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Cohort profile: the Funen Diabetes Database—a population-based cohort of patients with diabetes in Denmark

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ABSTRACT

Purpose Detailed population-based data are essential to understanding the epidemiology of diabetes and its clinical course. This article describes the Funen Diabetes Database (FDDB). The purpose of the FDDB was to serve as a shared electronic medical record system for healthcare professionals treating patients with diabetes. The cohort can also be used for research.

Participants The FDDB covers a geographical area of almost 500 000 Danish inhabitants. It currently includes 3691 patients with type 1 diabetes, 19 085 patients with type 2 diabetes, 292 patients with other types of diabetes and 5992 patients with an unknown type of diabetes. Patients have been continuously enrolled from general practitioners and endocrinology departments in the Funen area in Denmark since 2003. Patients undergo a clinical work-up at their first diabetes contact and during follow-up visits. The information collected includes type of diabetes contact, blood pressure, height, weight, lifestyle factors (smoking, exercise), laboratory records (eg, haemoglobin A1c and cholesterol levels), results from foot examinations (eg, pulse, cutaneous sensitivity and ankle brachial index), results from eye examinations (eg, degree of retinopathy assessed by retinal photo and eye examination), glucose-lowering drugs and diabetic complications.

Findings to date The FDDB cohort was followed for a total of 212 234 person-years up to 2016. A cross-sectional study described the prevalence of diabetic retinopathy and its associated risk factors. The clinical outcomes of patients with type 1 diabetes, type 2 diabetes and latent autoimmune diabetes in adults have been assessed. Linkage to population-based medical registries with complete follow-up has enabled the collection of extensive continuous data on general practice contacts, diagnoses and procedures from hospital contacts, medication use and mortality.

Future plans The FDDB serves as a strong data resource that will be used in future studies of diabetes epidemiology with focus on occurrence, risk factors, treatment, complications and prognosis.

Strengths and limitations of this study

- The Funen Diabetes Database (FDDB) is an ongoing general practice and hospital cohort of patients with type 1 diabetes, type 2 diabetes and other forms of diabetes (eg, latent autoimmune diabetes in adults) covering a geographical area of almost 500 000 Danish inhabitants.
- The FDDB database is a detailed resource of healthcare data for research, including baseline and follow-up data on blood pressure, body mass index, lifestyle factors (smoking habits and weekly exercise), results from foot and eye examinations, glucose-lowering drugs, and cardiovascular and non-cardiovascular diabetes complications.
- A total of 29 060 patients have been included in the database between June 2003 through November 2018. The FDDB has been used in several observational studies and will serve as an important resource in future studies through linkage with the extensive network of Danish registries.
- Weaknesses of the cohort are a lack of information on certain life style factors, missing data for some of the recorded variables and the absence of biobank material.

INTRODUCTION

With more than 500 million people living with diabetes worldwide, the disease is an important and growing public health concern.[1 2] Despite improvements in prevention and treatment,[3 4] diabetes remains a major cause of morbidity, disability, loss of productive life-years and mortality.[5] In addition, an increasing prevalence of diabetes has given rise to a high prevalence of cardiovascular disease, eye disease, kidney disease, and amputations worldwide.

Population-based cohorts with access to comprehensive clinical data are essential to understanding the current and future epidemiology of diabetes, including its occurrence, clinical course and complications, and the effectiveness and safety of antidiabetic treatments. Improving the knowledge on diabetes may enable tailored prevention strategies and reduce the risk of or delay onset of for

example, vision loss or cardiovascular diseases through timely interventions.

Denmark has a long tradition of registry-based diabetes research, and a few specific diabetes registries have been established, including the Danish Adult Diabetes Database, Vejle Diabetes Biobank and Danish Centre for Strategic Research in Type 2 Diabetes project cohort, which are described in detail elsewhere.[6–8] The Funen Diabetes Database (FDDB) represents an important and detailed resource for diabetes research that can be of value in generating new knowledge. In contrast to the existing diabetes registries in Denmark, the FDDB is an electronic record of general practice and hospital medical encounters with detailed routine clinical and longitudinal data on patients with diabetes. In this article, we describe the FDDB and how it can be used in clinical epidemiological research.

COHORT DESCRIPTION

Study participants and recruitment

The Danish healthcare system is government-funded, ensuring free access to healthcare at hospitals and general practitioners for all inhabitants, including patients with diabetes.[9] A unique 10-digit identifier assigned to all inhabitants at birth or on immigration by the Danish Civil Registration System allows exact individual-level linkage of all health and administrative registries. In Denmark, general practitioners is the patient's primary contact point to the healthcare system, and when necessary, general practitioners refer patients to specialists and hospital care. Most patients with type 1 diabetes are treated at hospital outpatient diabetes clinics, while patients with type 2 diabetes are primarily managed in the primary healthcare sector.

The FDDB was launched in 2003 as a web-based database, serving as a digital healthcare platform used for daily clinical work and electronic communication among all healthcare providers involved in the treatment of patients with diabetes, in the geographical area of Funen, Denmark, including hospital physicians, general practitioners and specialists (eg, ophthalmologists), while engaging patients as active partners. Data from routine clinical practice are manually recorded in the web-based database, while biomarker test results are automatically transferred to the database from the central laboratory. Thus, no other data are automatically extracted from any other electronic media either from the hospital or the general practitioners.

All data from the FDDB are also deposited at the Department of Clinical Epidemiology at Aarhus University Hospital and can be used for research purposes.

