Type 2 diabetes in real-life: Population-based Danish studies of incidence, prognosis, and treatment effectiveness

PhD dissertation

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Thesis papers

Study I: 24 year trends in the incidence and mortality of type 2 diabetes - A Danish population-based study (In draft).

Study II Trends in HbA_{1c} and LDL Cholesterol in Patients with Type 2 Diabetes Receiving First-Time Treatment in Northern Denmark, 2000-2017: Population-Based Sequential Cross-Sectional Analysis (*Diabetes Care* 2019; November: e1-e3).

Study III Differences Between Randomized Clinical Trial Patients and Real-World Initiators of the Glucagon-Like Peptide 1 Receptor Agonist Liraglutide (*Diabetes Care* 2018; 41: e133–5)

Study IV Clinical characteristics and glucose-lowering drug utilization among patients initiating liraglutide in Denmark: a routine clinical care prescription study (*Journal of Diabetes* 2019; 11: 690–4).

Table of Contents

Abbreviations

ACCORD	The Action to Control Cardiovascular Risk in Type 2 Diabetes
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation
DPP	Diabetes Prevention Program
DPS	Diabetes Prevention Study
HbA_{1c}	Hemoglobin A1c
OGTT	Oral Glucose Tolerance Tests
FPG	Fasting Plasma Glucose
GLD	Glucose Lowering Drug
LABKA	The Clinical Laboratory Information System
LLD	Lipid-Lowering Drug
LDL	Low Density Lipoprotein
LEAD	Liraglutide Effect and Action in Diabetes
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
T2D	Type 2 Diabetes
UKPDS	United Kingdom Prospective Diabetes Study Group
WHO	World Health Organization

Introduction

"Diabetes" has been described in historical records for thousands of years, possibly even dating back to ~3,400 BC during ancient Egypt's First Dynasty [1]. Naturally, the condition described in the historical documents evolves around what physicians of the times were able to experience and understand, initially involving descriptions of conditions with excess urine [1]. The first descriptions including glycosuria ("honey urine" that attracted ants and flies) are from ancient Hindu texts three millennia later [1]. In 1769, William Cullen was the first to distinguish this condition from a condition that solely involved polyuria (Diabetes Insipidus) by adding the "Mellitus" (meaning "sweet" [taste]) to Diabetes [1].

The understanding of diabetes continued to evolve gradually. This included the histological finding of the islets of Langerhans in the human pancreas (1869), and recognizing that removing the pancreas from dogs resulted in fatal diabetes (late 1800s), and the discovery and isolation of insulin (1920s). Of course, this soon led to insulin treatment of patients with elevated blood glucose. Thus enabling patients to survive, although without being cured, led to a new focus on long-term complications from living with diabetes [2]. This eventually led to the recognition of distinct types of diabetes based on whether a patient needed treatment with insulin, and later again (late 1990s) a change in diabetes definitions based on the pathogenesis of diabetes (e.g. type 1 and type 2 diabetes [T2D]). In recent decades, knowledge and understanding of diabetes continue to evolve gradually, including changing diagnostic methods and thresholds for diagnosis [3].

Obviously, the archetypical patient diagnosed with and initiating treatment for diabetes has changed in the course of this long period since the first discovery of diabetes. In recent decades, this may have had important clinical implications as many key clinical trials (forming the basis of contemporary treatment guidelines for effective diabetes treatment) were performed when the diabetes definition, the diagnostic thresholds, and even diagnostic methods were all quite different from what they are today. In this dissertation, I examine the time trends in patient characteristics, diabetes treatment and its effectiveness, and the incidence and prognosis of newly treated T2D patients in Denmark. I also examine differences between randomized clinical trial participants and real-world initiators of one of the most utilized newer glucose-lowering drugs (GLDs) in Denmark, liraglutide, and their HbA_{1c} reduction. In this, the

dissertation aims to suggest and demonstrate a new method for examining whether randomized clinical trial efficacy translates into real-world effectiveness in diabetes patients.

Aims

The overall aims of this dissertation were to:

1) **examine time trends in HbA_{1c} levels, lipid management, incidence, and prognosis in early type 2 diabetes in Denmark (studies I + II) and**
2) **examine differences in patient characteristics between real-world users of newer glucose-lowering drugs (exemplified by liraglutide) and participants in key randomized controlled trials, and how these differences influence the generalizability of trial efficacy into treatment effectiveness (studies III + IV).**

Diabetes classification and diagnosis

A range of different criteria were used for diabetes diagnosis prior to the 1980s. To resolve this, an expert committee established a single set of criteria [4]. They elected to predict a diabetes-specific microvascular outcome, namely diabetic retinopathy, and based this prediction on glucose levels. Three prospective studies were available at the time, in which 1,123 patients were followed for up to 3 to 8 years after a 2-hour oral glucose tolerance test (OGTT). Among these patients, 77 patients developed diabetic retinopathy. There were no further glucose evaluations following the initial OGTT. Despite this, a fasting plasma glucose (FPG) of ≥140 mg/dL (7.77 mmol/L) or a 2-hour OGTT value ≥200mg/dL (11.1 mmol/L) was selected as diagnostic threshold for diabetes. The OGTT was considered the diagnostic gold standard, despite being based on the outcome of 77 patients with unknown glucose status for years prior to developing the outcome [4]. Thus, in the mid-1980s diabetes was classified according to insulin dependency, and diagnosis was based on a OGTT or fasting glucose [5]. When the diagnostic criteria were re-evaluated in the mid-1990s, one challenge was the limited mutual agreement between the diagnostic methods: only one-quarter to half of patients with a 2-hour OGTT value ≥200mg/dL (11.1 mmol/L) also had fasting glucose ≥140 mg/dL (7.77 mmol/L) [4]. It was considered "very disruptive" to change the

OGTT diagnostic value because many epidemiological studies were based on these values [4]. For this reason, at the end of the 1990s, consensus arose around a classification based on the pathogenesis of diabetes and a diagnosis based on lower fasting glucose thresholds that would yield a diabetes prevalence equal to that found when using OGTT ≥200mg/dL (11.1 mmol/L) (fasting glucose ≥126 mg/dL/7.0 mmol/L) [3,4]. During the 1990s and 2000s, there was a continued search for a diagnostic option that would inconvenience both the patient and the physicians to a lesser extent than fasting glucose and the 2-hour OGTT [6]. Consequently, in 2011, the World Health Organization (WHO) concluded that HbA_{1c} could also be used for diagnostic testing [6]. These changes to the diagnostic criteria expanded the definition of T2D. This resulted in a change regarding which patients fulfilled the diagnosis criteria and would receive treatment, this consequently impacted the incidence and prevalence of T2D [3]. According to contemporary definitions, most forms of diabetes can be classified as follows (cited from the American Diabetes Association [ADA] 2019 [7]):

- Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency)
- Type 2 diabetes (due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance)
- Gestational diabetes mellitus […] (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)
- Specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young […], diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation)

Starting in 2011 (2012 in Denmark), the diagnosis of T2D may be based upon *either* FPG *or* a 2-hour OGTT *or* HbA_{1c} as shown below (cited from ADA 2019) [7,8]:

- FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.
- 2-h PG ≥200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
- HbA_{1c} ≥6.5% (48 mmol/mol). […]
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

The HbA_{1c} value reflects a patient's mean glucose over the preceding 90–120 days, and has been used since the 1990s for monitoring the glycemic status of already diagnosed T2D patients. The main reason for the introduction of HbA_{1c} as a diagnostic option was to make diagnosing diabetes simpler. For this reason, it is obvious why HbA_{1c} has become the most used T2D diagnostic option since its introduction. However, there is only partial overlap between patients receiving a T2D diagnosis when using the different diagnostic methods. A study identifying 1,158 patients with incident T2D detected through screening used all three diagnostic methods (OGTT, FPG, HbA_{1c}); while patients by definition had at least one positive diagnostic test, only 7% were diagnosed positive with all three simultaneously [9]. Patients diagnosed with different T2D diagnostic methods may represent different disease phenotypes or stages and might thus have a different prognosis [10]; the diagnostic changes may thus have changed the basic epidemiology of diabetes [11].

Diabetes incidence trends

According to the WHO, the number of patients worldwide living with (mostly type 2) diabetes has increased from 108 million in 1980 to 422 million in 2014 (corresponding to an increase in prevalence from 4.7% to 8.5%) [12]. This increase is mostly accredited to lifestyle changes, including an increasing prevalence of obesity [12]. A similar dramatic increase in the prevalence of T2D has been seen in Denmark during the same period, and is projected by some to continue at least until 2030 [13].

A major reason for the increasing prevalence has been earlier and better treatment of T2D, resulting in patients living longer with the disease. While increasingly earlier treatment has a permanent effect on T2D prevalence, the effect on incidence is temporary. Most studies on T2D incidence (with sufficient granularity to examine year-by-year trends) show a reduction in incidence in the years following the introduction of HbA_{1c} as a diagnostic option (Table 1). Some studies have even suggested that this decrease may somehow be the result of the introduction of HbA_{1c} [14,15] as a diagnostic option, but no studies that had data allowing for the examination of this hypothesis have been found.

To explore time trends in T2D incidence, I performed a literature search on PubMed in October 2019. I used the terms: "(("Diabetes Mellitus") AND Incidence) AND trend". I limited the search to studies within the last 5 years (allowing for information after HbA_{1c} introduction) and to English language manuscripts. This yielded 1,927 results. Following screening of the titles, I read the abstracts of 43 of the papers. I excluded publications that exclusively reported prevalence trends, since it is hard to interpret whether a change in prevalence is caused by changes in incidence or mortality [16]. Additionally, I searched the reference lists of all selected articles. Table 1 shows the 15 papers resulting from the literature search.

Table 1. Incidence trends in T2D

First author, journal (year)	Setting, period, study design	Mode of diagnosis	Underlying population	Persons with diabetes	Annual incidence/prevalence	trend
Fox et al., Circulation (2006) [17]	Framingham heart study, 1970s-1990s, cohort study	Fasting plasma glucose ≥7.0 mmol/L or treatment with either insulin or a hypoglycemic agent	3,104	162	Incidence: 2.0%, 3.0%, and 3.7% among women and 2.7%, 3.6%, and 5.8% among men in the 1970s, 1980s, and 1990s, respectively	Increasing
Alharbi et al., Diabetes Research and Clinical Practice Journal (2014) [18]	Arabian Gulf States, 1980-2012, review	"WHO criteria"	Not reported	Not reported	Prevalence: increased from 10.6% in 1989 to 32.1% in 2009	Increasing
Geiss et al., JAMA (2014) [19]	US NHIS, 1980-2012, cross sectional	Self or proxy reported (survey)	664,969 adults 20-79 years	428	Incidence/1000 persons 3.2 (1990), 8.8 (2008), 7.1 (2012)	Increase until late 2000s, subsequent decline
Abraham et al., Diabetes Care (2015) [20]	Framingham heart study, 1970s-2000s, cohort study	Fasting glucose ≥126 mg/dL or use of antidiabetic medication	4,795	217	Rates of diabetes per 1,000 individuals were 2.6, 3.8, 4.7, and 3.0 (women) and 3.4, 4.5, 7.4, and 7.3 (men) in the 1970s, 1980s, 1990s, and 2000s	Increasing for men. Increasing for women until 1990s, then declining
Jansson et al., Diabetic Medicine (2015) [21]	Entire Swedish population, 2005-2013, cohort study	Those who received antidiabetic drugs between 1 July 2005 and 30 June 2013	Not reported	240,871	Incidence: 4.34 and 3.16 per 1000 individuals in men and women, respectively	Decline, driven by decrease among >65 years last two years of study

Nichols et al., American Journal of Epidemiology (2016) [22]	US, 2006-2011, cohort study	ICD-9 diabetes codes (in- or outpatient), or HbA1c > 6.5%, or fasting plasma glucose ≥ 126 mg/dl or any GLD prescribed	~7 million insured adults aged 20 years or older	289,050	Incidence / 1000 persons : 10.8 (2006) to 11.5 (2011)	Increase was statistically insignificant
Green et al., Clinical Epidemiology (2015)[23]	Entire Danish population, 2000-2011, cohort study	Diagnosis codes (ICD-8 or ICD-10) for diabetes, regular or elevated glucose measurements, prescription redemption GLD	Not reported	497,232	Standardized Incidence Rate / 100,000 person years: 36 (2000) – 62 (2011)	Increasing
Sharma et al., BMJ open (2016) [24]	550 general practices throughout the UK, 2000-2013	Diagnosis in UK primary care database	8,838,031	203,639	Incidence: 3.69 per 1000 person years (2000) to 3.99 (2013) for men; and from 3.06 (2000) to 3.73 (2013) for women	Increasing
Sousa-Uva et al., Primary Care Diabetes (2016) [25]	Volunteer GP sentinel network in spain, 1992- 2015	Family doctors reported all new cases of Diabetes in their patients' lists	Not reported	Not reported	incidence / 100.000 persons: Increase from 262 (1992-94) peaking (2010-12) with subsequent fall to 630 (2013-15)	Increasing. Decline last period of study (from 2010-12 to 2013-15).
Weng et al., Diabetes Research and Clinical Practice (2016) [26]	US claims database, 2007-2012	GLD prescription	24,517,156	152,252 (2007) 147,011 (2012)	Decline from 1.1% (2007) to 0.65%. (2012)	Declining
Norhammar et al., Diabetologia (2016) [27]	Sweden, 2006-2013, Population based	GLD prescription	~8 million	253,689	Decline from 460 (2006) to 399 (2013) per 100,000 persons	Declining

Ruiz et al., Diabetologia (2018) [28]	Norway, 2009-2014, Population based	ICD-10 diagnosis code from hospital or code from primary care (ICPC-2) and GLD prescription redemption	3,227,454	75,496	609 (2009) to 398 (2014) per 100,000 Person years	Declining.
Mayer-Davis et al., New England Journal of Medicine (2017) [29]	US, five study centers, 2002-2012	Physician´s diagnosis of diabetes (T1D or T2D) in the medical record at age < 20 years	4.9 million youths	Not reported	226 (2002) to 322 (2012) per year	Increasing markedly among youths
Liu et al., International Journal of Environmental Research and Public Health (2019) [30]	China, Global Burden of Disease 2017 survey, 1990-2017	Collected from the Global Burden of Disease 2017 Study.	Not reported	Not reported	From figure per 100,000: from 180 (1990) to 250 (2017)	Slow increase until 1998. Sharp increase until late 2000s. Significant decrease until 2017.
Abbreviations: GP: general Practitioner, WHO: World Health Organization, T1D: Type 1 Diabetes, T2D: Type 2 Diabetes						

Diabetes mortality trends

I performed a literature search on PubMed using the terms: (("diabetes mellitus") AND "mortality") AND "trends". I limited the search to studies within the last 5 years (allowing for information after HbA_{1c} introduction) and to English language manuscripts. This yielded 677 results. Following the screening of titles, I read the abstracts of 43 of the papers and limited my study to papers reporting all-cause mortality. I also searched the reference lists of the papers. The 13 papers resulting from the search are shown in Table 2.

With few exceptions [31], most studies on T2D mortality trends compare annual mortality trends among the prevalent T2D population. The most recent mortality studies find a convergence between mortality rates of T2D patients and general population controls until the introduction of HbA_{1c} [32–34]; i.e., they suggest that mortality has decreased relatively more in T2D patients than in the general population of similar age. Recently, however, a Swedish population-based study found that all-cause mortality increased again among T2D diabetes patients from 2010-11 to 2012-13 and 2014, which was not seen in matched general population controls [32]. A UK study similarly reported all-cause mortality increased in T2D from 2012 to 2014 in contrast to a continued decline among population controls [34]. Finally, a US study that included the most recent data analyzed National Health Interview Survey data from 1988-2015 at 5- or 6-year intervals and did not find a mortality increase from 2005-2009 to 2010-2015 – possibly due to a lack of granularity of the data (and because time was modeled as a continuous variable) [33]. These previous studies on T2D mortality trends abstain from commenting on the increases in mortality in the most recent years, possibly because only modest numbers of data points are available.

Table 2: Mortality trends in T2D

First author, journal (year)	Setting, period	Baseline rate	Study end rate	Difference (%)	Relevant comparison	Mode of diagnosis	Patient type	mortality trend
Ringborg et al., Diabetic Medicine (2008) [35]	Uppsala County, Sweden, 1996-2003	5.4%	4.1%	-1.3 ppt. (-24%)	none	ICD-9, ICD-10 diabetes code, or GLD prescription, or elevated plasma glucose	prevalent	Declining
Forssas et al., Scandinavian Journal of Public Health (2010) [36]	Finland, Population-based, 1991-2002	4.2% (women), 6.3% (men)	2.7% (women), 4.3% (men)	-1.6 ppt (-36%) (women), -2.0 ppt. (-32%) (men)	no	ICD-9, ICD-10 diabetes code, or GLD prescription	prevalent	Declining
Li et al., Journal of the Formosan Medical Association [37,38]	Taiwan, Population based, 2000-2014	1.2%	1.0%	-0.2 ppt. (-17%)	no	>2 outpatient visits or at least one admission within one year with ICD-9 coded diabetes	Prevalent	Declining until 2013. Increasing last year of study
Lind et al., Diabetologia (2013) [39]	Ontario, Canada and the UK, 1996-2009	1.9%	1.2%	-0.7 ppt. (-37%)	yes	Age 20 years, and at least one hospitalization or two physicians claims for diabetes within 2 years	Prevalent	Declining, converging with controls
Karpati et al., Population Health Metrics (2014) [40]	Israel, 2004-2012	1.4%	1.1%	-0.3 ppt. (-21%)	no	HbA1c tests, glucoses tests, diagnoses, and GLDs	prevalent	Declining
Butala et al., JAMA internal medicine (2014) [41]	Yale New Haven, US, 2000-2012	3.6%	2.2%	-1.4 ppt (-39%)	yes	Diabetes diagnosis during admission	Prevalent	Declining, converging with controls
Green et al., Clinical	Denmark, 2000-2011	5.7%	3.9%	-1.8 ppt (-32%)	no	Diagnosis codes (ICD-8 or ICD-10)	Prevalent	Declining

First author, journal (year)	Setting, period	Baseline rate	Study end rate	Difference (%)	Relevant comparison	Mode of diagnosis	Patient type	mortality trend
Epidemiology (2015) [23]						for diabetes, regular or elevated glucose measurements, prescription redemption for GLD		
Harding et al., Diabetes Care (2016) [42]	Australia, 2000-2011	9.7%	7.9	- 1.8 ppt (-19%)	no	Physician-reported diagnosis to database	Prevalent	Declining
Read et al., Diabetologia (2016) [31]	Scotland, 2004-2013	2.0 %	1.8%	-0.2 ppt (-10%)	no	Physician-coded diabetes in national diabetes database	Incident	Declining
Norhammar et al., Diabetes Care (2016) [27]	Sweden, 2006-2013	1.6%	1.4%	-0.2 ppt (-9%)	yes	GLD prescription	Prevalent	Declining
Zghebi et. al., Diabetes, Obesity and Metabolism (2017) [34]	UK, 2004-2014	3.2%	2.2%	-1.0 ppt (31%)	yes	Primary care database with at least one T2D code at age >15 years	Probably prevalent	Declining
Rawshani et al., New England Journal of Medicine (2017) [32]	Sweden, 1998-2014	4.1%	3.4%	-1.3 ppt (17%)	yes	Consenting individuals included in the Swedish National Diabetes Register	Prevalent	Declining until end 2000s. Subsequent increase in difference from controls
Kim et al., Diabetes and Metabolism	South Korea, 2003-2013	1.4%	0.9 %	-0.5 ppt (36%)	yes	Diabetes codes ICD-10 in national sample database	prevalent	Declining

First author, journal (year)	Setting, period	Baseline rate	Study end rate	Difference (%)	Relevant comparison	Mode of diagnosis	Patient type	mortality trend
Journal (2018) [43]								
Gregg et al., The Lancet (2018) [33]	US NHIS, 1985-2015	2.3%	1.5%	-0.8 ppt (35%)	yes	Self-reported from survey.	prevalent	Declining. Low granularity.

Diabetes treatment: evolving guidelines and treatment targets based on key clinical trials

Evidence-based best practice for early diabetes detection has evolved markedly in the past decades following the publication of the Diabetes Prevention Program (DPP) and the Finnish Diabetes Prevention Study (DPS), which showed that diabetes could be prevented in people with impaired glucose tolerance [44,45]. Evidence-based guidelines for treatment of diabetes have also evolved markedly; starting with a stronger focus on glycemic control after the publication of the UKPDS results. This was followed by attention to other cardiovascular risk factors, including lipid control, after the Steno 2 Study showed that intensive multifactorial target-driven intervention led to markedly better outcomes in patients with longstanding T2D. At the same time the ACCORD and ADVANCE studies showed that glucose lowering alone did not improve macrovascular outcomes [46–49]. Findings from key diabetes trials are presented in Table 3.

Good glycemic control with use of GLDs and good lipid control, using mainly statins, are key factors in all contemporary guidelines for diabetes treatment, and HbA_{1c} targets of at least <7.0% have been widely accepted since the early 2000s. More intensive targets of <6.0% were examined in the ACCORD trial, but a previously unrecognized harmful effect from overly strict glucose management [7,50–52] was found. Primary LDL targets of 2.6 mmol/l for patients age >40 years and without overt cardiovascular disease were introduced in the ADA recommendations in 2005 [53]. That same year, a more intensive target of 1.8 mmol/l was introduced for patients with diabetes and overt cardiovascular disease as a direct consequence of the CARDS trial [53,54]. Indeed, following the publication of the CARDS trial the discussion focused on whether statin treatment should be withheld from any T2D patients [53].

In parallel with this evidence and the emphasis on achieving these treatment targets that has emerged during the recent 2 or 3 decades, the incidence of classic diabetes complications (lower extremity amputation, myocardial infarction, stroke, end-stage renal disease, blindness, hyperglycemic death, and an increased all-cause mortality) has reportedly declined markedly in high-income countries [55]. Possible explanations for these improvements are likely to be: 1) improved clinical care, including lower thresholds for initiating treatment, more intensive treatment targets, and more available treatment options, but also 2) earlier and more complete detection of previously undiagnosed T2D due to increased

awareness among physicians and patients [46,56]. However, there are few large population-based data sources available on time trends in diabetes with regard to management with GLDs and statins and the achievement of treatment targets [57], i.e., data necessary to substantiate how and whether T2D treatment has actually improved on the population level over the years.

Diabetes treatment: clinical trials and their generalizability

Evidence-based treatment guidelines for diabetes are based on evaluations of all available clinical research [51,52,58]. However, most of these trials recruited patients with T2D during periods in which the diagnostic criteria were different, and blood lipids and hypertension were less strictly regulated than today. The T2D patients included in the most recently conducted trial, EMPA-REG outcome, were recruited during 2010-2013, making it unlikely that a single T2D diabetes patient in any of the pivotal trials listed in Table 3 was diagnosed using HbA_{1c} [59].

Randomized controlled trials (RCTs) are considered the gold standard for determining the efficacy and safety of newly developed or already marketed medications [60]. A successful randomization removes confounding both by indication and by unknown confounding factors, thus improving the ability to show the effect of a drug in a selected trial population. This may come at the expense of generalizability: treatment results have been shown on occasion to be much less favorable than expected [61–63], and the risk of adverse drug effects may be higher among patients treated in everyday clinical practice. The probability that real-world patient populations differ considerably from RCT participants likely contributes to this discrepancy. Key differences may include age, comorbidities, ethnicity, co-medications, disease severity and duration, and adherence to medications [64], as RCT participants are often selected on the basis of these criteria. Thus, the generalizability of trial findings to real-world T2D patients remains poorly understood.

