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Prevalence, vascular complications, and level of health care treatment in individuals with type 2 and type 1 diabetes mellitus

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A dissertation for the degree of Philosophiae Doctor June 2022

Table of contents

List of Figures

List of Tables

Acknowledgements

This has been an incredible journey, and I would like to thank everyone who has made this work possible. First, to Tor Claudi for introducing me to the project. It has been a joy working with a respected colleague like you. I want to thank my supervisors, Tore Julsrud Berg, Anne Karen Jenum, and Knut Tore Lappegård, for enduring with me and being there through all these years. Tore for guiding me despite geographical distance and Knut Tore for always having an open door. To statistician Marthe Larsen, this work would not have been possible without your assistance. I am so grateful you have been there all along, always with a clear head and unparalleled generosity. To Karianne at Noklus, for answering my countless questions. Thanks to friends and colleagues. Thank you, Nils, for sound advice, life's most important ski trip, and for leading the way when I have been wobbling. Thank you, Amalie, Ida, Liv, and Benjamin, for your advice, honest feedback, and meaningful conversations. To Grethe for drawing the beautiful front page. To the Department of Medicine at Nordland Hospital, Bodø, and especially Cecile Vasset, for constantly facilitating so that I could combine research and clinical work as I have wanted. Thanks to my family, mom, dad, Åge, Arne Martin, and Knut Arild, for all the hours and days you have lined up so I could complete this journey.

But most of all, to the love of my life and best friend, Kjetil. No words are big enough to express my gratitude for all the help, understanding, encouragement and support throughout these years. Thank you! To our beautiful children Markus, Aleksander, and Hennie thank you for patiently following from the sidelines.

There is a time for everything and a season for every activity under the heavens. Now we have come to the end of this road, and I am infinitely grateful for the opportunity I have been given.

Abbreviations

Anti-GAD	Anti glutamate acid decarboxylase
Anti-IA 2	Anti tyrosine phosphatase
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
CKD	Chronic kidney disease
eGFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
GLP-1RA	Glucagon-like-peptide-1 receptor agonists
GP	General Practitioner
HbA1c	Glycated haemoglobin A1c
ICPC	International Classification of Primary Care
IDF	International Diabetes Federation
LADA	Late Autoimmune Diabetes in the Adult
LDL	Low-density lipoprotein
MODY	Maturity Onset Diabetes of the Young
Noklus	Norwegian Organization for Quality Improvements of Laboratory Examinations
NDR-A	The Norwegian Diabetes Register for Adults
MAR	Missing at random
MNAR	Missing not at random
OR	Odds ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PTA	Percutaneous transluminal angioplasty
ROSA 4	The Rogaland-Oslo-Salten-Akershus-Hordaland study, 2014
SES	Socioeconomic status
SGLT-2	Sodium-glucose cotransporter-2
TIA	Transient ischemic attacks
UACR	Urine Albumin-to-Creatinine Ratio
VIF	Variance inflation factor

List of papers

Paper 1

The total prevalence of diagnosed diabetes and the quality of diabetes care for the adult population in Salten, Norway. Kristina B. Slåtsve, Tor Claudi, Knut Tore Lappegård, Anne Karen Jenum, Marthe Larsen, John G. Cooper, Sverre Sandberg, Tore Julsrud Berg. Scand J Public Health. 2022 Mar;50(2):161-171. DOI: 10.1177/1403494820951004.

Paper 2

Factors associated with treatment in primary versus specialist care: A population-based study of people with type 2 and type 1 diabetes. Kristina B. Slåtsve, Tor Claudi, Knut Tore Lappegård, Anne Karen Jenum, Marthe Larsen, Kjersti Nøkleby, John G. Cooper, Sverre Sandberg, Tore Julsrud Berg. Diabetic Medicine. https://doi.org.10.1111/dme.14580

Paper 3

Level of education is associated with coronary heart disease and chronic kidney failure in individuals with type 2 diabetes: A population-based study. Kristina B. Slåtsve, Tor Claudi, Knut Tore Lappegård, Anne Karen Jenum, Marthe Larsen, Kjersti Nøkleby, Katrina Tibballs, John G. Cooper, Sverre Sandberg, Esben Selmer Buhl, Karianne Fjeld Løvaas, Tore Julsrud Berg. Submitted after revisions.

Summary

Background and aims: The total prevalence of diabetes and vascular complications is increasing. Hence, it is essential to provide diabetes treatment according to the *National clinical guideline for the management of diabetes* and allocate individuals to the right level of health care in line with the *National guideline for prioritization in specialist health care – Endocrinology and endocrine surgery*. The aims of this thesis were to assess the prevalence of diagnosed type 2 and type 1 diabetes and the status of diabetes treatment in Salten, Norway. Moreover, to study the association between education level and vascular complications in individuals with type 2 diabetes born in Norway.

Methods: We used data from the Rogaland-Oslo-Salten-Akershus-Hordaland study (ROSA 4) and The Norwegian Diabetes Register for Adults. The dataset included all individuals diagnosed with type 2 and type 1 diabetes living in Salten, Norway. Differences in cardiovascular risk factors, the prevalence of vascular complications, and attained treatment targets between type 2 and type 1 diabetes were studied in regression analyses. In individuals with type 2 diabetes, factors associated with treatment in specialist care were studied in multilevel regression models with specialist care as the outcome variable and population, general practitioner, and practice characteristics as exposure variables. The nationwide ROSA 4 data were analysed in multivariable multilevel regression models to study the association between education level and vascular complications. Associations with the outcomes are presented as odds ratios with 95% confidence intervals and corresponding p-values.

Results: The total diabetes prevalence in all age groups was 3.8%. The prevalence of type 2 diabetes was 3.4%, and type 1 diabetes was 0.45% in all age groups. Coronary heart disease was more prevalent in individuals with type 2 diabetes than in those with type 1 diabetes (23.1% vs 15.8%). The HbA1c treatment target of ≤ 53 mmol/mol (≤ 7.0%) was reached in 61.1% of individuals with type 2 diabetes and 22.5% with type 1 diabetes. In individuals with type 2 diabetes, 67.3% of those treated in primary care and 30.4% treated in specialist/shared care reached the HbA1c treatment target. Moreover, 16% of individuals with type 2 diabetes received treatment in specialist care. Higher HbA1c levels, insulin use, coronary heart disease, retinopathy, and general practitioners' urban location were positively associated with treatment in specialist care in individuals with type 2 diabetes. Education level was not associated with treatment in specialist care. In individuals with type 2 diabetes born in

Norway, higher education was associated with lower odds for coronary heart disease and chronic kidney disease compared to compulsory education when adjusting for age, sex, HbA1c, low-density lipoprotein cholesterol, systolic blood pressure, smoking, and diabetes duration.

Conclusion:

The total prevalence of diabetes was slightly lower than reported in comparable studies. As expected from priority guidelines, the results showed that individuals with type 2 diabetes treated in specialist care had higher HbA1c levels and more vascular complications. Higher education levels were associated with lower odds for coronary heart disease and chronic kidney disease in individuals with type 2 diabetes in a country where everyone has equal access to health care. A greater focus on socioeconomic status may be warranted to reduce unacceptable variations in health care.

1 Introduction

1.1 Background

The global diabetes prevalence has increased substantially over the last decades (1). The diabetes epidemic represents significant challenges for affected individuals, their families, and communities worldwide. Diabetes is an important cause of coronary heart disease (CHD), stroke, chronic kidney disease, blindness, and lower-limb amputations and is among the top ten causes of mortality worldwide. Diabetes and cardiovascular disease (CVD) are complex diseases affecting many parts of the health services, placing considerable pressure on specialist health care (2).

To ensure a standardised national treatment and to improve patient outcomes, the Norwegian Directorate of Health (Helsedirektoratet) publishes the *National clinical guideline for management of diabetes* (Nasjonal faglig retningslinje for diabetes) with recommended treatment targets for diabetes care (3). Coordination between primary and specialist levels of diabetes care is crucial. According to the Norwegian Directorate of Health's *National guideline for prioritization in specialist health care – Endocrinology and endocrine surgery* (Endokrinologi og endokrinkirurgi, Prioriteringsveileder), individuals with type 2 diabetes should mainly be treated in primary care and referred to specialist care for acute and late complications, following poor glycemic control or in other situations where the individual is at high risk for developing diabetes complications. Individuals with type 1 diabetes should receive treatment in specialist care (4). Additionally, all individuals with diabetes should be referred to ophthalmologists for regular retinal screening.

Socioeconomic disparities regarding vascular diseases were shown as early as in the first Framingham study in the 1950s (5). In that study, the incidence of CHD in a general population was significantly associated with education level, with the highest CHD incidence amongst those in the lowest education levels. In the Whitehall I study beginning in 1967, men in the lowest employment grade, classified by job title, had 3.6 times higher CHD mortality compared to men in the highest employment grade, even after adjustments for the established risk factors weight, blood pressure (BP), plasma glucose, cholesterol, smoking, and physical activity (6). Following these studies, several studies on diabetes have shown that socioeconomic conditions affect access to and the quality of diabetes care (7).

Type 2 diabetes can be cured, or the onset delayed. Although both pathophysiology and risk factors associated with type 2 diabetes are well known, the incidence and prevalence of the disease are rising worldwide (1). Early detection of the disease, effective therapies, thorough follow-up, and allocating individuals at high risk to specialist care may prevent or delay long-term vascular complications, thus reducing morbidity and mortality.

The Rogaland-Oslo-Salten-Akershus study (ROSA 4) has assessed the quality of care in Norway, including complication rates and adherence to clinical guidelines, delivered to type 2 diabetes patients in primary care based on the *National clinical guideline for management of diabetes* (8-12). However, knowledge on the status of diabetes type 2 and type 1 treatment with regards to cardiovascular risk factors, the prevalence of vascular complications and attained treatment targets is lacking, as is the status of diabetes treatment based on the *National guideline for prioritization in specialist health care – Endocrinology and endocrine surgery*.

1.2 Definitions and characteristics of type 2 and type 1 diabetes

Type 2 diabetes is the most common type of diabetes, accounting for over 90% of diabetes cases worldwide. Type 2 diabetes is a complex and heterogeneous metabolic disease with persistent hyperglycemia due to relative insulin deficiency. The onset is slow, and the development is considered a result of hyperinsulinemia, increased peripheral insulin resistance, defects in the insulin-producing and secreting beta-cells of the pancreas, and loss of beta-cell mass by 20% to 65% at diagnosis (13). Increased insulin resistance is mainly a result of lifestyle, including an unhealthy diet, sedentary behaviour, and obesity (14). Additional pathophysiological changes include dysregulation of protein, carbohydrate, and lipid metabolism.

Type 1 diabetes is characterized by the destruction of the beta-cells within the pancreas, followed by insulin deficiency. The onset is acute. Both genetic predisposal and environmental factors trigger the autoimmune response, but a minority do not have a detectable immune response. Latent autoimmune diabetes in the adult (LADA) is a condition with autoantibodies towards beta-cells, resulting in gradual loss of beta-cells. In contrast to type 1 diabetes, most individuals are not absolutely insulin dependent at the time of diagnosis,

and insulin production declines gradually (15). LADA usually will progress to resemble type 1 diabetes over the years.

There are also other types of diabetes. Maturity-onset diabetes of the young (MODY) is characterized by autosomal dominant inheritance, absence of β-cell autoimmunity, and sustained beta-cell function of the pancreas (16). Mutations in 14 different genes have been identified (16). Diabetes can also be caused by diseases in the pancreas, i.e. pancreatitis (17).

Diagnostic criteria for diabetes are glycated haemoglobin (HbA1c) ≥ 48 mmol/mol (≥ 6.5%), or fasting plasma glucose ≥ 7.0 mmol/L, and/or glucose ≥ 11.1 mmol/L two hours after a glucose tolerance test (3). Blood tests, including autoantibodies against insulin-producing beta-cells in the pancreas, usually anti glutamate acid decarboxylase (anti-GAD), and fasting C-peptide at diagnosis, may be helpful and sometimes necessary to classify diabetes as type 2, LADA, or type 1. Diabetes type 1 is anti-GAD positive. Moreover, individuals with type 1 diabetes have low fasting C-peptide (preferably < 0.3 nmol/L). LADA is anti-GAD-positive but has higher C-peptide at diagnosis (usually > 0.3 nmol/L). Type 2 is anti-GAD negative. Autoantibodies to tyrosine phosphatase (anti-IA2; an intracellular part of a protein phosphatase), insulin (IAA), and zinc transporter T8 (anti-ZnT8) are additional markers for beta-cell destruction (18).

1.3 Diabetes epidemiology

Epidemiology is the study of the distribution of diseases and determinants of diseases in a population (19). The goal of epidemiology is to improve health by understanding the causes of disease variation. Prevalence is defined as the number of individuals with the factor or disease in the study population at a particular time (20). The prevalence of diabetes reflects the disease burden. Incidence is defined as the number of new cases occurring during a specified time period in a population of known size (20).

Both the total prevalence and the incidence of diabetes increase worldwide. In 2014 the global age-standardised diabetes prevalence was 9.0% in men and 7.9% in women. The prevalence was lowest in north-western Europe, with a crude prevalence of 7.9% in men and 5.8% in women (21). In 2021, the estimated prevalence of diabetes was 10.5% in the global adult population (20-79 years) (1). By 2045, the number is expected to rise to more than 12%.

However, the disease burden is possibly much higher. It is estimated that 240 million people have undiagnosed diabetes, meaning that one-in-two adults with diabetes are unaware that they have the condition (1).

There has also been a steady rise in the prevalence of diabetes in Norway over the last decades. In 2004, the estimated prevalence of self-reported diabetes mellitus was 3.4% in individuals aged ≥ 30 years and 2.3% in all age groups (22). From 2009 to 2014, the estimated prevalence of type 2 diabetes increased from 4.9% to 6.1% in the age group 30 to 89 years (23). In 2020, more than 4.1% of the population, 221 000 individuals, had blood glucose-lowering drugs dispensed, and an estimated 260 000 to 280 000 people live with known diabetes in Norway. If we assume 270 000 individuals have known diabetes; this gives a prevalence of 5%. Approximately 60 000 people have undiagnosed diabetes (24, 25).

Type 1 diabetes can occur at any age. The incidence increases with age up to puberty and is higher among those aged < 15 years than among 15–29 year-olds. The International Diabetes Federation (IDF) estimates from 2021 indicate that around 108 200 children and adolescents aged < 15 years are diagnosed with type 1 diabetes globally per year (1). The incidence varies greatly between countries, with the highest incidences in children and adolescents in the Scandinavian countries (26).

1.4 Risk factors for type 2 diabetes

Risk factors for type 2 diabetes can be divided into modifiable and non-modifiable risk factors (24). Modifiable risk factors include overweight and obesity, physical inactivity, intrauterine development or prematurity disturbances, impaired fasting glucose or impaired glucose tolerance, metabolic syndrome, dietary factors, diabetogenic drugs, depression, obesogenic/diabetogenic environment, and low socioeconomic status. Obesity and a sedentary lifestyle are the main modifiable risk factors (27). Non-modifiable risk factors include age, family history or genetic predisposition, ethnicity, history of gestational diabetes, and polycystic ovary syndrome.

1.5 Diabetes vascular complications

Vascular complications are traditionally divided into macrovascular and microvascular complications. Macrovascular complications include CHD, myocardial infarction,

cerebrovascular disease (stroke), and peripheral artery disease and are not specific to diabetes. Microvascular complications include diabetic kidney disease/nephropathy, neuropathy, and retinopathy.

Type 2 diabetes increases the risk of vascular diseases by about two-fold compared to those without diabetes (28). While the microvascular complications of type 2 diabetes are a significant cause of morbidity, mortality is mainly driven by the macrovascular complications CHD and stroke.

The vascular complications of diabetes have been reported to decline worldwide (29, 30). However, as many individuals with type 2 diabetes remain undiagnosed and untreated, many presents with complications already at diagnosis. In a Danish study, one-third of individuals with type 2 diabetes had diabetes complications around the time of diagnosis (31). In a Norwegian study, CHD was diagnosed before type 2 diabetes was diagnosed in 48% of the individuals (32).

In the following sections, definitions, prevalence, and risk factors for developing the different vascular complications of diabetes included in the thesis are presented.

1.5.1 Cardiovascular disease

Cardiovascular disease (CVD) includes CHD, cerebrovascular disease/stroke, and peripheral artery disease.

Prevalence: CVD is the major macrovascular complication of type 2 diabetes. In a systematic review, the global prevalence of CVD in individuals with type 2 diabetes was 32.2% (33). A Swedish study reported a prevalence of CVD of 34% in individuals with type 2 diabetes requiring glucose-lowering drugs (34).

Risk factors: Inadequate glycaemic control, hypertension, elevated levels of low-density lipoprotein (LDL) cholesterol, and smoking are established risk factors for CVD shown to be reduced by improved management of diabetes treatment (35-37). CVD is the leading cause of morbidity and mortality in individuals with diabetes (38).

1.5.2 Coronary heart disease

CHD occurs when the arteries supplying the blood flow to the heart are narrowed or blocked by atherosclerotic plaque. CHD is also known as coronary artery disease, ischaemic heart disease, or atherosclerotic heart disease. According to the IDF Diabetes and CVD report, CHD includes angina pectoris, myocardial infarction, heart failure, and sudden coronary death (39).

Prevalence: In a systematic literature review including 42 articles, and 3 833 200 individuals, the reported prevalence of CHD was 21.2% in individuals with type 2 diabetes (33).

Risk factors: Hyperglycemia, dyslipidemia, and insulin resistance lead to endothelial dysfunction, alterations in platelet function and coagulation, oxidative stress, and low-grade inflammation, all contributing to the formation of atherosclerotic plaque (40, 41). In a meta-analysis that included nearly 700 000 individuals from 102 prospective studies, diabetes was associated with an approximately two-fold excess risk of CHD, also after adjustments for risk factors (28).

1.5.3 Stroke

Stroke can result from cerebral infarction (blocking a blood vessel) or cerebral haemorrhage (rupture of a blood vessel) and is one form of cerebrovascular disease. In individuals with diabetes, chronic hyperglycemia leads to vascular endothelial dysfunction and microvascular changes at cellular and genetic levels.

Prevalence: In a systematic literature review including 39 studies and 3 901 505 individuals, the reported prevalence of stroke was 7.6% in individuals with type 2 diabetes (33).

Risk factors: Risk factors for ischemic stroke in individuals with diabetes include hypertension, atherosclerosis, smoking, and atrial fibrillation (40).

1.5.4 Diabetic kidney disease

Diabetic kidney disease is a clinical diagnosis and a common name for various kidney diseases defined by elevated excretion of urine albumin or reduced glomerular filtration rate (GFR), or both (42). According to *Kidney Disease: Improving Global Outcomes (KDIGO)*

2012, Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease, chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health (43). CKD is classified based on cause, estimated GFR (eGFR) category, and albuminuria category. Criteria for CKD are decreased eGFR < 60 ml/min/1.73 m^2 or other markers of kidney disease, i.e. albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, or structural abnormalities detected by imaging (43). Diabetic nephropathy, characterised by hypertension, progressive albuminuria, glomerulosclerosis, and declining eGFR, is the most common cause of CKD in individuals with diabetes (44). Individuals with type 1 diabetes have a higher risk of CKD than individuals with type 2 diabetes (45). In type 2 diabetes, hypertension often exists prior to kidney disease, and hypertension leads to a progression of kidney disease (45).

Prevalence: The reported prevalence of CKD is 25-40% in individuals with diabetes (46, 47).

Risk factors: The pathogenesis of CKD is complex and multifactorial, and age, sex, predisposing genes, hyperglycemia, hypertension, smoking, dyslipidemia, and insulin resistance are recognised risk factors (46). Intensified glucose regulation is not expected to have the same effect on hypertensive kidney damage/nephrosclerosis as diabetic nephropathy seen in individuals with type 1 diabetes.

1.5.5 Diabetic foot complications

Diabetic foot complications are caused by chronic pathological processes such as neuropathy, peripheral artery disease, and impaired wound healing (48). Peripheral artery disease is a narrowing of the arteries other than those supplying the heart or the brain. The condition increases the risk of foot ulcers (49). Other factors involved in the development of foot ulcers in individuals with diabetes are peripheral neuropathy (sensory, motor, and autonomic) and trauma, which in Western countries are most often caused by tight shoes (50). Peripheral artery disease may require treatment with an invasive procedure called percutaneous transluminal angioplasty (PTA) used to open a blocked artery or arterial surgery to re-route the blood supply around the blocked artery.

Prevalence: Peripheral artery disease has been reported in 29% of individuals with diabetes (51). The lifetime incidence of a foot ulcer has been estimated to be 19% to 34% (49).

Risk factors: Smoking is a well-known risk factor for peripheral artery disease, as well as age, diabetes duration, hypertension, and dyslipidemia (52). The most important risk factors for foot ulcers are neuropathy and peripheral artery disease (53). Moreover, foot deformity and previous history of diabetic foot ulcers or lower limb amputation are associated with diabetic foot ulcers (50).

1.5.6 Diabetic retinopathy

Diabetic retinopathy is a progressive condition with microvascular alterations. The diagnosis is based on examining the retina with disease severity and classification assessment (54). Treatment is initiated based on severity.

Prevalence: The prevalence of diabetic retinopathy is higher in Western countries compared to Middle-East and Asian countries (55). Studies in the European population have shown a prevalence of diabetic retinopathy of 37–94% in type 1 diabetes and 16–38% in type 2 diabetes.

Risk: Diabetes duration, hyperglycemia, and hypertension are the most important risk factors for progression to vision loss (55).

1.6 Diabetes care in Norway

The following sections briefly present the Norwegian health care system, the organization of care for individuals with type 2 and 1 diabetes, the *National clinical guideline for management of diabetes*, recommended treatment targets, and The Norwegian Diabetes Register for Adults (NDR-A).

1.6.1 The Norwegian health care system

The government funds the public health care system in Norway. Every citizen has the right to be registered with a general practitioner (GP), responsible for all necessary primary health care services. The GP is a gatekeeper in the health care system. If examinations or treatment in specialist care are considered needed, the GP is responsible for referral to the specialist

health services. Residents aged 16 years and over must pay an annual deductible, in 2014, 2105 NOK (approximately 233 EUR) for doctor's visits and drug prescriptions before becoming eligible for an exemption card, covering further drug prescriptions and visits in primary and specialist care. In-hospital treatments are free.

1.6.2 National clinical guideline for management of diabetes

The Norwegian Directorate of Health publishes Norwegian national professional guidelines. The guidelines cover disease prevention, diagnosis, treatment, rehabilitation, and treatment organization when there is a need for a national standard and often on issues with professional disagreement or discrepancy in practice.

The first attempt to make an overall plan to improve diabetes treatment in Norway was launched in 1980 when the Norwegian Diabetes Association (Norges Landsforbund for sukkersyke) set up a committee with the mandate to issue recommendations for better diabetes care (56). In 1984 the first initiative was made to create a group within the Norwegian Society for General medicine (Norsk Selskap for allmennmedisin [NSAM]). The group's mandate was to develop a diabetes control form for primary care and create an action program for diabetes care in general practice settings. The Norwegian action program for diabetes was published in 1988 and revised in 1995, 2000, and 2004-2005; the latter was posted online. After 2005, The Norwegian Directorate of Health took over the responsibility for auditing the guidelines, and the new *National clinical guideline for management of diabetes* was published in 2009. The last guideline was published in 2016 based on GRADE methodology (3) and updated in 2019. Today's guidelines have 13 chapters covering, among other things, diagnosis of diabetes, assessment, organization of diabetes care, and medical treatment.

1.6.3 Assessment of risk in high-risk individuals

According to the *National clinical guideline for management of diabetes*, the GP should assess the risk of undiagnosed diabetes in people with diabetes in a close family, in case of obesity or physical inactivity, and people of Asian or African origin (3).

1.6.4 Treatment targets

The Norwegian guidelines have recommendations for glycaemic control, BP control, and lipid control. The treatment targets will be briefly presented in the following sections.

Glycaemic control

For most individuals with type 2 diabetes, the HbA1c treatment target is around 53 mmol/mol (7%) (3). A lower treatment target, HbA1c, around 48 mmol/mol (6.5%), is considered in younger and newly diagnosed individuals. A treatment target between 53-64 mmol/mol (7.0-8.0%) is accepted in individuals with longer diabetes duration, comorbidity, and risk of hypoglycaemia.

Blood pressure control

Antihypertensive treatment is recommended in individuals with BP > 140/90 mmHg (3), with a treatment target of < 135/85 mmHg. A treatment target of 130/80 mmHg should be considered for younger individuals with microvascular complications, especially nephropathy, and those at increased risk of stroke. Higher treatment targets, 150/85 mmHg, are considered in individuals over 80 years of age, individuals with isolated systolic hypertension, orthostatism, or drug side effects.

Lipid control

In current national guidelines, statin therapy is recommended in individuals aged 40-80 years without known cardiovascular disease if LDL-cholesterol > 2.5 mmol/L or when the overall risk is high. In individuals with known CVD (defined as CHD, ischemic stroke or TIA, and peripheral atherosclerosis), intensive statin therapy with LDL-cholesterol < 1.8 mmol/L is recommended.

Lifestyle and treatment of overweight and obesity

Adults with type 2 and 1 diabetes are recommended to be physically active with moderate to high intensity for a minimum of 150 minutes per week. A diet in line with the Norwegian Directorate of Health's dietary advice is recommended. However, an individually adjusted intake of starch and sugar is suggested as starch and sugar affect blood glucose. Individuals with type 2 diabetes and overweight or obesity should be offered a minimum 6-month

structured lifestyle treatment program in primary care with a 5-10% permanent weight loss goal. Anyone who wants to quit smoking should be offered structured help to quit.

1.7 The organization of care for individuals with diabetes: Level of care

According to the *National clinical guideline for management of diabetes*, follow-up, and treatment of individuals with type 2 diabetes usually take place in primary care (3). The *National guideline for prioritization in specialist health care – Endocrinology and endocrine surgery* strongly suggest that individuals with poor blood glucose control, late complications, macrovascular disease, or other complicating other conditions should be referred to specialist care with an indicative deadline of 12 weeks before starting treatment. Individuals with type 1 diabetes should be offered interdisciplinary follow-up in specialist care with at least one visit per year (3).

Hickman has defined shared care as “the joint participation of hospital consultants and general practitioners in the planned delivery of care for patients with a chronic condition, informed by an enhanced information exchange over and above routine discharge and referral notices" (57). In the papers included in this thesis, “shared care” is used to describe individuals visiting primary and specialist care in the defined period.

1.8 The Norwegian Diabetes Register for Adults

The Norwegian Diabetes Register for Adults (NDR-A) was established in 2006 and is run by the Norwegian Organization for Quality Improvements of Laboratory Examinations (Noklus). The NDR-A offers a national electronic form (Noklus diabetes window for general practice) developed by Noklus. The form interacts with the GPs’ journal systems and works as an add-on program to their electronic medical records. The form is a clinical tool summarizing risk factor control and it provides a checklist for recommended tasks at the annual review in a one-screen display. Moreover, the application acts as a collection tool for the register as it supports reporting to NDR-A. Reporting to NDR-A is optional. The software is free and can be downloaded from the internet. In 2014 approximately 25 500 individuals were registered in NDR-A, of whom about 16 000 had type 2 diabetes, and 8400 had type 1 diabetes.

Noklus also offers a complete diabetes record to hospitals and outpatient clinics, interacting with the hospital's journal system. In 2014, 32 of approximately 45 outpatient clinics reported to NDR-A, and in 2021 all 52 diabetes outpatient clinics in Norwegian hospitals reported to the register.

2 Aims of the thesis

The overall aim of this thesis was to assess the total prevalence of diagnosed diabetes and contribute to new knowledge on the status of diabetes treatment in Salten, Northern Norway. Furthermore, to provide new insight on the associations between education level and vascular complications in individuals with type 2 diabetes. The specific objectives of the three papers included in the thesis were:

1. To assess the prevalence of diagnosed type 2 and type 1 diabetes in all age groups of the population in the geographical area of Salten, Norway. To describe and compare cardiovascular risk factors, the prevalence of vascular complications, and attained treatment targets according to national guidelines in adults with type 2 and type 1 diabetes.

2. First, to identify the proportion and characteristics of individuals with type 2 diabetes and type 1 diabetes treated in primary, shared, and specialist care in the geographical area of Salten, Norway. Second, to determine the proportion of individuals with type 2 diabetes reaching HbA1c treatment targets. Third, identify clinical risk factors, GP, and practice characteristics associated with type 2 diabetes treatment in specialist care.

3. To assess whether there is an association between education level and diabetes vascular complications in individuals with type 2 diabetes born in Norway.

3 Materials and Methods

3.1 The ROSA 4 study

The first ROSA study investigating the quality of diabetes care in general practice was conducted in 1995 in Rogaland and Salten and initiated by Tor Claudi and John Cooper. They both were working as GPs at the time. Data from 1688 patients visiting 77 GPs in 33 GP practices were collected. The study was called ROSA, named by the geographical areas included: **Ro**galand and **Sa**lten. The following two studies were conducted in 1999/2000 and 2005, undertaken by Tor Claudi, John Cooper, and Anne Karen Jenum (58, 59). The ROSA 4 study from 2014 was the fourth study in this project. GPs in five strategically selected counties in three of the four Norwegian Health Regions participated. Nationwide, the ROSA 4 study invited 367 GPs working in 106 practices into the study, and 282 GPs working in 77 practices accepted the invitation. This corresponds to a response rate of 77% for the individual GP and 73% for GP practices. All 82 GPs in Salten accepted the invitation. Noklus (see chapter 1.8) led the data collection in ROSA 4 and was responsible for data storage and administration.

3.2 Setting

The Salten region in Nordland County is localised in and around Bodø, the largest city in the area. The Salten region covers eight municipalities: Bodø, Fauske, Hamarøy, Steigen, Saltdal, Beiarn, Gildeskål, and Sørfold (Figure 1). In the present study, Meløy municipality was also included. The Salten region (including Meløy) covers an area of approximately 10 000 km^2 and had a total population of 80 338 as of 31 December 2014, of whom 49 731 were living in Bodø (60). Table 1 shows the selected population demographics of Salten and Norway.

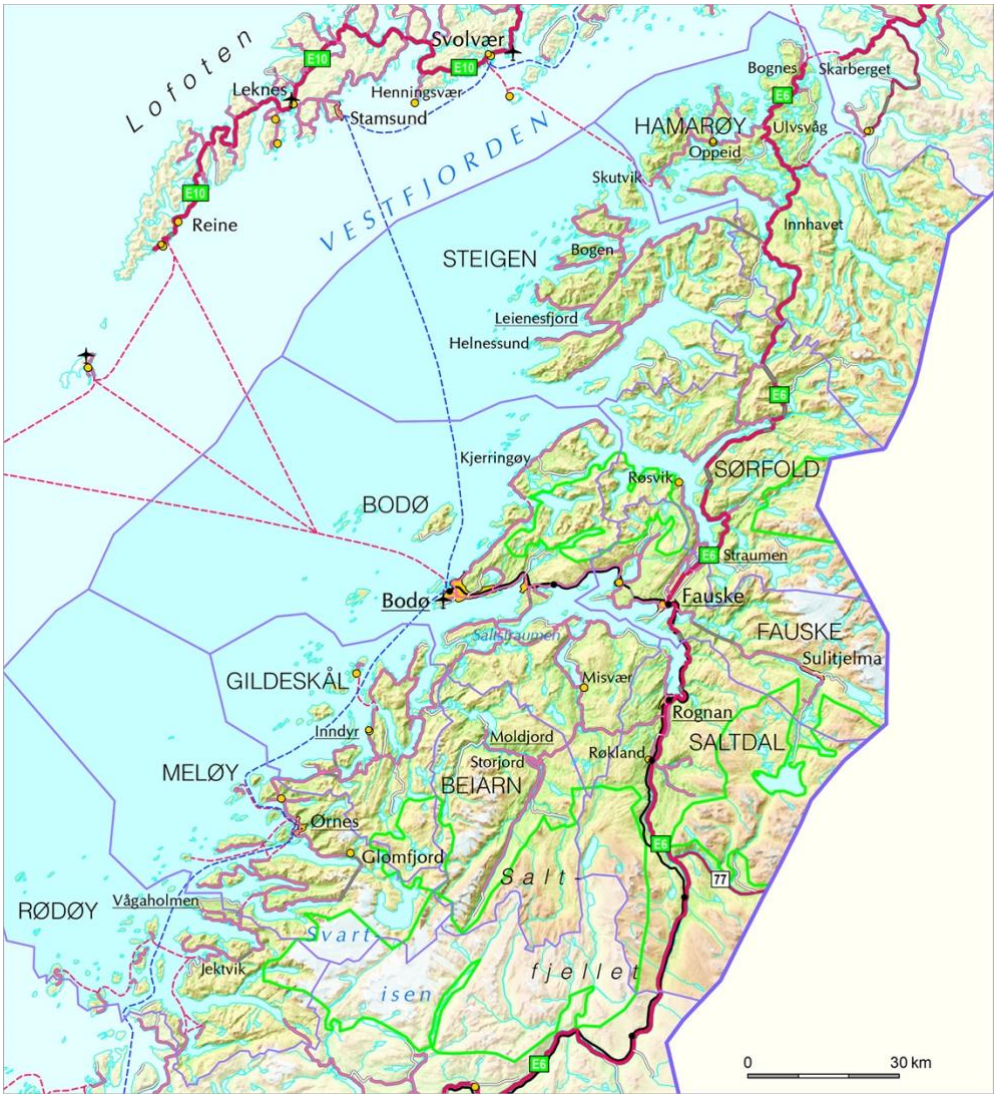

Figure 1. Map showing the Salten area in Northern Norway.

