Type 2 diabetes
in general practice in Norway
- status, time trends, and quality of care

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Contents

Scientific environment

The thesis was performed at the Department of Global Public Health and Primary Care, University of Bergen, and at the Department of Medicine, Stavanger University Hospital. Main supervisor was Professor Sverre Sandberg, University of Bergen (UiB) / Norwegian Organization for Quality Improvement of Laboratory Examinations (Noklus). Co-supervisors were Professor Geir Thue (UiB, Noklus), PhD Svein Skeie (Stavanger University Hospital (SUS), PhD Siri Carlsen (SUS, Noklus) and PhD Ingvild Dalen (SUS).

We collaborated with John Cooper (SUS, Noklus), Karianne Fjeld Løvaas (Noklus), Tone Vonheim Madsen (Noklus), Professor Anne Karen Jenum (University of Oslo (UiO)), PhD Tore Julsrud Berg (Oslo University Hospital), PhD Anh Thi Tran (UiO), PhD Bjørn Gjelsvik (UiO), Kjersti Nøkleby (UiO), and Tor Claudi (Nordland Hospital).

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Abbreviations

ACE	Angiotensin-converting enzyme
ADA	American Diabetes Association
ARB	Angiotensin II receptor blocker
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DPN	Diabetic peripheral neuropathy
DPP4i	Dipeptidyl peptidase-4 inhibitors
EB	Empirical Bayes
EHR	Electronic Health Record
eGFR	Estimated Glomerular Filtration Rate
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GP	General practitioner
HDL-c	HDL cholesterol
ICC	Intraclass correlation coefficient
ICPC	International Classification of Primary Care

IDF	International Diabetes Federation
LADA	Latent autoimmune diabetes in adults
LDL-c	LDL cholesterol
MICE	Multiple imputation by chained equations
MLE	Maximum likelihood estimation
MODY	Maturity Onset Diabetes of the Young
MOR	Median odds ratio
Noklus	Norwegian Organization for Quality Improvement of Laboratory Examinations
NDV	The Norwegian Diabetes Register for Adults
OR	Odds ratio
PTA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trials
ROSA 3	Rogaland-Oslo-Salten-Alta survey, 2005
ROSA 4	Rogaland-Oslo-Salten-Akershus-Hordaland survey, 2014
SBP	Systolic blood pressure
SGLT2i	Sodium-glucose co-transporter-2 inhibitors
SU	Sulfonylureas
T-chol	Total cholesterol
TIA	Transient ischemic attacks

TZD	Thiazolidinedione
UACR	Urine Albumin-to-Creatinine Ratio

Abstract

Background and objectives: People with type 2 diabetes have increased risk of vascular complications and premature death. Good glycaemic control and adequate management of cardiovascular risk factors can reduce the risk of complications and mortality. Diabetes care is dependent on lifestyle changes, possible medication and self-management, with main follow-up by general practitioners (GPs). The aims of the thesis were to assess status of type 2 diabetes care in general practice in Norway in 2014, analyse time trends 2005-2014, and identify factors associated with the quality of care.

Methods: Data from the Rogaland-Oslo-Salten-Akershus-Hordaland study (ROSA 4) consists of ~ 10 000 people with type 2 diabetes in general practice in Norway in 2014, and was compared with results from the Rogaland-Oslo-Salten-Alta study (ROSA 3) in 2005. ROSA 4 data was analysed in multilevel regression models with 1) care processes to detect microvascular complications and 2) the achievement of HbA1c, blood pressure and LDL-cholesterol targets as dependent variables, and characteristics related to patients (level 1), GPs (level 2) and practices (level 3) as independent variables. Associations with the outcomes were presented as odds ratios with 95% confidence intervals, and corresponding p-values. Variations in the outcomes were visualised with empirical Bayes estimates. Variance decomposition was presented as intraclass correlation coefficients and median odds ratios at GP- and practice levels.

Results: Between 2005 and 2014 we observed high performance (>85%) of blood tests and blood pressure, but still very low recordings of procedures to detect microvascular complications. About 30% was tested annually for albuminuria and diabetic neuropathy, ~ 60% achieved the HbA1c target, and ~ 50% achieved the blood pressure target, while ~ 50% achieved the LDL-cholesterol target in 2014. This was an increase from 2005. We observed substantial variation in the care processes,

where ~ 40% of the variation in the recording of two or more microvascular procedures was due to differences among GPs within practices. There was significant variation in the achievement of HbA1c, blood pressure and LDL-cholesterol targets, but the variation due to differences among GPs within practices was <6%. Several patient factors were associated with care processes and risk factor control; e.g. age, ethnicity, diabetes duration, and a history of macrovascular complications. GPs with long lists of patients and responsibility for less than 25 people with type 2 diabetes were associated with poor performance of microvascular screening procedures, while being a specialist in general practice was associated with more frequent recordings of the care processes. The strongest predictor of microvascular screening was GP usage of a structured diabetes form (OR 2.65). People attending GPs who were regular users of the form were also associated with higher achievement of HbA1c and LDL-cholesterol targets. Furthermore, practices with routines for annual diabetes review were associated with higher probability of performing care processes (OR 1.92).

Conclusions: Risk factor control improved the last decade, but not the care processes. There were still major gaps in the annual recording of microvascular screening procedures. Variation in care processes and achievement of targets existed among GPs within practices, although most of the variation was at the patient level. People < 50 years, and those with a history of macrovascular complications were less likely to have had screening procedures performed to detect microvascular complications, and to achieve treatment targets. GP usage of a structured diabetes form was associated with both improved care processes and risk factor control, and routines for annual diabetes review was associated with more recordings of microvascular screening procedures. We suggest that structure and good routines for annual review may improve the quality of diabetes care, and the use of a diabetes form is highly recommended.

List of Publications

Paper 1

Bakke Å, Cooper JG, Thue G, Skeie S, Carlsen S, Dalen I, Løvaas KF, Madsen TV, Oord ER, Berg TJ, Claudi T, Tran AT, Gjelsvik B, Jenum AK, Sandberg S. **Type 2 diabetes in general practice in Norway 2005-2014: moderate improvements in risk factor control but still major gaps in complication screening.** *BMJ Open Diab Res Care 2017; 5:e000459. Doi: 10.1136/bmjdrc-2017-000459*

Paper 2

Bakke Å, Tran AT, Dalen I, Cooper JG, Løvaas KF, Jenum AK, Berg TJ, Madsen TV, Nøkleby K, Gjelsvik B, Claudi T, Skeie S, Carlsen S, Sandberg S* and Thue G*. **Population, general practitioner and practice characteristics are associated with screening procedures for microvascular complications in Type 2 diabetes care in Norway.** *Joint senior authors.

Diabet Med. 2019 Nov; 36(11):1431-1433. Doi: 10.1111/dme.13842.

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Paper 3

Bakke Å, Dalen I, Thue G, Cooper JG, Skeie S, Berg TJ, Jenum AK, Claudi T, Løvaas KF, Sandberg S.

Variation in the achievement of HbA1c, blood pressure and LDL-cholesterol targets in type 2 diabetes in general practice and characteristics associated with risk factor control.

Diabet Med. 2019, Epub ahead of print, Oct 25. Doi:10.1111/dme.14159.

1. Introduction

1.1 Aetiology

Type 2 diabetes is a heterogeneous disease with considerable phenotypic variation (1). More than 400 genetic variants are associated with type 2 diabetes risk (2). However, they explain only little of the phenotypic variation (2). The aetiology is multifaceted. Individuals develop type 2 diabetes due to a combination of defects in beta cell function, beta cell mass, insulin action, glucagon secretion/action, incretin secretion/action and fat distribution (1).

The main defects in glucose metabolism are insulin resistance and impaired insulin secretion, parts of "the ominous octet" of hyperglycaemia, Figure 1 (3).