Table 3 selected key trials of T2D treatment

Key trial name	Recruitment period	Publication	Main finding (cited conclusions)
The United Kingdom Prospective Diabetes Study (UKPDS) [46]	1977-91	1998	*Intensive blood-glucose control by either sulphonylureas or insulin substantially decreases the risk of microvascular complications, but not macrovascular disease, in patients with T2D. None of the individual drugs had an adverse effect on cardiovascular outcomes. All intensive treatment increased the risk of hypoglycemia.*
UKPDS 10 year follow-up [65]	1977-91	2008	*Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients.*
Steno 2 [47]	1993	2008	*In at-risk patients with T2D, intensive intervention with multiple drug combinations and behavior modification had sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes.*
Finish Diabetes Prevention study (DPS) [66]	1993-1998	2001	*T2D can be prevented by changes in the lifestyles of high-risk subjects.*
Diabetes Prevention Program (DPP) [67]	1996-1999	2002	*Lifestyle changes and treatment with metformin both reduced the incidence of diabetes in persons at high risk. The lifestyle intervention was more effective than metformin.*
The CARDS trial[54]	1997-2001	2004	*Atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with T2D without high LDL-cholesterol. No justification is available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with T2D should receive statins. The debate about whether all people with this disorder warrant statin*

Key trial name	Recruitment period	Publication	Main finding (cited conclusions)
			treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld.
VADT study [68]	2000-2003	2009	*Intensive glucose control in patients with poorly controlled T2D had no significant effect on the rates of major cardiovascular events, death, or micro-vascular complications, with the exception of progression of albuminuria*
VADT 10 year follow-up [69]	2000-2003	2015	*After nearly 10 years of follow-up, patients with T2D who had been randomly assigned to intensive glucose control for 5.6 years had 8.6 fewer major cardiovascular events per 1000 person-years than those assigned to standard therapy, but no improvement was seen in the rate of overall survival.*
ADVANCE [49]	2001-2002	2008	*A strategy of intensive glucose control, involving gliclazide (modified release) and other drugs as required, that lowered the glycated hemoglobin value to 6.5% yielded a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy*
PROactive study [70]	2001-2002	2005	*Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with T2D who have a high risk of macrovascular events.*
ACCORD [71]	2001-2005	2008	*As compared with standard therapy, the use of intensive therapy to target normal glycated hemoglobin levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events. These findings identify a previously unrecognized harm of intensive glucose lowering in high-risk patients with T2D.*
EMPA-REG outcome [59]	2010-2013	2015	*Patients with T2D at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.*

Key trial name	Recruitment period	Publication	Main finding (cited conclusions)
LEADER [72]	2010-2012	2016	*In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with T2D mellitus was lower with liraglutide than with placebo.*

Methods

Setting

All studies described in this PhD thesis were carried out using only Danish data. The Danish National Health Service provides universal, tax-supported healthcare, guaranteeing unfettered access to general practitioners, hospitals, and partial reimbursement for prescribed drugs. Unambiguous linkage of data from all sources at the individual level is possible via the unique central personal registry number assigned to all Danish residents at birth or immigration [73]. Studies III and IV were restricted to Northern Denmark (Region Nord and Region Midt), where long-term laboratory data were available.

Data sources

The Danish Civil Registration System (studies I-IV):

The Danish Civil Registration System (CRS) was established in 1968 and contains personal information including sex and date of birth, and is updated daily with respect to vital status and residency for all Danish residents [74].

The Danish National Patient Registry (studies I-IV)

The Danish National Patient Registry (DNPR) contains data on dates of admission and discharge from all Danish somatic hospitals since 1977 and records of emergency and outpatient specialist clinics visits since 1995 [75]. Each hospital encounter is recorded in the DNPR with one primary diagnosis and potentially multiple secondary diagnoses, coded using the International Classification of Diseases, Eighth Revision (ICD-8) until the end of 1993 and Tenth Revision (ICD-10) thereafter [75].

The Danish National Prescription Registry (studies I-IV)

The Danish National Prescription Registry covers all prescriptions redeemed at any pharmacy in Denmark since 1995. Prescription medicines are partially reimbursed. The registry data include information on drug type, package dose, size, and strength [76].

Clinical Laboratory Information System database (studies I-IV)

Complete laboratory results from tests ordered in primary care and hospitals in Northern Denmark have been recorded since 2000 in the Clinical Laboratory Information System (LABKA) database. Data are available in LABKA for the 1985-1999 period, but are incomplete [77].

Study designs

Within the Danish healthcare databases, we conducted three population-based cross-sectional studies (II -IV). In study I, we employed a matched cohort design where patients with T2D were matched with patients from the general population serving as comparators (Table 4).

Table 4: Methods summary

	Study I	Study II	Study III	Study IV
Objectives	To investigate changes during 24 years in incidence and all-cause mortality for patients with incident T2D. To compare these trends to secular mortality trends in the general population and examine the consequences from the introduction of HbA_{1c}.	To examine 18-year changes in early HbA_{1c} and lipid testing and control among people initiating GLDs.	To examine the proportion of real-world initiators of liraglutide, ineligible for participation in the phase III randomized clinical trials of liraglutide (LEAD 1-5), and their HbA_{1c} reduction.	To examine clinical characteristics and glucose-lowering drug utilization among patients initiating liraglutide in Denmark.
Design	Incidence study & population-based cohort study, with matched general population comparators.	Population-based cross-sectional study.	Population-based cross-sectional study.	Population-based cross-sectional study.
Study region and period	Nationwide, 1995-2018.	Northern Denmark, 2000-2017.	Northern Denmark, 2009-2015.	Northern Denmark, 2009-2015.
Study population/ exposures	Part 1: population of Denmark. Part 2: Incident T2D patients defined by: prescription redemption of first ever GLD among unlikely T1D patients.	Incident T2D patients defined by: Prescription redemption of first ever GLD at age > 30 years.	Patients with first ever prescription redemption of liraglutide.	Patients with first ever prescription redemption of liraglutide.
Study outcomes	Part 1: Diabetes Incidence. Part 2: All-cause mortality.	LLD treatment initiation; LDL and HBA_{1c} target achievement; total HbA_{1c} reduction.	Proportion of patients eligible for trial participation. 6-month HbA_{1c} reduction.	Proportions receiving liraglutide outside approved indications.
Matching	Age and Sex (with replacement).	-	-	-
Co-variables	Matching stratification, multivariate adjustment.			

	Study I	Study II	Study III	Study IV
Statistics	Standardization, Cox-regression, Poisson regression modelling.	Mean difference. 95% confidence interval.	Mean difference. 95% confidence interval.	Descriptive statistics.
Confounder control	Matching, restriction, stratification, multivariate adjustment.	-	-	-
Stratification	Sex, age, comorbidity, $HbA_{1c,}$ calendar year of GLD initiation.	Calendar year of GLD initiation.	Trial eligibility.	Trial eligibility.
Sensitivity analysis	Restriction to Northern Denmark with available laboratory data. Limitation to one year follow up for all included patients. Additional adjustment for cardiovascular diseases and drugs, and diabetes complications. Cox regression. Standardization.		Calendar periods.	Calendar periods.

Abbreviations: LEAD: Liraglutide Effect and Action in Diabetes

Study populations and exposures

For all studies (I-IV), we aimed to study all, or groups of, patients with T2D in Denmark. However, most T2D patients are diagnosed by their general practitioner. General practitioners do not contribute directly to the Danish diagnosis registries, and this direct method for identifying new diabetes patients was thus not available. Furthermore, plasma glucose measurements taken and analyzed locally by general practitioners were also not available. Instead, we identified patients among the entire Danish population that had ever redeemed any prescription for any GLD, as we considered this a proxy for diabetes. We used different methods in the studies to further ascertain whether patients had T2D, type 1 diabetes, or received GLD treatment for other causes.

Study I: We conducted a population-based cross-sectional analysis in Denmark based on health care data for 1994-2018. We identified incident T2D patients by the date of their first-ever redemption of a GLD prescription and defined this as their index date (defined as the redemption date of a first prescription for any drug with an Anatomical Therapeutic Chemical classification system (ATC) code starting with A10). We excluded patients that prior to this date had not resided in Denmark for at least 1 year. To ensure truly newly treated patients, we excluded patients that redeemed their first GLD before January 1, 1995 (data were available from 1994 but not throughout the entire calendar year). Patients that redeemed a prescription for insulin before age 30 or any GLD before age 15 were excluded as likely being type 1 diabetes patients. At the time of diagnosis, we matched each patient with five controls from the general Danish population, based on age and sex, defining this as their index date. Consequently, T2D was defined as the exposure.

Study II: We conducted a population-based cross-sectional analysis in Northern Denmark (with 1.8 million inhabitants ~32% of Denmark's population) based on health care data for 1995-2017. We identified and included all people living in Northern Denmark from January 1, 2000 to December 31, 2017 who redeemed their first-ever GLD prescription (with a documented window of at least 5 years without GLD use). The initiation date of GLD treatment was the index date. To focus on people with

T2D, all patients below age 30 at the time of initial GLD treatment were excluded, as they were likely to have either type 1 diabetes or polycystic ovarian syndrome.

Studies III and IV: We conducted these cross-sectional studies in Northern Denmark based on health care data from 2009-2015. We linked existing population-based medical databases covering all prescriptions redeemed at any pharmacy in Denmark [76], laboratory data, and diagnoses for the region's 1.8 million inhabitants as described in more detail previously. The cohort included individuals who lived in Northern Denmark for 1 year before redeeming a first-time liraglutide prescription (ATC code A10BJ02) between 2009 and 2015. After the study period, liraglutide was approved for treatment of obesity, thus this use of the drug did not affect the present studies.

Statistical analyses

The applied statistical analyses are presented in Table 4 and will be summarized below.
Statistical analyses were performed using R statistics version 3.5.1. This same program was used for data management in studies I-II, while data management for studies III-IV was performed using SAS 9.4.

For study I, we computed age as well as age and sex standardized incidence rates of T2D. We used a Poisson model to calculate relative risk estimates, comparing all-cause mortality of T2D patients in later time periods to earlier periods. We similarly compared age- and sex-matched comparators from the general population to earlier periods. For both groups, we calculated absolute mortality rates using a contrast matrix assuming sex = male, age = 60 years, and Charlson score = 0. Because of a suspicion that the changing mortality trend might be driven by changes in 1-year mortality, we calculated age standardized mortality rates at five 1-year intervals after T2D treatment initiation and stratified by calendar year. To further assess the robustness of the model assumptions in the Poisson model, we calculated the relative risk estimates using a Cox-regression model. We sought to handle confounding by using matching, adjustment, and stratification.
For study II, we calculated 95% confidence intervals (95% CIs), assuming a Poisson distribution. We calculated mean HbA_{1c} reductions by year of diagnosis, and stratified this by baseline HbA_{1c}.

For studies III+IV, we assessed the proportions eligible for trial participation. We calculated mean HbA_{1c} before initiating liraglutide and 6 months after. We calculated 95% CIs, assuming a Poisson distribution. We calculated mean HbA_{1c} reductions (before – after) using patients with both before and after values. We stratified this analysis by trial eligibility, by each eligibility criteria separately, and (as a sensitivity analysis) by calendar period.

Results

Incidence and mortality trends (study I)

In our cohort, we identified 417,986 patients with incident T2D in Denmark from 1995 through 2018, along with ~2 million matched comparators. We followed T2D patients for a total of 3.3 million person-years. During the last year of the study period, 2.8% of all incident T2D patients had no HbA_{1c} test prior to GLD initiation, compared with 78% in the first year. **Figure 1** shows an increasing incidence for T2D until 2011, and a subsequent decline following the introduction of HbA_{1c} as a diagnostic option (top panel). It also shows that the increase was most pronounced among patients with an HbA_{1c} below 7%, while the number of patients with higher HbA_{1c} was more stable (bottom panel).

Figure 1: T2D Incidence trends. (next page) (Study I). ***The upper panel*** *depicts age-standardized incidence rates (SIRs) of type 2 diabetes with 95% confidence intervals by calendar year of diagnosis. Similarly, the* ***middle panel shows*** *SIRs by age categories at diagnosis. The* ***lower panel*** *shows among diabetes patients living in Northern Denmark at diagnosis, the incidence rate per 100,000 persons, and their most recent* HbA_{1c} *measurement before first glucose-lowering drug (GLD) redemption (index date).*

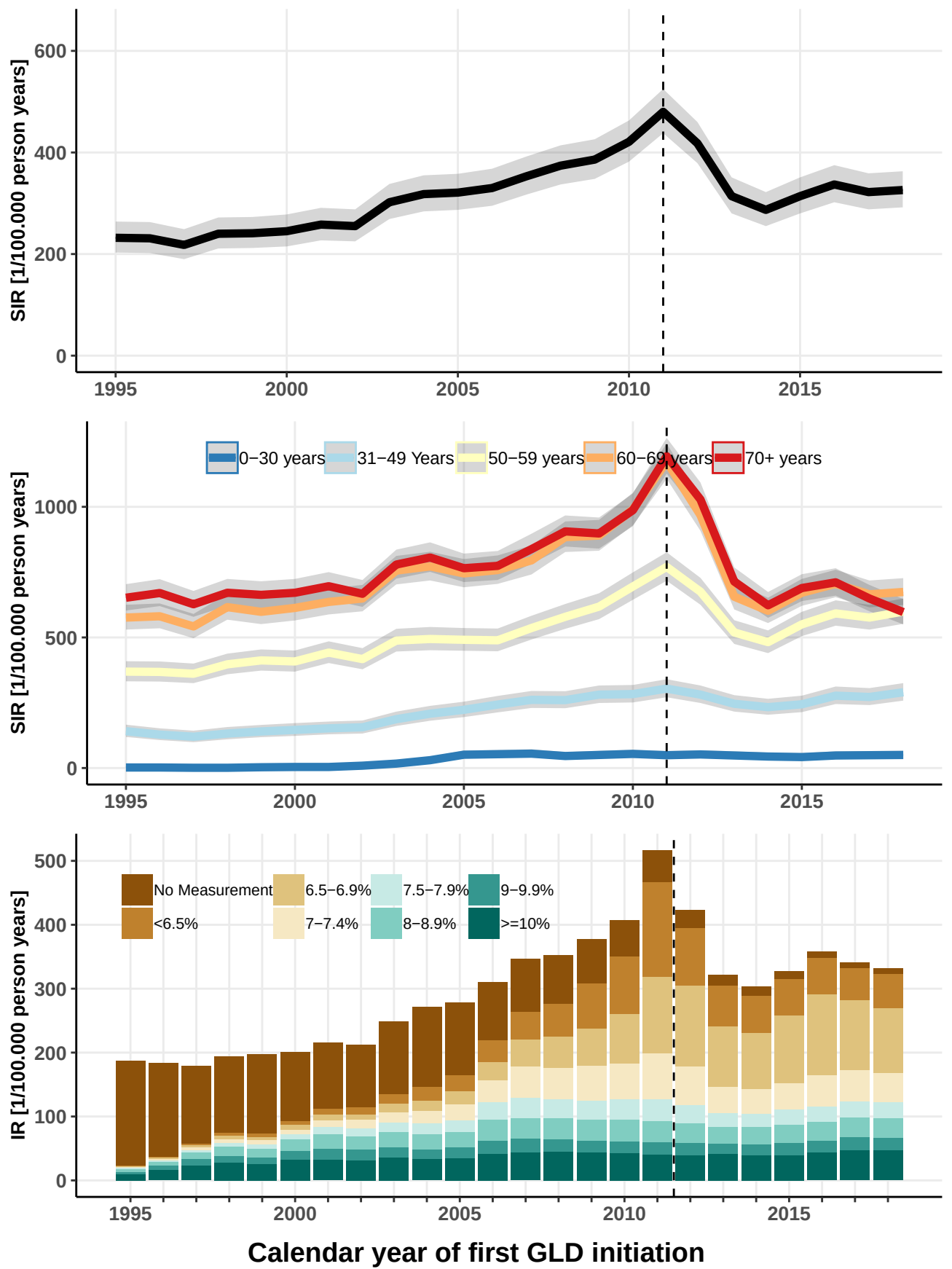
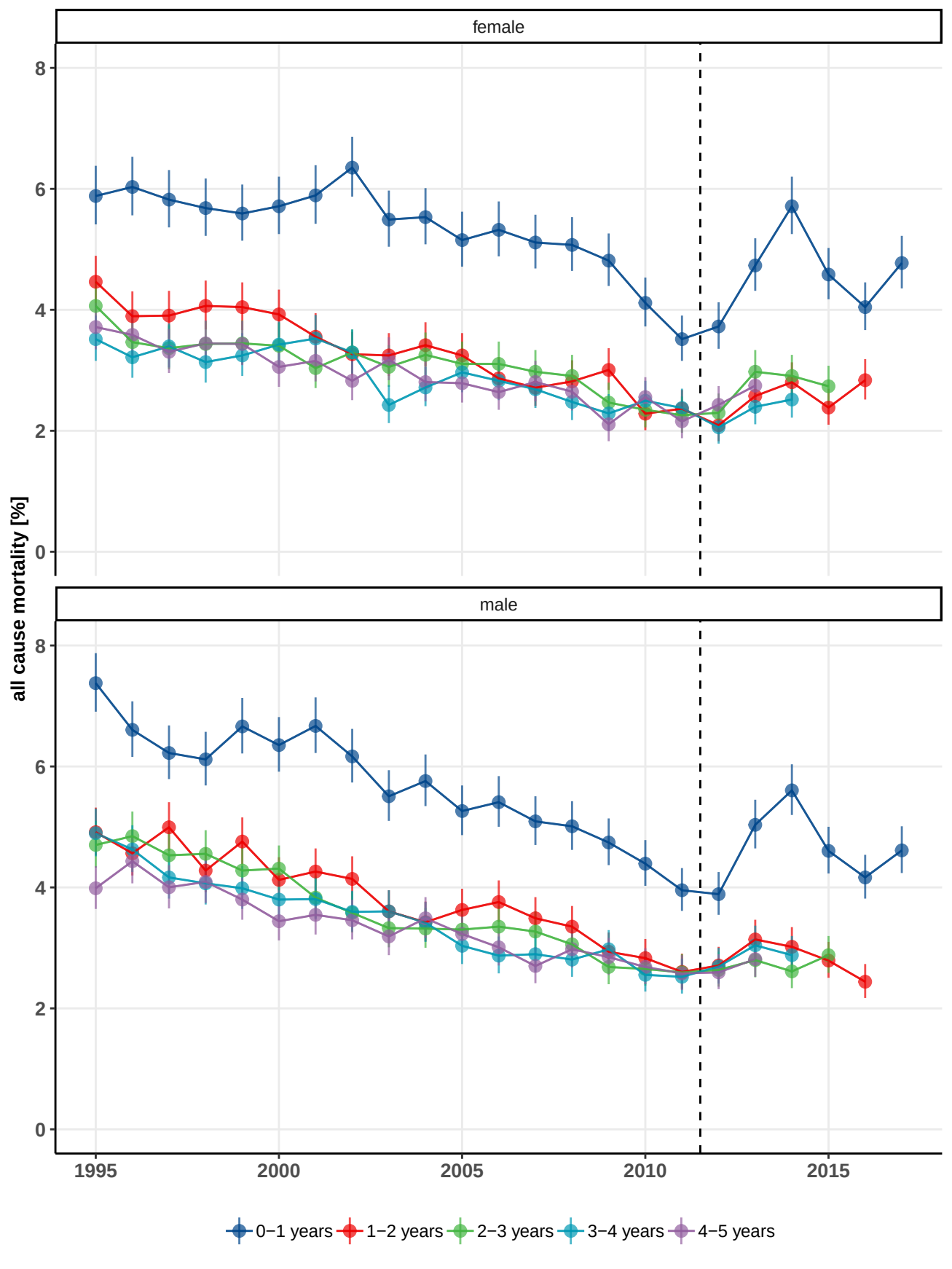

SIR [1/100.000 person years]
600
400
200
0
1995
2000
2005
2010
2015
SIR [1/100.000 person years]
0–30 years
31–49 Years
50–59 years
60–69 years
70+ years
1000
500
0
1995
2000
2005
2010
2015
IR [1/100.000 person years]
No Measurement
<6.5%
6.5–6.9%
7–7.4%
7.5–7.9%
8–8.9%
9–9.9%
>=10%
500
400
300
200
100
0
1995
2000
2005
2010
2015
Calendar year of first GLD initiation

Table 5: Mortality risk and mortality rate ratio by cohort and diagnosis period of diabetes. (Study I).

	DIABETES COHORT						COMPARATOR COHORT				
Period of diagnosis	**Persons N**	**Risk time (years)**	**Events N**	**Mortality rate (95% CI)**	**Rate ratio (95% CI) - crude**	**Rate ratio (95% CI) – adjusted***	**Persons N**	**Events N**	**Mortality rate (95% CI)**	**Rate ratio (95% CI) - crude**	**Rate ratio (95% CI) – adjusted***
1995-1997	34,641	457,345	23,576	68.48 (66.39-70.64)	1 (1-1)	1 (1-1)	173,169	94,662	39.57 (38.93-40.22)	1 (1-1)	1 (1-1)
1998-2000	37,135	466,571	22,594	60.82 (58.95-62.75)	0.94 (0.92-0.96)	0.89 (0.87-0.9)	185,635	87,805	37.19 (36.59-37.81)	0.94 (0.93-0.95)	0.94 (0.93-0.95)
2001-2003	42,612	500,281	21,325	53.21 (51.56-54.91)	0.83 (0.81-0.84)	0.78 (0.76-0.79)	213,022	81,081	34.72 (34.15-35.3)	0.84 (0.83-0.84)	0.88 (0.87-0.89)
2004-2006	52,161	554,526	19,455	47.34 (45.86-48.88)	0.68 (0.67-0.69)	0.69 (0.68-0.7)	260,749	72,490	31.93 (31.4-32.47)	0.7 (0.69-0.71)	0.81 (0.8-0.81)
2007-2009	61,817	545,278	17,049	41.74 (40.42-43.11)	0.61 (0.59-0.62)	0.61 (0.6-0.62)	309,013	62,195	29.14 (28.65-29.64)	0.62 (0.62-0.63)	0.74 (0.73-0.74)
2010-2012	74,863	501,413	14,184	35.81 (34.64-37.01)	0.55 (0.54-0.56)	0.52 (0.51-0.53)	374,222	52,250	26.71 (26.25-27.18)	0.58 (0.58-0.59)	0.67 (0.67-0.68)
2013-2015	53,966	222,848	7,000	40.99 (39.49-42.55)	0.61 (0.59-0.63)	0.6 (0.58-0.61)	269,761	20,006	24.17 (23.68-24.67)	0.5 (0.49-0.51)	0.61 (0.6-0.62)
2016-2018	59,791	87,163	2,936	44.17 (42.17-46.26)	0.65 (0.63-0.68)	0.64 (0.62-0.67)	298,889	6,784	21.92 (21.31-22.55)	0.44 (0.43-0.45)	0.55 (0.54-0.57)

Table 5 (study I) *shows the all-cause mortality for incident diabetes patients and comparators, by calendar period of diagnosis. Patients with diabetes experienced a reduction in all-cause mortality that exceed that of age- and sex-matched general population comparators. This trend, however, was reversed starting from 2013-2015, after which increasing mortality rates were observed for diabetes patients, but not for comparators. *Adjusted for age, sex, and comorbidities. The Poisson regression included all available follow-up. 95% CI: 95% confidence interval.*

Figure 2 (next page) (study I). Age-standardized all-cause mortality by calendar year in men and women with first-treated type 2 diabetes. Denmark, 1995-2018. *The figure shows the all-cause mortality by different follow-up periods following diagnosis. The majority of the increase in mortality rates occurs in the period from 0 to 1 year following diagnosis, while mortality in the follow-up periods after the first year increased less.*


female
male
all cause mortality [%]
0
2
4
6
8
1995
2000
2005
2010
2015
0−1 years
1−2 years
2−3 years
3−4 years
4−5 years

Trends in HbA1c and LDL cholesterol in patients with type 2 diabetes (study II)

Study II was conducted and submitted as a full-length paper, but published as a letter as requested by the journal's chief editor. We omitted several results from the letter due to the constraints of the letter format. Some of the data presented here in the dissertation are results that were omitted from the publication.

During the 2000-2017 period, we identified 94,175 patients who initiated GLDs while living in Northern Denmark. Patient characteristics and complications at the time of GLD initiation are shown in Table 6. Patients' median age was 63 years and most were male (56%). One-third of patients (35%) had one or more comorbidities included in the CCI (Table 6). From 2000-2006 to 2012-2017, there was an increase in the recorded baseline prevalence of macrovascular complications (from 21.0% to 24.5%), diabetic retinopathy (6.7% to 10.1%), peripheral diabetic neuropathy (1.1% to 1.5%), microalbuminuria (1.9% to 2.8%), peripheral vascular disease (4.5% to 5.1%), and cerebrovascular disease (8.7% to 9.9%). However, there was a decrease in the proportion of patients with myocardial infarction (8.1% to 7.5%) and congestive heart failure (6.8% to 4.7%). As well, eGFR improved from a median of 70 ml/min/1.73m^2 to 77 ml/min/1.73m^2. The changes in mean and median age at GLD initiation are shown in Figure 3. The two were similar until diverging after 2005.