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There had been a structured collaboration between primary and specialist care (the diabetes outpatient clinic at the Department of Medicine, Nordland Hospital, Bodø) for at least ten years before 2014. As part of The Northern Norway Diabetes plan 2008-2013, diabetes education was offered to community health personnel. The plan described the shortcomings of diabetes treatment in hospitals in Northern Norway and advised on measures necessary to improve health care quality. No other health regions have had a similar structured approach to improving the care for diabetes patients. The plan was revised in 2013; the work led by Tor Claudi emphasised increasing GPs' use of the Noklus diabetes form and reporting to NDR-A, more structured teaching from specialist care diabetes teams to municipal health care services, and better data solutions interacting between primary and specialist care.

There are and have not been any private diabetologists in the Salten area.

Table 1. Population demographics of the Salten region and Norway 31 December 2014. Data were obtained from Statistics Norway (60).

	Salten (n = 80 338)	**Norway (n = 5 165 802)**
Age (mean)	39.5	38.9
Proportion > 60 years %	21.3	20.3
Sex, men %	50.6	50.3
Educational attainment of the population, %	-	-
Compulsory education	35.1	26.9
Upper secondary education	43.5	40.9
Higher education	21.4	32.2
Recipients of disability benefit, %	14.0	9.7
Immigrants and Norwegian-born to immigrant parents, country background, %	-	-
Total	8.2	15.6
Africa	1.7	2.0
Asia	2.0	4.9

3.3 Data sources

This thesis is based on data from the following sources:

- The ROSA 4 study:
  I. Individual-level patient data from primary care
  II. GP data with information about participating GPs, their staff, and organization
- The Norwegian diabetes register for Adults (NDR-A):
  Individual-level patient data from the diabetes outpatient clinic/specialist care in Bodø
- Statistics Norway (Statistisk sentralbyrå)

Supplementary sources:

- The pediatric clinic at Nordland Hospital in Bodø
- The municipal administration in the municipalities of Salten (Bodø, Fauske, Hamarøy, Steigen, Saltdal, Beiarn, Gildeskål, Sørfold, and Meløy).

The ROSA 4 study and NDR-A are the primary data sources in this thesis and were the basis of all three papers.

This thesis also includes information from four other registries and sources:

1) In Paper 2 and Paper 3, individual data from ROSA 4 and NDR-A were linked to Statistics Norway due to the unique Norwegian personal identification number with the possibility to obtain information on individual education levels.
2) In Paper 1, the number of children < 18 years of age with diabetes living in the Salten area was obtained from the paediatric clinic at Nordland Hospital in Bodø.
3) Individuals permanently living in nursing homes receive health services in the institution and are generally not in contact with their GP. The total number of individuals permanently residing in nursing homes in Salten in 2014 was obtained by contacting each municipality administration centre in Salten by phone during the winter of 2018. Based on this number, we estimated the number of individuals with diabetes in this population and included it in prevalence estimates in Paper 1.
4) In Paper 1, the total number of individuals alive and residing in the nine municipalities in Salten by 31 December 2014 was obtained from Statistics Norway, available online (60).

Table 2 shows diabetes type, geographical area, and data sources included in Paper 1, 2, and 3.

Table 2. Participants, geographical area, and data sources in Paper 1, 2, and 3.

	Paper 1	Paper 2	Paper 3
Diabetes type	Type 2 and type 1, MODY, diabetes caused by disease in the pancreas	Type 2 and type 1	Type 2
Excluded	Other types of diabetes	Other types of diabetes	Other types of diabetes Individuals born outside Norway
Geographic area	One region (Salten)	One region (Salten)	Five regions
Data sources	ROSA 4 NDR-A The pediatric clinic Municipality centres in Salten Statistics Norway	ROSA 4 NDR-A Statistics Norway	ROSA 4 Statistics Norway
ROSA 4/ NDR-A data linked Statistics Norway	No	Yes	Yes
Individuals included in analyses	3091/3027	3009	8192
GPs included in analyses	-	82	-

3.4 Data collection

The ROSA 4 data collection from primary care was performed by four study nurses, one in each study region (one nurse covering Oslo and Akershus). The study nurses visited each GP office included in the study between February 2015 and April 2016 and read and punched data from each diabetes patient's file. The electronic medical record system identified all patients with a diabetes diagnosis (T89 Insulin-dependent diabetes and T90 Non-insulin-dependent diabetes, in the International Classification of Primary Care [ICPC]) over a three-year period. The diabetes diagnoses set by the GPs were validated by the study nurses during data collection, as were data for interactions with specialist care (referrals to and discharge

notes from specialist care [diabetes outpatient clinic, internists, and ophthalmologists]). Data not suitable for electronic capture (year of diabetes diagnosis, height, weight, risk factors, history of vascular complication) were recorded. Data from specialist care were collected from NDR-A without data validation by a research nurse.

Data from primary care were securely transferred to the ROSA 4 database at Noklus as encrypted files via the secure health net (Helsenett). The ROSA 4 patient file was linked to Statistics Norway for information about patients' education, workforce status, and ethnicity.

3.5 Study design and participants

All three studies had a cross-sectional design. In total prevalence analyses in Paper 1, we included all individuals with diagnosed diabetes visiting primary care from 1 January 2012 to 31 December 2014 and all visiting specialist care (hospital outpatient clinic) from 31 October 2013 to 31 December 2014 (Figure 2). In prevalence analyses, we also included MODY and diabetes caused by diseases in the pancreas. The study did not include other types of diabetes, i.e., gestational diabetes and diabetes insipidus. In further analyses, we included all individuals with diagnosed diabetes visiting primary care and all consenting individuals visiting specialist care. We only included those with diabetes living and registered in Salten. The total number of individuals residing in Salten on 31 December 2014 was obtained from Statistics Norway. To include subgroups in the population not included in ROSA 4 study, the number of children < 18 years of age with diabetes was obtained and included in the prevalence analyses. The number of individuals permanently living in nursing homes was obtained (Bodø: 253, Fauske: 81, Saltdal: 39, Meløy: 55, Gildeskål: 35, Steigen: 32, Beiarn: 22, Hamarøy: 28, Sørfold: 25; a total of 570) and the number of individuals with diabetes in this populations was estimated based on previous prevalence data for this population.

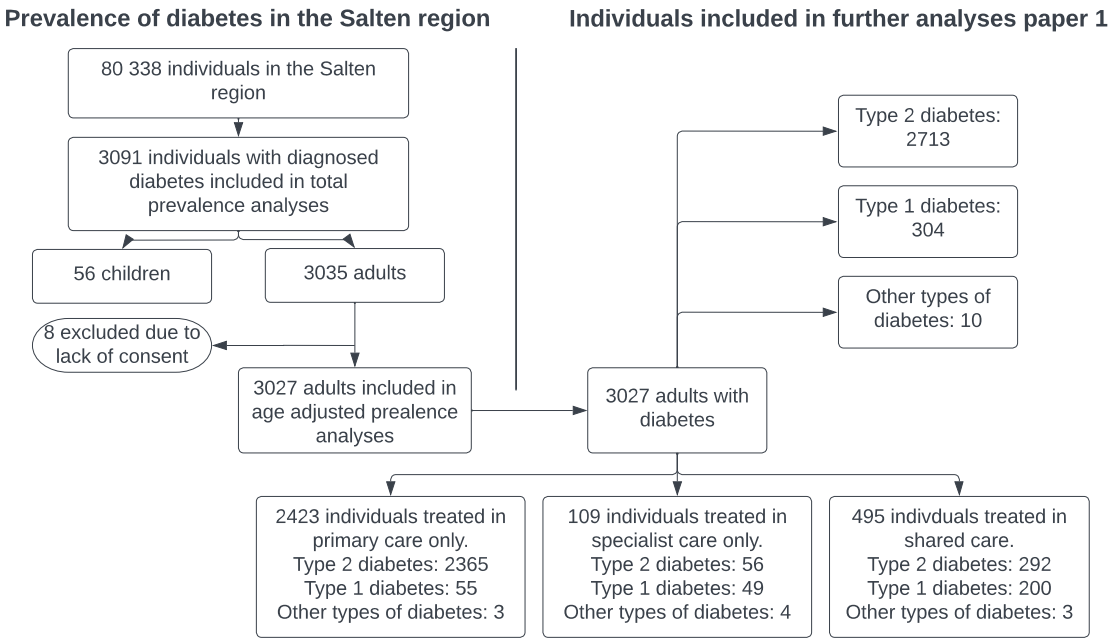

Figure 2. Flowchart Paper 1. Estimation of diabetes prevalence and overview of individuals included in the study grouped by diabetes type and level of care.

In Paper 2, we included individuals diagnosed with type 2 or type 1 diabetes visiting primary care and all consenting individuals visiting specialist care from 1 January 2012 to 31 December 2014 (Figure 3). The linkage to Statistics Norway was done after the publication of Paper 1. In the linking process, it was decided to change the inclusion period in specialist care. In Paper 1, we included patients visiting specialist care between 31 October 2013 and 31 December 2014. In Paper 2, the time interval was changed to between 1 January 2012 and 31 December 2014. Consequently, more individuals were registered as visiting specialist care or shared care in Paper 2 than in Paper 1. The total number of individuals included in the study also changed. All individuals were given new identification numbers in the linking process, and changes between the two data sets could therefore not be traced.

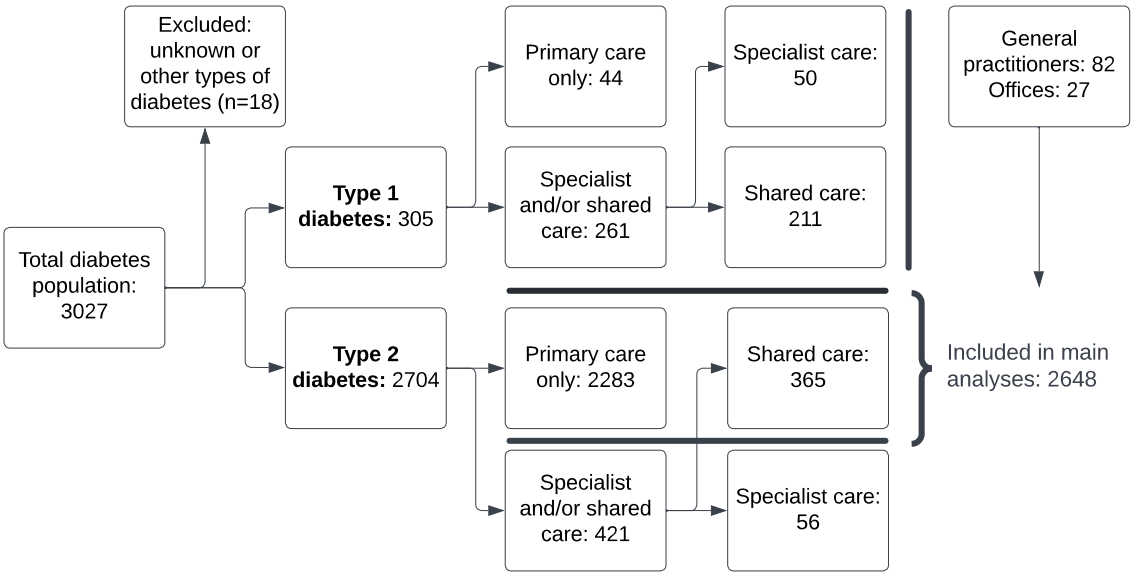

Figure 3. Flowchart Paper 2. Individuals included in analyses Paper 2, diabetes type and level of care.

In Paper 3, the study population consisted of individuals with type 2 diabetes born in Norway and visiting primary care in five regions in Norway between 1 January 2012 and 31 December 2014: Nordland, Rogaland, Hordaland, Oslo, and Akershus (Figure 4).

Figure 4. Patient data from five Norwegian regions were collected in the ROSA 4 study and included in the analyses in Paper 3.

Created with BioRender.com

3.6 Variables

Individual characteristics

Table 3 shows variable descriptions of patient characteristics included in Paper 1, 2, and 3.

Table 3. Variable descriptions of sample characteristics included in Paper 1, 2 and 3

	Paper 1	Paper 2	Paper 3
Patients characteristics			
Sex	men/women	men/women	men/women
Age	continuous	continuous	continuous
Age at diagnosis	continuous	continuous	continuous
Diabetes type	3 categories	2 categories	_
Diabetes duration	continuous	continuous	continuous
BMI	continuous	continuous	continuous
Smoking	yes/no	_	yes/no
Education level	_	3 categories	3 categories
Born outside Europe	_	yes/no	_
Attending hospital outpatient clinic	yes/no	yes/no	_
Cardiovascular risk factors and attained treatment targets			
HbA1c	continuous, 2 categories	continuous, 3 categories	continuous
Systolic blood pressure, mmHg	continuous, 2 categories	continuous, 2 categories	continuous
Diastolic blood pressure, mmHg	continuous, 2 categories	continuous, 2 categories	continuous
LDL cholesterol, mmol/L	continuous, 4 categories	continuous, 4 categories	continuous
Prescribed medication			
Glucose lowering agents	yes/no	_	_
Insulin	yes/no	yes/no	yes/no
Antihypertensive agents	yes/no	yes/no	yes/no
Lipid lowering medication	yes/no	yes/no	yes/no
Lipid lowering medication with CHD	yes/no	yes/no	yes/no
Lipid lowering medication with no CHD	yes/no	yes/no	yes/no
Acetylsalicylic acid	yes/no	yes/no	yes/no
Vascular complications	yes/no	yes/no	yes/no
Macrovascular complications	yes/no	_	_
Coronary heart disease	yes/no	yes/no	yes/no
Stroke	yes/no	yes/no	yes/no
PTA/arterial surgery	yes/no	yes/no	yes/no
History of foot ulcer	yes/no	yes/no	yes/no
Lower limb amputation	yes/no	yes/no	yes/no
Foot complications	_	_	yes/no
Nephropathy (eGFR, ml/min)	3 categories	3 categories	_
Chronic kidney disease (eGFR <60 ml/min/1.73m^2)	_	_	yes/no
Retinopathy	3 categories	3 categories	yes/no

Abbreviations: BMI: body mass index, PTA: percutaneous transluminal angioplasty.

Patient characteristics included sex, age, and diabetes type: 1) type 2 diabetes, 2) type 1, including latent autoimmune diabetes in the adult (LADA), 3) other types (including MODY or pancreatitis), diabetes duration and ethnicity defined as born outside Europe. Education was categorised as compulsory/primary education (completed primary and lower secondary school), upper secondary school/secondary education (completed upper secondary school), and higher/tertiary education (completed education beyond upper secondary school). Moreover, individuals registered with a visit to the hospital diabetes outpatient clinic in the defined period were categorised as attending specialist care. Individuals registered in primary and specialist care in the defined period were classified as receiving shared care. Body mass index (BMI) was used as a continuous variable.

Cardiovascular risk factors and attained treatment targets. Cardiovascular risk factors included HbA1c, systolic BP, diastolic BP, LDL-cholesterol, and smoking status. Treatment targets were as follows: HbA1c < 53 mmol/mol (< 7.0%), BP < 135/80 mmHg in individuals treated with antihypertensive agents and < 140/85 mmHg if untreated, LDL-cholesterol < 3.5 mmol/L if untreated, and < 1.8 mmol/L and < 2.5 mmol/L in treated individuals with and without CHD, respectively.

Prescribed medication included glucose-lowering agents (metformin, sulfonylurea, acarbose, glitazone, and insulin), antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium antagonists, thiazides), lipid-lowering medication (statins) and acetylsalicylic acid.

Vascular complications included CHD (angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass surgery), stroke, PTA, or arterial surgery, history of foot ulcer, lower limb amputation, nephropathy or chronic kidney disease and retinopathy.

In Paper 1, the composite variable macrovascular complications included CHD (angina pectoris, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass surgery), stroke, PTA, and arterial surgery. In Paper 3, the composite variable foot complications included PTA, arterial surgery, foot ulcer, and lower limb amputation. Serum creatinine was measured in µmol/l, and eGFR was calculated using the CKD-EPI equation. In Paper 1 and 2 eGFR was divided into ≥ 60 ml/min/1.73m^2, 30-59 ml/min/1.73m^2

and < 30 ml/min/1.73m^2. In Paper 3, chronic kidney disease was defined as eGFR < 60 ml/min/1.73m^2. In Paper 1 and 2, retinopathy was divided into treated and untreated, whereas these were combined in Paper 3.

In case of discrepancies in the registration of an individual's vascular complication in primary and specialist care, we chose to register the individual with the complication.

Table 4 shows variable inclusion periods for Paper 1, 2, and 3, as inclusion periods differed slightly between papers.

Table 4. Patient and variable inclusion periods in Paper 1, 2, and 3, by the level of care.

	Paper 1		Paper 2		Paper 3
Variables	**Primary care**	**Specialist care**	**Primary care**	**Specialist care**	**Primary care**
	All adults (≥ 18 years) with a diagnosis of diabetes 1 Jan. 2012 to 31 Dec. 2014	All adults (≥ 18 years) visiting 31 Oct. 2013 to 31 Dec. 2014	All adults (≥ 18 years) with a diagnosis of diabetes 1 Jan. 2012 to 31 Dec. 2014	All adults (≥ 18 years) visiting 1 Jan. 2012 to 31 Dec. 2014	All adults (≥ 18 years) with a diagnosis of diabetes 1 Jan. 2012, to 31 Dec. 2014
Characteristics					
Diabetes duration	2014 minus year of diagnosis	2014 minus year of diagnosis	2014 minus year of diagnosis	2014 minus year of diagnosis	2014 minus year of diagnosis
Height	If ever registered	If ever registered	If ever registered	If ever registered	If ever registered
Weight	15 months	15 months	15 months	36 months	15 months
BMI	15 months	15 months	15 months	36 months	15 months
Vascular complications					
Retinopathy	If ever registered	If ever registered	If ever registered	If ever registered	If ever registered
Coronary heart disease	If ever registered	If ever registered	If ever registered	If ever registered	If ever registered
Stroke	If ever registered	If ever registered	If ever registered	If ever registered	If ever registered
Diabetic foot ulcer	If ever registered	If ever registered	If ever registered	If ever registered	If ever registered
Risk factors					
HbA1c	15 months	15 months	36 months	36 months	36 months
Blood pressure	15 months	15 months	15 months	36 months	15 months
Lipids	36 months	36 months	36 months	36 months	36 months
Creatinine/eGFR	36 months	36 months	36 months	36 months	36 months
Medication	Prescriptions 15 months and if registered manually	If registered manually	Prescriptions 36* months and if registered manually	If registered manually	Prescriptions 36 months

Timeframes: 12 months: 1 January 2014 to 31 December 2014. 15 months: 1 October 2013 to 31 December 2014. 36 months: 1 January 2012 to 31 December 2014. * Unfortunately there is a typo in Paper 2 (15 months). The correct timeframe is 36 months.

General practitioners and practice characteristics

In Paper 2, general practitioner and -practice characteristics were included as independent variables, and the variables are listed in Table 5.

Table 5. Variable descriptions of general practitioner and practice characteristics included in analyses in Paper 2.

	Paper 1	Paper 2	Paper 3
General practitioners characteristics			
Age	_	continuous	_
Sex	_	men/women	_
Medical education in Norway	_	yes/no	_
Specialist in general practice	_	yes/no	_
Years working as GP	_	continuous	_
Workload (patients on list)	_	continuous	_
No. of people with T2D per GP	_	continuous	_
No. Of people with shared care	_	continuous	_
User of a structured diabetes form	_	yes/no	_
General practice characteristics			_
Urban location	_	yes/no	_
Diabetes nurse employed	_	yes/no	_

We have information about participating GPs (age, sex, specialist status, age, country of origin, and medical degree), staff members, and care organization. The GP was registered as a user of the structured Noklus form if more than 50% of the form was completed in a minimum of ten patients or in more than 50% of the GP's patients with diabetes.

In Paper 1, the *National clinical guideline for management of diabetes* from 2009 was used as a reference for good quality. The *National guideline for prioritization in specialist health care – Endocrinology and endocrine surgery* represents the national standard for which diabetes patients should be offered shared care.

3.7 Statistical methods

3.7.1 Regression analyses

Linear regression models were used for continuous outcome variables, and logistic regression models were used for categorical outcome variables. Regular regression modeling assumes independent observations. If this assumption is not met, multilevel analyses are used to account for clustering. Clustering can be seen at different levels. The following is an example: Patients seen by the same GP for a given condition may receive more similar treatment than those treated for the same condition by different GPs. Moreover, there may be clustering at the GP practice level due to, for example, GPs knowledge exchange and patients attending a GP practice tend to have some similarities. To account for this clustering, we used mixed-effect logistic regression.

3.7.2 Direct and indirect effects

The effect of an independent variable X on a dependent variable Y can be expressed as X $\rightarrow$ Y. Sometimes, parts of this effect can occur through another mediating (mediator) variable Z: X influences Z, which in turn influences Y (61). The direct effect is the effect of the independent variable X on the dependent variable Y absent the mediating variable Z (62). The indirect effect is the effect of the independent variable X on the dependent variable Y that works through the mediating variable Z. The total effect of X on Y is the combined effect of the indirect and direct effects.

3.7.3 Imputation of missing data

Epidemiological studies often involve handling missing data. Researchers can choose to study observations without missing data, complete case analyses, or use imputation techniques to study all observations. To avoid selection bias in Paper 3, we used the statistical technique of multiple imputations to handle missing data. We used an imputation method called multiple imputations by chained equation (MICE) to impute datasets with complete data. First, the multiple imputation procedure replaces each missing value with numerous possible values (63). MICE can handle continuous, binary, unordered, and ordered categorical variables (64). Continuous variables are handled by predictive mean matching, and logistic regression is used to impute dichotomous variables. Missing data are replaced by independent simulated sets of values, and *m* numbers of imputed datasets are produced. Second, each imputed data set is analysed separately. Third, estimates from the multiple data sets are combined.

The multiple imputation method is designed to reflect the uncertainty surrounding the missing values accurately. The method is usually performed under the missing at random (MAR) assumption, but it may also be performed under specific missing, not at random (MNAR) assumptions (65). In Paper 3, the method was used under the assumption that data were missing at random (MAR).

We included the following variables in the multiple imputation models: I) Patient-level variables: age, sex, age at diagnosis, diabetes duration, education level, county, BMI, HbA1c, systolic and diastolic BP, LDL-cholesterol, smoking status, CHD, stroke, foot ulcer, amputation, arterial surgery, retinopathy, eGFR, prescription of lipid-lowering drugs, oral glucose-lowering drugs, acetylsalicylic acid, insulin. II) GP level variables: age, sex, specialist status, use of a structured diabetes form. III) Clustering variables: GP identification number and practice identification number.

3.7.4 Statistical analyses Paper 1, 2, and 3

Descriptive statistics were used to summarise the data in all three papers. Categorical variables were presented with frequencies and percentages, and continuous variables were presented with means and standard deviations (SD) or medians with interquartile range (IQR) according to the distribution. We addressed the normality of variables by visual inspection of histograms.

Paper 1: To estimate the crude prevalence of diabetes, the total number of diabetes cases identified from ROSA 4, NDR-A, and the paediatric clinic was used as the nominator, and the total number of individuals alive and residing in the nine municipalities in Salten by 31 December 2014, was used as the denominator. The diabetes prevalence estimates were stratified by diabetes type, 10-year age group, and sex. We estimated the total diabetes prevalence using the Norwegian proportion of immigrants from Asia and Africa and by including the estimated number of individuals with diabetes permanently living in nursing homes in Salten. Age standardisation was performed using the age distribution of the Norwegian population by 31 December 2014. Univariable and multivariable linear and logistic regression models were used to compare variables of interest between type 2 and 1 diabetes. We adjusted for age, sex, and diabetes duration in the multivariable models due to

possible confounding between diabetes type and the outcomes of interest. Differences in complications and cardiovascular risk factors between diabetes types were calculated using the margins command to estimate Average adjusted predictions and average marginal effects with 95% confidence intervals (CI). Marginal effects tell us how a dependent variable change when an independent variable changes and other variables are assumed to be held constant (66).

Paper 2: We used multivariable mixed-effects logistic regression to estimate the odds of being treated in specialist care (outcome variable). Characteristics of population, GP, and practices were exposure (independent) variables. We ran separate models for each exposure variable and adjusted for age, sex, diabetes duration, and education as fixed effects in the models due to possible confounding between outcome and the different exposure variables. GP practice was included as a random effect in the models.

Paper 3: We performed multilevel multiple imputations of the missing variables using the function mice.impute.ml.lmer in the statistical software package R, making 25 datasets to reduce potential selection bias rising from a high proportion of missing information on BMI, BP, LDL-cholesterol, smoking status, and retinopathy. Multiple imputation models were used under the assumption that data were missing at random.

Analyses of associations between education and outcomes were performed using a mixed-effect logistic regression model for binary outcomes on imputed data and complete cases. In Model 1, we adjusted for age and sex as these are considered potential confounders. In Model 2, we additionally adjusted for the potential mediators HbA1c, LDL-cholesterol, systolic BP, smoking, and diabetes duration to estimate the direct effect of education level. County was included as a random effect in all models. We included the same number of individuals in unadjusted analyses as in adjusted models 1 and 2 for each outcome in complete case analyses. Results were presented as unadjusted and adjusted odds ratios (OR) with 95% CI.

In Model 1, we wanted to find the total effect of education on vascular complication rates. We therefore adjusted for the potential confounders age and sex. In Model 2, we wanted to identify the direct effect of education level on vascular complications and therefore adjusted for potential mediators: HbA1c, LDL-cholesterol, systolic BP, smoking, and diabetes duration.

Statistical analyses were performed using STATA, versions 14, 15, and 16.1 (StataCorp, LP, College Station, Texas, USA). Multiple imputations were done in R version 3.6.2 (R Core Team. R: A language and environment for statistical computing. Foundation for Statistical Computing, Vienna, Austria). The significance level was set at 0.05 for all analyses.

3.8 Ethical considerations

The ROSA 4 study was approved by the Regional Ethical Committee West (REK 2014/1374, REK Vest) with permission to collect retrospective patient data from general practice without informed consent and to link the ROSA 4 data file with data from national registers (Statistics of Norway). Data from patients attending the outpatient clinic was only obtained from individuals consenting to send their data to the Norwegian Diabetes Registry for Adults. The project had a strong user involvement during planning and project management. The Norwegian Diabetes Association informed about the study and the possibility of withdrawing from it on their website.

3.9 Funding

Data collection of the ROSA 4 was funded by 1.2 million NOK from the pharmaceutical industry (6 different companies), 1.05 million NOK from the Norwegian Diabetes Association, 300 000 NOK from the Diabetes Project in The Northern Norway Regional Health Authority, 25 000 NOK from Nordland Hospital Bodø, 125 000 NOK from the University of Oslo and 250 000 NOK from the Endocrinology Research foundation, Stavanger. The pharmaceutical companies have one member in the advisory group but no influence on study methods or interpretation of results. Northern Norway Regional Health Authority (Helse Nord) supported the PhD doctoral program of the candidate.

4 Results – summary of papers

4.1 Paper 1

The objective of Paper 1 was to present the total prevalence of type 2 and type 1 diabetes in Salten, Norway, and to describe and compare cardiovascular risk factors, the prevalence of vascular complications, and attained treatment targets according to the *National clinical guideline for management of diabetes* in adults with type 2 and type 1 diabetes in Salten. We included data from 3091 individuals with diabetes in the total prevalence analyses. In further analyses, we included 3027 adults in total; all individuals diagnosed with diabetes visiting the 82 GPs in 26 practices (100% of the invited) in the Salten area and all consenting individuals (98.7%, 604 out of 612 individuals) visiting the diabetes outpatient clinic/specialist care.

4.1.1 Prevalence of diabetes

The prevalence of total diabetes in all age groups was 3.8% (Figure 8). The prevalence of type 2 diabetes was 3.4%, and the prevalence of type 1 diabetes was 0.45%. In the age group 30-89 years, the prevalence of type 2 diabetes was 5.3%. Among the 3027 adults aged ≥ 18 years with diabetes, 2713 (89.6%) had type 2, and 304 (10.0%) had type 1 diabetes. Ten individuals (0.3%) had other types of diabetes (MODY or pancreatitis-induced diabetes).

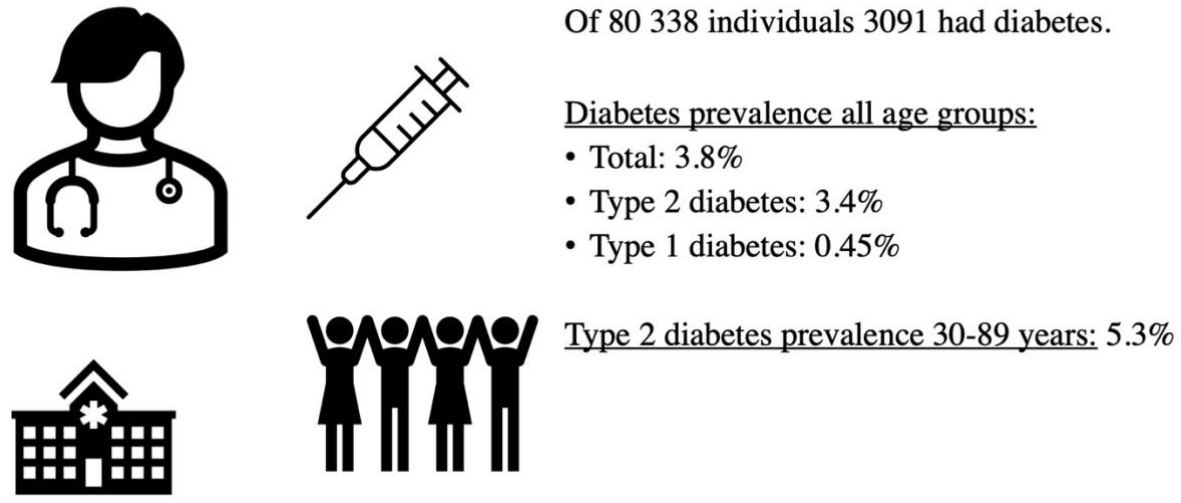

Figure 5. Diabetes prevalence in the Salten region.

4.1.2 Prevalence of vascular complications

The crude prevalence of any macrovascular complication was higher in type 2 diabetes patients than in type 1 diabetes (29.2% vs 13.0%, $p < 0.001$). Likewise, the crude prevalence of CHD was higher in type 2 diabetes than in type 1 diabetes patients (24.1% vs 10.2%, $p < 0.001$). The prevalence of CHD remained significantly more prevalent in individuals with type 2 diabetes when adjusting for age, sex, and diabetes duration than in individuals with type 1 diabetes (23.1% vs 15.8%, $p = 0.019$).

4.1.3 Cardiovascular risk factors

The HbA1c treatment target of ≤ 53 mmol/mol (≤ 7%) was reached by 61.1% of individuals with type 2 diabetes and 22.5% of those with type 1 diabetes. Individuals with type 2 diabetes had higher BP than those with type 1 diabetes; adjusted mean BP values were 136/78 mmHg and 131/74 mmHg. Mean values of HbA1c were lower in type 2 diabetes patients than in type 1 diabetes patients: 7.1% and 7.5%, respectively.

We concluded that the prevalence of diagnosed type 2 diabetes was slightly lower than anticipated. CHD was more prevalent in individuals with type 2 diabetes than in those with type 1 diabetes. Glycaemic control was not satisfactory in most individuals with type 1 diabetes.

4.2 Paper 2

The objective of this paper was to identify the proportion and characteristics of individuals with type 2 and type 1 diabetes treated in primary, specialist, and shared care. Furthermore, we aimed to identify the proportion of individuals with type 2 diabetes reaching HbA1c treatment targets and the clinical risk factors and general practitioner and practice characteristics associated with treatment in specialist care. Data from 2704 individuals with type 2 diabetes, 305 individuals with type 1 diabetes, and 82 GPs were included in the analysis.

4.2.1 Level of care

Among individuals with type 2 diabetes, 13.5% were treated in shared care and 2.1% in specialist care only. Among individuals with type 1 diabetes, 14.4% received treatment in primary care only.

4.2.2 HbA1c treatment target

Approximately two-thirds (67.3%) of type 2 diabetes patients in primary care reached the HbA1c treatment target of ≤ 53 mmol/mol (≤ 7.0%), compared to 30.4% in specialist/shared care.

