MORTALITY, CAUSES OF DEATH AND END-STAGE RENAL DISEASE IN TYPE 1 DIABETES

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PREFACE

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Summary of the thesis

Background

Type 1 diabetes is one of the most common chronic diseases in children and young adults in Norway. It represents a significant burden to the patients and their families, requiring lifelong treatment with insulin as well as day-to-day monitoring. In addition, type 1 diabetes constitutes a substantial burden to society due to the morbidity and mortality caused by diabetes complications and diabetes associated diseases. In the pre-insulin era death was caused by diabetic coma. Due to the implementation of insulin therapy the cause of death in patients with type 1 diabetes shifted to being dominated by long-term complications, like renal and cardiovascular diseases (CVD). Major advances in treatment of type 1 diabetes have occurred since the 1980s. However, diabetes-related deaths still occur in people with short duration of diabetes, without signs of long-term complications. Few studies have evaluated temporal trends in mortality and causes of death in cohorts diagnosed more recently. In addition, reports on causes of death in cohorts diagnosed in late adolescence and young adulthood with long-term follow-up are scarce. Studies have shown that at this age, adherence to treatment is poorer and the risk of acute diabetic complications higher than during childhood.

The presence of renal disease is recognized as the major predictor of mortality in type 1 diabetes. The incidence of end-stage renal disease (ESRD) among individuals with type 1 diabetes has to our knowledge not previously been evaluated in Norway.

Objectives

The overall objective was to study mortality and causes of death in nationwide, population-based cohorts diagnosed with type 1 diabetes at age <15 years and 15-29 years in Norway. We also aimed to estimate the incidence of ESRD in the cohort diagnosed at age 15-29 years.
**Methods**

Paper I and II were based on data from the nationwide, population-based Norwegian Childhood Diabetes Registry (NCDR), a registry including newly diagnosed individuals with childhood-onset type 1 diabetes (0-14 years). Individuals were diagnosed in 1973-1982 and 1989-2012, and followed from date of diagnosis until date of death, emigration or to September 30, 2013 by linkage to the National Population Register. The diagnosis period was split into three time periods, 1973–1982, 1989–1998 and1999–2012, to assess temporal trends in mortality. We assessed causes of death in two ways, by linking to the nationwide Norwegian Cause of Death Register and by a clinical review committee evaluating medical records, autopsy reports and death certificates. Clinical information was collected from the relevant hospitals and medical offices. We calculated standardized mortality ratios (SMRs) to compare mortality and causes of death with that of the general population.

In paper III, a nationwide, population-based cohort diagnosed with type 1 diabetes at age 15-29 years during 1978-1982 was followed from diagnosis until death, emigration or September 30, 2013. Mortality and causes of death were assessed by the same methods as used in paper I and II. Linkage to the Norwegian Renal Registry (NRR) provided information on whether ESRD was present and on the date renal replacement therapy (RRT) was started. This allowed us to estimate the incidence of ESRD by diabetes duration.

**Results**

Among the 7,884 individuals with childhood-onset diabetes, 249 (3.2%) individuals died during a mean follow-up of 16.8 (range 0.0–40.7) years. Mortality was between three and four times higher than in the general population in Norway, matched for age, sex and calendar year, and was significantly elevated in all age bands. We identified a significantly decreasing trend in cumulative mortality up to 14 years of follow-up over
the study period. The leading cause of death before the age of 30 years was acute complications, after the age of 30 years cardiovascular death was predominant. Mortality due to CVD and violent death was higher in people with type 1 diabetes than in the general population in both sexes combined, but for suicide, only in women. The risk of death from acute complications was approximately half in women compared with men and it did not change with more recent year of diagnosis.

In the cohort diagnosed with type 1 diabetes at age 15-29 years (n=719) and followed for mean 29.6 (range 0.05–35.8) years, 4.6% (33 persons) developed ESRD and 20.6% (148 persons) died. Mortality was between four and five times higher than in the general population in Norway. Mean time from diagnosis of type 1 diabetes to ESRD was almost 24 years. Death was caused by acute or chronic diabetic complications in more than 50% of the cases and by violent death in about 20% of the cases. Death was related to alcohol in 15% of the deceased. Mortality due to CVD was about seven times higher than in the general population and mortality associated with alcohol was between five and ten times higher than in the general population.

Conclusions

Our study demonstrates that in spite of improved diabetes care, people with type 1 diabetes remain at a markedly higher risk of mortality compared with the general population. Both acute and chronic complications caused substantial premature mortality, implying a need for better prevention and treatment of diabetic complications. Mortality has declined among people diagnosed most recently (1999–2012) compared with those diagnosed in the earliest period (1973–1982). However, we observed no decrease in mortality due to diabetes-related causes during the study period. Our study suggests that increased awareness about alcohol-related deaths should be encouraged in clinics providing diabetes care. The cumulative incidence of ESRD was relatively low compared with previous studies assessing the incidence of ESRD in type 1 diabetes cohorts.
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**Disclaimer**

This study has used data from the Norwegian Cause of Death Registry. The interpretation and reporting of these data is the sole responsibility of the authors, and no endorsement by the Norwegian Cause of Death Registry is intended nor should be inferred.
Abbreviations

β-cells  Beta cells
ACEi    Angiotensin-Converting Enzyme inhibitor
ADA     The American Diabetes Association
AHA     The American Heart Association
CVD     Cardiovascular Disease
CHD     Coronary Heart Disease
DCCT    Diabetes Control and Complications Trial
DERI    Diabetes Epidemiology Research International
DKA     Diabetic Ketoacidosis
EDIC    Epidemiology of Diabetes Interventions and Complications
ESRD    End-Stage Renal Disease
EURODIAB PCS  EURODIAB Prospective Complication Study
GP      General Practitioner
GPRD    General Practice Research Database
HbA1c   Hemoglobin A1c
HR      Hazard Ratio
ICD     International Classification of Diseases
IDF     International Diabetes Federation
IHD     Ischemic Heart Disease
MODY    Maturity-Onset Diabetes of the Young
NRR     Norwegian Renal Registry
NCDR    Norwegian Childhood Diabetes Registry
PDR     Proliferative Diabetic Retinopathy
PYR     Person-Years
RRT     Renal Replacement Therapy
SMR     Standardized Mortality Ratio
UK      United Kingdom
UAE     Urinary Albumin Excretion
WHO     World Health Organization
List of publications

Paper I

*Diabetologia.* 2015 Aug; 58(8):1779-86

Paper II


Paper III

Gagnum V, Stene LC, Joner G, Skrivarhaug T: Long-term Mortality and End-Stage Renal Disease in a Type 1 Diabetes Population Diagnosed at Age 15-29 Years in Norway.  
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INTRODUCTION

Historical perspective
The polyuric state of diabetes was described in an Egyptian papyrus dating from 1550 BC. However, a clearly recognizable description of type 1 diabetes was given for the first time by Araetus of Cappodocia in the second century AD; he was the first to use the term "diabetes”, which comes from Greek and means "to pass through". The sweetness of the diabetic urine was probably recognized for the first time by two Indian physicians in 400-500 BC, they also associated one type of diabetes with youth and another with obesity. The term "mellitus" or "from honey" was added later on because of the sweet taste of the urine (1). The discovery of insulin in 1922 was one of the greatest medical breakthroughs in history and led to dramatic improvement in life expectancy of patients with type 1 diabetes.

Etiology of diabetes
Diabetes mellitus is a complex metabolic disorder of multiple etiologies, but can broadly be grouped into two main entities: type 1 diabetes and type 2 diabetes. The etiology of type 1 diabetes is multifactorial. There is clear evidence of genetic susceptibility and environmental factors triggering an autoimmune destruction of the beta cells (β-cells), leading to absolute insulin deficiency (2-4). The environmental triggers (for example nutritional or infective) initiating the pancreatic β-cell destruction remain largely unknown, but the process usually begins long before the manifestation of clinical symptoms (5). Type 2 diabetes may range from predominantly insulin resistance to a predominantly secretory defect with or without insulin resistance (6). Although the etiology of and risk factors for type 1 and type 2 diabetes are quite different, both result in chronic hyperglycemia leading to long-term complications like nephropathy, retinopathy, neuropathy and CVD. Diabetes also occurs as a result of specific genetic defects in the β-cell function. The best known of the defects in the insulin secretion is the maturity-onset diabetes of the young (MODY)-family, a group of autosomal dominant inherited disorders characterized by
hyperglycemia at an early age (7). Diabetes can also develop secondary to other conditions such as infections, diseases of the endocrine pancreas, or it might be drug induced. Type 1 diabetes accounts for more than 95% of childhood-onset diabetes in Norway (8).

Incidence of type 1 diabetes
According to the International Diabetes Federation (IDF) there are large differences worldwide in the incidence of childhood-onset (<15 years) diabetes, estimates are displayed in figure 1. Approximately 86,000 children under 15 years of age develop type 1 diabetes annually (9). Norway has the fourth highest incidence of childhood-onset diabetes in the world, after Finland, Sweden and Kuwait (9-11). The incidence of type 1 diabetes diagnosed before 15 years of age has increased in most studied populations over the past two to three decades (10, 12, 13). However, trends from Sweden and Finland have indicated that the incidence may have leveled off in the past years (14, 15). In Norway the incidence rate of type 1 diabetes among children (<15 years) was stable at about 33 per 100,000 person-years during 2004–2012 (16), although the estimate was higher in 2015, 36.5 per 100,000 person-years (8). Recent data from EURODIAB concerning the incidence trends of childhood-onset type 1 diabetes during 1989-2013 indicated a continued rise up to 2013. The rate of increase was highest in low-incidence countries (17).
Treatment and monitoring of type 1 diabetes

When insulin was introduced in 1922 it completely changed the lives of patients with type 1 diabetes. Since then there have been many improvements in diabetes care. The 1970s and 1980s marked a turning point in the treatment of diabetes. Innovations such as blood glucose readers and strips measuring blood glucose revolutionized the management of diabetes and facilitated self-management. New types of insulin have been developed and there have been major technological improvements like more user-friendly insulin pens, insulin pumps and continuous glucose monitoring. In 1968, an American scientist discovered that sugar attached to hemoglobin could be used to determine how well the blood glucose had been controlled in the previous two to three months. This discovery led to the creation of the glycated hemoglobin (A1C) test. During the last decades Hemoglobin A1c (HbA1c) measurements have played an important role in assessing glycemic levels (18, 19). Repeated monitoring of HbA1c about every third month is recommended as part of the patients continuing diabetes care to see whether an optimal metabolic control is achieved (20). Pirart, a Belgian doctor, was the first to describe the relationship between hyperglycemia and
microvascular complications. In the period 1947-1973 he divided more than 4,000 patients into groups based on their level of blood glucose control, he observed more complications in patients with poor glycemic control (21). The Oslo study (22-24), the Stockholm study (25) and the Diabetes Control and Complications Trial (DCCT) (26) showed that maintaining the blood glucose level close to normal, delayed and slowed the onset of chronic diabetic complications. Modern intensive insulin therapy has become the standard of care in Norway, consisting of either multiple daily injections or continuous subcutaneous insulin infusion by insulin pumps. The proportion using insulin pumps among children with type 1 diabetes in Norway has increased from 9% in 2001 to 72% in 2015 (8). During the last decades there have also been large improvements in treating comorbidities and complications of diabetes. Monitoring of albumin secretion in the urine is an important tool for evaluating microvascular complications in diabetes. If microalbuminuria is detected Angiotensin-converting enzyme inhibitors (ACEi) are recommended regardless of blood pressure (27-29). Prevention and treatment of CVD are critical issues in diabetes care, as outlined in consensus guidelines (30). Whether modern diabetes management has resulted in lower mortality in type 1 diabetes needs to be explored further.

Complications of type 1 diabetes

Type 1 diabetes is a progressive chronic disease with multiple complications, including premature death. Long-term complications consist of both microvascular and macrovascular complications (31).