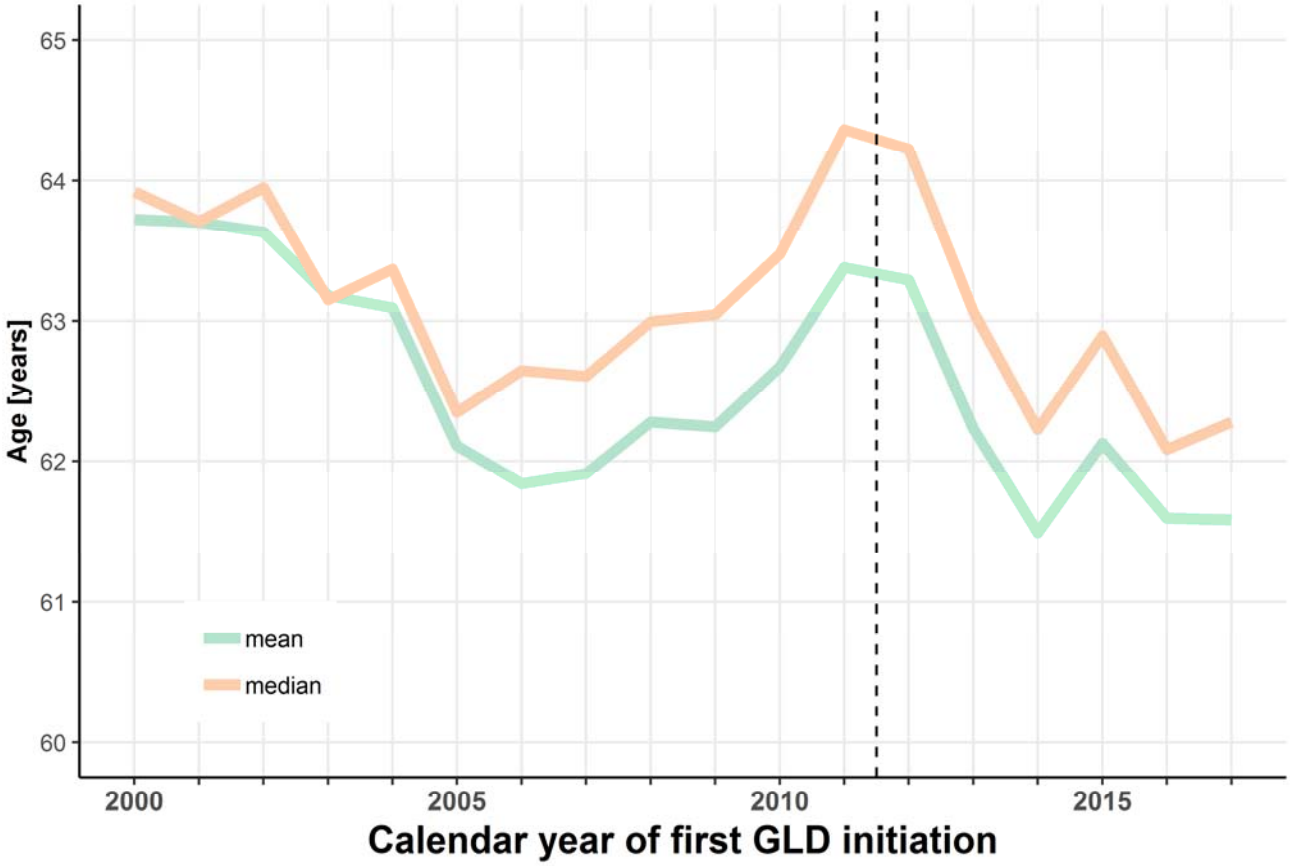
Table 6: Clinical characteristics of 94,175 first-time initiators of glucose-lowering drugs in Northern Denmark, 2000-2017. (study II)

	2000-2005		2006-2011		2012-2017		Total	
	n	%	n	%	n	%	n	%
Sex								
Female	**10,334**	45.2	**16,395**	44.5	**14,958**	43.4	**41,687**	44.3
Male	**12,514**	54.8	**20,488**	55.5	**19,486**	56.6	**52,488**	55.7
Age								
Median age (IQR)	**64.1**	(52,75)	**62.6**	(52,72)	**62.5**	(52,72)	**63.2**	(52, 73)
Pre-treatment* HbA_{1c}								
No measurement	**10,338**	45.2	**5,730**	15.5	**1,089**	3.2	**17,157**	18.2
<6.5	**1,380**	6.0	**6,759**	18.3	**5,456**	15.8	**13,595**	14.4
6.5-6.9	**1,202**	5.3	**6,367**	17.3	**11,362**	33.0	**18,931**	20.1
7-7.4	**1,543**	6.8	**5,353**	14.5	**4,830**	14.0	**11,726**	12.5
7.5-7.9	**1,385**	6.1	**3,132**	8.5	**2,513**	7.3	**7,030**	7.5
8-8.9	**2,188**	9.6	**3,331**	9.0	**3,000**	8.7	**8,519**	9.0
9-9.9	**1,548**	6.8	**1,961**	5.3	**1,868**	5.4	**5,377**	5.7
>=10	**3,264**	14.3	**4,250**	11.5	**4,326**	12.6	**11,840**	12.6
Median HbA_{1c} (IQR)	**8.3**	(7.1,10)	**7.1**	(6.5,8.4)	**7.0**	(6.6,8.2)	**7.2**	(6.6,8.6)
Macrovascular complications	**4,866**	21.3	**8,912**	24.2	**8,275**	24.0	**22,053**	23.4
Diabetic retinopathy	**1,613**	7.1	**3,334**	9.0	**3,502**	10.2	**8,449**	9.0
Diabetic peripheral neuropathy	**299**	1.3	**738**	2.0	**803**	2.3	**1,840**	2.0
Microalbuminuria (>= 2 positive tests)	**434**	1.9	**829**	2.2	**1,054**	3.1	**2,317**	2.5
eGFR † ($ml/min/1.73m^2$) median, (IQR)	**78**	(63,93)	**88**	(73,100)	**89**	(73,100)	**87**	(70,99)
Myocardial infarction	**1,849**	8.1	**2,986**	8.1	**2,452**	7.1	**7,287**	7.7
Congestive heart failure	**1,620**	7.1	**1,911**	5.2	**1,649**	4.8	**5,180**	5.5
Peripheral vascular disease	**1,077**	4.7	**1,816**	4.9	**1,673**	4.9	**4,566**	4.8
Cerebrovascular disease	**2,033**	8.9	**3,381**	9.2	**3,313**	9.6	**8,727**	9.3

Charlson Comorbidity Index (CCI) score ‡								
0	**12,289**	53.8	**21,548**	58.4	**20,526**	59.6	**54,363**	57.7
1	**5,138**	22.5	**7,507**	20.4	**6,415**	18.6	**19,060**	20.2
2	**2,772**	12.1	**4,100**	11.1	**3,942**	11.4	**10,814**	11.5
>=3	**2,649**	11.6	**3,728**	10.1	**3,561**	10.3	**9,938**	10.6

*Abbreviations: IQR: 25th and 75th percentile. *Pre-treatment: latest measurement within 12 months before initiating first glucose-lowering drug treatment. † eGFR: estimated Glomerular Filtration Rate. ‡ The Charlson Comorbidity Index (CCI) includes 19 major disease categories, ascertained from each individual's complete hospital contact history before the date of the first redeemed prescription* ***for a glucose-lowering drug. Diabetes and diabetes with end-organ damage were omitted from the CCI.***

Figure 3: mean and median age trends among first-ever glucose-lowering drug initiators (study II)



HbA_{1c}

The proportion of patients with at least one HbA_{1c} test within 12 months after GLD initiation increased from 53% (95% CI 52 to 55) in 2000 to 95% (95% CI 94 to 95) in 2016 (data available throughout 2017) (Figure 4: 1A). Concurrently, mean pre-treatment HbA_{1c} decreased from 9.2% (95% CI 9.1 to 9.3) in 2000 to 7.9% (95% CI 7.8 to 7.9) in 2017, with a nadir of 7.3% occurring in 2011. For mean post-treatment HbA_{1c}, a smaller decline was seen from 7.1% (95% CI 7.0 to 7.2) to 6.6% (95% CI 6.6 to 6.6) during 2000-2016. (Figure 4: 1B). The proportion of patients achieving post-treatment HbA_{1c} targets of <6.5% or <7% increased from 37% (95% CI 34 to 39) to 56% (95% CI 55 to 57) and from 54% (95% CI 52 to 57) to 81% (95% CI 80 to 82) during 2000-2017, respectively (Figure 4: 1C). Patients with a pre-treatment HbA_{1c} below 6.5% did not experience a post-treatment HbA_{1c} reduction, while patients in higher pre-treatment HbA_{1c} categories had increasingly large post-treatment reductions (Figure 4: 1E). The post-treatment reduction in HbA_{1c} by pre-treatment category showed little change throughout the observation period (Figure 4: 1E). The proportion of initiators with an HbA_{1c} ≥10% decreased from 34% (95% CI 34 to 36) to 15% (95% CI 14 to 16), while the proportion of patients with a pre-treatment HbA_{1c} ≥6.5%-6.9% increased from 7% (95% CI 6 to 9) to 34% (95% CI 33 to 36) during the observation period. The proportion of GLD initiators with a pre-treatment HbA_{1c} below the diagnostic threshold of 6.5% (n = 13,594) increased from 7% (95% CI 6 to 9) in 2000 to 31% (95% CI 30 to 32) in 2011 (prior to the introduction of HbA_{1c} as a diagnostic criterion), and then fell again to 12% (95% CI 11 to 13) in 2017 (Figure 4 1D).

LDL cholesterol

The proportion of patients who had at least one blood lipid test within 12 months following their first-ever GLD treatment increased from 82% (95% CI 81 to 84) in 2000 to 99% (95% CI 99 to 99) in 2016. The proportion receiving LLD therapy within 12 months quintupled from 12% (95% CI 11 to 13) to 61% (95% CI 60 to 62) from 2000 to 2016 but declined after peaking at 68% (95% CI 67 to 69) in 2011 (Figure 4: 2A). Mean pre-treatment LDL cholesterol declined from 3.5 mol/l (95% CI 3.4 to 3.6) in 2000 to 2.8 mol/l (95% CI 2.8 to 2.9) in 2017, while the mean post-treatment value declined from 3.3 mmol/l (95% CI 3.2 to 3.3) in 2000 to 2.3 mmol/l (95% CI 2.3 to 2.4) in 2016 (Figure 4: 2B). The proportion of patients achieving LDL cholesterol post-treatment targets of <1.8 mmol/l or <2.6 mmol/l increased from

5% (95% CI 3 to 6) in 2000 to 29% (95% CI 28 to 30) in 2016 and from 23% (95% CI 20 to 26) in 2000 to 65% (95% CI 63 to 66) in 2016, respectively (Figure 4: 2C).

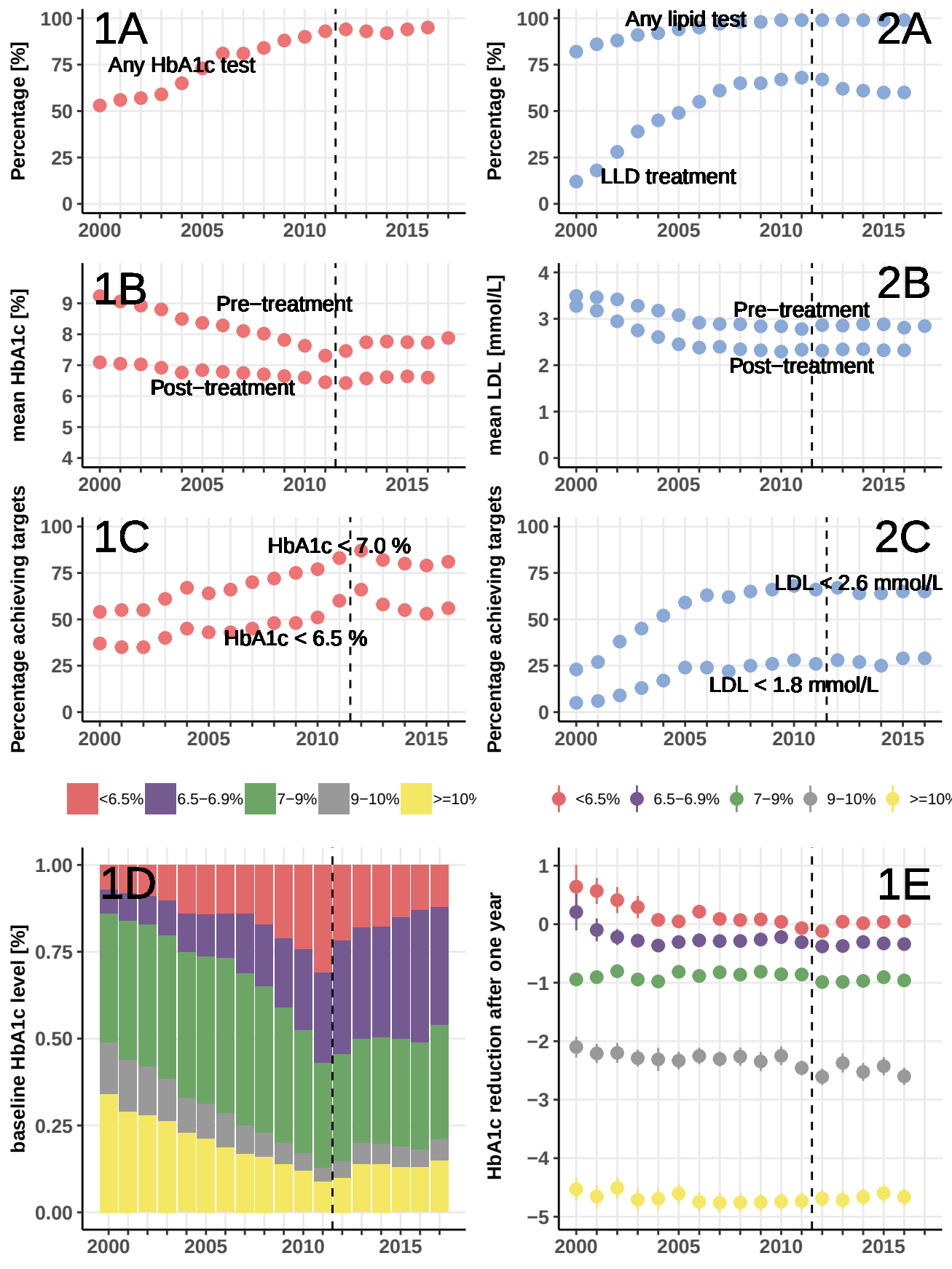

1A
Any HbA1c test
Percentage [%]
2A
Any lipid test
LLD treatment
Percentage [%]
1B
Pre−treatment
Post−treatment
mean HbA1c [%]
2B
Pre−treatment
Post−treatment
mean LDL [mmol/L]
1C
HbA1c < 7.0 %
HbA1c < 6.5 %
Percentage achieving targets
2C
LDL < 2.6 mmol/L
LDL < 1.8 mmol/L
Percentage achieving targets
<6.5%
6.5−6.9%
7−9%
9−10%
>=10%
1D
baseline HbA1c level [%]
1E
HbA1c reduction after one year
2000
2005
2010
2015

Figure 4 (opposite page). Lipid and HbA_{1c} trends among first-time initiators of glucose-lowering drugs (GLDs) in Northern Denmark, 2000-2017. (Study II)

Blue circles depict lipids and red circles depict HbA_{1c}. Confidence intervals are shown as vertical small lines; however, they are narrow and are usually hidden by the point estimates.Vertical dashed line depicts the introduction of HbA_{1c} as a diagnostic criterion in February 2012. Pre-treatment: latest measurement within 12 months before first-time GLD treatment; Post-treatment: measurement closest to 12 months following treatment initiation (within 6-18 months). ***1A:*** *Proportion of incident type 2 diabetes patients in Northern Denmark who received HbA_{1c} testing within 1 year, by calendar year of GLD initiation.* ***1B:*** *Mean pre-treatment and post-treatment HbA_{1c} by calendar year of GLD initiation.* ***1C:*** *Proportion of patients achieving HbA_{1c} treatment targets (<6.5% [48 mmol/mol], <7% [53 mmol/mol]) at 12 months following GLD initiation, by calendar year of GLD initiation.* ***1D:*** *Proportions of pre-treatment HbA_{1c} categories for first-time glucose-lowering drug (GLD) initiators by calendar year of first GLD use.* ***1E:*** *Mean pre- to post-treatment HbA_{1c} reduction following 12 months of treatment by calendar year of first GLD use and pre-treatment HbA_{1c} category among the 64,094 initiators with both a pre- and post-treatment measurement.* ***2A:*** *Proportion of incident type 2 diabetes patients in Northern Denmark who received lipid testing, and/or lipid-lowering drug (LLD) prescriptions within one year, by calendar year of GLD initiation.* ***2B:*** *Mean pre-treatment and post-treatment low-density lipoprotein (LDL) cholesterol levels, by calendar year of GLD initiation* ***2C:*** *Proportion of patients achieving LDL treatment targets (1.8 mmol/l, 2.6 mmol/l) at 12 months following GLD initiation.*

Differences between RCT patients and real-world liraglutide initiators (studies III and IV)

A total of 9,251 first-time users of liraglutide in Northern Denmark between 2009 and 2015 were identified and included in the analysis. We assessed patients as eligible or ineligible for participation in the Liraglutide Effect and Action in Diabetes (LEAD) trials based on their characteristics, comorbidities, and medication use.

Overall, 73% of all real-world liraglutide users would have been ineligible for any of the LEAD trials. We found that among the first third of patients to receive liraglutide during our study period, 76% were ineligible for trial participation. This proportion decreased slightly to 72% for patients in the second third of patients, and to 70% for patients in the last third of users.

We performed sensitivity analyses, in which we disregarded previous insulin treatment (total proportion ineligible = 62%), the requirement for previous non-insulin GLD treatment (total proportion ineligible = 72%), or both (total proportion ineligible = 59%). When we accounted for the newest findings from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) - trial [72] by ignoring the exclusion criterion of "clinically significant CVD (cardiovascular disease)" in addition to the two previous criteria, 45% of real-world users would still have been ineligible for trial participation, primarily due to the HbA_{1c} criterion (Table 8).

Table 8. Trial exclusion and HbA_{1c} reductions among patients by eligibility for participation in the LEAD 1-5 trials (study III).

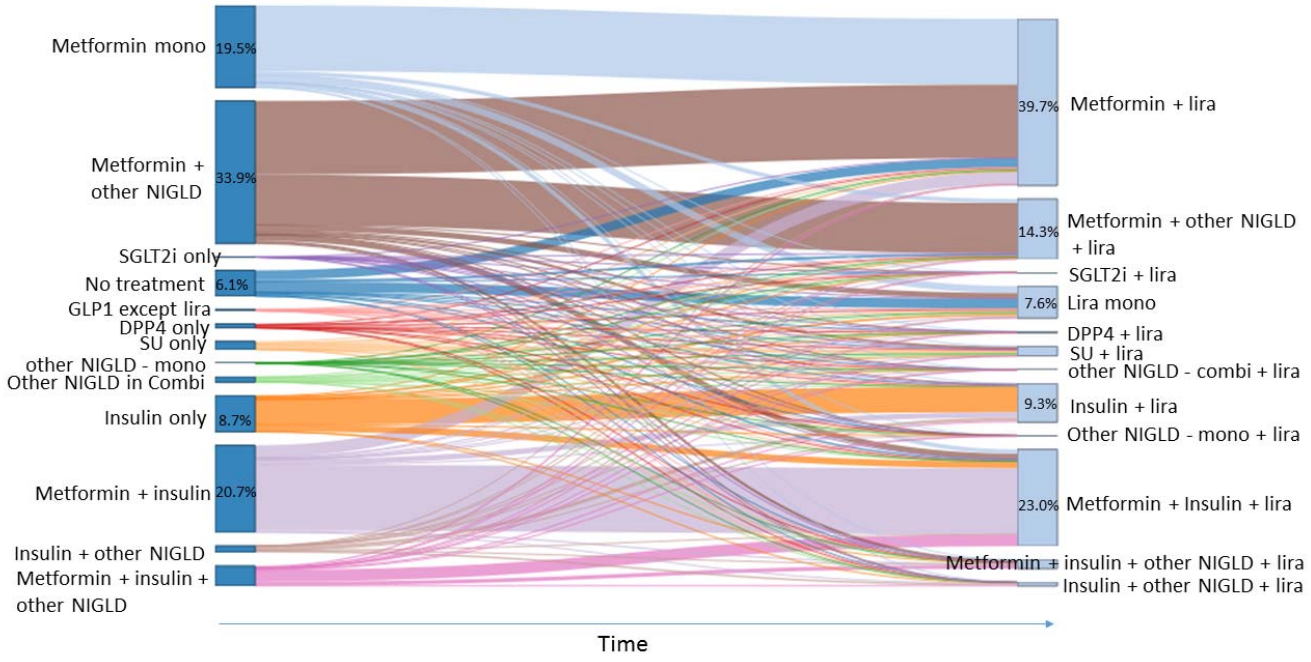
	Would have been excluded		Mean HbA_{1c} % before liraglutide initiation (95% CI)	Mean HbA_{1c} % 6 months after liraglutide initiation (95% CI)	Mean HbA_{1c} % change (95% CI)
	n	%			
Total	9,251	100	8.6 (8.6 to 8.6)	7.6 (7.6 to 7.7	-1.0 (-1.0 to -0.9)
Excluded for any one of the below	6,768	(73.2)	8.7 (8.7 to 8.7)	7.7 (7.7 to 7.7)	-1.0 (-1.0 to -0.9)
Not excluded for any of the below	2,583	(26.9)	8.4 (8.3 to 8.4)	7.5 (7.4 to 7.5)	-0.9 (-1.0 to -0.9)
Ongoing non-insulin GLD therapy for less than 3 months	1,051	(11.4)	8.8 (8.7 to 8.9)	7.7 (7.6 to 7.8	-1.1 (-1.2 to -1.0)
HbA_{1c} level	2,522	(27.3)	9.1 (9.0 to 9.2)	7.8 (7.7 to 7.9)	-1.3 (-1.4 to -1.2)
Age <18 years	8	(0.1)	8.6 (6.0 to 11.1)	6.7 (-1.0 to 14.4)	-2.5 (-16.3 to 11.3)
Age >80 years	147	(1.6)	8.5 (8.2 to 8.7)	7.6 (7.4 to 7.8)	-0.9 (-1.1 to -0.6)
Insulin treatment last 3 months	3,414	(36.9)	8.8 (8.7 to 8.8)	8.00 (7.9 to 8.0)	-0.8 (-0.8 to -0.7)
Impaired liver function	86	(0.9)	9.2 (8.8 to 9.6)	7.7 (7.3 to 8.0)	-1.7 (-2.1 to -1.2)
Hepatitis B or C positive	27	(0.3)	9.1 (8.5 to 9.7)	8.5 (7.6 to 9.3)	-0.6 (-1.3 to 0.1)
Impaired renal function	395	(4.3)	8.6 (8.5 to 8.8)	7.7 (7.6 to 7.8)	-0.9 (-1.0 to -0.7)
Clinically significant active CVD	2,646	(28.6)	8.7 (8.6 to 8.7)	7.7 (7.7 to 7.8)	-0.9 (-1.0 to -0.9)
Cancer	326	(3.5)	8.5 (8.4 to 8.7)	7.6 (7.5 to 7.8)	-0.9 (-1.1 to -0.8)
Clinically significant disease	1,029	(11.2)	8.6 (8.4 to 8.6)	7.6 (7.5 to 7.7	-1.0 (-1.1 to -1.0)

	Would have been excluded		Mean HbA_{1c} % before liraglutide initiation (95% CI)	Mean HbA_{1c} % 6 months after liraglutide initiation (95% CI)	Mean HbA_{1c} % change (95% CI)
Recurrent hypoglycemia	46	(0.5)	8.5 (8.0 to 9.0)	8.1 (7.7 to 8.5)	-0.5 (-0.9 to 0.0)
Use of drugs that interferes with glucose	439	(4.8)	8.6 (8.4 to 8.7)	7.5 (7.4 to 7.6)	-1.0 (-1.2 to -0.9)
Alcohol or substance abuse	389	(4.2)	8.9 (8.6 to 9.1)	7.8 (7.6 to 7.9)	-1.1 (-1.3 to -0.9)
Mental incapacity	246	(2.6)	8.9 (8.6 to 9.1)	7.8 (7.5 to 8.0)	-1.1 (-1.4 to -0.9)
Current/ intention of breastfeeding or pregnant	25	(0.3)	7.8 (7.1 to 8.5)	7.1 (6.5 to 7.7)	-0.9 (-1.5 to 0.2)

Among 9,251 real-world initiators of liraglutide in Northern Denmark. Exclusion criteria: As present in all LEAD 1-5 studies. Abbreviations: GLD, Glucose Lowering Drugs; CVD, Cardiovascular Disease; CI, Confidence Intervals.