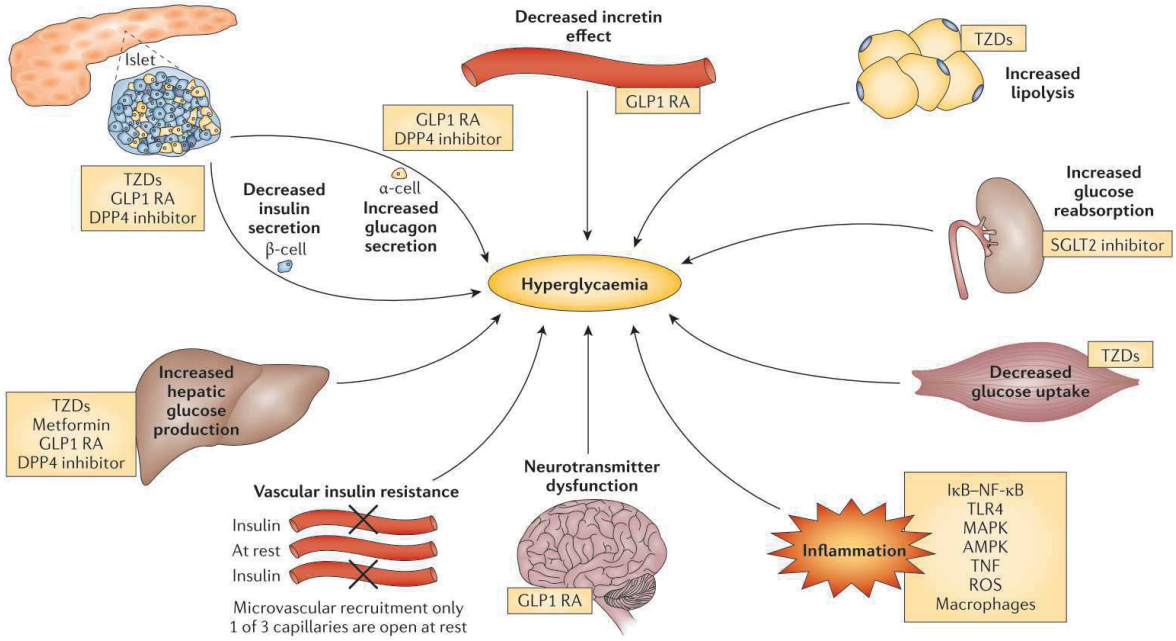


Figure 1. The «ominous octet» of hyperglycaemia in type 2 diabetes, with sites of actions for antihyperglycaemic agents. TZD, thiazolidinedione. GLP1 RA, glucagon-like peptide 1 receptor agonist. DDP4, dipeptidyl peptidase 4. SGLT2, sodium-glucose co-transporter-2. To the "ominous octet" is added vascular insulin resistance and inflammation, making the "decadent decoplet". Reprinted with permission from Springer Nature: Nature, DeFronzo et al. (3), Copyright 2015.

Lifestyle factors such as obesity, physical inactivity, smoke and unhealthy diet, contribute to the pathophysiological disturbances. Increasing adiposity is the most important risk factor for development of type 2 diabetes (3).

The aetiology may influence treatment response and susceptibility to complications (3). However, diabetes progression and treatment response is better predicted by simply using phenotypic measures as age, gender, body mass index (BMI) and HbA1c, rather than assigning patients to groups based on e.g. insulin resistance and insulin deficiency (4).

1.2 Epidemiology

The International Diabetes Federation (IDF) estimates that ~ 450 million people have diabetes worldwide (9% between 18-99 years), and the number will increase to ~ 700 million in 2045 (10%) (5). The age-standardized prevalence was lower in the Africa Region and in Europe, compared with the other regions. The prevalence was slightly higher in men. The likeliest explanation of the global increase in diabetes prevalence is changes towards sedentary lifestyle and urbanization, and better healthcare services improving the life expectancy for people living with diabetes (5).

In Norway, about 245 000 people have known diabetes (6). The prevalence of diabetes strongly increases with age, with the highest proportion at the age of 80 years (6). Type 2 diabetes accounts for ~ 90% of all diabetes cases (3). From 2009 to 2014, the incidence of type 2 diabetes decreased in the Norwegian population, while the prevalence increased from 4.9% to 6.1%, probably due to earlier diagnosis and longer longevity (7). The 75 gram oral glucose tolerance test, together with fasting blood glucose, have been used to diagnose diabetes since the late 1990s. However, in 2012, HbA1c $\geq$ 6.5% ($\geq$ 48 mmol/mol) was recommended as a diagnostic criteria.

1.3 Risks of type 2 diabetes

People with diabetes are at risk of acute and chronic complications. Acute complications consist of diabetes ketoacidosis, hyperosmolar hyperglycaemic non-ketotic coma, and hypoglycaemia, and will not be discussed further. Chronic complications consist of micro- and macrovascular complications. Microvascular complications include diabetic kidney disease, neuropathy, and retinopathy. Macrovascular complications consist of myocardial infarction, coronary heart disease, cerebrovascular disease, and peripheral artery disease. In addition, heart failure has recently been recognized as a cardiovascular complication of diabetes.

Six pathways that mediate vascular damage in the presence of hyperglycaemia have been recognized; the polyol pathway that increases oxidative stress, enhanced production of advanced glycated end products, activation of protein kinase-C, increased hexosamine pathway activity, and higher formation of reactive oxygen species (8). Organ damage may be accelerated by age, gender, diabetes duration, insulin resistance, hypertension, dyslipidemia, endothelial dysfunction, activation of plasminogen activator inhibitor, visceral obesity, non-alcoholic fatty liver disease, and genetic determinants of individual susceptibility (3, 8, 9).

1.3.1 Diabetic kidney disease

Diagnosis: Diabetic kidney disease is diagnosed by the presence of albuminuria, decreased estimated glomerular filtration rate (eGFR), or both (10).

Occurrence: The prevalence of diabetic kidney disease lies between 20% and 40% (11, 12). In newly diagnosed type 2 diabetes in the UK, moderately increased albuminuria was found in ~ 13-17% (13). The UKPDS showed that the development of albuminuria is correlated to glycaemic control, blood pressure control and diabetes duration (14-16).

Risk: Previously, albuminuria was thought to be the first marker of diabetic kidney disease. However, in type 1 diabetes, a decline in eGFR has been shown to precede

the onset of moderately elevated albuminuria (17, 18). Nevertheless, an increase in albuminuria is correlated with progression to end-stage renal disease (19), cardiovascular disease (CVD), and all-cause mortality (20). Albuminuria and eGFR are independently associated with CVD and death (11, 21-23). The risk of CVD and mortality has been shown to increase linearly with urine albumin-to-creatinine ratio (UACR), but exponentially with eGFR drop (24). Thus, a combination of UACR and eGFR and is more accurate in predicting CVD risk and mortality (11, 24).

1.3.2 Diabetic neuropathy

Diagnosis: Diabetic neuropathy is a diagnosis of exclusion (25). It can be divided into diabetic peripheral neuropathy (DPN) and autonomic neuropathy (including hypoglycaemia unawareness, cardiac autonomic neuropathy, gastrointestinal neuropathies, and genitourinary disturbances) (25). Autonomic neuropathy will not be discussed further. Peripheral neuropathy includes defects in small and large nerve fibers. Large-fiber function can be assessed by vibration perception using a 128-Hz tuning, and a 10-g monofilament test. Protective sensation can be measured by the 10-g monofilament test. The monofilament test is widely used in clinical practice due to simplicity and low cost (26). A systematic review concludes that the monofilament test is a useful clinical tool for detecting peripheral neuropathy and identifying people at high risk for ulceration and amputation (27). Other diagnostic tools for DPN are the self-administered Michigan Neuropathy Screening Instrument that has been used in large clinical trials (28-31), a biothesiometer, and the Neuropad screening test.

Occurrence: The prevalence of DPN is ~ 20% (32, 33). In newly diagnosed people, sensory neuropathy is present in ~ 10% (13). Fifty percent of DPN may be asymptomatic, thus recognition of neuropathy and implementation of foot care is important to delay and prevent adverse outcomes (25). The prevalence of DPN is related to glycaemic control, duration of diabetes, dyslipidemia, and smoking (34).

Risk: Impaired monofilament test is a strong predictor of foot ulcers and amputations, together with absent pedal pulses, and a history of prior ulcers (26). Other risk factors for ulcers and amputations are foot deformities, callus, peripheral arterial disease,

proteinuria, retinopathy, visual impairment, high BMI, high waist circumference, insulin use and cigarette smoking (25, 26, 35). Diabetic foot ulcers are strongly correlated to death (36, 37). In those with a history of ulcer and additional peripheral vascular disease, 5-year survival rate was 35% in UK (38). Integration of diabetes foot care including standardized screening in general practice, more podiatrists in the community and improvement of effective care pathways to secondary care has reduced foot ulcer incidence and major amputation incidence in South England (38, 39).

