRs and 95% CIs.

Compared with HbA1c levels <7%, higher HbA1c levels at diagnosis were associated with a higher prevalence of microvascular complications [e.g., HbA1c 7–8%, aPR: 1.35, 95% confidence interval (CI): 1.12–1.62] and of both micro- and macrovascular complications [aPR: 1.48, 95% CI: 1.14–1.91], but not of macrovascular complications [aPR: 0.91, 95% CI: 0.76–1.08] (Table 2). Similarly, we found a relationship between high baseline fasting blood glucose levels (>7.5 mmol/L) and the presence of microvascular complications, but no association with either macro- or combined micro-/macrovascular complications (Table 1). In contrast, high C-peptide  $\geq$  800 pmol/L was associated with macrovascular complications [aPR 1.34, 95% CI: 1.00–1.80], but not microvascular complications [aPR 0.97, 95% CI: 0.71–1.33] or both micro- and macrovascular complications [aPR: 1.07, 95% CI: 0.68–1.69].

Higher age and male sex were both associated with presence of macrovascular complications and both micro- and macrovascular complications (Table 1). In contrast, the presence of microvascular complications was only increased in persons aged  $\geq$ 70 years and did not differ by sex.

For the remaining metabolic syndrome-related factors, we found that central obesity, high baseline triglyceride ( $\geq$ 1.7), low baseline HDL cholesterol (<1.3), and use of anti-hypertensive drugs were all associated with presence of macrovascular and both micro- and macrovascular complications (Tables 1 and 2). Similar associations were found for high waist-hip ratio (>1.0) and BMI. Regarding microvascular complications, we found an

association with high blood pressure [aPR: 1.27, 95% CI: 1.08–1.50] and high triglyceride level [aPR: 1.31, 95% CI: 1.12–1.52]. The prevalence of microvascular complications was lower in patients using lipid-lowering drugs (99.5% used statins), while the prevalence of macrovascular and both micro- and macrovascular complications was increased.

Smoking was associated with macrovascular complications, but not with microvascular or both micro- and macrovascular complications (Table 2). In the subsample with biobank information, high baseline CRP (>3.0 mg/L) was associated with presence of macrovascular and both micro- and macrovascular complications, but not with microvascular complications.

Of interest, most associations were very robust to further adjustment for central obesity assessed by WHR categories, as seen in Supplementary Tables A.2 and A.3.

Overall, the sensitivity analysis restricted to patients with maximized probability of having newly detected diabetes showed consistent results with the main analysis (Supplementary Tables A.4 and A.5). This included similar associations between HbA1c levels and complications as observed in the main analysis. Further adjustment for WHR categories in these subcohorts did not change the estimates materially (Supplementary Tables A.6 and A.7).

#### 3.3. Characteristics associated with individual complications

Characteristics associated with individual micro- and macrovascular complications are presented in Supplementary Tables A.8–A.11. Statistical precision was limited, but some interesting tendencies were noted. For macrovascular complications, central obesity, high waist-hip ratio (>1.0), physical inactivity, high blood pressure, and smoking were more closely associated with peripheral vascular disease than with the other complications. High C-peptide was most strongly associated with cerebrovascular disease. In contrast, very high HbA1c values of 9% or more tended to be associated with ischemic heart disease, but not with cerebrovascular disease. For microvascular complications, an increased HbA1c level of 7% or more was associated with both retino-, neuro-, and nephropathy. Male sex was associated with neuropathy and nephropathy, but not with retinopathy. Obesity, high C-peptide, and dyslipidemia tended to be associated with nephropathy, but not with the other microvascular complications. Smoking was related to neuropathy.

### 4. Discussion

Our findings from the nationwide DD2 study cohort show that one-third of newly or recently diagnosed T2D patients have hospital-diagnosed micro- and macrovascular complications already around time of diagnosis. Of concern, this suggests that many patients have their T2D diagnosed on the basis of already having developed diabetes complications. While keeping in mind the limitations of a cross-sectional analysis, the observed associations of dysglycemia-related factors with microvascular complications, and metabolic syndrome related factors with macrovascular complications corroborate hypotheses about different underlying pathophysiological mechanisms.