Less than half of liraglutide initiators initiated treatment in combinations that were in accordance with the originally approved indications (Figure 5), with little change throughout the period 2009-2015.

Figure 5 (study IV): Glucose-lowering drugs used 100 days before (left-hand side) and 100 days after (right-hand side) first-time redemption of a liraglutide prescription.



Liraglutide initiators most often transitioned from therapy with metformin plus another non-insulin glucose-lowering drug (NIGLD; 33.9%), metformin monotherapy (19.5%), metformin plus insulin (20.7%), insulin monotherapy (8.7%), or no glucose-lowering drug (6.1%). Percentages show the proportion of all patients within different drug groups before (left-hand side) and after (right-hand side) first-time redemption of a liraglutide prescription. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; SGLT2i: sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea drugs.

Discussion

In study I, we found a change from increasing to declining incidence trends, a change coinciding with the 2012 introduction of HbA_{1c} as a diagnostic option. We saw opposite trends for mortality following T2D diagnosis: a decrease until 2011, followed by increasing mortality. In study II, we found that monitoring and treatment of blood glucose and cholesterol levels had improved considerably from 2000 to 2017, but with heterogeneity from 2012 and with room for further improvements. In studies III and IV, we found that three in four real-world liraglutide initiators exhibited clinical characteristics that would have led to ineligibility for the trials that led to approval of liraglutide for T2D patients. We presented and applied a new method for evaluating whether the efficacy seen in clinical trials translated into real-world clinical effectiveness.

Strengths and limitations

Study I

We conducted a population-based cohort study in a setting with uniform access to health care, complete registration of hospital admissions, and complete follow-up until death or emigration, all of which minimize selection biases due to selective inclusion or prognostically non-random loss to follow-up. However, several limitations should be considered regarding the interpretation of our findings. Unlike guidelines from the mid-1990s, contemporary guidelines recommend initiation of GLDs 3 months following confirmed diagnosis if glucose targets are not achieved through lifestyle interventions [7]. This may, in combination with increased opportunistic screening for T2D, transiently inflate the observed increases in diabetes incidence and have introduced a lead time bias on mortality in our study: if patients are diagnosed earlier in their disease trajectory, their mortality will appear to decline. However, similar findings were observed by numerous studies using different methods to define T2D and covering parts of our observation period, thus corroborating our findings on T2D incidence and prognosis. Furthermore, earlier initiation of GLDs is an improvement in T2D treatment, and the change in prognosis from time of treatment initiation is not biased because of this, but is a result of this change.

Study II

In study II (as well as the other studies), we studied only patients receiving GLD at a pharmacy. However, a proportion (<10%) of T2D patients never initiates the prescribed pharmacological treatment after the

first prescription issued from their physician (primary non-compliance) [78]. Moreover, some patients are not prescribed treatment by their physicians despite having a clear medical indication for treatment [78]. This can be a result of clinical inertia by the physician, or caused by patients' reluctance to visit the physician, accept treatment, or buy the medication [79]. Thus, patients never adequately examined for T2D or patients unwilling to accept the physicians' recommendations are by design not included in the present study. With generally increasing attention to diabetes, a higher proportion of the general population with no previously known diabetes may have been offered a screening fasting glucose or HbA_{1c} test by a general practitioner in 2017 than 2000, possibly introducing a length time bias by diagnosing more diabetes cases in the population with a milder progression trajectory, or lead time bias by diagnosing the same patients with diabetes earlier in their disease course. Our data do not allow us to examine the changes in the time from diabetes diagnosis to treatment initiation, since the true diabetes diagnosis date (typically by a general practitioner) is not known to us.

The LABKA database of blood tests is virtually complete in the study period for patients tested in Northern Denmark [77], but a small proportion of patients may have had tests outside the region while maintaining an address within the region. Since the majority of patients (97%) had an HbA_{1c} test performed within 1 year of diagnosis during 2016-17, this is unlikely to significantly affect results, and can furthermore reasonably be presumed to have been constant throughout the period.

HbA_{1c} was first introduced as a diagnostic criterion for T2D in 2012 [8], and did not see widespread usage at the beginning of the observation period. At the beginning of the observation period, HbA_{1c} tests were more likely to be ordered by specialists, while general practitioners increasingly started to order HbA_{1c} measures during later years. Being treated by a specialist may be related to a higher pre-treatment HbA_{1c} and could bias the estimate toward a more pronounced decline in pre-treatment HbA_{1c} during the observation period. However, in the Danish health care system, the general practitioners serve a gate-keeper function for secondary or tertiary care and examine all patients before referral, unless very acutely admitted. We believe that only a small proportion of patients would have been referred to secondary diabetes care without first initiating any pharmacological GLD treatment, limiting the confounding impact on pre-treatment HbA_{1c}. Furthermore, before HbA_{1c} measurement became widely available and usual, blood glucose was often monitored by patient self-testing, and presumably some patients still

exclusively monitor blood glucose using this method. Thus, the proportion of patients being adequately monitored may be underestimated when only available laboratory data are considered. Since post-treatment HbA_{1c} was estimated using measurements taken 6-18 months after treatment initiation, patients who did not survive to receive the post-treatment measurement could not contribute with information, thus potentially introducing bias. However, since this proportion was small (<5%), it is unlikely to have markedly influenced the results.

Due to higher costs, LDL cholesterol testing was also used more selectively at the beginning of the study period, potentially introducing bias with regard to the mean pre- and post-treatment LDL cholesterol trends by calendar year. If patients tested at the beginning of the observation period on average had a higher mean LDL cholesterol, this would bias the time trend toward a stronger decline over time in pre-treatment LDL cholesterol. However, the magnitude of the decline in LDL cholesterol seen in the general population during recent decades is of a similar magnitude, thus substantiating our findings [80].

During the observation period, the economic compensation for hospitals increasingly depended on the coding practice at the hospitals, creating an incentive for more zealous registration, but also favoring some registrations over others [81]. We found that most characteristics and comorbidities sensitive to increasing coding rates (i.e. condition present or not present) tended to increase, while characteristics based on the values of measurements (eGFR, HbA_{1c}, and LDL cholesterol) declined or improved (e.g.: while median eGFR improved, more patients were found to have microalbuminuria). While some events may be more sensitive to changes in coding practice, some of the events (e.g., myocardial infarction, cerebrovascular disease, and peripheral vascular disease) are known to be reliably coded, with positive predictive values exceeding 90% [75,82]. One possible explanation why an increasing number of patients already had diabetes-related complications at the time of treatment initiation could be that patients may initiate diabetes treatment with exercise and diet alone. If these patients are increasingly examined for the presence of complications, this may explain why many patients already have diabetes-related complications at the time of pharmacological treatment initiation.

Study III and Study IV

The use of the nationwide Danish prescription registry [76,83] ensures complete information of all redeemed prescriptions from the centralized database, including liraglutide. Due to limitations of administrative data, some LEAD 1-5 trial criteria were not available for evaluation, e.g., uncontrolled blood pressure and BMI. Considering that these conditions are both frequent and associated with T2D, we likely underestimated the proportion of patients that would have been ineligible for inclusion in the LEAD 1-5 trials. Although comorbidities may have been misclassified to some extent, the Danish National Patient Registry has documented high positive predictive values for major diseases [75]. For some conditions (i.e., hospital-coded obesity), the completeness of the registries is unknown, but presumed to be low. For comorbidities included in trial exclusion criteria, low sensitivity would have led to further underestimation of the proportion of real-world liraglutide initiators who would have been ineligible for the LEAD 1-5 trials.

Interpretation

Study I

We believe our findings on T2D incidence trends provide evidence suggesting a causal relation between the introduction of HbA_{1c} as a diagnostic option and the subsequent decline in T2D incidence, especially among the elderly. While HbA_{1c} is one among several diagnostic options (including 2-hour oral glucose-tolerance testing and fasting plasma-glucose), it remains the most convenient method for patients and physicians, requiring less time, planning, and discomfort, while at the same time being promoted through economic encouragements in Denmark [84]. Indeed, its convenience was the main reason for the investigation of HbA_{1c} as a diagnostic option [85]. All three diagnostic options for T2D and their thresholds were validated by their ability to predict diabetic retinopathy rather than mortality [85]. It appears plausible that patients diagnosed using different methods may have different prognoses, as a patient may fulfill the diagnostic requirements for one method, but not the others, thus representing different disease phenotypes or stages. We believe our findings imply that a significant proportion of incident diabetes patients with blood glucose in the diabetic range but normal (or pre-diabetic) HbA_{1c} levels remains undiagnosed and untreated. In effect, this entails that the reported declines in T2D incidence may be an artefact resulting from a new diagnostic practice. If that is the case, we would expect a subsequent transient increase in T2D incidence if these untreated diabetes patients experience

further increases in blood glucose and are diagnosed at a later date. Although we did see a return of an increasing T2D incidence trend in the most recent years, more data are needed in order to assess whether this is transient. Another possible interpretation of our findings is that the increasing incidence during the 2000s is caused by earlier diabetes detection resulting in lead time bias, thereby impacting both incidence and mortality trends temporarily.

Study II

The increasing proportion of new T2D patients receiving HbA_{1c} and lipid testing shows that physicians in Denmark have intensified monitoring of HbA_{1c} and LDL cholesterol since the turn of the millennium. The ADDITION-EUROPE trial, including patients from the Netherlands, the UK, and Denmark, found that opportunistic diabetes screening is feasible in general practice, and identifies a population at high cardiovascular risk, despite only mild HbA_{1c} elevation [86]. The study, published in 2011, found that intensive multifactorial treatment improves CVD (cardiovascular disease) risk factors (HbA_{1c} and LDL) and a reduction of CVD risk (first CVD event hazard ratio 0.83, 95% CI 0.65 to 1.05) [87]. These findings helped strengthen the idea that early T2D detection and intensive CVD risk factor management are important and feasible. During the period from 2000-2011, we found the pre-treatment HbA_{1c} declined more than post-treatment HbA_{1c}. This indicates that testing for T2D may have become more common and that clinicians increasingly use a lower threshold for treatment initiation. However, this may not represent patients being diagnosed at an earlier disease stage, but rather a group of patients who previously remained undiagnosed, being diagnosed with less severe T2D (and a lower HbA_{1c}). This is supported by our finding of the reductions in the proportions of initiators with a pre-treatment HbA_{1c} >9% (75 mmol/mol) and a corresponding increase in the proportion of patients with an HbA_{1c} <7% (53 mmol/mol) or even <6.5% (48 mmol/mol). The lower pre-treatment values could appear to have driven the large increase in the proportion of patients achieving HbA_{1c} targets since: 1) achieving a treatment target is more likely when already close to the target, and 2) post-treatment reductions in HbA_{1c} stratified by pre-treatment HbA_{1c} were somewhat stable over time, The decline in the proportion of patients achieving treatment targets since 2012 coincides with the introduction of HbA_{1c} as a diagnostic tool in February that year [8]. From 2011 to 2017, the proportion of patients initiating treatment with an HbA_{1c} below the diagnostic threshold (but likely still having T2D if tested using OGTT or fasting plasma-glucose) decreased dramatically. Oral glucose-tolerance testing or fasting plasma-glucose remains viable

diagnostic approaches, but the relative convenience of HbA_{1c} has made this the de-facto diagnostic test in Denmark. Preventing the (estimated) one-third of dysglycemic patients with an HbA_{1c} below the diagnostic threshold from initiating GLD treatment could in fact explain the 32% decrease in the incidence of T2D from 2012-2016 we reported in paper I, and which starkly contrasts with the 102% increase from 1995-2011 prior to the introduction of HbA_{1c} as a diagnostic tool [88].

The proportion of patients receiving lipid lowering drugs (LLD) within 1 year of first GLD quintupled during the observation period, while the pre-treatment LDL declined; thus, physicians initiated treatment more often despite the generally lower LDL cholesterol levels. This resulted in a 3- to 5-fold increase in the proportion of patients achieving current guideline targets for LDL cholesterol.

To our knowledge, our study is the first population-based study (defined as involving all cases in a geographically defined area) to examine time trends in HbA_{1c} and LDL cholesterol testing, results, and target achievements. A US study that included 4,926 adults with self-reported diabetes (and thus prevalent diabetes) in a national survey found that from 1999-2010 the proportion of patients achieving HbA_{1c} <7.0% (53 mmol/mol) increased from 44% to 53%, both noticeably lower proportions than our findings of 54% to 83% over the same time period. However, this can be attributed to the fact that the study involved patients with prevalent diabetes and thus included patients with a much longer duration than in the present study. In the US study, the proportion of patients achieving LDL cholesterol <2.6mmol/l increased from 35.3% to 56.2%, similar to our findings [89]. Comparable to our findings, Gu et al. found that among 4,860 patients in the United States with self-reported diabetes, the proportion reporting treatment with LLDs increased from 26% to 50% from 1999 to 2014, although the increase was smaller and from a higher starting level than in our study [90]. A Japanese study among 9,956 patients with prevalent T2D in 2013 estimated that 53% had achieved an HbA_{1c} <7% (53 mmol/mol) and 66% had achieved an LDL <3.1 mmol/mol [91], both markedly lower than our findings in 2013. While these previous studies all reported improvements in the proportion that achieved HbA_{1c} targets over time, our current study indicates that these improvements may be driven mainly by a change toward lower disease severity at the time of treatment initiation, rather than primarily being a result of more efficient treatment of blood glucose. This trend was, however, to some extent offset by the introduction of HbA_{1c} as a

diagnostic criterion, which appears to have excluded some dysglycemic patients from being diagnosed with T2D and initiate GLD treatment.

Study III and Study IV

To the best of our knowledge, studies III and IV are the first to analyze in detail the differences between the populations included in the LEAD 1-5 trials and real-world patients initiating liraglutide in a population-based routine clinical care setting. For patients eligible for trial participation, we found a mean reduction in HbA_{1c} of -0.9% (95% CI -1.0 to -0.9) after 6 months. The LEAD 1-5 trials found similar HbA_{1c} reductions 6 months after initiation (except LEAD 3 that followed patients for 12 months): -1.1% (LEAD 1), -1.0% (LEAD 2), -0.8% (LEAD 3), -1.5% (LEAD 4), and -1.3% (LEAD 5). All patients in the LEAD 1-5 trials had very similar baseline HbA_{1c} (means from 8.3% to 8.5%) comparable to real-world patients assessed eligible for trial participation in the present study (8.4% [95% CI 8.3 to 8.4).

Patients enrolled in RCTs likely exhibit healthier behavior, including higher medication adherence, and are encouraged to tolerate more side effects, compared with non-participants. Carls et al. found a 0.8% larger absolute reduction in HbA_{1c} with another new GLD, GLP-1 RA, among RCT participants (decrease of 1.3%) compared with real-world users (decrease of 0.5%). The authors concluded that poor adherence is the primary reason for reduced real-world effectiveness of GLP-1 RA. While adherence is not directly addressed in our study; some exclusion criteria for the RCTs directly address a patient's ability to adhere to the trial regimen (e.g., uncontrolled hypoglycemia, drug and alcohol abuse, and mental incapacity) to ensure selection of a study population with as high adherence as possible. This allows an effect to be detected in an intention-to-treat analysis [92]. The pronounced observed comorbidity in our study population, compared to the trial participants, could imply a possible lower effectiveness of liraglutide, more side effects, or unknown adverse effects in the real-world users compared with trial participants. It may even be associated in itself with risk of poorer adherence. However, we did not find a smaller reduction in HbA_{1c} among our real-world users (neither among the eligible nor the ineligible for trial participation).

A substantial proportion of our real-world users would have been excluded from LEAD 1-5 due to clinically significant CVD. After concerns had been raised about the cardiovascular safety of some GLDs

[72,93], regulatory authorities mandated cardiovascular safety assessments of new diabetes treatments [94]. This led to the LEADER trial [72], which reported non-inferiority for liraglutide vs. placebo for death from CVD, non-fatal myocardial infarction, and non-fatal stroke, while liraglutide reduced the occurrence of the three-point major adverse CVD event endpoints, CVD death, and all-cause mortality. The LEADER trial was published in 2016, i.e., after the study period of our analysis and included patients with pre-existing CVD or at high risk of CVD. Consequently, based on prevailing CVD criteria, most participants in LEADER (~80%) would have been ineligible for inclusion in the previous LEAD 1-5 trials [72,95–99]. However, even when we disregarded both pre-existing CVD and presence/type of previous GLD use (including insulin) as exclusion criteria in the analysis, almost half of the real-world liraglutide users (45%) remained ineligible for trial inclusion.

Generalizability and implications

Studies I and II

The observed trends in incidence and mortality of T2D are likely generalizable to other high-income countries that have seen similar changes in diet and lifestyle and also have implemented international diabetes guidelines throughout recent decades.

We found that from 2000 to 2017, patient characteristics, pre-treatment HbA_{1c}, and post-treatment LDL cholesterol changed substantially. The increase in the proportion of patients achieving HbA_{1c} targets from 2000-2011 was seen concurrently with a change in patient baseline characteristics toward less severe T2D cases, rather than treatment-related larger absolute reductions in HbA_{1c} levels. As cardiovascular risk in T2D patients is further reduced by an increase in treatment with LLDs, this indicates that patients with newly treated T2D in 2017 overall have different risk profiles than patients initiating treatment in 2000, both before and after treatment initiation. We also found that despite dramatic increases in treatment with LLDs, four in ten newly GLD treated T2D patient remain untreated with LLDs.

Our findings suggest that the introduction of HbA_{1c} as a diagnostic criterion precludes some patients with dysglycemia but normal (or pre-diabetic) HbA_{1c} levels from initiating relevant GLD treatment, and that this group may constitute around one in three dysglycemic patients with diabetes. We believe the

mechanisms giving rise to our findings are international in nature and are likely generalizable to other industrialized societies.

Studies III and IV

Our findings suggest that the efficacy of liraglutide on HbA_{1c} levels seen in RCTs translates into real-world effectiveness both for patients who would have been eligible as well as ineligible for the LEAD 1-5 trials. However, patient characteristics used as exclusion criteria in the LEAD 1-5 trials were common among real-world users of liraglutide. Thus, our findings underscore the importance of post-marketing observational studies. While subsequent RCTs and the present study have established the efficacy of liraglutide in patients ineligible for the LEAD 1-5 trials, safety data are urgently needed for patients with common comorbidities.

Conclusions and perspectives

We found that from 2000 to 2017, the "typical" incident T2D patient's characteristics, baseline HbA_{1c}, and target achievement of HbA_{1c} and LDL cholesterol changed substantially, reflecting substantial changes in clinical practice. There is, however, still room for improvement, especially of the proportion of patients initiating lipid-lowering therapy. We found evidence suggesting that the change in diagnostic criteria in 2011 led to a substantial number of dysglycemic patients (those fulfilling the FPG and/or the OGTT diagnostic criteria but not the HbA_{1c} criterion) no longer being diagnosed and treated for diabetes.

Our findings suggest a causal association between the introduction of HbA_{1c} as a diagnostic option for T2D and the subsequent decline in incidence and concomitant worsening of prognosis. However, despite significant changes in patient characteristics and prognosis over time and despite the differences observed between real-world initiators of GLDs and RCT participants, at least in the case of liraglutide, we found that the efficacy observed in clinical trials that enrolled patients prior to the introduction of the HbA_{1c} criterion translates into real-world effectiveness afterwards. However, whether this is also the case with other GLDs used in the treatment of type 2 diabetes remains to be examined.

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Summary

Abstract (Dansk)

Type 2 diabetes (T2D) har i de seneste årtier set væsentlige ændringer i sygdommens klassifikation, diagnostiske kriterier og tærsklen for iværksættelse af anti-diabetisk behandling. Disse ændringer kan potentielt have påvirket både forekomst af diabetes, prognosen samt profilen på / karakteristika af den "typiske" diabetes patient som opstarter anti-diabetisk behandling.

De overordnede formål med denne afhandling var: 1) undersøge udviklingen over tid i behandlingen af blodsukker og kolesterol i blodet hos patienter med T2D, samt at undersøge udviklingen i forekomst og prognose af T2D. 2) at undersøge forskellen mellem patienter i den kliniske hverdag og de patienter som deltog i de store lodtrækningsforsøg der dannede grundlag for godkendelse af nyere anti-diabetisk behandling. 3) at demonstrere og anvende en ny metode til at undersøge om denne forskel påvirker de konklusioner der kan overføres fra lodtrækningsforsøgenes patienter til patienter i den kliniske hverdag

Vi anvendte nationale befolkningsdækkende registre (1995-2018) med data over hospitalskontakter, indløste recepter, dødelighed og laboratorie-prøver til at udføre studierne.

I studie I fandt vi at forekomsten af T2D var støt stigende fra 1995 til 2011, for brat at falde fra 2012 til 2018. Den overordnede dødelighed blandt ny-behandlede T2D patienter faldt fra 1995 til 2011 men steg efterfølgende frem til 2017. Disse ændringer i 2012 var tidsmæssigt sammenfaldende med indførelsen af måling af HbA_{1c} (langtidsblodsukker) som en diagnostisk mulighed. I studie II fandt vi at monitorering og behandling af blodsukker og kolesterol har forbedret sig markant fra 2000 til 2017, om end der fortsat er plads til yderligere forbedring. I studierne III og IV fandt vi at tre fjerdedele af patienter behandlet med liraglutid i den kliniske hverdag ville være blevet ekskluderet fra deltagelse i de lodtrækningsforsøg der førte til godkendelse af diabetesbehandling med liraglutid. Vi præsenterer og anvender i afhandlingen en ny metode til at evaluere hvorvidt den effekt man har fundet i kliniske lodtrækningsforsøg af anti-diabetisk medicin kan genfindes iblandt patienter behandlet i den kliniske hverdag. Vi fandt at patienter fra den kliniske hverdag som kunne have deltaget i de kliniske lodtrækningsforsøg for liraglutid havde reduktioner af HbA_{1c} i samme størrelsesorden som både de patienter som ikke kunne have deltaget, og som de patienter som deltog i lodtrækningsforsøgene.

Abstract (English)

Recent decades have seen significant changes in type 2 diabetes disease classification, diagnostic criteria, and the threshold for treatment initiation. These changes could potentially affect both basic diabetes epidemiology trends and the prognosis and profile of the typical type 2 diabetes patient initiating treatment. Furthermore, changes in profiles of the typical patients diagnosed with type 2 diabetes may affect the generalizability of key trials with regard to contemporary diabetes populations.

The overall aims of this dissertation were to 1) examine time trends in HbA_{1c} and lipid management, and prognosis in early T2D in Denmark and 2) examine how differences in patient characteristics between participants in key randomized controlled trials influence the generalizability of trial efficacy into treatment effectiveness among real-world users of newer glucose-lowering drugs.

We used Danish administrative population-based register-data (1995-2018) on hospital contacts, prescription redemptions, mortality, and laboratory results to perform the studies.

In study I, we found a change from increasing to declining incidence of T2D, a change temporally coinciding with the 2012 introduction of HbA_{1c} measurement as a diagnostic option. We saw opposite trends for mortality following diagnosis: a decrease until 2011, followed by increasing mortality. In study II, we found that monitoring and treatment of blood glucose and cholesterol had improved considerably from 2000 to 2017, but with heterogeneity from 2012 and with room for further improvements. In studies III and IV, we found that three in four real-world liraglutide initiators exhibited clinical characteristics that would have led to ineligibility for the trials that led to approval of liraglutide for diabetes patients. We presented and applied a new method for evaluating whether the efficacy seen in clinical trials translated into real-world clinical effectiveness. Overall, trial in-eligible patients experienced similar reductions in HbA_{1c} compared to both real-world patients eligible for the trials and patients originally participating in the trials.

Appendices

Paper I

Paper II

Paper III

Paper IV

Paper I

Trends over 24 year in type 2 diabetes incidence and mortality: A Danish population-based study

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ABSTRACT

Background: In 2011 the World Health Organization recommended glycated haemogolobin (HbA_{1c}) as a measure for diagnosing type 2 diabetes (T2D). This may have changed basic T2D epidemiology. We examined temporal changes in T2D incidence and mortality during 1995-2018.

Methods: In this population-based cohort study, we included 417,986 individuals with a first-ever redemption of a glucose-lowering drug for T2D. We calculated annual age-standardized incidence rates of T2D. We then used Poisson regression to investigate changes over 3-year calendar periods (1995-1997 to 2016-18.) in all-cause mortality among the T2D patients and a matched comparison cohort from the general population.

