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ORIGINAL ARTICLE

Design and methodology of the PRIMETIME 1 cohort study: PRecIsion MEdicine based on kidney TIssue Molecular interrogation in diabetic nEphropathy

Karina Haar Jensen [1,2], Frederik Persson [2], Ditte Hansen[3,4], Iain Bressendorff[3], Marie Møller[3], Peter Rossing [2,4], Eva Gravesen[5], Vanja Kosjerina[2,6], Dorte Vistisen[2] and Rikke Borg[1,4]

[1]Department of Medicine, Zealand University Hospital, Roskilde, Denmark, [2]Steno Diabetes Center Copenhagen, Herlev, Denmark, [3]Department of Nephrology, Copenhagen University Hospital – Herlev and Gentofte Hospital, Herlev, Denmark, [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [5]Department of Pathology, Copenhagen University Hospital – Herlev and Gentofte Hospital, Herlev, Denmark and [6]Department of Endocrinology, University Hospital Bispebjerg-Frederiksberg, Copenhagen, Denmark

Correspondence to: Karina Haar Jensen; E-mail: khr@regionsjaelland.dk

ABSTRACT

Background. Clinical features of diabetic kidney disease alone cannot differentiate between the histopathology that defines diabetic nephropathy (DN) and non-diabetic nephropathy (NDN). A kidney biopsy is necessary to make the definitive diagnosis of DN. However, there is no consensus on when to perform a kidney biopsy in individuals with diabetes and kidney disease. Furthermore, the implications of NDN versus DN for management, morbidity and kidney prognosis are unclear. To address the gap in knowledge, we aimed to create a national retrospective cohort of people with diabetes and a performed kidney biopsy.

Methods. Adults diagnosed with diabetes in Denmark between 1996 and 2020 who had a kidney biopsy performed were included. The cohort was established by linking a nationwide diabetes registry with the Danish Pathology Registry. Data from 11 national registries and databases were compiled. The type of kidney disease was classified using a three-step analysis of Systematized Nomenclature of Medicine codes reported in relation to the histopathological examinations of kidney tissue. The final cohort and classification of kidney disease was as follows: out of 485 989 individuals with diabetes 2586 were included, 2259 of whom had type 2 diabetes. We were able to classify 599 (26.5%) with DN, 703 (31.1%) with NDN and 165 (7.3%) with mixed disease in individuals with type 2 diabetes. In individuals with type 1 diabetes, 132 (40.4%) had DN, 73 (22.3%) NDN and 39 (11.9%) mixed disease. The remaining could not be classified or had normal histology. The overall median (Q1–Q3) follow-up time was 3.8 (1.6–7.2) years.

Conclusions. This cohort is a novel platform based on high-quality registry data for important longitudinal studies of the impact of kidney disease diagnosis on prognosis. With regular updates of data from the Danish registries, the presented follow-up will increase over time and is only limited by emigration or death.

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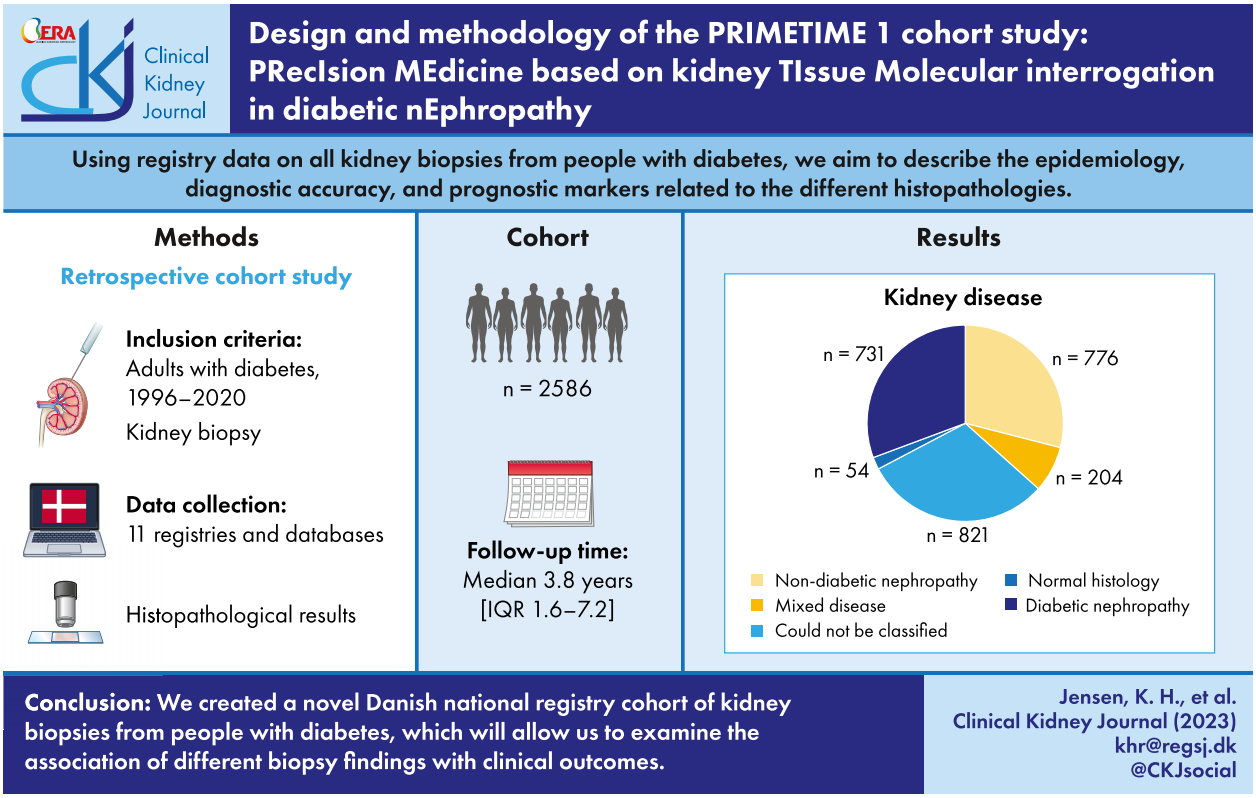
LAY SUMMARY