Microvascular complications

The microvascular complications mainly affect the eyes, the kidneys, the peripheral and the autonomic nervous system, resulting in retinopathy, nephropathy and neuropathy, all representing clinical hallmarks of type 1 diabetes (figure 2) (32).
Diabetic retinopathy is the most common microvascular complication. A study of retinopathy starting in 1980–1982, examined the prevalence of retinopathy in people diagnosed with diabetes <30 years of age and on insulin within 1 years of diagnosis (33). After 15 years 98% had developed background retinopathy, the earliest clinical signs of diabetic retinopathy including microaneurysms, small outpouchings from retinal capillaries, and dot intraretinal hemorrhages. After 35 years 62% had developed proliferative diabetic retinopathy (PDR), involving the formation of new blood vessels that develop from the retinal circulation. Improved diabetes care has been associated with a reduction in PDR. At 20 years’ diabetes duration, type 1 patients examined in 2007–2011 had less PDR than type 1 patients examined 1980–1996: 18 vs. 43% (34). The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemic control conferred a significant risk reduction for microvascular complications compared with conventional treatment (26). After completion of the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients. The EDIC-study demonstrated that there was a memory effect of improved glycemic control (35)

Diabetic nephropathy and end-stage renal disease
Diabetic nephropathy is one of the most severe complications of type 1 diabetes and occurs as a result of microvascular lesions in the renal glomeruli. It is recognized as the major predictor of premature death (36-38). The FinneDiane study, including 4,201 adults with type 1 diabetes, showed that the risk of premature death increased with more severe kidney status (38), figure 3. Microalbuminuria was defined by a urinary albumin excretion (UAE) of 20–200 µg/min, macroalbuminuria by a UAE >200 µg/min, and normoalbuminuria by a UAE <20 µg/min in two of three consecutive urine collections.
The natural history of diabetic nephropathy progresses from normoalbuminuria, through a subclinical stage of microalbuminuria, to overt proteinuria and eventually ESRD. At 20 years’ duration of type 1 diabetes about one third have developed microalbuminuria and approximately 15-25% have developed persistent proteinuria (37, 39-41). Diabetic nephropathy is the main cause of ESRD in the western countries (42). In Norway, 32% of all incident cases with ESRD registered in the NRR in 2015 was noted with the diagnosis diabetes (43).

There are publications on the incidence of ESRD in type 1 diabetes reported from several countries. In the United States, the cumulative incidence of ESRD was 14.2% at 25 years diabetes duration for patients diagnosed with type 1 diabetes in 1965-1979 (44). Another study from the United States showed that the cumulative incidence of ESRD at 25 years diabetes duration was 9.3% in patients diagnosed with type 1
diabetes during 1970-1980 (45). The same study showed that the incidence was reduced by 70% compared with those diagnosed during 1922-1969. The lower incidence of ESRD observed in those diagnosed with type 1 diabetes more recently was explained by improvements in glycemic and blood pressure control during the last decades. In Finland, the cumulative incidence of ESRD was 7.8% at 30 years diabetes duration for patients diagnosed with type 1 diabetes between 1965 and 1999, the incidence was lower in patients diagnosed in more recent years (46). In a Swedish cohort diagnosed with type 1 diabetes between 1977 and 1995, the cumulative incidence of ESRD was lower, being 3.2-5.3% at 30 years (47). Declining incidence of ESRD by increasing year of diagnosis has been reported in several studies comparing the incidence in older cohorts with the incidence in newer cohorts (44, 46-48). These results are in line with the improvements in diabetes care, including the renoprotective treatment with ACEi. A report from Norway showed that the incidence of diabetic nephropathy in Norway was low, 7.8% in a population with duration of type 1 diabetes between 19 and 30 years (49). The incidence of ESRD among patients with type 1 diabetes in Norway has, to our knowledge, not been assessed before.

**Macrovascular complications**

Macrovascular complications consist of peripheral artery disease (PAD), coronary heart disease (CHD) and cerebrovascular disease, all caused by atherosclerosis in the arteries. Unlike microvascular complications, which are unique to diabetes mellitus, diabetic cardiovascular disorders are clinically similar to CVD in people without diabetes mellitus. However, mortality and morbidity due to CVD are markedly increased in individuals with type 1 diabetes compared with the general population (50). A study of the large United Kingdom (UK) General Practice Research Database (GPRD), comprising data from >7,400 patients with type 1 diabetes with a mean (±SD) age of 33 (± 14.5) years and a mean diabetes duration of 15 (±12) years showed that cardiovascular events occurred on average 10 to 15 years earlier than in matched non-diabetic control subjects (51). The majority of individuals with long-standing type 1 diabetes will develop one or more of these major complications, many of which
cause or contribute to premature death (52). However, in the EDIC-study, the effect of intensive therapy showed a reduction in CVD by 50% in the previously intensively treated group compared with the control group during a mean follow-up of 17 years (35).

Inflammation is a central pathological process of atherosclerosis (53), it is suggested that inflammation is more predominant in patients with type 1 diabetes (54). Elevated inflammatory markers in patients with type 1 diabetes have been associated with an atherogenic lipid profile (55) and with microvascular complications and CVD (56), this may contribute to accelerated atherosclerosis in youth with type 1 diabetes. It has been shown that atherosclerosis starts in childhood and adolescence (57, 58). In all patients the clinical presentation of CHD is very late in the pathophysiological process of atherosclerosis. However, cardiovascular events occur earlier in patients with type 1 diabetes than in the general population, often two decades after the diagnosis of type 1 diabetes, which in some patients may be by age 30 years (59). A family history of type 2 diabetes, early CVD, lipid disturbances and hypertension are independent predictors of carotid intima–media thickness in young patients (<32 years) with type 1 diabetes, and could therefore predispose these patients to atherosclerosis (60). A review by the American Diabetes Association (ADA) and the American Heart Association (AHA) presenting a scientific statement concerning CVD in type 1 diabetes, concluded that important targets for risk reduction include hypertension, proteinuria, obesity, HbA1c, lipid levels, and smoking (61). High rates of cardiovascular risk factors have been documented in children and adolescence in Norway (62). However, the prevalence of smoking was much lower in Norway than what has been reported from Germany and the United States (63, 64). We also know that the prevalence of smoking among Norwegian patients above 15 years of age fell from 18% in 2001 to 5% in 2005 (65). It has been suggested that type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality (66).
Nephropathy may also influence the timing of cardiovascular events. Historical data suggest that CHD and PAD followed the development of overt nephropathy, which increased the risk of CVD many times (67). However, the decline in kidney disease in patients with type 1 diabetes by 60% in the past several decades has not been accompanied by a corresponding fall in rates of CVD (48). The AHA and ADA review argue that this suggests that other factors contribute to CVD events (68).

Acute complications
Diabetic ketoacidosis (DKA) and severe hypoglycemia are major life-threatening acute complications of type 1 diabetes associated with insufficient or excessive insulin treatment, respectively. Both are, in theory, preventable. The risk of DKA in patients with established type 1 diabetes is 1-15/100 person-years (69-73). The most recent numbers from the NCDR showed that the risk of DKA was 3% in 2015 (8). The risk is higher in children with inferior glycemic control or previous episodes of DKA, peripubertal and adolescent girls, patients with psychiatric disorders, and those with difficult family circumstances (including lower socioeconomic status and lack of appropriate health insurance) (74). Reports from the United States, Germany and Austria have shown annual incidence of severe hypoglycemia at 15-19/100 person-years (70, 75). Low HbA1c has become a minor risk factor for severe hypoglycemia in those diagnosed during 2004-2012 compared with those diagnosed during 1995-2003 (75). The frequency of severe hypoglycemia was reduced by half between 2008 and 2013, reported in a large Danish registry (76). In a Norwegian study including 3,299 individuals, the incidence of severe hypoglycemia decreased significantly from 14.4 to 4.2/100 person-years between 2001 and 2013 (77).
Mortality

The prognosis of type 1 diabetes is strongly dependent on the methods available for its diagnosis and treatment and has therefore changed dramatically over the last century and between different countries across the world. Before the introduction of insulin therapy, individuals with type 1 diabetes died within months after the onset of symptoms (78). Early studies of type 1 diabetes showed a major reduction in mortality during the decades after insulin was introduced. As demonstrated by the Joslin Clinic in the United States, mortality rates declined substantially during this period, mortality rates were 360-824/1,000 person-years in 1897-1914, 61-75/1,000 in 1922-1926 and 1.0-14.4/1,000 in 1950-1961, in the age range 10-30 years (78). In Norway, Westlund registered mortality among 3,832 patients discharged for the first time with diabetes diagnosis in Oslo during the years 1925-1955. Patients were traced to death or to the year 1961. 2,677 deaths were recorded. Mortality rates up to 30 years of age were 38/1,000 person years in 1925-1940, 13/1,000 in 1941-1959, and 9/1,000 in 1951-1961. The distribution of causes of death shifted from mostly acute complications in the 1920s and 1930s to being dominated by renal and cardiovascular complications after the 1940s (79, 80). Several large, population-based studies in different parts of the world have given important knowledge concerning the mortality in people with type 1 diabetes. The excess mortality in childhood-/adolescent-diagnosed type 1 diabetes, based on a systematic review, is displayed in figure 4 (81). The review observed a significant 5 % reduction in mortality for each 1-year increase in the mid-year of study follow-up. Results from mortality studies until the initiation of the work with this thesis will be discussed in the introduction, while some of most recent studies (81-88) will be discussed in the general discussion section.
Figure 4 SMR (log scale) and mid-year of study follow-up with fitted negative binomial regression (81). Reproduced with permission from Springer.
European data on early mortality in childhood-onset (<15 years) type 1 diabetes in the EURODIAB registers from 12 countries (n=28,887) was reported by Patterson et al. The overall SMR was 2.0, varying from 0 to 4.7 between countries, showing little relationship with the incidence rate or the gross domestic product. One-third of deaths were directly attributable to diabetes, and DKA was mentioned in the majority of such deaths (89).

The EURODIAB Prospective Complication Study (The EURODIAB PCS) is a clinic-based prospective cohort study that examined 3,250 type 1 diabetes patients between 1989 and 1991. Data from EURODIAB PCS have given important information on risk factors for morbidity and mortality in type 1 diabetes (90-92). Participants were aged between 15 and 60 years and were recruited from 31 centers in 16 European countries. Type 1 diabetes was defined as diabetes diagnosed before age 36 years with a continuous need for insulin within one year of diagnosis. Important risk factors for all-cause mortality were age, waist-to-hip ratio, pulse pressure, and non-HDL cholesterol. All microvascular complications were especially strong risk markers for mortality (90).

The British Diabetic Association Cohort Study provided detailed all-cause and cause-specific mortality rates by sex and attained age. The cohort consisted of 23,752 individuals with type 1 diabetes diagnosed before 30 years of age, identified during 1972-1993 and followed up to 1997. The authors reported all-cause mortality rates in patients with diabetes to exceed those in the general population at all ages; SMR was 4.0 in women and 2.7 in men (93). Acute diabetic complication was the greatest single cause of death under the age of 30 years, while CVD was responsible for the greatest proportion of deaths from the age of 30 years and onwards (94). The risk of cerebrovascular mortality was raised at all ages (95) and death due to Ischemic Heart Disease (IHD) was especially high in young adult women (50). Mortality data from the UK has also been reported from the UK GPRD. Five sex- and age-matched control
subjects were selected (n=38,518) for each individual with type 1 diabetes (n=7,713). They confirmed that increased mortality rates in individuals with type 1 diabetes were apparent across all age-bands (overall-hazard ratio [HR] 4.5). They also found high absolute and relative risks of CVD, and greater relative risks in women than men compared with those without diabetes (51, 96).