Results: From 1995 up to the 2012 introduction of HbA_{1c} as a diagnostic option in Denmark, the annual standardized incidence rate (SIR) of T2D doubled, from 252 to 509 per 100,000 persons. From 2012 onwards T2D incidence declined by 32%, reaching 344 per 100,000 persons in 2018. Declining incidence was predominantly observed in people aged 60+ years. The decline was driven by fewer T2D patients starting treatment with an HbA_{1c} measurement <6.5% or without prior HbA_{1c} testing. Mortality following a T2D diagnosis decreased by 48% between 1995-1997 and 2010-2012, from 68 deaths per 1000 person-years (95% confidence interval (CI): 65-70) to 36 deaths per 1000 person-years (95% CI: 36-38) (adjusted mortality rate ratio: 0.52 (95% CI: 0.51-0.53). After the nadir in 2010-2012, mortality increased again by 23% to 44 per 1,000 person-years (95% CI: 42-46) during 2016-2018, driven by an increase in T2D mortality during the first year following diagnosis.

Conclusions: Our findings suggest an association between introduction of HbA_{1c} as a diagnostic option and the subsequent reduction in T2D incidence and increase in mortality.

INTRODUCTION

Estimated global type 2 diabetes (T2D) prevalence has increased from 108 million adults in 1980 to 422 million in 2014[1]. Prevalence is predicted to nearly double by 2030[2], but any projections are sensitive to developing trends in incidence of T2D and changes in subsequent prognosis.

Diagnosis of T2D has relied traditionally on either fasting blood glucose measurements or 2-hour oral glucose tolerance testing[3,4]. More convenient diagnostic options have been pursued for decades, and in 2011 the World Health Organization concluded that HbA_{1c} could be used for T2D diagnosis, as an alternative to the two established diagnostic methods[3]. However, there is limited overlap among T2D patients identified using the three different diagnostic tools, as only 7% may be diagnosed using all three methods[5]. As well, HbA_{1c} may have become the most commonly used diagnostic tool after 2012[6]. The impact of the recent introduction of HbA_{1c} on both diabetes incidence and mortality is poorly understood[4].

Three recent studies of T2D incidence trends in affluent countries included less than three years of data following introduction of HbA_{1c} as a diagnostic option[7–9], hampering evaluation of recent changes in incidence. A US and a Danish study suggested declining T2D incidence rates after introduction of HbA_{1c}, but lacked laboratory data to further explore the role of HbA_{1c} testing in diagnosed individuals[10,11]. Recent landmark studies showed that all-cause mortality among adults with T2D in the US and Sweden continuously declined and approached general population mortality until the late 2000s, but that excess mortality from diabetes again may be on the rise [12,13].

We aimed to investigate temporal changes over 24 years in incidence and all-cause mortality among patients first treated for T2D during 1995-2018. We compared these trends to secular mortality trends in the general population and examined the consequences of introducing HbA_{1c} as a diagnostic option in 2012.

METHODS

Study design, setting, and participants

We conducted a population-based longitudinal study covering the entire population of Denmark (5.8 million inhabitants) based on national healthcare data for 1990-2018. All analyses involving laboratory tests were limited to the population residing in Northern Denmark (1.8 million inhabitants), where these data were available. The Danish National Health Service provides universal tax-supported healthcare, guaranteeing unfettered access to general practitioners, hospitals, and partial reimbursement for prescribed drugs. The unique personal registry number assigned to all Danish residents at birth or immigration makes unambiguous linkage of data sources at the individual level possible in Denmark[14].

Data sources

We linked four existing population-based medical databases in our study[15]. The Danish National Prescription Registry covers all prescriptions redeemed at any pharmacy in Denmark since 1994[16]. The Danish National Registry of Patients (DNRP) contains data on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and records of emergency and outpatient specialist clinic visits since 1995[17]. Each hospital encounter is recorded in the DNRP with one primary diagnosis and potentially multiple secondary diagnoses, coded since

1994 using the *International Classification of Diseases, Tenth Revision* (ICD-10). Since 1990 laboratory results from tests ordered in primary care practices and hospitals in Northern Denmark have been recorded in the Clinical Laboratory Information System (LABKA) database[18]. The Danish Civil Registration System (CRS)[19] was established in 1968 and provides daily updates on the age, sex, vital status, and residency of all inhabitants[19].

Diabetes patients and general population comparators

We identified patients with incident treated T2D by the date of their first-ever redemption of a glucose-lowering drug prescription (Anatomical Therapeutic Chemical classification system [ATC] code starting with A10) and defined this as their diagnosis date. We excluded patients who had not resided in Denmark for at least one year prior to this date. To ensure inclusion of truly incident patients, we excluded those who redeemed any glucose-lowering drug before 1 January 1995. Patients who redeemed insulin before age 30 (ATC starting with A10A) or any glucose-lowering drug before age 15 were excluded as likely having type 1 diabetes[20]. On the T2D diagnosis date we matched each patient with five comparators drawn from the general Danish population, based on age (year of birth) and sex, defining the respective patient's diagnosis date as their index date.

Comorbidities and mortality

We obtained information on comorbid conditions included in the Charlson Comorbidity Index CCI),[17,21] constructed from inpatient or outpatient hospital encounters (all recorded primary or secondary diagnoses) in the DNRP during the five years before and including the diagnosis/index date. We categorized the severity of comorbidity using the CCI score (excluding

diabetes),[22] adapted for use with hospital discharge data.[23] We computed the total CCI score for each individual, defining four categories of comorbidity: a total score of 0 (no comorbidity), a total score of 1 (moderate comorbidity), a total score of 2 (severe comorbidity), or a total score ≥ 3 (very severe comorbidity). The CRS was used to link data on all-cause mortality and migration status of each patient and comparator until the end of 2018.[14]

HbA_{1c}

For each patient, the latest available HbA_{1c} measurement within one year before diagnosis of diabetes was obtained from the LABKA database. We used the following values to categorize baseline HbA_{1c} level: no measurement available, <6.5%, 6.5%-6.9%, 7.0%-7.4%, 7.5%-7.9%, 8.0%-8.9%, 9.0%-9.9%, and ≥10%[24].

Statistical analysis

We first compiled descriptive characteristics for all T2D patients according to 3-year calendar periods of diagnosis. To assess changes in incidence of T2D over time, we plotted standardized incidence rates (SIRs) of T2D for each calendar year, standardized to the age and sex distribution of the population of Denmark in the year 2012. Next, we restricted the population to Northern Denmark where laboratory data was available, and calculated and plotted incidence rates (IRs) of T2D associated with different baseline HbA_{1c} categories.

To evaluate temporal changes in all-cause mortality among incident T2D patients, for each calendar year we calculated and plotted the all-cause mortality risk during 0-<1 years, 1-<2 years, 2-<3 years, 3-<4 years, and 4-<5 years after T2D diagnosis, separately for men and

women and age-standardized to the incident T2D population in 2012. Next, we followed T2D patients and their population comparators from the matched diagnosis/index date, until death, migration, first diabetes diagnosis (in comparators), or end of follow-up, whichever came first. We plotted cumulative unadjusted mortality by 3-year calendar periods of diagnosis. We used a Poisson regression model to plot mortality rates per 1,000 person years for T2D patients and comparators, using all available follow-up time (maximum follow-up time = 24 years). We then examined changes over 3-year calendar periods in all-cause mortality rates, using the first period 1995-1997 as the reference period and calculating mortality rate ratios adjusted for changes over time in age, sex, and comorbidity (CCI score). In a sensitivity analysis, we repeated the mortality rate ratios calculations substituting a Cox-regression model for the Poisson model.

RESULTS

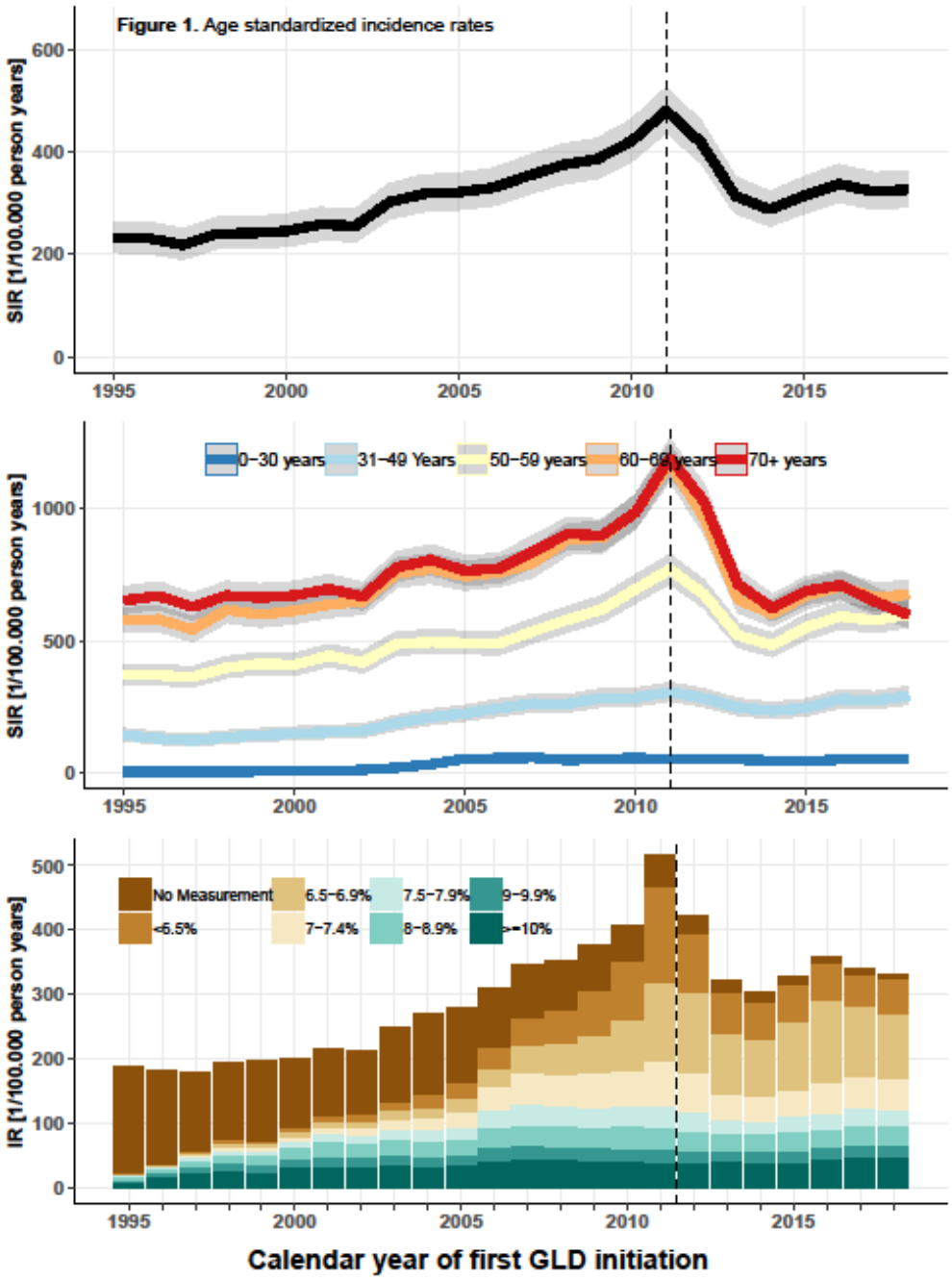
Patient characteristics

We identified 417,986 patients treated for T2D for the first time from 1995 through 2018 in Denmark and 2,084,460 matched comparators. For each 3-year calendar period, baseline characteristics of the T2D patients at inclusion are presented in **Table 1** and those of the comparators in **Supplementary Table 1**. Median age was 60.7 years (IQR: 49.1-70.8 years). We followed the T2D patients for a total of 3.3 million person-years. Median age at first treatment fell from 62.1 years in 1995-1997 to 59.0 years in 2016-2018, while sex distribution remained stable (54% male). The proportion with severe/very severe hospital-diagnosed comorbidity (CCI score >=2) increased from 15% to 19% during the study period. Median pre-treatment HbA_{1c} values decreased substantially, from 9.50% in 1995-1997 to 7.09% in 2016-2018. An HbA_{1c}

nadir of 6.90% occurred in 2010-2012, when 25% of patients (=lower quartile) had a HbA_{1c} measurement of less than 6.40% at treatment initiation (**Table 1**).

Incidence

From 1995 up to the 2012 introduction of HbA_{1c} as a diagnostic option, the annual SIR of T2D per 100,000 people more than doubled from 252 (CI) to 509 (CI). From 2012 to 2018 the annual SIR then declined by 32% to 344 per 100,000 persons (**Figure 1: top**). SIRs increased for men and women in all age groups until 2011, but the subsequent decline was predominantly observed in the older age groups (**Figure 1: middle, and Supplementary Figure 2: middle)**. Thus, in the age group ≥60 years, both men and women had a 45% decline in diabetes incidence in the three years from 2011 to 2014 (**Figure 1: middle and Supplementary Figure 2: middle)**. The decline in incidence was almost entirely driven by a reduction in patients who started treatment with an HbA_{1c} measurement below the new diagnostic HbA_{1c} threshold of 6.5% or without a previous HbA_{1c} measurement (**Figure 1: bottom)**.



Mortality

The all-cause mortality risks within 0-<1 years, 1-<2 years, 2-<3 years, 3-<4 years, and 4-<5 years after diagnosis were similar in men and women with T2D **(Figure 2).** The mortality risk in the first year (0-<1 years) was clearly higher than subsequent one-year mortality risks. This early period also showed the greatest variation in mortality risk, when findings before and after the

diagnostic change in 2012 were compared. The adjusted mortality rate per 1,000 person-years among T2D patients over the whole study period decreased by 48%, from 68 deaths during 1995-1997 to 36 deaths during 2010-2012 (adjusted MMR: 0.52 [95% CI: 0.51-0.53]) **(Table 2)**. The mortality rate subsequently increased by 23% to 44 (95% CI: 42-46) during 2016-18, corresponding to an adjusted MRR of 0.65. The increase in mortality during the study period after 2012 was driven almost entirely by an increase in short-term mortality. During the 17 years leading up to 2012, T2D mortality rates continuously decreased and converged between T2D patients and age- and sex-matched population comparators (**Supplementary Figure 3**). In the following six years (up to 2018), rates diverged again, caused by an increase in mortality in T2D patients and a continued decrease in mortality in the general population (**Table 2, Supplementary Figure 3**).

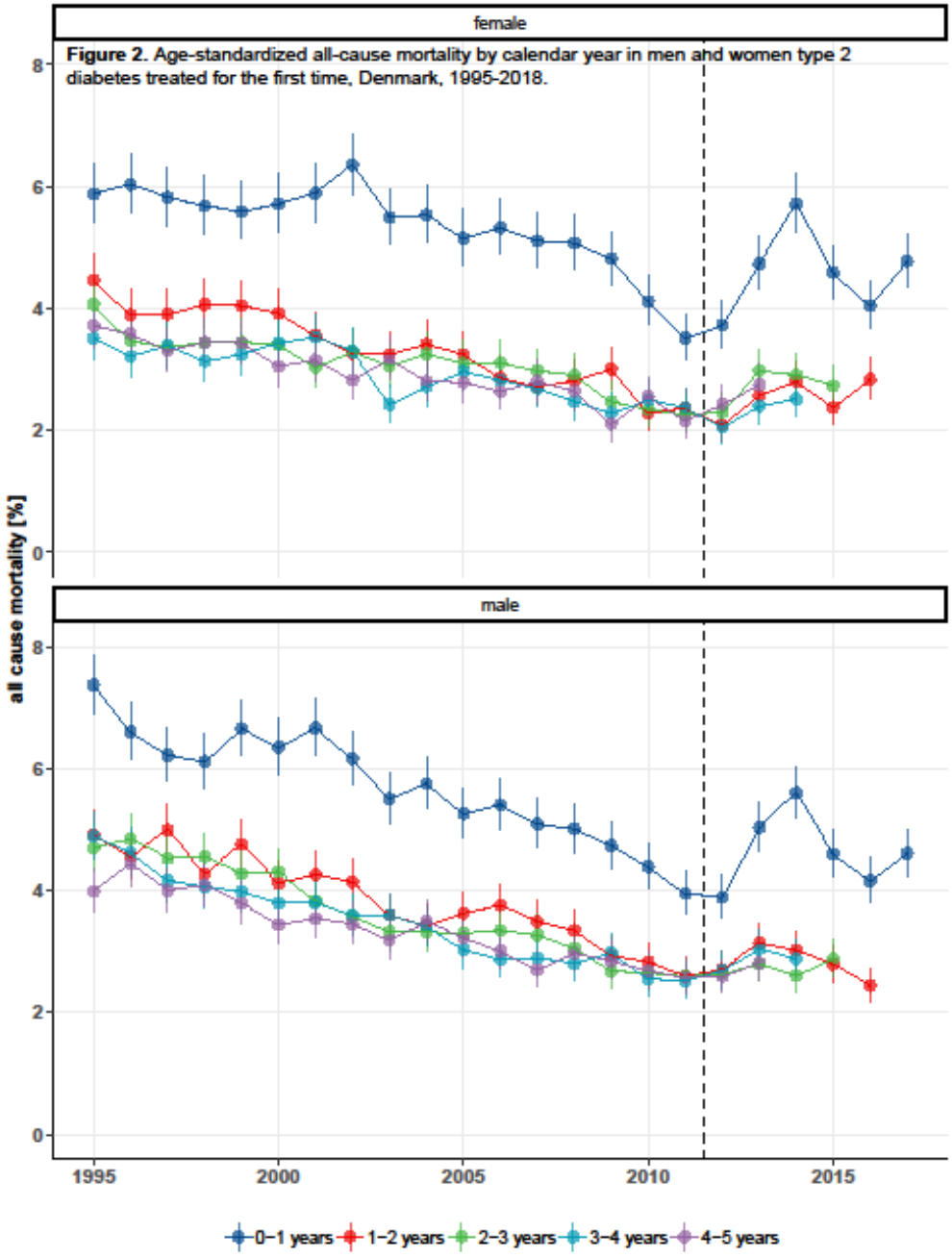


Figure 2. Age-standardized all-cause mortality by calendar year in men and women type 2 diabetes treated for the first time, Denmark, 1995-2018.

DISCUSSION

We observed a twofold increase in the incidence of T2D in Denmark between 1995 and 2011, when HbA_{1c} was first introduced as a primary diagnostic criterion. During the same 17 years, mortality following a T2D diagnosis halved. Between 2012 and 2018 we found a marked decline

in T2D incidence, driven by fewer elderly patients and fewer with a baseline HbA_{1c} <6.5% who started T2D treatment. In parallel, T2D mortality rates climbed back to pre-2012 levels.

Comparison with other studies

Our population-based study used 24 consecutive years of data to examine associations between HbA_{1c}, T2D incidence, and all-cause mortality. The continuously increasing incidence and improving prognosis of T2D that we observed during the 2000s accords with findings from previous US[9,12,25–27], UAE[28], Norwegian[7], Swedish[8,13,29,30], Finnish[31] Danish[32], UK[33–35], Spanish[36], and Australian[37] studies[38]. Most of these studies were based on T2D data before the introduction of HbA_{1c} for diagnostic purposes[9,25,40,41,26–28,30–32,37,39] or included only few data points following this change[8,9,12,13,27,33,34,36,40], hampering assessment of subsequent changing trends. We were unable to identify other population-based incidence studies that included time trends of HbA_{1c} levels at diagnosis. A recent Norwegian study reported declining T2D incidence during 2009-2014, similar to our findings, but did not include information on HbA_{1c} or T2D mortality. In the US, where HbA_{1c} for diagnosis was introduced as early as 2010, a decline in diabetes incidence began a few years earlier than we observed[10], supporting that reductions in T2D incidence might be partly driven by the introduction of HbA_{1c} as a diagnostic option.

With few exceptions[34], previous studies have reported evolving mortality time trends among prevalent, not incident, T2D patients. However, even in recent studies many prevalent T2D patients were diagnosed before the diagnostic changes. Thus, any impact of the HbA_{1c} diagnostic option on T2D mortality preferably should be studied in newly incident T2D patients, as in our study. Nonetheless, several studies comparing mortality trends in prevalent T2D patients versus

general population comparators reported a convergence in mortality rates among T2D patients and comparison subjects, up to the introduction of HbA_{1c}[12,13,35], corroborating our findings. For later periods, a Swedish population-based study found that a continuous decline in all-cause mortality in prevalent T2D diabetes patients began to reverse in 2010-11, while mortality rates continued to decrease in matched controls[13], also in line with our findings. A UK study similarly reported all-cause mortality increases in T2D patients from 2012 to 2014, in contrast with continued decline among controls[35]. A US study based on the National Health Interview Survey reported a continuous T2D mortality decrease between 1988-1994 and 2010-2015, but pooling of the most recent years may have masked recent changes in mortality trends[12]. Authors of previous studies that suggested increasing T2D mortality trends in most recent years generally abstained from commenting on the increases, possibly because few data points were available to assess the mortality increases with certainty.

Strengths and limitations

We conducted a population-based cohort study in a setting with uniform access to health care, complete registration of hospital admissions, drug prescriptions, laboratory data, and complete follow-up until death or emigration. This reduced selection biases stemming from selective inclusion of specific hospitals, health insurance systems, or age groups.

Several limitations should be considered in interpreting our findings. Increased opportunistic screening for T2D and earlier initiation of glucose-lowering drugs following T2D diagnosis[42] would tend to temporarily inflate increases in T2D incidence, introducing a lead time bias resulting in apparent decreased mortality. As well, we could only identify and follow patients from the date of their first glucose-lowering drug treatment and had no means to assess patients

with exclusively diet-treated T2D. At the same time, earlier detection and initiation of therapy can be considered causal factors in the improvement of T2D prognosis over time. We were able to adjust for changes in comorbidity over 24 years, using previously validated diagnoses in the DNRP (with positive predictive values exceeding 90%) and included in the CCI. Still, improved ascertainment of comorbidities over time may have contributed to more complete comorbidity adjustment in recent years, and thus to overestimation of mortality improvements compared with earlier years.

Generalizability, implications, and conclusions

The observed trends in T2D epidemiology may apply to other high-income countries with similar trends in lifestyle risk factors and similar T2D diagnosis and therapy guideline changes in recent decades. It is made clear in recent guidelines that HbA_{1c} is just one among several T2D diagnostic options, which still include both 2-hour oral glucose-tolerance testing and fasting plasma-glucose testing. Nonetheless, HbA_{1c} testing is clearly the most convenient method for patients and physicians in everyday clinical practice, as it requires no fasting and less time, planning and discomfort. Denmark also offers financial inducements for HbA_{1c} testing[3,44]. Of note, all three options for T2D diagnosis and their thresholds have been validated by their ability to predict diabetic retinopathy, rather than mortality[3]. There is currently much discussion that a considerable proportion of T2D patients may fulfill the diagnostic requirements of one method, but not the others [5,45]. Patients diagnosed with different T2D diagnostic methods may represent different disease phenotypes or stages and thus have a different prognosis[46]. We believe our findings suggest that a significant proportion of incident T2D patients, with blood glucose in the diabetic range but normal (or pre-diabetic) HbA_{1c} values of less than 6.5%, remained

undiagnosed and untreated after 2012. In effect, this indicates that reported declines in T2D incidence may be an artifact resulting from a new diagnostic option. If that is the case, we might expect a later compensatory increase in T2D incidence when initially untreated diabetes patients experience further increases in blood glucose and HbA_{1c} values and are eventually diagnosed. Indeed, we observed a return to an increasing T2D incidence trend in the most recent years. However, more data are needed to evaluate whether this trend is transient. The dramatic decline in T2D incidence starting in 2012 coincided with increasing early T2D mortality, possibly because increased use of HbA_{1c} removed T2D patients with normal or pre-diabetic HbA_{1c} (and potentially better short-term prognosis) from the pool of treated T2D patients.

In conclusion, we found that the incidence of first-time treatment of T2D doubled while T2D mortality halved during the 17 years between 1995 and 2011. After introduction of HbA_{1c} as the primary diagnostic criterion in 2012, we saw a marked decline in T2D incidence and a resurgent increase in mortality, driven by fewer patients with baseline HbA_{1c} <6.5% who initiated T2D treatment. Our findings suggest that not all patients have been correctly diagnosed with T2D since the introduction of HbA_{1c} as the primary diagnostic option, leading to risk of undertreatment and possibly worse outcomes. These findings may have implications for clinical practice and suggest that physicians should consider other diagnostic options more often when patients present with borderline increased HbA_{1c} values.

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writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. RWT is the guarantor.

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Prior Presentation: the study has not been presented elsewhere.

Ethics approval: Not needed for purely registry-based studies in Denmark.

Patient involvement

Patients were not involved in posing the research question, choosing the outcome measures, or in the design or implementation of the study. There are no plans to involve patients in dissemination of the results.

Data sharing: No additional data available.