Kidney disease is a severe and common complication of diabetes. To improve individualized treatment for kidney disease in diabetes, there persists a need to advance knowledge concerning diagnostic accuracy, disease course, secondary diseases and prognostic markers within this field. Therefore, we established the PRIMETIME 1 (PRecIsion MEdicine based on kidney TIssue Molecular interrogation in diabetic nEphropathy) study. The study is a large Danish national study with comprehensive national registry data on all individuals with diabetes who have undergone a kidney biopsy. This paper describes the rationale, design and methodology of creating this cohort, and demonstrates a novel method of classifying kidney disease based on national registry data. With the PRIMETIME 1 cohort study, we have established a unique opportunity to study biopsy-proven kidney disease in diabetes in the future.

GRAPHICAL ABSTRACT



Keywords: chronic kidney disease, diabetic kidney disease, diabetic nephropathy, kidney biopsy, registries

INTRODUCTION

Diabetic kidney disease (DKD) is a severe complication of diabetes that leads to increased risk of kidney failure and cardiovascular diseases, as well as the excess mortality associated with diabetes [1–5]. In most cases, the diagnosis of DKD is based on clinical characteristics such as persistent albuminuria, hypertension, decline in kidney function, and absence of clinical or laboratory evidence of other kidney or urinary tract disease [6, 7].

However, studies suggest that many individuals with diabetes and kidney disease will suffer from non-diabetic nephropathy (NDN) or have a mixed pathology of kidney lesions [4, 5, 8].

A more precise diagnosis of kidney disease caused by diabetes is based on histological examination of kidney biopsies, and in this case, is termed diabetic nephropathy (DN). In daily clinical practice, kidney biopsies are not used as a systematic diagnostic tool for kidney disease in diabetes. Clinical indication for a kidney biopsy is a frequent discussion among specialists in daily clinical practice. Furthermore, practice varies between clinics and countries [9, 10].

Persisting severe (>1 g/day) or rapidly increasing proteinuria despite optimal treatment, absence of retinopathy, hematuria and rapid decrease in kidney function are some of the indications for performing a kidney biopsy [9]. However, since the clinical characteristics of DKD overlap with features of non-DKD, clinical characteristics alone cannot reliably differentiate between the two. At present, only a kidney biopsy can give an accurate diagnosis and classify the structural staging of the kidney disease [4, 5, 9, 11].

Some studies show kidney outcomes to be better in NDN compared with DN, and a histopathological diagnosis of DN or NDN may be decisive [8, 12]. For instance, in many cases, glomerular and tubulointerstitial diseases caused by NDN will benefit from individualized treatments such as immunosuppressive therapy. Recent years have provided several new and important treatments in addition to renin–angiotensin system inhibitors, such as sodium-glucose cotransporter-2 inhibitors, the nonsteroidal mineralocorticoid receptor antagonist finerenone and potentially glucagon-like peptide-1-receptor agonists for treatment in DKD, although in DKD the potential of precision medicine and diagnostics has yet to be further developed and utilized [13–16].

To improve precision medicine for kidney disease in diabetes, there is a need to address the gap in knowledge concerning epidemiology, diagnostic accuracy and prognostic markers within this field. To answer some of these questions, we are establishing the PRIMETIME 1 (PRecIsion MEdicine based on kidney TIssue Molecular interrogation in diabetic nEphropathy) cohort. The purpose of this paper is to describe the rationale, design and methodology of creating this cohort, and classifying kidney disease based on registry data.

MATERIALS AND METHODS

Study design, population and setting

The study was approved by the Danish Data Protection Agency and Danish Health Data Agency (j-No: SDC-2017-026 and FSEID-00003715).

We created a cohort by compiling data from several nationwide Danish registries and databases linked at person level using the unique personal identification number given to all Danish residents at birth or at immigration [17].

The PRIMETIME 1 cohort aimed to include all Danish adults with diabetes registered between 1996 and 2020 who have undergone a kidney biopsy. Originating from the national researcher-initiated diabetes cohort, called the DMreg, a data search was carried out in the Danish Pathology Registry by the Danish Health Data Authority Research Service. The search was based on registered Systematized Nomenclature of Medicine (SNOMED) codes corresponding to having undergone a kidney biopsy (specified in Supplementary data, Table S1).

The DMreg consists of all Danish individuals with diabetes from 1996 until 1 May 2020. DMreg is constructed on existing population-based registries and databases, and is not only based on relevant International Classification of Diseases (ICD)-8/10 codes but also on diabetes-defining information from several other sources. DMreg contains 485 989 individuals with diabetes and details concerning the constructions have been described elsewhere [18, 19].