1.3.3 Diabetic retinopathy

Diagnosis: Diabetic retinopathy is diagnosed by examination of retina, and consists of mild, moderate, and severe nonproliferative and proliferative retinopathy. Additionally, people with diabetes have higher risk of diabetic macular oedema, cataract and glaucoma (40), but those will not be discussed further.

Occurrence: Diabetic retinopathy affects ~ 25% of people with type 2 diabetes (9). Between 10 to 20% have retinopathy at the time of diagnosis (13, 41). Those not screened promptly after the diabetes diagnosis had higher proportion of severe non-proliferative or proliferative retinopathy (42). The United Kingdom Prospective Diabetes Study (UKPDS) and more recent studies have shown that the prevalence of diabetic retinopathy is strongly correlated with glycaemic control and diabetes duration (43-45). The percentage of referable retinopathy increases with HbA1c-levels (41). Furthermore, diabetic nephropathy, and non-healing foot ulcers were independent risk factors of progression from non-proliferative to proliferative retinopathy in a retrospective cohort among all types of diabetes patients (USA) (46).

Risk: A systematic review and meta-analysis, showed that in 2015 about 3% of blindness among adults aged 50 years or older was due to diabetic retinopathy in Western Europe, with an increasing tendency from 1990 (47). In this report cataract was the leading cause of blindness worldwide. However, the findings do not undermine that diabetic retinopathy is still a major cause of blindness, and many of these cases could be avoided by appropriate treatment.

1.3.4 CVD and mortality

Diagnosis: Cardiovascular disease (CVD) have traditionally consisted of coronary heart disease, myocardial infarction, stroke and peripheral artery disease, and is the definition used in the thesis.

Occurrence: In a systematic review, CVD was shown to affect 32% of people with type 2 diabetes globally (48). Independent of conventional risk factors, diabetes confers a doubled excess risk for coronary heart disease, stroke and vascular deaths (49, 50). In a UK study, about 18% of people with type 2 diabetes had a first cardiovascular presentation during the median 5.5 years of follow-up (51). The most common initial presentation was peripheral artery disease (16%) and heart failure (14%) (51).

Risk: The excess relative risk for cardiovascular disease and death is higher in women, in young individuals <55 years, and in people diagnosed with type 2 diabetes aged forty years or less (50, 52, 53). Furthermore, the relative and absolute risk of vascular events are increased with long diabetes duration, and microvascular complications (21, 54).

1.4 Guidelines

1.4.1 Screening procedures to detect microvascular complications

National guidelines recommend an annual diabetes review that include identification of possible microvascular complications (55).

Detection of diabetic kidney disease: It is recommended to assess urinary albumin and eGFR at least once a year to identify people at risk of developing renal dysfunction (25, 54, 55).

Detection of diabetic peripheral neuropathy: An assessment of diabetic peripheral neuropathy should be performed by using a 10-g monofilament test annually (25, 55). Furthermore, palpation of distal foot pulses, and inspection of foot deformities and callus are recommended to identify people at moderate and high risk of developing

foot ulcers. General self-care education to prevent foot complications should be provided for patients with moderate to high-risk of developing foot ulcers, and they are recommended to wear specialized therapeutic footwear (25, 55).

Detection of diabetic retinopathy: At the time of diagnosis, all patients with type 2 diabetes should be referred to an ophthalmologist for an eye examination including fundus photography (55). Further eye controls depend on the initial findings, however in the absence of retinopathy, a fundus photo with evaluation every other year should be sufficient.

1.4.2 Risk factor control

1.4.2 a) Glycaemic control

An HbA1c target of < 7.0% (53 mmol/mol), with avoidance of hypoglycaemia, and individualisation according to diabetes duration, comorbidity and age, is recommended in current national guidelines (55). In newly diagnosed people, a lower target of about 6.5% (48 mmol/mol) can be considered, while a higher target of 7.0-8.0% (53-64 mmol/mmol) can be accepted for people with a long diabetes duration, severe comorbidities or high risk of hypoglycaemia.

HbA1c and the effects on vascular complications in general: The UKPDS study of ~ 3000 newly diagnosed people with type 2 diabetes showed that early glycaemic control led to a reduction in micro- and macrovascular complications after 10-years follow-up (16, 44, 56). The "legacy effect" of early glycaemic control has also been demonstrated in a recent study with ~ 35 000 people and newly diagnosed type 2 diabetes from the USA followed for 13 years (57). HbA1c levels ≥ 6.5% (≥ 48 mmol/mol) in the 1st year after diagnosis were associated with increased micro- and macrovascular events, while levels ≥ 7.0% (≥ 53 mmol/mol) were associated with increased mortality (57).

HbA1c and the effects on diabetic kidney disease: Intensive glycaemic control with HbA1c < 6.5% (< 48 mmol/mol) in type 2 diabetes has delayed onset and progression of albuminuria and end-stage-renal disease in large randomized trials (58-62).

Furthermore, treatment with new antihyperglycaemic agents such as SGLT2 inhibitors have renoprotective effects, GLP-1 RAs lower albuminuria, and both reduce the risk of cardiovascular disease and death (63).

HbA1c and the effects on diabetic peripheral neuropathy: Intensive glycaemic control delayed onset and progression of peripheral neuropathy in type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) Study (28). They found a significant association between mean HbA1c and neuropathy. However, in type 2 diabetes, the association has been less convincing. Intensive glucose control did not reduce nerve events in a meta-analysis of four trials (59). On the other hand, normalizing HbA1c in people with a short diabetes duration improved results for all neurophysiological tests (64). Furthermore, higher baseline HbA1c and steeper slopes of HbA1c trajectories were associated with DPN in people with screen-detected diabetes (35). Current guidelines recommend that glucose control should be optimized to slow the progression of neuropathy (25, 55).

HbA1c and the effects on diabetic retinopathy: Large RCTs have shown that optimized glycaemic control prevent and/or delay the onset and progression of diabetic retinopathy in type 1 and type 2 diabetes (16, 65-69).

HbA1c and the effects on cardiovascular outcomes and mortality: A meta-analysis of three randomized studies in type 2 diabetes proposed that an HbA1c reduction was associated with reduced non-fatal myocardial infarction, without beneficial effects on mortality (70). On the other hand, glycated haemoglobin level was a strong predictor of myocardial infarction, stroke, and death from any cause in Sweden (71). There appeared to be a linear relationship between major adverse cardiovascular events and HbA1c in a meta-analysis including only studies with newer type 2 diabetes agents with little hypoglycaemic risk (72).

1.4.2 b) Blood pressure control

The current national guidelines recommend to start antihypertensive treatment when office BP is > 140/90 mmHg, and with treatment targeting a BP < 135/85 mmHg. (In 2009 guidelines the intervention threshold was > 140/85 mmHg, with treatment target of ≤ 135/80 mmHg) (54, 55). Stricter targets (130/80 mmHg) may be applied in young people, in those with microvascular complications (especially in diabetic kidney disease), and in people with high risk of stroke (55). Higher targets can be accepted in older people, people with ortostatism, and other side effects.

Blood pressure and the effects on diabetic kidney disease: In a meta-analysis of large scale randomized studies in people with type 2 diabetes, a systolic BP < 130 mmHg reduced the risk of albuminuria (73). Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) are shown to have similar renoprotective effect (74).

Blood pressure and the effects on diabetic retinopathy: A systolic BP < 130 mmHg reduced the risk of retinopathy (73). Another recent meta-analysis of RCTs, and a Cochrane review of RCTs supported a beneficial effect of lowering blood pressure to prevent diabetic retinopathy for about 5 years. However, no significant effect on progression of retinopathy was observed (75, 76).

Blood pressure and the effects on cardiovascular disease and mortality: Different classes of antihypertensive medication were shown to have similar effects on cardiovascular outcomes in a large meta-analysis (73). They found that a systolic BP < 140 mmHg conferred to a reduction in mortality and cardiovascular events, while a systolic BP < 130 mmHg reduced the stroke risk. There are conflicting evidence whether a systolic BP < 120 mmHg is beneficial. In a recent analysis, a systolic BP < 120 mmHg reduced cardiovascular events in people receiving standard glycaemic control, HbA1c > 7.0% (> 53 mmol/mol), but not in those with intensive glycaemic control, HbA1c < 6.0% (< 42 mmol/mol) (77). These data may suggest that episodes of severe hypoglycaemia might have diminished the potential benefits of lowering systolic blood pressure (78).