The Diabetes Epidemiology Research International (DERI) mortality study is an ongoing follow-up study launched in 1986 to examine mortality in four population-based cohorts in Finland (n=5,146), Japan (n=1,428), the United States (the Allegheny cohort, n=1,075) and Israel (n=681). DERI has given comparable data from countries that differ in the incidence of type 1 diabetes. All patients included were diagnosed in 1965-1979, at age < 18 years and treated with insulin from diagnosis. The causes of death were determined by reviewing death certificates, medical records and autopsy reports. The DERI-group showed that mortality in Japan was much higher than in the other countries, mainly due to diabetes-related complications and renal disease (97). Diabetes contributed to death in 96% of deaths in Japan, 83% in Israel, 75% in the United States and 64% in Finland (97). Another large study, using several registries showed a large geographic variation in mortality ratios, for example, individuals in Bulgaria were 10 times more likely to die than those in Norway prior to the age of 25 years. Mortality rates were highest in Japan, Russia and Eastern Europe (98). In 2003 Asao el al. reported mortality data from Finland and Japan, SMR was 3.7 and 12.9, respectively. They showed dramatic improvements in mortality in Japan, and a temporal trend of lower absolute and relative mortality rates for those diagnosed in the 1970s rather than the 1960s (99). More recently both all-cause and cause-specific mortality has been reported from the Allegheny County Type 1 Diabetes Registry, which has been part of the DERI-study. They showed improved survival in more recently diagnosed cohorts (1975-1979), but there was still a major excess mortality compared with the general population (SMR 5.6) (100). After 20 years duration of diabetes, more than 70% of all deaths were due to long-term complications (59).
In Norway, mortality in people with type 1 diabetes was reported for the first time by Joner & Patrick in a nationwide, population-based cohort in 1991 (101). The cohort consisted of individuals with childhood-onset type 1 diabetes, diagnosed in 1973-1982 and maximum follow-up of 15.5 years; the overall mortality rate was 1.1/1,000 person-years and SMR 2.2. In 2003, causes of death were assessed in the same cohort, but with longer duration of diabetes (mean diabetes duration of 24 years). The overall mortality rate was 2.2/1,000 person-years and SMR 4.0 (102). In that study a clinical review committee concluded on the causes of death. There have been major advances in the management of type 1 diabetes since the 1970s, but recent data on the long-time effect on all-cause and cause-specific mortality does not exist in Norway.

Researchers from the Steno Diabetes Center in Copenhagen, Denmark have several publications on long-term follow-up of individuals with type 1 diabetes (52, 103, 104). In a study (n=2,930) assessing the influence of calendar year of diagnosis on mortality, they showed that the prognosis for patients with type 1 diabetes improved by 30-40% during the diagnosis period 1933-1972. They also showed that time since diagnosis was the major determinant of relative mortality, increasing until 20 years after diagnosis, thereafter declining (105). In a study assessing the effect of proteinuria on mortality they found that the relative mortality was extremely high in individuals with persistent proteinuria, SMR peaked at about 100 at age 35 years. Those who did not develop proteinuria had a relatively low SMR of about 2 (36). More recently a Danish study assessing time trends in mortality among 4,821 patients with type 1 diabetes from 2002-2011 showed that mortality rates were greater in patients with type 1 diabetes than in those without diabetes (106). Further, the mortality rate decreased faster in individuals with type 1 diabetes compared with that of the background population. Nephropathy was identified as the main driver of the excess mortality.

In Sweden, several population-based studies have assessed mortality in cohorts with type 1 diabetes. Short-term mortality in 3,228 patients with childhood-onset diabetes
was reported to be very low (only 10 deaths), however still about twice as high as in the general population (107). In another population-based study with maximum duration of type 1 diabetes of 13.5 years they identified a high frequency of unexplained deaths in bed (108). Dahlquist et al. explored this further, they compared five non-diabetic control subjects matched for sex, age and year of death with deceased type 1 diabetes cases and identified a very large proportion of unexplained deaths in the cohort with type 1 diabetes (109). Mortality studies in cohorts with age at diagnosis 15-34 years reported approximately double risk of mortality in type 1 diabetes cases compared with the general population. Hypoglycemia and ketoacidosis played a relatively small role compared with the impact from social and mental dysfunction, and from careless use of alcohol or drugs (110-112), emphasizing the role of socioeconomic factors in diabetes care.

In Finland, a large population-based cohort including patients diagnosed with type 1 diabetes before 30 years of age between 1970 and 1999 (n=17,306) was followed to the end of 2007. The overall SMR was 3.6 in the early-onset (0-14 years) cohort and 2.8 in the late-onset (15-29 years) cohort. They reported improved survival over time in patients with early-onset type 1 diabetes, while survival in patients with late-onset type 1 diabetes had deteriorated since the 1980s (113). IHD-specific mortality was explored in the same population, the results showed that the risk of mortality due to IHD was exceptionally high in women with early-onset type 1 diabetes compared with women in the background population (21.6 [95% CI 17.2–27.0])

In many countries in the world mortality among children with type 1 diabetes is largely unknown. It is believed that many cases remain undiagnosed and that the deaths are attributed to malaria, gastroenteritis or other infections (97). 41% of individuals with Insulin-Dependent Diabetes Mellitus (IDDM) died within five years in a study from Tanzania, and half of these deaths were attributed to ketoacidosis (114). A systematic literature review of papers published on epidemiology and public health implications of diabetes in Sub-Saharan Africa during 1999-2011, reported five-year mortality proportions in patients with diabetes between 4% and 57% (115).
Barriers to accessing diagnosis and treatment included lack of diagnostic tools, glucose monitoring equipment and high cost of diabetes treatment. Insulin was unaffordable in many cases and the supply was irregular.

**Causes of death**

*Mortality due to acute diabetic complications*
Ideally, near normal survival should be expected before the onset of long-term complications. However, the excess mortality seen in people with diabetes dying before age 30 years is mainly explained by acute diabetic complications (59, 94, 102). A Finnish study assessed time trends in mortality and found mortality due to acute complications to increase significantly during follow-up in individuals diagnosed at age 15-29 years, while there was a non-significant tendency to increase in those diagnosed at age 0-14 (113). Most studies using register data to examine causes of death do not distinguish between DKA and hypoglycemia, as these are both noted as “diabetic coma” in the International Classification of Diseases (ICD). However, some studies look closer at the cause of acute complications and report mortality due to DKA at higher rates than hypoglycemia (89, 102, 116, 117), although not all studies are consistent (118).

*Mortality due to long-term diabetic complications*
The Steno Diabetes Center reported cause-specific mortality in individuals diagnosed with type 1 diabetes (age <30) before 1943 and followed until 1984. They aimed to identify factors of prognostic value by comparing patients dying within 35 years of diagnosis of diabetes with patients surviving for 40 years or more. Among patients surviving for more than 40 years 53% had no major complications (52). Among deaths within 35 years after diagnosis of diabetes, more than 50% were due to renal disease, compared with only 5% of the deaths after 40 years duration. Deaths from CVD showed an opposite trend (52). In contrast, Secrest et al. found that renal disease was the underlying cause of death in only 17% of deaths before 35 years diabetes duration.
in the Allegheny County Type 1 Diabetes Registry, diagnosed during 1965-1979 (59). Fewer renal deaths are probably the result of major improvements in the treatment of type 1 diabetes and renal failure. Long-term follow-up of the participants in the DCCT/EDIC have shown a reduction in CVD associated with intensive diabetes therapy (35). A large Scottish registry linkage study (n=19,000) compared patients with type 1 diabetes with the non-diabetic general population. They reported a decline in the relative risks for CVD and total mortality associated with type 1 diabetes. However, type 1 diabetes continued to be associated with higher CVD and death rates than the non-diabetic population (119).

Violent death
Violent death, including accidents, intoxications and suicides, is a frequent cause of death in young people. It is well known that hypoglycemia affects the cognitive functions (120), this may result in higher risk of accidents. A higher risk of traffic incidents in individuals with type 1 diabetes is suggested by some, but not all studies (121-124). In a prospective study from the United States as many as 52% of the drivers with type 1 diabetes reported at least one hypoglycemia-related mishap over a 12 months period (125). However, in a Swedish population-based case-control study, mortality due to traffic accidents was comparable to that seen in the general population (109). A recent review article reported higher risk of violent death in individuals with type 1 diabetes compared with the general population (SMR; 2.5 [1.7-3.9] in women and 1.8 [1.3-2.5] in men) (87). Further, another systematic review looking specifically at the risk of suicide in people with type 1 diabetes indicated increased risk of suicides, although there was no clear consensus regarding the level of the increased risk (126). A population-based study has reported higher risk of psychiatric disorders in children and adolescents with type 1 diabetes (127). This may indicate that the psychological burden of living with a chronic disease is substantial.
**Sudden, unexpected death**

In 1991 a report on sudden, unexplained deaths was published (128). In total 22 young (12-43 years old) and apparently healthy people with type 1 diabetes were found dead in their beds. Among the 22 deceased individuals, 20 were found in an undisturbed bed, without signs of sweating or terminal struggle, and no clear cause of death was identified on autopsy. This particular type of sudden death is referred to as the “dead in bed syndrome”. Information on this syndrome have later been published in several countries; Norway (129), Sweden (109), Denmark (130), the UK (116), the United States (131), Canada (132) and Australia (133). Two studies have reported that sudden, unexpected deaths occur in > 20% of all deaths among patients with type 1 diabetes younger than 50 years, compared to 1-5% in a matched general population (109, 133). The “dead in bed syndrome” and sudden unexpected death can appear as much as 10 times as often in type 1 diabetes compared with the general population. Higher risk in men and in those with inferior metabolic control is suggested (131). The exact cause of the “dead in bed syndrome” is unknown. Hypoglycemia and cardiac autonomic dysfunction are implied as predisposing factors. Studies have demonstrated prolonged QTc (QT interval corrected for heart rate)-interval during hypoglycemia (both induced and spontaneous) among people with type 1 diabetes and with both normal and impaired cardiac autonomic function (134-138). Long-standing type 1 diabetes may lead to reduced parasympathetic activity and increased sympathetic activity, which could result in increased susceptibility to ventricular arrhythmias (139, 140). In addition, many people with duration of diabetes more than 10 years have hypoglycemia associated autonomic failure, signifying that glucagon and adrenaline are not secreted adequately in response to hypoglycemia and thereby prolonging hypoglycemic episodes (141).
Classification of causes of death

When assessing causes of death, the death certificate and the ICD-codes are of great importance. Some studies have assessed the validity of the causes of death noted on the death certificates by using additional clinical notes and autopsy reports. In 1976 a Swedish study used the Swedish Twin Registry to validate cause-of-death certification in 1,156 deaths. They concluded that Swedish death certificate data was fairly valid with regard to cancer, cerebrovascular disease, IHD and respiratory diseases, but not for diabetes mellitus (142). Mühlhauser et al. compared different methods of determining the causes of death in a cohort with type 1 diabetes; determined by a clinical review committee, by the information on the death certificates, and by the ICD-codes. Only 1 of 4 deaths due to hypoglycemia and 4 of 7 deaths due to DKA were reported on the death certificates. However, the review committee agreed with what was noted on the death certificates in cases when myocardial infarction, stroke and accidents were the underlying causes of death. The authors concluded that death certificates alone are not reliable when reporting the actual causes of death in individuals with type 1 diabetes (143). The ability of physicians to complete death certificates accurately was evaluated by Messite et al. in a study from the United States. In that study the correct cause of death was identified in only 50-60% of the cases and there was a substantial underreporting of mortality from both circulatory diseases and diabetes (144). These studies underscores the importance of assessing causes of death in type 1 diabetes in greater detail than what is possible just from considering the death certificates and ICD-codes. Population-based studies using a clinical review committee to determine the causes of death probably provide more reliable cause-specific morality rates. This is important in order to explore details concerning the premature mortality existing in patients with type 1 diabetes.
AIMS OF THE STUDY

The overall objective of this thesis was to characterize mortality and causes of death in nationwide, population-based cohorts with type 1 diabetes:

- In childhood-onset (<15 years) type 1 diabetes diagnosed in 1973-1982 and 1989-2012 (Paper I and II)
- In Type 1 diabetes diagnosed at age 15 and 29 years in 1978-1982 (Paper III)

The specific aims were:

- To determine mortality in individuals with type 1 diabetes diagnosed at age <15 years and 15-29 years by diabetes duration and sex (Paper I and III).