Thus, data included in the FDDB are intended for clinical and administrative use but can also be used for diabetes research. The database is ongoing with continuous patient enrolment. To be included in the FDDB, patients must have a prevalent or incident diagnosis of diabetes according to current diagnostic criteria used for diabetes. For example, patients were mainly diagnosed with type 2 diabetes based on elevated fasting glucose or a positive oral glucose tolerance test before 2012, but thereafter were mainly diagnosed by means of elevated haemoglobin A1c (HbA1c) levels.[10] As of 2019, Funen covers a population of 498 566 inhabitants.[11] Odense University Hospital is one of the four main university hospitals in Denmark and has around 1000 beds, serving as a tertiary centre for the Region of Southern Denmark.[12] The Funen area also has a few smaller regional hospitals in Svendborg, Fåborg, Nyborg and Middelfart. Inclusion in the registry occurred automatically if two HbA1c measurements from a patient were recorded in the laboratory system (covering hospitals and general practitioners) less than 12 months apart in combination with a physician confirming the diagnosis of diabetes. These criteria were used in the early years of the database to capture all patients with prevalent diabetes, outpatient clinic patients (mainly the Department of Endocrinology at Odense University Hospital, and to a lesser extent the regional hospitals in Svendborg, Fåborg, Nyborg and Middelfart), patients from general practice physicians and private working ophthalmologists. In the early years after 2003, general practice physicians and private working ophthalmologists were paid a small fee when providing patients with annual diabetes control.

In a study that focused on retinal changes among patients with diabetes, an estimated 80% of patients with diabetes in the Funen area were enrolled in the registry.[13] Because the five Danish administrative regions are considered to be relatively homogeneous concerning populations and healthcare systems,[14] with the Funen area having a mixed rural–urban population of similar socioeconomic background as the rest of Denmark, the FDDB comprises a sample of patients with diabetes that is considered representative of diabetic patients in the whole Danish population. Data collection is included as part of normal daily clinical care of patients; therefore, the frequency of data recording is mainly determined by patient need, age and comorbidity. The FDDB includes measured and self-reported healthcare data related to diabetes.

Data collection

All patients are recorded with a 10-digit identifier, age, sex, diabetes contact date and type of diabetes contact (routine, annual status, clinical dietitian, diabetes school, outpatient status and other contacts). The FDDB comprises systolic and diastolic blood pressure measurements from the office setting, home setting or over 24 hours. Anthropometric measures, including weight, height, body mass index (BMI; kg/m^2), and waist measures, self-reported weekly physical exercise, smoking status (never, daily, former, occasional) and daily glucose measurements are also captured. Biomarkers that are used in routine clinical practice for diagnosis, screening, monitoring and prognosis of patients are automatically transferred from the laboratory information system to

the database. These biomarkers include HbA1c, estimated average glucose, creatinine (plasma concentration and urine clearance), urine albumin (concentration and amount excreted per minute), urine albumin/creatinine ratio, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol and triglycerides. In addition, glutamic acid decarboxylase (GAD) autoantibodies and C-peptide are measured in a subset of patients. The hospital laboratory is accredited in accordance with the standards for medical laboratory testing specified by the *International Organisation for Standardisation*.[15]

The FDDB also records data on insulin treatment, including information on insulin type and dose. Data are also available on the type and dose of treatment with oral glucose-lowering drugs, including biguanid (metformin), glucagon-like peptide-1 analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, DPP-4 inhibitors in combination with metformin, sodium/glucose cotransporter 2 inhibitors, glinides, glitazones, alpha-glucosidase inhibitors and sulfonylurea.

Data on routine standardised foot examinations are also recorded in the database. The foot examination includes an assessment of cutaneous sensitivity by means of vibration, biothesiometry and monofilament test. It also comprises a pulse assessment, whether or not the foot was considered 'at risk', the presence of foot ulcer, whether the patient underwent amputation of the lower limb, and data on the ankle brachial index (ratio).

A retinal examination and eye examination are an integrated part of the routine assessment of patients with diabetes. In the setting of the FDDB, the retinal examination was and is conducted by appropriately trained healthcare providers at Odense University Hospital and/or by any of 14 accredited private ophthalmologists. The examination includes ophthalmic images taken by nurses, optometrists and ophthalmologists, or six-field fundus images of 45°, or two-field fundus images of 45°. Authorised healthcare providers graded the images according to the International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scale.[16]

The FDDB also records information on diabetes complications, including cardiovascular conditions (angina pectoris, myocardial infarction, ischaemic stroke, vessel surgery, intermittent claudication and heart failure), other conditions (kidney failure and dialysis), diabetes-related conditions (severe hypoglycaemia and ketoacidosis) and pregnancy.

The FDDB can be used as a stand-alone resource, but the full potential is enabled through linkage to other administrative and health registries. Data on migration, date of death and civil status are provided from the Civil Registration System.[9] The Danish National Patient Registry contains data on all admission and discharge dates, surgical procedures, hospital treatments (eg, dialysis), and primary and secondary discharge diagnoses from Danish hospitals since 1977.[17] Data on most of the diabetes complications mentioned above (eg, cardiovascular diseases and hypoglycaemia) are considered more complete and accurate than data in the FDDB. The FDDB is also linkable to the Danish National Health Service Prescription Database, which contains data on all prescriptions dispensed in Danish community pharmacies for reimbursed medicines since 2004.[18] Linkage to the Danish Cancer Registry, which has recorded data on cancer diagnoses since 1943, allows for investigation into the link between diabetes and cancer. Information on cause-specific mortality are retrieved from the Danish Register of Causes of Death. Statistics Denmark holds data on socioeconomic variables (ie, education, gross income and employment). The National Health Insurance Service Registry comprises data on the number of and type of healthcare services provided by general practitioners, dentists, physiotherapists and chiropractors since 1990. The data recorded in the FDDB are also used for clinical quality control.

Patient and public involvement

No patient involved.

Characteristics of study participants

The characteristics of the patients in the diabetes cohorts on enrolment in the database or, if missing, at the earliest observation closest to the first contact date are given in table 1. A total of 29 060 patients were enrolled in the FDDB by November 2018, encompassing 3691 patients with type 1 diabetes, 19 085 patients with type 2 diabetes, 292 with other types of diabetes and 5992 with an unknown type of diabetes. The number of patients with an unknown type of diabetes is relatively high, but according to the median age of 63 years and 56% redeemed a prescription for metformin, a considerable proportion of these patients likely suffer from type 2 diabetes. In addition, 4927 of the patients with unknown diabetes had no contact date recorded, and these patients likely represent patients seen only by ophthalmologists.