1.4.2 c) Lipid control

Current national guidelines recommend that all people with diabetes between the age of 40 and 80 years, without cardiovascular disease, should should receive statins in the presence of LDL-c > 2.5 mmol/L. In people with known cardiovascular disease, everybody should receive statins targeting an LDL-c of < 1.8 mmol/L. The 2019 European Society of Cardiology guidelines support the national guidelines, however, in addition they recommend that in people at very high CV risk, the LDL-c should be < 1.4 mmol/mol, with ezetimibe as add-on to statins if the target is not reached initially (54).

Lipids and the effects on diabetic peripheral neuropathy: In the EURODIAB and a more recent study, dyslipidemia was associated with the incidence of neuropathy (34, 79).

Lipids and the effects on diabetic retinopathy: A meta-analysis of RCTs in type 1 and type 2 diabetes found that lipid-lowering agents protect against progession of diabetic retinopathy (80).

Lipids and the effecst on cardiovascular disease and mortality: Reports from meta-analyses of RCTs showed that levels of LDL-c are strongly related to cardiovascular disease and death in people with type 2 diabetes (81). There was a linear relation of LDL-c level and myocardial infarction, coronary death or revasularisation, and stroke (81), and even people at low 5-year cardiovascular risk benefit from statin therapy with fewer major vascular events (82). In people with diabetes and acute coronary syndrome addition of ezetimibe to a statin has been shown to be beneficial, with reductions in myocardial infarction and ischaemic stroke (83, 84).

1.4.2 d) Lifestyle modification

Guidelines advocate lifestyle intervention including smoking cessation, moderate-to-vigorous physical activity at a minimum of 150 minutes per week, and reduced

calorie intake. In people with overweight and obesity, a sustained weight loss of 5-10% is recommended.

Smoke: Smoking is independently associated with neuropathy (79), and with high risk of myocardial infarction, stroke and mortality in people with type 2 diabetes (85). Smoking cessation would substantially lower cardiovascular risk.

Physical activity: Exercise can improve glycaemic control, reduce cardiovascular risk factors, and contribute to weight loss (86). Higher levels of physical activity in people with diabetes are associated with lower total mortality risk, and lower CVD mortality risk (87).

Weight loss: The Look AHEAD trial found no significant reduction of CVD in the intensive weight loss intervention group (88). However, in a cohort analysis of people with screen-detected type 2 diabetes in the ADDITION-Cambridge trial, loss of ≥ 5% body weight during the first year after diagnosis was associated with improvements in HbA1c, lipids and lower incidence of CVD and mortality (89).

1.5 Multifactorial management

There is emerging evidence of multifactorial management to reduce cardiovascular risk in people with type 2 diabetes (71, 90-95). The ADDITION-Europe showed a small, non-significant reduction in vascular complications after 5-years follow-up (96-98). However, the 10-year modelled cardiovascular risk was significantly lower in the group with intensive multifactorial treatment, compared with routine care (99). In the Steno-2 trial, 160 people with type 2 diabetes and microalbuminuria were randomized to either multifactorial intervention, or conventional treatment. The intervention group received treatment with ACE inhibitors or ARBs, betablockers and aspirin, and aimed at HbA1c < 6.5% (< 48 mmol/mol), total cholesterol < 4.5 mmol/L, BP < 130/80 mmHg (93) together with lifestyle recommendations. After 7.8 years of follow-up, micro- and macrovascular complications were reduced

by ~ 50% in the intesifyed treatment-group (92). Furthermore, after 21 years of follow-up, people in the intervention group achieved renal benefits (100), lived in median 7.9 years longer than in the conventional-treated group (95), and had a 70% reduction in hospitalization for heart failure (94). The BARI 2D trial assessed cardiovascular events in ~ 2000 people with type 2 diabetes and coronary disease followed up for five years (101). The number of uncontrolled risk factors (HbA1c, BP, lipids) was strongly associated with death, myocardial infarction and stroke. Similarly, there was a substantial decrease in risk of cardiovascular disease and death with a combined reduction in HbA1c, BP and lipids in ~ 13 000 people with type 2 diabetes in the Swedish National Diabetes Register (102). In another study from Sweden, the cardiovascular risk and mortality decreased by each risk factor at target (HbA1c, systolic BP, LDL-c, albuminuria, and smoking) in ~ 300 000 people with type 2 diabetes with 5.7 years follow-up (71).

1.6 Type 2 diabetes care in Norway

1.6.1 General practice

Most people with type 2 diabetes are followed in general practice. In Norway, 99% of the general population are registered with a specific general practitioner who acts as a gate-keeper. In 2014, there were ~ 4500 GPs, with a mean list size of ~ 1100 patients (103). Five percent of GPs belonged to single GP practices. The mean GP age was 48 years, 40% were females and 53% were specialists in general practice (103, 104). Mean number of consultations per day were 19, higher than Sweden/Finland/Iceland (~13 consultations per day), but lower than Denmark (~24 consultations per day) (105). In addition to clinical days at the practice, Norwegian GPs provide a broad specter of services compared with other OECD-countries, practicing at child health clinics, schools, nursing homes, prisons or acting as chief physicians in the municipalties (106). Only a minority of Norwegian GP practices have employed a nurse in contrast to other European countries (e.g. Sweden, Finland, Denmark, the Netherlands, England, Scotland), but no official number exists. The Norwegian GPs

have to full-finance all the ancillary staff and their pensions. The majority of GPs are remunerated with a mix of fee-for-service and capitation fee (70/30%), while only four percent have a fixed salary (103, 105). Diabetes specific processes of care that leads to a tariff are measurements of HbA1c, glucose, albuminuria and an annual diabetes review. Consultation fees and medical expences are covered by the state, although patients have to make a small annual contribution of approximately 2000 NOK (~ 200 EUR).

1.6.2 The Norwegian Diabetes Register for Adults

The Norwegian Diabetes Register for Adults (NDV) was established in 2006 and is a medical quality register financed by the Government. The University Hospital of Bergen is the owner of the registry, and responsible for data storage, while the Norwegian Organisation for Quality Improvement of Laboratory Examinations (Noklus) run the registry. It is based on informed consent from patients, and contains data on patient characteristics (age, gender, and ethnicity), cardiovascular risk factors, laboratory results, micro- and macrovascular complications, and records of medication. Patient age, gender, medication, and results from blood tests are electronically transferred to the database. All other information is completed in an electronic form by GPs or ancillary staff, and data is transferred to the register on an annual basis.

In 2014, approximately 16 000 people with type 2 diabetes were registered in the Norwegian Diabetes Registry (coverage 8%). On the other hand, the registry only received data from ~ 4 800 people treated by 362 GPs for the 2014 annual report (i.e. < 3% of the type 2 diabetes population, and 8% of all GPs in Norway) (107). In 2018, 37 000 people with type 2 diabetes were included in the registry (coverage 17%), while the registry received data on ~ 16 000 people and 1275 GPs the corresponding year (i.e. 8% people with type 2 diabetes, and 26% of all practicing GPs in Norway). The coverage in secondary care was higher; 45 of 51 outpatient

clinics (87%) reported to the registry in 2018, including data from 70% of people with type 1 diabetes in Norway.

GPs in the registry receive annual feedback on outcome measures and processes of care, and local reports are available.

People with type 2 diabetes included in the Norwegian Diabetes Registry are probably patients of diabetes interested GPs, and the results may be biased. It has therefore been necessary to perform repeated cross-sectional studies from a representative population to assess the quality of care in Norway, the ROSA-studies.

1.6.3 The ROSA-studies

The ROSA-studies are cross-sectional surveys of the quality of type 2 diabetes care in Norway, where ROSA 4 is the foundation of this thesis. The abbreviation stems from the first letters in the two initial participating regions. The first study, ROSA 1, was initiated by two GPs (Tor Claudi and John G. Cooper) who in 1995 wanted to assess the quality of diabetes care in general practice in Norway. They invited GPs in their respective areas. With a response rate of 100%, GPs from some selected regions in **Ro**galand County, and all GPs in the **Sa**lten area in Nordland participated. In ROSA 1, two research nurses personally visited all practices and reviewed the patients' case notes for care processes, intermediate outcomes (HbA1c, BP, and total cholesterol), smoking status, and medication. In ROSA 2 and 3, more patients, GPs and practices were included from other parts of the country, and the data collection was facilitated by the help of GPs and/or research nurses. A fourth survey was initiated to assess further time trends in the quality of care in 2014, the ROSA 4 study, which is the base for this thesis. Noklus, who runs the Norwegian Diabetes Register for Adults, led the data collection in ROSA 4 and was responsible for data storage and administration. Table 1 is an overview of the included number of patients, GPs, practices and regions in the ROSA-studies.