- To characterize the causes of death in individuals with type 1 diabetes diagnosed at age < 15 years and 15-29 years (Paper II and III).

- To explore time trends in mortality and causes of death in childhood-onset type 1 diabetes diagnosed between 1973 and 2012 (Paper I and II).

- To compare all-cause and cause-specific mortality in type 1 diabetes with the general Norwegian population, matched for age, sex and calendar year (Paper I, II and III).

- To estimate the incidence of ESRD by diabetes duration in a cohort with approximately 30 years duration of type 1 diabetes (Paper III).
MATERIALS AND METHODS

Data sources

Study population
Paper I and II are based on data from the NCDR, a population-based, nationwide registry including all new-onset cases of childhood-onset (0-14 years) diabetes in Norway (10, 16, 145). The study population consisted of two nationwide cohorts diagnosed during 1973-1982 and 1989-2012 (n=7,884). Individuals diagnosed during 1973-1982 were registered retrospectively by Joner et al. in 1978 (1973-1977) and 1984 (1978-1982), using identical methods for the two 5-year periods (145). Briefly, a questionnaire was sent to all medical and pediatric departments in Norway. All 19 pediatric departments and 60 out of 63 medical departments responded. The hospitals reported all new cases of diabetes mellitus in the age groups <15 years. All the reported hospital cases were on insulin treatment when leaving the hospital, the assumption was made that the large majority had type 1 diabetes. Data was also collected from The National Insurance Institution since young persons with diabetes mellitus were entitled to a basic allowance as a compensation for their diet expenses. The completeness of ascertainment in this cohort with childhood-onset (<15 years) diabetes was estimated to more than 98% (146). In Norway nearly all children diagnosed with type 1 diabetes are referred and treated in hospital pediatric departments. Since 1989 all pediatric departments have reported newly diagnosed cases prospectively. The completeness of ascertainment in the NCDR has been estimated to 91% in the period 2005-2008 (16). Between 1983 and 1988 data was not collected nationwide, individuals diagnosed during this period were therefore not included in the study. Individuals registered with the diagnosis type 2 diabetes or monogenic diabetes in the NCDR were not included in the study. Type 2 diabetes diagnosed at age 0-14 years is rare in Norway, according to data from the NCDR, patients with type 2 diabetes represent less than 1% of children and adolescents treated in pediatric departments (8). Since 2002, patients in the NCDR have been screened for monogenic diabetes. Monogenic diabetes accounts for less than 2% of patients in this age group (147). The study population, consisting of 7,897 individuals, was linked to
the National Population Register, 13 individuals were not matched for follow-up due to missing data or error in identification. In paper II we excluded additional six individuals because it was discovered from medical records that they did not have type 1 diabetes (three with Cystic Fibrosis, two with Downs syndrome and one with another syndrome in which diabetes was considered secondary). All of these individuals were diagnosed in 1973-1982. We also excluded individuals diagnosed before six months of age (n=7) because we did not want to include those with possibly transient neonatal diabetes. After these exclusions, the study population consisted of 7,871 individuals with type 1 diabetes (figure 5). Causes of death have previously been reported in the cohort diagnosed during 1973-1982 (102), however in this study the cohort was followed until September 30, 2013 (82 new deaths). Causes of death among individuals diagnosed during 1989-2012 have not been examined in detail before.

Figure 5 Flow chart showing the cases that were excluded from the study population with childhood-onset diabetes diagnosed in 1973-1982 and 1989-2012 during the study (paper I and II).
In paper III the cohort was population-based and nationwide, consisting of individuals diagnosed with type 1 diabetes at age 15 to 29 years, during 1978-1982 (n=719). The cohort was initially collected retrospectively in 1988-1990 by the same method as described above (146). The completeness of ascertainment in the cohort, based on two independent sources (the National Insurance Institution and hospital records), was estimated to 87.8% (146). The quality of the data, initially retrieved before 1991, has subsequently been enhanced by linkage to additional sources of information and quality assurance procedures in the NCDR. The cohort consisted of 784 cases in 1991, but was reduced to 719 cases during this process (figure 6).

![Flow chart showing the original cohort with age at diagnosis 15-29 years and the cleaning process that reduced the cohort to the 719 followed in paper III.](image)

Both those with diabetes diagnosed before age 15 years and those diagnosed between age 15 and 29 years represented quite homogenous populations of almost exclusively ethnic Norwegians with good access to a public health care system. The Norwegian health care system is inexpensive for the patient and insulin is free of cost.
Health Registries

Norway has excellent nationwide population-based registries giving unique possibilities to do large-scale epidemiological research. Data was retrieved from four nationwide, population-based registries (figure 7). We performed linking of registries using the unique national personal identification number assigned to all inhabitants in Norway. Individuals were followed from date of diagnosis to date of death, emigration or September 30, 2013, and in paper III also to date of ESRD.

The Norwegian Childhood Diabetes Registry

The National Population Registry
- Alive, dead, emigrated
- Date of death and emigration

The Norwegian Cause of Death Registry
- Causes of death

The Norwegian Renal Registry
- ESRD
- Date of ESRD

Figure 7 Illustration of the registry linkage of the NCDR to three national registries using the unique personal identification number

The Norwegian Childhood Diabetes Registry

NCDR was established in 2006 by merging of two research registries, The Norwegian Diabetes Registry and The Norwegian Childhood Diabetes and Quality project. The population-based Norwegian Diabetes Registry was established in 1989 and all incident cases of diabetes diagnosed before 18 years of age were registered. The
NCDR is a prospective, population-based, nationwide registry that systematically registers all incident cases of childhood-onset diabetes, and monitors certain quality indicators of diabetes care in children and adolescents. NCDR includes data on childhood-onset diabetes since 1973, and diabetes care outcome since 2001. Signed consent is obtained from each patient and/or the parents, before the patient is registered, less than 1% refuses to sign. NCDR was founded with the objectives to improve the diagnostics, classifications and treatment of childhood-onset diabetes, surveillance of incidence of diabetes in children and adolescents, surveillance of quality of diabetes care in Norwegian pediatric departments, and to stimulate to research in diabetes (148).

The National Population Registry

The National Population Registry contains important information concerning everyone who either is or has been a resident in Norway. We linked the cohorts with type 1 diabetes to the National Population Registry to determine the survival or emigration status as of September 30, 2013.

The Norwegian Cause of Death Registry

The Norwegian Cause of Death Registry is a nationwide registry managed by the Norwegian Institute of Public Health that covers all deaths in Norway. Norwegians who die abroad are also registered. The doctors calling the deaths report to the Norwegian Cause of Death Registry, by completing the death certificate. The official cause of death statistics is based on death certificates and is prepared in accordance with the ICD, World Health Organization (WHO). With this system, mortality can be compared across countries and cause-specific time-trends can be followed. Norway implemented the 10th revision of ICD in 1996. In the Norwegian Cause of Death Registry death certificates are run through a semi-automatic coding program that selects the underlying cause of death according to rules set by the WHO. The
diagnoses on the death certificate are examined and controlled to check that they are plausible for a person of the specified age or sex; this is performed to ensure that the Cause of Death Registry provides valid data.

The Norwegian Renal Registry

The NRR is a nationwide registry containing data on all patients in Norway receiving RRT since 1980. It was formally constituted in 1994 by collaboration between the Norwegian Renal Association and Oslo University Hospital, Rikshospitalet. National data on RRT had been collected within the Renal Association since 1980 in a less formalized manner, and the transplant center had stored data on transplanted patients since the late sixties. Since the mid-90ies, a process of transition from a pure epidemiological registry into a quality-oriented registry has progressed. The 25 national centers are responsible for reporting data from day one on all patients receiving RRT for chronic renal failure within their area. Based on annual crosschecks, reporting is considered to be 100%. Treatment of acute renal failure is not reported unless the failure turns out to be irreversible, in which case the whole treatment period is included (43). In paper II we obtained information from the NRR about ESRD among the deceased individuals with childhood-onset diabetes. In paper III we estimated the cumulative incidence of ESRD by linking the cohort aged 15-29 years at diagnosis of diabetes to the NRR.
Data collection

To review the causes of death we collected medical information about the deceased in addition to retrieving all death certificates. The Norwegian Regional Committee for Research Ethics gave permission to obtain medical records and medical autopsy reports. We obtained existing medical records by contacting regional and/or local hospitals. If we were not able to obtain medical records from the hospitals or if we needed additional clinical information, we contacted the doctor signing the death certificate or the patients’ general practitioner (GP), if noted on the death certificate.

The clinical details noted in the medical records varied widely and gave us insight into the varying quality of historical records. We contacted the Forensic Medicine Institutes (Division of Forensic Sciences, Norwegian Institute of Public Health; Gade Laboratory of Pathology, University of Bergen; Department of Pathology, Stavanger University Hospital; Department of Pathology and Medical Genetics, St Olavs University Hospital; Department of Pathology, University Hospital of Tromsø) and the departments of pathology in Norway to obtain the forensic autopsy reports or medical autopsy reports, if any. We received information on whether an autopsy had been performed from the Norwegian Cause of Death Registry. In most of the forensic reports a brief police report was also included. If we needed additional reports from the police, we contacted the local police department.

The available clinical information

Paper II: An autopsy was performed in 51% of the deceased. We obtained and considered 122 of 123 autopsy reports, 98 forensic autopsy reports, all including police reports, and 24 medical autopsy reports. In total we had access to medical records from primary or secondary care for 171/234 (73%) cases. In total, 66 patients died in hospital, medical records from terminal admission were available in almost all cases (64/66) and autopsy was performed in 23% (15/66). Among those who did not die in hospital (n=168) an autopsy was performed more frequently (64%, 107/168). In eight patients, the only source of information was the death certificate, in seven of these cases the review committee decided that the information on the death certificates was
sufficient to conclude on the cause of death (six accidents and one suicide). In one case death was sudden and unexplained.

Paper III: An autopsy was performed in 51% of the cases. All autopsy reports were available. Among the deceased individuals, 40% (59/146) died in hospital, medical records from terminal admission were available in most cases (56/59), 41% were autopsied. Among those who did not die in hospital (n=87) an autopsy was performed in 58% (50/87) and medical records were available in 72% (63/87). The medical records in these cases were either from previous visits or admissions to the hospital (n=19), clinical notes by the doctor certifying death and writing the death certificate (n=4) or a combination of the two (n=40).
Classification of the causes of death

In paper II we used a clinical committee, consisting of two pediatric diabetologists, one nephrologist and one forensic pathologist to review the causes of death. The review committee assessed all available information regarding the deceased. The causes of death were grouped as follows:

1. Acute diabetic complications: including DKA and hypoglycemia. The diagnosis of DKA was either made at autopsy or in hospital before death occurred. Death due to hypoglycemia was divided into two groups by degree of certainty after evaluating the clinical information available: death due to hypoglycemia (blood sugars near time of death available), and death probably due to hypoglycemia, if it was implied by other circumstances and signs.

2. Cardiovascular deaths: including death from all CVD (death from IHD, cerebrovascular disease or other CVD).

3. Renal death: including death from renal failure.

4. Other, diabetes related deaths: including death from diabetes related infections and other diabetes related complications that were not classified as acute complications, CVD or renal disease.

5. Violent death: including fatal accidents, intoxications and suicide.

6. Other, not diabetes related deaths: including all other causes of death, including infections not related to diabetes and any form of cancer.

7. Sudden, unexplained death: including sudden, unexpected deaths in which the committee was unable to state the cause of death. Sudden, unexpected deaths in which the committee concluded on a cause of death, was grouped into the relevant category. This category included the “dead in bed syndrome”. The criteria for the “dead-in-bed syndrome” were considered fulfilled in individuals without a history of long-term complications, observed in good health the day before, found dead in an undisturbed bed and autopsy not informative (128).
In paper III we assessed the causes of death using the same method; however, the clinical committee consisted only of two pediatric diabetologists. The causes of death were grouped into four larger groups. All contained subgroups corresponding to the classification in paper II:

1. Acute complications: including DKA and hypoglycemia.

2. Chronic complications: subdivided into death from renal failure, cardiovascular deaths (death from IHD, cerebrovascular disease or other CVD) and other diabetes complications.