There were slightly more men than women with type 1 diabetes, type 2 diabetes and other types of diabetes. As expected, the median age of patients with type 2 diabetes (62 years, IQR: 53–70) was higher than that of patients with type 1 diabetes (42 years, IQR: 27–55). For patients with other types of diabetes, the median age was 56 years (IQR: 45–67), and it was higher in patients with unknown types of diabetes (63 years, IQR: 54–72). A higher proportion of patients was enrolled in the cohort during 2003–2005 relative to later time periods. This likely reflects the inclusion of patients with prevalent diabetes in the beginning of the database coverage period, together with the economic incentives for general practitioners and private working ophthalmologists to enrol patients in the cohort in the early years after the launch of the database.

The median systolic and diastolic blood pressure were slightly higher in type 2 diabetic patients (135 mm Hg, IQR: 125–149 mm Hg and 80 mm Hg, IQR: 75–87 mm Hg) than among patients with type 1 diabetes (128 mm Hg, IQR: 117–140 mm Hg and 78 mm Hg, IQR: 70–84 mm

Table 1 Baseline characteristics of patients with diabetes mellitus recorded in the Funen Diabetes Database, Denmark, 2003–2018

Type of diabetes	Type 1 diabetes	Type 2 diabetes	Other types of diabetes	Unknown type of diabetes
Number of patients	3691 (100%)	19 085 (100%)	292 (100%)	5992 (100%)
Sex				
Female	1548 (42%)	8046 (42%)	120 (41%)	2644 (44%)
Male	2143 (58%)	11 039 (58%)	172 (59%)	3348 (56%)
Age				
Median age, years (IQR)	42 (27–55)	62 (53–70)	56 (45–67)	63 (54–72)
<39	1725 (47%)	1094 (6%)	47 (16%)	414 (7%)
40–59	1363 (37%)	7176 (38%)	123 (42%)	1947 (32%)
60–79	555 (15%)	9607 (50%)	114 (39%)	3118 (52%)
80+	48 (1%)	1208 (6%)	8 (3%)	513 (9%)
Enrolment year				
2003–2005	2193 (59%)	8000 (42%)	39 (13%)	214 (4%)
2006–2010	684 (19%)	6007 (31%)	53 (18%)	2121 (35%)
2011–2015	537 (15%)	4226 (22%)	125 (43%)	2866 (48%)
2016–2018	277 (8%)	852 (4%)	75 (26%)	791 (13%)
First diabetes contact type				
Routine	2286 (62%)	6629 (35%)	98 (34%)	326 (5%)
Annual status	509 (14%)	5499 (29%)	21 (7%)	225 (4%)
Clinical dietitian	158 (4%)	1076 (6%)	27 (9%)	156 (3%)
Diabetes school	57 (2%)	748 (4%)	8 (3%)	207 (3%)
Outpatient clinical	71 (2%)	418 (2%)	5 (2%)	16 (0%)
Other contact	384 (10%)	2582 (14%)	61 (21%)	135 (2%)
No contact type recorded	226 (6%)	2133 (11%)	72 (25%)	4927 (82%)
Diabetes duration, median years (IQR)	11 (3–24)	2 (0.5–7)	0.5 (0.3–2)	0.5 (0.3–1)
Blood pressure in the consultation (mm Hg), median (IQR)				
Systolic	128 (117–140)	135 (125–149)	125 (116–136)	130 (120–140)
Diastolic	78 (70–84)	80 (75–87)	80 (70–85)	80 (74–87)
Missing	152 (4%)	2736 (14%)	45 (15%)	4964 (83%)
Anthropometric measurements, median (IQR)				
Weight, kg	74 (65–84)	89 (77–103)	72 (61–84)	86 (75–103)
Missing	154 (4%)	2563 (13%)	44 (15%)	4946 (83%)
Height, cm	174 (167–181)	171 (164–178)	172 (164–178)	172 (164–178)
Missing	179 (5%)	3154 (17%)	48 (16%)	5032 (84%)
Body mass index, kg/m^2	25 (22–27)	30 (27–35)	24 (21–28)	29 (26–34)
Missing	196 (5%)	3277 (17%)	51 (17%)	5046 (84%)
Waist, cm	93 (82–104)	107 (98–118)	98 (86–105)	104 (97–116)
Missing	3411 (92%)	14 080 (74%)	273 (93%)	5876 (98%)
Exercise, median hours per week (IQR)	3.5 (1.6–7.0)	3.0 (0.5–5.0)	2.0 (0.0–5.0)	2.0 (0.0–4.0)
Missing	407 (11%)	4510 (24%)	79 (27%)	5223 (87%)
Self-monitoring, median number of blood glucose measurements per week (IQR)	21 (8–28)	1 (0–7)	14 (1–28)	1 (0–10)