Data on kidney biopsies delivered from the Danish Pathology Registry were stored safely and the following exclusion criteria were implemented: (i) no material from the kidney or material with other topography than kidney tissue; (ii) material not confirmed as a biopsy or with origin from procedure other than biopsy; (iii) kidney biopsy from solid tumors, both benign and malignant (hematologic malignancies were not excluded); (iv) kidney transplant, graft/donor kidney biopsies; (v) individuals aged <18 years at the time of diabetes diagnosis; (vi) biopsies taken before diabetes diagnosis; and (vii) individuals who emigrated before diagnosis was made from the biopsy.

Exclusion criteria, defined by codes, were based on prevalent codes in the originally identified population. Exclusion criteria are described in detail in Supplementary data, Table S2.

Before data cleaning, all prevalent SNOMED codes were exported and the codes were translated into text by searching the SNOMED code on https://www.patobank.dk, and if not available here, identified in the official SNOMED classification sheet published by the Danish Health Data Authority [20]. Following this, the texts were translated into English.

SNOMED

Pathology reports are often based on serial codes describing the findings and results of the examination, but the applied system and coverage in kidney biopsy registries are not unified internationally [21]. One coding system used in pathology reporting is the Systematized Nomenclature Of Medicine second edition (SNOMED II), which is used for pathology reporting in Denmark [22].

SNOMED II is organized in a multiaxial hierarchy, where each axis is represented by a letter followed by five-digit codes resenting a unique encoded text. The pathologist operates with the six following axes: topography [i.e. type of organ and anatomical orientation (T-codes)], procedure or histopathological technique applied (P-codes), morphology (M-codes), disease (S-codes), function (F-codes) and etiology (Æ-codes). It is mandatory for Danish pathologists to report at least one T- and one M-code. All reported codes are stored in the Danish Pathobank and the Danish Pathology Registry [23, 24].

Origin and availability of data

Data from the DMreg, the Danish Pathology Registry and an additional nine registries and databases were stored at Statistics Denmark, the independent official and central authority for Danish Statistics [25]. All data will be updated regularly. The 11 registries and databases present a wide range of data for further studies and an overview of time coverage and type of data is provided in Table 1.

Preliminary baseline data

We assembled data on gender, type of diabetes and duration of diabetes at biopsy from the DMreg. Data on body mass index were compiled from Steno Diabetes Center Copenhagen Electronic Patient Record (SDCC EPR) and the Danish Adult Diabetes Registry, and were defined as the measurement closest to date of biopsy and no more than 2 years before or after biopsy. Estimated glomerular filtration rate (eGFR) and urine albumin–creatinine ratio (UACR) were defined as the measurement closest to date of biopsy and no more than 1 year before biopsy. eGFR was extracted from the Register of laboratory results. Furthermore, eGFR was obtained from SDCC EPR , and in this case calculated from serum and plasma creatinine (using the Chronic Kidney Disease Epidemiology Collaboration equation 2009). UACR data were assembled from the Register of laboratory results and the Danish Adult Diabetes Registry.

We also report follow-up time calculated as time from biopsy until emigration, death or 31 December 2020.

Classification of kidney disease

The free-text part of the histopathology report is considered to be micro-data, and this type of information is not permitted to

Table 1: Databases and registries in the PRIMETIME 1 cohort (note that reported content in registries is not complete, but mostly limited to content of relevance for this present study).

Database/registry	Period	About
CPR Register and Register of Demography [35, 36]	Data since 1968	A national registry driven by the CPR office. SHDS holds a copy of the registry for internal use and use in research. Data on personal ID number, migrations and vital status among others
Danish Adult Diabetes Registry (DVDD) [37]	Data from outpatient clinics since 2004. Data from General Practitioners since 2008, although paused between 2014 and 2017	A national clinical quality database. Data are held by RKKP and covers annual status on diabetes patients, including various clinical and laboratory measurements.
National Health Insurance Service Register [38]	Data since 1990	Data held by SHDS and DST. Contains data on vital status, services supported by public welfare performed by general practitioners, specialized doctors and podiatrists among others
Danish Pathology Register (LRP) [30]	Data since 1970, complete since 1997	Registry held by SHDS. In 1997 it became mandatory for all pathologists to report pathology data electronically, not directly in the Danish Pathology Register. In 1999 the National Danish Pathology Data Bank was established as a tool for direct recording by pathologists, and these data are referred to the Danish Pathology Register
Danish Register of Causes of Death (DAR) [39]	Data since 1970	Data held by SHDS and DST. National data regarding cause and date of death. The source of information is a medical certificate fulfilled by inquest
Danish Registry of Diabetic Retinopathy (DiaBase) [40]	Outpatient data since 2007, nationwide in 2010. Data from private practice ophthalmologists since 2013	A clinical national quality database held by RKKP. Data cover nationwide annual registrations of eye examinations in patients with diabetes reported by Departments of Ophthalmology and Ophthalmologists in private practice
National Patient Register (NPR) [41–43]	Founded in 1976. From 1995 data from all public psychiatric, somatic and emergency department contacts. Data from private sector are incomplete	Data held by SHDS and DST. By law it is required for Danish hospitals to report standardized data to the registry. Data covers diagnosis and procedures related to the contacts, among others. Furthermore, data on certain treatments, e.g. surgery, and examinations plus specific administrative data, such as date of admission and discharge
Register of laboratory results (LAP_F) [44]	Data since 2015. Some regions have reported further historical data to the database	Data held by SHDS and DST. Hospital laboratory analyses performed at departments of clinical biochemistry and clinical immunology on blood samples, urine, joint and spinal fluids. “Region Midt” does not report results from clinical biochemistry analyses. “Region Zealand” and “Region South” do not report results from clinical immunology analysis
The Danish National Prescription Registry (DNPR) [45]	Data since 1995	Data held by SHDS and DST. National information on all prescription drugs dispensed at community pharmacies