3. Violent death: subdivided into fatal accidents, intoxications and suicides.

4. Other, not diabetes related deaths: all other causes of death, also including infections not related to diabetes, any form of cancer and sudden, unexplained deaths.

The committee looked for cases of “dead-in-bed”, defined in the same way as in paper II. We aimed to identify factors that might have contributed to death. A particular focus was on deaths related to alcohol or drug abuse, defined by ICD-10 codes in accordance with the definition used by the Norwegian Institute of Public Health (149).
Statistical methods

To assess mortality compared with the general population in Norway we calculated SMRs. All SMRs were calculated by attained age and sex as the ratio of the observed to the expected number of deaths. We based the calculations of the cause-specific SMRs on the ICD-code for the underlying cause of death (violent death; including accidents, intoxications and suicides [V01-V99, W00-X59, X4n, X60-X84, F10.0-F19.0], suicides [X60-X84], cancer [C00-C97], CVD [I00-I99], IHD [I20-I25] and cerebrovascular disease [I60-I69]). All ICD-8 and ICD-9 codes were translated into ICD-10 codes. Since we know that “diabetes” might reflect both acute and a variety of long-term complications, we examined the other ICD-10 codes listed on the death certificate if the underlying cause of death was “diabetes” (E10.0-E10.9, except E10.5 that was classified as cardiovascular death). If an ICD-code indicating cardiovascular death was identified anywhere on the death certificate, the case was defined as cardiovascular death. In paper III we also calculated SMR for alcohol-related deaths (E24.4, F10.0, F10.2, F10.4, F10.7, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, Q86.0, X45, X65, Y15). This was done in two ways; based on the underlying cause of death, and based on all ICD-codes listed on the death certificate. SMRs for acute diabetic complications were not estimated, since hypoglycemia and DKA cause death almost exclusively in individuals with diabetes.

In all three papers the follow-up period for each patient was calculated from the date of the first insulin injection to the date of death, emigration or September 30, 2013, whichever occurred first. We estimated the cumulative mortality by years from diagnosis using the Kaplan-Meier method. Differences between curves were tested by the log-rank test. We used years since diagnosis as time-scale also in the Cox regression models to estimate unadjusted and adjusted HRs.

In paper I and II we obtained all-cause mortality rates for the Norwegian population in one-year calendar year and age groups for each sex, from Statistics Norway. In paper II and III cause-specific mortality rates in the Norwegian population, in five-year calendar periods and age groups, for each sex were obtained from the Norwegian
Cause of Death Registry. Each patient contributed to the total person-years the time they spent within each age band and calendar period.

In paper I the diagnosis period was split into three time periods, 1973-1982, 1989-1998 and 1999-2012, to assess temporal trends in mortality risk up to 14 years after diagnosis. Since the age composition of the individuals in three time periods of diagnosis were different, and SMR differed by attained age, we estimated age-adjusted SMRs with 95% CIs for the three time periods by first stratifying by 10-year attained age groups in each time period, and then pooling the stratum-specific SMRs (Mantel–Haenszel method). The purpose of this was to make the comparison of the three diagnosis periods less influenced by the differences in attained age across the three periods. Finally, in paper I we estimated the risk difference for men and women by subtracting the mortality rate of the general population in Norway with the corresponding age and calendar time, from the mortality rate of the diabetic population.

We used Cox regression models to estimate unadjusted and adjusted HRs for the association between all-cause (paper I) or cause-specific mortality (paper II), sex and year of diagnosis. Year of diagnosis was modelled as a continuous (linear) covariate (no deviations from linearity were indicated in categorical analyses). We estimated the slopes separately in the cohorts 1973-1982 and 1989-2012 and found them to be similar; we also found the linearity assumption to hold across the range of diagnosis years. The proportional hazards assumption was found to hold after testing and assessing plots of scaled Schoenfeld residuals for each cause of death.

In paper III we also used Cox regression models to estimate unadjusted and adjusted HRs for the association between mortality, sex and ESRD. ESRD was handled as a time-varying covariate. We assessed the cumulative incidence of ESRD using the Kaplan-Meier method, we also analyzed the data considering death as competing risk using the Fine and Gray model (stcompet- and stcrreg-function in Stata).
A significance level of 5% was used in all analyses. We used Stata, version 13 (StataCorp LP, College Station, TX, USA) and SPSS version 21.0 (SPSS, Chicago, IL, USA) for data handling and analyses.
Ethical considerations
In health research the privacy and integrity of the participants in the study must be ensuring, data must be stored safely, and the data collected must be used meaningfully (150). The Norwegian Regional Committee for Medical and Health Research Ethics approved the present study. A specific ethical consideration in this study was looking into medical records and autopsy reports of deceased individuals that naturally could not consent to the use of their clinical data. The Norwegian Regional Committee for Medical and Health Research Ethics gave exemption from confidentiality and permission to look into medical records of the deceased without obtaining permission of next of kin. All data collected were de-identified and stored safely. Only the clinical information that was relevant to assess the cause of death was reviewed by the four members of the clinical committee. Furthermore, all members of the clinical review committee were medical doctors used to handle confidentiality. We believe that the aims of our study were important and relevant to the whole population with type 1 diabetes in Norway and that the study could provide useful information to public health and in clinical practice. Finally, we have made an effort to optimize publication of the results, which ultimately may make a difference with respect to communicating results to policymakers, other researchers, the public and the relevant patients.
Approvals

We obtained the following approvals:

- The Norwegian Regional Committee for Research Ethics approved the study protocol; reference number 2012/1939, date: December 12, 2012. They gave exemption from confidentiality and permission to look into medical records of the deceased without obtaining permission of next of kin.

- The Director of Public Prosecutions approved the study protocol and gave permission to obtain the forensic reports, including police reports on June 6, 2014.

- The hospital's Privacy and Data Protection Officer approved the study protocol on April 17, 2013.

- The NCDRs steering committee approved the study protocol and the use of data from the NCDR on May 8, 2013.

- The National Population Registry approved the study protocol on July 16, 2013.

- We applied The Norwegian Institute of Public Health to obtain data from the Norwegian Cause of Death registry concerning the deceased. This was approved on May 23, 2014.

- The NRR approved the study protocol on March 25, 2014 and provided data on all individuals receiving RRT.
SUMMARY OF RESULTS

Paper I

“All-cause mortality in a nationwide cohort of childhood-onset diabetes in Norway 1973-2013”

Among the 7,884 individuals with childhood-onset diabetes (<15 years of age), representing 132,420 person-years, 249 individuals (3.2%) died during a mean follow-up of 16.8 (range 0.0-40.7) years. Mortality was lower in woman compared with men (HR 0.50 [95% CI 0.38, 0.65]) and higher in individuals aged 10–14 years at diagnosis compared with those aged 0–9 years at diagnosis (HR 1.86 [95% CI 1.45-2.40]). Mortality rates were between three and four times higher in individuals with type 1 diabetes compared with the general population (SMR 3.6 [95% CI 3.1-4.0]). SMR increased by attained age and was significantly elevated in all 10-year age groups. SMRs were similar in males and females, but excess mortality assessed by risk difference was higher in males (figure 8).

Figure 8 All-cause mortality rates per 1,000 person-years (PYR) by calendar periods in the childhood-onset type 1 diabetes cohort and the background population, males (M) and females (F) with 95% CI. Reproduced with permission from Springer (paper I).
Temporal trends in mortality assessed by cox regression analysis showed that mortality decreased significantly by 49% (HR 0.51, 95% CI 0.28-0.93; p=0.03) for those diagnosed in 1999-2012 compared with those diagnosed in 1973-1982. In addition, there was a significantly decreasing trend in cumulative mortality up to 14 years of follow-up over the three time periods of diagnosis (figure 9). The SMRs showed a declining tendency from 3.8 to 2.2 over the three time periods of diagnosis, however this was not statistically significant.

**Figure 9** Cumulative mortality in 7,884 individuals with childhood-onset diabetes by time period of diagnosis, \(p_{\text{trend}}=0.018\). Modified from paper I.
Among the 7,871 individuals with type 1 diabetes diagnosed before 15 years of age, 3.1% (n=241) died during a mean follow-up of 16.8 (range 0.0-40.7) years. More than half of the deaths were due to causes that were related to diabetes (130/241, 53.9%). The leading cause of death before 30 years of age was acute complications (34.5%, 41/119), figure 10. CVD caused the majority deaths occurring after 30 years of age (33.6%, 41/122). Acute complications still caused 18% of all deaths among those dying after age 30 years. In 13.3% of individuals (32/241; 26 men) death was sudden and unexplained. Death was categorized as “dead in bed” in 5% (12/241; 11 men) of the deceased.

**Figure 10** Causes of death in 234 individuals with childhood-onset Type 1 diabetes diagnosed in 1973-2012 in Norway, age 2-55 years. The data are sorted by age at death. Reproduced with permission from John Wiley and Sons, (paper II).

Death from CVD (SMR 11.9 [95% CI 8.6-16.4]) and violent death (SMR 1.7 [95% CI 1.3- 2.1]) was significantly elevated in both sexes combined, but for suicide, only in
women (SMR 2.5 [95% CI 1.2-5.3]). Death due to traffic accidents and cancer occurred at similar rates in individuals with type 1 diabetes as in the general population. The risk of death for women with type 1 diabetes compared with men with type 1 diabetes was significantly lower for all diabetes-related deaths combined (HR 0.52 [95% CI 0.36–0.76]), for acute complications (HR 0.43 [95% CI 0.25–0.76]), for violent death (HR 0.33 [95% CI 0.16–0.66) and for sudden unexplained death (HR 0.27 [95% CI 0.11–0.65]). We observed no significant change with more recent year of diagnosis in the risk of death due to diabetes-related causes in total, or due to acute complications more specifically (HR 1.02 [95% CI 0.98-1.05]).
During 30 years’ (mean 29.6 [range 0.05–35.8]) follow-up of individuals diagnosed with type 1 diabetes at age 15-29 years during 1978-1982, 20.6% (148 individuals) died. The risk of mortality was about half in women compared with men with type 1 diabetes (HR 0.5 [95% CI 0.4-0.8, p<0.001]). The cumulative mortality by years since diagnosis was 6.0% (95% CI 4.5-8.0) at 10 years, 12.2% (95% CI 10.0-14.8) at 20 years and 18.4% (95% CI 15.8-21.5) at 30 years. Mortality rates were between four and five times higher compared with the general population (SMR 4.4 [95% CI 3.7-5.1]). The excess mortality was similar for men (SMR 4.5 [95% CI: 3.8-5.5]) and women (SMR 3.9 [95% CI: 2.9-5.3]). SMRs were higher in the lower age bands, being 6.7 (95% CI 3.9-11.5) at 15-24 years and 7.3 (95% CI 5.2-10.1) at 25-34 years compared with the higher age bands, being 3.7 (95% CI 2.7-4.9) at 45-54 years and 3.9 (95% CI 2.6-5.8) at 55-65 years. Death was caused by chronic diabetic complications (32.2%), acute diabetic complications (20.5%), violent death (19.9%) or any other cause (27.4%). Among individuals dying due to chronic complications, CVD caused death in 94% (44/47) and renal failure caused death in 6% (3/47). ESRD caused or contributed to death in 13/14 cases when present. The risk of death due to acute complications was lower in women compared with men (borderline significant; HR 0.47 [95% CI 0.21-1.02]). However, there was no difference in the risk of death due to chronic complications. According to the death certificate, death was related to alcohol in 15% of the cases. SMR for alcohol-related death was 6.8 (95% CI 4.5-10.3), for cardiovascular death 7.3 (95% CI 5.4-10.0), and for violent death 3.6 (95% CI 2.3-5.3), figure 11. Death due to cancer was comparable with the general population. The cumulative incidence of ESRD by years since diagnosis of diabetes was 1.4% (95% CI 0.7-2.7) at 20 years and 4.8% (95% CI 3.4-6.9) at 30 years. Mean time from diagnosis of type 1 diabetes to ESRD was 23.6 (range 14.2-33.5) years. There was no significant difference in the risk of developing ESRD between men and women.
Figure 11 Standardized mortality ratios for the underlying cause of death. Data are given for 719 individuals with type 1 diabetes diagnosed between 15 and 29 years of age in 1978-1982, followed until September 2013. *SMR for alcohol-related death was calculated for underlying and contributing causes of death. Reproduced with permission from the American Diabetes Association (paper III).
METHODOLOGICAL CONSIDERATIONS