4.2.3 Factors associated with treatment in specialist care

HbA1c was associated with treatment in specialist care: per one-unit increase in HbA1c measured in %, the adjusted odds for treatment in specialist care increased by 54% (OR 1.54, 95% CI 1.39 to 1.71). Further, individuals with CHD (OR 1.99, 95% CI 1.47 to 2.68), retinopathy (OR 2.78, 95% CI 1.97 to 3.93), and foot ulcer (OR 5.55, 95% CI 2.94 to10.48) were more likely to be treated in specialist care. Higher GP age was associated with treatment in specialist care (OR 1.01, 95% CI 1.00 to 1.02), as was the urban location (OR 1.53, 95% CI 1.18 to 1.98). On the other hand, GP's use of a structured diabetes form (OR 0.53, 95% CI 0.40 to 0.69) and having a diabetes nurse employed (OR 0.64, 95% CI 0.50 to 0.82) were associated with lower odds for treatment in specialist care (Figure 10).

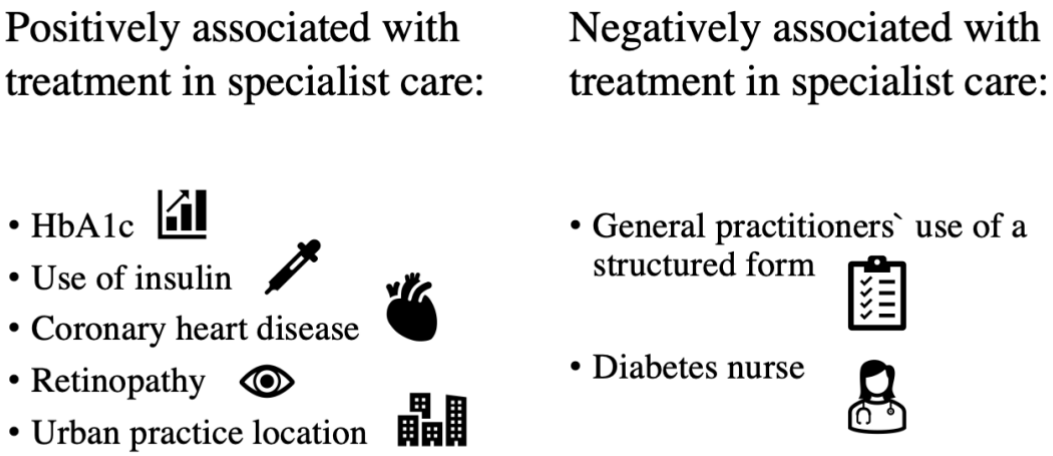

Figure 6. Factors associated with treatment in specialist care.

We concluded that individuals with type 2 diabetes treated in specialist care had higher HbA1c and more vascular complications than individuals treated in primary care, as expected from priority guidelines. The use of a structured diabetes form and diabetes nurses seem to support type 2 diabetes follow-up in primary care.

4.3 Paper 3

In Paper 3, the objective was to examine the relationship between education level and vascular complications among individuals with type 2 diabetes born in Norway. Data from 8192 patients from the ROSA 4 study were included in the analysis, of whom 33.9% 2789 patients) had completed primary school education, 48.9% (4016 patients) high school education, and 16.9% (1387 patients) university education.

4.3.1 Education level and vascular complications

The prevalence of CHD was 25.9% in those with primary school education and 23.0% and 16.9% in those with high school and university education, respectively. The prevalence of stroke was 9.6%, 7.4% and 6.6%, respectively, chronic kidney disease (eGFR < 60 ml/min) 23.9%, 16.8% and 12.6% and retinopathy 13.9%, 11.5% and 11.7%, respectively.

Higher education levels were associated with lower odds for CHD compared to compulsory education in both unadjusted and adjusted analyses on imputed data. When adjusting for age and sex in Model 1, OR for CHD in individuals with upper secondary education was 0.84 (95% CI 0.74 to 0.95) compared to individuals with compulsory education. Individuals with higher education had 42% lower odds for CHD (OR 0.58, 95% CI 0.49 to 0.70) compared to individuals with compulsory education. After adjusting for age, sex, HbA1c, LDL-cholesterol, systolic BP, smoking, and diabetes duration in Model 2, individuals with upper secondary education had 17% lower odds for CHD (OR 0.83, 95% CI 0.73 to 0.93). Those with higher education had 41% lower odds for CHD (OR 0.59, 95% CI 0.49 to 0.71) than individuals with primary education.

In both models, individuals with upper secondary and higher education had lower odds of chronic kidney disease than individuals with compulsory education. Moving from Model 1 to Model 2, the results remained largely unchanged as those with upper secondary education had 17% lower odds (OR 0.83, 95% CI 0.72 to 0.95), and those with tertiary education had 26%

and 25% lower odds (OR 0.74, 95% CI 0.60 to 0.92 and OR 0.75, 95% CI 0.60 to 0.93) compared to compulsory education.

Education level was associated with foot complications in Model 1 but not in Model 2 due to an overall p-value of 0.68. Similarly, education level was associated with retinopathy in Model 1 but not in Model 2.

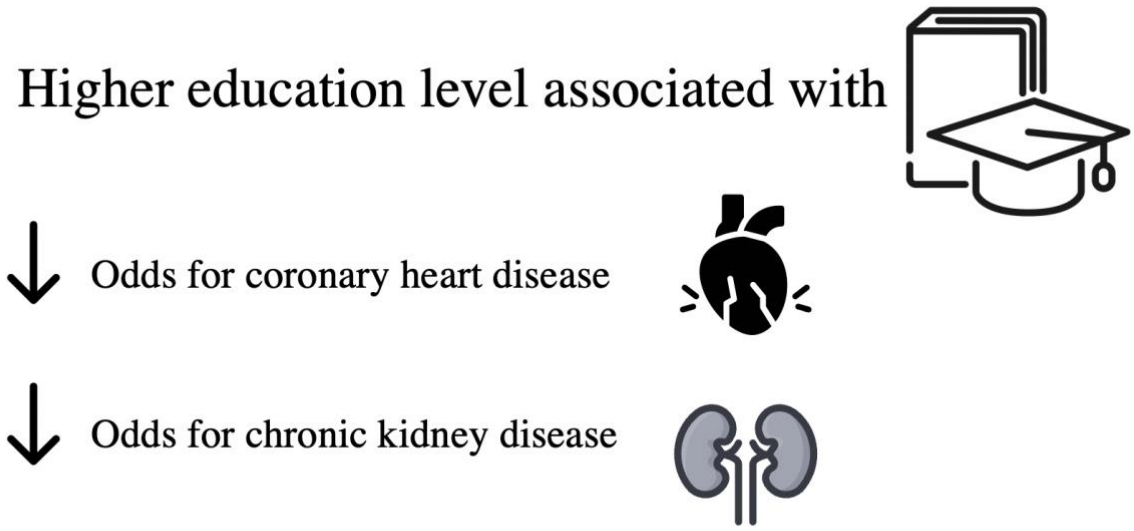

Figure 7. Education level and vascular complications in type 2 diabetes.

We concluded that in a country with equal access to health care, higher education levels were associated with lower odds for CHD and chronic kidney disease. These results remained after adjusting for risk factors. Greater focus on risk reduction in individuals with type 2 diabetes and low education level may be warranted.

Figure 8 shows a summary of results in Paper 1, 2, and 3.

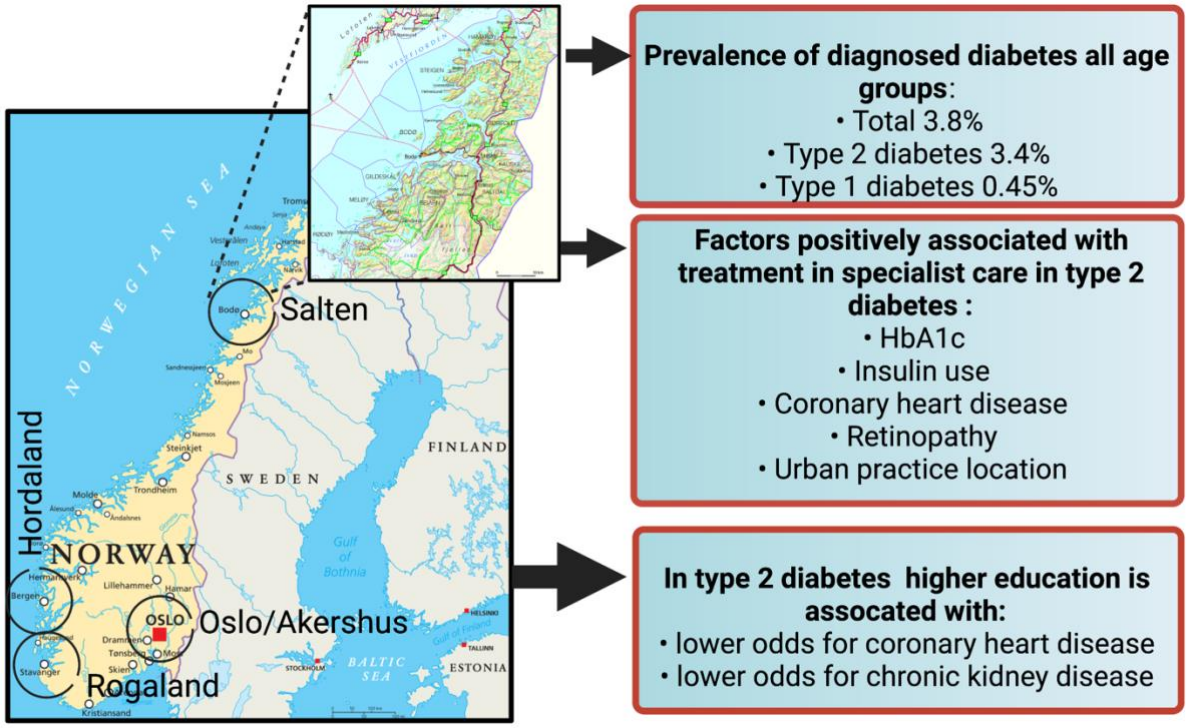

Figure 8. Summary of results Paper 1, 2, and 3.

Created with BioRender.com

5 Discussion of methodology

The main objectives of this thesis were to describe the prevalence of diagnosed type 2 and type 1 diabetes in Salten, Northern Norway, assess the status of diabetes treatment and factors associated with type 2 diabetes treatment in specialist care, and study the association between education level and vascular complications in individuals with type 2 diabetes born in Norway. When interpreting the results presented in this thesis, the complexities in diabetes treatment and care and the disease itself must be kept in mind. But just as important, evaluating results from epidemiological studies requires judging whether the observed association between the independent and the dependent variable is accurate or introduced by a systematic or random error or by confounding. The study's validity must be considered, defined as "the degree to which inferences drawn from a study are valid" (19, p. 287). There are two types of study validity, internal and external validity (19). This and other methodological considerations will be discussed in the following.

5.1 Study design

All three papers were based on registry data with a cross-sectional design. Cross-sectional studies, conducted in a population at a specific time and place, can measure disease frequency and factors that may cause disease simultaneously (20).

In Paper 1, we aimed to estimate the prevalence of known type 2 and type 1 diabetes and the proportion of individuals reaching recommended treatment targets identical for the two diabetes types. The cross-sectional design allowed estimating the prevalence of diagnosed diabetes and vascular complications and the proportion reaching treatment targets. Moreover, the design permitted comparing risk factors, attained treatment targets and vascular complications between diabetes types. In Paper 2, we aimed to identify the proportions and characteristics of individuals treated in primary, specialist and shared care and the proportion of individuals with type 2 diabetes reaching the HbA1c treatment target at the time of the study. The cross-sectional design was considered suitable to answer these aims.

In Paper 2, we also aimed to describe factors associated with treatment in specialist care in individuals with type 2 diabetes. I acknowledge that a prospective cohort study would be the best design to study the association between risk factors, vascular complications, and level of

care. A cross-sectional design cannot show directions of associations, and causal interferences are impossible (20). Moreover, the time order of cause and effect cannot necessarily be determined in a cross-sectional study (19). The following acts as an example: in the ROSA 4 study, we do not know whether risk factor variables included in the analyses in Paper 2 were measured and recorded before or after the referral and treatment in specialist care. Additionally, treatment duration in specialist care and the potential effect of any treatment interventions initiated in specialist care was unknown. If the aim had been to study which factors included in the analyses caused treatment in specialist care, we would need a prospective design. This consideration also applies to Paper 3 as we used a cross-sectional design to study the association between education level and vascular complications and cannot show causal relationships.

Cohort effects are a particular issue in cross-sectional studies. The cohort effect can be described as a "Variation in health status that arises from the different causal factors to which each birth cohort in the population is exposed as the environment and society change" (19, p. 119). In Paper 3, we aimed to study the relationship between SES, measured by education, and vascular complications in individuals with type 2 diabetes born in Norway. We considered education status the most appropriate measure for SES as it is relevant regardless of age and working status. However, the meaning and importance of education levels differ across cohorts, both qualitatively and quantitatively, and may have been altered by the accessibility to education over time (67). Moreover, access to and the structure of educational systems in Norway have changed over time (68). Economic factors such as income, social-psychological factors such as coping resources and social support, and health knowledge and behaviour such as exercise and nutrition may affect the relationship between education and health (69). In Norway, primary school was previously seven or nine years, but in 1997 ten years of primary school was introduced. No individuals in the ROSA 4 study have attended primary school after this. To account for a potential cohort effect in Paper 3, the correlation between age and education level was assessed using Pearson's correlation coefficient. The correlation was 0.28, indicating a small strength of association. Repeating the analysis in Paper 3 and including age as a categorical variable (18-55, 55-70, and > 70 years) in Model 2 did not change the ORs (results not shown). Still, this does not exclude a potential cohort effect. In performing a longitudinal study, cohort effects can be circumvented.

5.2 Internal validity

The study's internal validity refers to whether the provided results and inferences drawn from the study are correct for the study population. Internal validity may be expressed as “the degree to which a study is free from bias or systematic error” (19, p. 287). Bias is a systematic error that affects comparison groups unequally (20). This leads to an incorrect estimate of the association between exposures and outcomes. The definition of bias relates to the design and procedures of the study and may influence the study's internal validity and create false patterns. Error is defined as “an act, assertation, or belief that is not right” (20). In epidemiological studies of humans and health, errors are inevitable but must be recognised and reflected on (20).

Bias can, for simplicity, be divided into either *selection* (of the population) bias or *information bias***,** also called measurement bias or misclassification bias (20). Selection bias arises from procedures used to select the study population and from factors that influence study participation (19). Information bias arises from measurement errors.

Selection bias, information bias, and confounding can influence the study’s validity.
The following sections will discuss the study design, potential selection bias, information bias, and confounding in the current study and how it was handled.

5.2.1 Missing data and the risk of selection bias

Selection bias is a well-known problem in epidemiological studies. It can occur when the probability of being included in a study, referring to the choice of the study population, is influenced by the exposure and outcome or by factors affecting the exposure and outcome in a causal way (70). Consequently, the association between exposure and outcome in individuals included in the study and selected for analyses differs from the association among those eligible for the study (70). Selection bias may result in distortion of the estimated associations between exposure and outcome due to systematic bias in selecting the study population or systematic differences in characteristics of participants and non-participants (19).

Nationwide, 282 GPs working in 77 practices were included in the ROSA 4 study. All adult patients diagnosed with diabetes on each GP’s list were included. Four research nurses visited the GP offices included in the ROSA 4 study to collect data unsuitable for electronic capture,

searching electronic health records for missing data to complete the data collection. All adult age groups were included in the study. Moreover, all GPs in Salten were included in the study, ensuring a 100% GP participation rate in Salten. The study was conducted in a setting where all citizens in principal have equal access to the health care system. The individual's medical costs are only a part of the actual medical costs, independent of the level of care or the medical examinations and investigations performed by medical staff. The factors mentioned above reduce selection bias, also called health care access bias, occurring because of selective inclusions linked to, i.e., health insurance systems or age (71). However, individuals permanently living in nursing homes and therefore not cared for by a GP were not included in the study. Therefore, comorbid individuals of high age, and potentially poor glycaemic control, may have been excluded from the study.

Despite the action taken during the data collection to minimise the amount of missing data, some variables had a high proportion of missing data. Missing data can lead to bias, as some groups are more likely to have missing data. In our study, information on BMI was missing in 50% of individuals with type 2 diabetes treated in primary care only. We assume there are several reasons for missing BMI. In a Portuguese study, missing data on self-reported height and weight used to measure BMI was associated with age, education, smoking, and level of physical activity in women (72). In our study, height and weight were most likely measured by the doctor or other staff members. One possible explanation for missing BMI can be that BMI was missing due to selective measurement by the GP, i.e. BMI was not given attention in the consultation if the patient appeared to be of average weight. Due to the high proportion of missing data on BMI, this variable was not included as an exposure variable in the main analyses in Paper 2. Therefore, we could not measure the association between BMI and treatment in specialist care.

Missing data is a frequent problem in cross-sectional studies (73), as in our study. There has been no consensus regarding the best way to handle missing data. The most frequently used method is complete case analyses. However, if several variables have missing data, complete case analyses will exclude larger or smaller parts of the original sample leading to a loss of power. Studies of inadequate sample size and thereby low power have an increased risk of a type II error: the null hypothesis is incorrectly accepted (74).

In Paper 3, we handled missing data by the multiple imputation approach to impute the missing variables and avoid bias due to missing data. The statistical technique of multiple imputations methods can overcome selection bias, as individuals with incomplete data are included in the analyses (75).

The risk of bias due to missing data depends on why data are missing (75). The reasons for missing data are most often classified as data missing completely at random, missing at random, and missing not at random. Sterne et al. define data missing completely at random as "There are no systematic differences between the missing values and the observed values" (75). Missing at random is defined as "Any systematic difference between the missing values and the observed values can be explained by differences in observed data" (75). If we assume data are missing at random but not completely at random, results from complete case analyses may be biased. It is stated that "missing at random" is not a property of the data but rather an assumption that justifies the analyses. (75). The assumption that data are missing at random may be reasonable if we include variables predictive of missing data in a variable of interest in the imputation procedure. If the dependent variable carries information on the missing independent variable, this information must be used in the imputation procedure. Bias can be avoided only if enough variables predictive of missing values are included in the multiple imputation procedure. The assumption that data are missing at random is not reasonable if the variables predictive of missing data are excluded (75).

The following is an example: In a model of the association between education level and CHD, which includes systolic BP as an independent variable, systolic BP may have some missing values. When imputing missing systolic BP values, on average, individuals with CHD should have higher BP values than those without CHD. Failure to include the CHD outcome when imputing the missing systolic BP values would falsely weaken the association between education level and CHD. When missing data have been imputed, the analyses are repeated and can be compared with results from the original analyses.

The extent and distribution of valid numbers in complete cases in Paper 3 are presented in Table 1, Paper 3. BMI had approximately 50% missing data, retinopathy approximately 40% missing data, smoking approximately 20%, BP about 14% and LDL-cholesterol about 18% missing data. All other variables had less than 6% missing data. We assumed that data were missing at random (MAR), but there is no method or test to ensure that data are missing at

random based on the observed data (75). Only minimal differences were seen when comparing observed and imputed values in Paper 3. There were no essential differences between complete case analyses and results based on multiple imputations. This supports that the results from datasets with imputed data are valid.

We consider the risk of selection bias to be limited and our efforts to handle missing data in Paper 3 as appropriate and sufficient to judge that our estimates are not severely biased.

5.2.2 Information bias

Information bias results from systematic differences in information collection, recall, recording, analyses or information handling in a study (76). Misclassification is a type of information bias.

Sampling

The ROSA 4 data collection in primary care was performed over a limited time by a limited number of trained study nurses and standardised according to a protocol and thereby identical for all individuals included in the study. All four study nurses, one in each region, received the same information and training to ensure consistent data sampling, reducing intra- and interobserver variability. Data quality was guaranteed using predefined search keywords tested in a pilot. This approach should reduce systematic differences in data collection and registration of risk factors and vascular complications to a minimum. Data from specialist care in Salten were collected from the Diabetes outpatient clinic in Bodø. Two doctors worked in close collaboration during the inclusion period, ensuring the equal registration of patient data.

The fact that we do not have information on individuals not in contact with their GP in the defined time period must not be neglected. This may have affected the prevalence estimates, but only to a minimal extent, as we believe the number of individuals to be small. We included the estimated number of individuals with type 2 diabetes permanently living in nursing homes in the prevalence estimates. Nevertheless, we do not have information on individuals referred to specialist care but not attending for unknown reasons. This may have affected the analyses on factors associated with specialist care in Paper 2.

Misclassification and measurement error

Misclassification occurs when the characteristic under study is qualitative, and a person is included in a wrong category or population subgroup (20). This misclassification may be due to observational or measurement errors. Misclassification may be random, known as non-differential misclassification, with misclassifications in both directions not dependent on other variables. These errors will only cancel each other out when measuring the disease frequency, as in Paper 1, but not in studies of association, leading to an underestimation of effect (20). Differential classification error occurs when the errors differ between groups and depend on other variables (77). Measurement error refers to errors in measurement.

Individuals unintentionally classified with the wrong diabetes type is a type of non-differential misclassification, and if present, misclassification would affect the prevalence estimates in Paper 1. However, we believe misclassification is a minor issue. The diabetes diagnosis was based on the GPs and outpatient clinic doctors' clinical diagnoses and ICPC-codes, supported by measurements of beta-cell autoantibodies and C-peptide when indicated. Moreover, diabetes diagnoses were manually validated by research nurses during data collection. Consistent data collection in primary care reduces the risk of differential misclassification. During data linking to Statistics Norway, it was decided that if an individual's diagnosis differed in primary and specialist care, the diagnosis from specialist care was recorded (affecting 20 individuals).

Information on age and sex was available in the 11-digit personal identification number: the first six digits reflect the individual's date of birth (DDMMYY). A 9th digit is an even number for females and an uneven number for males. Information regarding education level was obtained by linkage to Statistics Norway; hence measurement errors are unlikely. Yet, Norwegian-born individuals who received education abroad may not have been correctly registered in Statistics Norway and may have been classified in lower education groups. We assume the number of individuals misclassified is low. However, education obtained abroad is self-reported in individuals born outside Norway, and misclassification may be more common. Moreover, we cannot exclude a possible interaction between country of birth and education level, and the potential effect of education on health may vary with ethnicity. Due to this, we excluded individuals born outside Norway from the analyses in Paper 3.

Laboratory values: All GP laboratory results (HbA1c, LDL-cholesterol, creatinine) were drawn from the electronic health records. All GPs in Salten and the diabetes outpatient clinic used the same laboratory at Nordland hospital, reducing the inter-instrument variation in Paper 1 and 2. HbA1c may have been analysed at the GP office. In all papers, we used the latest laboratory value registered. In Paper 1 and 2, analyses were repeated using mean laboratory values in individuals registered with shared care and values recorded both at the GP and diabetes outpatient clinic. This did not change the results (data not shown).

Laboratory HbA1c, BP, and LDL-cholesterol values were dichotomised in Paper 1 and 2 to assess the proportion reaching national guideline treatment targets. Systematic differences in LDL-cholesterol measured fasting or non-fasting may have occurred, but the extent is unknown. Measurement variability may lead to non-differential misclassification in both directions, but correcting for measurement bias has been shown to have little effect on the percentage of patients reaching the HbA1c treatment target (78). The albuminuria test was recorded, but unfortunately, due to the design of the Noklus diabetes form used in the data collection, it was not possible in hindsight to decide whether the recorded variables regarding albuminuria were urine albumin or urine albumin-creatinine ratio (UACR). The apparatus used by GPs differed between practice offices, and not all devices measured UACR. Due to this, we had no data on albuminuria.

Prescribed medication: Prescriptions of glucose-lowering drugs, antihypertensive medication, lipid-lowering medication, and acetylsalicylic acid by GPs and at the diabetes outpatient clinic were automatically registered and transferred to the Norwegian Diabetes Registry. Prescriptions done exclusively by other specialists may not have been recorded, underestimating medication prescription in Paper 1, and biasing estimates of factors associated with treatment in specialist care in Paper 2. We do not have information on medication compliance. If individuals registered as medication users were non-compliant, this would bias our estimates in Paper 2, resulting in an overestimate/underestimation of the true effect. If medication compliance or prescription by others than GPs and the diabetes outpatient clinic were associated with other individual patient characteristics, this would lead to differential misclassification, and estimated associations with the outcome in Paper 2 (treatment in specialist care) would be biased. However, we do not believe this to be a complicating issue. In hindsight, we discovered a typo in Paper 2, as the medication

prescriptions were between 1 January 2012, not 31 October 2013 as unfortunately written, and 31 December 2014. The editor has been made aware of this unfortunate typo.

In recent years several new glucose-lowering drugs have entered the market. In fall 2015, after this study was conducted, the new LDL-cholesterol lowering proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were approved for use in Norway. Consequently, our results regarding medication are not generalisable to today's situation. Clopidogrel, a platelet aggregation inhibitor prescribed to 98 individuals visiting primary care in Salten, was not included in the analyses.

Vascular complications: Non-differential misclassification may have occurred during registrations of vascular complications, believed to be present only to a minimal extent as all GPs' medical records were searched during data collection. The ophthalmologist performs screening for retinopathy, sending a report to the GP where the result from the examination is registered. If reports were not sent, a bias is possible. However, all private ophthalmologists and the ophthalmologist outpatient clinic at Nordlandssykehuset in Salten were contacted by phone, and all reported sending their results to the GPs. Reporting status in the other geographical areas included in Paper 3 is unknown as well as whether a possible bias may have influenced the estimated associations in Paper 3.

More intense screening for outcomes or surveillance among exposed individuals (i.e., known vascular complications) than among unexposed individuals may lead to ascertainment bias. In our study, this may have affected the doctors' recording of information on vascular complications. If an already known diabetes complication requires contact with a doctor, other factors (i.e., medication prescription) may be associated with the frequency of doctor visits. It is unknown whether this has distorted the association in our studies.

We had no reliable data on albuminuria, as recorded data were urine albumin or UACR. In kidney disease stages 1 and 2, eGFR is normal, elevated, or mildly decreased (60-89 ml/min/1.73m^2). By only including eGFR, we may have underestimated the prevalence of kidney damage, as the use of eGFR < 60 underestimates chronic disease cases. However, we did not use the > 3-month duration requirement for CKD diagnosis, which can lead to an overestimation of CKD prevalence (79). We acknowledge that using the creatinine-based CKD-EPI equation can provide inaccurate estimates of actual GFR in individuals with high or

low muscle mass. Moreover, it is well known that serum creatinine is affected by dietary intake of red meat or other precursors of creatinine (79).

GP and practice characteristics: The GPs' country of birth, country of medical education, and specialist status were self-reported in a questionnaire and assumed to be reliable.

5.2.3 Confounding and correlation

Confounding can be defined as "to mix together" and refers to a distortion of the estimated association between an exposure and an outcome due to the presence of another factor (or factors), explaining all or part of the observed association (19). A confounding variable refers to a variable associated with both the independent and dependent variables. During data analyses using stratification, multivariable analysis, or standardisation, confounders can be controlled for. Age, sex, and diabetes duration were considered the most likely confounding factors in our studies, and multivariable analysis can be used to control for more than one confounder at the same time. In Paper 1, age, sex, and diabetes duration were included in the multivariable analyses. In Paper 2, we additionally included education level due to the possible confounding between the outcome and the different exposure variables. In Paper 3, age and sex were considered the most important confounding factors based on relevant literature. Therefore, they were included in the analyses of the association between education level and vascular complications. Balancing between the total adjustment for several covariates and the risk of over-adjustment bias with loss of power must be addressed. Only covariates considered necessary have been included.

Correlation may be defined as the "degree to which variables change together. How closely two (or more) variables are related." (19, p. 60) Multicollinearity can occur in regression analyses when two or more independent variables are highly correlated, thereby not providing independent information in the regression model (80). Diabetes duration was included as a mediator in Paper 3. The association between age and diabetes duration was assessed using Spearman's rank correlation coefficient, a nonparametric measure of the statistical dependence between the rankings of two variables. Age and diabetes duration had a Spearman correlation coefficient of 0.28, indicating a weak relationship between the two variables, and consequently, both variables were included in the analyses.

5.2.4 Statistical considerations

In Paper 1, we reported the age-adjusted prevalence of diabetes using the age distribution in Norway. Age adjustment is a statistical process applied to disease rates, allowing areas with different age structures to be compared, e.g., Salten and Norway (Table 1). In 2014, 12.4% of the Norwegian population were immigrants born outside Norway, compared to 7.1% of the Salten population. Immigrants from Africa and Asia, including Turkey, accounted for 1.5% vs 1.3% and 3.5% vs 1.7% in Norway and Salten, respectively. By standardising to the Norwegian immigrant population from Africa and Asia in the 30-89 years age group, using an estimated diabetes prevalence of 15% (81), the prevalence estimates in Salten only changed from 5.3% to 5.4%.

If the study sample size is small, type II errors are more likely to occur (74). A type II error occurs when we declare no differences or associations between study groups when there actually are. In other words, the null hypothesis is incorrectly accepted (74). In paper 1, some significant tests had low power to detect differences between groups due to the low number of people with type 1 diabetes, potentially threatening the study's internal validity. In Paper 3, the trend of lower OR for higher education groups was present for all vascular complications, but there were few observations for some complications. As a result, there may be uncertainty related to the estimates and the statistical significance of the estimates. For example, the ORs for retinopathy in those with upper secondary and higher education were similar, but the p-values differed. This was related to the number of individuals with higher education and the total number with retinopathy in this group, which affected the statistical power to detect a difference.

In Paper 2, we ran separate models for each exposure/independent variable adjusted for the considered confounding variables age, sex, diabetes duration, and education level included as fixed effects in the models. We excluded individuals with specialist care only and those not registered with a GP, as these had no GP or practice characteristic variables recorded. It was desirable to include GP and practice characteristic variables in the analyses. Different statistical approaches were discussed. As an alternative, multivariable mixed-model logistic regression with variable selection based on statistical significance in univariate analyses was discussed. Due to the proportion of missing values for several variables, this alternative resulted in a low number of individuals included in the analyses. Performing sensitivity analyses (using single imputation with the mean value for continuous variables and best-case

value for categorical variables) in addition to the complete case analyses was discussed but not performed. Sensitivity analyses were considered problematic and challenging to handle in an appropriate way regarding GP and practice variables such as age, sex, medical education in Norway ("yes"/"no"), and urban location ("yes"/"no"). Multiple imputation methods were not chosen due to the non-random missing data pattern, as individuals with specialist and shared care had fewer missing values.

Consequently, we chose to run separate models for each exposure variable. No sensitivity analyses were performed. Clustering was addressed by including GP practice as a random effect in the models. BMI was not included in the models due to a large number of missing values.

In Paper 3, our aim was to study the association between education level and vascular complications in individuals with type 2 diabetes. We excluded individuals born outside Norway due to the possible interaction between country of birth and education level. Missing data were handled with multiple imputations to minimise bias. Age and sex were considered confounders in the pathway between education level and vascular complications. Adjustments for potential mediators and which mediators to include were discussed. A mediator may be defined as: "a variable that occurs in a causal pathway from a causal (independent) variable to an outcome (dependent) variable. It causes variation in the outcome variable, and itself is caused to vary by the original causal variable. Such a variable will be associated with both the causal and the outcome variable" (19, p. 152).

We used directed acyclic graphs (DAGs) as a practical and visual aid when discussing and choosing variables to include in the statistical models. Unmeasured potential mediating factors discussed in the section above could not be included. Therefore, alternative, more advanced statistical approaches to analyse the effects of education level on vascular complications were not an option.

5.2.5 Summary of internal validity

The extensive study population in Salten, including all individuals with diagnosed diabetes visiting primary and specialist care, and the accurate data collection ensuring high-quality data hopefully ensures that the results obtained in this study are of high internal validity.

However, the risk for non-differential bias cannot be completely ruled out. Moreover, multiple imputations reduce the risk of selection bias. Linkage to Statistics Norway ensured objective information on individual education levels. Due to the high number of variables included in the data set, we could include both confounders and potential mediating factors in the statistical models. We consider the associations reported to be valid and reliable estimates. Overall, we regard the results from this study to be of sufficient internal validity.

5.3 External validity

External validity refers to what extent the provided results obtained in a study are generalisable to other populations or groups that did not participate in the study. Several aspects regarding external validity in this thesis must be addressed.

Results from Paper 1 and 2 are based on data from individuals living in Salten, Northern Norway. The population and living conditions in Salten may differ from other parts of Norway or the country as a whole concerning age, education level, immigration, and the proportion of disability benefits. Demographic features of the population of Salten and Norway were obtained from Statistics Norway. Compared to Norway, the people of Salten were older, and the proportion of individuals from Africa and Asia was lower in 2014. To account for differences in age and country of origin between Salten and Norway, we estimated the diabetes prevalence based on the Norwegian age distribution and the Norwegian proportion of immigrants from Africa and Asia.