Table 1: Continued

Database/registry	Period	About
DMreg [46]	Valid information from 1996 up until 1 May 2020	A register constructed on existing population-based healthcare registers. The register intends to include all people with diabetes[a] in Denmark and has information on gender, birthdate, type of diabetes and first event of retinopathy (only those treated in-hospital). Data stored at DST
SDCC Electronic Patient Record (SDCC EPR)	Data since 1993	Data held by SDCC and the Capital Region. Data cover information on maculopathy and retinopathy, neuropathy, blood pressure, history of foot ulcers, and alcohol and smoking status
Tissue Utilisation Register (VAR) [47]	Data since 2004	Data held by SHDS. According to Danish law people have the right to decide that their biological material (with a few exceptions) only can be used for their own diagnosis and treatment, and not for research. To obtain these rights patients must register within the Tissue Utilisation Register

[a]Diabetes defining information: (i) at least two relevant ICD-8/10 codes, (ii) at least two purchases of anti-diabetic medication, (iii) one purchase of anti-diabetic medication and one relevant ICD-8/10 code, (iv) registration in the Danish Adult Diabetes Registry; (v) at least one registration of podiatry; or (vi) at least one diabetic eye examination. The earliest date of occurrence of these diabetes-defining information acts as a proxy for the date of diagnosis in the DMreg.
DST, Statistics Denmark; ID number, a 10-cifered unique personal ID number called the CPR number (the first 6 cifers represents the person's birthday and birth year; cifers 5–7 represent century of birth; and cifer 10 tells us the person's gender); RKKP, the Danish Clinical Quality Program—National Clinical registries; SDCC, Steno Diabetes Center Copenhagen; SHDS, Danish Health Data Authority.

be stored at Statistics Denmark. Thus, available data from the Danish Pathology Registry consisted of SNOMED codes. We conducted a three-step analysis of prevalent SNOMED codes identified in the PRIMETIME 1 population to stratify our population into groups according to their histological findings: DN, NDN, mixed disease (DN plus NDN), normal histology and biopsies that could not be classified (Fig. 1).

Since one biopsy procedure could be represented by more than one biopsy core and each core could represent different histopathological patterns, the term biopsy will refer to all part

Figure 1: Defining kidney disease, a three-step analysis. Morphology -, disease-, function-, and etiology-SNOMED codes are categorized into eleven code types in step one of the classification algorithm. In step two the combinations of the code types, grouped in step one, define kidney disease within each kidney biopsy material. Step three defines the kidney disease within each individual i.e. first conclusive biopsy. SNOMED, Systematized Nomenclature Of Medicine.
†Three nephrologists and one nephropathologist individually performed a manual assessment of all the SNOMED codes.
*SNOMED codes divided into the following eleven types: *Acceptable DN code*, code that is acceptable in addition to DN codes and where findings still indicate diabetic nephropathy. Code is nonspecific to diabetic nephropathy and cannot be accepted in addition to NDN code when classified as having non-diabetic nephropathy; *Acceptable NDN code*, code which is acceptable in addition to an NDN code and where findings still indicate nondiabetic nephropathy. Code non-specific for non-diabetic nephropathy and cannot be accepted in addition to DN code when classified as DN; *Acceptable NDN or DN code*, code which is acceptable in addition to an NDN code or a DN code and where findings still indicate non-diabetic nephropathy or diabetic nephropathy, respectively. Non-specific code, neither nondiabetic nephropathy nor diabetic nephropathy; *DN code*, code indicating diabetic nephropathy; *Freetext code*, code referring to free text; *Grading code*, code referring to the grading of morphological findings; *Location code*, code referring to orientation; *NDN code*, code specific for non-diabetic nephropathy; *Normal code*, codes referring to normal pathology; *Unspecific code*, code non-specific for either diabetic nephropathy or non-diabetic nephropathy. Moreover, so ambiguous that the code cannot be accepted in either diabetic nephropathy or nondiabetic nephropathy; *quality code*, code concerning the quality of biopsy material or quality of examination.