Study design
Our study has several strengths. First, it is based on cohorts that are nationwide and population-based, with high completeness of ascertainment (16, 145, 146). All individuals were followed from date of diagnosis. Second, we linked nationwide registries using the unique personal identification number assigned to all inhabitants of Norway. By linking to the National Population Registry nearly all patients were followed for survival and emigration. This excluded the problem with lost to follow-up, a limitation in studies that do not use registry linkage, or that have less complete registries and therefore depend on tracing the patients in other ways. Only a few of the deceased individuals did not have a match in the Norwegian Cause of Death Registry, possibly due to death outside Norway (personal notification from the Cause of Death Registry). The fact that the study population was nationwide and population-based with high completeness of ascertainment, and that few individuals were lost to follow-up makes selection bias unlikely. This is a strength regarding the generalizability of the results compared with studies only reporting data from selected regions or clinics. We believe that our data are representative of the Norwegian type 1 diabetes population diagnosed before 30 years of age, and probably of type 1 diabetes populations in countries following the same international guidelines in diabetes care and with a health care system that is well developed and inexpensive for the patients. However, a limitation in our study is being restricted to only a few demographic variables (age at diagnosis, year of diagnosis and sex), not including socioeconomic or clinical variables. Even though we had access to medical records for the deceased we did not have information about clinical risk factors like HbA1c, blood pressure and lipid status for the majority of patients. This underscores the importance of collecting this kind of information systematically in registries. In Norway, modern-day advances in diabetes treatment like multiple daily injection therapy and self-monitoring of blood glucose were introduced in the 1980s. Most individuals in our cohorts have likely benefited from this, although probably to a larger degree in those diagnosed more recently. However, as much as 94% of the individuals who died from CVD were
diagnosed with childhood-onset diabetes in 1973–1982, the estimates we present regarding long-term complications may not be representative of individuals diagnosed today.

We consider the cohorts to represent only type 1 diabetes patients and believe that there are few misclassifications. Individuals noted with the diagnosis type 2 diabetes or monogenic diabetes in the NCDR were not included in the study population. After valuable comments from reviewers we excluded 7 cases diagnosed before 6 months of age in our work with paper II, this was done to exclude those with transient neonatal diabetes. Type 2 diabetes diagnosed between 0 and 14 years of age is infrequent in Norway and thereby unlikely to influence the results (8). Paper III is based on a cohort collected retrospectively in the period 1988-1990. Patients were diagnosed with type 1 diabetes at age 15 to 29 years, in 1978-1982 (146). The cohort diagnosed at age 15-29 years might include a few individuals with type 2 diabetes, although type 2 diabetes diagnosed at this age was probably infrequent in Norway during this period.

Studies performed in type 1 diabetes-cohorts are the preferred way to evaluate mortality and causes of death in type 1 diabetes. Studies that rely solely on death certificates to determine diabetes status will underestimate the number of individuals with diabetes because of underreporting of diabetes on the death certificates (151). In our study diabetes was noted on the death certificate in 74.8% (Paper I and II) and 68.2% (Paper III) of the deceased, meaning that about 30% of the deaths would have been lost if not using a study design of cohorts with type 1 diabetes. In addition we note that the proportion of cases with diabetes noted on the death certificate varied depending on the cause of death, indicating that cohort studies are even more important when exploring causes of death. For example, if assessing the frequency of violent deaths among individuals with type 1 diabetes, as much as 70% of the deaths would not have been identified (diabetes was mentioned on the death certificate in only 30 % of the violent deaths). It is not necessarily so that diabetes should always be
mentioned on the death certificate if an individual has diabetes, however, in many cases the role of diabetes might be of interest to determine.
Causes of death

ICD-codes are used to classify the causes of death noted on death certificates. These codes are widely used in epidemiological research, for example to assess population health in order to make priorities in health care. Using ICD-codes from health registries in research is relatively inexpensive and easily available when compared to collecting clinical data. However, there are limitations in research using only health registries when assessing causes of death. The reliance on death certificates and ICD-codes as the only sources of information concerning the cause of death can provide data of insufficient reliability (152). This might have implications on conclusions drawn from epidemiological research. The quality of the data in the Norwegian Cause of Death Registry relies on the quality of the information on the death certificates. Few Norwegian physicians have specific training in reporting cause of death statements, and even with the available instructions on the death certificates it is known that the causes of death are still reported improperly. Lu et al. demonstrated increasing prevalence of incorrect causal sequences among reported diagnoses on death certificates involving diabetes during the period 1985-2005 (153). They also found variability in the way of coding the underlying cause of death across time and in different populations. A possible explanation could be the substantial increase in reporting of comorbidities among deaths with mention of diabetes. A strength in our study is assessing causes of death in two ways, using data from the Norwegian Cause of Death Registry to compare causes of death in patients with type 1 diabetes with the general population, and using a clinical committee to explore the causes of death in greater detail.

“Diabetes” (E10.0-E10.9) was noted as the underlying cause of death in the Cause of Death Registry for 53.8% (126/234) of the cases in paper II (table 1) and 39.0% (57/146) of the cases in paper III (table 2). Only considering the underlying cause of death in cohorts with type 1 diabetes might be inadequate. For instance, the ICD coding rules will select diabetes as the underlying (primary) cause of death in the following chain of events: the immediate cause of death (Ia) could be myocardial
infarction, the intermediate cause of death (the cause of Ia): IHD (Ib) and the underlying cause of death, the condition initiating the events that leads to death (Ic), diabetes. Diabetes is only one of several known risk factors for CVD; others are hypertension, dyslipidemia, overweight, inactivity and smoking. One could therefor argue that the cardiovascular event (ex. IHD) should be noted as the underlying cause of death when a well-defined cardiovascular event precedes death and diabetes is a preexisting condition, diabetes could then be noted as contributing condition. Harding et al. argue this in their publication assessing sensitivity and specificity of mortality codes in identifying cardiovascular deaths (154). Their conclusion was that national mortality codes underestimate the true proportion of CHD and stroke deaths by 13.6% and 50.8%, respectively. We have address this issue in our study by considering all causes listed on the death certificate when calculating SMR for CVD (see under section “Statistical methods”) and by using a clinical review committee to explore the causes of death in detail.

Classification
Correct determination of the cause of death is essential. In our study a clinical review committee concluded on the causes of death by a thorough evaluation of death certificates, medical records, autopsy reports and police reports. Using a clinical review committee is regarded the most reliable method for evaluation of causes of death (143, 155). The four members of the clinical committee in paper II had relevant clinical experience that was useful in evaluating causes of death in individuals with type 1 diabetes. The experience from the work of the review committee in paper II was used in the smaller review committee in paper III. The review committee reclassified the causes of death in 145/234 cases in paper II (table 1) and 71/146 in paper III (table 2). We considered a case as reclassified if the conclusion of the review committee differed from the underlying cause of death. We considered all cases with the underlying cause of death “diabetes” as reclassified even though some were grouped as DKA or hypoglycemia that clearly is diabetes-related, however, the code E10.0
(diabetic coma) does not distinguish between hypoglycemia and DKA, the committee therefore added valuable information in these cases.

<table>
<thead>
<tr>
<th>Underlying cause of death, n (%)</th>
<th>Total</th>
<th>Diabetes</th>
<th>Circulatory</th>
<th>Suicide</th>
<th>Violent*</th>
<th>Cancer</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>234</td>
<td>126</td>
<td>18</td>
<td>20</td>
<td>32</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>43</td>
<td>41</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>20</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>49</td>
<td>29</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suicide</td>
<td>23</td>
<td>1</td>
<td>0</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Violent*</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cancer</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>1</td>
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<tr>
<td>Other</td>
<td>25</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td>Sudden, unexplained</td>
<td>32</td>
<td>27</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total reclassified</td>
<td>145</td>
<td>126</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1 Reclassification of the cause of death by the clinical committee in 234 individuals with age at diagnosis < 15 years, paper II. The underlying causes of death were retrieved from the Norwegian Cause of Death Registry. *including intoxications and accidents
Table 2 Reclassification of the cause of death by the clinical committee in 146 individuals with age at diagnosis 15-29 years, paper III. The underlying causes of death were retrieved from the Norwegian Cause of Death Registry. *including intoxications and accidents

<table>
<thead>
<tr>
<th>Reclassified by the clinical review committee, n (%)</th>
<th>Total</th>
<th>Diabetes</th>
<th>Circulatory</th>
<th>Suicide</th>
<th>Violent*</th>
<th>Cancer</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total deaths</td>
<td>146</td>
<td>57 (39.0)</td>
<td>22 (15.1)</td>
<td>8 (5.5)</td>
<td>20 (13.7)</td>
<td>18 (12.3)</td>
<td>21 (14.4)</td>
</tr>
<tr>
<td>Diabetic ketoacidosis</td>
<td>20 (13.7)</td>
<td>19 (33.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>10 (6.8)</td>
<td>8 (14.0)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>1 (5.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CVD</td>
<td>44 (30.1)</td>
<td>16 (28.0)</td>
<td>20 (91.0)</td>
<td>0</td>
<td>0</td>
<td>8 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>3 (2.1)</td>
<td>3 (5.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Suicide</td>
<td>8 (5.5)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>7 (87.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Violent*</td>
<td>21 (14.4)</td>
<td>0</td>
<td>0</td>
<td>1 (12.5)</td>
<td>19 (95.0)</td>
<td>0</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Cancer</td>
<td>19 (13.0)</td>
<td>1 (1.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (11.0)</td>
<td>4 (7.0)</td>
<td>1 (4.5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>11 (52.3)</td>
</tr>
<tr>
<td>Sudden, unexplained</td>
<td>5 (3.4)</td>
<td>5 (8.8)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total reclassified</td>
<td>71 (48.6)</td>
<td>57 (100)</td>
<td>2 (9.1)</td>
<td>1 (12.5)</td>
<td>1 (5.0)</td>
<td>0</td>
<td>10 (42.9)</td>
</tr>
</tbody>
</table>

The work to classify the causes of death posed several challenges. First of all, the quality of the review process was dependent on the number of autopsies performed and the medical records available. In the cohorts combined, about 50% of the deceased were autopsied. We found this to be surprisingly few, considering the relatively young age at death in the cohorts. This was a limitation in the work of the clinical review committee. Although it is substantially higher than in the general population in Norway, around 18% of all deaths in Norway were autopsied in 1986, decreasing to only 8.3% in 2010 (156). For example, in those with childhood-onset diabetes and age at death <40 years (n=188), 44% (82/188) were not autopsied and among the cases that were not autopsied 12 individuals died sudden and unexplained. In those with onset of diabetes between 15 and 29 years who died before 40 years of age (n=64), 32% were
not autopsied. In several cases it was difficult to determine the cause of death because death occurred at home and no autopsy was performed. In these cases recorded information from the relatives, medical records or police reports about the circumstances of death was valuable.