Moreover, education levels differed in Salten and Norway, as 21.4% of the population in Salten had higher education compared to 32.2% of the general Norwegian population in 2014 (Table 1). Education level is associated with type 2 diabetes prevalence, and the prevalence of type 2 diabetes is higher in individuals with lower education levels (82, 83). Our reported prevalence of type 2 diabetes in Paper 1 may not be generalisable to the Norwegian population with higher education levels. Furthermore, individuals permanently living in nursing homes and not cared for by a GP were not included in the analyses, and our results are not generalisable to these populations. We do not know whether the focus on diabetes treatment and measures to improve the quality of care in the area may have affected our results.

In Paper 3, we included individuals with type 2 diabetes in five Norwegian regions. GPs were invited into the study, and it is questionable whether included individuals and GPs are representative of Norway. Still, we believe the study population to be representative of Norway, as both urban and rural areas in five regions were included. We only included individuals born in Norway in the analyses. Due to this, the results may not be representative of populations of other countries' origins. Moreover, Norwegian schools and universities are without significant tuition fees, and the government provides loans and scholarships to cover living costs during higher education. The results may not be representative of countries with different school systems.

Diabetes treatment is evolving, and in recent years, the introduction of the new glucose-lowering drugs sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like-peptide-1 receptor agonists (GLP-1RA) have changed treatment recommendations. For example, a systematic review and meta-analysis evaluating treatment with SGLT-2 inhibitors or GLP-1RA in individuals with type 2 diabetes, including 764 trials, reported lowered all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure compared to placebo, standard care, or other glucose-lowering drugs (84). Thus, our reported vascular complication prevalence estimates may not represent today's or future situations.

Overall, we consider the results from Paper 1 and 2 to be valid for the Norwegian adult population and other populations with similar characteristics and similar health care systems at the time of the study. We believe that the results from Paper 3 are generalisable to individuals with type 2 diabetes born in Norway and countries with similar health care systems.

6 Discussion of results

6.1 Prevalence of diabetes

In Paper 1, we present the estimated total prevalence of diagnosed diabetes and the prevalence of type 2 and 1 diabetes in different age groups. The total diabetes prevalence in all age groups was 3.8%, whereas the prevalence of type 2 diabetes in all age groups was 3.4%, and 4.4% in age > 20 years. Previous Norwegian studies have reported prevalence estimates of known diabetes as follows: 2.3% (all age groups) (22), 4.3% (age > 20 years) (85), 5.5% in women and 7.9% in men (40-84 years) (86) and 6.1% (type 2 diabetes, 30-89 years) (23), the latter corresponding to our reported prevalence of 5.3% in the age group 30-89 years. In a Swedish study, the total age-standardised prevalence of pharmacologically and non-pharmacologically treated diabetes was 46.9 per 1000 in 2012 (87). In a Danish study, the overall prevalence of type 2 diabetes was 4.4% in the age group 0 to 99 years in 2016 (88). In the same study, the prevalence of type 1 diabetes was 0.5%, corresponding to our reported prevalence of 0.45% in all age groups.

When comparing diabetes prevalence data, we must be aware that diabetes type and the age groups included in analyses, data sources, and the use of screening can affect the estimates. The increasing number of individuals living with diabetes may be related to altered screening procedures and recommendations, including opportunistic screening, increased life expectancy, better treatments, the health care system becoming better at detecting undetected diseases earlier, and improvements in the prevention of cardiovascular disease. Results from pooled data from population-based studies showed that 39.7% of the rise in the number of people with diabetes was due to population growth and ageing, 28.5% due to the increase in age-specific prevalence, and 31.8% due to the interaction of the two (21).

Previous Scandinavian studies have reported that 17% to 25% of individuals with diabetes are undiagnosed (86, 89). However, recently published results from the HUNT Study, a Norwegian population-based study including about 50 000 individuals, showed that the prevalence of diabetes was 6.0% in the age group ≥ 20 years, of whom 11.2% were previously undiagnosed (90). The proportion of undiagnosed diabetes will vary with the diagnostic tools and criteria applied.

As our prevalence estimates are lower than estimates from comparable studies, it is reasonable to question whether the prevalence in Salten is actually lower, or the estimates are affected by some of the abovementioned factors, or a short inclusion time. In Paper 1, we included individuals visiting primary care for the last three years. Consequently, we may have failed to include individuals with known diabetes and irregular follow-up, potentially affecting our prevalence estimates being too low. However, in 2014, 76% of individuals 50 to 66 years of age visited their GP (60). Of individuals 67 to 79 years, 85% saw their GP in 2014.

In 2011, the World Health Organization advised HbA1c to be used to diagnose diabetes (91). The cut-off was set at 6.5%. Results from a recently published Danish study showed that the incidence of type 2 diabetes increased before the 2012 introduction of HbA1c as a diagnostic option, but the incidence declined from 2012 to 2018 (92). The decline was explained by a drop in individuals diagnosed with type 2 diabetes resulting from the new diagnostic option. A stable incidence of type 2 diabetes from 2006 to 2013 was also reported in a Swedish study (34). A decline in incidence has also occurred in the United States of America after implementing HbA1c testing for diagnosing diabetes (93). It is unknown whether the introduction of HbA1c testing as a diagnostic tool has affected our prevalence estimates.

6.2 Achievement of treatment targets and prevalence of vascular complications

Our results in Paper 1 show that 61.1% of individuals with type 2 diabetes reached the HbA1c treatment target of ≤ 53 mmol/mol (≤ 7%), 62.5% reached the BP treatment target of ≤ 140/85 mmHg if untreated, and 36.2% of those treated reached the BP treatment target of ≤ 135/80 mmHg. Our reported proportion of people reaching treatment targets is higher than pooled target achievement rates from a meta-analysis including 24 studies worldwide; glycaemic control 42.8% (95% CI 38.1–47.5%), BP 29.0% (22.9–35.9%), and LDL-cholesterol, 49.2% (39.0–59.4%) (94). There were considerable variations in the achievement of treatment targets and no evidence of improvements between 2006 and 2012 (94). Previous results from the ROSA 4 study showed that the achievement of HbA1c, BP, and LDL-cholesterol targets varied significantly between GPs and practices. Individuals < 50 years, BMI ≥ 30 kg/m^2, and known macrovascular disease were less likely to achieve targets (10).

Although comparing vascular complication rates across studies and countries may be challenging due to differences in populations, inclusion criteria, and other methodological issues such as definitions of diseases, our findings regarding cardiovascular risk factors and complications are generally in line with other studies. In a recently published study from the United Kingdom with data from primary care database and diabetes registry, the prevalence of CHD in individuals with type 2 diabetes were 19% and 24% (95), compared to our reported prevalence of 24% in all individuals with type 2 diabetes included in Paper 1. The prevalence of stroke was 5.3%, and 6.4% (95) compared to 7.7% in our study. These results align with a systematic literature review including 57 papers reporting that 32.2% of individuals with type 2 diabetes had CVD, 21.2% had CHD, and 7.6% had stroke (33). The prevalence of type 2 diabetes-related microvascular and macrovascular complications differs, and the highest prevalence is found in Europe (96).

In the last 20 years, rates of diabetes vascular complications, myocardial infarction, stroke, and lower-limb amputations have decreased in high-income countries (97). Rates of complications have declined more for macrovascular than for microvascular complications. The reductions are explained by improved risk factors, earlier diagnosis, and better care organization.

In a recent study, chronic kidney disease was the most prevalent complication (12.3%) at the time of type 2 diabetes diagnosis, while CVD was among the least prevalent complications at 3.3%. The median time to a type 2 diabetes complication incidence ranged from 3.0 to 5.2 years. Neuropathy, CKD and CVD had high incidence rates (98). CHD is generally considered a complication of diabetes, but the awareness of diagnosing type 2 diabetes among patients with CHD is increasing. In the ROSA 4 study of 10 255 individuals with type 2 diabetes, of the 2260 individuals with CHD, 47.9% were diagnosed with CHD $\geq$ 1 year before type 2 diabetes (32). These patients were older, more often male, more often smokers, and had a lower educational level than patients with CHD diagnosed after type 2 diabetes. According to national guidelines, it is recommended to measure serum glucose in all patients admitted with stroke (99).

The detection of vascular complications is affected by the doctors' screening procedures. In the ROSA 4 study, 31.5% of individuals with type 2 diabetes had a test for albuminuria, 27.5% for a monofilament test, and 60.0% for eye examination (9). Only 12.3% had all three

microvascular screening procedures performed as recommended (9). Young age (< 50 years) and macrovascular disease were negatively associated with the albuminuria test and eye examination performance. The GP's use of the structured diabetes form was associated with improved screening for microvascular complications. In contrast, GPs with a high workload, defined as the number of individuals on the GPs list per day, recorded fewer procedures (9). Patients of GPs performing more recommended diabetes procedures (including measurements of HbA1c, LDL-cholesterol, albuminuria, blood pressure, and recorded foot examination) had lower CVD risk and better glycaemic control (11). Still, the question is whether high scores on process indicators are associated with better patient outcomes in everyday practice.

Treatment of type 2 diabetes and CVD varies between countries, and sulfonylureas, historically the second most commonly used antidiabetic drug after metformin, have been associated with an increased risk of cardiovascular events and mortality (100). However, a randomised clinical trial showed non-inferiority of sulfonylurea to the dipeptidyl peptidase-4 inhibitor linagliptin regarding the first occurrence of a cardiovascular event over a median of 6.3 years in individuals with elevated cardiovascular risk (101).

The Diabetes Control and Complications Trial (DCCT) demonstrated that tight blood glucose control effectively reduced diabetic retinopathy, nephropathy, and neuropathy in individuals with insulin-dependent diabetes (102). Still, even optimal blood glucose control did not prevent complications. In a recently published study, individuals with type 2 diabetes optimally treated with total cholesterol ≤ 4 mmol/L, triglycerides ≤ 1.7 mmol/L, HbA1c ≤ 53 mmol/mol (≤ 7.0%), systolic blood pressure < 140mm Hg, or < 130 mm Hg if high risk and nonsmoking, had a 21% higher CVD risk compared with controls (95). This is in contrast to a Swedish study reporting that individuals with type 2 diabetes who had five risk-factor variables (HbA1c ≤ 53 mmol/mol (≤ 7.0%), systolic BP < 140 mmHg, diastolic BP < 80 mmHg, no albuminuria or smoking, and LDL-cholesterol level < 2.5 mmol/L) had little or no excess risk of death, myocardial infarction, or stroke compared to the general population (103).

In a meta-analysis, reducing LDL-cholesterol with a statin reduced the risk of major vascular events by 21% per 1 mmol/L reduction of LDL-cholesterol during a mean follow-up of 4.3 years in individuals with diabetes (104). Furthermore, a recently published study showed that

individuals from the lowest BMI, HbA1c, systolic BP and LDL-cholesterol population quartile had 3.9, 3.8, 1.9, and 0.9 years of additional life expectancy, respectively, compared with those from the highest BMI, HbA1c, systolic BP, and LDL-cholesterol population quartile (105).

The effects of physical activity on atherosclerosis in a general population are well known. In a systematic review and meta-analysis of 48 randomised controlled trials, exercise training was associated with a 20–25% reduction in overall and cardiac mortality compared to usual care (106). Exercise improves hyperglycemia and insulin sensitivity by normalising myocardial oxidative stress, lipotoxicity, and systemic inflammation in diabetes and has emerged as an effective synergistic therapy to combat cardiovascular complications (107). Moreover, physical activity modulates microRNAs as an immediate response, inducing significant cardio-protection (107).

6.3 Level of diabetes care

In Tudor Hart's famous essay in The Lancet 1971, "The Inverse Care Law", the link between inequalities in health and inequity in access to care was expressed as the idea that "the availability of good medical care tends to vary inversely with the need of the population served". Four decades later, data used in the present thesis was collected. Our results show that in patients with type 2 diabetes, HbA1c, the individual's use of insulin, CHD, retinopathy, and urban practice location were positively associated with receiving treatment in specialist care, indicating that patients in specialist care had more severe disease. Using a structured diabetes form and a diabetes nurse employed in primary care were negatively associated with treatment in specialist care. Equal access to quality services irrespective of people's socio-economic circumstances is essential to improving health and overcoming inequalities. In our study, education level was not associated with treatment in specialist care.

6.4 Education level and vascular complications

The number of studies on the association between individual-level socioeconomic status (SES), as opposed to geographical indices of SES, and vascular complications in individuals with diabetes is scarce. In a systematic review from 2019, including 28 studies conducted in high-income countries over ten years, the authors conclude that the strength of the association between SES and diabetes complications was highly variable, dependent on the type of SES,

and analyses were insufficiently adjusted for risk factors (108). Most studies showed an association between SES, measured at individual or geographical levels, and complications. However, some of these studies were done on selected groups regarding age and sex and did not adjust for important confounders or mediators. Many studies did not have access to individual-level data on education level and were not conducted in a setting where everyone has equal access to health care (108).

In Paper 3, we had all the data available to study the association between education level and vascular complications in an equal health access Norwegian setting. Our results showed an association between education level and CHD and CKD, in line with previous studies (7, 109-112). In a recently published Norwegian study on individuals with type 1 diabetes, lower education was significantly associated with a higher risk of acute myocardial infarction. Similar trends were found in matched controls without diabetes (113). Our results align with previous studies on a general population (114-117). Mendelian randomisation studies can assess the causal effect of a risk factor on an outcome, and low education is identified as a causal risk factor in developing CHD (118). In a Mendelian randomisation study of more than 500 000 individuals in a general population, BMI, systolic blood pressure, and smoking behaviour mediated around 40% of the effect of education on CHD, leaving half of the effect of education unexplained (119). In a computer-generated study in a general population, both men and women in the low-SES group had doubled the rate of myocardial infarction and CHD deaths per 10 000 person-years compared with individuals with higher SES (120). A higher burden of traditional CHD risk factors explained 40% of the excess CHD events in those with low SES. Other factors associated with low SES explained the remaining 60% of these events.
There is growing knowledge of the genetic relationship between type 2 diabetes and CHD, indicating that not only is type 2 diabetes an epidemiological risk factor for CHD, but it is also a genetic risk factor for CHD (121). In a recent study on the relationship between type 2 diabetes and CHD, the authors conclude that type 2 diabetes is an epidemiological and genetic risk factor for CHD (121). Polygenic predisposition to CHD, i.e., identifying common genetic variants across the genome, is strongly associated with atherosclerotic burden in individuals with type 2 diabetes (122). The effect is largely independent of traditional clinical risk factors.

In individuals with low SES, the increased burden of CVD may be attributable to biological, behavioural, and psychosocial risk factors more prevalent in underprivileged individuals

(123). A recently published Italian study showed that depression in individuals with type 2 diabetes was associated with a 2.3-fold risk of developing acute complications and a 1.6-fold risk of developing long-term complications (124). To further complicate the picture, results from a previous ROSA 4 study showed that those with macrovascular disease and lower education levels had lower odds of receiving microvascular screening procedures (9), an indication that SES also influences access to care. The importance of information on education level is acknowledged, and information on the patient's education level was included in the Noklus diabetes form offered to specialist care in 2020 and primary care in 2019.

The fact that controlling for risk factors in our study only to a small extent changed the effect of education level on vascular complications does not mean that risk factor control is less important. It could still be the most effective intervention in reducing inequalities.

6.5 The complex relationship between SES and diabetes outcomes

To adequately reveal the complex relationship between education level and vascular complications was beyond the scope of this thesis. The mechanisms by which SES influences health have been extensively studied. Brown's conceptual framework integrates the many dimensions that may explain how SES influences diabetes health outcomes (125). SES is linked to diabetes outcomes through health behaviours, access to care, and care processes such as BP measurement and screening for vascular complications. Characteristics of the person with diabetes, the health care provider, communities, neighbourhoods, and health care systems are identified as distal mediators acting through the central mechanisms and potentially explaining the link between SES and health behaviours, access to care, care process, and diabetes outcomes. The level of education affects the individual's ability to turn information into practical measures and behaviour and affects access to recourses, employment-related problems, and social exclusion in those unemployed. Inadequate health literacy, defined as "a measure of patients' ability to read, comprehend, and act on medical instructions," was independently associated with worse glycaemic control and higher rates of retinopathy (126).

In a recent Danish study, the low socioeconomic position was associated with a lower probability of initiating SGLT-2 inhibitors or GLP-1RA (127). This indicates differences in diabetes treatment according to SES, possibly affecting the development of vascular complications.

Quality indicators are used to identify and improve the quality of care. Quality indicators can be divided into structure indicators (organisational aspects, martial and human resources), process indicators related to the performance of practitioners (number or quality of consultations, laboratory tests, drug prescription), and outcome indicators (128, 129). An important aspect is that health outcomes also are affected by other factors than health care, such as environment, lifestyle, nutrition, and poverty (130). The abovementioned factors contribute to the complex relationship between SES and diabetes outcomes.

7 Conclusions

This thesis showed that the total prevalence of diagnosed diabetes in Salten, 2014 was slightly lower than estimated in previous Norwegian studies. Glycaemic control was inadequate in most individuals with diabetes, as only 61.1% of individuals with type 2 diabetes and 22.5% of individuals with type 1 diabetes reached the HbA1c treatment target of ≤ 53 mmol/mol (≤ 7.0%). We found that approximately two-thirds of type 2 diabetes patients treated in primary care reached the HbA1c treatment target compared to one-third of individuals in specialist/shared care. Individuals with type 2 diabetes treated in specialist care had more vascular complications than those treated in primary care, as expected from the *National clinical guideline for management of diabetes*. Further, insulin use and GP urban practice localisation were positively associated with treatment in specialist care. Higher education levels were associated with lower odds for CHD and CKD in individuals with type 2 diabetes born in Norway, indicating inequalities in health by SES. These associations remained after adjusting for known risk factors.

Our data bring new information about diabetes treatment target achievement and identify gaps in quality of care regarding recommendations in the *National clinical guideline for management of diabetes*. Moreover, we have identified an association between education level and vascular complications in a Norwegian setting where everyone, in principle, has equal access to health care. These findings suggest that additional attention should be paid to those in lower education groups.

8 Implications and future perspectives

Regularly repeated representative population surveys are essential to estimate the future burden of diabetes and to obtain estimates of diagnosed and undiagnosed diabetes. As only a low proportion of individuals with diabetes reach the recommended treatment targets, also shown in this thesis, it is crucial to obtain a better understanding of patient, physician, and healthcare system-related factors contributing to the lack of adherence to clinical guidelines or obstacles in diabetes treatment. Improving risk factor control may contribute to a reduction in future vascular complications. The best ways to prevent future CVD events are educating the general population from childhood, increasing the knowledge of healthy food, encouraging and facilitating physical activity even from primary school, and eradicating smoking (131). In addition, subgroups in the general population and among individuals with diabetes needing closer attention and follow-up must be identified. The potential effect of adding SES to risk scoring models or as an additional factor should be considered.

Public health interventions targeting disadvantaged population groups may reduce inequalities in health. Health illiteracy varies between populations and is less prevalent in lower SES groups. A greater focus on improving health literacy may help close the inequality gap. Future research should focus on a better understanding the underlying mechanisms responsible for the observed differences in vascular complications according to SES, affecting individuals in lower SES groups to a greater extent.

The increasing burden of diabetes also calls for strengthening primary care. A greater focus on strategies for handling diabetes in primary care, including considering transferring work tasks to other medical staff members, is warranted. The effects of these measures must be evaluated. Just as important, information on the impact of referral to and treatment in specialist care in individuals with type 2 diabetes should be studied. Is referral associated with better risk factor control, intensified treatment or lifestyle interventions? A deeper understanding of the patients' perspective on diabetes treatment and how treatment and self-management can be improved can be obtained by qualitative studies.

Further research investigating diabetes prevalence and vascular complications trends and levels of care may include:

- Repeated cross-sectional studies on the prevalence of diabetes and vascular complications
- Longitudinal studies to monitor risk factors and vascular complications across education groups for developing preventive strategies
- Randomised controlled intervention studies on lifestyle
- Qualitative studies, including patients and GPs, to improve knowledge regarding communication, socioeconomic differences, and diabetes care.

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Paper 1

Slåtsve, K.B., Claudi, T., Lappegård, K.T., Jenum, A.K., Larsen, M., Cooper, J.G., Sandberg, S. & Berg, T.J. (2022).

The total prevalence of diagnosed diabetes and the quality of diabetes care for the adult population in Salten, Norway

Scandinavian Journal of Public Health, 50(2), 161-171.

Scandinavian Journal of Public Health, 1–11

ORIGINAL ARTICLE

The total prevalence of diagnosed diabetes and the quality of diabetes care for the adult population in Salten, Norway

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Abstract

Objective: To assess the total prevalence of types 1 and 2 diabetes and to describe and compare cardiovascular risk factors, vascular complications and the quality of diabetes care in adults with types 1 and 2 diabetes in Salten, Norway. *Research design and methods:* Cross-sectional study including all patients with diagnosed diabetes in primary and specialist care in Salten, 2014 (population 80,338). Differences in cardiovascular risk factors, prevalence of vascular complications and attained treatment targets between diabetes types were assessed using regression analyses. *Results:* We identified 3091 cases of diabetes, giving a total prevalence in all age groups of 3.8%, 3.4% and 0.45% for types 2 and 1 diabetes, respectively. In the age group 30–89 years the prevalence of type 2 diabetes was 5.3%. Among 3027 adults aged 18 years and older with diabetes, 2713 (89.6%) had type 2 and 304 (10.0%) type 1 diabetes. The treatment target for haemoglobin A1c (≤7.0%/53 mmol/mol) was reached in 61.1% and 22.5% of types 2 and 1 diabetes patients, respectively. After adjusting for age, sex and diabetes duration we found differences between patients with types 2 and 1 diabetes in mean haemoglobin A1c (7.1% vs. 7.5%, $P<0.001$), blood pressure (136/78 mmHg vs. 131/74 mmHg, $P<0.001$) and prevalence of coronary heart disease (23.1% vs. 15.8%, $P<0.001$). *Conclusions:* The prevalence of diagnosed type 2 diabetes was slightly lower than anticipated. Glycaemic control was not satisfactory in the majority of patients with type 1 diabetes. Coronary heart disease was more prevalent in patients with type 2 diabetes.

Keywords: *Diabetes, type 1 diabetes, type 2 diabetes, prevalence, vascular complication, primary healthcare*

Significance of this study

What is already known about this subject?

Studies reporting the prevalence of diabetes in Norway and worldwide have mostly been based on self-reported data, diagnoses in electronic medical records, registry data, or the use of blood glucose-lowering drugs.

What are the new findings?

Based on validated data collected from all physicians treating individuals with diabetes in a geographically defined area, the total prevalence of diagnosed type 2 and type 1 diabetes in Salten was 3.4% and 0.45%, respectively. More type 2 diabetes patients than type 1 diabetes patients reached the haemoglobin A1c

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Date received 24 March 2020; reviewed 15 May 2020; 4 June 2020; 3 July 2020; accepted 10 July 2020

DOI: 10.1177/1403494820951004
journals.sagepub.com/home/sjp

(HbA1c) treatment target. The patterns of cardiovascular risk factors (HbA1c and blood pressure) differed significantly between type 2 and type 1 diabetes patients. Patients with type 2 diabetes had lower mean HbA1c, whereas patients with type 1 diabetes had lower mean blood pressure. The adjusted prevalence of coronary heart disease (CHD) was 23.1% and 15.8% in type 2 and type 1 diabetes patients, respectively.

How might these results change the focus of research or clinical practice?

We found a slightly lower prevalence of diabetes than anticipated. Furthermore, we identified quality gaps in the treatment that differed by type of diabetes. This knowledge can be used in quality improvement strategies.

Introduction

Type 1 and type 2 diabetes are complex metabolic diseases that differ in pathophysiology and treatment. The global prevalence of diabetes in adults (age 18–99 years) in 2017 was estimated to be 8.4% and a worrisome increase is predicted worldwide in the coming years [1]. Pooled data from population-based studies found a global age-standardised diabetes prevalence of 9.0% in men and 7.9% in women in 2014 [2]. In Norway the prevalence of type 2 diabetes was reported to be 6.1% (age 30–89 years) in 2014 [3].

Compared to people without diabetes, patients with type 2 diabetes have a 15% increased risk of all-cause mortality, and the mortality is higher in younger age groups [4]. Inadequate glycaemic control, hypertension, elevated levels of low-density lipoprotein (LDL) cholesterol and smoking are established risk factors for cardiovascular disease (CVD) shown to be reduced by improved management of diabetes [5,6]. Repeated Norwegian cross-sectional surveys have shown improvements in the achievement of diabetes treatment targets over time [7]. Although the treatment targets are identical in type 1 and type 2 diabetes, identifying subgroups in need of closer follow-up and overcoming the barriers achieving treatment targets will be more important in the coming years.

There is a lack of real-world data describing the total population with diagnosed diabetes within a geographical area with validated clinical data. We hypothesise that the prevalence of diagnosed diabetes differs from studies based on self-reported data, administrative registries without validated diagnoses, or health surveys with a risk of selection bias. Our first objective was therefore to describe the prevalence of diagnosed type 1 and type 2 diabetes in all age groups in the geographical area of Salten, Norway. Furthermore, we aimed to identify gaps in the quality of care for type 1 and type 2 diabetes patients in this population by comparing cardiovascular risk factors, vascular complications and attained treatment targets according to national guidelines.

Research design and methods

The present cross-sectional study is part of the ROSA 4 (Rogaland-Oslo-Salten-Akershus-Hordaland) study, assessing the quality of diabetes care within an integrated healthcare system in 2014 [7]. The study was approved by the Regional Ethical Committee West (REK 2014/1374, REK Vest), with permission to collect data from general practice without written consent. Data from the outpatient clinic included patients consenting to send their data to the Norwegian Diabetes Registry for Adults.

The public healthcare system in Norway is financed through government funding. Every citizen has the right to be registered with a general practitioner (GP). Residents aged 16 years and older must pay an annual deductible, in 2014 approximately €233 for doctors' visits and drug prescriptions before getting free essential drugs and appointments in primary and specialist care. In-hospital treatments are free.

Setting

The Salten region in Northern Norway has a total population of 80,338 as of 31 December 2014, covers approximately 10,000 km^2, nine municipalities and one town (approximately 50,000 inhabitants). A diabetes action plan was launched in 2009 facilitating a close collaboration between GPs in the area and the diabetes outpatient clinic at the only hospital that serves all diabetes patients in need of specialist care. There are no private diabetologists in the region. In 2014 the prevalence of immigrants born outside Norway was lower in Salten than in Norway as a whole (7.1% vs. 12.4%). The proportions of immigrants from Africa and Asia were 1.3% and 1.5% in Salten (compared to 1.7% and 3.5%, in Norway), respectively.

Data collection

To be able to include all patients with diabetes living in Salten, we used four independent data sources. First, data collected from primary care included all patients with known diabetes visiting a GP from 1 January 2012 to 31 December 2014. All GPs (n=82)

were invited to take part in the study and all accepted. The data collection was facilitated using a software program from the Norwegian Diabetes Registry for Adults, which identified all adults (⩾18 years) with a diagnosis of diabetes (T89 and T90 in the International Classification of Primary Care (ICPC)) in the defined time period. Predefined variables were extracted from the electronic medical records for each patient. A research nurse scrutinised all primary care electronic medical records including mandatory copies of patient reports from all types of specialist care visits, to verify electronically captured data and collect missing data not suitable for electronic capture. The data collection was performed from April to December 2015. Second, relevant data from all adult patients with diabetes visiting the hospital diabetes outpatient clinic from 31 October 2013 to 31 December 2014 were collected. Third, information on the number of patients with diabetes in the paediatric population was obtained from the paediatric clinic at the same hospital. Fourth, each municipality included in the study was contacted by phone to provide information about the number of people permanently living in nursing homes with no follow-up by a GP.

Variables

Diabetes was categorised as type 1 diabetes including latent autoimmune diabetes of adults (LADA), type 2 diabetes and by other types (including maturity-onset diabetes of the young (MODY) or pancreatitis). The diagnosis of diabetes type was based on the doctor's clinical diagnosis supported by measurements of beta cell antibodies and C-peptide when necessary. Information on patient characteristics, processes of care, intermediate outcomes, complications, medication and information on GPs and GP practices was registered. For the majority of patient variables, we included the last registered value in the period 1 October 2013 to 31 December 2014 (Supplemental Table I). Eye examination, creatinine/estimated glomerular filtration rate (eGFR) and lipids were registered for the period 1 January 2012 to 31 December 2014 and smoking habits 2010–2014. Data from the most recent visit were used in the analyses. If data in patients visiting both primary and specialist care clinic differed, the most adverse or recent outcome/complication was used.

Type 1 and type 2 diabetes treatment targets were identical and based on the Norwegian national treatment guidelines from 2009: HbA1c 7.0% or less (53 mmol/mol); intervention threshold for blood pressure greater than 140/85 mmHg with treatment target of 135/80 mmHg or less; total cholesterol 4.5 mmol/L or less and LDL-cholesterol 3.5 mmol/L or less with treatment target for LDL-cholesterol 1.8 mmol/L or less and 2.5 mmol/L or less for individuals with and without known CHD, respectively [8].

Statistical analyses

To estimate the crude prevalence of diabetes, we used the total number of diabetes cases identified, including number of cases from the paediatric clinic as the nominator.

The denominator was the total number of individuals alive and residing in each of the nine municipalities in Salten by 31 December 2014 according to Statistics Norway. The prevalence estimates were stratified by diabetes type, 10-year age groups and sex. We also estimated the total prevalence using the proportion of immigrants in Norway and by including the estimated number of people with diabetes permanently living in nursing homes.

Descriptive statistics are presented as percentages, means with standard deviations (SDs) or medians with interquartile range (IQR). Bivariate parametric and non-parametric tests were used as appropriate.

Both univariable and multivariable linear and logistic regression models were used to compare variables of interest between diabetes types. In the multivariable models, we adjusted for age, sex and diabetes duration due to possible confounding between diabetes type and the outcomes of interest. We present average adjusted predictions (AAPs) and average marginal effects (AMEs) with 95% confidence intervals (CIs) and *P* values from univariable and multivariable regression. Crude attained treatment targets are presented in figures and AAPs for attained treatment targets are presented in the text. The significance level was set at 0.05 for all analyses. All statistical analyses were performed using STATA/SE 14 (StataCorp LP, College Station, Texas, USA).

After excluding duplicates, patients with gestational diabetes, patients who were not registered with an address or not residing in Salten, and those registered as dead (n=4), we studied 3035 adults with diabetes. Furthermore, 56 children (<18 years), all with type 1 diabetes, were included in the sample of 3091 persons used to calculate the total prevalence (Supplemental Figure 1). In 2014, the total number of people permanently living in nursing homes was 570, and we estimated the number of people with diabetes in this population to be 90–95 [9].

The clinical dataset of adults used in further analyses included 3027 patients obtained from 82 GPs in 26 practices (100% of the invited) and all consenting

patients (n=604, 98.7%) visiting the diabetes outpatient clinic (Supplemental Figure 2). Age-adjusted prevalence was calculated by adding the number of children with diabetes to this dataset, giving a sample of 3083 patients.

Results

Prevalence of diabetes

The total prevalence of diagnosed diabetes was 3.8% and increased with age up to 80 years (Figure 1). In adults aged 20 years and older the prevalence was 4.9%. The overall prevalence of type 2 diabetes (all age groups) was 3.4%; 4.4% in those aged 20 years and older and 5.3% in the age group 30–89 years. Type 2 diabetes was more prevalent in men than in women in all age groups. The prevalence of type 1 diabetes (all age groups) and in the age group 20 years and older was 0.45% and 0.49%, respectively.

When we extrapolated the proportion of immigrants from Asia and Africa in Norway to diabetes prevalence in Salten, with a prevalence of diabetes in this group set to 15%, the prevalence of diabetes in the 30–89 years age group increased marginally from 5.3% to 5.4% [10]. Age standardisation using age distribution from the Norwegian population by 31 December 2014 did not change the prevalence estimates. Including the estimated number of people with type 2 diabetes permanently living in nursing homes changed the total prevalence estimate (all age groups) from 3.8% to 3.9–4.0%.

Characteristics of adults with diabetes

Type 2 and type 1 diabetes accounted for 89.6% and 10.0%, respectively. Ten patients (0.3%) had other types of diabetes. The sample included 2713 patients with type 2 diabetes with a mean age of 67 years, median diabetes duration of 7 years (Table I) and a mean body mass index (BMI) of 30.5 kg/m^2. The majority (56.4%) of type 2 diabetes patients were men and they were younger than women, also at the time of diagnosis. Among the 304 patients with type 1 diabetes, the mean age was 47 years and median diabetes duration of 19 years.

In the total dataset, 2423 patients (80.1%) had their follow-up in primary care only, 109 (3.6%) in hospital outpatient clinic only and 495 (16.4%) had shared care (Supplemental Figure 2).