Continued

Table 1 Continued

Type of diabetes	Type 1 diabetes	Type 2 diabetes	Other types of diabetes	Unknown type of diabetes
Missing	400 (11%)	5570 (29%)	86 (29%)	5326 (89%)
Smoking status				
Never	1582 (50%)	5729 (41%)	87 (40%)	315 (40%)
Daily smoker	836 (26%)	3237 (23%)	71 (33%)	206 (26%)
Former smoker	699 (22%)	4808 (35%)	56 (26%)	257 (32%)
Occasionally	52 (2%)	137 (1%)	≤5	15 (2%)
Missing	522 (14%)	5174 (27%)	≤80	5199 (87%)
Laboratory records, median (IQR)				
HbA1c, mmol/mol	66 (55–79)	51 (44–63)	54 (44–68)	48 (43–56)
Missing	30 (1%)	93 (0%)	11 (4%)	242 (4%)
Estimated average glucose, mmol/L	10.3 (8.9–12.4)	8.2 (7.3–10.0)	8.7 (7.4–10.7)	7.7 (7.0–9.0)
Missing	52 (1%)	115 (0.6%)	20 (7%)	242 (4%)
Creatinine, µmol/L	82 (70–93)	83 (71–96)	72 (60–87)	77 (66–91)
Missing	49 (1%)	82 (0%)	6 (2%)	205 (3%)
Creatinine clearance, mL/min	47.2 (28.2–80.4)	47.4 (27.0–78.6)	52.5 (42.6–71.0)	55.0 (33.0–78.6)
Missing	3285 (89%)	16 874 (88%)	260 (89%)	5514 (92%)
Urine albumin creatinine ratio, mg/g	10.6 (4.4–27.4)	15.9 (8.0–39.8)	15.0 (7.0–38.0)	11.0 (6.0–29.0)
Normal (<30 mg/g)	2410 (76%)	11 318 (69%)	150 (70%)	3254 (76%)
Microalbuminuria (30–299 mg/g)	636 (20%)	4545 (28%)	54 (25%)	935 (22%)
Macroalbuminuria (≥300 mg/g)	112 (4%)	648 (4%)	10 (5%)	109 (3%)
Missing	533 (14%)	2574 (13%)	78 (27%)	1694 (28%)
Total cholesterol, mmol/L	4.7 (4.1–5.5)	4.8 (4.1–5.6)	4.6 (3.9–5.6)	4.4 (3.8–5.2)
Missing	89 (2%)	212 (1%)	24 (8%)	338 (6%)
HDL cholesterol, mmol/L	1.5 (1.2–1.9)	1.2 (1.0–1.5)	1.4 (1.1–1.7)	1.2 (1.0–1.5)
Missing	98 (3%)	262 (1%)	24 (8%)	359 (6%)
LDL cholesterol, mmol/L	2.6 (2.1–3.2)	2.6 (2.0–3.3)	2.6 (1.8–3.2)	2.4 (1.9–3.1)
Missing	99 (3%)	266 (1%)	24 (8%)	359 (6%)
Triglyceride, mmol/L	1.0 (0.7–1.5)	1.7 (1.2–2.5)	1.4 (0.9–2.2)	1.6 (1.1–2.3)
Missing	99 (3%)	254 (1%)	22 (8%)	352 (6%)
GAD autoantibody positivity (>25 IU/L)	332 (40%)	58 (15%)	14 (37%)	9 (26%)
Missing	2815 (76%)	18 687 (98%)	254 (87%)	5958 (99%)
C-peptide, pmol/l	162 (33–352)	1074 (717–1529)	604 (273–956)	1019 (596–1484)
Missing	1961 (53%)	10 608 (56%)	94 (32%)	5303 (89%)
Glucose-lowering drugs*				
Insulin	1282 (93%)	1758 (15%)	130 (70%)	1095 (21%)
Biguanid (metformin)	188 (14%)†	7416 (64%)	57 (31%)	2855 (56%)
GLP-1 analogues	0 (0%)	0 (0%)	0 (0%)	0 (0%)
DPP-4 inhibitors	8 (1%)	432 (4%)	≤5	125 (2%)
DPP-4 inhibitors in combination with metformin	≤5	251 (2%)	≤5	113 (2%)
SGLT-2 inhibitors	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Glinides	8 (1%)†	358 (3%)	≤5	73 (1%)
Glitazones	≤5	61 (1%)	0 (0%)	25 (0%)

Continued

Table 1 Continued

Type of diabetes	Type 1 diabetes	Type 2 diabetes	Other types of diabetes	Unknown type of diabetes
Alpha-glucosidase inhibitors	0 (0%)	20 (0%)	0 (0%)	6 (0%)
Sulfonylurea	89 (6%)†	2409 (21%)	19 (10%)	616 (12%)

All variables are defined at the date of registry inclusion or, if missing, at the closest observation thereafter.
*For this tabulation, the cohort was restricted to January 2005 onwards due to data availability from the prescription database, which was used for this analysis. Data were redeemed prescriptions within 1 year before or after inclusion in the cohort. Patients may have used more than one drug category, or no drugs, in this period; therefore, the percentages do not add up to 100%.
†Some of these patients likely represent patients suspected to have type 2 diabetes before the final diagnosis of type 1 diabetes was made.
DPP4, dipeptidyl peptidase-4; GAD, glutamic acid decarboxylase; GLP, glucagon-like peptide-1; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT-2, sodium/glucose cotransporter 2.

Hg) or other types of diabetes (125 mm Hg, IQR: 116–136 mm Hg and 80 mm Hg, IQR: 70–85 mm Hg). Similarly, the median BMI was higher among patients with type 2 diabetes (30 kg/m^2, IQR: 27–35 kg/m^2) than patients with type 1 diabetes (25 kg/m^2, IQR: 22–27 kg/m^2) or other types of diabetes (24 kg/m^2, IQR: 21–28 kg/m^2). Patients with type 1 diabetes performed more weekly physical exercise than patients with type 2 and other types of diabetes. Of patients with type 1 diabetes and type 2 diabetes, 26% and 23%, respectively, were daily smokers.