Study	Study year	People with type 2 diabetes	No. of practices	No. of GPs	Counties/ regions
ROSA 1 (108)	1995	*n* ≈ 1500	33 practices	73 GPs	Ro, Sa
ROSA 2 (109)	2000	*n* ≈ 2000	59 practices	169 GPs	Ro, O, Sa
ROSA 3 (110)	2005	*n* ≈ 5500	60 practices	204 GPs	Ro, O, Sa, A
ROSA 4	2014	*n* ≈10000	77 practices	282 GPs	Ro, O, Sa, Ak, H

Table 1. Overview of the ROSA-studies. Ro, Rogaland County. Sa, Salten in Nordland county. O, Oslo County. A, Alta city in Finnmark County. Ak, Akershus County. H, Hordaland County.

Between 1995 and 2005 results from the ROSA 2 and 3 studies showed a considerable improvement in risk factor control to prevent CVD; Mean HbA1c declined with 0.6 percentage points (6 mmol/mol), systolic blood pressure was reduced with almost 10 mmHg, and total cholesterol was lowered with 1.3 mmol/L (110). Correspondingly, the percentage with performed processes of care increased significantly; 40% more people had a cholesterol test measured, smoking habits documented, and eye examination performed, and 20% more people were tested for albuminuria. More information on the ROSA 3 and ROSA 4 studies will be described in detail later (see 4.1).

1.7 How can quality of care be assessed

In Donabedian's model from the 80's, quality of care can be assessed according to structure, process and outcome (111). Structure includes the setting of diabetes care with material- and human resources, and organizational structure. Process includes what is done in giving and receiving care, i.e. patients' seeking of care and carrying it out, and GPs' implementations and recommendations. Outcome denotes the effects of care. In other words, quality of care depends on the health care system, on the performance of practitioners, and on patient contribution (111).

The healthcare system carries responsibility for the quality of care. This includes organizing of diabetes care, with easy access to care in the communities, availability of enough qualified GPs and nurses, incentives, feedback-systems, and structure that may facilitate diabetes care.

The performance of GPs consists of two elements; one practical and the other interpersonal (111). Practical performance depends on the GPs knowledge and judgement, and time to offer the best follow-up and treatment according to current knowledge. Interpersonal performance is contingent on communication between the patient and the GP, where preferences of care are exchanged. The interpersonal process is closely linked to success in practical care and implementation of guidelines. Although it is important, information about interpersonal performance is not easily available. The management of the interpersonal processes by the GPs, influence the implementation of care by and for the patients (111).

Furthermore, the patients themselves are responsible for the failure or success of care as they seek care and carry it out. Accordingly, the GPs may occasionally be blameless in some cases where care, as implemented by the patients, are found to be inferior. Appropriate assessment of type 2 diabetes care can thus be difficult.

To summarize, the quality of care can be assessed at several levels, i.e. the patient level, GP level or the practice/healthcare system levels.

1.8 Quality improvement strategies

Numerous trials have been performed to improve the quality of type 2 diabetes care, targeting the patients, the GPs and the practice/healthcare system.

Targeting the patient: Apart from different medical interventions to improve glycaemic-, BP control and lipids, multifactorial intervention in the Steno-2 trial showed decline in HbA1c, BP, cholesterol and UACR, and reduced vascular complications (92). A multifaceted approach with structured diabetes self-management education in high-risk people with microalbuminuria has also showed benefits in other studies (112). Counselling interventions have been shown to be effective in reducing HbA1c (e.g. intervention by multidisciplinary teams, home counselling visits, and SMS-based interventions) (113). A systematic review of RCTs found significant improvements in glycaemic and BP control in peer-led interventions aiming at medication adherence (114). Finally, more people achieved Hba1c, BP and LDL-c targets with individualized targets in the Netherlands (115).

Targeting the GP: In an electronic questionnaire in the Netherlands, GPs' preferred interventions to improve guideline adherence were small interactive meetings, audit and feedback, organizational interventions, and interactions with local opinion leaders (116). Financial incentives, educational materials and big group meetings were of least interest (116). A systematic review showed little evidence that educational interventions targeting GPs have an effect on patient outcomes (117). Reviews of systematically reviews suggested that "electronic decision support, educational meetings, outreach visits, audit and feedback, and tailored interventions are probably effective", but the effects on implementation of guidelines were most often moderate and effect sizes varied (118, 119). Benchmarking of GPs in the multinational OPTIMISE study led to improved BP- and LDL-c control (120). Passive intervention strategies like publication of guidelines are often insufficient to behavioural changes, and a review in progress plan to study active implantation strategies to change GP behaviour (121).

Targeting the practice/healthcare system: Introduction of a quality and outcome framework led to significant improvements in care process and intermediate outcomes in the UK (122). Multifaceted improvement initiatives on multidisciplinary teams have resulted in better HbA1c (123, 124). A systematic review and meta-analysis of RCTs with nurse-led interventions showed reduced HbA1c, lipids and increased smoking cessation (125). Another meta-analysis of RCTs showed that organizational interventions (e.g. revision of professional roles, and skill mix changes) achieved better glycaemic control than patient-centred interventions (e.g. patient education, peer support, and telephone support), and in particular in people with baseline HbA1c > 9.5%) (> 80 mmol/mol) (126). A systematic review of RCTs on telemedicine found moderate improvements in HbA1c (127).

1.9 Variation in diabetes care

In diabetes care it is expected that national guidelines are implemented for care processes and treatment targets. Furthermore, it is desirable that the variation in health care services are reduced so that all people receive equal evidence based guidance and treatment. However, in a real-world setting, variation in the quality of diabetes care is present. Annual reports from the Swedish National Diabetes Register and from the UK National Diabetes Audit (2014 and 2018) visualize variation in care processes and target achievement between regions (12, 128-130). The least variation was observed in the performance of blood checks and BP measurements (128), a greater variation was in the performance of the monofilament test, while the greatest variation was observed in the performance of the albuminuria test in both countries (12, 128-130). Further, a moderate variation between regions was observed in the achievement of targets. Both registries emphasize that the variation is not a direct measure of quality of care, but an alert to investigate the differences further (12, 129).

A core function in quality improvement strategies is to reduce unwarranted variation (128, 131, 132). Based on Donabedian's model (111), the variation in the quality of

care can be attributed to the patient-, GP- or practice level, and even further, at a higher level, involving healthcare systems and countries.

In this PhD project the aim was to assess the available quality indicators of type 2 diabetes care in general practice in Norway 2014, with time trends from 2005. Furthermore, we wanted to quantify and explore the variation in quality of care at different levels, and identify factors associated with care processes and the achievement of treatment targets.

2. Aim and objectives

The overall aim of this PhD project was to assess status, time trends, and factors associated with quality of care of type 2 diabetes in general practice in Norway. The specific objectives were:

Paper 1

To assess status of type 2 diabetes care in general practice in Norway in 2014, and to describe time trends in quality of care from 2005 to 2014.

Paper 2

To identify factors associated with the performance of microvascular screening procedures (albuminuria, monofilament, and eye examination) in general practice in Norway in 2014.

Paper 3

To describe variation in the achievement of HbA1c, blood pressure, and LDL-cholesterol targets in Norway in 2014, and to assess patient-, general practitioner- and practice characteristics associated with risk factor control.

3. Overview of papers 1-3

3.1 Paper 1

The quality of type 2 diabetes care in Norwegian general practice in 2014 (ROSA 4, n = 9464) was compared with data from 2005 (ROSA 3, n = 5463) in regression models. The performance of blood tests and blood pressure measurements were high in both years. The low recordings in 2005 of BMI and screening procedures to detect microvascular complications (albuminuria, monofilament, eye examination) were still low in 2014. There was a significant change in medication. The mean glycaemic control was similar, while mean blood pressure and lipids improved, and more people achieved recommended targets for HbA1c, blood pressure, and lipids. We observed no reduction in the proportion of patients with vascular complications (Figure 2).