Prevalence of vascular complications

The crude prevalence of any macrovascular complication and CHD was higher in type 2 diabetes than in type 1 diabetes patients, while the prevalence of diagnosed retinopathy was substantially higher in patients with type 1 diabetes (Table II). After adjustments for age, sex and diabetes duration, CHD remained significantly more prevalent in type 2 than in type 1 diabetes patients (23.1% vs. 15.8%, P=0.019), whereas retinopathy differences became borderline significant. Moreover, 0.7% of type 2 and 0.5% of type 1 diabetes patients were in dialysis, and 0.3% of type 2 and 0.9% of type 1 diabetes patients had undergone kidney transplantation. Information was registered in 48.9% type 2 diabetes and 70.4% type 1 diabetes patients.

Cardiovascular risk factors and prescriptions of blood glucose-lowering medications

After adjusting for age, sex and diabetes duration, we found differences in mean HbA1c (7.1% vs. 7.5%, P<0.001) and blood pressure (136/78 mmHg vs. 131/74 mmHg, P<0.001) but not in LDL-cholesterol between patients with type 2 and type 1 diabetes (Table III). The proportion of current smokers was 18.6% in both type 2 and type 1 diabetes patients.

Among type 2 diabetes patients, 64.5% were prescribed one or more antihyperglycaemic agents, whereas 35.5% were treated with lifestyle alone. Oral antihyperglycaemic treatment was prescribed to 42.1%. Insulin was used as the only treatment in 12.3% and insulin in combination with other glucose-lowering drugs was used by 10.1%. Furthermore, 20.4% of type 2 diabetes patients were prescribed two antihyperglycaemic agents and 28.1% were prescribed three or more.

Attained treatment targets

Substantially more type 2 diabetes patients than type 1 diabetes patients reached the HbA1c treatment target of 7.0% or less/53 mmol/mol or less, 61.1% versus 22.5% (Figure 2, crude analyses). After adjustments for age, sex and diabetes duration, the difference between diabetes types was reduced to 57.4% versus 45.2% (P=0.003).

In patients using antihypertensive agents, 36.2% type 2 and 47.2% type 1 diabetes patients had blood pressure of 135/80 mmHg or less. After adjustments we found no difference between diabetes types (P=0.144). If not on medication, type 2 and type 1

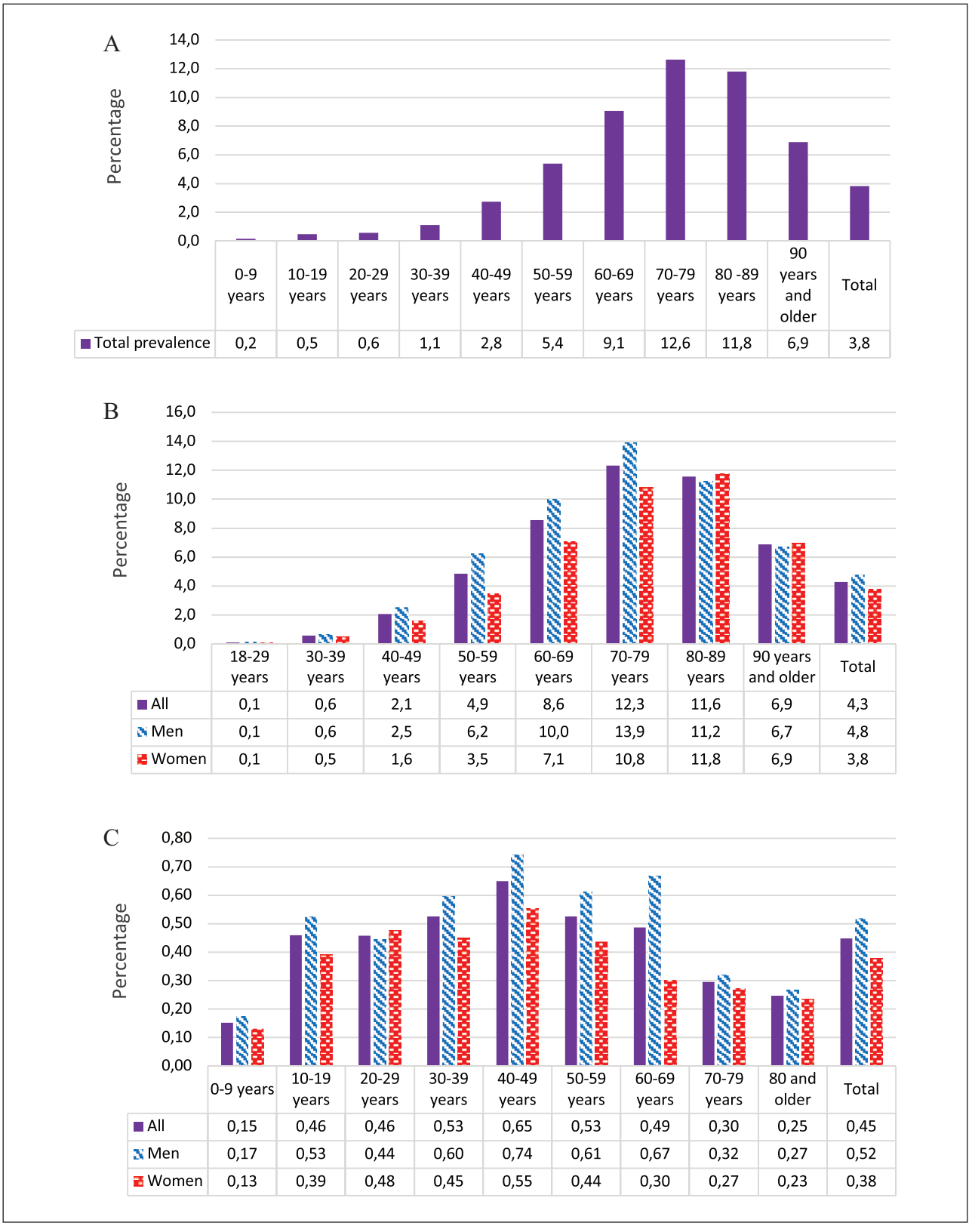
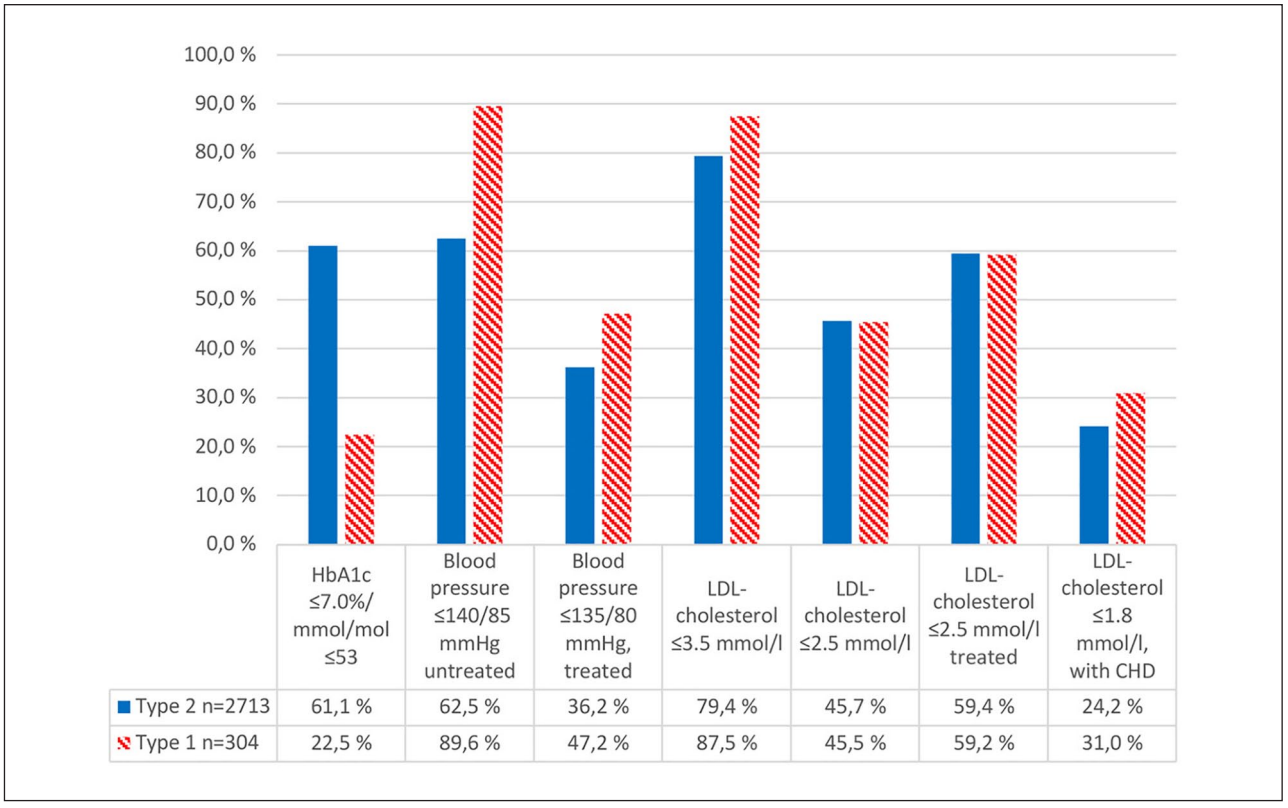


Figure 1. Total prevalence of diabetes and by diabetes type, %.
(a) Total prevalence, all diabetes types, %. (b) Type 2 diabetes prevalence, %. (c) Type 1 diabetes prevalence, %.



	HbA1c ≤7.0%/ mmol/mol ≤53	Blood pressure ≤140/85 mmHg untreated	Blood pressure ≤135/80 mmHg, treated	LDL-cholesterol ≤3.5 mmol/l	LDL-cholesterol ≤2.5 mmol/l	LDL-cholesterol ≤2.5 mmol/l treated	LDL-cholesterol ≤1.8 mmol/l, with CHD
Type 2 n=2713	61,1 %	62,5 %	36,2 %	79,4 %	45,7 %	59,4 %	24,2 %
Type 1 n=304	22,5 %	89,6 %	47,2 %	87,5 %	45,5 %	59,2 %	31,0 %

Figure 2. Attained crude treatment targets in all adults with diabetes in Salten, Norway.

diabetes patients differed in the proportion having blood pressure of 140/85 mmHg or less (62.5% vs. 89.6%), and these differences persisted after adjustments ($P<0.001$). In patients using lipid-lowering agents, the treatment target for LDL-cholesterol (⩽2.5 mmol/L) was reached in 59.4% of type 2 and 59.2% of type 1 diabetes patients.

Discussion

By including all patients with diagnosed diabetes in a geographical area, the present study identifies the true prevalence of diagnosed diabetes in all age groups and diabetes-related vascular complications in adults with type 1 and type 2 diabetes. The total prevalence of type 2 and type 1 diabetes in all age groups was 3.4% and 0.45%, respectively. In adults aged 20 years and older the prevalence of type 2 and type 1 diabetes was 4.4% and 0.49%. CHD was more prevalent in type 2 than in type 1 diabetes, also after adjusting for known confounders, 23.1% versus 15.8%, respectively. Type 2 diabetes patients had higher blood pressure and lower HbA1c than type 1 diabetes patients before and after adjustments. Substantially more type 2 than type 1 diabetes patients reached the HbA1c treatment target even after adjustments, 57.4% versus 45.2%, respectively.

Prevalence of diabetes

First, our estimates of diabetes prevalence in Salten are lower than global estimates and estimates from the USA and most parts of Europe. A study on US adults (aged ⩾20 years) found a prevalence of type 1 and type 2 diabetes of 0.5% and 8.5%, respectively [11]. A Swedish registry-based study reported a total diabetes prevalence of 4.7% in all age groups in 2012, but had no information on diabetes subtypes [12].

A Norwegian study from 2006 based on self-reported data, had an attendance rate of 56% and reported a prevalence of known diabetes of 4.3% in the age group 20 years and older; 4.9% in men and 3.9% in women [13]. Another study on self-reported diabetes from 2004 reported a prevalence of 2.3% in all age groups, and 3.4% among those aged 30 years and older [14].

We consider a recent Norwegian registry-based study with an estimated prevalence of type 2 diabetes of 6.1% in the age group 30–89 years [3] to be the most relevant comparison for our findings of a

Table I. Characteristics and vascular complications of all adults with diabetes in Salten, Norway.

	Type 2 diabetes, *n*=2713				Type 1 diabetes, *n*=304			
	Valid data, *n* (%)	All	Men	Women	Valid data, *n* (%)	All	Men	Women
Patient characteristics								
Sex, *n* (%)	2713 (100)		1530 (56.4)	1183 (43.6)	304 (100)		177 (58.2)	127 (41.8)
Age (years), mean (SD)	2713 (100)	65.6 (12.7)	64.0 (12.1)	67.7 (13.2)	304 (100)	46.7 (15.7)	47.2 (15.3)	45.9 (16.4)
Age at diagnosis (years), mean (SD)	2522 (93.0)	56.9 (12.5)	55.6 (12.0)	58.7 (12.9)	300 (98.7)	25.9 (17.2)	25.8 (17.0)	25.9 (17.7)
BMI (kg/m^2), mean (SD)	1532 (56.4)	30.5 (6.0)	30.4 (5.9)	30.6 (6.2)	282 (92.8)	26.5 (4.5)	26.5 (4.1)	26.6 (5.1)
Diabetes duration (years), median (IQR)	2522 (93.0)	7 (3–12)	7 (3–12)	7 (4–13)	300 (98.7)	19 (11–30)	20 (11–31)	18 (9–29)
Attending hospital outpatient clinic, *n* (%)	2713 (100)	348 (12.8)	225 (14.7)	123 (10.4)	304 (100)	107 (84.3)	142 (80.2)	107 (84.3)
Complications								
Macrovascular complications, *n* (%)	2680 (98.8)	782 (29.2)	530 (35.0)	252 (21.6)	284 (93.4)	37 (13.0)	24 (14.5)	13 (11.0)
Coronary heart disease, *n* (%)	2684 (98.9)	646 (24.1)	443 (29.2)	203 (17.4)	284 (93.4)	29 (10.2)	19 (11.5)	10 (8.5)
Stroke, *n* (%)	2690 (99.2)	206 (7.7)	133 (8.8)	73 (6.2)	284 (93.4)	12 (4.2)	8 (4.8)	4 (3.4)
PTA/art. surgery, *n* (%)	2680 (98.8)	67 (2.5)	47 (3.1)	20 (1.7)	284 (93.4)	9 (3.2)	6 (3.6)	3 (2.5)
History of foot ulcer, *n* (%)	2686 (99.0)	62 (2.3)	39 (2.6)	23 (2.0)	283 (93.1)	18 (6.4)	12 (7.2)	6 (5.1)
Lower limb amputations, *n* (%)	2690 (99.2)	27 (1.0)	20 (1.3)	7 (0.6)	284 (93.4)	6 (2.1)	5 (3.0)	1 (0.9)
Retinopathy, all *n* (%)	2088 (77.0)	243 (11.6)	169 (14.1)	74 (8.3)	266 (87.5)	139 (52.3)	90 (59.2)	49 (43.0)
Untreated	–	194 (9.3)	133 (11.1)	61 (6.9)	–	93 (35.0)	61 (40.1)	32 (28.1)
Treated	–	49 (2.4)	36 (3.0)	13 (1.5)	–	46 (17.3)	29 (19.1)	17 (14.9)
Nephropathy, (eGFR, ml/min), *n* (%)	2594 (95.6)	–	–	–	294 (96.7)	–	–	–
≥60		2178 (84.0)	1264 (86.9)	914 (80.3)	–	283 (96.3)	165 (98.2)	118 (93.7)
30–59	–	365 (14.1)	1665 (11.3)	200 (17.6)	–	9 (3.1)	2 (1.2)	7 (5.6)
<30	–	51 (2.0)	26 (1.8)	25 (2.2)	–	2 (0.7)	1 (0.6)	1 (0.8)

Data are presented as means with standard deviation (SD), median with interquartile range (IQR) or percentage.
BMI: body mass index; eGFR: estimated glomerular filtration rate; Macrovascular complications: coronary heart disease (angina/myocardial infarction/percutaneous coronary intervention/bypass), stroke, percutaneous transluminal angioplasty or arterial surgery; PTA/art. surgery: percutaneous transluminal angioplasty or arterial surgery.

Table II. Observed and adjusted vascular complications of all adults with diabetes in Salten, Norway.

Complications	Type 2, *n*=2713		Type 1, *n*=304		Observed difference	Adjusted difference[b]	*P* value margins, observed	*P* value margins, adjusted
	Observed	Adjusted[a]	Observed	Adjusted[a]				
Macro-vascular complications, % (95% CI)	29.2 (27.5 to 31.0)	27.9 (26.3 to 29.5)	13.0 (9.1 to 16.9)	22.4 (15.7 to 29.1)	16.2 (11.9 to 20.4)	5.5 (–1.5 to 12.5)	<0.001	0.123
Coronary heart disease, % (95% CI)	24.1 (22.5 to 25.7)	23.1 (21.6 to 24.7)	10.2 (6.7 to 13.7)	15.8 (10.0 to 1.6)	13.9 (10.1 to 17.7)	7.3 (1.2 to 13.5)	<0.001	0.019
Stroke, % (95% CI)	7.7 (6.7 to 8.7)	7.3 (6.4 to 8.3)	4.2 (1.9 to 6.6)	9.9 (4.3 to 15.5)	3.4 (0.9 to 6.0)	–2.5 (–8.3 to 3.2)	0.008	0.384
PTA/art. surgery, % (95% CI)	2.5 (1.9 to 3.1)	2.7 (2.0 to 3.3)	3.2 (1.1 to 5.2)	3.0 (0.4 to 5.5)	–0.7 (–2.8 to 1.5)	–0.3 (–3.0 to 2.4)	0.536	0.841
Foot ulcer, % (95% CI)	2.3 (1.7 to 2.9)	2.8 (2.0 to 3.7)	6.4 (3.5 to 9.2)	2.5 (0.8 to 4.3)	–4.1 (–7.0 to –1.2)	0.3 (–1.8 to 2.5)	0.006	0.774
Lower limb amputations, % (95% CI)	1.0 (0.6 to 1.4)	1.1 (0.6 to 1.7)	2.1 (0.4 to 3.8)	1.0 (–0.1 to 2.2)	–1.1 (–2.8 to 0.6)	0.1 (–1.3 to 1.6)	0.205	0.843
Retinopathy, % (95% CI)	11.6 (10.3 to 13.0)	15.5 (13.9 to 17.0)	52.3 (46.3 to 58.3)	21.0 (16.0 to 25.9)	–40.6 (–46.8 to –34.5)	–5.5 (–11.1 to 0.0)	<0.001	0.052
Nephropathy, (eGFR, ml/min), mean (95% CI)	83 (82 to 84)	85 (84 to 86)	103 (100 to 105)	87 (85 to 89)	–20 (–22 to –17)	–2 (–4 to 0)	<0.001	0.116

[a]Average predictions adjusted for age, sex and diabetes duration.
[b]Average marginal effects.
CI: confidence interval; eGFR; estimated glomerular filtration rate; Macrovascular complications: coronary heart disease (angina/myocardial infarction/percutaneous coronary intervention/bypass), stroke, percutaneous transluminal angioplasty or arterial surgery; PTA/art. surgery: percutaneous transluminal angioplasty or arterial surgery.

slightly lower prevalence of 5.3% in the same age group, although with a slightly higher prevalence of 5.4% based on sensitivity analyses. The registry study was based on national databases only and lacked validation of diagnosis from clinical records. In contrast, in the present study we used information from electronic records in primary and specialist care, with manually validated diagnoses. Our prevalence estimates may therefore be more accurate.

Explanations for the discrepant prevalence findings could, however, also be related to differences in rates of opportunistic screening, undiagnosed cases, trends for underlying risk factors, such as BMI, all-cause mortality in the diabetes population and the ethnic composition when the studies were performed. Many people with type 2 diabetes are still undiagnosed [15].

Cardiovascular risk factors and complications

Our findings regarding cardiovascular risk factors and complications are generally in line with other studies. A recent systematic review on patients with type 2 diabetes reported that CVD affected 32.2% and 21.2% had CHD [16]. A Swedish study including type 2 diabetes patients requiring glucose-lowering drugs reported a CVD prevalence of 34% [17]. Other studies on type 2 diabetes patients have reported a CVD prevalence of 17% to 23%, 18% in men and 14% in women [7], [18–21]. The differences in crude rates of CVD and CHD between diabetes types can partly be explained by differences in age, sex and diabetes duration, as seen in our adjusted analyses where these differences were less pronounced. Furthermore, the pathophysiological process leading to CVD in type 1 and type 2 diabetes differs [22].

Attained treatment targets

Only 22.5% of type 1 diabetes patients reached the HbA1c treatment target versus 61.1% of type 2 patients. This is comparable to other studies including both type 1 and type 2 diabetes patients reporting proportions of 52% to 57%, and 54.2% in type 2 diabetes patients [23–26]. We also identified inadequate lipid control as the treatment target for LDL-cholesterol was reached in only 60% in patients receiving lipid-lowering medication.

Strengths and limitations

The strengths of the present study include the large sample size obtained within an integrated and defined health system and the use of real-world data obtained

Table III. Observed and adjusted cardiovascular risk factors and prescribed medication in all adults with diabetes in Salten, Norway.

	Type 2 (*N*=2713)			Type 1 (*N*=304)			Adjusted difference[c]	*P* value for adjusted
	Valid numbers (%)	Observed	Adjusted[b]	Valid numbers (%)	Observed	Adjusted[b]		
HbA1c, %, mean (95% CI)	2435 (89.8)	7.0 (7.0 to 7.1)	7.1 (7.0 to 7.2)	289 (95.1)	8.1 (8.0 to 8.3)	7.5 (7.4 to 7.7)	–0.4 (–0.6 to –0.3)	<0.001
HbA1c, mmol/mol, mean (95% CI)	2435 (89.8)	53 (53 to 54)	54 (54 to 55)	289 (95.1)	66 (64 to 67)	59 (57 to 61)	–4.8 (–6.8 to –2.7)	<0.001
Systolic blood pressure, mmHg, mean (95% CI)	2277 (83.9)	137 (137 to 138)	136 (136 to 137)	288 (94.7)	127 (126 to 129)	131 (129 to 133)	5.4 (2.9 to 8.0)	<0.001
Diastolic blood pressure, mmHg, mean (95% CI)	2277 (83.9)	78 (78 to 78)	78 (78 to 78)	288 (94.7)	74 (73 to 75)	74 (72 to 75)	4.5 (3.0 to 5.9)	<0.001
LDL-cholesterol, mmol/l, mean (95% CI)	2408 (88.8)	2.8 (2.7 to 2.8)	2.8 (2.7 to 2.8)	288 (94.7)	2.7 (2.6 to 2.8)	2.8 (2.6 to 2.9)	–0.0 (–0.1 to 0.1)	0.915
With CHD, mmol/l	587 (21.6[1]) (90.9[2])	2.5 (2.4 to 2.5)	2.5 (2.4 to 2.5)	29 (9.5[1]) (100[2])	2.1 (1.9 to 2.4)	2.1 (1.7 to 2.4)	0.4 (0.0 to 0.8)	0.051
No CHD, mmol/l	1795 (66.2[1]) (88.1[2])	2.9 (2.8 to 2.9)	2.8 (2.8 to 2.9)	240 (78.9[1]) (94.1[2])	2.8 (2.7 to 2.9)	2.9 (2.8 to 3.1)	–0.1 (–0.2 to 0.1)	0.242
Prescribed lipid-lowering agents, mmol/l	1345 (49.6[1]) (96.1[3])	2.5 (2.5 to 2.6)	2.5 (2.4 to 2.5)	98 (32.2[1]) (100[3])	2.5 (2.3 to 2.7)	2.7 (2.5 to 2.8)	–0.2 (–0.4 to 0.0)	0.095
No lipid-lowering agents, mmol/l	1063 (39.2[1]) (80.9[4])	3.1 (3.1 to 3.2)	3.1 (3.0 to 3.1)	190 (62.5[1]) (92.2[4])	2.8 (2.7 to 2.9)	2.8 (2.7 to 3.0)	0.2 (0.0 to 0.4)	0.016
Current smoking, *n* (%)	2309 (85.1)	430 (18.6)	18.9 (17.2 to 20.5)	291 (95.7)	54 (18.6)	12.8 (7.1 to 18.4)	6.0 (0.0 to 12.2)	0.050
Using antihypertensive agents, *n* (%)	2713 (100)	1806 (66.6)	–	304 (100)	108 (35.5)	–	–	–
Groups of antihypertensive agents, *n* (%)								
ACE/AII blockers	2713 (100)	1435 (52.9)	54.3 (52.4 to 56.3)	304 (100)	85 (28.0)	23.5 (16.7 to 30.3)	30.8 (23.4 to 38.2)	<0.001
Beta blockers[a]	–	790 (29.1)	–	–	24 (7.9)	–	–	–
Calcium antagonists[a]	–	750 (27.6)	–	–	24 (7.9)	–	–	–
Thiazides[a]	–	741 (27.3)	–	–	30 (9.9)	–	–	–
Number of antihypertensive agents, *n* (%)								
1	–	492 (18.1)	–	–	44 (14.5)	–	–	–
2	–	552 (20.4)	–	–	34 (11.2)	–	–	–
≥3	–	762 (28.1)	–	–	30 (9.9)	–	–	–
Lipid-lowering medication, *n* (%)	2713 (100)	1399 (51.6)	53.1 (51.1 to 55.1)	304 (100)	98 (32.2)	29.0 (22.1 to 35.9)	24.1 (16.6 to 31.5)	<0.001
Lipid-lowering medication with CHD	–	471 (72.9)	75.0 (71.6 to 78.5)	–	26 (89.7)	77.2 (58.3 to 96.1)	–2.2 (–21.6 to 17.3)	0.827
Lipid-lowering medication with no CHD	–	915 (44.9)	46.7 (44.4 to 49.0)	–	70 (27.5)	22.1 (14.6 to 29.5)	24.6 (16.5 to 32.8)	<0.001
Acetylsalicylic acid, *n* (%)	2713 (100)	917 (33.8)	33.2 (31.4 to 35.0)	304 (100)	51 (16.8)	23.6 (17.3 to 29.9)	9.6 (2.8 to 16.4)	0.006

1: % of total population (type 1 or type 2 diabetes).
2: % of subpopulation with or without known CHD.
3: % of subpopulation prescribed lipid-lowering medication.
4: % of subpopulation not prescribed lipid-lowering medication.
[a]Data only from general practice.
[b]Average predictions adjusted for age, sex and diabetes duration.
[c]Average marginal effects.
HbA1c: haemoglobin A1c; CI: confidence interval; LDL: low-density lipoprotein; CHD: coronary heart disease.

from both primary and specialist care in a geographically defined area. The diabetes diagnoses were based on the physicians' clinical diagnoses and validated during data collection. No financial incentives related to pay-for-performance were operating at the time of the study. A limitation may be that we only included patients in primary care who had been in contact with their GP in the period 1 January 2012 to 31 December 2014. This may have excluded some individuals infrequently visiting their GPs.

The prevalence of type 2 diabetes varies considerably between ethnic groups [27,28]. By standardising to the Norwegian immigrant population, the prevalence estimate in Salten only changed by 0.1%. Due to the low number of persons with type 1 diabetes the power to detect differences between diabetes types was limited. Finally, we lack information about individualised treatment targets based on age, multimorbidity and individual preferences.

Identifying gaps in treatment and prevention followed by quality improvement strategies to improve risk factor control may contribute to a further reduction in the individual risk of diabetes complications.

Conclusion

The present study provides benchmark estimates on the prevalence of diagnosed type 1 and type 2 diabetes in a Norwegian geographically defined population showing a slightly lower prevalence of type 2 diabetes than a recent estimate based on registry data. Glycaemic control was not satisfactory in the majority of patients with type 1 diabetes. CHD and hypertension were more prevalent in patients with type 2 diabetes. Continued monitoring of both diabetes prevalence and diabetes-related risk factors and complications is necessary to target interventions in subgroups in need of more intensive treatment.

Acknowledgements

The authors would like to thank Elin Røst, research nurse in Salten, and Karianne Fjeld Løvaas at the Norwegian Organization for Quality Improvement of Laboratory Examinations, Haraldsplass Deaconess Hospital, Bergen, for participating in the study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Helse Nord supports the PhD doctoral programme of KBS. The data collection of the ROSA 4 study was supported financially with grants from the Norwegian Diabetes Association, a consortium of six pharmaceutical firms (AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis), Helse Nord, the Endocrinology Research Foundation, Stavanger and the University of Oslo.

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Supplemental material

Supplemental material for this article is available online.

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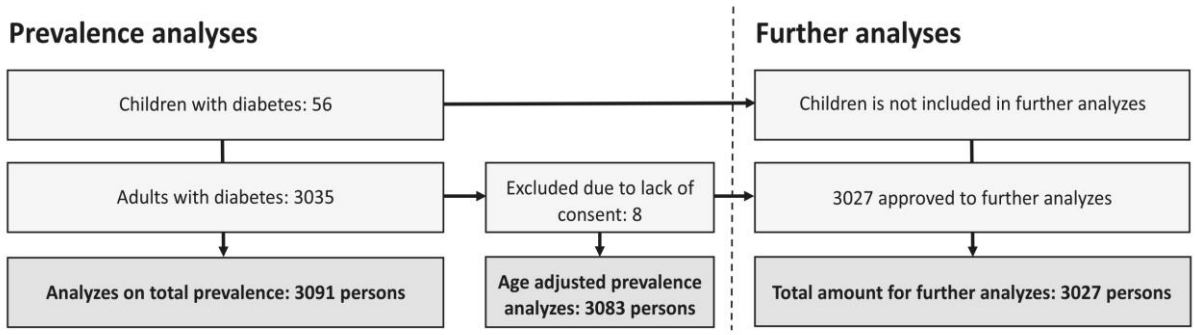
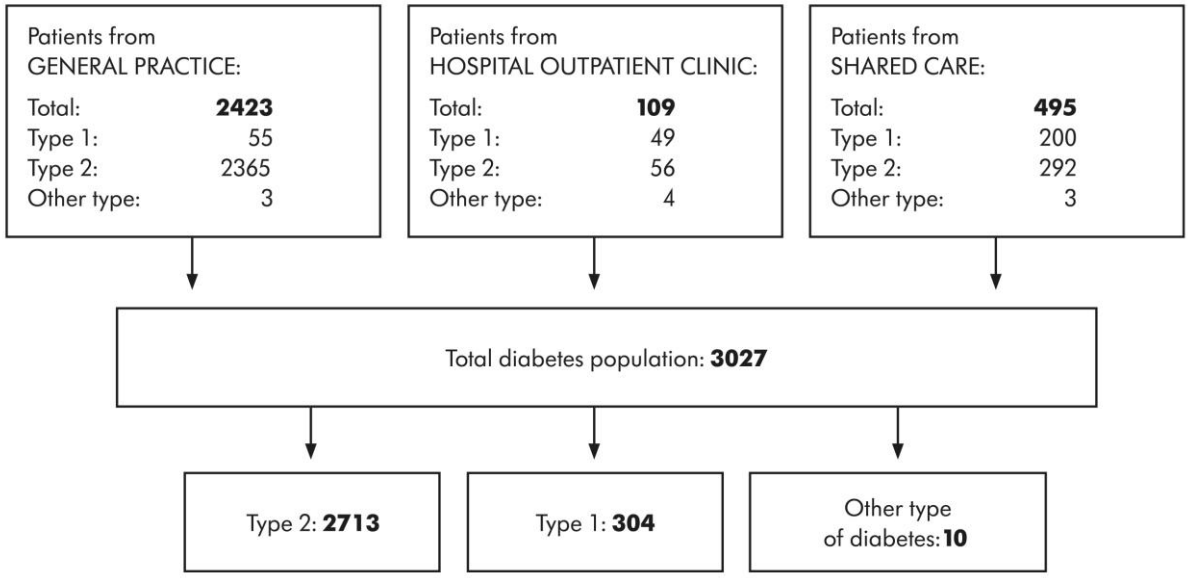
Supplementary Figure 1: Flowchart of patients



Supplementary Figure 2: Adults patients included in the study: Diabetes type and source of data collection. Shared care includes patients visiting both general practice and specialist care.



Paper 2

Slåtsve, K.B., Claudi, T., Lappegård, K.T., Jenum, A.K., Larsen, M., Nøkleby, K., Cooper, J.G., Sandberg, S. & Berg, T.J. (2021).

Factors associated with treatment in primary versus specialist care: A population-based study of people with type 2 and type 1 diabetes

Diabetic Medicine, 38(7), e14580.

Received: 29 December 2020 | Accepted: 28 March 2021

DOI: 10.1111/dme.14580

DIABETIC Medicine

RESEARCH: CARE DELIVERY

Factors associated with treatment in primary versus specialist care: A population-based study of people with type 2 and type 1 diabetes

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Funding information
Helse Nord supports the PhD doctoral program of KBS. The data collection of the ROSA 4 study was supported financially with grants from the Norwegian Diabetes Association, a consortium of six pharmaceutical firms (AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk and Sanofi Aventis), Helse Nord, the Endocrinology Research Foundation, Stavanger, and the University of Oslo.