Median HbA1c at enrolment was lower in patients with type 2 diabetes (51 mmol/mol, IQR: 44–63 mmol/mol) or other types of diabetes (54 mmol/mol, IQR: 44–68 mmol/mol) than in patients with type 1 diabetes (66 mmol/mol, IQR: 55–79 mmol/mol). Patients with type 2 diabetes were more likely to have microalbuminuria (urine albumin/creatinine ratio between 30 and 299 mg/g) than patients with type 1 and other types of diabetes. At enrolment, median total cholesterol and LDL levels were similar among patients with type 1 diabetes (4.7 mmol/L, IQR: 4.1–5.5 mmol/L and 2.6 mmol/L, IQR: 2.1–3.2), type 2 diabetes (4.8 mmol/L, IQR: 4.1–5.6 mmol/L and 2.6 mmol/L, IQR: 2.0–3.3) and other types of diabetes (4.6 mmol/L, IQR: 3.9–5.7 and 2.6 mmol/L, IQR: 1.8–3.2). GAD autoantibody positivity was present in 40% of patients with type 1 diabetes, whereas 76% had missing information on this variable. As expected, the C-peptide level was substantially higher among patients with type 2 diabetes than among patients with type 1 diabetes. The vast majority of type 1 diabetes patients had a record of redeeming an insulin (93%) prescription in the Danish National Health Service Prescription Database within 1 year before or after inclusion in the cohort. A majority (64%) of type 2 diabetic patients redeemed a prescription with metformin alone or in combination with DPP-4 inhibitors at the time of inclusion in the cohort and 15% were treated with insulin; less frequently, glucose-lowering drugs, such as sulfonylurea (21%) and DPP-4 inhibitors (6%), were used.

Information on foot status variables according to type of diabetes is shown in table 2. Approximately 4%–9% of patients had no foot sensitivity and 18%–25% had reduced foot sensitivity assessed by biothesiometry, monofilament test or vibration test. Approximately 4%–9% had no foot pulse and 3%–5% had a foot ulcer at registry inclusion. Eye status is reported in table 3. The prevalence and severity of diabetic retinopathy were more pronounced in patients with type 1 diabetes than in patients with type 2 diabetes.

FINDINGS TO DATE

Diabetes-related morbidity and mortality

To understand the burden of diabetes-related morbidity and mortality in the FDDB cohort, we linked the cohort to the Danish National Patient Registry and Civil Registration System. In this analysis, we followed patients from their first diabetes contact until any outcomes (incident or recurrent), death or end of follow-up using all available diagnostic *International Classification of Diseases 10th Revision* codes (table 4).

Median follow-up was 11.3 years (IQR: 6.0–13.6 years) for patients with type 1 diabetes, 8.1 years (IQR: 4.8–11.7 years) for patients with type 2 diabetes and 4.1 years (IQR: 1.9–8.0 years) for patients with other types of diabetes.

Number of events and rates (unadjusted and age-standardised) are given in table 4. During 212 234 person-years of follow-up for the entire diabetic cohort, 10 038 cardiovascular events (angina pectoris, myocardial infarction, ischaemic stroke, vessel surgery, intermittent arterial claudication or heart failure) occurred; 2415 were recorded with kidney failure, and less frequent complications were severe hypoglycaemia and ketoacidosis. During follow-up, 6265 patients died.

Key findings

The FDDB cohort has proven useful in previous publications, and several studies are ongoing.[13 19 20] In a cross-sectional study of 4374 adults, measurement of fasting C-peptide and the presence or absence of GAD autoantibodies at first hospital admission with diabetes could be used to define a subgroup of patients with clinically relevant differences in glycaemic control and markers of cardiovascular disease risk (BMI, blood pressure, lipid profile and liver enzymes).[20] Another cross-sectional study based on data from the FDDB

Table 2 Foot status of patients with diabetes mellitus recorded in the Funen Diabetes Database, Denmark, 2003–2018

	Type 1 diabetes		Type 2 diabetes		Other types of diabetes		Unknown type of diabetes	
	Left	Right	Left	Right	Left	Right	Left	Right
Sensitivity (vibration, biothesiometry or monofilament test)								
None	277 (8%)	282 (8%)	1282 (9%)	1287 (9%)	10 (4%)	9 (4%)	66 (7%)	65 (7%)
Reduced	602 (18%)	603 (18%)	3425 (23%)	3453 (23%)	56 (25%)	53 (23%)	163 (18%)	171 (19%)
Normal	2499 (74%)	2494 (74%)	10241 (69%)	10231 (68%)	162 (71%)	166 (73%)	662 (74%)	655 (74%)
Missing	313 (8%)	312 (8%)	4137 (22%)	4114 (22%)	64 (22%)	64 (22%)	5101 (85%)	5101 (85%)
Pulse								
No	197 (6%)	195 (6%)	1321 (9%)	1318 (9%)	11 (5%)	10 (4%)	74 (8%)	75 (8%)
Yes	3178 (94%)	3183 (94%)	13604 (91%)	13624 (91%)	212 (95%)	213 (96%)	810 (92%)	810 (92%)
Missing	316 (9%)	313 (8%)	4160 (22%)	4143 (22%)	69 (24%)	69 (24%)	5108 (85%)	5107 (85%)
Foot at risk								
No	2534 (75%)	2521 (75%)	9908 (68%)	9981 (68%)	156 (70%)	157 (70%)	530 (63%)	527 (62%)
Yes	824 (25%)	839 (25%)	4745 (32%)	4697 (32%)	67 (30%)	67 (30%)	317 (37%)	318 (38%)
Missing	333 (9%)	331 (9%)	4432 (23%)	4407 (23%)	69 (24%)	68 (23%)	5145 (86%)	5147 (86%)
Foot ulcer								
No	3245 (97%)	3228 (96%)	14227 (97%)	14150 (96%)	216 (97%)	218 (97%)	827 (95%)	828 (96%)
Yes	106 (3%)	128 (4%)	487 (3%)	588 (3%)	7 (3%)	6 (3%)	40 (5%)	38 (4%)
Missing	340 (9%)	335 (9%)	4371 (23%)	4347 (23%)	69 (24%)	68 (23%)	5125 (86%)	5126 (86%)
Amputation								
Above ankle	17 (1%)	14 (0%)	66 (0%)	66 (0%)	≤5	≤5	≤5	≤5
Below ankle	16 (0%)	18 (1%)	69 (0%)	66 (0%)	≤5	≤5	≤5	≤5
No	3331 (99%)	3336 (99%)	14247 (99%)	14282 (99%)	222 (100%)	223 (99%)	840 (100%)	840 (100%)
Missing	327 (9%)	323 (9%)	4703 (25%)	4671 (24%)	69 (24%)	67 (23%)	5148 (86%)	5149 (86%)
Ankle brachial index								
Median (IQR)	1.12 (1.00–1.20)	1.12 (1.00–1.20)	1.03 (0.94–1.14)	1.03 (0.94–1.14)	1.07 (1.00–1.15)	1.13 (1.00–1.16)	1.00 (0.91–1.13)	1.03 (0.95–1.11)
Missing	2249 (61%)	2245 (61%)	14641 (77%)	14636 (77%)	275 (94%)	275 (94%)	5907 (99%)	5905 (99%)