#### 4.1. Strengths and limitations

The main strength of this large cross-sectional study is its comprehensive and detailed assessment of lifestyle and clinical factors based on the DD2 database, DD2 biobank, and linkage with population-based health registries. These resources provide close to 100% completeness for demographic, clinical characteristics and prescription data for the newly diagnosed T2D patients in our study.<sup>17</sup>

**Table 1**

Prevalence of diabetes complications among 6958 patients with newly diagnosed type 2 diabetes in the DD2 cohort. Age- and gender-adjusted prevalence ratios are shown according to each patient characteristic.

Characteristic	All T2D patients	No complication (%)	Microvascular complication (%)	aPR (95% CI)	Macrovascular complication (%)	aPR (95% CI)	Micro- and macrovascular complications (%)	aPR (95% CI)
Main cohort	6958	4502 (64.7)	828 (11.9)		1186 (17.1)		442 (6.4)	
Sex								
Female	2927	2047 (69.9)	365 (12.5)	Ref (1.00)	374 (12.8)	Ref (1.00)	141 (4.8)	Ref (1.00)
Male	4031	2455 (60.9)	463 (11.5)	0.92 (0.81–1.05)	812 (20.1)	1.60 (1.43–1.79)	301 (7.5)	1.59 (1.32–1.93)
Age (years)								
<50	1220	973 (79.8)	142 (11.6)	Ref (1.00)	82 (6.7)	Ref (1.00)	23 (1.9)	Ref (1.00)
50–59	1790	1262 (70.5)	180 (10.1)	0.87 (0.70–1.07)	276 (15.4)	2.31 (1.82–2.92)	72 (4.0)	2.17 (1.36–3.44)
60–69	2517	1550 (61.6)	291 (11.6)	0.99 (0.82–1.20)	505 (20.1)	2.99 (2.40–3.74)	171 (6.8)	3.61 (2.35–5.55)
≥70	1431	717 (50.1)	215 (15.0)	1.28 (1.05–1.56)	323 (22.6)	3.44 (2.73–4.32)	176 (12.3)	6.60 (4.31–10.12)
Central obesity <sup>a</sup>								
No	570	393 (69.0)	63 (11.1)	Ref (1.00)	83 (14.6)	Ref (1.00)	31 (5.4)	Ref (1.00)
Yes	6378	4099 (64.3)	765 (12.0)	1.08 (0.85–1.38)	1103 (17.3)	1.33 (1.09–1.63)	411 (6.4)	1.38 (0.97–1.97)
Waist-hip ratio <sup>b</sup>								
≤0.95m/≤0.80f	772	506 (65.5)	95 (12.3)	Ref (1.00)	131 (17.0)	Ref (1.00)	40 (5.2)	Ref (1.00)
0.96–1.0m/0.81–0.85f	1437	911 (63.4)	180 (12.5)	0.99 (0.79–1.26)	261 (18.2)	1.12 (0.93–1.36)	85 (5.9)	1.22 (0.85–1.75)
>1.0m/>0.85f	4737	3074 (64.9)	553 (11.7)	0.92 (0.74–1.14)	793 (16.7)	1.21 (1.02–1.43)	317 (6.7)	1.75 (1.27–2.40)
Regular physical exercise								
Yes	2725	1847 (67.8)	304 (11.2)	Ref (1.00)	430 (15.8)	Ref (1.00)	144 (5.3)	Ref (1.00)
No	4232	2655 (62.7)	524 (12.4)	1.12 (0.98–1.28)	755 (17.8)	1.10 (0.99–1.23)	298 (7.0)	1.31 (1.08–1.58)
Use of lipid-lowering drugs								
No	2072	1537 (74.2)	304 (14.7)	Ref (1.00)	171 (8.3)	Ref (1.00)	60 (2.9)	Ref (1.00)
Yes	4886	2965 (60.7)	524 (10.7)	0.70 (0.62–0.80)	1015 (20.8)	2.31 (1.98–2.69)	382 (7.8)	2.35 (1.81–3.07)
Use of anti-hypertensive drugs								
No	1967	1548 (78.7)	232 (11.8)	Ref (1.00)	151 (7.7)	Ref (1.00)	36 (1.8)	Ref (1.00)
Yes	4991	2954 (59.2)	596 (11.9)	0.94 (0.81–1.10)	1035 (20.7)	2.28 (1.93–2.70)	406 (8.1)	3.19 (2.27–4.49)
Fasting blood glucose (mmol/L)								
<6.5	1548	996 (64.3)	159 (10.3)	Ref (1.00)	278 (18.0)	Ref (1.00)	115 (7.4)	Ref (1.00)
6.5–7.0	917	611 (66.6)	86 (9.4)	0.92 (0.71–1.17)	167 (18.2)	1.00 (0.85–1.19)	53 (5.7)	0.80 (0.59–1.09)
7.0–7.5	751	482 (64.2)	80 (10.7)	1.05 (0.82–1.36)	147 (19.6)	1.07 (0.90–1.28)	42 (5.6)	0.75 (0.54–1.06)
≥7.5	2146	1424 (66.4)	245 (11.4)	1.16 (0.96–1.41)	350 (16.3)	0.95 (0.83–1.10)	127 (5.9)	0.92 (0.72–1.16)
C-peptide (pmol/L)								
<550	295	202 (68.5)	36 (12.2)	Ref (1.00)	39 (13.2)	Ref (1.00)	18 (6.1)	Ref (1.00)
550–800	853	606 (71.0)	90 (10.6)	0.84 (0.58–1.21)	120 (14.1)	1.00 (0.72–1.40)	37 (4.3)	0.65 (0.38–1.12)
≥800	4652	2932 (63.0)	552 (11.9)	0.97 (0.71–1.33)	847 (18.2)	1.34 (1.00–1.80)	321 (6.9)	1.07 (0.68–1.69)
CRP (mg/L)								
≤3.0	627	429 (68.4)	62 (9.9)	Ref (1.00)	114 (18.2)	Ref (1.00)	22 (3.5)	Ref (1.00)
>3.0	403	254 (63.0)	35 (8.7)	0.86 (0.58–1.29)	87 (21.6)	1.42 (1.11–1.81)	27 (6.7)	2.34 (1.34–4.07)