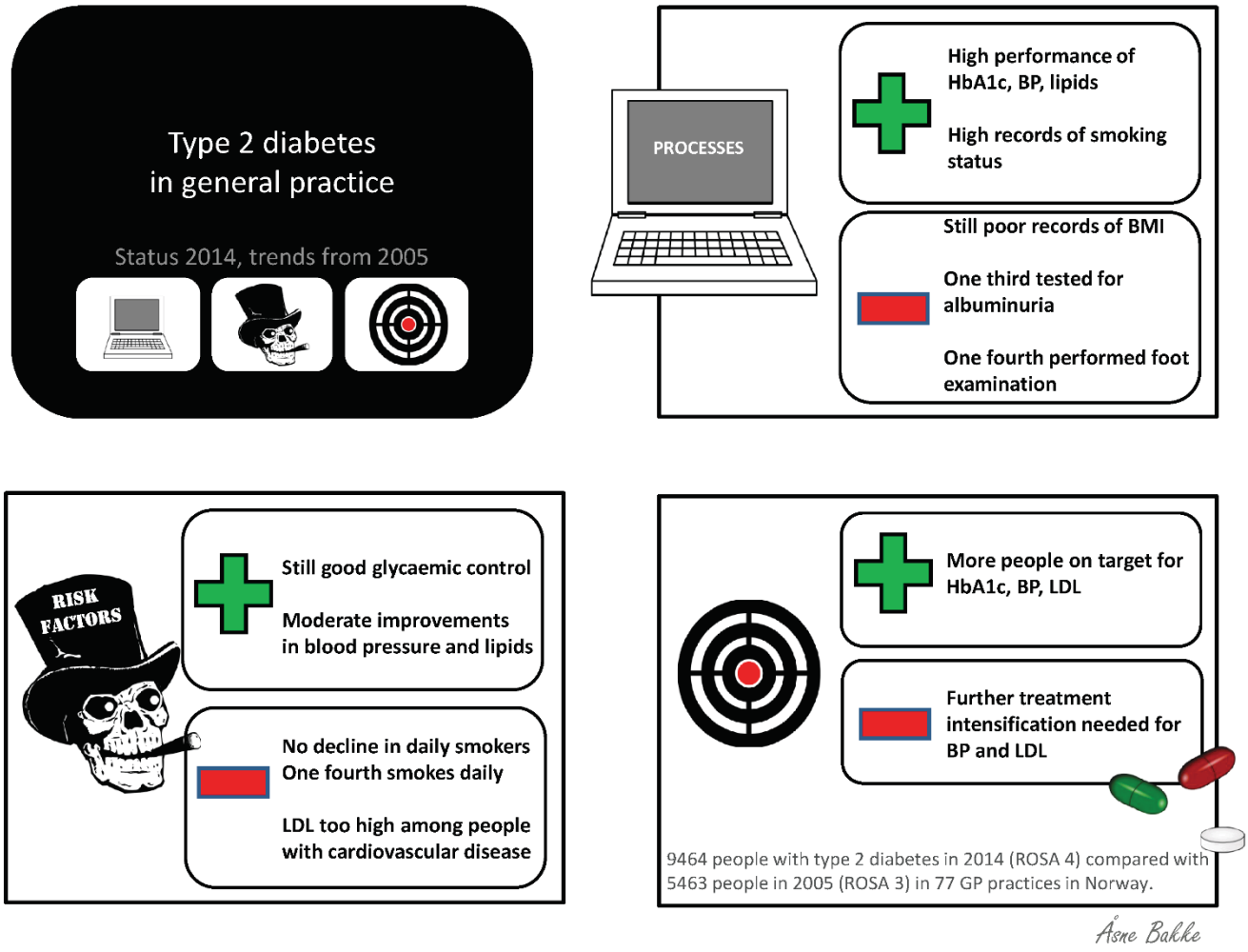


Figure 2. Graphical abstract of paper 1. Illustrations from openclipart.org.

3.2 Paper 2

Factors associated with the performance of microvascular screening procedures (albuminuria, monofilament, and eye examination) were identified in multilevel modelling. People with type 2 diabetes and a duration of one year or more in the ROSA 4 study (n = 8246), with their 281 general practitioners at 77 practices were included. Young people < 50 years were less likely to have an albuminuria test and eye examination recorded. People with macrovascular disease had fewer screening procedures performed. The performance varied among GPs and practices. GP specialists performed the procedures more often, while higher GP age and increasing list size reduced the odds of performing the procedures. GPs who used a structured diabetes form had almost three times higher odds of recording the recommended procedures (Figure 3).

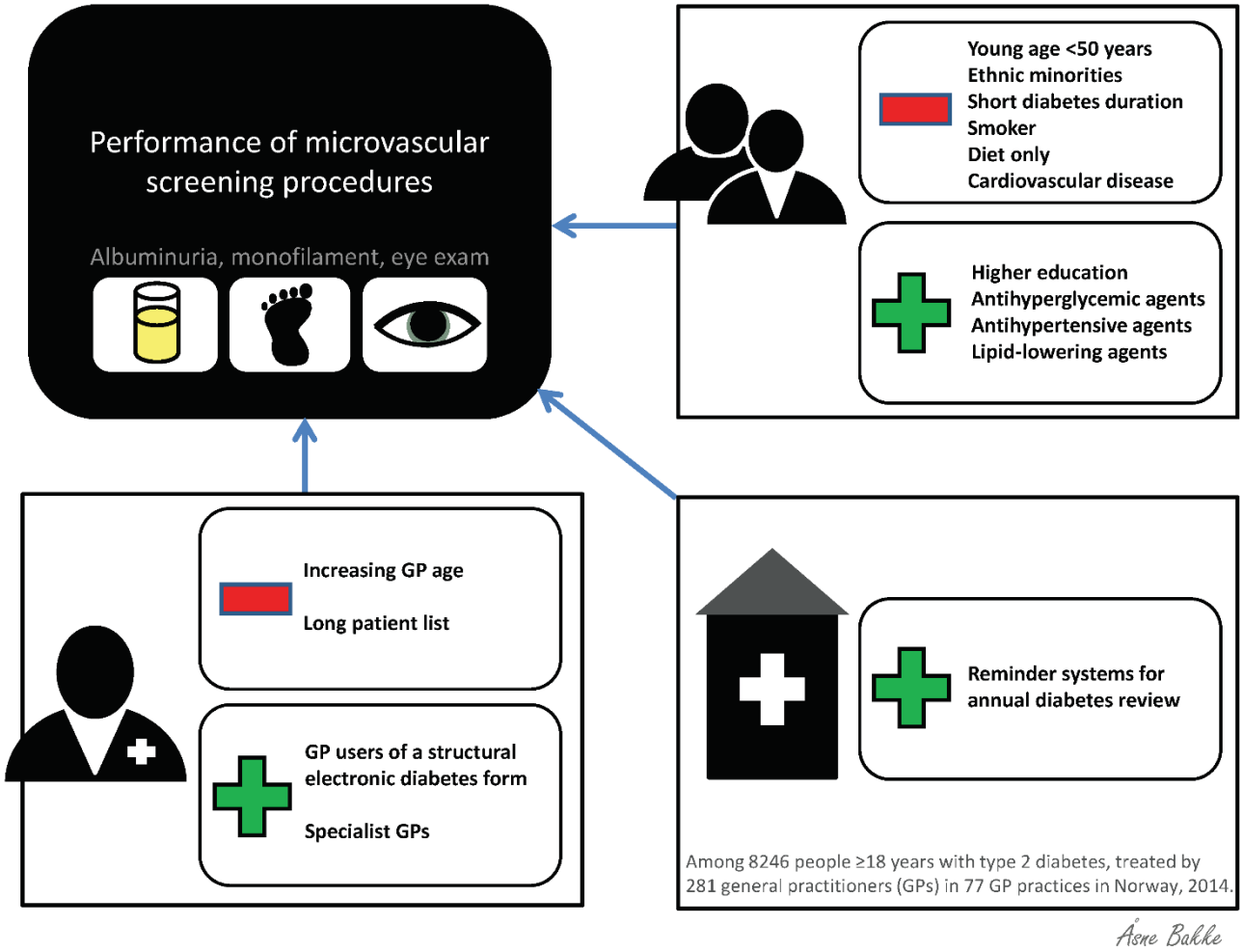


Figure 3. Graphical abstract of paper 2, with ≥ 2 microvascular screening procedures as the composite outcome.