Abstract

Aims: The objectives of this study are to identify the proportion and characteristics of people with type 1 and 2 diabetes treated in primary, specialist and shared care and to identify the proportion of persons with type 2 diabetes reaching HbA_{1c} treatment targets and the clinical risk factors and general practitioner and practice characteristics associated with treatment in specialist care.

Methods: Population-based cross-sectional study including all adults ≥18 years diagnosed with diabetes in primary and specialist care in Salten, Norway. We used multivariable mixed-effects logistic regression models with level of care as outcome variable and population, general practitioner, and practice characteristics as exposure variables.

Results: Of 2704 people with type 2 diabetes, 13.5% were treated in shared care and 2.1% in specialist care only. Of 305 people with type 1 diabetes, 14.4% received treatment in primary care only. The HbA_{1c} treatment target of 53 mmol/mol (7.0%) was reached by 67.3% of people with type 2 diabetes in primary care versus 30.4% in specialist care. HbA_{1c}, use of insulin, coronary heart disease, retinopathy and urban

practice location were positively associated with treatment in specialist care. General practitioners' use of a structured form and a diabetes nurse were negatively associated with specialist care.

Conclusions: Of people with type 2 diabetes, 16% were treated in specialist care. They had higher HbA_{1c} and more vascular complications, as expected from priority guidelines. The use of a structured diabetes form and diabetes nurses seem to support type 2 diabetes follow-up in primary care.

What's new?

- The increasing prevalence of diabetes calls for an optimal utilization of healthcare resources.
- Individuals with type 2 diabetes treated in specialist care had higher HbA_{1c} and more vascular complications than those treated in primary care only and were thus rightly allocated. General practitioner's (GP's) use of a structured diabetes form and diabetes nurses were negatively associated with treatment in specialist care.
- The use of structured diabetes forms and diabetes nurses in primary care may reduce the workload in specialist care.

1 | INTRODUCTION

The prevalence of diabetes is increasing worldwide and so is the proportion of people living with diabetes and vascular complications and the overall healthcare related costs of the disease.[1] The goal of diabetes care is to reduce vascular complications and prolong high quality of life.[2] Several studies have shown the importance of glucose-lowering therapy, blood pressure and lipid control in reducing the risk of cardiovascular outcomes.[3] Preventing or postponing vascular complications will reduce both the individual and the societal burden of the disease.

Accordingly, this calls for an efficient, evidence-based and cost-effective organization of diabetes healthcare. The World Health Organization supports the trend of chronic care shifting from the secondary to the primary healthcare sector because a strong primary care service is essential to meet the observed worldwide challenges related to diabetes.[4] Finding the right balance between levels of care and identifying individuals who may benefit from treatment in specialist care is essential. This will also facilitate optimal utilization of available healthcare resources.

The pathophysiology, aetiology and treatment of type 2 diabetes (T2D) and type 1 diabetes (T1D) differ. Optimal care should integrate individual, medication and provider factors.[5] As there are no international guidelines on allocation to primary or specialist care of persons with T2D, both guidelines and organization differ between countries.[6,7] The Norwegian diabetes guidelines state that individuals with T1D should be treated in specialist care. Individuals with complicated T2D should be referred to specialist care. Studies on people with T2D have shown that socio-economic status (SES) influences follow-up in many ways, including individual capabilities, health-related behaviours, access to care, processes of care and risk of complications.[8,9]

Given the two levels of care (primary and specialist care) in people with T2D, it is important to evaluate the current patterns of management of the population of people with diabetes, as well as the characteristics of general practitioners (GPs) and GP practices associated with treatment levels.

We hypothesized that people with T2D treated in specialist care have more complex diseases with less achievement of treatment targets and more vascular complications than those treated in primary care only. Thus, we aimed to identify the proportion and characteristics of people with T2D and T1D treated in primary, shared and specialist care as well as the proportion of people with T2D reaching HbA_{1c} treatment targets. Furthermore, our aim was to identify clinical risk factors, GP and practice characteristics associated with T2D treatment in specialist care.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design and setting

We used data from the Norwegian cross-sectional study ROSA 4 including all adults (≥18 years) with T1D and T2D living in the Salten region as at 31 December 2014.[10,11] The ROSA 4 study was approved by the Regional Ethical Committee West (REK 2014/1374, REK Vest), with

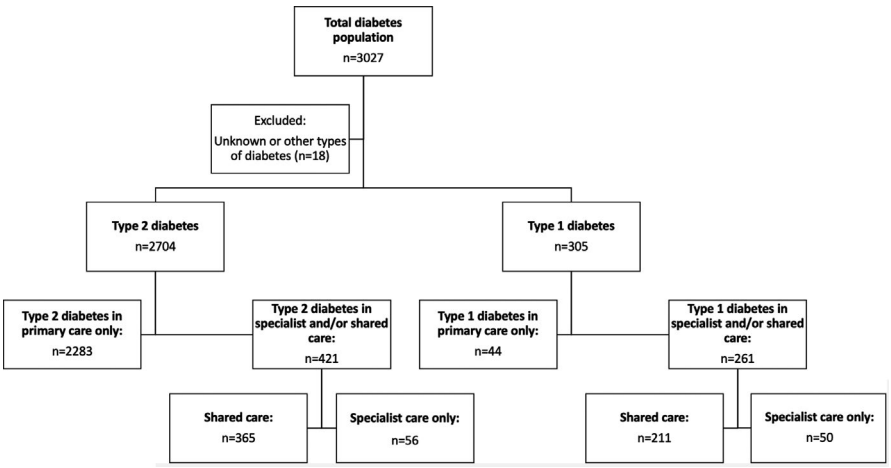

FIGURE 1 Study population according to level of care; primary, specialist or shared care

permission to collect data without written consent from all individuals with diabetes visiting primary care. Data on individuals visiting specialist care were collected in those consenting to send their data to the Norwegian Adult Diabetes Registry.

All residents in Norway have equal access to primary and specialist healthcare services free of charge once their own contribution to medical services has exceeded the annual limit (approximately 233 EUR in 2014). All residents are assigned to one GP, who cares for a maximum of 2500 individuals. The GP acts as a gatekeeper to specialist healthcare as specialists cannot see patients without referral.

Norwegian diabetes guidelines state that individuals with T1D ought to be treated in specialist care with individualized follow-up and at least one annual consultation.[12] In most people with T2D, cost-effective diabetes care can be provided in a primary care setting,[13-15] with at least one visit per year. GPs can use a software tool (Noklus diabetes application) that lists recommended tasks in the annual review and allows the performance of these tasks to be reported to the Norwegian Adult Diabetes Registry. Additional support from specialist care is recommended in individuals with poor glycaemic control, severe diabetes complications or complicating co-morbidities.[12] The Priority Guideline for Diabetes in the Specialist Health Service covers rights and deadlines for assessment of referrals to the specialist health service and ensures equality in clinical practice.[16] People with T2D without severe vascular complications or co-morbidities and reaching treatment targets are generally returned to primary care.[16] Diabetes nurses in Norway have additional education, some at master level, enabling them to independently provide lifestyle advice, educate on the use of insulin and contribute to better diabetes management.

Salten is a geographical area in Norway, both urban and rural, with a population of 80 338, 83 GPs and one diabetes outpatient clinic (i.e., diabetes specialist care) but no private diabetologists as of 31 December 2014. The total prevalence of diagnosed diabetes in Salten was 3.8% in 2014, 3.4% for T2D and 0.45% for T1D.[10] As a result of a regional diabetes action plan, there has been a close cooperation between diabetes specialist care and GPs in this region during the last 20 years.

2.2 | Population

The study population covered all individuals registered with T2D and T1D visiting primary care and all consenting individuals with T2D and T1D visiting the diabetes outpatient clinic ($n = 682$ out of 690 [98.8%]) between 1 January 2012 and 31 December 2014. After excluding individuals with gestational and other types of diabetes (maturity-onset diabetes of the young [MODY] or pancreatitis, $n = 18$) from the total diabetes sample ($n = 3027$), the final study sample included 3009 individuals: 2704 with T2D and 305 with T1D (Figure 1). Individuals registered with primary care follow-up had visited their GP for diabetes and were not treated in specialist care during the study period. Individuals registered with specialist care had one or more visits at the diabetes outpatient clinic. This group included individuals with specialist care only and individuals with consultations in both primary and specialist care, defined as shared care. All GPs and GP practices in the area were invited, and all GPs agreed to participate in the study.

2.3 | Data sources

In primary care, all individuals ≥18 years with diabetes (T89 and T90 in the International Classification of Primary Care) registered in electronic medical records from 1 January 2012 to 31 December 2014 were included. Predefined data were extracted according to a protocol.[11] Data quality was ensured by an experienced research nurse visiting all GPs to verify data and search for missing data in the electronic medical records, including reports from specialists. The search had been

tested in a pilot ensuring the accuracy of key search words used. Data from the only outpatient clinic were obtained from the Norwegian Adult Diabetes Registry and included all consenting individuals treated at the clinic. Information about education level and country of birth was obtained from 'Statistics Norway' and linked to the electronic health records. Information about the GPs and GP practices was collected by a questionnaire, with 96.3% response rate.

2.4 | Variables

A detailed description of variables used in the present study has been published.[11] In short, the following population variables were registered: sex, age, diabetes duration, body mass index (BMI), medication, HbA_{1c}, blood pressure (BP), total cholesterol, low-density lipoprotein (LDL) cholesterol, creatinine and vascular complications (retinopathy, nephropathy, neuropathy, foot ulcer, lower limb amputation, coronary heart disease [CHD], stroke, percutaneous transluminal angioplasty/arterial surgery). Serum creatinine was measured in μmol/L, and estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. We used the last registered value within 3 years for HbA_{1c}, BP, lipids and eGFR. BP values in primary care were registered within 15 months (Table S1). We used the most adverse outcome or complication in the analyses if registrations in primary and specialist care differed in individuals with shared care. Medications were extracted from the GP's electronic prescription records from 1 October 2013 to 31 December 2014, and from GP and specialist database registrations. The classification of diabetes type was based on the doctor's clinical diagnoses, supplemented by measurements of beta cell antibodies and C-peptide when indicated.[10]

Variables regarding GPs included sex, age, medical education in Norway (yes/no), specialist status, workload defined as number of people on the list, number of individuals with T2D listed and the use of a national structured electronic diabetes form with an annual review template supplying data to the Norwegian Adult Diabetes Registry. Practice variables included location (urban/rural) and diabetes nurse employed. Urban/rural status was defined as living in the only city (Bodø) versus small towns or rural areas.

Treatment targets were based on the key recommendations in the Norwegian diabetes guidelines from 2009 [12] : HbA_{1c} ≤53 mmol/mol (7.0%), intervention threshold for BP >140/85 mmHg with treatment target ≤135/80 mmHg, LDL cholesterol ≤3.5 mmol/L without lipid lowering therapy and ≤1.8 mmol/L with and ≤2.5 mmol/L without known CHD.

Education was categorized as: (1) pre-primary and primary education (completion of compulsory school) or less (≤10 years), (2) secondary education (high school 11–13 years) and (3) tertiary education (university >13 years).

3 | STATISTICAL ANALYSES

Descriptive statistics are presented as frequencies and percentages (categorical variables), means with standard deviations or medians with interquartile range (IQR) (continuous variables). Nephropathy was categorized for descriptive purposes according to standard categorization (eGFR ≥60, 30–59 and <30 ml/min/1.73 m^2).

We used multivariable mixed-effects logistic regression to analyse the odds of being treated in specialist care and population, GP and practice characteristics as exposure variables. We ran separate models for each exposure variable. We adjusted for age, sex, diabetes duration and education as fixed effects in the models due to possible confounding between outcome and the different exposure variables. GP practice was included as a random effect in the models. BMI was not included in the models due to a high level of missing values. In the regression analyses, we excluded 56 (2.1%) individuals with T2D treated in specialist care only due to lack of information on GP and practice characteristics and individuals not registered with a GP. Odds ratios (ORs) and 95% confidence intervals (CIs) were presented for univariable and multivariable results.

All statistical analyses were performed using STATA/SE 14 (StataCorp, LP).

4 | RESULTS

4.1 | Population characteristics in primary, specialist and shared care

In individuals with T2D, 84.4% (n = 2283) were treated in primary care only, 2.1% (n = 56) in specialist care only and 13.5% (n = 365) in shared care (Table 1). Individuals treated in primary care only had mean age 66.4 (SD =12.6) years, compared with 64.1 (SD =13.0) and 60.7 (SD =12.9) years in specialist and shared care, respectively. The proportion of men was 54.9%, 69.9% and 63.0% in primary, specialist and shared care, respectively. In primary care, 16.7% of individuals with T2D had university education, compared with 28.6% and 20.8% in specialist and shared care, respectively. The prevalence of CHD was 23.1% in primary care, 40.0% in specialist care and 28.8% in shared care. For retinopathy, the prevalence was 7.6%, 44.8% and 29.4%, respectively.

In individuals with T1D, the majority were treated in specialist and shared care, but 14.4% (n = 44) were treated in primary care only (Table 2). Among those treated in primary care only, mean age was 51.4 (SD =18.3) years, compared with 43.7 (SD =14.2) years in specialist care and 47.0 (SD =15.7) years in shared care. Median diabetes duration was 16 (IQR: 7–33), 25 (IQR: 14–36) and 19 (IQR: 11–28) years, respectively.

TABLE 1 Type 2 diabetes persons characteristics, cardiovascular risk factors, prescribed medication and vascular complications

	Type 2 diabetes, *n* = 2704					
	Primary care only, *n* = 2283		Shared care, *n* = 365		Specialist care only, *n* = 56	
	Valid numbers, *n* (%)		Valid numbers, *n* (%)		Valid numbers, *n* (%)	
Patient characteristics						
Age (years), mean (SD)	2283 (100)	66.4 (12.6)	365 (100)	60.7 (12.9)	56 (100)	64.1 (13.0)
Men, *n* (%)	2283 (100)	1254 (54.9)	365 (100)	230 (63.0)	56 (100)	39 (69.9)
Diabetes duration (years), median (IQR)	2093 (91.7)	6 (3–11)	365 (100)	12 (7–17)	56 (100)	11 (7–19)
Age at diagnosis (years), median (IQR)	2093 (91.7)	59 (51–67)	365 (100)	48.0 (41–56)	56 (100)	52.0 (42–61)
BMI (kg/m^2), mean (SD)	1142 (50.0)	30.1(5.9)	361 (98.9)	31.7 (6.1)	54 (96.4)	29.9 (5.8)
Education	2261 (99.0)	—	361 (98.9)	—	56 (100)	—
Primary school, *n* (%)	—	829 (36.7)	—	116 (32.1)	—	11 (19.6)
High school/craftmanship, *n* (%)	—	1054 (46.6)	—	170 (47.1)	—	29 (51.8)
University, *n* (%)	—	378 (16.7)	—	75 (20.8)	—	16 (28.6)
Born outside Europe, *n* (%)	2283 (100)	71 (3.1)	365 (100)	7 (1.9)	56 (100)	3 (5.4)
Cardiovascular risk factors						
HbA_{1c}, %, mean (SD)	2212 (96.9)	6.9 (1.1)	365 (100)	7.9 (1.4)	56 (100)	7.4 (1.3)
HbA_{1c}, mmol/mol, mean (SD)	2212 (96.9)	51.4 (11.9)	365 (100)	62.4 (15.3)	56 (100)	57.6 (14.6)
Systolic blood pressure, mmHg, mean (SD)	1855 (81.3)	138 (16)	365 (100)	135 (15)	55 (98.2)	133 (15)
Diastolic blood pressure, mmHg, mean (SD)	1855 (81.3)	78 (10)	365 (100)	77 (10)	55 (98.2)	73 (11)
LDL cholesterol, mmol/L, mean (SD)	1987 (87.0)	2.8 (0.9)	365 (100)	2.7 (1.0)	54 (96.4)	2.6 (0.9)
With CHD, mmol/L, mean (SD)	469 (89.3[a])	2.5 (0.9)	105 (100[a])	2.4 (1.0)	14 (100[a])	2.3 (0.8)
No CHD, mmol/L, mean (SD)	1511 (86.3[a])	2.9 (0.9)	260 (100[a])	2.8 (0.9)	21 (100[a])	2.6 (1.0)
Prescribed lipid lowering agents, mmol/L	1204 (93.8[a])	2.6 (0.9)	277 (100[a])	2.5 (0.9)	31 (100[a])	2.4 (0.8)
No lipid lowering agents, mmol/L, mean (SD)	783 (78.4[a])	3.2 (0.9)	88 (100[a])	3.1 (0.9)	23 (92.0[a])	2.9 (0.9)
Prescribed medication						
Antihypertensive agents, *n* (%)	2283 (100)	1645 (72.1)	365 (100)	277 (75.9)	56 (100)	37 (66.1)
Insulin, *n* (%)	2283 (100)	320 (14.0)	365 (100)	245 (67.1)	56 (100)	38 (67.9)
Lipid lowering medication, *n* (%)	2283 (100)	1284 (56.2)	365 (100)	277 (75.9)	56 (100)	31 (55.4)
Lipid lowering medication with CHD, *n* (%)	525 (100)	428 (81.5)	105 (100[a])	100 (95.2)	14 (100[a])	12 (85.7)
Lipid lowering medication with no CHD, *n* (%)	1750 (100)	850 (48.6)	260 (100[a])	177 (68.1)	21 (100[a])	11 (52.4)
Acetylsalicylic acid, *n* (%)	2283 (100)	844 (37.0)	365 (100)	162 (44.4)	56 (100)	18 (32.1)
Complications						
Coronary heart disease, *n* (%)	2275 (99.6)	525 (23.1)	365 (100)	105 (28.8)	35 (62.5)	14 (40.0)
Stroke, *n* (%)	2281 (99.9)	186 (8.2)	365 (100)	19 (5.2)	35 (62.5)	3 (8.6)
PTA/arterial surgery, *n* (%)	2274 (99.6)	45 (2.0)	364 (99.7)	22 (6.0)	34 (60.7)	2 (5.9)
History of foot ulcer, *n* (%)	2278 (99.8)	27 (1.2)	365 (100)	30 (8.2)	34 (60.7)	6 (17.7)
Lower limb amputations, *n* (%)	2282 (100)	17 (0.7)	365 (100)	10 (2.7)	34 (60.7)	0 (0)

(Continues)

TABLE 1 (Continued)

	Type 2 diabetes, $n = 2704$					
	Primary care only, $n = 2283$		Shared care, $n = 365$		Specialist care only, $n = 56$	
	Valid numbers, n (%)		Valid numbers, n (%)		Valid numbers, n (%)	
Retinopathy, all, n (%)	1717 (75.2)	131 (7.6)	348 (95.3)	101 (29.4)	29 (51.8)	13 (44.8)
Untreated	—	114 (6.6)	—	73 (21.3)	—	9 (31.0)
Treated	—	17 (1.0)	—	28 (8.2)	—	4 (13.8)
Nephropathy, (eGFR, ml/min/1.73 m^2), n (%)	2167 (94.9)	—	365 (100)	—	56 (100)	—
≥60	—	1932 (89.2)	—	332 (91.0)	—	44 (78.6)
30–59	—	209 (9.6)	—	29 (8.0)	—	9 (16.1)
<30	—	26 (1.2)	—	4 (1.1)	—	3 (5.4)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PTA, percutaneous transluminal angioplasty.

Data are presented as means with standard deviation (SD), median with interquartile range (IQR) or percent. Specialist care = Hospital diabetes outpatient clinic.

[a]Percentage of subpopulation with/without coronary heart disease (CHD) and prescribed/not prescribed lipid lowering medication.

4.2 | General practitioner and practice characteristics

For the 82 GPs included in the study, mean age was 44.7 (SD =11.2) years, 58.1% were men and median years working as GP was 9 (IQR: 3–24) (Table 3). A diabetes nurse was employed in 53.9% ($n = 14$) of the 27 practices.

4.3 | Attained treatment targets in primary and specialist care in people with T2D

In individuals with T2D, the HbA_{1c} treatment target of 53 mmol/mol (7.0%) was reached by 67.3% (95% CI [65.3, 69.2]) in primary care versus 30.4% (95% CI [26.2, 35.0]) in specialist/shared care (Figure 2). In primary care, 6.7% ($n = 148$) had HbA_{1c} values >69 mmol/mol (8.5%), of whom 45.9% ($n = 68$) were younger than 60 years. There were no differences between levels of care in the proportion of individuals with T2D reaching treatment targets for BP and LDL cholesterol.

4.4 | Clinical and GP characteristics associated with treatment in specialist care setting

In adjusted analyses, HbA_{1c} was positively associated with treatment in specialist care (OR =1.54, 95% CI [1.39, 1.71]), as the odds for specialist care treatment increased by 54% per one-unit increase in HbA_{1c} (%) (Table 4). Diabetes-related complications such as CHD (OR =1.99, 95% CI [1.47, 2.68]), retinopathy (OR =2.78, 95% CI [1.97, 3.93]) and foot ulcer (OR =5.55, 95% CI [2.94, 10.48]) were also positively associated with treatment in specialist care. The use of a structured diabetes form and a diabetes nurse employed at the GP's office were both associated with reduced odds for treatment in specialist care (OR =0.53, 95% CI [0.40, 0.69] and OR =0.64, 95% CI [0.50, 0.82], respectively). GP's age and urban location were positively associated with treatment in specialist care (OR =1.01, 95% CI [1.00, 1.02] and OR =1.53, 95% CI [1.18, 1.98], respectively). In unadjusted analyses, education was not associated with treatment in specialist care.

5 | DISCUSSION

The present study shows that 15.6% of people with T2D in Salten, Norway, were treated in specialist care (shared care or specialist care only). They were younger, more likely to be men and had higher HbA_{1c} levels, less achievement of HbA_{1c} treatment target and a higher prevalence of CHD, foot ulcer and retinopathy compared with individuals treated in primary care only. The GP's age and urban practice location were positively associated with treatment in specialist care, and the GP's use of a structured diabetes form and a diabetes nurse employed at the GP practice were associated with reduced odds for treatment in specialist care. In people with T1D, 14.4% were treated in primary care only.

In accordance with our hypothesis, people with T2D treated in specialist care had more vascular complications and less achievement of treatment targets than those treated in primary care, despite their younger age, indicating a more complex disease.

Our findings are in line with previous studies on T2D reporting that specialists often see younger individuals that are more likely to be men with more vascular complications and higher HbA_{1c} levels living in urban centres.[17-19] Individuals

TABLE 2 Type 1 diabetes persons characteristics, cardiovascular risk factors, prescribed medication and vascular complications

	Type 1 diabetes, *n* = 305					
	Primary care only, *n* = 44		Shared care, *n* = 211		Specialist care only, *n* = 50	
	Valid numbers, *n* (%)		Valid numbers, *n* (%)		Valid numbers, *n* (%)	
Patient characteristics						
Age (years), mean (SD)	44 (100)	51.4(18.3)	211 (100)	47.0 (15.7)	50 (100)	43.7 (14.2)
Men, *n* (%)	44 (100)	30 (68.2)	211 (100)	114 (54.0)	50 (100)	34 (68.0)
Diabetes duration (years), median (IQR)	40 (90.9)	16 (7–33)	211 (100)	19 (11–28)	50 (100)	25 (14–36)
Age at diagnosis (years), median (IQR)	40 (90.9)	35 (16–50)	211 (100)	23 (12–38)	50 (100)	17 (11–26)
BMI (kg/m^2), mean (SD)	27 (61.4)	27.1 (5.0)	210 (99.5)	26.4 (4.6)	50 (100)	26.4 (4.2)
Education	43 (97.7)	—	210 (99.5)	—	50 (100)	—
Primary school, *n* (%)	—	13 (30.2)	—	55 (26.2)	—	11 (22.0)
High school/craftmanship, *n* (%)	—	20 (46.5)	—	91 (43.3)	—	23 (46.0)
University, *n* (%)	—	10 (23.3)	—	64 (30.5)	—	16 (32.0)
Born outside Europe, *n* (%)	44 (100)	1 (2.3)	211 (100)	3 (1.4)	50 (100)	0 (0)
Cardiovascular risk factors						
HbA_{1c}, %, mean (SD)	34 (77.3)	7.8 (1.7)	211 (100)	8.3 (1.4)	50 (100)	7.9 (1.4)
HbA_{1c}, mmol/mol, mean (SD)	34 (77.3)	61.8 (18.1)	211 (100)	67.2 (15.2)	50 (100)	63.4 (15.6)
Systolic blood pressure, mmHg, mean (SD)	30 (68.2)	134 (15)	211 (100)	126 (14)	50 (100)	128 (17)
Diastolic blood pressure, mmHg, mean (SD)	30 (68.2)	74 (11)	211 (100)	74 (9)	50 (100)	73 (10)
LDL cholesterol, mmol/L, mean (SD)	31 (70.5)	2.9 (1.1)	210 (99.5)	2.7 (0.8)	49 (98.0)	2.6 (0.6)
With CHD, mmol/L, mean (SD)	6 (100[a])	2.3 (0.7)	22 (100[a])	2.0 (0.7)	4 (100[a])	2.6 (1.0)
No CHD, mmol/L, mean (SD)	25 (65.8[a])	3.1 (1.1)	188 (99.5[a])	2.7 (0.8)	24 (100[a])	2.7 (0.5)
Prescribed lipid lowering agents, mmol/L	16 (94.1[a])	2.8 (1.1)	82 (100[a])	2.5 (1.0)	11 (100[a])	2.6 (0.6)
No lipid lowering agents, mmol/L, mean (SD)	15 (55.6[a])	3.1 (1.1)	128 (99.2[a])	2.8 (0.7)	38 (97.4[a])	2.7 (0.6)
Prescribed medication						
Antihypertensive agents, *n* (%)	44 (100)	17 (38.6)	211 (100)	86 (40.8)	50 (100)	15 (30.0)
Lipid lowering medication, *n* (%)	44 (100)	17 (38.6)	211 (100)	82 (38.9)	50 (100)	11 (22.0)
Lipid lowering medication with CHD, *n* (%)	6 (100)	6 (100)	22 (100)	20 (90.9)	4 (100)	4 (100)
Lipid lowering medication with no CHD, *n* (%)	38 (100)	11 (29.0)	189 (100)	62 (32.8)	24 (100)	5 (20.8)
Acetylsalicylic acid, *n* (%)	44 (100)	11 (25.0)	211 (100)	41 (19.4)	50 (100)	6 (12.0)
Complications						
Coronary heart disease, *n* (%)	44 (100)	6 (13.6)	211 (100)	22 (10.4)	28 (56.0)	4 (14.3)
Stroke, *n* (%)	44 (100)	4 (9.1)	211 (100)	8 (3.8)	28 (56.0)	0 (0)
PTA/arterial surgery, *n* (%)	44 (100)	3 (6.8)	211 (100)	5 (2.4)	28 (56.0)	1 (3.6)
History of foot ulcer, *n* (%)	44 (100)	0 (0)	211 (100)	17 (8.1)	28 (56.0)	2 (7.1)
Lower limb amputations, *n* (%)	44 (100)	0 (0)	211 (100)	6 (2.8)	28 (56.0)	0 (0)
Retinopathy, all, *n* (%)	34 (77.3)	14 (41.2)	203 (96.2)	103 (50.7)	30 (60.0)	34 (80.0)

(Continues)

TABLE 2 (Continued)

	Type 1 diabetes, $n = 305$					
	Primary care only, $n = 44$		Shared care, $n = 211$		Specialist care only, $n = 50$	
	Valid numbers, n (%)		Valid numbers, n (%)		Valid numbers, n (%)	
Untreated	—	7 (20.6)	—	71 (35.0)	—	15 (50.0)
Treated	—	7 (20.6)	—	32 (15.8)	—	9 (30.0)
Nephropathy, (eGFR, ml/min/1.73 m^2), n (%)	35 (79.5)	—	210 (99.5)	—	50 (100)	—
≥60	—	33 (94.3)	—	205 (97.6)	—	50 (100)
30–59	—	2 (5.7)	—	4 (1.9)	—	0 (0)
<30	—	0 (0)	—	1 (0.5)	—	0 (0)

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; PTA, percutaneous transluminal angioplasty.

Data are presented as means with standard deviation (SD), median with interquartile range (IQR) or percent. Specialist care = Hospital diabetes outpatient clinic.

[a]Percentage of subpopulation with/without coronary heart disease (CHD) and prescribed/not prescribed lipid lowering medication.

TABLE 3 Characteristics of general practitioners ($n = 82$) and practices ($n = 27$)

	Valid numbers	
General practitioners characteristics ($n = 82$)		
Age (years), mean (SD)	76	44.7 (11.2)
Men, n (%)	74	43 (58.1)
Medical education in Norway, n (%)	75	54 (72.0)
Specialist in general practice, n (%)	75	37 (49.3)
Years working as GP, median (IQR)	72	9 (3–24)
Workload (patients on list), median (IQR)	78	989 (826–1224)
No. of people with T2D per GP, median (IQR)	82	31 (20–46)
No. of people with shared care, median (IQR)	82	4 (2–6)
General practitioner office characteristics ($n = 27$)		
Diabetes nurse employed, n (%)	26	14 (53.9)
Urban location, n (%)	26	14 (53.9)

Abbreviations: GP, general practitioner; IQR, interquartile range; T2D, type 2 diabetes.

treated in specialist care are more likely to be monitored according to guidelines, with achievement of adequate HbA_{1c} levels [19-22]; the last stands in contrast to our findings of higher HbA_{1c} levels in specialist care. Whether follow-up in specialist care positively affects HbA_{1c}, hypertension, vascular complications or improves survival is unclear, as results are conflicting.[17,23-26]

In a recent Norwegian study on people with T2D, the GP's use of a structured diabetes form was associated with 23% higher odds of achieving the HbA_{1c} treatment target and 17% higher odds of achieving LDL cholesterol target.[27] In our study, the GP's use of a structured diabetes form and a diabetes nurse employed at the office were both associated with reduced odds for treatment in specialist care. This may indicate a more structured diabetes review and increased knowledge and competence in diabetes treatment, all leading to less need for referrals to specialist care. Whereas GP characteristics such as sex, specialist status and workload were not associated with treatment in specialist care, urban location was. This indicates geographical proximity to the specialist care to be of importance. The reason for this is unknown but could possibly be caused by short transport distance to specialist care or patients' preferences.

Previous studies in people with T2D have reported that SES influences follow-up at multiple levels, including access of care.[8] In the present study, education was not associated with treatment in specialist care, indicating no differences in access to healthcare according to SES. However, only 91 patients treated in specialist care had university education.

According to Norwegian diabetes guidelines,[12] all individuals with T1D have the right to specialist care. Yet, our study surprisingly showed that 14.4% were treated in primary care only. A longitudinal cohort study from the UK including 113 young people with T1D reported that 3% did not attend any clinic and 22% were cared for exclusively by their GPs at follow-up.[28] In a Finnish study, individuals with T1D received follow-up in primary care without compromising good quality and patient satisfaction.[29] Others report associations between specialist care and lower HbA_{1c} levels; however, individuals in specialist care also reported higher education and income levels.[30] A higher proportion of diabetes duration spent in specialist care delayed the development of certain diabetes late complications.[31] To our knowledge, large studies on level of care and disease severity in individuals with T1D are scarce.