DD2: the Danish Centre for Strategic Research in Type 2 Diabetes; aPR: adjusted prevalence ratio; CI: confidence interval.

Data available in total DD2 cohort (n = 6958) for central obesity (n = 10 missing); for waist-hip ratio (n = 12 missing); for regular physical activity (n = 1 missing). Data currently available in the DD2 biobank for fasting blood glucose (n = 5362); for C-peptide (n = 5800); and for CRP (n = 1030).

<sup>a</sup> Central obesity = waist circumference > 94 (men) and > 80 (women).

<sup>b</sup> Waist-hip ratio: m = males; f = females.

Our study also has important limitations. Firstly, the cross-sectional design of our study leads to intrinsic uncertainty as to whether given diabetes complications preceded or followed the diagnosis of T2D and some of the patient characteristics, making it difficult to draw firm conclusions about the direction of exposure-outcome associations. Secondly, although the DD2 project aims to enroll newly diagnosed T2D patients, some may have been diagnosed with diabetes several years before enrolment,<sup>22</sup> which may have led to an overestimation of the true complication prevalence at diabetes debut. Thirdly, the DD2 cohort may represent patients whose newly diagnosed T2D is more severe than average in Denmark, as initial enrolment took place in hospital specialist outpatient clinics in about half of the cases.<sup>17</sup> This may represent an example of Berksonian-like bias if an undiagnosed diabetic complication leads patients to seek medical attention in secondary health care, thus causing T2D to be diagnosed and the patient to be enrolled in the DD2, with a possible overestimation of the average complication

prevalence in early T2D. However, since 2013, the number of patients recruited by GPs has increased rapidly and by 2016 characteristics of the cohort appear to be representative of all newly diagnosed T2D patients in Denmark.<sup>6</sup> Fourth, assessment of complications exclusively through hospital contact diagnoses leads to likely underestimation, especially for microvascular complications, but probably less so for macrovascular complications. Thus, when comparing with results from RCTs, it must be kept in mind that our complication data are not derived from a structured evaluation following briefly after diagnosis, leading to a likely underestimation.

#### 4.2. Comparison with previous literature

The lower prevalence of individual diabetes complications in our cohort compared with older studies may originate in earlier and more complete detection of T2D cases in recent years, or be due to improvements over time in clinical management<sup>23</sup> which seem to have

**Table 2**  
Prevalence of diabetes complications in the subcohort of 5115 DD2 patients who currently can be linked to the DDDA. Age- and gender-adjusted prevalence ratios are shown according to patient characteristics.