Table 3 Eye status of patients with diabetes mellitus recorded in the Funen Diabetes Database, Denmark, 2003–2018

	Type 1 diabetes		Type 2 diabetes		Other types of diabetes		Unknown type of diabetes	
	Left	Right	Left	Right	Left	Right	Left	Right
Retinopathy (examined by retinal photo or ophthalmoscopy)*								
No (grade 0)	1909 (57%)	1892 (56%)	13137 (83%)	13155 (83%)	167 (90%)	161 (87%)	3780 (94%)	3808 (94%)
Minimal (grade 1)	489 (15%)	510 (15%)	1125 (7%)	1115 (7%)	9 (5%)	12 (6%)	159 (4%)	135 (3%)
Moderate (grade 2)	419 (12%)	412 (12%)	967 (6%)	961 (6%)	7 (4%)	10 (5%)	59 (1%)	59 (1%)
Pre-proliferative (grade 3)	147 (4%)	155 (5%)	233 (1%)	241 (2%)	≤5	≤5	11 (0%)	13 (0%)
Proliferative, laser treatment (grade 4)	358 (11%)	354 (11%)	248 (2%)	245 (2%)	≤5	≤5	15 (0%)	12 (0%)
Missing	335 (9%)	337 (9%)	3263 (17%)	3266 (17%)	107 (37%)	107 (37%)	1950 (33%)	1947 (32%)
Vitrectomy								
No	3161 (98%)	3154 (98%)	14880 (100%)	14887 (100%)	175 (100%)	174 (100%)	3695 (100%)	3700 (100%)
Yes	69 (2%)	78 (2%)	64 (0%)	62 (0%)	0 (0%)	0 (0%)	5 (0%)	5 (0%)
Missing	461 (12%)	459 (12%)	4141 (22%)	4136 (22%)	117 (40%)	118 (40%)	2292 (38%)	2287 (38%)
Eye examination (visual acuity)								
Median (IQR)	1.0 (0.8–1.0)	1.0 (0.8–1.0)	0.9 (0.0.7–1.0)	0.9 (0.0.7–1.0	1.0 (0.8–1.0)	1.0 (0.8–1.0)	0.9 (0.7–1.0)	0.8 (0.7–1.0)
Missing	371 (10%)	371 (10%)	3357 (18%)	3347 (17%)	110 (38%)	110 (38%)	1959 (33%)	1955 (33%)

Categories of 'not gradable' and 'not evaluated' are not shown; therefore, the percentages do not add up to 100%.

Table 4 Number of and incidence rates (unadjusted and age-standardised) for diabetes-related conditions during follow-up according to diabetes type

	Type 1 diabetes			Type 2 diabetes			Other types of diabetes			Unknown type of diabetes		
	No. of events	Rate per 1000 person-years	Age-standardised rate per 1000 person-years*	No. of events	Rate per 1000 person-years	Age-standardised rate per 1000 person-years*	No. of events	Rate per 1000 person-years	Age-standardised rate per 1000 person-years*	No. of events	Rate per 1000 person-years	Age-standardised rate per 1000 person-years*
Cardiovascular diseases												
Angina pectoris	268	8.45 (7.47–9.49)	15.01 (12.89–17.14)	2397	18.81 (18.06–19.57)	17.57 (16.86–18.29)	10	9.08 (4.35–15.51)	11.18 (2.96–19.40)	320	13.45 (12.01–14.96)	13.41 (11.94–14.89)
Myocardial infarction	147	4.45 (3.76–5.20)	8.54 (6.97–10.10)	1006	7.05 (6.62–7.49)	6.55 (6.13–6.96)	6	5.03 (1.84–9.78)	7.76 (0.75–14.76)	136	5.12 (4.30–6.02)	5.10 (4.24–5.96)
Ischaemic stroke	169	5.18 (4.43–5.99)	9.22 (7.61–10.82)	1266	8.92 (8.44–9.42)	8.17 (7.72–8.63)	9	7.65 (3.49–13.39)	9.98 (2.41–17.55)	179	6.81 (5.85–7.85)	6.75 (5.75–7.74)
Vessel surgery	113	3.44 (2.83–4.10)	5.61 (4.44–6.79)	887	6.28 (5.87–6.70)	5.79 (5.40–6.18)	≤5	N/A	N/A	100	3.81 (3.10–4.59)	3.68 (2.95–4.40)
Intermittent claudication	107	3.23 (2.65–3.78)	5.26 (4.12–6.39)	764	5.24 (4.87–5.62)	4.73 (4.39–5.08)	9	7.42 (3.39–13.00)	6.96 (1.87–12.06)	138	5.18 (4.35–6.08)	4.99 (4.15–5.82)
Heart failure	148	4.49 (3.80–5.24)	9.24 (7.55–10.93)	1595	11.32 (10.77–11.88)	10.37 (9.85–10.89)	7	5.85 (2.34–10.91)	7.03 (1.00–13.07)	252	9.65 (8.49–10.88)	9.75 (8.53–10.96)
Other conditions												
Kidney failure	313	10.05 (8.97–11.19)	14.52 (12.57–16.47)	1793	12.78 (12.20–13.38)	12.01 (11.44–12.59)	8	7.04 (3.03–12.68)	9.60 (1.90–17.30)	301	11.85 (10.55–13.22)	11.88 (10.52–13.23)
Dialysis	84	2.53 (2.02–3.10)	3.18 (2.38–3.99)	214	1.44 (1.25–1.64)	1.33 (1.15–1.52)	≤5	N/A	N/A	34	1.24 (0.86–1.69)	1.19 (0.79–1.59)
Diabetes-specific conditions												
Hospitalisation for hypoglycaemia	680	23.31 (21.59–25.09)	28.32 (25.53–31.11)	797	5.43 (5.06–5.81)	4.96 (4.61–5.31)	22	19.11 (11.97–27.88)	19.30 (9.92–28.68)	152	5.62 (4.76–6.55)	5.70 (4.78–6.62)
Ketoacidosis	414	13.17 (11.93–14.47)	11.33 (9.83–12.84)	157	1.05 (0.89–1.22)	1.07 (0.89–1.25)	≤5	N/A	N/A	48	1.75 (1.29–2.28)	1.95 (1.39–2.51)
Pregnancy	196	6.27 (5.42–7.18)	2.67 (2.27–3.07)	80	0.54 (0.43–0.67)	1.11 (0.86–1.36)	≤5	N/A	N/A	19	0.70 (0.42–1.05)	1.04 (0.57–1.51)
All-cause mortality†	536	15.93 (14.61–17.31)	31.06 (28.05–34.07)	4711	31.46 (30.57–32.37)	28.18 (27.36–29.00)	40	32.42 (23.16–43.21)	40.76 (26.29–55.23)	978	35.42 (33.24–37.67)	34.93 (32.72–37.13)