3.3 Paper 3

We described variation in the achievement of HbA1c, BP and LDL-c targets and identified factors associated with the achievement of treatment targets for HbA1c, BP and LDL-c in multilevel modelling. People with type 2 diabetes and a duration of ≥ 6 months in the ROSA 4 study (n = 9342), 281 GPs and 77 practices were included. The proportion achieving treatment targets varied significantly between GPs and practices. People with age < 50 years, BMI ≥ 30 kg/m^2, and known macrovascular disease were less likely to achieve targets. GPs who used a structured diabetes form had higher odds of achieving the HbA1c and LDL-c targets. However, our model explained only a small part of the total variation in risk factor control (Figure 4).

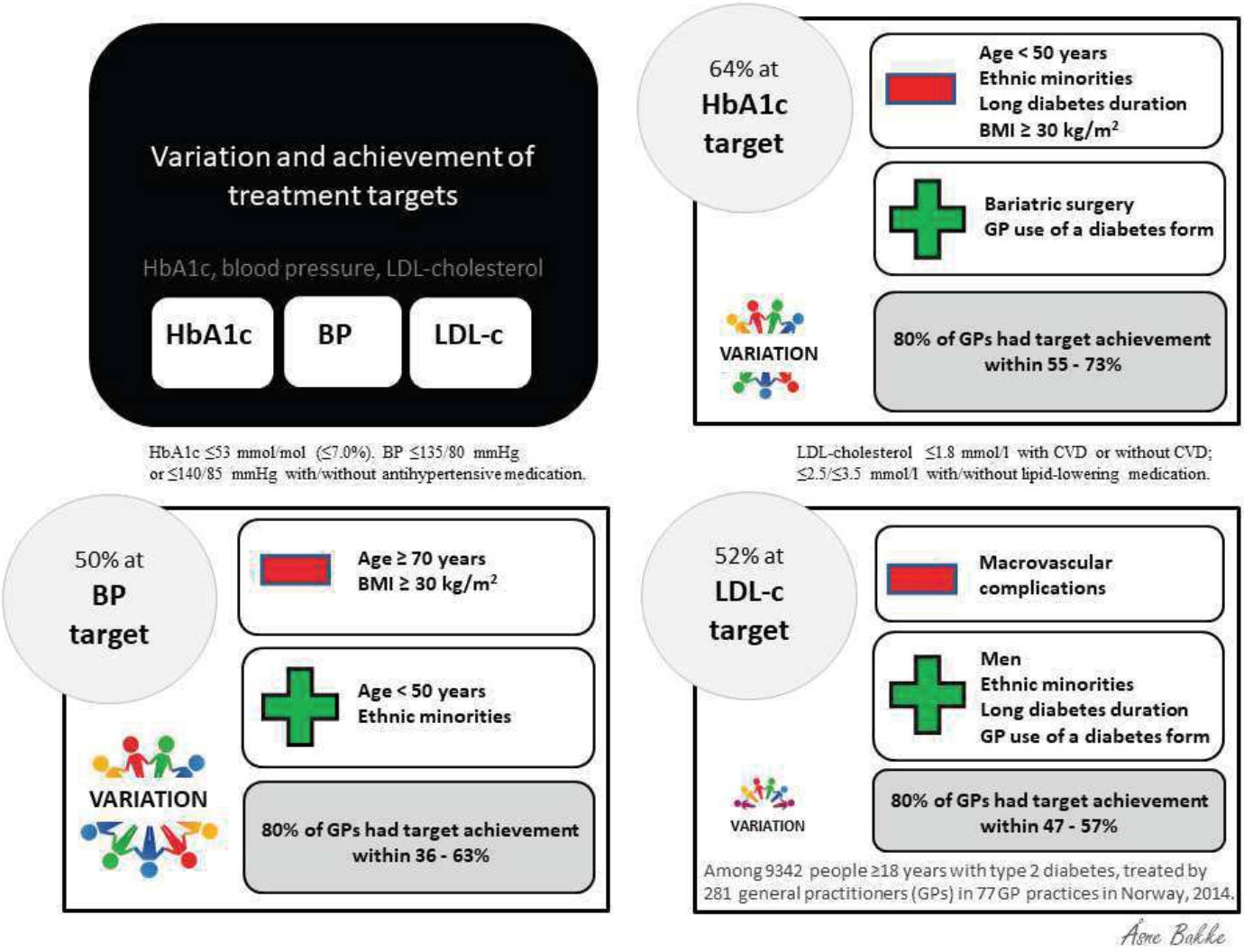


Figure 4. Graphical abstract of paper 3, with variation in the achievement of targets and characteristics associated with risk factor control. Illustration by pixabay.com.

4. Materials and methods

4.1 Recruitment and data collection

The ROSA 3 study

In the Rogaland-Oslo-Salten-Alta (ROSA 3) study, data was collected from 2005 and included 60 of 66 invited practices (response rate 91%), 205 GPs, and 6892 patients with diabetes, located in four counties (Alta, Nordland, Oslo and Rogaland) (Figure 5). In ROSA 3, each practice was visited by one of two diabetes nurses. The software Mediata AS identified people with diabetes and captured data from the electronic health records, while the nurses searched the patients' case notes and supplemented the data file.

Figure 5. Counties included in ROSA 3, Norway. Map modified from pixabay.com.

The ROSA 4 study

The Rogaland-Oslo-Salten-Akershus-Hordaland (ROSA 4) study, with data from 2014, was the base for all three papers. An invitation was sent to 106 practices with 367 GPs, in five of Norway's 19 counties (Figure 6, Table 2). The study included mainly the same practices in Nordland as in ROSA 3, while only a few practices were the same in Oslo and Rogaland. Two counties differed from the studies; Alta in Finnmark County was included in ROSA 3, while Hordaland County was included in ROSA 4.

The practices were located in urban and rural areas, and in some districts with a high proportion of ethnic minorities. The response rate among practices varied between counties, ranging from 43% in Oslo to 100% in Nordland and Rogaland. In total, 77 practices (response rate 73%) and 282 GPs (response rate 77%) were included. All GPs within each practice participated, with all their diabetes patients, n = 11 428.

Figure 6. Counties included in ROSA 4, Norway. Map modified from pixabay.com.

County	Municipality /district	Included / invited practices	Practices' response rate	Included GPs	Included patients
Akershus	Bærum, Skedsmo	10 / 13	78%	47	1 593
Hordaland	Fyllingsdalen, Laksevåg, Fjell	10 / 20	50%	41	1 810
Nordland	Salten	26 / 26	100%	78	3 079
Oslo	Groruddalen, Østensjø	12 / 28	43%	52	2 731
Rogaland	Sandnes, Stavanger	19 / 19	100%	64	2 215
Total		77 / 106	77%	282	11 428

Table 2. Number of practices, general practitioners (GPs) and diabetes patients in ROSA 4, stratified by county.

A customized software (Mediata AS) identified all people ≥ 18 years with a diabetes diagnosis (T89 and T90 in the International Classification of Primary Care (ICPC)) between 2012 and 2014. Laboratory results and prescribed medication were extracted automatically from the electronic health records (EHRs). The diabetes diagnosis was mainly set by GPs according to current national guidelines, with results from oral glucose tolerance tests, fasting blood glucose, or HbA1c measurements, and people with a diagnosis before the age of 40 were also included. Four research nurses visited each practice between January 2015 and April 2016 and scrutinized the EHRs. For each included patient, they verified the diabetes diagnosis in case of ambiguity. They collected patient information not suitable for electronic capture (year of diabetes diagnosis, measurements of blood pressure, height, and weight, smoking status, performance of foot- and eye examination, vascular complications). Furthermore, they gathered information from available specialist reports. Medication was extracted from the GPs' electronic prescription files. Data on ethnicity and education were obtained from Statistics Norway. Noklus at Haraldsplass Deaconess Hospital was

responsible for organizing data collection, together with storage of data and administrating research access to the database. Two questionnaires were used to gather GP and practice characteristics (completed in 99% and 100% of cases) (Appendix).

4.2 Ethics

The ROSA 3 and ROSA 4 studies were approved by the Regional Ethical Committee in Norway with exception from informed consent (06/811 and 2014/1374 REK Vest).