Medical records and autopsy reports were collected from hospitals and GPs nationwide. We succeeded in retrieving all but one autopsy report; the main reason for the high success rate was that information on whether an autopsy was performed and where it was performed was registered in the Norwegian Cause of Death Registry. Retrieving the medical records was more difficult because some adults with type 1 diabetes are treated in hospitals and some are treated in primary care. We observed that the greater the time lap between death and follow-up, the more difficult it was to find clinical information relevant to determine the cause of death. There were several reasons for this: some institutions no longer existed, the GP might have retired or relocated, or it was difficult to locate where the deceased had been receiving health care. We used the place of death and the home address registered in the National Population Registry to reason on which hospital the deceased might have attended. We also used the death certificates to retrieve the name of the GP or the doctor writing the death certificate. The data collection and the evaluation of the causes of death were more straightforward if the patient died in hospital or was autopsied, in which clinical notes were quite easily available.

Classification of the causes of death is difficult and can be done in several ways. In patients dying due to long-term complications our impression was that in many cases they had complex medical histories and several complications coexisted. Distinguishing death due to CVD from death due to renal failure was complicated when both existed. The clinical review committee decided to classify a case as renal death only if the immediate cause of death was renal disease. If the immediate cause of death was CVD and the patient had ESRD as a preexisting condition, it was classified
as CVD, and ESRD as a contributing factor. One could also argue the opposite. However, since treatment of patients with ESRD is of high quality in Norway and this allows patients to live long with renal failure we considered it most correct to ascribe deaths as renal deaths only if death could be attributed directly to renal failure. We are aware that this might give mortality rates due to renal death lower than in other similar studies (59, 97). In paper III we decided to estimate mortality rates for the whole contribution of ESRD (ESRD caused or contributed to death) to enhance comparison with other studies.

In terms of acute complications, the true nature of a “diabetic coma” in retrospect is often difficult to determine, leading to a grouping in many studies of “unspecified diabetic coma”. It is well known that fatal hypoglycemia is difficult to diagnose postmortem because glucose concentrations in blood or vitreous fluid drops rapidly in the post mortem period and can therefore not be trusted (157). We used blood sugar near time of death (if available) as an indicator of death due to hypoglycemia. Without any information on blood sugar close to death we attributed death to hypoglycemia under the following circumstances: no other cause of death was revealed, circumstances and signs pointed in the direction of hypoglycemia and there was additional information on previous history of serious hypoglycemia attacks. We are aware that this way of defining death due to hypoglycemia has its limitations, even when scrutinizing all details available in the medical records. One might suspect that some of the deaths categorized as sudden and unexplained might actually have been deaths caused by hypoglycemia, in addition, among the cases noted as “dead in bed” the role of hypoglycemia is unclear. This could lead to underestimation of the true number of deaths attributable to hypoglycemia. However, overestimation is also possible since the cases considered as “possible due to hypoglycemia” could actually be caused by other conditions like for example undiagnosed epilepsy.

Medical records and police reports are important to gain more information on how diabetes influences violent deaths. Registry data does not provide sufficient detailed
information on this. However, still when obtaining all available information, the role of diabetes in violent deaths is difficult to determine. Among the violent deaths a forensic autopsy was performed in 61% (34/56) of people with childhood-onset diabetes and in 86% (25/29) of people with age at onset between 15-29 years. It is difficult to determine the role of diabetes if a forensic autopsy is not performed. Table 3 gives detailed information on the forensic autopsies that was available in determining the role of diabetes in violent deaths among individuals with childhood-onset diabetes. For example, a forensic autopsy was performed in only 9 of 23 accidents, thereby making the influence of diabetes on the accidents difficult to evaluate in the remaining 14 cases. In paper II the review committee classified 10/56 violent deaths as diabetes related, four due to intoxication and six due to accidents. In none of the traffic accidents (n=13) the role of diabetes was clear, even though we knew that the deceased was the driver in seven cases it was difficult to assess whether hypoglycaemia played a role. In two cases (2/7) hypoglycaemia was considered unlikely at autopsy, in two cases (2/7) the accident was probably due to alcohol and in the remaining three cases (3/7) diabetes could have influenced on the accident, however this was not clear. A limitation was the low frequency of forensic autopsies (4/7), even though a forensic autopsy might not give the complete answer to this question.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Suicide</th>
<th>Intoxications</th>
<th>Accidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>56</td>
<td>23</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Forensic autopsies, n (%)</td>
<td>34 (61)</td>
<td>16 (70)</td>
<td>9 (90)</td>
<td>9 (39)</td>
</tr>
<tr>
<td>Death related to diabetes, n (%)</td>
<td>10 (18)</td>
<td>0 (0)</td>
<td>4 (40)</td>
<td>6 (26)</td>
</tr>
</tbody>
</table>

Table 3 Violent deaths, forensic autopsies and relation to diabetes in childhood-onset type 1 diabetes.
DISCUSSION OF RESULTS
The results of this thesis extend and expand on previous published data on mortality in childhood-onset type 1 diabetes in Norway. The long period of diagnosis (January 1, 1973- December 31, 2012) and follow-up (January 1, 1973- September 30, 2013) have allowed us to look for time trends in mortality and causes of death.

We explored mortality and the incidence of ESRD in individuals diagnosed with type 1 diabetes in adolescence and young adulthood (15-29 years) with up to about 30 years duration of diabetes. Mortality and ESRD, in individuals diagnosed with type 1 diabetes at this age, have to my knowledge not previously been assessed in Norway.

All-cause mortality compared with the general population
We identified higher mortality rates in people with type 1 diabetes compared with the general population in Norway, SMR being 3.6 in childhood-onset diabetes and 4.4 in those with onset of diabetes between 15 and 29 years of age. In the cohorts SMRs were significantly elevated in all 10-years age groups, showing that both at younger and older age, people with type 1 diabetes die at higher rates compared with a matched general population. Although, the results may not be generalizable to patients older than the maximum age at end of follow-up, 55.3 years and 64.9 years in those diagnosed at age <15 years and 15-30 years, respectively. A recent mortality study from Denmark following a type 1 diabetes population for 24 years reported SMR at 4.8 (95%CI 3.5-6.2) (158). A systematic review of mortality in childhood-/adolescent-diagnosed type 1 diabetes including 13 relevant publications with mortality data describing 23 independent studies, was published in 2015 (81). Excess mortality was reported to be present worldwide, with marked variation between studies, ranging from a SMR of 0 in a small cohort from Iceland where no deaths were observed, to 8.5 in a study from Cuba. Excess mortality was, however, less marked in more recent studies (figure 4) and in countries with lower infant mortality. In contrast to most studies concerning mortality in type 1 diabetes, a recent study from the DCCT/EDIC-cohort demonstrated mortality rates in patients with type 1 diabetes similar to the general population. SMR was 0.88 (95% CI 0.67-1.16) in the intensively treated group
and 1.31 (95% CI 1.05-1.65) in the conventionally treated group (86). However, these results may not be generalizable to other populations with type 1 diabetes. First of all, the participants of the DCCT were enrolled in a randomized clinical trial that required adherence to a specific regimen over time, thereby including highly motivated patients and probably exclude patients with psychosocial problems. Also, the selection criteria for DCCT excluded those with hypertension, severe dyslipidemia or other serious comorbidities. The glycemic control in the DCCT-cohort was probably better than what was achieved in our nationwide and population-based cohorts. In addition, mortality rates in the Norwegian general population are lower than in the United States, thereby giving a higher relative difference. This could probably explain some of the discrepancies in relative mortality. Another study from the DCCT/EDIC with long-term follow-up showed a modestly lower mortality rate in those initially receiving intensive therapy compared with those receiving conventional therapy at 27 years follow-up, although the risk-reduction was small (85).

Recently, Lind et al. explored mortality and glycemic control (82). They followed individuals with type 1 diabetes (n=33,915) for mean 8 years between 1998 and 2011 and demonstrated that even patients with very good glycemic control (HbA1c <7%) had risk of death from any cause and from cardiovascular causes twice as high as in a matched general population. The risk increased with increasing HbA1c to about 8 times that of the general population for HbA1c-levels above 9.7. A limitation of our study was that we did not have information about HbA1c or other risk factors for the majority of patients. We could therefore not provide information on how the mortality risk in Norwegian patients is influenced by metabolic control, but we assume that the results provided by Lind et al. probably are similar in Norway.

**Time trends in mortality**
Life expectancy has improved in the general population over the recent decades, partly explained by lower mortality rates for CVD (159). It is probable that individuals with
type 1 diabetes have benefited from the improvements in prevention and treatment of
CVD as seen in the general population. We know that management of type 1 diabetes
has improved during the same period (32, 48, 160, 161). Recently, large registry-based
studies from Sweden and Australia showed that the increase in the remaining life
expectancy at age 20 years was very similar in individuals with type 1 diabetes and in
the general populations during the same period; 2002-2006 and 2007-2011 in the
Swedish study, 1997-2003 and 2004-2010 in the Australian study. The gap in life
expectancy compared with the general populations was approximately 10-13 years in
both countries (83, 84). The Swedish study also showed that mortality rates for
cardiovascular-related mortality decreased significantly from 2002-2010 for those with
type 1 diabetes. In paper I we showed a declining trend in absolute mortality up to 14
years after diagnosis during 1973-2013. When we compared those diagnosed in 1999-
2012 with those diagnosed in 1973-1982 the cox regression analysis showed a
significant decrease in mortality of 49% (HR 0.51[95% CI 0.28, 0.93]). Some studies
have reported temporal decline in mortality (100, 106, 113, 162). However, because
studies differ in populations, diagnosis periods, duration of diabetes and age at
diagnosis comparisons between studies are difficult. The SMRs for all-cause mortality
in paper I tended to decrease by more recent diagnosis year, although not significantly.
However, it is probably most relevant to emphasise the absolute decline in mortality
among patients with type 1 diabetes, in the context with a very low and declining
mortality in the background population. A Danish study assessing time trends in
mortality among patients with type 1 diabetes (2002-2011) showed that mortality rates
in patients with type 1 diabetes decreased over the study period, faster than that of the
background population (106). We note that care needs to be taken when drawing
conclusions by comparing SMRs between countries with differences in underlying
mortality rates. A larger relative difference may still by a smaller difference in
absolute terms (figure 12 and 13).

In paper II we explored time trends in cause-specific mortality in childhood-onset
diabetes. We were not able to demonstrate decreased risk of mortality due to diabetes-
related causes in total or due to acute complications specifically. The results we report are in accordance with a large Finnish study of individuals diagnosed with type 1 diabetes between 1970 and 1999, showing a non-significant trend towards increase in acute complication-related deaths in early onset type 1 diabetes (113). An explanation might be that the health care system is focusing primarily on acute treatment of physical illness while there might be an unmet need for preventive health care service, focusing on patient education. Death due to CVD seemed to decline during the study period. This is in line with the Swedish study by Petrie et al. showing decreasing cardiovascular-related mortality in individuals with type 1 diabetes (84). Our results concerning cause-specific time trends must be interpreted with caution due to the few deaths in each group of causes, leading to limited statistical power to detect minor to moderate changes over time.

**Sex differences in mortality**

In both paper I and paper III all-cause mortality was about twice as high in male compared with female patients, while the SMRs were similar, this probably reflects higher mortality rates in men compared with women in the general population at this age in Norway. The mortality rates of men and women were higher in all attained age groups compared with the general population matched for sex, age and calendar year (figure 12 and 13). This is in line with earlier published data from Norway (102), but widely different from results from the United States. In the United States they reported SMR for women nearly three times that of men and the male to female rate ratio was 0.8, clearly confirming that any sex advantage in mortality is lost in women with type 1 diabetes (100). Furthermore, a systematic review compared excess mortality in women and men with type 1 diabetes (87). They reported sex-specific SMRs or HRs based on data from 26 studies. The review concluded that women had a 40% excess risk of all-cause mortality and twice the excess risk of fatal vascular events compared with men. This result was consistent across the year of study at baseline and the duration of follow-up, part of the diverging results between studies could be explained by differences in background mortality rates between the sexes. Hence, in studies from
countries in which the mortality rates in women were similar to, or higher than mortality rates in men, there was a greater excess risk in women than in men. This supports the results from our study where the mortality rate in the background population was lower for women than for men in these age groups and thereby posed a possible explanation on why the all-cause SMRs for men and women were similar (figure 12 and 13).
Figure 12 Mortality rates in men diagnosed with type 1 diabetes at age 15-29 years in 1978-1982 by attained age (age 15-65 years), paper III.