The diagnosis codes are given in online supplementary file 1. Unless otherwise specified, outcomes were defined according to the *International Classification of Diseases 10th Revision* codes recorded in the Danish National Patient Registry with access to discharge diagnoses until 2016 and surgery/procedure data until 2014. All inpatient and outpatient hospital diagnoses were used. Hypoglycaemia and ketoacidosis also included emergency room diagnoses.
*Age-standardised to the age distribution in year 2003.
†All-cause mortality was recorded in the Civil Registration System.

that included 17 152 patients with diabetes reported a prevalence of diabetic retinopathy of 21% among type 2 diabetes patients, increasing to 54% among patients with type 1 diabetes. Risk factors for more severe diabetic retinopathy were age, duration of diabetes, HbA1c level, creatinine level and urine albumin. Based on the literature, the prevalence of diabetic retinopathy was fairly comparable to diabetic patients from cohorts in similar countries, including Sweden[21] and Wales,[22] supporting that the FDDB comprises a relatively representative sample of patients with diabetes. The FDDB has also been used to study the prognosis related to diabetes.[19] Patients with latent autoimmune diabetes in adults (LADA), representing ~10% of patients with type 2 diabetes with circulating islet autoantibodies as seen in type 1 diabetes mellitus, were identified and followed for subsequent mortality and cardiovascular outcomes. During a median follow-up period of 7 years, the study found that patients with both type 1 diabetes and type 2 diabetes had higher cardiovascular outcome rates (HR: 1.2, 95% confidence interval (CI) 0.7–2.0; and HR 1.2, 95% CI 0.8 to 1.8) and mortality (HR 2.2, 95% CI 1.5 to 3.2; and HR 1.4, 95% CI 1.0 to 1.9) than patients with LADA.

Strengths and limitations

The FDDB offers one of the most comprehensive records of clinical data on diabetes to date. The database comprises detailed clinical data with longitudinal and multiple records per patient. Although formal validation studies have not yet been performed, the FDDB is based on physicians' assessment of all available medical record data for each patient, and thus considered to be accurate. Serial examinations are recorded to track the clinical course and incidence of diabetic complications over time. Denmark's universal healthcare system and the possibility of exact individual-level data linkage provides unlimited possibilities for epidemiological and clinical studies. Data from Danish registries generally have high validity. For example, the Danish National Patient Registry sustains positive predictive values exceeding 90% for most cardiovascular outcomes, surgeries and interventions,[23 24] and the positive predictive value is 70%–80% for diabetic polyneuropathy.[25] On the other hand, the positive predictive value is much lower for diabetic foot ulcers (55%) in the Danish National Patient Registry.[25] Thus, if foot ulcers is the subject of investigation, the FDDB may be of enormous value.

All registry studies are vulnerable to participant attrition and missing data. In general, the proportion of missing data was lower among patients with type 1 and type 2 diabetes than it was for other types of diabetes. The proportion of missing data also varied according to specific variables. For example, the proportion of missing data was low for HbA1c and creatinine but higher for other variables, such as C-peptide and ankle brachial index. To deal with missing data issues, data from the FDDB can be linked to other Danish registries where the missing data could be available. In addition, it is recommended that multiple imputation techniques are employed to handle missing data. In epidemiological terms, the population of Denmark represents an open dynamic cohort with known dates of entry and exit with complete follow-up, censored only at emigration or death. Therefore, selection bias is minimised.

Although registry inclusion of patients does not entirely reflect the recent increase in the prevalence and incidence of diabetes and not all diabetic patients are captured by the FDDB, the registry is population-based and considered relatively representative of diabetic patients in Denmark. Supporting this notion, the age and sex composition, BMI, and blood pressure in the type 2 diabetic population of the FDDB are comparable to the Danish Centre for Strategic Research in Type 2 Diabetes project cohort.[6] Moreover, the age and sex composition, use of glucose-lowering drugs and HbA1c levels are similar to Danish type 2 diabetes patients who recently started glucose-lowering drugs in everyday clinical care in other regions of Denmark, such as Northern Denmark.[4 26] The FDDB lacks data on dietary habits, certain lifestyle factors (eg, alcohol consumption) and genetic predisposition, and it does not comprise biobank material. Gestational diabetes is not routinely captured in the FDDB, nor is ethnicity (the population of the Funen area comprises around 90% ethnic Danes). Left truncation or lack of data before the year 2003 is also a challenge for studies examining very long-term outcomes.