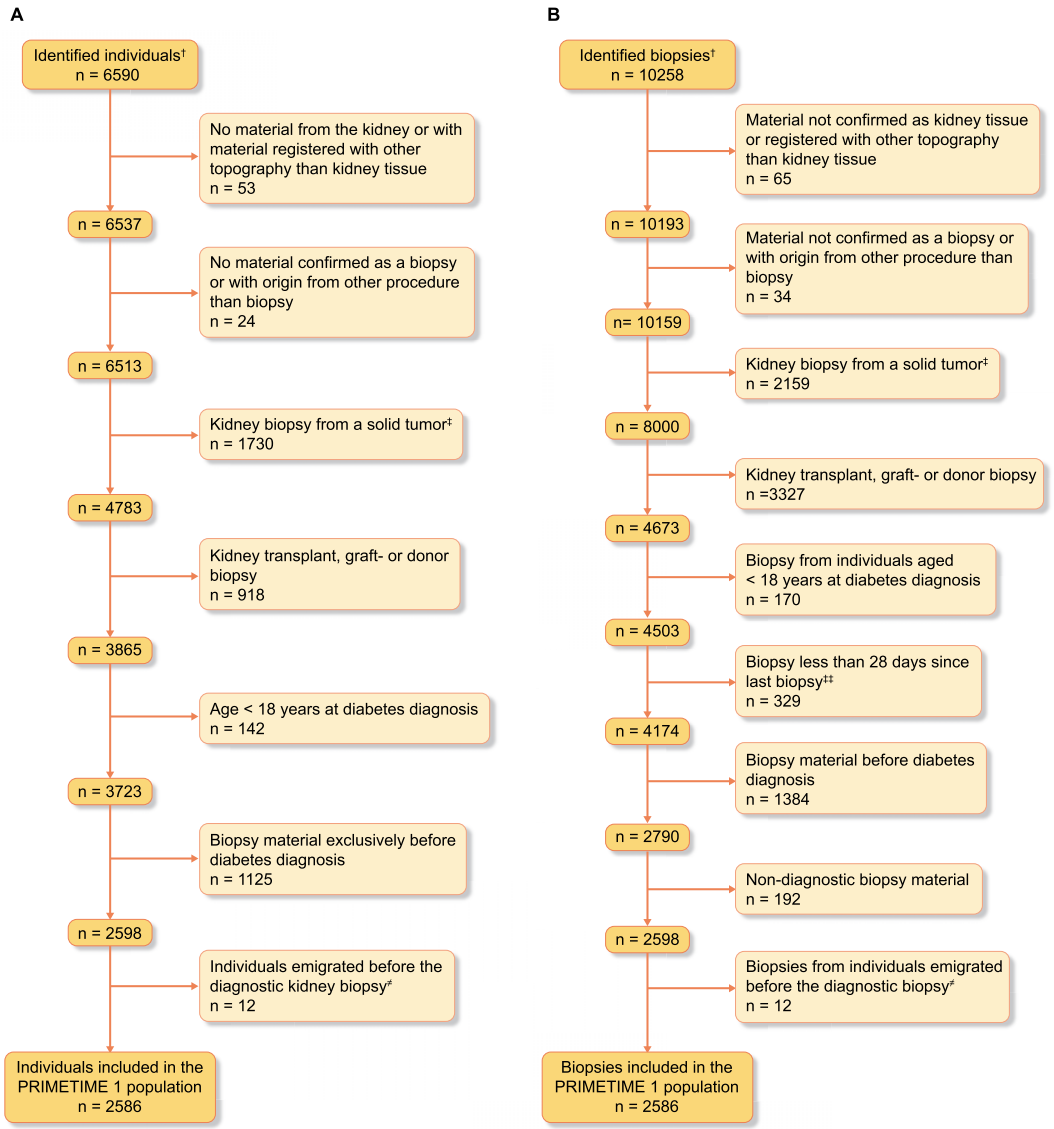


Figure 2: Flowchart illustrating the process of inclusion and exclusion (A) identification of The PRIMETIME 1 population and (B) identification of kidney biopsy selection. SNOMED, Systematized Nomenclature Of Medicine, a multiaxial coding system.
†The Danish Health Data Authority Research Service identified all individuals with diabetes having a previously performed kidney biopsy. ‡Solid tumor-biopsies are defined as malignant and non-malignant tumors (exclusive hematologic malignancy). ††If the interval between multiple biopsies from one individual is <28 days, all the biopsy material is considered as one biopsy procedure. ≠It is allowed to have emigrated if the individual immigrated again before the diagnostic biopsy.

elements of a biopsy, meaning all core biopsies. All kidney biopsies performed and examined within 28 days were evaluated as one biopsy within each individual.

Classification of kidney disease, Step 1

The first step involves assessing all morphology, disease, function and etiology codes represented in the cohort. Three nephrologists and one nephropathologist individually performed manual assessment in step one. The codes were categorized in one of the following 11 code types: DN, NDN, Acceptable in DN, Acceptable in NDN, Acceptable in NDN or DN, Free text, Quality, Location, Grading, Unspecific and Normal (definitions are shown in Supplementary data, Table S3). In cases of disagreement, a final decision was reached by consensus.

Some SNOMED codes were considered as ambiguous. As an example, the disease codes "Diabetes Mellitus" and "Sarcoidosis" can potentially be clinical information and are not necessarily based on the pathoanatomical examination [26]. To minimize potential misclassification, ambiguous codes could not be used for classification of DN or NDN code types.