Characteristic	All T2D patients	No complication (%)	Microvascular complication (%)	aPR (95% CI)	Macrovascular complication (%)	aPR (95% CI)	Micro- and macrovascular complications (%)	aPR (95% CI)
Subcohort	5115							
High blood pressure (mm Hg) <sup>a</sup>								
No	1575	1012 (64.3)	173 (11.0)	Ref (1.00)	278 (17.7)	Ref (1.00)	112 (7.1)	Ref (1.00)
Yes	3261	2013 (61.7)	450 (13.8)	1.27 (1.08–1.50)	572 (17.5)	0.94 (0.83–1.07)	226 (6.9)	0.92 (0.74–1.14)
Smoking								
No	3903	2464 (63.1)	490 (12.6)	Ref (1.00)	676 (17.3)	Ref (1.00)	273 (7.0)	Ref (1.00)
Yes	941	579 (61.5)	127 (13.5)	1.08 (0.90–1.30)	177 (18.8)	1.20 (1.04–1.40)	58 (6.2)	1.07 (0.82–1.41)
BMI (kg/m <sup>2</sup> )								
<25	500	309 (61.8)	73 (14.6)	Ref (1.00)	78 (15.6)	Ref (1.00)	40 (8.0)	Ref (1.00)
25–29	1291	800 (62.0)	156 (12.1)	0.84 (0.65–1.08)	222 (17.2)	1.10 (0.87–1.40)	113 (8.8)	1.05 (0.74–1.48)
30–34	1147	692 (60.3)	141 (12.3)	0.84 (0.65–1.09)	231 (20.1)	1.37 (1.09–1.73)	83 (7.2)	1.01 (0.70–1.47)
≥35	897	554 (61.8)	145 (16.2)	1.11 (0.85–1.45)	150 (16.7)	1.39 (1.08–1.80)	48 (5.4)	0.85 (0.56–1.31)
HDL cholesterol (mmol/L) <sup>b</sup>								
≥1.3m/≥1.0f	2061	1246 (60.5)	297 (14.4)	Ref (1.00)	356 (17.3)	Ref (1.00)	162 (7.9)	Ref (1.00)
<1.3m/<1.0f	969	558 (57.6)	152 (15.7)	1.01 (0.84–1.22)	181 (18.7)	1.37 (1.16–1.61)	78 (8.1)	1.37 (1.06–1.78)
Triglycerides (mmol/L)								
<1.7	2410	1573 (65.3)	261 (10.8)	Ref (1.00)	415 (17.2)	Ref (1.00)	161 (6.7)	Ref (1.00)
≥1.7	2348	1430 (60.9)	330 (14.1)	1.31 (1.12–1.52)	424 (18.1)	1.16 (1.03–1.31)	164 (7.0)	1.23 (1.00–1.52)
HbA1c (%)								
<7.0	3592	2298 (64.0)	413 (11.5)	Ref (1.00)	651 (18.1)	Ref (1.00)	230 (6.4)	Ref (1.00)
7.0–8.0	824	500 (60.7)	126 (15.3)	1.35 (1.12–1.62)	129 (15.7)	0.91 (0.76–1.08)	69 (8.4)	1.48 (1.14–1.91)
8.0–9.0	303	182 (60.1)	43 (14.2)	1.30 (0.96–1.74)	57 (18.8)	1.19 (0.93–1.52)	21 (6.9)	1.50 (0.97–2.30)
≥9.0	313	187 (59.7)	52 (16.6)	1.53 (1.17–2.01)	47 (15.0)	1.00 (0.76–1.32)	27 (8.6)	2.14 (1.46–3.13)

DD2: the Danish Centre for Strategic Research in Type 2 Diabetes; DDDA: the Danish Diabetes Database for Adults; aPR: adjusted prevalence ratio; CI: confidence interval. Data available in DDDA cohort (n = 5115); for blood pressure (n = 279 missing); for smoking (n = 271 missing); for BMI (n = 1280 missing); for HDL (n = 2085 missing); for triglycerides (n = 357 missing); and for HbA1c (n = 83 missing).

<sup>a</sup> High blood pressure = defined as no (systolic blood pressure < 130 or diastolic blood pressure < 85) and as yes (systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85).