The present study shows an overall adherence in the Salten region to the Norwegian diabetes guidelines recommendation

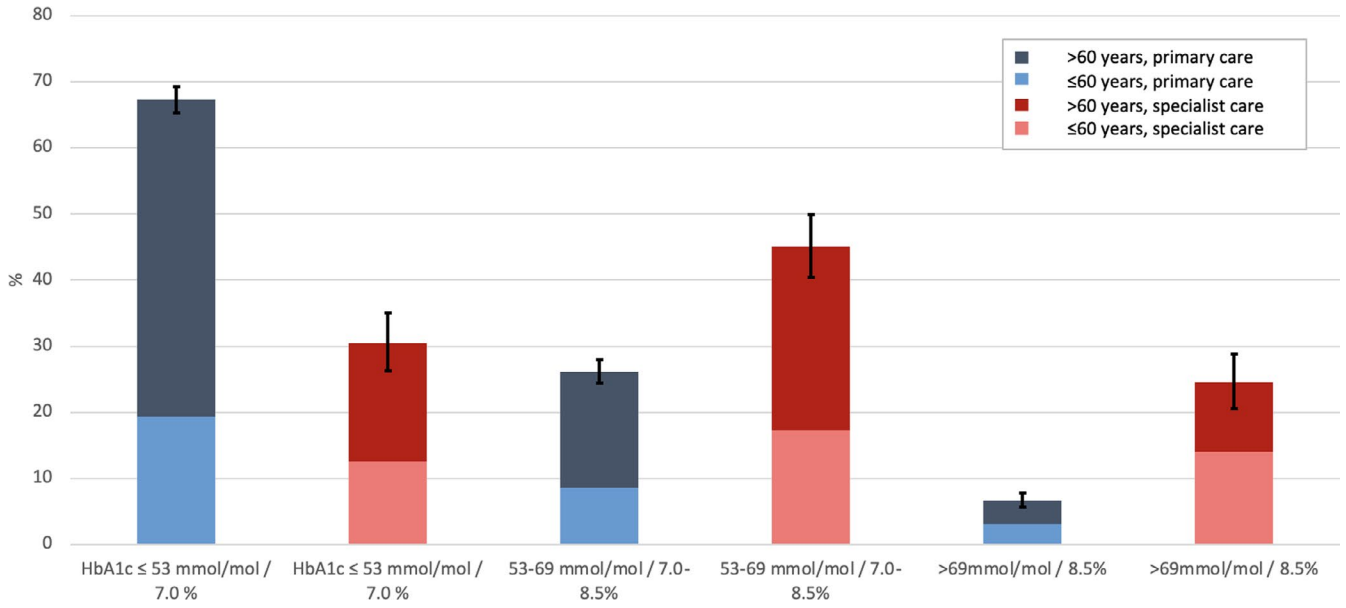

FIGURE 2 HbA_{1c} in people with type 2 diabetes in primary versus specialist/shared care. Error bars represent 95% confidence intervals

that individuals with T2D and poor glycaemic control or complicating co-morbidities should be treated in specialist care.[12] This may partly be a result of a longstanding, systematic co-operation between the hospital and the GPs in the local municipalities. Nevertheless, 46% of patients with HbA_{1c} values >69 mmol/mol (8.5%) treated in primary care were younger than 60 years. Although factors such as the individuals' preferences and medical or social disabilities can influence the decision of level of care, these findings are worrisome. Effective use of resources and a more efficient healthcare service will benefit both individuals and the society. Individual assessments are necessary when deciding level of care. GPs may have a more holistic approach to diabetes care, whereas fragmented healthcare delivery can affect the individual's experience negatively.[32]

The strengths of the present study include a data collection ensuring complete and accurate data on all adults with T2D and T1D and all GPs in a well-defined geographical area, resulting in an adequate sample size. Linkage to 'Statistics Norway' ensured information on education level. Further, in Norway, individuals have equal access to healthcare, and the study was done in the absence of financial incentives related to pay-for-performance. Our study is limited by its cross-sectional design, as we do not have information on the development of risk profile over time, in particular not the risk profile at the time of referral and during treatment in specialist care. In addition, factors such as co-morbidity, the individual's preferences, frailty and social conditions may influence the decision to refer and care for people with T2D in specialist care, not shown in this study. Excluding 56 individuals with T2D treated in specialist care only due to lack of information on GP and practice characteristics from the regression analyses may have introduced some selection bias. Salten is fairly representative of Norway, except for a lower proportion of immigrants born outside Norway than the Norwegian average in 2014 (7.1% vs. 12.4%). The study findings might be generalizable to other parts of Norway and possibly to countries with a similar system. Generalization of these results to other countries with a different organization of healthcare should be made with caution.

In conclusion, the present study shows that on the whole, people with T2D were appropriately allocated to primary and specialist care according to age, hyperglycaemia and vascular complications. However, surprisingly many individuals with T1D were treated exclusively in primary care. The use of a structured diabetes form and diabetes nurses may support T2D follow-up in primary care leading to better organization of diabetes healthcare for the benefit of the individual. Further longitudinal studies on better risk stratification as a guide for allocation of individuals between primary and specialist care should be performed.

ACKNOWLEDGEMENTS

The authors thank Elin Røst, research nurse in Salten, Ståle Nymo at Nordland Hospital and Karianne Fjeld Løvaas at the Norwegian Organization for Quality Improvement of Laboratory Examinations, Haraldsplass Deaconess Hospital, Bergen, for participating in the study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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TABLE 4 Odds ratio (OR) for treatment in specialist care for different patient characteristics, risk factors and general practitioner and practice variables of people with type 2 diabetes

	Type 2 diabetes			
	Unadjusted results		Adjusted results	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Patients characteristics				
Age (years)	0.97 (0.96, 0.97)	<0.001	—	—
Men	1.40 (1.11, 1.76)	0.004	—	—
Diabetes duration (years)	1.11 (1.09, 1.13)	<0.001	—	—
Education	—	0.097	—	—
Primary school	0.87 (0.67, 1.12)	0.271	—	—
High school/craftmanship	1	—	—	—
University	1.23 (0.91, 1.65)	0.170	—	—
Cardiovascular risk factors				
HbA_{1c}, %	1.81 (1.66, 1.97)	<0.001	1.54 (1.39, 1.71)	<0.001
Systolic blood pressure, mmHg	0.99 (0.98, 1.00)	0.021	0.99 (0.99, 1.00)	0.207
Diastolic blood pressure, mmHg	0.98 (0.97, 0.99)	0.002	0.96 (0.95, 0.98)	<0.001
LDL cholesterol, mmol/L	0.85 (0.75, 0.97)	0.012	0.95 (0.81, 1.10)	0.473
Prescribed medication				
Antihypertensive agents	1.22 (0.94, 1.58)	0.128	1.50 (1.11, 2.02)	0.008
Insulin	12.52 (9.77, 16.05)	<0.001	9.87 (7.30, 13.36)	<0.001
Lipid lowering medication	2.45 (1.90, 3.16)	<0.001	2.96 (2.17, 4.03)	<0.001
Acetylsalicylic acid	1.36 (1.09, 1.70)	0.007	1.92 (1.44, 2.55)	<0.001
Complications				
Coronary heart disease	1.35 (1.05, 1.72)	0.018	1.99 (1.47, 2.68)	<0.001
Stroke	0.62 (0.38, 1.01)	0.052	0.69 (0.40, 1.18)	0.172
PTA/arterial surgery	3.19 (1.89, 5.37)	<0.001	3.32 (1.81, 6.10)	<0.001
History of foot ulcer	7.47 (4.38, 12.72)	<0.001	5.55 (2.94, 10.48)	<0.001
Retinopathy	5.05 (3.77, 6.77)	<0.001	2.78 (1.97, 3.93)	<0.001
General practitioner and practice characteristics				
Age (years)	1.01 (1.00, 1.02)	0.010	1.01 (1.00, 1.02)	0.043
Men	1.12 (0.89, 1.41)	0.345	1.15 (0.89, 1.49)	0.298
Medical education in Norway	0.83 (0.64, 1.07)	0.150	0.88 (0.65, 1.17)	0.378
Specialist in general practice	1.05 (0.84, 1.32)	0.665	0.86 (0.67, 1.12)	0.262
Workload (no patients on list)	1.00 (1.00, 1.00)	0.325	1.00 (1.00, 1.00)	0.129
No. of people with T2D per GP	0.99 (0.98, 1.00)	0.001	0.99 (0.98, 1.00)	0.007
Diabetes nurse employed	0.68(0.54, 0.85)	0.001	0.64 (0.50, 0.82)	<0.001
User of a structured diabetes form	0.62 (0.49, 0.79)	<0.001	0.53 (0.40, 0.69)	<0.001
Urban location	1.42 (1.12, 1.79)	0.004	1.53 (1.18, 1.98)	0.001

Abbreviations: CI, confidence interval; GP, general practitioner; IQR, interquartile range; PTA, percutaneous transluminal angioplasty; T2D, type 2 diabetes.
Adjusted results: adjusted for age, sex, diabetes duration and education.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Slåtsve KB, Claudi T, Lappegård KT, et al. Factors associated with treatment in primary versus specialist care: A population-based study of people with type 2 and type 1 diabetes. *Diabet Med*. 2021;38:e14580. https://doi.org/10.1111/dme.14580

Supplementary

Table 1 Variable extraction in primary care and hospital outpatient clinic.

Variables	**Primary care:** All adults (≥18 years) with a diagnosis of diabetes Jan. 1st, 2012 to Dec. 31st, 2014	**Hospital outpatient clinic**: All adults (≥18 years) visiting Jan. 1st, 2012 to Dec. 31st, 2014
Characteristics		
Diabetes duration	2014 minus year of diagnosis	2014 minus year of diagnosis
Height	If ever registered	If ever registered
Weight	15 months	36 months
BMI	15 months	36 months
Complications		
Microvascular complications		
Retinopathy	If ever registered	If ever registered
Macrovascular complications		
Coronary heart disease	If ever registered	If ever registered
Stroke	If ever registered	If ever registered
Diabetic foot ulcer	If ever registered	If ever registered
Processes of care		
HbA1c	36 months	36 months
Blood pressure	15 months	36 months
Lipids	36 months	36 months
Creatinine/eGFR	36 months	36 months
Medication	Prescriptions 15 months and if registered manually	If registered manually

Retinopathy: Non-proliferative and proliferative retinopathy.
Coronary heart disease: Acute myocardial infarction, angina, percutaneous coronary intervention/coronary artery bypass surgery.
Stroke: Excluding transient ischemic attacks.
15 months: Oct. 1st, 2013 to Dec. 31st, 2014.
24 months: Jan. 1st, 2013 to Dec. 31st, 2014.
36 months: Jan 1st, 2012 to Dec. 31st, 2014.

Paper 3

Slåtsve, K.B., Claudi, T., Lappegård, K.T., Jenum, A.K., Larsen, M., Nøkleby, K., … Berg, T.J.

Level of education is associated with coronary heart disease and chronic kidney failure in individuals with type 2 diabetes: A population-based study

Submitted manuscript.

Level of education is associated with coronary heart disease and chronic kidney disease in individuals with type 2 diabetes: A population-based study

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Manuscript word count: 3020/4000

Abstract word count: 246/300

Key words:

Diabetes Mellitus, Type 2, Diabetes Complications, Glycated Hemoglobin A, Coronary Disease, Stroke, Diabetic Nephropathies, Retinal Diseases, Socioeconomic Factors.

Abstract (245/300 words)

Introduction: To study the relationship between education level and vascular complications in individuals with type 2 diabetes in Norway.

Research design and methods: Multiregional population-based cross-sectional study of individuals with type 2 diabetes in primary care. Data were extracted from electronic medical records in the period 2012-2014. Information on education level was obtained from Statistics Norway. Using multivariable multilevel regression analyses on imputed data we analysed the association between education level and vascular complications. We adjusted for age, sex, HbA1c, low-density lipoprotein cholesterol, systolic blood pressure, smoking and diabetes duration. Results are presented as odds ratios (OR) and 95% confidence intervals (CI).

Results: Of 8192 individuals with type 2 diabetes included, 34.0% had completed compulsory education, 49.0% upper secondary education and 16.9% higher education. The prevalence of vascular complications in the three education groups were: Coronary heart disease 25.9%, 23.0% and 16.9%, stroke 9.6%, 7.4% and 6.6%, chronic kidney disease (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2) 23.9%, 16.8% and 12.6% and retinopathy 13.9%, 11.5% and 11.7%, respectively. Higher education was associated with lower odds for coronary heart disease (OR 0.59; 95% CI 0.49-0.71) and chronic kidney disease (OR 0.75; 95% CI 0.60-0.93) compared to compulsory education when adjusting for age, sex, HbA1c, low-density lipoprotein cholesterol, systolic blood pressure, smoking and diabetes duration.

Conclusions: In a country with equal access to health care, high education level was associated with lower odds for coronary heart disease and chronic kidney disease in individuals with type 2 diabetes.

What is already known on this topic:

Socioeconomic status affects several aspects of type 2 diabetes care, but the association between individual-level socioeconomic status and diabetes vascular complications is less known.

What this study adds:

High education level was associated with lower odds for coronary heart disease and chronic kidney disease in individuals with type 2 diabetes.

How this study might affect research, practice or policy:

Education level should be considered when caring for individuals with type 2 diabetes and included as a factor when assessing diabetes vascular risk.

INTRODUCTION

Diabetes mellitus is one of the world's most common chronic diseases. Extensive research has shown that socioeconomic status (SES) affects several aspects of type 2 diabetes care. SES is associated with the prevalence of type 2 diabetes, time to diagnosis, access to diabetes care, quality of care, measurement of processes of care, glycaemic control and diabetes related mortality, all in disfavour of those with low SES.(1-7) In a systematic review and meta-analysis people with low SES had higher HbA1c levels than people with high SES.(8) Differences in smoking, body mass index (BMI), systolic BP and cholesterol across educational groups have been shown to be persistent over time, with a more unfavourable pattern in the lowest education group.(9)

Only a few studies have assessed the association between individual-level SES, as opposed to geographical indices of SES, and diabetes vascular complications.(10) Data are often insufficient to conclude that the gradient is independent of glycaemic control.(10) Information on individual level SES is often lacking in clinical databases as this often requires linking to national registries. SES includes education, occupation and income, variables which cannot be used interchangeably as predictors of a hypothetical social dimension.(11) When comparing the three, all used in studies showing social inequalities in health, education has been shown to be the strongest predictor for the prevalence of diabetes.(11)

In Norway all inhabitants are assigned to a specific general practitioner and in principle have equal access to health care and medication free of charge (apart from a personal contribution limited to approximately 233 EUR in 2014). In a recent study, we found that education level was not associated with level of care (primary or specialist) in individuals with type 2 diabetes.(12) The total prevalence of diagnosed diabetes was 3.8%, and the prevalence of type 2 diabetes was 3.4% (13).

There is a lack of studies on the associations between individual-level SES and diabetes vascular complications in a European setting, where everyone has equal access to health care. We therefore aimed to assess the relationship between SES as measured by education, and vascular complications in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study design and setting

We used data from the Norwegian ROSA 4 study, a cross-sectional study of quality of diabetes care in adults (≥18 years) with type 2 diabetes. Norwegian schools and universities do not charge students tuition fees. The ROSA 4 study was approved by the Regional Ethical Committee West (REK 2014/1374, REK Vest) with permission to collect data from general practice without written consent, and has been described in detail elsewhere.(14)

Population

The study population consisted of individuals with type 2 diabetes visiting or in contact with primary care in three out of four health regions in Norway between January 1st, 2012, and December 31st, 2014. Due to the possible interaction between country of birth and education level, the potential effect of education on health varying with ethnicity, and the fact that education completed before immigration to Norway is self-reported, we excluded individuals born outside Norway (n=2015). Furthermore, after excluding those registered as dead (n=4) and individuals with missing education status (n=27), the final study sample included 8192 individuals.

Data sources

We included individuals ≥18 years registered with type 2 diabetes in electronic medical records (T89 and T90 in The International Classification of Primary Care). As described in detail earlier, predefined data were extracted according to a protocol and medical records were screened by four experienced research nurses in order to reduce the number of missing data (14) (Supplementary file 1). Vascular complications were determined based on general practitioners' diagnosis or discharge summaries/outpatient letters from specialist care. Information about highest attained education level and country of birth was obtained from Statistics Norway, the Norwegian statistics bureau, and linked to the electronic health records.

Variables

A detailed description of variables in the ROSA study has been published previously.(14) In the current study, the following variables were used: sex, age, diabetes duration, body mass index (BMI), place of residence/county, medication, HbA1c, blood pressure (BP), total cholesterol, low-density lipoprotein (LDL) cholesterol, creatinine and vascular complications

(coronary heart disease (CHD) (including angina pectoris, myocardial infarction, percutaneous coronary intervention or coronary artery bypass surgery), stroke, chronic kidney disease (CKD), retinopathy, foot complications (percutaneous transluminal angioplasty (PTA)/arterial surgery, foot ulcer and lower limb amputation)). Due to small numbers, the groups with PTA/arterial surgery, foot ulcer and lower limb amputation were combined in the regression analyses. S-creatinine was measured in µmol/l and estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. CKD was defined as eGFR <60 ml/min/1.73m^2.

We used the most recent value of HbA1c, LDL-cholesterol and eGFR recorded during the last 3 years and weight and BP recorded during the last 15 months (Supplementary Table 1). Medications were extracted from the general practitioners' electronic prescription records from January 1st, 2012, to December 31st, 2014.

We chose education as an indicator for SES because it was available for all participants regardless of employment status, and it has been shown to be a good proxy for SES.(15) Education was categorized as: 1) completed compulsory education or less (≤10 years), 2) upper secondary education (11-13 years) and 3) higher education (university or similar, >13 years).

Statistical analyses

Descriptive statistics are presented as frequencies and percentages for categorical variables, mean ± standard deviation (SD) or medians with interquartile range (IQR) for continuous variables. Due to a high proportion of missing data on BMI, BP, LDL-cholesterol values, smoking status and retinopathy, and in order to reduce potential bias in complete case analyses, we performed multilevel multiple imputation of the missing variables using the package mice.impute.ml.lmer in R, making 25 datasets. Multiple imputation models were used under the assumption that data were missing at random. Vascular complications were registered as "yes", "no" or "unknown". In the imputed regression analyses, "unknown" status for vascular complications was defined as not registered with complication. Summary statistics for imputed data are presented as means and proportions with 95% confidence interval (CI).

Analyses of associations between education and outcomes were performed using mixed-effect logistic regression model for binary outcomes on imputed data and complete cases. In Model 1 we adjusted for age and sex, as these are considered potential confounders. In Model 2 we additionally adjusted for the potential mediators HbA1c, LDL-cholesterol, systolic BP,

smoking, and diabetes duration to estimate the direct effect of education level. County was included as a random effect in all models. In complete case analyses, we included the same number of individuals in unadjusted analyses and model 1 and 2 for each outcome.
We report unadjusted and adjusted odds ratios (OR) with 95% CI. The significance level was set at 0.05 for all analyses. Imputation was done in R. Other statistical analyses were performed using STATA/SE 16.1 (StataCorp, LP, College Station, Texas, USA).

RESULTS

Population characteristics and vascular complications

The study included 8192 individuals born in Norway with type 2 diabetes, 34.0% had completed compulsory education, 49.0% upper secondary education and 16.9% higher education (Table 1).

Table 1. General characteristics in individuals with type 2 diabetes according to education level.

	Compulsory education, n=2789		Upper secondary education, n=4016		Higher education, n=1387	
Patient characteristics	Valid numbers, n (%)		Valid numbers, n (%)		Valid numbers, n (%)	
Age (years), mean (SD)	2789 (100)	69.1 (13.8)	4016 (100)	67.4 (12.1)	1387 (100)	65.4 (11.8)
Men, n (%)	2789 (100)	1289 (46.2)	4016 (100)	2350 (58.5)	1387 (100)	874 (63.0)
Diabetes duration (years), median (IQR)	2620 (93.9)	8 (3-13)	3796 (94.5)	7 (3-12)	1326 (95.6)	7 (3-12)
Age at diagnosis (years), median (IQR)	2620 (93.9)	61 (50-69)	3796 (94.5)	59 (51-67)	1326 (95.6)	58 (50-65)
BMI (kg/m^2), mean (SD)	1255 (50.0)	30.5 (6.3)	1918 (47.8)	30.2 (5.8)	674 (48.6)	29.7 (5.7)
Smoking, n (%)	2260 (81.0)	642 (28.4)	3258 (81.1)	707 (21.7)	1102 (79.5)	157 (14.3)
Cardiovascular risk factors						
HbA1c, %, mean (SD)	2707 (97.1)	7.0 (1.2)	3885 (96.7)	6.9 (1.1)	1336 (96.3)	6.9 (1.1)
HbA1c, mmol/mol, mean (SD)	2708 (97.1)	53 (13)	3886 (96.7)	52 (12)	1336 (96.3)	52 (12)
Systolic blood pressure, mmHg, mean (SD)	2428 (87.1)	137 (17)	3537 (87.9)	136 (16)	1214 (87.4)	135 (15)
Diastolic blood pressure, mmHg, mean (SD)	2428 (87.1)	77 (10)	3537 (87.9)	78 (9)	1214 (87.4)	79 (9)
LDL-cholesterol, mmol/L, mean (SD)	2285 (81.9)	2.8 (1.0)	3380 (84.2)	2.7 (0.9)	1170 (84.4)	2.8 (0.9)
Prescribed medication						
Insulin, n (%)	2789 (100)	549 (19.7)	4016 (100)	673 (16.8)	1387 (100)	181 (13.0)
Per oral glucose lowering, n (%)	2789 (100)	1856 (66.6)	4016 (100)	2667 (66.4)	1387 (100)	874 (63.0)
Lipid lowering medication, n (%)	2789 (100)	1723 (61.8)	4016 (100)	2496 (62.2)	1387 (100)	796 (57.4)
Lipid lowering medication with CHD, n (%)	721 (100*)	595 (82.5)	920 (100*)	800 (87.0)	234 (100*)	202 (86.3)
Lipid lowering medication with no CHD, n (%)	2060 (73.9*)	1123 (54.5)	3086 (76.8*)	1689 (54.7)	1150 (82.9*)	593 (51.6)
Acetylsalicylic acid, n (%)	2789 (100)	1200 (43.0)	4016 (100)	1577 (39.3)	1387 (100)	500 (36.1)
Vascular complications						
Coronary heart disease, n (%)	2781 (99.7)	721 (25.9)	4006 (99.8)	920 (23.0)	1384 (99.8)	234 (16.9)
Stroke, n (%)	2786 (99.9)	266 (9.6)	4008 (99.8)	296 (7.4)	1385 (99.9)	91 (6.6)
Chronic kidney disease, eGFR <60 ml/min/1.73m^2, n (%)	2662 (95.4)	635 (23.9)	3813 (94.9)	640 (16.8)	1297 (93.5)	163 (12.6)
Retinopathy, all, n (%)	1669 (59.8)	132 (13.9)	2496 (62.2)	288 (11.5)	888 (64.0)	104 (11.7)
Foot complications	2789 (100)	166 (6.0)	4016 (100)	207 (5.2)	1387 (100)	49 (3.5)
PTA/arterial surgery, n (%)	2779 (99.6)	67 (2.4)	3996 (99.5)	96 (2.4)	1382 (99.6)	17 (1.2)
History of foot ulcer, n (%)	2785 (99.9)	101 (3.6)	4009 (99.8)	121 (3.0)	1387 (100)	37 (2.7)
Lower limb amputations, n (%)	2787 (100)	25 (0.9)	4011 (99.9)	38 (0.9)	1386 (100)	6 (0.4)

Abbreviations: BMI: body mass index. PTA: percutaneous transluminal angioplasty. eGFR: estimated glomerular filtration rate.
* % of subpopulation with/without CHD and prescribed/not prescribed lipid lowering medication.

Individuals with compulsory education had an (mean ± SD) age of 70.0 ± 13.8 years, compared to 67.4 ± 12.1 in the group with upper secondary education and 65.4 ± 11.8 years in those with higher education. The proportion of men was 46.2%, 58.5% and 63.0% in compulsory, upper secondary and higher education groups, respectively. There were no apparent differences in HbA1c, systolic BP and LDL-cholesterol values according to education levels, the latter despite more frequent statin prescription in individuals with CHD in upper secondary and higher education groups. All vascular complications were most prevalent in the compulsory education group. The prevalence of CHD was 25.9% in those with compulsory education, compared to 23.0% and 16.9% in those with upper secondary and higher education, respectively. The prevalence of stroke was; 9.6%, 7.4% and 6.6%, respectively, CKD; 23.9%, 16.8% and 12.6% and retinopathy; 13.9%, 11.5% and 11.7%, respectively.

Numbers of vascular complications according to education level in complete case analysis are shown in Figure 1. In individuals in the compulsory education group, 13.5% were registered with two vascular complications, compared to 10.3% and 7.1% in upper secondary and higher education groups, respectively. Baseline characteristics after imputations remained largely unchanged (Supplementary Table 2).

Education and vascular complications

Upper secondary and higher education levels were associated with lower odds for CHD compared to compulsory education in unadjusted analyses on imputed data (Table 2).

Table 2. Odds ratio (OR) and 95% confidence interval (CI) for having vascular complications in type 2 diabetes patients, by education level.

	Unadjusted		Model 1		Model 2	
Coronary heart disease	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education level		<0.001		<0.001		<0.001
Compulsory education	1		1		1	
Upper secondary education	0.86 (0.77, 0.96)	0.007	0.84 (0.74, 0.95)	0.004	0.83 (0.73, 0.93)	0.003
Higher education	0.59 (0.50, 0.69)	<0.001	0.58 (0.49, 0.70)	<0.001	0.59 (0.49, 0.71)	<0.001
Stroke						
Education level		0.001		0.037		0.066
Compulsory education	1		1		1	
Upper secondary education	0.75 (0.63, 0.90)	0.001	0.81 (0.68, 0.97)	0.021	0.81 (0.68, 0.97)	0.025
Higher education	0.67 (0.52, 0.86)	0.001	0.78 (0.60, 1.01)	0.061	0.82 (0.63, 1.07)	0.141
Chronic kidney disease (eGFR <60 ml/min/1.73m^2)						
Education level		<0.001		0.006		0.008
Compulsory education	1		1		1	
Upper secondary education	0.64 (0.57, 0.73)	<0.001	0.83 (0.72, 0.96)	0.010	0.83 (0.72, 0.96)	0.010
Higher education	0.46 (0.39, 0.56)	<0.001	0.74 (0.60, 0.92)	0.006	0.75 (0.60, 0.93)	0.009
Retinopathy						
Education level		0.097		0.025		0.166
Compulsory education	1		1		1	
Upper secondary education	0.84 (0.70, 0.99)	0.048	0.80 (0.67, 0.95)	0.012	0.84 (0.69, 1.01)	0.061
Higher education	0.85 (0.67, 1.07)	0.154	0.80 (0.63, 1.01)	0.058	0.91 (0.70, 1.17)	0.442
Foot complications						
Education level		0.003		0.005		0.068
Compulsory education	1		1		1	
Upper secondary education	0.85 (0.69, 1.05)	0.128	0.84 (0.68, 1.04)	0.113	0.89 (0.72, 1.11)	0.306
Higher education	0.57 (0.41, 0.79)	0.001	0.58 (0.42, 0.81)	0.001	0.67 (0.48, 0.94)	0.021

Model 1 is adjusted for age and sex, and model 2 is adjusted for age, sex, HbA1c, LDL-cholesterol, systolic blood pressure, smoking and diabetes duration. County is included as a random effect in all models, and the analyses are done on imputed data.

After adjusting for age and sex (Model 1) individuals with upper secondary education had an OR for CHD of 0.84 (95% CI 0.74-0.95) compared to those with compulsory education. In those with higher education OR for CHD was 0.58 (95% CI 0.49-0.70. After adjusting for age, sex, HbA1c, LDL-cholesterol, systolic BP, smoking and diabetes duration (Model 2), individuals with upper secondary and higher education had lower odds for CHD compared to compulsory education with an OR of 0.83 (95% CI 0.73-0.93) and 0.59 (95% CI 0.49-0.71), respectively. The results remained largely unchanged when repeating the analyses with age as a categorical variable (18-55, 56-70 and >70 years) in model 2 (data not shown).
Those with highest education had lower odds of CKD in all models (Table 2).
When moving from Model 1 to Model 2, the results remained largely unchanged as individuals with upper secondary education had an OR of 0.83 (95% CI 0.72-0.96) in both models and individuals with higher education had an OR of 0.74 (95% CI 0.60-0.92) in model 1 and OR of 0.75 (95% CI 0.60-0.93) in model 2, compared to those with compulsory education.
Higher education levels were associated with reduced odds for stroke in Model 1, but not in Model 2 due to an overall p value of 0.066. Education level was not associated with retinopathy in unadjusted analyses and Model 2. Foot complications were associated with education level in Model 1 and individuals with higher education had 42% reduced odds (OR 0.58; 95% CI 0.42-0.81) for the outcome compared to individuals with compulsory education. In Model 2 the OR was 0.67 (95% CI 0.48-0.94) in the same group, but education was not significantly associated with the outcome due to an overall p-value of 0.068.
Supplementary Table 3 shows the associations between outcomes and education in complete case analyses. A significant association was observed for education level and CHD in complete case analysis ($p<0.001$) but not for the other outcomes.

DISCUSSION

In this population-based cross-sectional study of individuals with type 2 diabetes born in Norway, the results show that higher education levels are associated with lower odds for CHD and CKD. These associations persisted after adjusting for the potential mediating cardiovascular risk factors HbA1c, LDL-cholesterol, systolic BP, smoking and diabetes duration. We found associations between education level and stroke, retinopathy and foot complications after adjusting for age and sex, but not statistically significant after adjusting for the abovementioned potentially mediating factors. The significant association between education level and CHD was found in both imputed and complete case analyses.

Our results show an association between education level, used as a marker of individual-level SES, and CHD in individuals with type 2 diabetes in a European country with equal access to health care, including both men and women in all age groups. Previous studies have reported similar findings, but the number of studies is low, representing selected populations and study designs with limitations.(7, 16-18) In the Whitehall cohort study the prevalence of heart disease in British male civil servants age 40-64 years was higher in the lowest social group (measured as employment grading).(7) These results are in line with a previous small survey on individuals with diabetes, a large diabetes study with self-reported data, and similar to a multinational study of highly selected individuals ≥55 years old diagnosed with type 2 diabetes after the age of 30 years with one or more macro- or microvascular diabetes complications or additional cardiovascular risk factors.(16-18) In our study the odds for CHD remained unchanged when adjusting for potentially mediating risk factors. This is in line with the findings from a computer simulation study of the general US population aged 35 to 64 years, reporting that traditional risk factors for CHD explained 40% of excess events among those with low SES, with the remaining 60% attributable to other risk factors.(19) We found that statin prescription was more frequent in high education groups. Due to our cross-sectional design, levels of LDL-cholesterol at the start of statin prescription and whether statin prescription was initiated before or after a cardiovascular event is not known.

Consistent with four other studies, CKD was more common among individuals with low as compared to high individual SES.(3, 7, 16, 18) Similar to a Chinese study we found no significant association between education level and stroke when adjusting for all risk factors.(17) Different from our findings most studies report an SES level gradient associated with retinopathy.(3, 4, 16, 17, 20-24) However, three of these studies included less than 1200 individuals. Low education level (≤ 9 years) increased the risk of retinopathy at time of diagnosis by 44% in Swedish individuals with type 2 diabetes and latent autoimmune diabetes in the adult (LADA).(25)

There are limited studies on the association between individual SES and foot complications. Two studies from France and Finland report an association between low SES and increased risk of the outcome.(2, 26) In a recent UK study on individuals newly diagnosed with type 2 diabetes, social deprivation, measured by a deprivation score, was an independent risk factor

for the development of diabetes related foot disease, peripheral vascular disease and lower limb amputation.(27)

Differences in vascular complications according to education level might be affected by social factors such as low income, employment insecurity, poor living conditions and chronic stress contributing to type 2 diabetes and acting as parts of a cyclical process both resulting from and contributing to adverse outcomes.(28) Poor health literacy is more common among individuals with low educational attainment.(29) Moreover, level of education is considered to affect the individual's ability to turn information into practical measures and behaviour, affects access to recourses, employment-related problems and social exclusion if unemployed. Among individuals with type 2 diabetes in primary care, inadequate health literacy has been independently associated with worse glycaemic control and higher rates of retinopathy.(30) In a Danish study, individuals with high education levels were favoured or more proactive in receiving services and more willing to accept rehabilitation services and seek specialist care.(31) In the diabetes population included in our study 34.0% had completed compulsory education, 49.0% upper secondary education and 16.9% higher education, compared to 26.9%, 40.9% and 32.2% in the general Norwegian population at the time of the study.

Comparing our results with other studies is complicated by differences in healthcare systems and insurance policies affecting health care delivery, possibly mediating the effect of education level on vascular complications. Furthermore, SES can be measured by income, level of education or occupational status. Each indicator measures different aspects of the socioeconomic gradient and may be more or less relevant to different health outcomes studied.(15) Income may change in a short time and a high proportion of our study population were, according to the mean age, retired, possibly affecting income. We therefore considered education status as the most appropriate measure for SES as it is relevant regardless of age and working status.

The main strengths in this study include the large sample size, individual register-based information on education level and the high-quality data collection done by experienced staff in a country with equal noninsurance-dependent access to health care and theoretically full availability of health care and higher education. Furthermore, the study included both men and women ≥18 years living in three out of four health regions in Norway, covering both urban and rural areas, ensuring that our findings are representative for individuals with type 2

diabetes born in Norway. Missing data were imputed, including missing measurement of HbA1c, BP, LDL-cholesterol, BMI, smoking status and diabetes duration, which may reduce the possibly biased estimates from complete case analyses. The imputation was done under the assumption that data were missing at random. However, we cannot exclude the possibility of sampling, ascertainment and detection bias. Although the trend of lower OR for higher education groups is present for all complications, there are few observations for some complications. Due to this there might be uncertainty related to the estimates, as seen for retinopathy.

A limitation is that the cross-sectional design prevents us from drawing conclusions regarding causality. Further, we did not have information on lifestyle factors like nutrition, diet including alcohol consumption and physical activity. Furthermore, heredity for disease, adherence to therapy and factors important in health care delivery affecting the risk of developing vascular complications is unknown. We lack information on cumulative lifetime exposure for potential risk factors and the development of risk profile over time. We had no information on albuminuria as a marker for CKD. Time period bias caused by timeframes up to 36 months for included variables, cannot be excluded, though 88.2% of HbA1c values, 73.9% of LDL-cholesterol values, and 83.1% of s-creatinine values were recorded within the last year.

The proportion of the population with higher education has changed in recent decades and longer education is now more common. Cohort effects may be present, as older cohorts will be over-represented among those with low education. Moreover, the meaning of education levels differs across cohorts, both qualitatively and quantitatively, and access to and structure of educational systems have changed over time. When tested, there was no significant interaction between education level and age in our study (data not shown). The OR for CHD remained largely unchanged when repeating the analyses using age as a categorical variable, but this does not exclude the cohort effect.