Classification of kidney disease, Step 2

An algorithm based on combinations of SNOMED codes types (assessed in Step 1) was applied and kidney disease was grouped based on the predefined principles (Fig. 1). Step 2 assigned each biopsy as having pathology suggesting DN, NDN, mixed disease, normal tissue or coding that could not be classified. Inadequate quality of material, lack of descriptive ambiguous and unclear

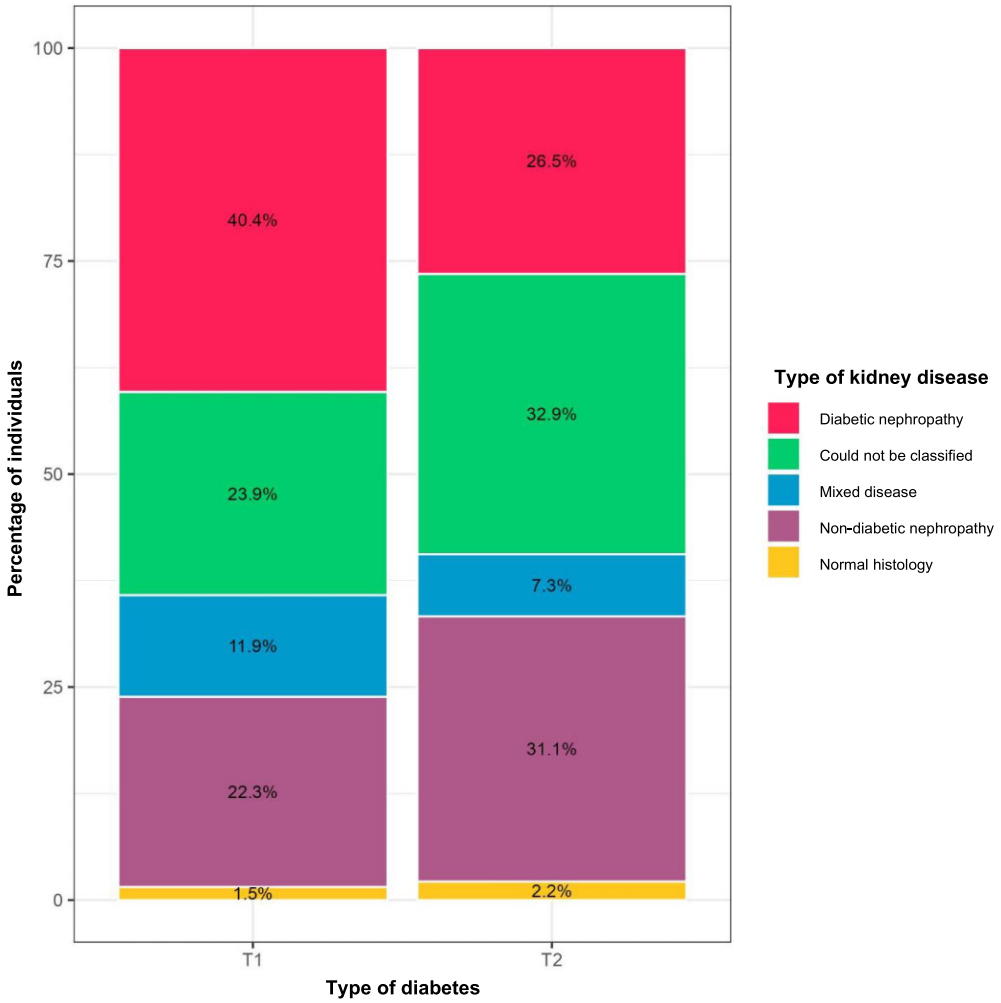


Figure 3: Defining kidney disease, results from the three-step analysis. The final type of kidney disease defined within individuals in The PRIMETIME 1 cohort according to type of diabetes.

combinations of SNOMED codes are examples of why some biopsies could not be classified.

Classification of kidney disease, Step 3

In Step 3, the type of kidney disease within each individual was classified as either DN, NDN, mixed disease, having normal histology or could not be classified. The first biopsy after diabetes diagnosis defined the type of kidney disease and repeat biopsies after diabetes diagnosis were excluded unless the result of the first biopsy was not diagnostic (i.e. normal or could not be classified). If the first biopsy was not diagnostic and the individual had more than one biopsy, then the first diagnostic biopsy was considered conclusive.

The final cohort and classification of kidney disease

After applying inclusion and exclusion criteria, a total of 2586 individuals with diabetes and a kidney biopsy were included (Fig. 2A). In total 231 unique morphology, disease, function and etiology codes were represented within the 2790 kidney biopsies (Fig. 2B). A complete list of the identified codes and results of the assessment process in Step 1 is provided in Supplementary data, Table S3.

As a result of the three-step analysis, individuals with type 2 diabetes (T2DM) were classified as having either DN ($n = 599$), NDN ($n = 703$) or mixed disease ($n = 165$) in their first conclusive biopsy after diabetes diagnosis. In type 1 diabetes (T1DM), $n = 132$ had DN, $n = 73$ NDN and $n = 39$ mixed disease. The remaining individuals could not be classified or had normal histology (Fig. 3).

The population consisted mostly of men (68%), and 87.4% had T2DM. Median (Q1–Q3) eGFR was 36 (20–64) mL/min/1.73 m^2 for those with T2DM and 35 (16–69) mL/min/1.73 m^2 for those with T1DM. Median (Q1–Q3) UACR was 1680 (313–3860) mg/g in T1DM and 955 (80–2730) mg/g in T2DM. The median (Q1–Q3) follow-up time was 3.8 (1.6–7.2) years. Preliminary baseline characteristics are presented in Table 2.

Table 2: Baseline characteristics of the PRIMETIME 1 cohort according to type of diabetes.