Figure 13 Mortality rates in women diagnosed with type 1 diabetes at age 15-29 years in 1978-1982 by attained age (age 15-65 years), paper III.
Age at diagnosis and mortality

In paper I the cumulative mortality was significantly higher in those diagnosed at age 10-14 years compared with 0-9 years. However, the SMRs were not significantly different between the two groups (SMR 3.2 vs 3.9). These findings are consistent with results from Finland and Japan (99, 113). In our study the results may be explained by the fact that those diagnosed at an older age have a systematically higher age during follow-up when using time since diagnosis as time-scale; the mean age at the end of follow-up in the group diagnosed at age 10-14 years was 29.1 vs 22.9 years for those diagnosed at age 0-9 years. Some studies have indicated that the prepubertal years of diabetes may contribute less to microvascular complications (163-165), but the opposite has also been reported (166).

In the cohort with age at diagnosis 15-29 years, SMR for all-cause mortality was comparable or higher than what we found in childhood-onset diabetes (3.1-4.0 vs 3.7-5.1). A possible explanation is that the age compositions in the two study populations are different, and we have shown in paper I and III that SMRs vary by attained age. This could affect the results, but probably to a small degree as SMRs in the age bands above 40 years are quite similar and seem to reach a plateau regardless of age at diagnosis. Adolescence or young adulthood is characterized by several changes in life, such as moving away from the care provided by the families. A possible explanation to the high mortality during the earliest 10 years with diabetes in the cohort diagnosed in adolescence and young adulthood, is that being diagnosed with a chronic disease in a period of life that poses more complex challenges than in childhood, could mean a higher risk of mortality. This hypothesis could also explain the high SMRs for those diagnosed at age 15-29 years during the earliest period with diabetes.
Causes of death

Mortality was dominated by acute complications and violent death up to 20 years after diagnosis, both in those diagnosed in childhood (figure 14) and at age 15-29 years (figure 15). Acute complications dominated to a larger degree among those diagnosed in childhood and violent death to a larger degree among those diagnosed in adolescence and young adulthood. This can probably be explained by the age differences in the cohorts when comparing by time since diagnosis. Long-term mortality was mainly caused by chronic complications, the pattern was most marked in the cohort with the higher attained age.

Figure 14 Causes of death in 234 individuals with type 1 diabetes diagnosed at age <15 years, displayed by years since diagnosis, modified from paper II.
Figure 15 Causes of death in 146 individuals with type 1 diabetes diagnosed at age 15-29 years, displayed by years since diagnosis, modified from paper III.
Early mortality

Death at onset of diabetes seems to be rare in Norway. We identified two cases that died at diagnosis due to DKA with cerebral oedema, at age 7 and 13 years. The high incidence of type 1 diabetes in Norway probably leads to high awareness of the diagnosis among health professionals. In addition glucometers are easily available to make the appropriate diagnosis. We believe that few children in Norway die due to DKA without being diagnosed with type 1 diabetes, although we cannot exclude this possibility completely. Low onset-mortality has also been reported from other countries (108, 118).

In a country with good access to healthcare, DKA is a condition that should be almost entirely preventable. In paper II we identified comorbidity with drug and alcohol misuse, or psychiatric disorders in 26% of deaths attributed to DKA. This might, to some extent, explain some of the deaths caused by DKA, but several young adults died at home with all necessary diabetes treatment available. In both childhood-onset diabetes and diabetes with onset in adolescence and young adulthood we found that the risk of death due to acute complications was twice as high in men compared with women. This is in contrast to a large study from the United States that reported mortality from diabetes-related causes higher in women (59), while similar mortality for men and women is also demonstrated (85, 94, 118). It is of great concern that death due to DKA is among the most common causes of death in young people with type 1 diabetes, and that the risk is twice as high in men compared with women in Norway. One might speculate about lower ability to the self-care in men. Our results indicate that a particular focus should be on prevention of acute complication in men.

In paper II and III SMR for intoxications and accidents combined, was high among men (<15 years at diagnosis [SMR 1.6] and 15-29 years at diagnosis [SMR 3.6]). Higher risk of violent death in individuals with type 1 diabetes was the conclusion in a recent review article including studies with age at diagnosis 0-30 years, 2.5 (95% CI
1.7-3.9) in women and 1.8 (95% CI 1.3-2.5) in men (87). It is suspected that hypoglycemia and impaired awareness of hypoglycemia increase the risk of accidents. We report higher mortality by suicide (two-fold) for women with childhood-onset type 1 diabetes compared with the general population, but no suicides were identified in women with type 1 diabetes diagnosed at age 15-30 years. It is possible that some suicides could be hidden among deaths categorized as due to acute complications. Based on these results it is difficult to draw robust conclusions and larger studies are probably needed. However, it has been shown that people with type 1 diabetes are at increased risk of suicide (126).

**Long-term mortality**

The high risk of long-term complications in people with type 1 diabetes is well known. Chronic complications caused a large proportion of deaths at diabetes duration more than 20 years (paper II and III). The main cause of death among those dying due to chronic complications was CVD. In individuals with age at diagnosis 15-29 years, the mortality rate for men with type 1 diabetes increased substantially after age 45-54 years (figure 12) compared with what is observed in the general population. A similar increase relative to the female general population can be seen about 10 years earlier in women with type 1 diabetes (figure 13). Causes of death at this age are mainly dominated by CVD (figure 14). Furthermore, both in paper II and III, the SMRs for CVD were higher in women compared with men, although most evident in the cohort with diabetes diagnosed at age 15-29 years. Several other studies have reported results similar to our findings (50, 59, 167, 168). In general, mortality rates for CVD are lower in premenopausal women than in men. However, type 1 diabetes seems to eliminate some of the female sex protection seen in the nondiabetic population.

**Alcohol-related mortality**

In paper III we identified that mortality rates associated with alcohol was about five to seven times higher in the cohort with type 1 diabetes compared with the general
population in Norway. Alcohol-related death was identified in about 15% of the deceased (figure 16).

Results concerning alcohol-related mortality have previously been reported from Finland (113). Finland and Norway are appropriate to compare as the countries share important population and welfare characteristics. However, there are significant differences in drinking levels and alcohol-related mortality, Finland is a higher-consuming country and Norway a lower-consuming country. The mortality rates for alcohol-related death are considerably higher in Finland than in the other Nordic countries (169). The markedly higher SMR in our cohort can probably be explained by the lower mortality rates for alcohol-related mortality in the general population in Norway. However, our study shows that people with type 1 diabetes have a much higher risk of alcohol-related deaths also in a country with substantially lower alcohol consumption and lower mortality related to alcohol. Our study indicates that diabetes is a major hazard to people with irregular lifestyle and with low ability to self-care. It
is important that clinicians are aware of the alcohol-related mortality when providing care to patients with type 1 diabetes.

**Sudden, unexplained death**

Sudden, unexplained deaths do not occur exclusively in individuals with type 1 diabetes. A study from The Netherlands assessing sudden deaths in individuals younger than 40 years of age reported the incidence to be 2.1/100,000 person-years, and higher in men than women (170). The comparable rate in our study regarding childhood-onset diabetes was about 10-times as high (24.2/100,000 person-years), but also showing higher incidence in men. This is similar to what was reported by Secrest et al. (131) and Koltin et al. (132) concerning sudden unexplained deaths in cohorts with type 1 diabetes. The male dominance is reported in several studies (129, 131, 133). The 5% of deaths attributed to “dead in bed” in individuals with childhood-onset diabetes was consistent with other studies (132), but lower than reported in a Swedish study (109). The youngest person was 11 years and died in 1992 after 7 years diabetes duration (table 4). We suspect that our estimate of “dead in bed” might be too low because autopsy was performed in only 60% of the cases that died sudden and unexplained (paper II). Hence, forensic autopsies should be performed more frequently to gain more knowledge on unexpected deaths in young people with type 1 diabetes. The underlying cause of death was in all cases “diabetes” in the Cause of Death Registry. We only identified one case of “dead in bed” among those with onset of diabetes at age 15-29 years.
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Table 4 Characteristics of individuals with childhood-onset type 1 diabetes classified as “dead in bed”, sorted by age at death. † in the Norwegian Cause of Death Registry. * Arterionephrosclerosis diagnosed at autopsy. F=female, M=male.
End-stage renal disease
A well-known predictor of mortality in type 1 diabetes is the presence and severity of renal disease (38, 82). Some studies suggest that people without renal complications have long-time survival comparable to the general population (38, 171). However, Lind et al. reported that even among patients with normoalbuminuria the risk of death was 2-4 times that of the general population. In our study the risk of death associated with ESRD in patients diagnosed at age 15-29 years, was between 8 and 9 (HR 8.7 [95% CI 4.8-15.5, p<0.0001]). The cumulative incidence of ESRD was 4.8% at 30 years diabetes duration. In general it is known that the incidence rates of ESRD are lower in Western European countries compared with the United States (172). According to a Norwegian population-based study this could not be explained by a lower prevalence of chronic kidney disease, but by a lower risk for ESRD among individuals with chronic kidney disease (172). Finland report higher cumulative incidence of ESRD compared to our results, 13.0% in women and 25.0% in men in a cohort with age at onset of diabetes ≥15 years, followed for 40 years (173). However, Sweden has reported results comparable to our numbers, 3.2-5.3% at 30 years (47). It has previously been published that the incidence of diabetic nephropathy in Norway was low compared with other countries, 7.8% in a population with duration of type 1 diabetes between 19 and 30 years (49). Low incidences of diabetic nephropathy and ESRD may indicate high quality of diabetes care in Norway.
CONCLUSIONS AND CLINICAL IMPLICATIONS

- All-cause mortality, although still higher in individuals with childhood-onset diabetes compared with the general population, has declined among children diagnosed most recently (1999–2012) compared with those diagnosed in the earliest period (1973–1982), probably reflecting improved diabetes care during the last decades.

- The high proportion of death due to acute complications, especially in males, reflects a need to focus on diabetes education and self-management.

- The large excess mortality from CVD underscores the importance of starting prevention at an early age. Guidelines should be followed, modifiable risk factors identified and lifestyle intervention should be recommended for all patients. This could have an impact on the long-term mortality.

- The relatively high proportion of alcohol-related death suggests that increased awareness of alcohol-related mortality should be encouraged in clinics providing diabetes care.

- Our estimates of the incidence of ESRD in individuals with type 1 diabetes were relatively low and we observed few deaths due to renal failure.

- We report excess death due to suicide compared with the general population. This may imply increased psychological vulnerability and reflect the burden of living with a chronic disease that requires high degree of self-management. We recommend early psychosocial support in diabetes management.

- We argue that the frequency of autopsies, especially in young individuals dying at home, should be higher in order to reveal a specific cause of death more frequently.
FUTURE STUDIES

• Continued long-term follow-up of individuals diagnosed with type 1 diabetes is important to provide more robust estimates of time trends in mortality and causes of death.

• A study assessing the socioeconomic influence on mortality in patients with type 1 diabetes in Norway is needed. This might give further insight concerning the excess mortality.

• A relatively high proportion of the deaths were sudden and unexplained. A study providing more clinical details concerning sudden, unexplained deaths could give further insight into this field.

• Studies assessing the influence of risk factors (especially HbA1c) on mortality. This has been recorded in the NCDR since 2001.

• We assessed the cumulative incidence of ESRD in a cohort diagnosed with type 1 diabetes in adolescence and young adulthood. Estimates should also be made in childhood-onset type 1 diabetes. This might give additional information on time trends concerning ESRD.

• Our study revealed excess death from alcohol-related causes. More details concerning alcohol consumption in patients with type 1 diabetes in Norway could be explored further.
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