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

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Figure 1. The upper panel depicts age- and sex-standardized incidence rates (SIRs) among patients treated for the first-time for type 2 diabetes with 95% confidence intervals by calendar year of diagnosis. Similarly, the **middle panel shows** SIRs by age categories. The **lower panel** shows the incidence rate stratified by baseline HbA_{1c} measurement at time of first treatment among diabetes patients living in Northern Denmark at time of diagnosis.

Figure 2. Age-standardized all-cause mortality by calendar year in men and women with type 2 diabetes treated for the first time, Denmark, 1995-2018.

Table 1. Sex, age, comorbidity, and HbA_{1c} values of patients initiating a glucose-lowering drug in Denmark, by calendar period of diagnosis.

	Calendar period of diagnosis							
	1995-1997	**1998-2000**	**2001-2003**	**2004-2006**	**2007-2009**	**2010-2012**	**2013-2015**	**2016-2018**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Overall	34,641	37,135	42,612	52,161	61,817	74,863	53,966	59,791
Sex								
Male	19,045 (55)	20,696 (56)	23,615 (55)	26,937 (52)	32,344 (52)	39,969 (53)	29,077 (54)	32,567 (54)
Female	15,596 (45)	16,439 (44)	18,997 (45)	25,224 (48)	29,473 (48)	34,894 (47)	24,889 (46)	27,224 (46)
Age (years)								
<50	8,479 (24)	8,248 (22)	10,021 (24)	14,964 (29)	17,404 (28)	18,402 (25)	15,523 (29)	17,377 (29)
50-59	7,115 (21)	8,771 (24)	10,154 (24)	11,023 (21)	12,468 (20)	15,350 (21)	11,468 (21)	13,779 (23)
60-69	7,874 (23)	8,638 (23)	10,218 (24)	12,769 (24)	16,424 (27)	21,350 (29)	13,354 (25)	13,755 (23)
70-79	7,399 (21)	7,471 (20)	7,891 (19)	8,766 (17)	10,517 (17)	13,861 (19)	9,416 (17)	10,738 (18)
80+	3,774 (11)	4,007 (11)	4,328 (10)	4,639 (9)	5,004 (8)	5,900 (8)	4,205 (8)	4,142 (7)
Median (IQR)	62.10 (50.20, 73.10)	61.70 (51.40, 72.70)	60.90 (50.80, 71.70)	60.00 (47.40, 70.30)	60.60 (47.90, 70.00)	61.80 (50.20, 70.50)	59.90 (47.90, 70.00)	59.00 (47.60, 69.90)
Comorbidity category								
No comorbidity	24,305 (70)	25,359 (68)	28,878 (68)	36,107 (69)	42,421 (69)	50,561 (68)	36,003 (67)	40,279 (67)
Moderate	5,329 (15)	5,968 (16)	6,817 (16)	7,972 (15)	9,397 (15)	11,491 (15)	7,854 (15)	8,357 (14)
Severe	2,994 (9)	3,388 (9)	3,888 (9)	4,387 (8)	5,453 (9)	7,101 (9)	5,170 (10)	5,788 (10)
Very severe	2,013 (6)	2,420 (7)	3,029 (7)	3,695 (7)	4,546 (7)	5,710 (8)	4,939 (9)	5,367 (9)

HbA_{1c} (%)*								
No measurement	8,357 (78)	6,581 (59)	5,926 (46)	6,128 (38)	4,195 (21)	2,462 (10)	824 (5)	528 (3)
<6.5	99 (1)	314 (3)	619 (5)	1,496 (9)	3,005 (15)	5,957 (24)	3,309 (19)	2,941 (15)
6.5-6.9	106 (1)	321 (3)	564 (4)	1,157 (7)	2,726 (14)	5,860 (24)	5,187 (29)	6,107 (32)
7-7.4	157 (1)	358 (3)	747 (6)	1,454 (9)	2,753 (14)	3,392 (14)	2,199 (12)	2,608 (14)
7.5-7.9	168 (2)	392 (4)	733 (6)	1,138 (7)	1,687 (8)	1,737 (7)	1,228 (7)	1,351 (7)
8-8.9	422 (4)	855 (8)	1,237 (10)	1,512 (9)	1,805 (9)	1,835 (7)	1,542 (9)	1,711 (9)
9-9.9	413 (4)	679 (6)	936 (7)	994 (6)	1,145 (6)	1,080 (4)	1,045 (6)	1,117 (6)
>=10	1,044 (10)	1,669 (15)	2,004 (16)	2,230 (14)	2,720 (14)	2,545 (10)	2,503 (14)	2,905 (15)
Median HbA_{1c} (IQR)	9.50 (8.10, 11.20)	9.00 (7.60, 10.90)	8.50 (7.30, 10.40)	7.80 (6.90, 9.60)	7.30 (6.60, 8.90)	6.90 (6.40, 7.90)	7.09 (6.60, 8.46)	7.09 (6.63, 8.55)

Categories of comorbidity were based on Charlson Comorbidity Index (CCI) scores of 0 (no comorbidity), 1 (moderate), 2 (severe), and ≥3 (very severe), Diabetes was excluded from the CCI score.

*HbA_{1c} results are limited to persons who resided in Northern Denmark at the time of their T2D diagnosis.

Table 2. Mortality risk and mortality rate ratios for patients treated for diabetes and age- and sex-matched comparators.

	Diabetes						Comparators				
Period of diagnosis	**Persons N**	**Risk time (years)**	**Events N**	**Mortality Rate / 1000 py**	**rate ratio (95% CI) – crude**	**rate ratio (95% CI) – adjusted***	**Persons N**	**Events N**	**Mortality Rate / 1000 py**	**rate ratio (95% CI) - crude**	**rate ratio (95% CI) – adjusted***
1995-1997	34641	457345	23576	68.48 (66.39-70.64)	1 (ref)	1 (ref)	173169	94662	39.57 (38.93-40.22)	1 (ref)	1 (ref)
1998-2000	37135	466571	22594	60.82 (58.95-62.75)	0.94 (0.92-0.96)	0.89 (0.87-0.9)	185635	87805	37.19 (36.59-37.81)	0.94 (0.93-0.95)	0.94 (0.93-0.95)
2001-2003	42612	500281	21325	53.21 (51.56-54.91)	0.83 (0.81-0.84)	0.78 (0.76-0.79)	213022	81081	34.72 (34.15-35.3)	0.84 (0.83-0.84)	0.88 (0.87-0.89)
2004-2006	52161	554526	19455	47.34 (45.86-48.88)	0.68 (0.67-0.69)	0.69 (0.68-0.7)	260749	72490	31.93 (31.4-32.47)	0.7 (0.69-0.71)	0.81 (0.8-0.81)
2007-2009	61817	545278	17049	41.74 (40.42-43.11)	0.61 (0.59-0.62)	0.61 (0.6-0.62)	309013	62195	29.14 (28.65-29.64)	0.62 (0.62-0.63)	0.74 (0.73-0.74)
2010-2012	74863	501413	14184	35.81 (34.64-37.01)	0.55 (0.54-0.56)	0.52 (0.51-0.53)	374222	52250	26.71 (26.25-27.18)	0.58 (0.58-0.59)	0.67 (0.67-0.68)
2013-2015	53966	222848	7000	40.99 (39.49-42.55)	0.61 (0.59-0.63)	0.6 (0.58-0.61)	269761	20006	24.17 (23.68-24.67)	0.5 (0.49-0.51)	0.61 (0.6-0.62)
2016-2018	59791	87163	2936	44.17 (42.17-46.26)	0.65 (0.63-0.68)	0.64 (0.62-0.67)	298889	6784	21.92 (21.31-22.55)	0.44 (0.43-0.45)	0.55 (0.54-0.57)

*Adjusted for age, sex and comorbidity**.** Abbreviations: py, person years; CI, confidence intervals

Supplementary Tables and Figures

Supplementary Table 1. Sex, age, comorbidity, and HbA_{1c} of comparison cohort, by calendar period of diagnosis.

Supplementary Table 2: Mortality rates and rate ratios comparing diabetes patients and comparators within diagnosis periods.

Supplementary Figure 1. Age standardized incidence rates for men and women.

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Supplementary Table 1. Sex, age, comorbidity, and HbA_{1c} of comparison cohort, by calendar period of diagnosis.

	Calendar period of diagnosis							
	1995-1997 N (%)	**1998-2000 N (%)**	**2001-2003 N (%)**	**2004-2006 N (%)**	**2007-2009 N (%)**	**2010-2012 N (%)**	**2013-2015 N (%)**	**2016-2018 N (%)**
Overall	173,169	185,635	213,022	260,749	309,013	374,222	269,761	298,889
Sex								
Male	95,201 (55)	103,457 (56)	118,047 (55)	134,653 (52)	161,688 (52)	199,794 (53)	145,343 (54)	162,802 (54)
Female	77,968 (45)	82,178 (44)	94,975 (45)	126,096 (48)	147,325 (48)	174,428 (47)	124,418 (46)	136,087 (46)
Age (years)								
<50	42,418 (24)	41,376 (22)	50,092 (24)	74,763 (29)	87,025 (28)	92,085 (25)	77,594 (29)	86,939 (29)
50-59	35,628 (21)	43,604 (23)	50,844 (24)	55,180 (21)	62,420 (20)	76,729 (21)	57,257 (21)	68,911 (23)
60-69	39,418 (23)	43,394 (23)	51,053 (24)	63,817 (24)	82,129 (27)	106,986 (29)	67,119 (25)	68,800 (23)
70-79	36,935 (21)	37,317 (20)	39,407 (18)	43,819 (17)	52,350 (17)	68,959 (18)	46,816 (17)	53,437 (18)
80+	18,770 (11)	19,944 (11)	21,626 (10)	23,170 (9)	25,089 (8)	29,463 (8)	20,975 (8)	20,802 (7)
Median (IQR)	62.10 (50.20, 73.10)	61.70 (51.40, 72.70)	60.90 (50.80, 71.70)	60.00 (47.40, 70.30)	60.60 (47.90, 70.00)	61.80 (50.20, 70.50)	60.00 (47.90, 70.00)	59.00 (47.60, 69.90)
Comorbidity category								
No comorbidity	139,837 (81)	147,641 (80)	168,098 (79)	207,016 (79)	242,993 (79)	287,920 (77)	208,678 (77)	230,860 (77)
Moderate	17,738 (10)	20,147 (11)	23,344 (11)	26,940 (10)	32,103 (10)	40,086 (11)	27,583 (10)	29,655 (10)
Severe	10,807 (6)	11,933 (6)	14,097 (7)	17,181 (7)	21,486 (7)	28,795 (8)	20,421 (8)	23,303 (8)
Very severe	4,787 (3)	5,914 (3)	7,483 (4)	9,612 (4)	12,431 (4)	17,421 (5)	13,079 (5)	15,071 (5)

Supplementary Table 2. Mortality rates and rate ratios comparing diabetes patients and comparators within diagnosis periods.

*Adjusted for age (= 60 years) and sex (= male)

**Adjusted for age (= 60 years), sex (= male), and comorbidities (CCI score = 0). Despite successful matching on age and sex, adjusting for age affected the estimate. This occurred because unlike patients with type 2 diabetes who can exit the cohort upon death, migration, or end of follow-up, members of the comparison cohort also can exit the study if they get T2D. This makes their contributions at different ages asymmetric. Continuing following comparators after a diagnosis of T2D introduces another type of bias (however the estimates are largely unaffected). It must be concluded that comparisons between T2D patients and comparators are uncertain.

Period of diagnosis	Mortality Rate diabetes cohort (95% CI)	Mortality Rate comparison cohort (95% CI)	comparisons	MRR T2D (95% CI) – unadjusted	MRR T2D (95% CI) partially adjusted*	MRR T2D (95% CI) – adjusted**	Rate difference
1995-1997	68.48 (66.39-70.64)	39.57 (38.93-40.22)	1 (ref)	1.49 (1.51-1.47)	1.80 (1.77-1.83)	1.69 (1.66-1.71)	28.9
1998-2000	60.82 (58.95-62.75)	37.19 (36.59-37.81)	1 (ref)	1.49 (1.51-1.47)	1.74 (1.71-1.76)	1.61 (1.59-1.64)	23.6
2001-2003	53.21 (51.56-54.91)	34.72 (34.15-35.3)	1 (ref)	1.47 (1.50-1.45)	1.64 (1.62-1.67)	1.52 (1.50-1.54)	18.5
2004-2006	47.34 (45.86-48.88)	31.93 (31.4-32.47)	1 (ref)	1.45 (1.47-1.43)	1.60 (1.58-1.63)	1.48 (1.46-1.51)	15.4
2007-2009	41.74 (40.42-43.11)	29.14 (28.65-29.64)	1 (ref)	1.45 (1.48-1.43)	1.56 (1.54-1.59)	1.44 (1.43-1.46)	12.6
2010-2012	35.81 (34.64-37.01)	26.71 (26.25-27.18)	1 (ref)	1.41 (1.43-1.38)	1.47 (1.44-1.50)	1.45 (1.33-1.38)	9.1
2013-2015	40.99 (39.49-42.55)	24.17 (23.68-24.67)	1 (ref)	1.82 (1.87-1.78)	1.92 (1.87-1.98)	1.69 (1.65-1.74)	16.8
2016-2018	44.17 (42.17-46.26)	21.92 (21.31-22.55)	1 (ref)	2.21 (2.31-2.12)	2.29 (2.19-2.39(	1.99 (1.91-2.08)	22.2

Supplementary Figure 1. The upper panel depicts age-standardized incidence rates (SIRs) of type 2 diabetes for men and women with 95% confidence intervals by calendar year of diagnosis. Similarly, the **middle panel shows** SIRs by age categories at diagnosis. The **lower panel** shows the incidence rate per 100,000 persons and their most recent HbA_{1c} measurement before diagnosis, among diabetes patients living in Northern Denmark at diagnosis.

Supplementary Figure 2. Proportion of patients diagnosed with type 2 diabetes each calendar year by baseline HbA_{1c} measurement.

Supplementary Figure 3. Cumulative unadjusted all-cause mortality (%) by calendar year of diagnosis.

Supplementary Figure 4. All-cause mortality rates (MRs) for the type 2 diabetes cohort and age- and sex-matched comparators with 95% confidence intervals by calendar year of diagnosis. Adjusted for age (= 60 years), sex (= male), and comorbidities (CCI score = 0).

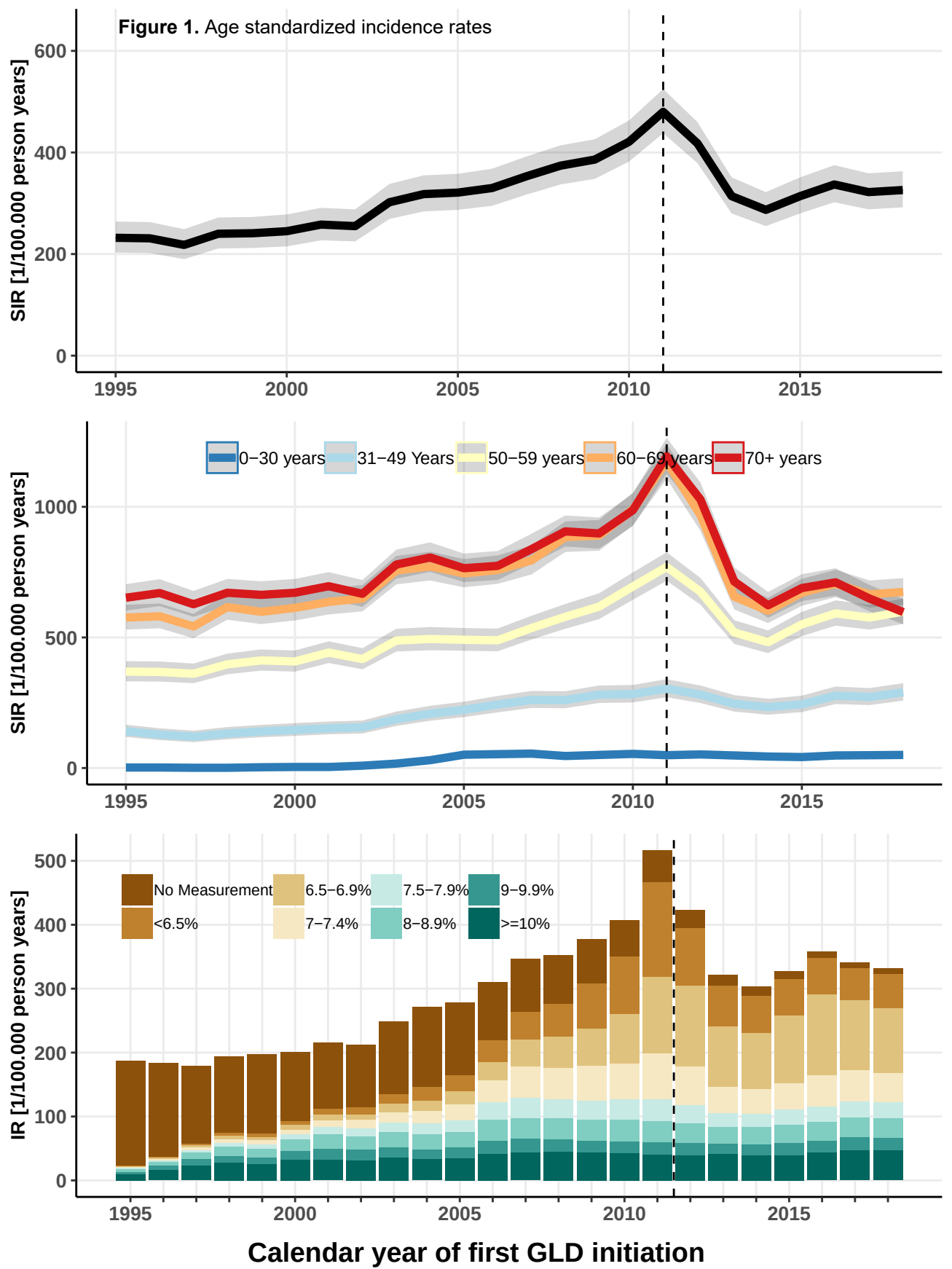


Figure 1. Age standardized incidence rates
SIR [1/100.000 person years]
600
400
200
0
1995
2000
2005
2010
2015
0−30 years
31−49 Years
50−59 years
60−69 years
70+ years
SIR [1/100.000 person years]
1000
500
0
1995
2000
2005
2010
2015
IR [1/100.000 person years]
500
400
300
200
100
0
No Measurement
<6.5%
6.5−6.9%
7−7.4%
7.5−7.9%
8−8.9%
9−9.9%
>=10%
1995
2000
2005
2010
2015
Calendar year of first GLD initiation

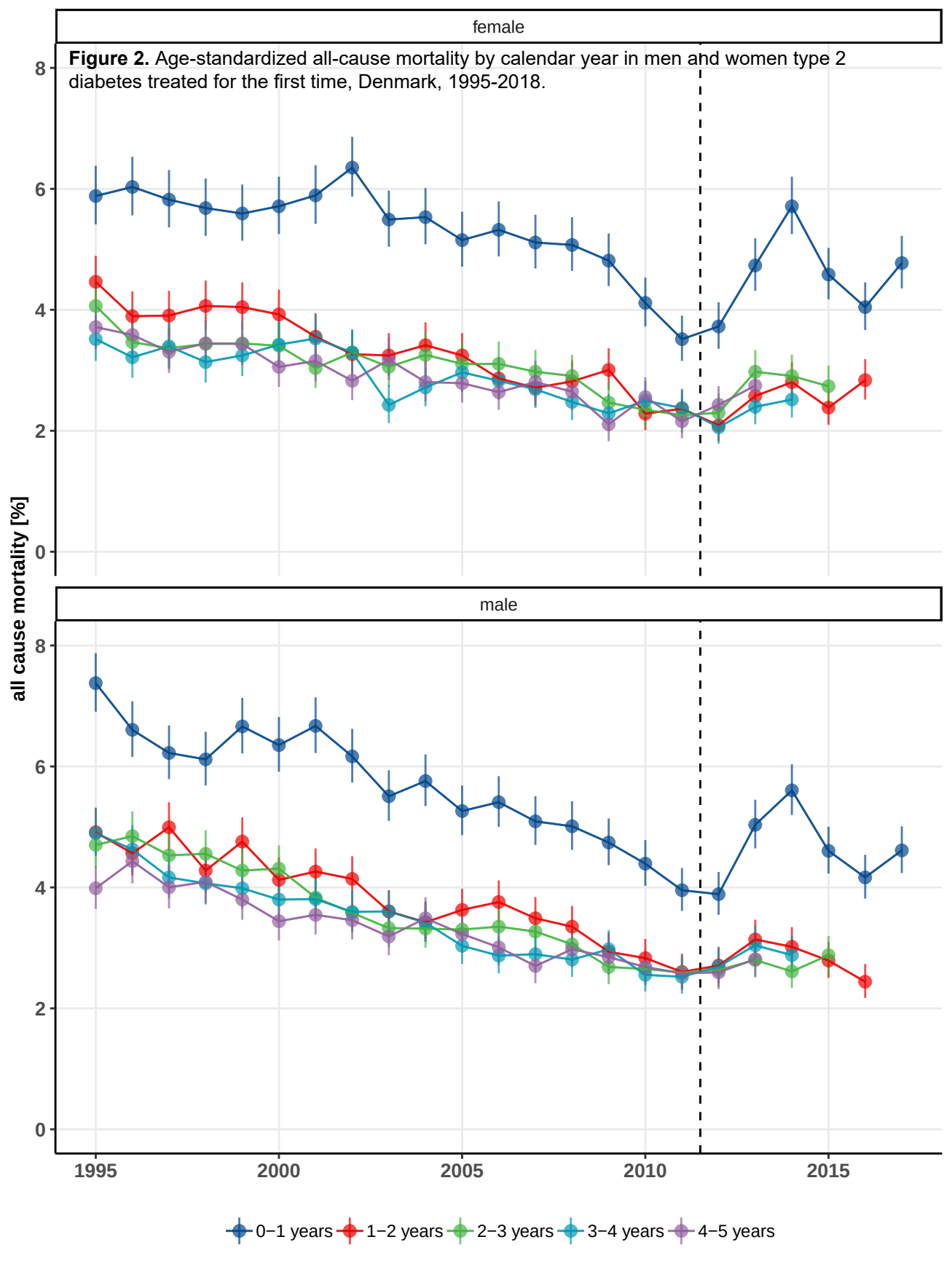
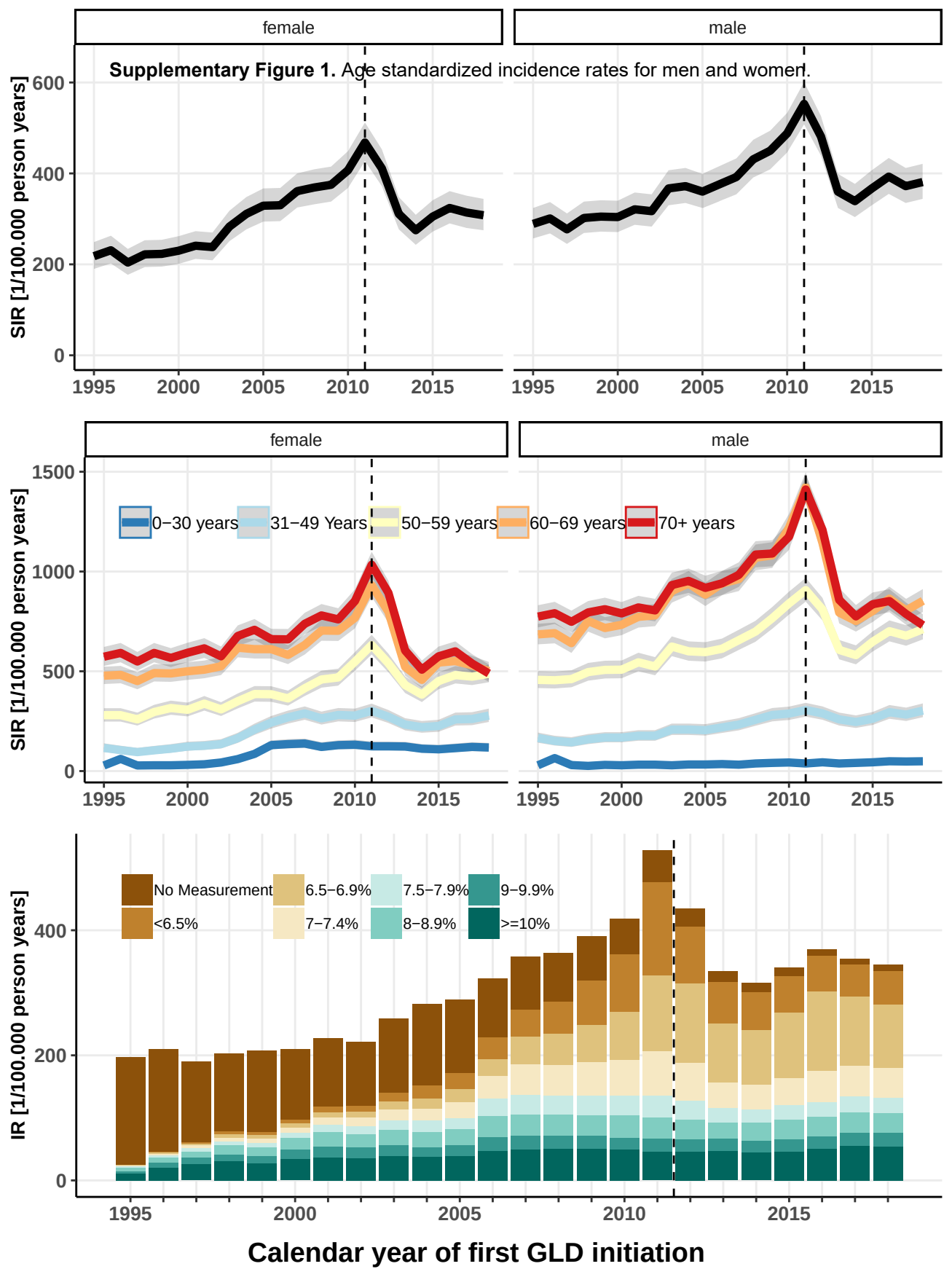
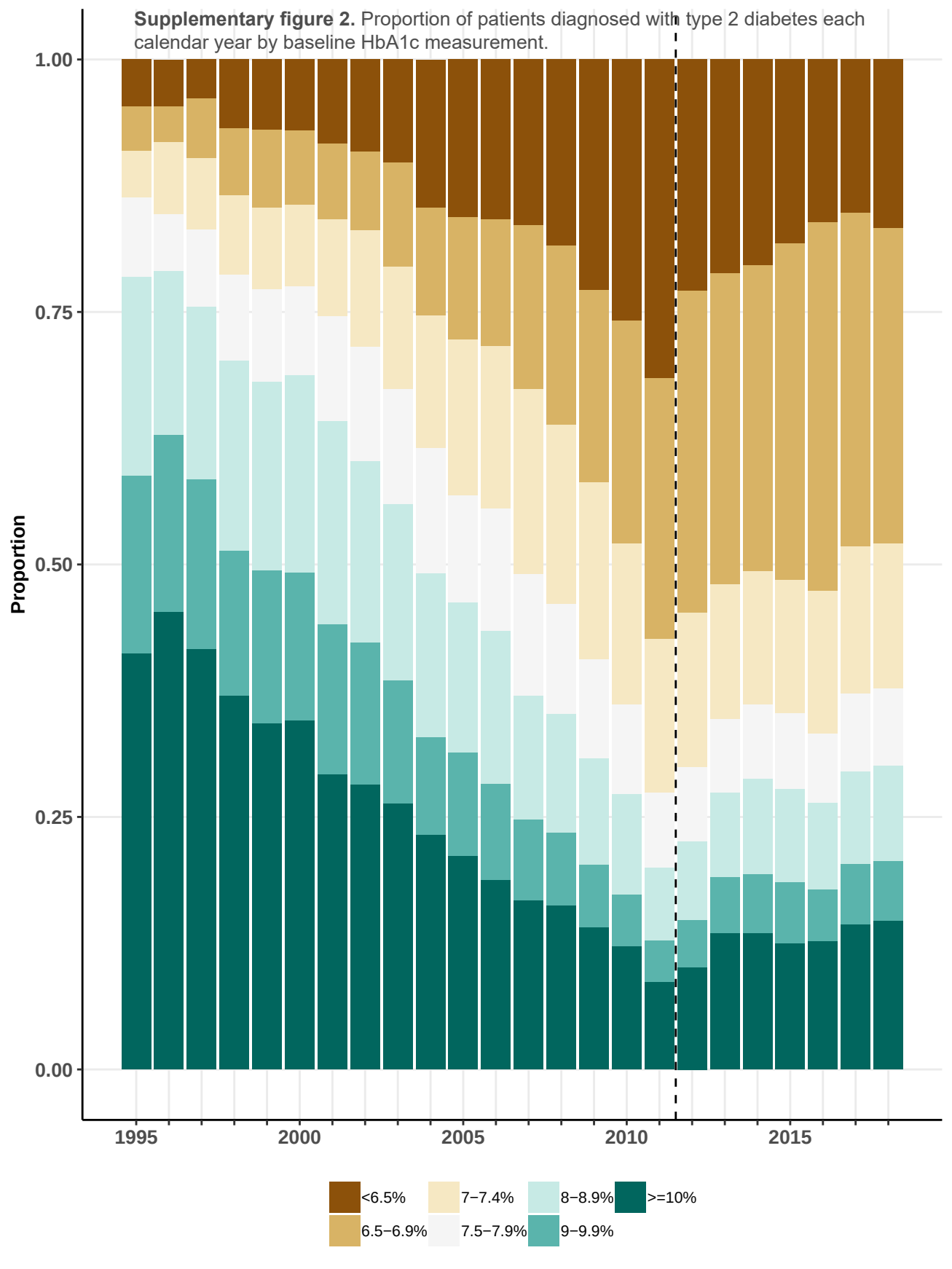