	Type 1 diabetes (N = 327)	Type 2 diabetes (N = 2259)	Overall (N = 2586)
Gender, *n* (%)			
Male	218 (66.7)	1540 (68.2)	1758 (68.0)
Female	109 (33.3)	719 (31.8)	828 (32.0)
Duration of diabetes at diagnostic kidney biopsy (years)			
Median (Q1–Q3)	12.1 (6.54–20.1)	7.21 (3.01–13.0)	7.70 (3.22–13.8)
Body mass index (kg/m^2)			
Mean (SD)	25.1 (4.50)	30.9 (6.24)	30.1 (6.36)
Missing, *n* (%)	160 (48.9)	1283 (56.8)	1443 (55.8)
eGFR (mL/min/1.73 m^2)			
Median (Q1–Q3)	36.5 (16–69)	36.0 (20–64)	36.0 (19–64)
Missing, *n* (%)	213 (65.1)	1108 (49.0)	1321 (51.1)
Category of eGFR, *n* (%)			
eGFR ≥90 mL/min/1.73 m^2	14 (4.3)	121 (5.4)	135 (5.2)
eGFR 60–89 mL/min/1.73 m^2	19 (5.8)	200 (8.9)	219 (8.5)
eGFR 45–59 mL/min/1.73 m^2	12 (3.7)	150 (6.6)	162 (6.3)
eGFR 30–44 mL/min/1.73 m^2	18 (5.5)	200 (8.9)	218 (8.4)
eGFR 15–29 mL/min/1.73 m^2	27 (8.3)	285 (12.6)	312 (12.1)
eGFR <15 mL/min/1.73 m^2	24 (7.3)	195 (8.6)	219 (8.5)
Missing	213 (65.1)	1108 (49.0)	1321 (51.1)
UACR (mg/g)			
Median (Q1–Q3)	1680 (313–3860)	955 (80.3–2730)	1020 (93.0–2860)
Missing, *n* (%)	208 (63.6)	1198 (53.0)	1406 (54.4)
Category of UACR, *n* (%)			
UACR <30 mg/g	12 (3.7)	171 (7.6)	183 (7.1)
UACR 30–299 mg/g	17 (5.2)	214 (9.5)	231 (8.9)
UACR ≥300 mg/g	90 (27.5)	676 (29.9)	766 (29.6)
Missing	208 (63.6)	1198 (53.0)	1406 (54.4)
Follow-up time (years)[a]			
Median (Q1–Q3)	4.8 (2.1–10.9)	3.7 (1.5–6.8)	3.8 (1.6–7.2)
Missing, *n* (%)	7 (2.1)	93 (4.1)	100 (3.9)

[a]The follow-up time was only calculated for those having their biopsy taken before 31 December 2020, as this is the date of the most recent update of registry data stored.

DISCUSSION

With the linkage of a nationwide diabetes registry and pathology registry, a large retrospective cohort of all adults with diabetes who have undergone a kidney biopsy was assembled. By converting SNOMED codes to a workable format we were able to categorize the type of kidney disease (DN, NDN and mixed disease) in 68% of our population. The population includes an almost equal fraction of NDN (30%) and DN (28%). One might predict DN to be present more often in people with diabetes, however these findings agree with previous studies performed on similar study populations and are to be expected as biopsies primarily are performed on clinical indications in cases suspicious for NDN. A systematic review and metanalysis by Fiorentino *et al.* reported that NDN was prevalent in up to 82.9% of individuals with diabetes. Numbers varied greatly between studies with the lowest reported prevalence being 3% [5]. Likewise, a review of 40 studies including individuals with T2DM reported a prevalence of NDN between 0% and 68.6% [4]. Both studies mainly included retrospective studies with a significant selection bias [4, 5].

Likewise, the kidney disease reported in our study is from individuals that were biopsied due to clinical features suggestive of NDN. Therefore, the prevalence of less frequently biopsied kidney diseases such as DKD or kidney diseases diagnosed with serological markers will presumably be underestimated. Furthermore, a large proportion of the population could not be classified according to their kidney disease from the available SNOMED codes. Therefore, the prevalence of each type of kidney disease should be interpretated with caution.

Strengths and limitations

The long-standing tradition of national, government-maintained population registration in Denmark offers a unique opportunity to work with high-quality registry data. As an example, the CPR Registry (Civil Registration System), essential for linking data on an individual level and tracking the population, is considered accurate and complete based on various mechanisms that control data, and a low prevalence of disappeared persons of around 0.3%. These conditions allow this study to have data completeness due to a long follow-up period only limited by emigration or death [27, 28].

Data in the Danish Pathology Registry are considered complete and valid. The electronic registration of kidney biopsies is mandatory and continuous troubleshooting and validation of data is incorporated in the Danish Pathology Registry, hence the kidney biopsy inclusion criteria should be adequate [24, 29, 30].

Also, identification of individuals with diabetes in Denmark is based on the DMreg which is considered to be almost complete due to its thorough construction [18, 19]. Therefore, we expect the study population to represent the target population.