CONCLUSIONS

In conclusion, our study indicates that even in a universal-access healthcare system such as the Norwegian one, education level is independently related to CHD and CKD. Low education level is an important risk factor for poor outcomes. Including education level as a factor when assessing diabetes vascular risk is important and should be considered when caring for individuals with type 2 diabetes. A greater understanding of the relationship

between SES and type 2 diabetes complications should be obtained, as the underlying driving mechanisms for the difference remain largely unknown.

Acknowledgements:
We thank the research nurses who collected the data and Ibrahimu Mdala, MS, for his statistical support.

Competing interests:
E.S. Buhl has received honoraria for medical consulting and lectures to Novo Nordisk, Sanofi Aventis and MundiPharma.

Funding:
Northern Norway Regional Health Authority supports the PhD doctoral program of KBS. The data collection of the ROSA 4 study was supported financially with grants from the Norwegian Diabetes Association, a consortium of six pharmaceutical firms (AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis), Northern Norway Regional Health Authority, the Endocrinology Research Foundation, Stavanger and the University of Oslo.

Availability of data and materials:
The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author if approved by the ethics committee.

Contributorship statement:
TJB, TC, AKJ, SS, and JC were responsible for the study design and collection of study data together with KFL. KBS and ML performed the statistical analyses. KBS wrote the first draft of the manuscript. KBS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors revised the manuscript for important intellectual content, provided constructive comments and insights, and assisted in manuscript revision. All authors read and approved the final manuscript.
All authors fulfil the criteria of authorship and agree to be accountable for all aspects of the work.

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Figure 1:
Title: Number of vascular complications in adults with type 2 diabetes in Norway according to education level.

Legend: Complications as defined in Table 1.
>3 complications: Compulsory education: 0.8%. Upper secondary education: 0.4%. Higher education: 0.2%.

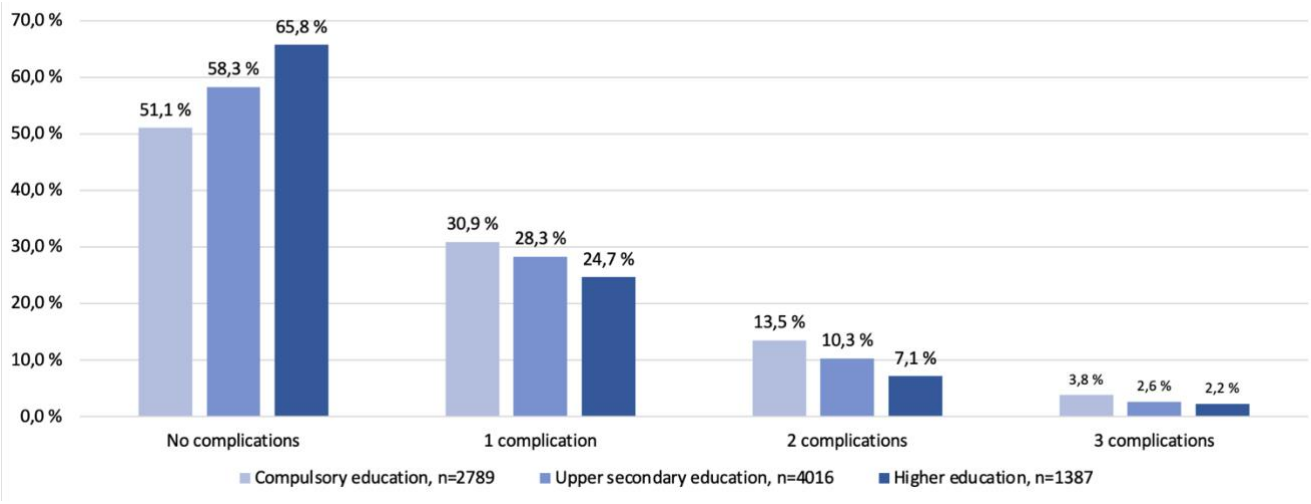
Supplementary files/tables:
File name: Supplementary File 1
File format: .docx
Title: Data sources and data collection:

File name: Supplementary Table 1
File format: .docx
Title of table: Variable extraction in general practice.
Legend: Retinopathy: Non-proliferative and proliferative retinopathy.

File name: Supplementary Table 2
File format: .docx
Title of table: General characteristics in individuals with type 2 diabetes according to education level, imputed data.
Legend: Abbreviations: BMI: body mass index. PTA: percutaneous transluminal angioplasty. eGFR: estimated glomerular filtration rate.

File name: Supplementary Table 3
File format: docx
Title of table: Odds ratio (OR) and 95% confidence interval (CI) for having vascular complications in individuals with type 2 diabetes, by education level, complete cases.
Legend: Model 1 is adjusted for age and sex, and model 2 is adjusted for age, sex, HbA1c, LDL-cholesterol, systolic blood pressure, smoking and diabetes duration. County is included as a random effect in all models, and the analyses are done on complete cases. Numbers presented for each complication are the total number of individuals included in the regression analyses.

Figure 1: Number of vascular complications in adults with type 2 diabetes in Norway according to education level.



Complications as defined in Table 1.

>3 complications: Compulsory education: 0.8%. Upper secondary education: 0.4%. Higher education: 0.2%.

Supplementary Table 1: Variable extraction in general practice.

Variables	**General practice:** All adults (≥18 years) with a diagnosis of diabetes Jan. 1st, 2012, to Dec. 31st, 2014
Characteristics	
Diabetes duration	2014 minus year of diagnosis
Height	If ever registered
Weight	15 months
BMI	15 months
Current smokers	No; if registered as non- smoker. Yes; if registered as current smoker the last 5 years and not changed smoking status
Vascular complications	
Coronary heart disease	If ever registered
Stroke	If ever registered
Retinopathy	If ever registered
PTA/foot ulcer/lower limb amputation	If ever registered
Processes of care	
HbA1c	36 months
Blood pressure	15 months
Lipids	36 months
Creatinine/eGFR	36 months
Medication	
Medication	Prescriptions 36 months

Retinopathy: Non-proliferative and proliferative retinopathy.

Supplementary Table 2. General characteristics in type 2 diabetes patients according to education level, imputed data.

Patient characteristics	Compulsory education, n=2789	Upper secondary education, n=4016	Higher education, n=1387
Age (years), mean (95% CI)	69.1 (68.6, 69.6)	67.4 (67.0, 67.7)	65.4 (64.8, 66.0)
Men, % (95% CI)	46.2 (44.4, 48.1)	58.5 (57.0, 60.0)	63.0 (60.5, 65.6)
Diabetes duration (years), mean (95% CI)	9.6 (9.3, 10.0)	9.0 (8.7, 9.2)	8.1 (7.8, 8.5)
Age at diagnosis (years), mean (95% CI)	59.5 (59.0, 60.0)	58.4 (58.0, 58.8)	57.2 (56.6, 57.8)
BMI (kg/m2), mean (95% CI)	30.1 (29.8, 30.3)	29.9 (29.6, 30.1)	29.4 (29.1, 29.8)
Smoking, % (95% CI)	28.2 (26.4, 30.0)	21.7 (20.2, 23.1)	14.6 (12.5, 16.7)
Cardiovascular risk factors			
HbA1c, %, mean (95% CI)	7.0 (7.0, 7.1)	6.9 (6.9, 7.0)	6.9 (6.8, 6.9)
HbA1c, mmol/mol, mean (95% CI)	53.1 (52.6, 53.6)	52.2 (51.8, 52.6)	51.7 (51.0, 52.3)
Systolic blood pressure, mmHg, mean (95% CI)	137 (136, 137)	136 (135, 137)	136 (135, 136)
Diastolic blood pressure, mmHg, mean (95% CI)	78 (77, 78)	78 (78, 79)	79 (79, 80)
LDL-cholesterol, mmol/L, mean (95% CI)	2.8 (2.8, 2.8)	2.7 (2.7, 2.8)	2.8 (2.7, 2.8)
Prescribed medication			
Insulin, % (95% CI)	19.7 (18.2, 21.2)	16.8 (15.5, 17.9)	13.0 (11.3, 14.8)
Per oral glucose lowering, % (95% CI)	66.5 (64.8, 68.3)	66.4 (64.9, 67.9)	63.0 (60.5, 65.6)
Lipid lowering medication, % (95% CI)	61.8 (60.0, 63.6)	62.2 (60.7, 63.7)	57.4 (54.8, 60.0)
Acetylsalicylic acid, % (95% CI)	43.0 (41.2, 44.9)	39.3 (37.8, 40.8)	36.0 (33.5, 38.6)
Complications			
Coronary heart disease, % (95% CI)	25.9 (24.2, 27.5)	23.0 (21.7, 24.3)	16.9 (14.9, 18.8)
Stroke, % (95% CI)	9.6 (8.5, 10.6)	7.4 (6.6, 8.2)	6.6 (5.3, 7.9)
Chronic kidney disease, eGFR <60 ml/min/1.73m^2, % (95% CI)	23.7 (22.1, 25.3)	16.6 (15.5, 17.8)	12.4 (10.6, 14.2)
Retinopathy, all, % (95% CI)	10.8 (9.6, 12.1)	9.2 (8.2, 10.2)	9.3 (7.7, 10.9)
PTA/arterial surgery, % (95% CI)	2.4 (1.8, 3.0)	2.4 (1.9, 2.9)	1.2 (0.6, 1.8)
History of foot ulcer, % (95% CI)	3.6 (2.9, 4.3)	3.0 (2.5, 3.6)	2.7 (1.8, 3.5)
Lower limb amputations, % (95% CI)	0.9 (0.5, 1.2)	0.9 (0.6, 1.2)	0.5 (0.1, 0.8)

Abbreviations: BMI: body mass index. PTA: percutaneous transluminal angioplasty. eGFR: estimated glomerular filtration rate

Supplementary Table 3. Odds ratio (OR) and 95% confidence interval (CI) for having vascular complications in type 2 diabetes patients, by education level, complete cases.

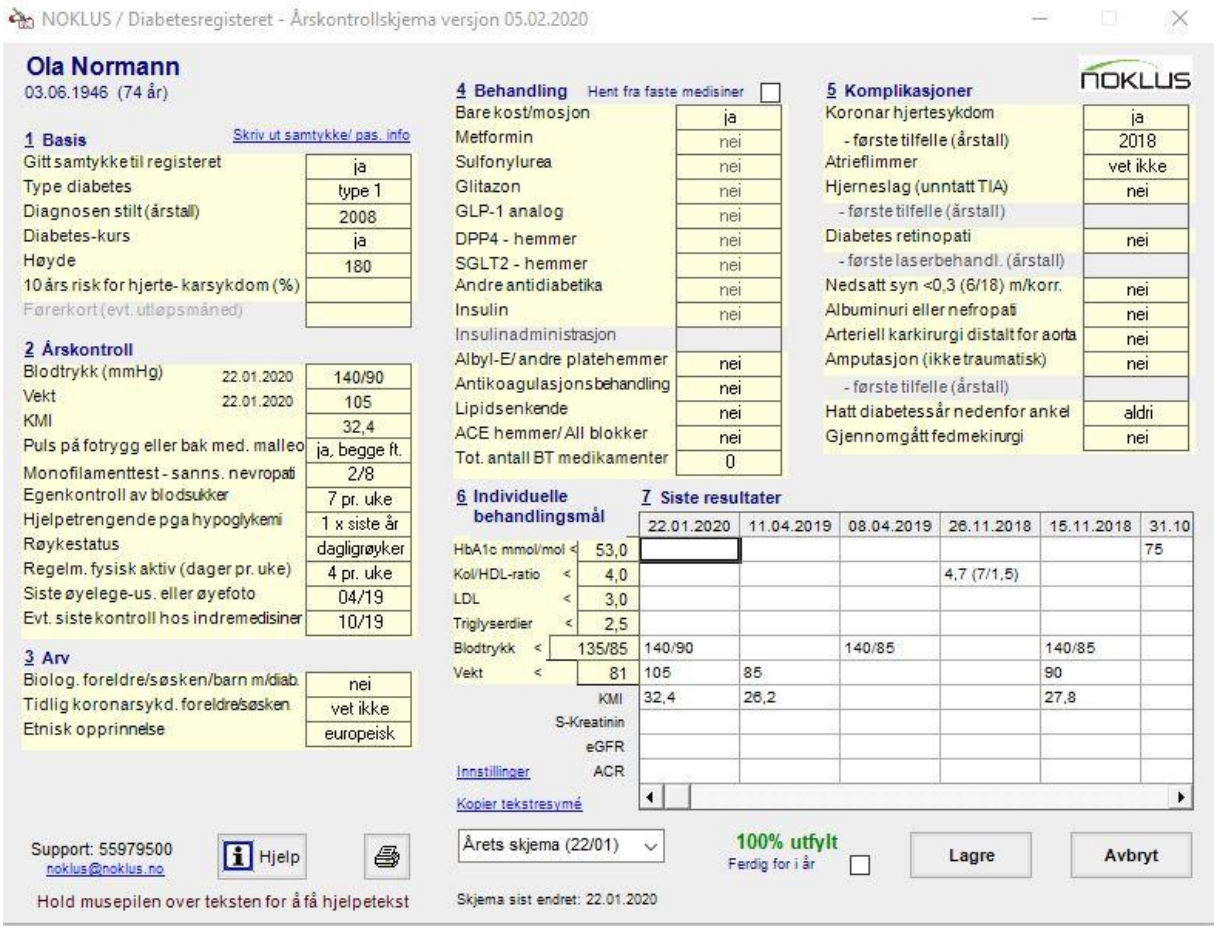
	Unadjusted		Model 1		Model 2	
Coronary heart disease, n=5073	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Education level		<0.001		<0.001		<0.001
Compulsory education	1		1		1	
Upper secondary education	0.84 (0.73, 0.97)	0.019	0.79 (0.68, 0.92)	0.003	0.79 (0.68, 0.92)	0.003
Higher education	0.56 (0.46, 0.69)	<0.001	0.54 (0.43, 0.67)	<0.001	0.54 (0.43, 0.68)	<0.001
Stroke, n=5080						
Education level		0.013		0.042		0.055
Compulsory education	1		1		1	
Upper secondary education	0.72 (0.57, 0.91)	0.006	0.74 (0.58, 0.94)	0.014	0.75 (0.59, 0.95)	0.017
Higher education	0.71 (0.51, 0.98)	0.039	0.78 (0.56, 1.09)	0.141	0.81 (0.58, 1.14)	0.225
Chronic kidney disease (eGFR <60 ml/min/1.73m^2), n=5057						
Education level		<0.001		0.093		0.128
Compulsory education	1		1		1	
Upper secondary education	0.67 (0.57, 0.79)	<0.001	0.83 (0.69, 1.00)	0.052	0.84 (0.69, 1.01)	0.065
Higher education	0.53 (0.42, 0.68)	<0.001	0.79 (0.60, 1.04)	0.093	0.81 (0.61, 1.07)	0.131
Retinopathy, n=3496						
Education level		0.243		0.067		0.304
Compulsory education	1		1		1	
Upper secondary education	0.83 (0.66, 1.05)	0.114	0.77 (0.61, 0.97)	0.028	0.82 (0.64, 1.05)	0.123
Higher education	0.83 (0.60, 1.13)	0.234	0.76 (0.56, 1.05)	0.098	0.89 (0.64, 1.25)	0.515
Foot complications, n=5089						
Education level		0.052		0.066		0.352
Compulsory education	1		1		1	
Upper secondary education	0.78 (0.59, 1.03)	0.083	0.77 (0.58, 1.03)	0.077	0.84 (0.63, 1.12)	0.238
Higher education	0.63 (0.41, 0.95)	0.026	0.64 (0.42, 0.98)	0.038	0.77 (0.50, 1.17)	0.219

Appendix

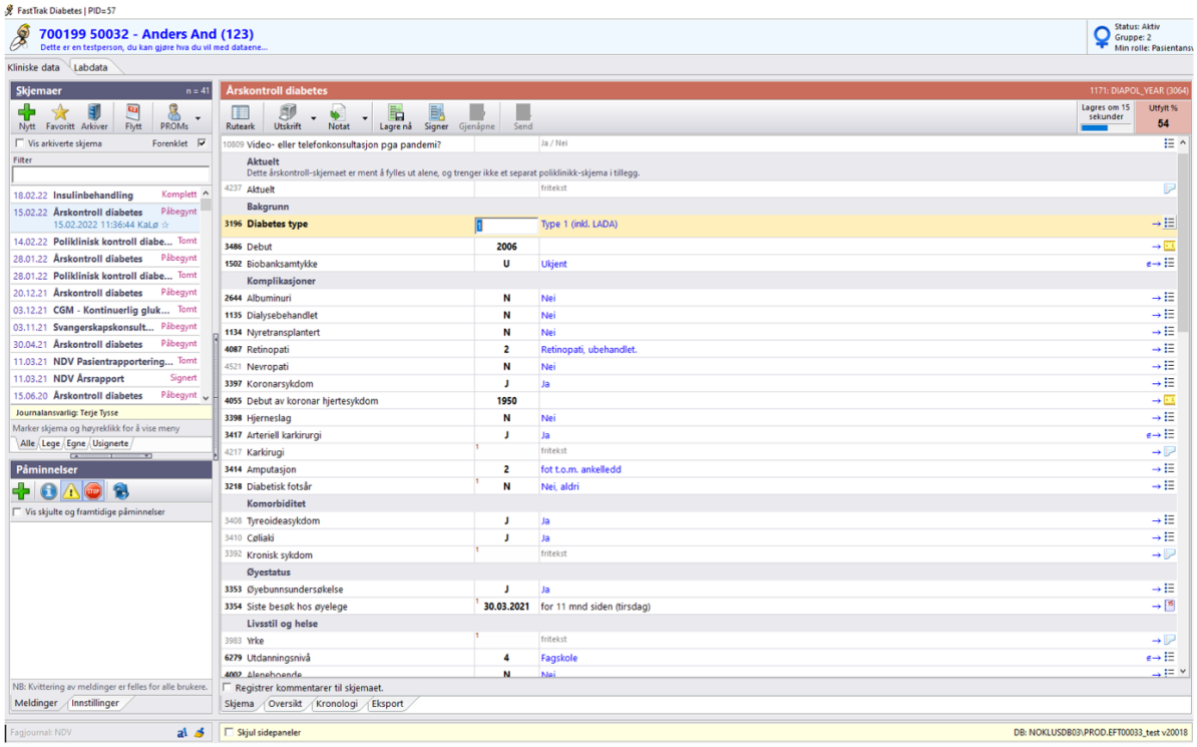
List of search words used by research nurses during data collection:

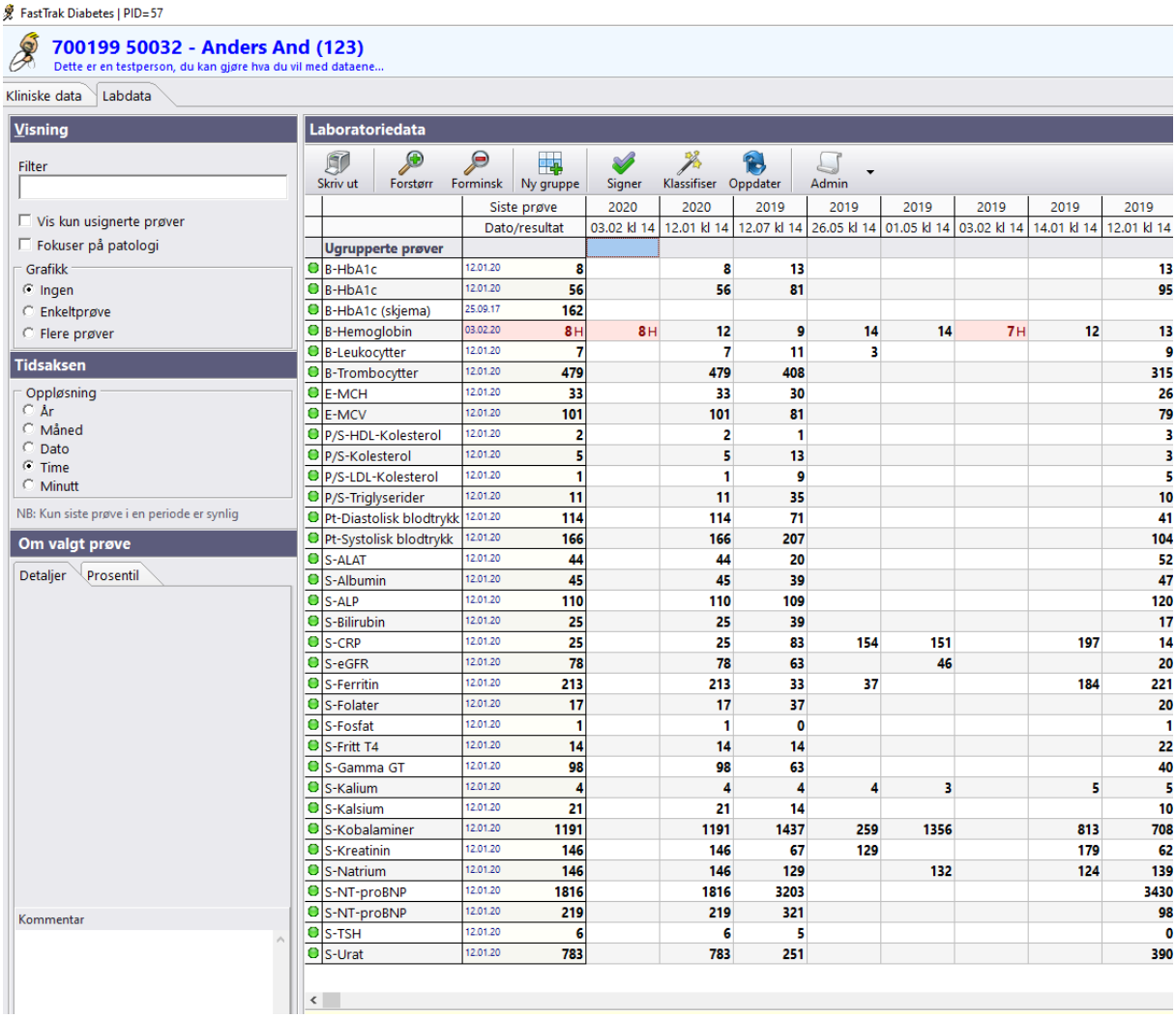
Søkeord basis og årskontroll	**Søkeord senkomplikasjoner**	**Sjekk epikriser**
Dia/diabetes/høyde/cm/meter /yde/gde/høgde/bt/blodtrykk/ Trykk/vekt/kg/puls/fot/sirk/ Mono/vibr/sens/nevrop/mikrofilament/røyk/øye/ Syn/auge/retino/visus	Hjert/koro/ angina/bypass/pci/ atrie/apop/hjerne/cereb Retino/øye/auge/syn/visus/nyre/nefro/transpl/ Dialy/claudicatio/pta/blokk/arterie/amput/ Sår/overvekt/fedme/bariatrisk/gastric	

The Noklus form developed for primary care:



The Noklus form developed for specialist care:





		Siste prøve	2020	2020	2019	2019	2019	2019	2019
		Dato/resultat	03.02 kl 14	12.01 kl 14	12.07 kl 14	26.05 kl 14	01.05 kl 14	03.02 kl 14	14.01 kl 14	12.01 kl 14
	Ugrupperte prøver									
	B-HbA1c	12.01.20 **8**		**8**	**13**					**13**
	B-HbA1c	12.01.20 **56**		**56**	**81**					**95**
	B-HbA1c (skjema)	25.09.17 **162**								
	B-Hemoglobin	03.02.20 **8** H	**8** H	**12**	**9**	**14**	**14**	**7** H	**12**	**13**
	B-Leukocytter	12.01.20 **7**		**7**	**11**	**3**				**9**
	B-Trombocytter	12.01.20 **479**		**479**	**408**					**315**
	E-MCH	12.01.20 **33**		**33**	**30**					**26**
	E-MCV	12.01.20 **101**		**101**	**81**					**79**
	P/S-HDL-Kolesterol	12.01.20 **2**		**2**	**1**					**3**
	P/S-Kolesterol	12.01.20 **5**		**5**	**13**					**3**
	P/S-LDL-Kolesterol	12.01.20 **1**		**1**	**9**					**5**
	P/S-Triglyserider	12.01.20 **11**		**11**	**35**					**10**
	Pt-Diastolisk blodtrykk	12.01.20 **114**		**114**	**71**					**41**
	Pt-Systolisk blodtrykk	12.01.20 **166**		**166**	**207**					**104**
	S-ALAT	12.01.20 **44**		**44**	**20**					**52**
	S-Albumin	12.01.20 **45**		**45**	**39**					**47**
	S-ALP	12.01.20 **110**		**110**	**109**					**120**
	S-Bilirubin	12.01.20 **25**		**25**	**39**					**17**
	S-CRP	12.01.20 **25**		**25**	**83**	**154**	**151**		**197**	**14**
	S-eGFR	12.01.20 **78**		**78**	**63**		**46**			**20**
	S-Ferritin	12.01.20 **213**		**213**	**33**	**37**			**184**	**221**
	S-Folater	12.01.20 **17**		**17**	**37**					**20**
	S-Fosfat	12.01.20 **1**		**1**	**0**					**1**
	S-Fritt T4	12.01.20 **14**		**14**	**14**					**22**
	S-Gamma GT	12.01.20 **98**		**98**	**63**					**40**
	S-Kalium	12.01.20 **4**		**4**	**4**	**4**	**3**		**5**	**5**
	S-Kalsium	12.01.20 **21**		**21**	**14**					**10**
	S-Kobalaminer	12.01.20 **1191**		**1191**	**1437**	**259**	**1356**		**813**	**708**
	S-Kreatinin	12.01.20 **146**		**146**	**67**	**129**			**179**	**62**
	S-Natrium	12.01.20 **146**		**146**	**129**		**132**		**124**	**139**
	S-NT-proBNP	12.01.20 **1816**		**1816**	**3203**					**3430**
	S-NT-proBNP	12.01.20 **219**		**219**	**321**					**98**
	S-TSH	12.01.20 **6**		**6**	**5**					**0**
	S-Urat	12.01.20 **783**		**783**	**251**					**390**

700199 50032 - Anders And

Statusrapport 28.02.2022

Bakgrunn

Diabetes type	Type 1 diabetes.	28.02.2022
Diabetes diagnose siden	2006	28.02.2022
Hjertesykdom i familien	Ja	14.02.2022

Livsstil

Røykevaner	Dagligrøyker.	28.02.2022
Mosjon	3 dager/uke	13.05.2020

Øyne og føtter

Hos øyelege	30.03.2021.	28.02.2022
Fotpuls	Ja, palpabel begge sider	28.02.2022

Komplikasjoner / Kroniske sykdommer

Øyne	Retinopati, ubehandlet.	28.02.2022
Albuminuri	Nei	15.02.2022
Perifer nevropati	Nei	28.02.2022
Koronarsykdom	Ja	28.02.2022

Astma

Behandling

Mot diabetes	Kun insulinbehandlet.	28.02.2022
Lipidsenkende	Nei	15.06.2020
Platehemmer	Ja	28.02.2022
Blodtrykksmidler	2 stk.	28.02.2022

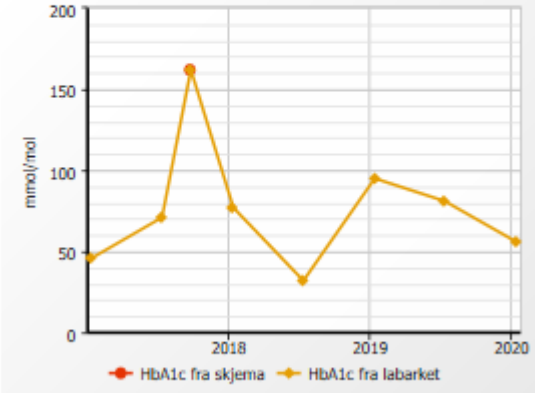
Medikamentell behandling

Legemidler i bruk	Indikasjon	Dose
Cozaar 50 mg	*angeotensin*	1 x 1
Fragmin 25000 IE/ml	*tromboseprofylakse*	0,2 ml x 1
Levaxin 0,15 mg	*hypothyreose*	5/uke
Stemetil 5 mg	*SVIMMELHET*	Maks 3/d

Plan videre

Vurdering/avtaler: Ny time om 3 mnd
Neste avtale lege: (ikke registrert)
Neste avtale spl: (ikke registrert)

Blodsukkerkontroll



Mål for HbA1c: **53 mmol/mol.** Status: Ikke nådd mål. 28.02.2022

AKR

The questionnaire used for the collection of data on GPs in the ROSA 4 study:

R O S A Kartlegging av diabetesomsorgen i Rogaland, Hordaland Salten og Oslo/Akershus

SPØRRESKJEMA TIL MEDARBEIDERE OG LEGER

Legekontor:……

Legekontoret har fellesliste Ja ☐ Nei ☐

- Fastlege 1:…… Spesialist i allmennmedisin ☐Ja ☐Nei
  Antall listepasienter:……
  Ant. dager/uke i kurativt arbeid ……..
  Kjønn……. Alder……
  Antall år som allmennlege i Norge:…….
  Fødeland:…….
  Utdannelsesland:…….
  Autorisasjonsår i Norge:……..
  Antall år bodd i Norge:…….

- Fastlege 2:…… Spesialist i allmennmedisin ☐Ja ☐Nei
  Antall listepasienter:……
  Ant. dager/uke i kurativt arbeid ……..
  Kjønn……. Alder……
  Antall år som allmennlege i Norge:…….
  Fødeland:…….
  Utdannelsesland:…….
  Autorisasjonsår i Norge:……..
  Antall år bodd i Norge:…….

- Fastlege 3:…… Spesialist i allmennmedisin ☐Ja ☐Nei
  Antall listepasienter:……
  Ant. dager/uke i kurativt arbeid ……..
  Kjønn……. Alder……
  Antall år som allmennlege i Norge:…….
  Fødeland:…….
  Utdannelsesland:…….
  Autorisasjonsår i Norge:……..
  Antall år bodd i Norge:…….

Totalt antall legevikarer som har vært innom legekontoret i 01.10.13-31.12.14:……..

ANDRE ANSATTE ved LEGEKONTORET:

Antall helsesekretærer/medisinske sekretærer:…… Stillingsprosent totalt……%

Antall sykepleiere ……..…… Stillingsprosent totalt……%

Antall bioingeniører ……. Stillingsprosent totalt……%

Antall «Annen medisinsk faggruppe»….. Stillingsprosent totalt……%

Diabetessykepleier (ja/ nei):…… Stillingsprosent totalt ……..%

Annen medarbeider med spesielt ansvar for diabetespasienter (ja/nei)…….

Fagruppe/stillingsprosent……..

SETT KRYSS VED RIKTIG SVARALTERNATIV (gjelder for hele legekontoret):

1	**REGISTER**	**JA**	**NEI**
	Bruker noen av medarbeiderne Noklus diabetesskjema?		
	Hvis JA, hva fylles ut av medarbeideren? Samtykke ☐ Basisdata ☐ Årskontrolldata ☐ Arv ☐ Komplikasjoner ☐		
2	**INNKALLING**		
	Har legekontoret en felles rutine for å kalle inn pasienter til diabetes årskontroll?		
	Er det noe rutine for å kalle inn de pasientene som ikke møter til diabetes årskontroll?		
3	**KURS MEDARBEIDERE**		
	Hvor mange medarbeidere ved legesenteret har deltatt på **kurs i diabetes** de siste 3 årene? Antall:……		
	Dersom noen har vært på kurs, hvilke kurs: (sett ring rundt det/de aktuelle) Diabetes forum, Noklus, egen faggruppe, industri, arbeidsgiver, sykehus, annet:……		
4	**KOST/LIVSSTILSVEILEDNING**		
	Har medarbeidere selvstendige oppgaver knyttet til det å gi **kostveiledning/livsstilsveiledning** til personer med diabetes?		
5	**EGENMÅLING BLODSUKKER**		
	Har medarbeidere selvstendige oppgaver knyttet til det å gi opplæring av pasienter i egenmåling av **blodsukker**?		
6	**INSULIN**		
	Har medarbeidere selvstendige oppgaver knyttet til det å gi opplæring ved oppstart av **insulin og/eller GLP1 analoger** hos pasienter med type 2 diabetes?		

	I tilfelle JA, hvilke oppgaver har du/dere? ……		
7	FØTTER		
	Har medarbeidere spesielle oppgaver ved oppfølging av **føttene** til personer med diabetes?		
	I tilfelle JA, hvilke oppgaver har du/dere? ……		
8	ÅRSKONTROLL		
	Har medarbeiderne spesielle oppgaver i tilknytning til årskontrollen?		
	I tilfelle JA, hvilke oppgaver har du/dere? ……		
9	ANNET		
	Har medarbeidere ekstra oppfølging av pasienter med diabetes som ikke er nevnt i dette spørreskjemaet? Kommenter……