Figure 2. Age-standardized all-cause mortality by calendar year in men and women type 2 diabetes treated for the first time, Denmark, 1995-2018.

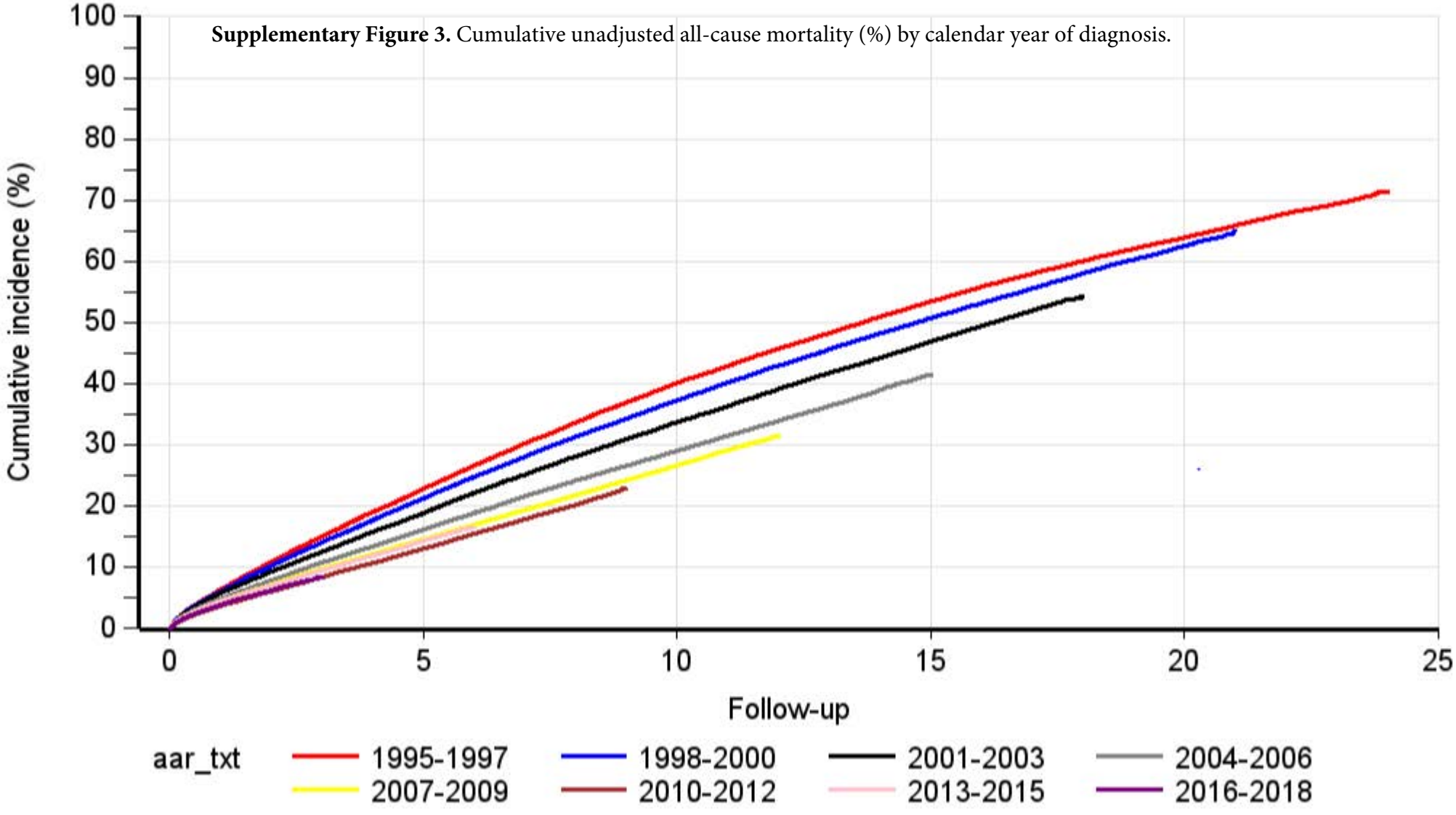


Supplementary Figure 1. Age standardized incidence rates for men and women.

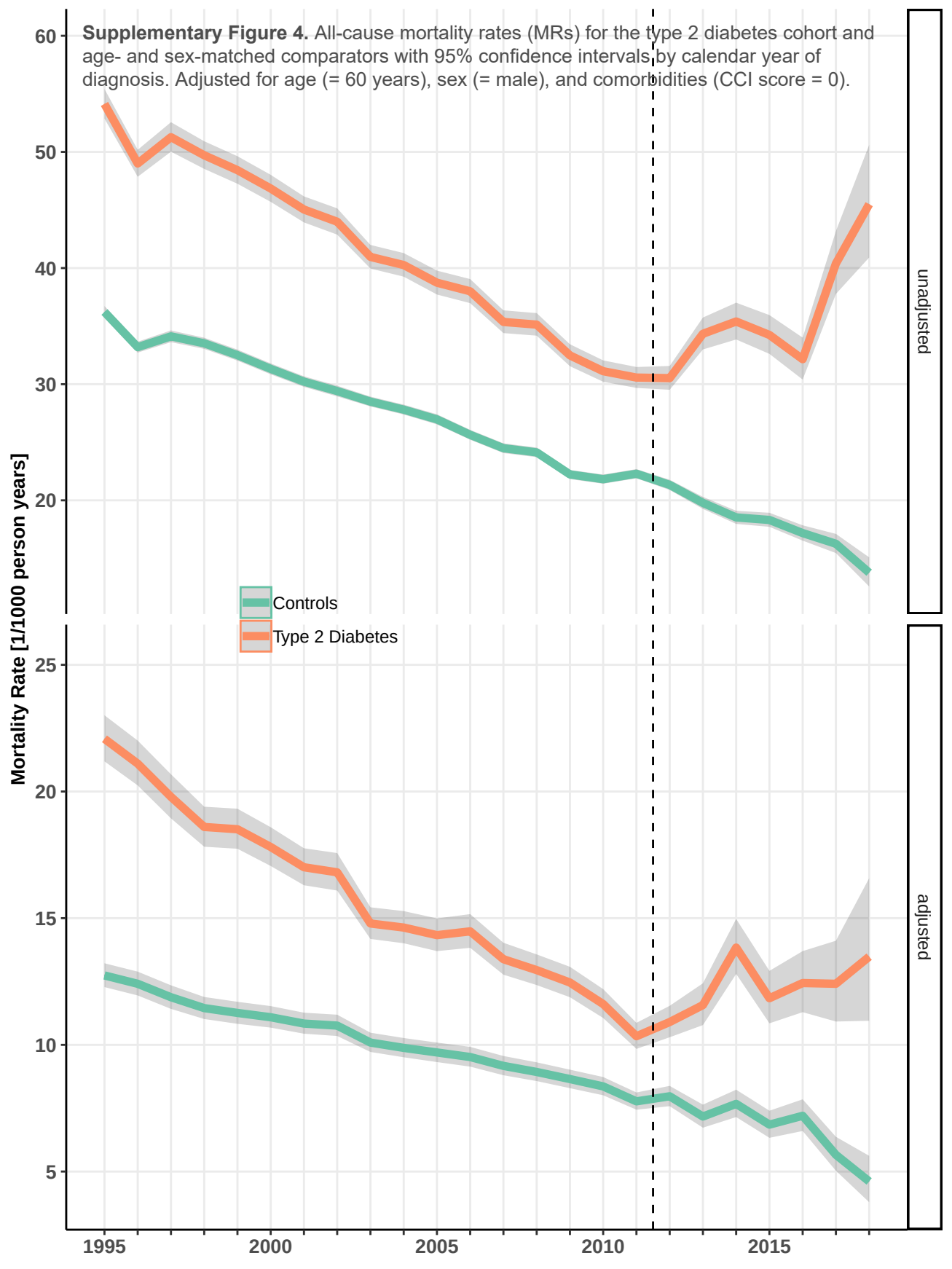
Supplementary figure 2. Proportion of patients diagnosed with type 2 diabetes each calendar year by baseline HbA1c measurement.



Supplementary Figure 3. Cumulative unadjusted all-cause mortality (%) by calendar year of diagnosis.



Supplementary Figure 4. All-cause mortality rates (MRs) for the type 2 diabetes cohort and age- and sex-matched comparators with 95% confidence intervals, by calendar year of diagnosis. Adjusted for age (= 60 years), sex (= male), and comorbidities (CCI score = 0).



Paper II

Trends in HbA_{1c} and LDL Cholesterol in Patients With Type 2 Diabetes Receiving First-Time Treatment in Northern Denmark, 2000–2017: Population-Based Sequential Cross-Sectional Analysis

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The evolving evidence base for early diabetes detection and intensive treatment over the recent decades has likely led to a change in the profile of patients initiating type 2 diabetes treatment (1–3). Knowing in which direction the clinical profile of patients with diabetes is moving is important because treatment guidelines rely on the generalizability of clinical trials to contemporary populations (3). Many of these trials were conducted when both the diagnostic criteria and treatment targets were quite different than today (1–3). Population-based data investigating long-term trends in diabetes management and treatment targets are scarce. We aimed to examine 18-year changes in HbA_{1c} and lipid testing and control among people initiating glucose-lowering drugs (GLDs) for type 2 diabetes. We performed one of the first population-based studies, using laboratory and health care databases covering the entire population of Northern Denmark (~1.8 million people) (4).

We identified people redeeming their first-ever GLD prescription at age ≥30 years. For all 94,175 GLD initiators 2000–2017, we examined pretreatment HbA_{1c} and lipid levels and proportions of testing. For initiators 2000–2016, we assessed 12 months posttreatment lipid-lowering therapy and achievement of glycemic and LDL cholesterol targets. Mean HbA_{1c} and LDL levels and reductions were plotted with 95% CIs.

Median age at first GLD treatment fell from 64 years in 2000 to 61 in 2017; 56% of the study population were men. The proportion of patients with at least one HbA_{1c} test within 12 months after GLD initiation increased from 53% (2000) to 95% (2016) (Fig. 1*A*). Concurrently, mean pretreatment HbA_{1c} decreased from 9.2% (77 mmol/mol) (2000) to 7.9% (63 mmol/mol) (2017), with a nadir occurring in 2011 (7.3% [56 mmol/mol]). For mean posttreatment HbA_{1c}, a smaller decline was seen from 7.1% (54 mmol/mol) (2000) to 6.6% (49 mmol/mol) (2016). (Fig. 1*B*). The proportion of patients achieving posttreatment HbA_{1c} target <7% (53 mmol/mol) increased from 54 to 81% during 2000–2016 and for target <6.5% (48 mmol/mol) increased from 37 to 56% (Fig. 1*C*). The proportion with a pretreatment HbA_{1c} below 6.5% (42 mmol/mol) increased from 7% in 2000 to 31% immediately preceding the 2012 introduction of HbA_{1c} as a diagnostic criterion. After the change in diagnostic criteria, the group with HbA_{1c} <6.5% before treatment dropped substantially, to only 12% in 2017 (Fig. 1*D*). As shown in Fig. 1*E*, GLD initiators below the current 6.5% diagnostic threshold did not experience any posttreatment HbA_{1c} reduction. In contrast, patients in successively higher pretreatment HbA_{1c} categories had increasingly large posttreatment reductions.

The proportion of patients who had at least one blood lipid test within 12 months following their first-ever GLD treatment increased from 82% (2000) to 99% (2016). The proportion receiving lipid-lowering therapy within 12 months quintupled from 12% (2000) to 61% (2016) but declined after peaking at 68% in 2011 (Fig. 1*F*). Mean pretreatment LDL cholesterol declined from 3.5 mmol/L (2000) to 2.8 mmol/L (2017), while the mean posttreatment value declined more, from 3.3 mmol/L (2000) to 2.3 mmol/L (2016) (Fig. 1*G*). The proportion achieving LDL cholesterol target <2.6 mmol/L increased from 23% (2000) to 65% (2016) and for target <1.8 mmol/L from 5% (2000) to 29% (2016) (Fig. 1*H*).

We found evidence that real-life patients with first-treated type 2 diabetes

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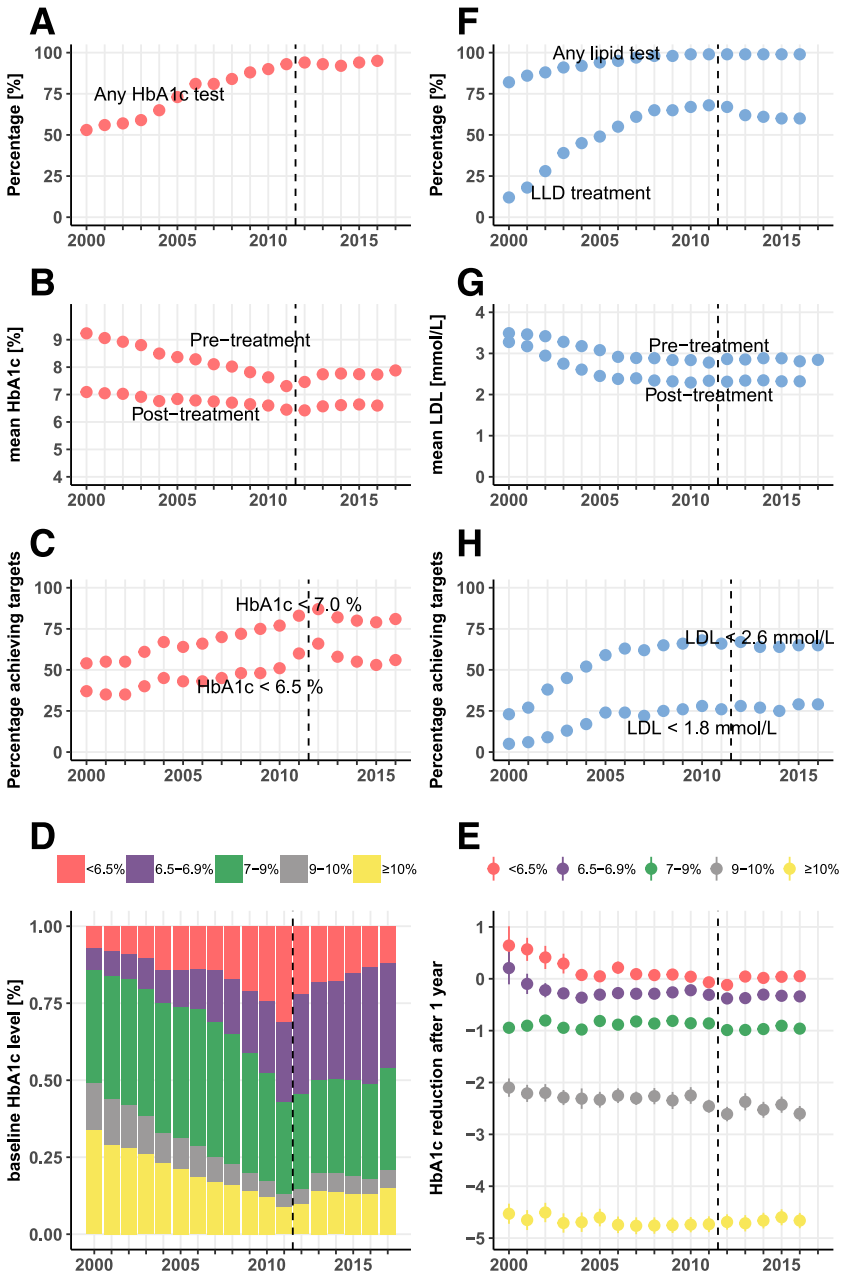

Figure 1—Lipid and HbA_{1c} trends among first-time initiators of GLDs in Northern Denmark, 2000–2017. Blue circles depict lipids, and red circles depict HbA_{1c}. Confidence intervals are shown as vertical small lines; however, they are narrow and are usually hidden by the point estimates. Vertical dashed lines depict the introduction of HbA_{1c} as a diagnostic criteria in February 2012. Pretreatment: latest measurement within 12 months before first-time GLD treatment; posttreatment: measurement closest to 12 months following treatment initiation (within 6–18 months). *A*: Proportion of patients with incident type 2 diabetes in Northern Denmark who received HbA_{1c} testing within 1 year, by calendar year of GLD initiation. *B*: Mean pretreatment and posttreatment HbA_{1c} by calendar year of GLD initiation. *C*: Proportion of patients achieving HbA_{1c} treatment targets (<6.5% [48 mmol/mol], <7% [53 mmol/mol]) at 12 months following GLD initiation, by calendar year of GLD initiation. *D*: Proportions of pretreatment HbA_{1c} categories for first-time GLD initiators by calendar year of first GLD use. *E*: Mean pre- to posttreatment HbA_{1c} reduction following 12 months of treatment by calendar year of first GLD use and pretreatment HbA_{1c} category among the 64,094 initiators with both a pre- and posttreatment measurement. *F*: Proportion of patients with incident type 2 diabetes in Northern Denmark who received lipid testing and/or lipid-lowering drug prescriptions within 1 year, by calendar year of GLD initiation. *G*: Mean pretreatment and posttreatment LDL cholesterol levels, by calendar year of GLD initiation. *H*: Proportion of patients achieving LDL treatment targets (1.8 mmol/L, 2.6 mmol/L) at 12 months following GLD initiation.

have changed markedly in the past 18 years. A large decline in HbA_{1c} levels before first-time GLD therapy is probably a main driver of the improvement in glycemic target achievement. Newer GLDs with a decreased risk of hypoglycemia may be another potential contributor. Of note, our investigated HbA_{1c} targets may not apply to all patients (3). Improvements in LDL cholesterol over time may relate to more intensive lipid-lowering therapy. Overall, recent developments likely reflect a combination of evolving clinical practices (earlier and more complete diabetes detection and coding practices), secular demographic changes, and true improvements in treatment. It is difficult to pinpoint one key driver of the observed changes. The main factors driving these changes—changing diagnostic and treatment guidelines, demography, and increasing treatment options—are seen in other Western countries (3). One study limitation is that HbA_{1c} measurements in early years may have been restricted predominantly to patients with anticipated glycemic control problems, which could lead to overestimation of HbA_{1c} improvements over time.

Although monitoring and treatment of glucose and cholesterol has improved considerably, there is room for further improvement, especially in proportions initiating lipid-lowering therapy. Finally, the introduction of HbA_{1c} for diagnosis of diabetes will have led to the exclusion of patients with blood glucose but not HbA_{1c} in the diabetic range from this study of GLD initiators.

Acknowledgments. Ethics approvial is not needed for purely registry-based studies in Denmark. Patients were not involved in setting the research question, the outcome measures, or the design or implementation of the study. There are no plans to involve patients in dissemination of the results.

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Novo Nordisk A/S. Project partners are listed on the website www.DD2.nu. The Department of Clinical Epidemiology, Aarhus University Hospital participates in the International Diabetic Neuropathy Consortium (IDNC) research program, which is supported by a Novo Nordisk Foundation Challenge Programme grant (grant no. NNF14SA000 6). The Department of Clinical Epidemiology is involved in studies with funding from various companies as research grants to (and administered by) Aarhus University. None of these studies are related to the current study.

The funder had no role in the study design, data analysis, interpretation of data, or writing of the manuscript.