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Collaborators All data from the FDDB are deposited at the Department of Clinical Epidemiology at Aarhus University Hospital. Researchers interested in collaboration can contact Steno Diabetes Center Odense, email: ouh.sdco@rsyd.dk

Contributors HB-N, JEH, and OH-N raised the funding. KA, PS, JEH, RWT, LP, JS, HTTS, OH-N and HB-N were involved in the study design. PS performed the statistical analyses. KA, PS, JEH, RWT, LP, JS, HTTS, OH-N and HB-N were involved in the interpretation of the results. KA wrote the initial drafts, and all authors commented on and approved the final manuscript.

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REFERENCES

1 Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet* 2017;389:2239–51.
2 Mayer-Davis EJ, Lawrence JM, Dabelea D, *et al*. Incidence trends of type 1 and type 2 diabetes among Youths, 2002-2012. *N Engl J Med* 2017;376:1419–29.
3 Thomsen RW, Baggesen LM, Søgaard M, *et al*. Early glycaemic control in metformin users receiving their first add-on therapy: a population-based study of 4,734 people with type 2 diabetes. *Diabetologia* 2015;58:2247–53.
4 Thomsen RW, Baggesen LM, Svensson E, *et al*. Early glycaemic control among patients with type 2 diabetes and initial glucose-lowering treatment: a 13-year population-based cohort study. *Diabetes Obes Metab* 2015;17:771–80.
5 Magliano DJ, Martin VJ, Owen AJ, *et al*. The productivity burden of diabetes at a population level. *Diabetes Care* 2018;41:979–84.
6 Christensen DH, Nicolaisen SK, Berencsi K, *et al*. Danish centre for strategic research in type 2 diabetes (DD2) project cohort of newly diagnosed patients with type 2 diabetes: a cohort profile. *BMJ Open* 2018;8:e017273.
7 Duelund-Jakobsen J, Worsoe J, Lundby L, *et al*. Management of patients with faecal incontinence. *Therap Adv Gastroenterol* 2016;9:86–97.
8 Petersen ERB, Nielsen AA, Christensen H, *et al*. Vejle Diabetes Biobank - a resource for studies of the etiologies of diabetes and its comorbidities. *Clin Epidemiol* 2016;8:393–413.
9 Schmidt M, Pedersen L, Sørensen HT. Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29:541–9.
10 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2019*. *Diabetes Care* 2019;42:S13–28.
11 Statistics Denmark. Available: https://www.dst.dk/en/Statistik/emner/befolkning-og-valg/befolkning-og-befolkningsfremskrivning/folketal [Accessed 3 Jun 2019].
12 Odense University Hospital's webpage. Available: http://en.ouh.dk/about-ouh/ [Accessed 3 Jun 2019].
13 Larsen MB, Henriksen JE, Grauslund J, *et al*. Prevalence and risk factors for diabetic retinopathy in 17 152 patients from the island of Funen, Denmark. *Acta Ophthalmol* 2017;95:778–86.
14 Henriksen DP, Rasmussen L, Hansen MR, *et al*. Comparison of the Five Danish Regions Regarding Demographic Characteristics, Healthcare Utilization, and Medication Use--A Descriptive Cross-Sectional Study. *PLoS One* 2015;10:e0140197.
15 Standardization IOf. ISO 15189:2012. Medical laboratoires — requirements for quality and competence: international organization for standardization, 2012. Available: https://www.iso.org/standard/56115.html
16 Wilkinson CP, Ferris FL, Klein RE, *et al*. Proposed International clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003;110:1677–82.
17 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al*. Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
18 Johannesdottir SA, Horváth-Puhó E, Ehrenstein V, *et al*. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:303–13.
19 Wod M, Thomsen RW, Pedersen L, *et al*. Lower mortality and cardiovascular event rates in patients with latent autoimmune diabetes in adults (LADA) as compared with type 2 diabetes and insulin deficient diabetes: a cohort study of 4368 patients. *Diabetes Res Clin Pract* 2018;139:107–13.
20 Wod M, Yderstræde KB, Halekoh U, *et al*. Metabolic risk profiles in diabetes stratified according to age at onset, islet autoimmunity and fasting C-peptide. *Diabetes Res Clin Pract* 2017;134:62–71.
21 Heintz E, Wiréhn A-B, Peebo BB, *et al*. Prevalence and healthcare costs of diabetic retinopathy: a population-based register study in Sweden. *Diabetologia* 2010;53:2147–54.
22 Thomas RL, Dunstan FD, Luzio SD, *et al*. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. *Br J Ophthalmol* 2015;99:64–8.
23 Adelborg K, Sundbøll J, Munch T, *et al*. Positive predictive value of cardiac examination, procedure and surgery codes in the Danish national patient registry: a population-based validation study. *BMJ Open* 2016;6:e012817.
24 Sundbøll J, Adelborg K, Munch T, *et al*. Positive predictive value of cardiovascular diagnoses in the Danish national patient registry: a validation study. *BMJ Open* 2016;6:e012832.
25 Christensen DH, Knudsen ST, Nicolaisen SK, *et al*. Can diabetic polyneuropathy and foot ulcers in patients with type 2 diabetes be accurately identified based on ICD-10 Hospital diagnoses and drug prescriptions? *Clin Epidemiol* 2019;11:311–21.
26 Svensson E, Baggesen LM, Johnsen SP, *et al*. Early Glycemic Control and Magnitude of HbA_{1c} Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators. *Diabetes Care* 2017;40:800–7.