The approach to categorize kidney disease based on national histopathology registry data in a stepwise analysis has, to our knowledge, not previously been performed. However, Helgstrand *et al.* used a somewhat similar method to define prostate cancer based on SNOMED codes, and researchers managed to validate the data internally and externally [31]. One significant difference from this study is that they had access to the free-text part of the histopathological report, which we do not. Therefore, analysis of SNOMED codes in our study is hampered by the fact that we could only extract the SNOMED codes, and not the final conclusion of the histopathology report. In the stepwise analysis, we acknowledge that some SNOMED codes, alone or in combination, are ambiguous. Some morphologic changes can be seen in both DN and NDN, and mixed disease. In addition, some of the SNOMED codes could potentially represent information given by the clinician and not be representative of the histopathological examination. We minimized the limitation introduced by the lack of the free-text part in the histopathological report by implementing a conservative approach in which only a clear-cut combination of SNOMED codes identified a case as DN, NDN or mixed disease, thus minimizing the risk of false-positive cases. This way of minimizing misclassification bias results in a relatively large group of biopsies that could not be classified. Optimization of the coding system within pathology with mandatory encoded biopsy diagnoses, and practice within the pathological departments, might provide even more workable data and would have reduced the biopsies that could not be classified within this study.

Although Denmark has one of the world's best registered populations the registry data on histopathology reporting has some limitations. The newest version of the SNOMED system is the international language SNOMED Clinical Term. However, SNOMED Clinical Term has not been implemented in histopathology reporting in Denmark, and data to the Danish Pathology Registry still has its origin in the SNOMED II system [22].

Next, the SNOMED II system introduces the possibility of variability in coding practice because of variations between departments and personnel, and changes in practice over time. However, due to the conservative approach when classifying type of kidney disease, we do not anticipate these variations to affect our study. Also, the vast number of codes incorporated in the SNOMED II system introduces a considerable number of coding possibilities. However, an effort to unify registered pathology data in a common, continuously revised guideline on the registration of pathoanatomic data was introduced in 1997 by the National Board of Health along with the introduction of a legal obligation for Danish pathologists to report pathology data [23].

Generalizability

The Danish population is relatively ethnically homogenous with only 5.8% and 2.9% being immigrants and descendants from non-Western countries, respectively, as of the second quarter of 2022 [32]. There are no useful data on the incidence of diabetic and non-diabetic kidney disease in general in chronic kidney disease, but in 2020 diabetes was the primary renal disease in kidney replacement therapy in 27.3% of Danish individuals, and similarly in 23% of European individuals [33]. We expect that the findings of the study will be generalizable to Western countries of similar demographics.

Internationally, coding systems reporting to kidney biopsy registries have a significant divergence, and proprietary systems seem to dominate over the SNOMED and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) coding system for primary kidney disease [21]. Unfortunately, this undermines the usefulness of kidney biopsy registries in comparing and aggregating data internationally.

The algorithm for classifying kidney disease was built on the SNOMED II system and can be applied to other populations using this system.

Our algorithm was built on prevalent SNOMED codes in the PRIMETIME 1 population and not on all potential SNOMED codes. This means SNOMED codes used rarely when encoding pathological examination of kidney tissue are less likely to be incorporated in this algorithm. However, we expect that over 20 years of national registered SNOMED codes represent applied coding to a large extent. Lastly, we plan to validate the described method.

CONCLUSIONS AND FUTURE PERSPECTIVES

The comprehensive description of the establishment of this cohort, and how registry data on kidney pathology can be used to classify kidney disease within diabetes, provides an in-depth understanding of opportunities and limitations within extensive use of registry data.

A large-scale repeated-measures dataset was assembled as part of the PRIMETIME 1 cohort and provides a unique opportunity to study biopsy-confirmed DN in future publications. The personal identification number secures information on the entire population with follow-up only limited by emigration or death. With regular updates from the Danish registries, follow-up will increase over time.

In order to improve personalized medicine in kidney disease in diabetes we aim to: (i) provide epidemiologic studies on morbidity and mortality of kidney disease in diabetes stratified by DN, NDN and mixed disease; (ii) associate the features of histopathology to clinical phenotype, clinical data, disease progression, comorbidity and mortality; and (iii) study the predictive value of clinical variables on disease course. The authors plan to validate these findings in an ongoing prospective study with research biopsies [34]. However, the strength of the present study is the long follow-up time.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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According to Danish law, ethical approval and patient consent are not required for registry studies. Access and use of the described register data are approved by the Danish Data Protection Agency and Danish Health Data Agency (j-No: SDC-2017-026 and FSEID-00003715).

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AUTHORS' CONTRIBUTIONS

R.B., F.P., D.H. and I.B. conceived the idea for the study. K.H.J. was responsible for data management, with contribution from V.K. K.H.J. and V.K. 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. K.H.J. wrote the initial draft and organized the writing process. All authors contributed to the study design and critically revised the article during the writing process. All authors gave final approval of the published version.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

F.P. reports receiving honoraria for lectures and consultancy from AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk and Sanofi. D.H. has reports receiving honoraria for lectures from Gedeon Richter and advisory board attendance from Pharmacosmos. I.B. reports honoraria for lectures from Bayer and Amgen. P.R. reports honoraria to Steno Diabetes Center Copenhagen for education and consultancy from Astellas, Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, Merck and Sanofi. D.V. holds shares in Novo Nordisk A/S and has received research grants from Bayer A/S, Sanofi, Novo Nordisk A/S and Boehringer Ingelheim. R.B. reports honoraria for education and consultancy from Astra Zeneca, Bayer, Mundipharma, Vifor and Boehringer Ingelheim. I.B., K.H.J. and M.M. receive funding from the Novo Nordisk Foundation. E.G. and V.K. report no conflicts of interest in this work.

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