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Author Contributions. J.S.K. reviewed the literature, organized the writing, and wrote the initial draft. J.S.K., A.H., D.R.W., and R.W.T. designed the study and directed the analyses, which were carried out by J.S.K. All authors participated in the discussion and interpretation of the results, critically revised the manuscript for intellectual content, and approved the final version. R.W.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Preliminary results of this work were presented in poster form at the 54th Annual Meeting of the European Association for the Study of Diabetes, Berlin, Germany, 1–5 October 2018, and as an oral presentation at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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Paper III

Differences Between Randomized Clinical Trial Patients and Real-World Initiators of the Glucagon-Like Peptide 1 Receptor Agonist Liraglutide

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Randomized controlled trials (RCTs) are considered the gold standard for determining efficacy and safety of new drugs. Successful randomization addresses known and unknown confounding when assessing a drug's effect among trial patients selected on strict inclusion and exclusion criteria (1). However, treatment results have been shown on occasion to be much less favorable than expected outside trial populations, often related to differences in age, comorbidity, disease severity, drug compliance, and/or comedication among patients treated in everyday clinical practice (1). The risk of adverse drug effects may also be higher among patients treated in routine clinical care.

Liraglutide, a glucagon-like peptide 1 receptor agonist, was quickly adopted by clinicians following its approval by the European Medicines Agency in 2009 and by the U.S. Food and Drug Administration in 2010. Approval was based on a number of phase III RCTs called the Liraglutide Effect and Action in Diabetes (LEAD) 1–5 trials (2).

We used data from Danish population-based medical databases to examine whether routine clinical care liraglutide initiators would have been eligible for participation in the phase III trials. Furthermore, their HbA_{1c} reduction on liraglutide was evaluated. We included all individuals who lived in northern Denmark and redeemed a first-time liraglutide prescription from 2009–2015 (n = 9,251). We adapted each LEAD 1–5 trial eligibility criterion (such as age, comorbid conditions, current drug use, HbA_{1c} level, etc.) to the Danish National Patient Registry, the Danish Prescription Registry, and the clinical laboratory information system, as appropriate (Table 1) (3). Exclusion criteria were largely similar in the LEAD 1–5 trials, and we used only exclusion criteria that were shared in all five trials. When exact information was unavailable in our databases (i.e., BMI and blood pressure), we assumed that patients would be eligible for trial participation.

Routine clinical care liraglutide users frequently had comorbidities that would have made them ineligible for the LEAD 1–5 trials, including "clinically significant cardiovascular disease" (29%) or "other significant disease" (11%) (Table 1). Further, 27% had HbA_{1c} levels outside the values needed for inclusion in the LEAD 1–5 trials, and 37% were on current insulin, another exclusion criterion in the LEAD 1–5 trials. Overall, 73% of all real-world liraglutide users would have been ineligible for any of the LEAD trials (Table 1). Approved indications expanded during 2009–2015 allowing for liraglutide therapy together with other glucose-lowering drug regimens (e.g., with insulin or as monotherapy) and a beneficial liraglutide effect in patients with cardiovascular disease emerged shortly after our study period (4). When we disregarded both previous glucose-lowering drug use and pre-existing cardiovascular disease as exclusion criteria, we found that 45% of real-world users would have been ineligible for RCT participation.

Overall, patients ineligible for LEAD 1–5 participation had a higher HbA_{1c} before initiating liraglutide (8.7% [72 mmol/mol])) than eligible patients (8.4% [68 mmol/mol]) (Table 1) but experienced similar HbA_{1c} reductions after 6 months (−1.0% [−11 mmol/mol] vs. −0.9% [−10 mmol/mol]).

We found that liraglutide users treated in clinical care settings in northern Denmark did not resemble patients included in the LEAD 1–5 trials, with almost three out of four routine clinical care initiators being classified as ineligible for the RCTs. Nevertheless, our findings suggest that the efficacy of liraglutide on HbA_{1c} seen in the LEAD trials translates into real-world effectiveness, both for eligible and noneligible patients. The LEAD 1–5 trials thus found similar reductions in HbA_{1c}

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Table 1—Real-world liraglutide initiators that would have been excluded from participation in the LEAD 1–5 trials and their HbA_{1c} reduction

Exclusion criteria for participation in LEAD 1–5 trials	Real-world patients that would have been excluded based on each criterion		Mean (95% CI) HbA_{1c} before liraglutide initiation		Mean (95% CI) HbA_{1c} 6 months after liraglutide initiation		Mean (95% CI) HbA_{1c} reduction	
	n	%	%	mmol/mol	%	mmol/mol	%	mmol/mol
All patients	9,251	100	8.6 (8.6, 8.6)	70 (70, 70)	7.6 (7.6, 7.7)	60 (60, 61)	−1.0 (−1.0, −0.9)	−11 (−11, −10)
Excluded for any of the following	6,768	73.2	8.7 (8.7, 8.7)	72 (72, 72)	7.7 (7.7, 7.7)	61 (61, 61)	−1.0 (−1.0, −0.9)	−11 (−11, −10)
Not excluded for any of the following	2,583	26.9	8.4 (8.3, 8.4)	68 (67, 68)	7.5 (7.4, 7.5)	58 (57, 58)	−0.9 (−1.0, −0.9)	−10 (−11, −10)
Ongoing noninsulin GLD therapy for <3 months	1,051	11.4	8.8 (8.7, 8.9)	73 (73, 74)	7.7 (7.6, 7.8)	61 (60, 62)	−1.1 (−1.2, −1.0)	−12 (−13, −11)
HbA_{1c} level outside range*	2,522	27.3	9.1 (9.0, 9.2)	76 (75, 77)	7.8 (7.7, 7.9)	62 (61, 63)	−1.3 (−1.4, −1.2)	−14 (−16, −13)
Age <18 years	8	0.1	8.6 (6.0, 11.1)	70 (42, 98)	6.7 (−1.0, 14.4)	50 (<0, 134)	−2.5 (−16.3, 11.3)	−28 (−155, 100)
Age >80 years	147	1.6	8.5 (8.2, 8.7)	69 (66, 72)	7.6 (7.4, 7.8)	60 (57, 62)	−0.9 (−1.1, −0.6)	−10 (−12, −7)
Current insulin treatment	3,414	36.9	8.8 (8.7, 8.8)	73 (72, 73)	8.00 (7.9, 8.0)	64 (63, 64)	−0.8 (−0.8, −0.7)	−9 (−9, −8)
Impaired liver function	86	0.9	9.2 (8.8, 9.6)	77 (73, 81)	7.7 (7.3, 8.0)	61 (56, 64)	−1.7 (−2.1, −1.2)	−19 (−23, −13)
Hepatitis B or C positive	27	0.3	9.1 (8.5, 9.7)	76 (69, 82)	8.5 (7.6, 9.3)	69 (60, 78)	−0.6 (−1.3, 0.1)	−7 (−14, 1)
Impaired renal function	395	4.3	8.6 (8.5, 8.8)	70 (69, 74)	7.7 (7.6, 7.8)	61 (60, 62)	−0.9 (−1.0, −0.7)	−10 (−11, −8)
Clinically significant active CVD	2,646	28.6	8.7 (8.6, 8.7)	72 (70, 72)	7.7 (7.7, 7.8)	61 (61, 62)	−0.9 (−1.0, −0.9)	−10 (−11, −10)
Cancer	326	3.5	8.5 (8.4, 8.7)	69 (68, 72)	7.6 (7.5, 7.8)	60 (58, 62)	−0.9 (−1.1, −0.8)	−10 (−12, −10)
Clinically significant disease	1,029	11.2	8.6 (8.4, 8.6)	70 (68, 70)	7.6 (7.5, 7.7)	60 (58, 61)	−1.0 (−1.1, −1.0)	−11 (−12, −11)
Recurrent hypoglycemia	46	0.5	8.5 (8.0, 9.0)	69 (64, 75)	8.1 (7.7, 8.5)	65 (61, 69)	−0.5 (−0.9, 0.0)	−6 (−10, 0)
Use of drugs that interfere with glucose	439	4.8	8.6 (8.4, 8.7)	70 (68, 72)	7.5 (7.4, 7.6)	58 (57, 60)	−1.0 (−1.2, −0.9)	−11 (−13, −10)
Alcohol or substance abuse	389	4.2	8.9 (8.6, 9.1)	74 (70, 76)	7.8 (7.6, 7.9)	62 (60, 63)	−1.1 (−1.3, −0.9)	−12 (−14, −10)
Mental incapacity	246	2.6	8.9 (8.6, 9.1)	74 (70, 76)	7.8 (7.5, 8.0)	62 (58, 64)	−1.1 (−1.4, −0.9)	−12 (−14, −10)
Current/intention of breastfeeding or pregnant	25	0.3	7.8 (7.1, 8.5)	62 (54, 69)	7.1 (6.5, 7.7)	54 (48, 61)	−0.9 (−1.5, 0.2)	−10 (−17, 2)

Among 9,251 real-world initiators of liraglutide in northern Denmark. Exclusion criteria as present in all LEAD 1–5 studies. CVD, cardiovascular disease; GLD, glucose-lowering drugs. *Last measured HbA_{1c} outside 7–11% (53–97 mmol/mol)/7–11% (53–97 mmol/mol)/7–10% (53–86 mmol/mol) range among patients receiving no/monotherapy/combination noninsulin glucose-lowering drug prescriptions before liraglutide initiation.

after 6 months (12 months in LEAD 3): between −0.8% (−9 mmol/mol) (LEAD 3) and −1.5% (−17 mmol/mol) (LEAD 4). However, our findings also underscore the importance of postmarketing observational studies based on real-world data. Although subsequent RCTs and the current study have established the efficacy of liraglutide in patients ineligible for the LEAD 1–5 trials, safety data are needed for patients with common comorbidities.

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Author Contributions. J.S.K., R.W.T., A.P., and F.K.K. designed the study. J.S.K. reviewed the literature. J.S.K., R.W.T., A.P., and H.T.S. directed the analyses. All authors participated in the discussion and interpretation of the results. J.S.K. organized the writing and wrote the initial draft. All authors critically revised the manuscript for intellectual content and approved the final version. R.W.T. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Paper IV

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RESEARCH LETTER

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Clinical characteristics and glucose-lowering drug utilization among patients initiating liraglutide in Denmark: a routine clinical care prescription study

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Highlights

- This population-based real-world prescription study characterized all new users of liraglutide in northern Denmark from 2009 to 2015.
- More than half (57%) the patients had liraglutide prescribed as part of drug combinations outside the originally approved indications.
- Comorbidities or diabetes complications were present in most patients, with the highest prevalence observed among the 73% of initiators who would have been ineligible for the Liraglutide Effect and Action in Diabetes (LEAD) 1-5 trials that led to liraglutide registration, underscoring the need for further post-marketing studies.

KEYWORDS
cross-sectional studies, diabetes pharmacology, drug utilization, glucagon-like peptide-1 receptor, liraglutide

To the Editor

The number of users of the glucagon-like peptide-1 (GLP-1) receptor agonist (GLP-1RA) liraglutide has grown substantially since its approval in Europe in 2009 and in the US in 2010. Routine clinical care drug users often differ considerably from participants of randomized trials in terms of age, comorbidities, and comedications, factors that may be of importance for a drug's, effect including cardiovascular outcomes, mortality, and risk of adverse events.[1] Thus, there is a need for post-marketing information on the prevalence and extent of comorbidity and off-label drug use among liraglutide users in everyday clinical practice.[2]

1 | METHODS

In this population-based cross-sectional study we linked existing population-based medical databases covering all redeemed prescriptions,[3] laboratory data, and hospital

outpatient and inpatient diagnoses for the 1.8 million inhabitants of northern Denmark, as described in more detail elsewhere.[4] The study cohort included 9251 individuals who initiated liraglutide between 2009 and 2015 and who had lived in northern Denmark continuously during the year prior to initiation. Liraglutide accounts for more than 90% of all GLP-1RA use in Denmark.[2] We first examined each patient's baseline glucose-lowering therapy use in the 100 days before liraglutide initiation. We then examined 100-day post-treatment initiation combinations. Finally, we ascertained diabetes complications and comorbidities present at the time of liraglutide initiation, based on patients' complete histories of drug prescriptions, hospital procedures, diagnoses, and laboratory tests. Patients were stratified based on eligibility (yes/no) to participate in the Liraglutide Effect and Action in Diabetes (LEAD) 1-5 trials (the Phase III trials that liraglutide approval was based upon) using definitions described in more detail elsewhere.[5] When reporting HbA1c and estimated glomerular filtration rate (eGFR), we used the most recent measurement within the 1-year period before liraglutide initiation.

1.1 | Ethics approval

Under Danish law, no ethics approval is required for register-based studies. This project was approved by the Danish Data Protection Agency (File no. 2014-54-0922).

2 | RESULTS

As shown in Figure 1, the most common glucose-lowering drug regimens preceding liraglutide initiation were as follows: metformin in combination with other non-insulin glucose-lowering drugs (34%); metformin + insulin (21%); metformin monotherapy (20%); and insulin monotherapy (9%). After liraglutide initiation, liraglutide was most often used in combination with metformin (40%), followed by metformin plus insulin (23%; Figure 1).

Liraglutide initiators were mostly male (59%) and had a median age of 59 years (interquartile range [IQR] 50-66 years). The median HbA1c before liraglutide initiation was 8.4% (IQR 7.5%-9.5%; Table 1).

More than half the patients (58%) had one or more microvascular complications, including previous hospital-diagnosed retinopathy (26%), neuropathy (7%), hospital-coded renal complications (8%), history of microalbuminuria (more than one positive test; 39%), and/or eGFR ≤60 mL/min per 1.73 m^2 (12%). A proportion of patients (29%) had a history of clinically significant hospital-diagnosed cardiovascular disease, including previous ischemic heart disease (23%), cerebrovascular disease (8%), heart failure (5%), and/or abdominal and/or peripheral vascular disease (11%). In total, comorbidities or complications were present in more than half of all liraglutide initiators, with prevalences much higher in the 73% of initiators who were ineligible for the LEAD trials than among the 27% patients who would have been eligible (macrovascular complications: 41% vs 6%; microvascular

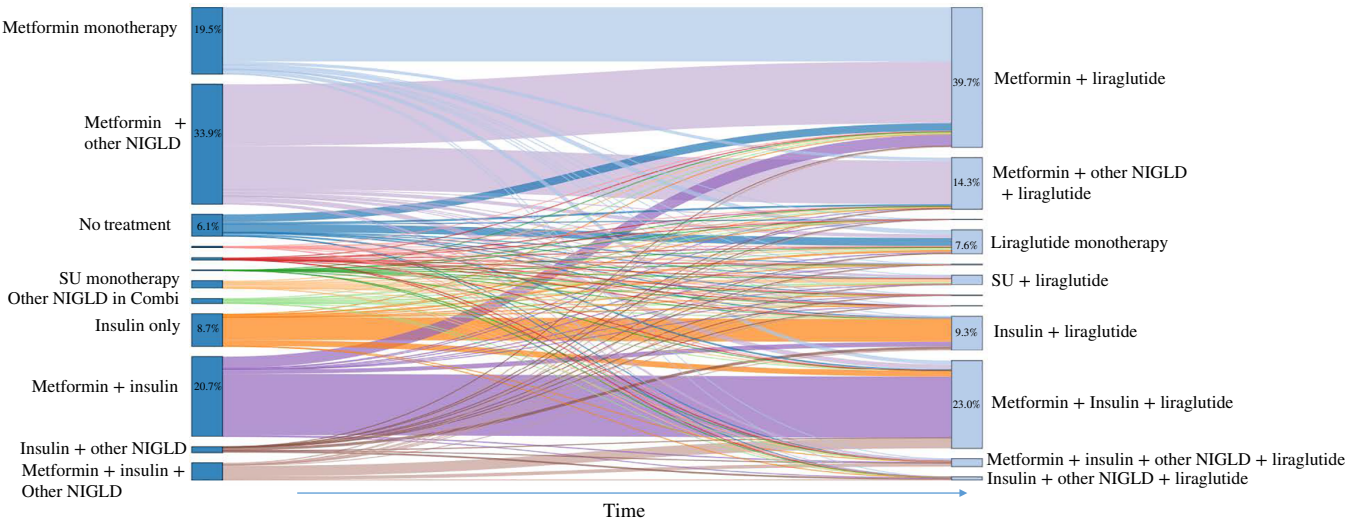

FIGURE 1 Glucose-lowering drugs used 100 days before (left-hand side) and 100 days after (right-hand side) first-time redemption of a liraglutide prescription. Liraglutide initiators most often transitioned from therapy with metformin plus another non-insulin glucose-lowering drug (NIGLD; 33.9%), metformin monotherapy (19.5%), metformin plus insulin (20.7%), insulin monotherapy (8.7%) or no glucose-lowering drug (6.1%). Percentages show the proportion of all patients within different drug groups before (left-hand side) and after (right-hand side) first-time redemption of a liraglutide prescription. DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide-1; SGLT2i: sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea drugs

TABLE 1 Clinical characteristics of 9251 real-world initiators of liraglutide in northern Denmark, 2009 to 2015

	Total	Would have been excluded from LEAD 1-5 trials	Would have been included in LEAD 1-5 trials
Overall	9251 (100)	6768 (73.2)	2483 (26.8)
Sex			
Female	3815 (41.2)	2788 (41.2)	1027 (41.4)
Male	5436 (58.8)	3980 (58.8)	1456 (58.6)
Age (y)			
0-30	134 (1.4)	99 (1.5)	35 (1.4)
31-59	4702 (50.8)	3262 (48.2)	1440 (58.0)
60-69	3106 (33.6)	2354 (34.8)	752 (30.3)
≥ 70	1309 (14.1)	1053 (15.6)	256 (10.3)
Median [IQR] age (y)	59.2 [50.2-66.4]	60.1 [51.1-67.1]	56.8 [48.7-66.4]
Calendar period of liraglutide initiation			
2009-11	4810 (52.0)	3631 (53.6)	1179 (47.5)
2012-13	2571 (27.8)	1828 (27.0)	743 (29.9)
2014-15	1870 (20.2)	1309 (19.3)	561 (22.6)
Baseline HbA1c (%; most recent in past 1 y)			
No measurement	221 (2.4)	170 (2.5)	51 (2.1)
< 6.5	408 (4.4)	408 (6.0)	0 (0)
6.5-6.9	663 (7.2)	649 (9.6)	14 (0.6)
7-7.4	1108 (12.0)	658 (9.7)	450 (18.1)
7.5-7.9	1297 (14.0)	785 (11.6)	512 (20.6)
8-8.9	2357 (25.5)	1544 (22.8)	813 (32.7)
9-9.9	1595 (17.2)	1075 (15.9)	520 (20.9)
≥ 10	1602 (17.3)	1479 (21.9)	123 (5.0)
Median [IQR] HbA1c (%)	8.4 [7.5-9.5]	8.5 [7.4-9.8]	8.2 [7.6-9.0]
Diabetes duration (y)			
< 1	622 (6.7)	484 (7.2)	138 (5.6)
1-<2	534 (5.8)	336 (5.0)	198 (8.0)
2-<3	597 (6.5)	380 (5.6)	217 (8.7)
≥ 3	7498 (81.1)	5568 (82.3)	1930 (77.7)
Macrovascular complications	2898 (31.3)	2752 (40.7)	146 (5.9)
Ischemic heart disease	2127 (23.0)	2001 (29.6)	126 (5.1)
Cerebrovascular disease	736 (8.0)	729 (10.8)	7 (0.3)
Abdominal and peripheral vascular disease	982 (10.6)	966 (14.3)	16 (0.6)
Microvascular complications[a]	5358 (57.9)	4223 (62.4)	1135 (45.7)
Eye complications	2414 (26.1)	1972 (29.1)	442 (17.8)
Neurological complications	657 (7.1)	582 (8.6)	75 (3.0)
Renal	726 (7.8)	646 (9.5)	80 (3.2)
Microalbuminuria[b]	3648 (39.4)	2865 (42.3)	783 (31.5)
eGFR <60 mL/min per 1.73 m^2	1107 (12.0)	994 (14.7)	113 (4.6)
CCI score[c]			
0	5652 (61.1)	3481 (51.4)	2171 (87.4)
1	1909 (20.6)	1697 (25.1)	212 (8.5)

TABLE 1 (Continued)

	Total	Would have been excluded from LEAD 1-5 trials	Would have been included in LEAD 1-5 trials
2	986 (10.7)	903 (13.3)	83 (3.3)
≥ 3	704 (7.6)	687 (10.2)	17 (0.7)
Atrial fibrillation	609 (6.6)	541 (8.0)	68 (2.7)
Hypertension	3614 (39.1)	3019 (44.6)	595 (24.0)
COPD	904 (9.8)	804 (11.9)	100 (4.0)
Renal disease	224 (2.4)	216 (3.2)	8 (0.3)
Rheumatic disease	305 (3.3)	283 (4.2)	22 (0.9)
Osteoarthritis	1520 (16.4)	1172 (17.3)	348 (14.0)
Osteoporosis or fracture	239 (2.6)	206 (3.0)	33 (1.3)
History of infections requiring hospitalization	3640 (39.3)	2952 (43.6)	688 (27.7)
Obesity	2833 (30.6)	2275 (33.6)	558 (22.5)
Mental disorders	3860 (41.7)	3047 (45.0)	813 (32.7)
Thrombocyte aggregation prophylaxis	4339 (46.9)	3527 (52.1)	812 (32.7)
Statins	7228 (78.1)	5320 (78.6)	1908 (76.8)
ACE inhibitors	4385 (47.4)	3265 (48.2)	1120 (45.1)
ARBs	2997 (32.4)	2276 (33.6)	721 (29.0)
Antihypertensive treatment	7567 (81.8)	5677 (83.9)	1890 (76.1)
Marital status			
Unmarried	1490 (16.1)	1054 (15.6)	436 (17.6)
Widowed	651 (7.0)	494 (7.3)	157 (6.3)
Divorced	1371 (14.8)	1058 (15.6)	313 (12.6)
Married	5557 (60.1)	4023 (59.4)	1534 (61.8)
Unknown	182 (2.0)	139 (2.1)	43 (1.7)

Note. Unless indicated otherwise, data are given as n (%). All categories are cross-sectional or retrospective, as appropriate.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LEAD, Liraglutide Effect and Action in Diabetes 1-5 (Phase III trials that liraglutide approval was based upon).

[a]Eye, neurological, or renal.

[b]Two or more positive tests.

[c]The Charlson Comorbidity Index (CCI) includes 19 major disease categories, ascertained from each individual's complete hospital contact history before the date of initial liraglutide treatment. Diabetes was excluded.

complication: 62% vs 46%; conditions in the Charlson comorbidity index: 49% vs 13%; Table 1).

3 | COMMENT

The initial indications for liraglutide approved by the European Medicines Agency in 2009 were: (a) use in combination with metformin or sulfonylurea, among patients with insufficient glycemic control despite a maximum tolerated dose of monotherapy with metformin or sulfonylurea; or (b) use in combination with metformin and a sulfonylurea or metformin and a thiazolidinedione in patients with insufficient glycemic control despite dual therapy.[6] In the present study, between 2009 and 2015, less than half (43%) of the routine clinical care patients initiated liraglutide in accordance with these original indications (see left-hand side of Figure 1), and there was little change during this period. The indication for liraglutide has since been broadened to include treatment in combination with basal insulin (2014) and as monotherapy (2016), covering all drug combinations shown in Figure 1. As seen in Figure 1, virtually no liraglutide plus insulin users during the period 2009 to 2015 were naïve to insulin at the time of liraglutide initiation (ie, liraglutide was used as an add-on to previous insulin treatment, not as cotherapy in tandem with insulin initiation).

In conclusion, we found that liraglutide was initially prescribed off-label for more than half of all liraglutide initiators. Moreover, comorbidities or complications were present

in more than half of all liraglutide initiators, with a distribution skewed towards the 73% of those we previously showed would have been ineligible for the LEAD 1-5 trials.[5] These data are important because the risk of potential adverse drug effects may be higher among multimorbid patients treated in everyday clinical practice, and in those with off-label drug treatment, than what has been observed among patients in randomized trials. Our aim was not to investigate drug safety, and our findings may not necessarily represent an increased risk to treated patients, yet these results underscore the need for further post-marketing observational and safety studies.

DISCLOSURE

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

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

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

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

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

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

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

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

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

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

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

40. Asbestose og kræft i lungehinderne. Danmark 1977-2005. *2008*.

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

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

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64. Martin Majlund Mikkelsen: Risk prediction and prognosis following cardiac surgery: the EuroSCORE and new potential prognostic factors. PhD thesis. *2011*.

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

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117. Clara Reece Medici: Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation. Research year report. *2016*.

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142. Frederikke Schønfeldt Troelsen: Risk and prognosis of primary liver, gallbladder, bile duct, and pancreatic cancer a negative CT scan of the abdomen: A Danish population-based cohort study. Research year report. *2019*.

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