<sup>b</sup> HDL cholesterol: m = males; f = females.

decreased the gap in life expectancy for persons with diabetes versus the general population.<sup>24</sup> The UKPDS study,<sup>4</sup> which enrolled patients with newly diagnosed diabetes referred by GPs, reported a 36% prevalence of retinopathy and an 11.5% prevalence of neuropathy. Our observed prevalence of 12.8% with retinopathy and 3.8% with neuropathy was more comparable with that reported among screen-detected T2D patients 5 years after diagnosis in the ADDITION study<sup>25</sup> (11% and 5.5%, respectively). Compared to our findings, the ADDITION study reported a much higher prevalence of nephropathy (23% vs. 3.4% in our study), likely because we were only able to assess nephropathy through manifest hospital diagnoses and not by albuminuria<sup>25</sup> leading to an underestimation. Among 9158 people newly diagnosed with T2D during 2003–2005 in a UK cohort study,<sup>26</sup> a lower proportion (1.7%) presented with microvascular conditions and cardiovascular complications (19.2%), compared with our study. A large population-based cohort study conducted in Sweden among patients with T2D and mean diabetes duration of 7.4 years<sup>27</sup> reported microalbuminuria in 16.6% and cardiovascular disease in 18.2% during the follow-up time of maximum 6 years. Another large Swedish cross-sectional population-based study<sup>28</sup> reported a prevalence of 12% of diabetic retinopathy among newly diagnosed T2D patients which corresponds well with our findings.

The pathophysiology leading to micro- versus macrovascular complications in T2D patients remains incompletely understood. Overall, RCTs have not demonstrated a substantial clinical effect of intensive glucose-lowering therapy on macrovascular outcomes in T2D patients, although there may be beneficial legacy effects of good early glucose control.<sup>29</sup> Also, recent RCTs<sup>10–13</sup> suggest that newer glucose lowering drugs reduce CVD risk beyond their glucose-lowering effect, by

affecting other CVD risk factors. Our cross-sectional observations confirm that risk factors related to the metabolic syndrome, e.g., central obesity, dyslipidemia, and hypertension, in addition to low physical activity, tobacco smoking, and older age, may be of greater importance than hyperglycemia per se for development of macrovascular complications. High C-peptide ≥ 800 pmol/L was associated with early macrovascular complications in our study in accordance with others' findings<sup>30</sup> and may reflect the insulin resistance underlying most of the metabolic syndrome.<sup>31</sup> In contrast, the fact that poor glycemic control per se reflected by a high HbA1c level was associated with microvascular but not macrovascular complications corroborates main findings from several randomized clinical trials<sup>3,32–34</sup> that tight glycemic control in T2D patients reduces the risk of microvascular complications by 10%–28%. Of note, high triglyceride levels, but not HDL cholesterol levels, were also associated with microvascular complications, and absence of lipid-lowering drug use was associated with microvascular complications at diagnosis. In analyses of individual complications, high triglyceride and low HDL cholesterol levels were clearly associated with nephropathy, consistent with a large case-control study<sup>35</sup> that reported strong associations between diabetic kidney disease, high triglyceride levels, and low HDL cholesterol levels. We did not find an association between retinopathy or neuropathy and high triglyceride or low HDL cholesterol levels, as other studies have reported.<sup>36,37</sup>

#### 4.3. Conclusion

In conclusion, almost one-third of newly or recently diagnosed T2D patients in the DD2 cohort presented with a likely diabetic

complication around disease onset. Our findings suggest that different phenotypical risk profiles exist for microvascular versus macrovascular complications, pointing to different pathophysiological mechanisms and a possible need to individualize preventive treatment strategies.

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### Author contributions

HBN, HTS and JR participated in designing the DD2 cohort. TPA, JR, JSN, DW, SF, AV, IB, JSC, HBN, HTS and RWT conceived of the study. IB was responsible for the biobank and the biochemical analyses. AG, RWT and HTS participated in the design of the study and KB performed the statistical analysis. AG initially drafted the article, with help by RWT and HTS. All other authors have critically reviewed the manuscript. All authors contributed substantially, revised the manuscript for intellectual content, and approved the final version to be submitted. AG 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.

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jdiacomp.2017.09.010>.

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