4.3 Participants and study design

Cross-sectional data from 10 248 people with type 2 diabetes in the ROSA 4 survey were the base for all three papers. We included people with type 2 diabetes and main follow-up in general practice, i.e. we excluded patients with more than one visit to an outpatient diabetes clinic in the study year, long-term residents in nursery homes, patients who were new to the GP the last 6 months, or who recently moved or died in the data collection period.

In paper 1 we included 5463 patients in ROSA 3 and 9464 in ROSA 4, with a diabetes duration of six months or longer.

In paper 2 we included people with a diabetes duration of one year or longer, so that GPs would have had the possibility to perform the microvascular screening procedures as recommended. Further, we excluded 137 patients with an unknown list holding GP, and 705 patients due to missing data on one or more of diabetes duration, ethnicity, and education. One GP was excluded, as he had only one patient with type 2 diabetes, and this patient had main follow-up in an outpatient clinic. Thus, 8246 patients in ROSA 4, with their 281 GPs, and 77 practices were eligible for analysis.

In paper 3 we wanted to analyze people with a diabetes duration of six months or more. Furthermore, we excluded 140 patients with an unknown list holding GP, leaving 9342 patients, 281 GPs, and 77 practices to study.

4.4 Outcomes

In paper 1 we assessed status of type 2 diabetes care in 2014, and time trends in general practice from 2005 to 2014 in Norway. We compared processes of care, medication, measurements and attained treatment targets, and vascular complications.

In paper 2 we identified factors associated with the performance of microvascular screening procedures in 2014; albuminuria test, monofilament test, and eye examination. The main outcomes were the performance of each procedure separately, and a composite of two or more microvascular screening procedures. Performance of the albuminuria and monofilament test were registered the last 15 months, while eye examination was registered the last 30 months.

In paper 3 we described variation in the achievement of HbA1c, BP and LDL-c targets, and patient, GP and practice characteristics associated with the achievement of risk factor control. The outcome was the achievement of treatment targets according to national diabetes guidelines in 2009; HbA1c ≤ 7.0% (≤ 53 mmol/mol), BP ≤ 135/80 mmHg with intervention threshold ≤ 140/85 mmHg, and LDL-c ≤ 1.8 mmol/L with cardiovascular disease, or without cardiovascular disease; LDL-c ≤ 2.5 with treatment, and LDL-c ≤ 3.5 mmol/L without treatment. We used the most recent measurement for HbA1c, BP and LDL-c the last 15 months, however, if none were available, the search period was extended backwards to 3 years (7.8% of HbA1c measurements, and 19.1% of LDL-c measurements).

4.5 Variables

Patient characteristics

Table 3 shows patient characteristics described in paper 1, and the patient characteristics used as explanatory variables in papers 2 and 3.

Patient characteristics	Paper 1	Paper 2	Paper 3
Demographics			
Gender	m/w	m/w	m/w
Age	Cont.	5-cat	5-cat
Ethnicity	Caucasian vs. others	W.Europe vs. others	**3-cat**
Education	-	3-cat	3-cat
Diabetes duration	Cont.	Per 5-year	Per 5-year
Smoking status	Current smoker y/n	Reg. current smoker y/n	**3-cat**
BMI	Cont.	-	**3-cat**
Bariatric surgery	y/n	Reg. surgery y/n	y/n
Processes of care			
HbA1c/BP/Lipids/eGFR	y/n	-	-
BMI assessment	y/n	-	-
Smoking habits registered	y/n	-	-
Albuminuria test	y/n	-	-
Monofilament test	y/n	-	-
Eye examination	y/n	-	-
Medication			
Antihyperglycaemic	4-cat	3-cat	-
Antihypertensive	y/n	y/n	-
Lipid-lowering	y/n	y/n	-
Laboratory results and target achievement			
HbA1c, % (mmol/mol)	Cont., 2-cat	Reg. HbA1c ≥ 8 (64)	-
BP, mmHg	Cont., 2-cat	Reg. BP > 140/85	-
Lipids, mmol/l	Cont., 2-cat	Reg. LDL > 3.5	-
Vascular complications			
Reduced eGFR, ml/min/1.73m^2	4-cat	Reg. eGFR < 45	**4-cat**
Absent monofilament	y/n	-	-
Foot ulcer/amputation	y/n	-	y/n
Retinopathy	y/n	-	-
CHD/stroke/PTA	y/n	Composite variable	Composite variable

Table 3. Overview of patient characteristics used in papers 1-3. Abbreviations; m/w, men/women. Cont., continuous variables. Cat, categories. W.Europe, Western Europe/North America. Y/n, yes/no. Reg., registered with risk factor, where missing observations are defined as "not registered with risk factor". BMI, body mass index. CHD, coronary heart disease. PTA, percutaneous transluminal angioplasty. Composite variable consisting of CHD, stroke, and PTA/peripheral arterial surgery.

Demographic variables included men/women, age, ethnicity (categorized in paper 1 as Caucasians vs. others, in paper 2 as Western Europeans/North Americans vs. others, and in paper 3 as Western Europeans/North Americans, South Asians and others), education (primary school, high school, and university). Furthermore, we included diabetes duration, smoking status (categorized in paper 1 as current smoker yes/no, in paper 2 as registered as current smoker (where missing variables were defined as not registered as current smoker), and in paper 3 as never smoked/ex-smoker/current smoker), BMI (categorized in papers 1 and 3 as BMI < 25, 25-29.9, ≥ 30 kg/m^2), and bariatric surgery (categorized in paper 1 as yes/no, and in paper 2 as registered with bariatric surgery yes/no, where missing variables were defined as not registered with surgery).

Processes of care was defined as a measurement of HbA1c, blood pressure, total cholesterol, HDL-cholesterol (HDL-c), LDL-cholesterol, creatinine/estimated glomerular filtration rate (eGFR), height and weight, registration of smoking status, albuminuria test, monofilament test, and eye examination.

Medication included antihyperglycaemic agents categorized in paper 1 as diet only/ agents excluding insulin/ insulin only/ agents including insulin, and in paper 2 categorized as diet only/ agents excluding insulin/ agents including insulin, antihypertensive drugs with subgroups in paper 1, and lipid-lowering therapy. Medication was based on GPs prescriptions the last 15 months.

Laboratory results and measurements were given for HbA1c, BP, total cholesterol, HDL-c, LDL-c, creatinine/eGFR. In paper 2 we defined HbA1c ≥ 8% (≥ 64 mmol/mol), BP > 140/85 mmHg, LDL-c ≥ 3.5 mmol/L, and eGFR < 45

ml/min/1.73m^2 as variables “registered with risk”, where missing variables were defined as “not registered with risk”.

Target achievement was accomplished if HbA1c was ≤ 7.0% (53 mmol/mol), BP ≤ 135/80 mmHg in treated, and ≤ 140/85 in untreated patients, and LDL-c was ≤ 1.8 mmol/L in people with CVD, and without CVD; ≤ 2.5 mmol/L in treated people, and ≤ 3.5 mmol/L in untreated people.

Vascular complications included diabetic retinopathy, diabetic nephropathy (albuminuria, eGFR < 60 mL/ min/ 1.73 m^2, dialysis, kidney transplantation), diabetic neuropathy (pathological 10g monofilament test, defined as absent sensation in one or more out of eight sites, foot ulcer, and lower limb amputation), coronary heart disease (CHD) (angina, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery), stroke (transient ischemic attacks (TIA) were included in 2005 and excluded in 2014, and percutaneous transluminal angioplasty (PTA)/ peripheral arterial surgery. In papers 2 and 3, a composite variable called macrovascular complications included CHD, stroke, and PTA/peripheral arterial surgery.

The most recent value was used for all measurements, however, we excluded values that were considered outdated. This was done slightly differently between papers. In paper 1 we wanted the inclusion periods in ROSA 4 to be as similar to ROSA 3 as possible, while we in papers 2 and 3 expanded the inclusion periods to reduce the number of missing data for regression modelling (Table 4).

Laboratory tests and measurements	**Paper 1** ROSA 3	ROSA 4	**Paper 2** ROSA 4	**Paper 3** ROSA 4
HbA1c	12 months	12 months	15 months	**3 years***
BP	12 months	**15 months**	15 months	15 months
Lipids	3 years	3 years	3 years	**3 years***
eGFR	3 years	3 years	3 years	3 years
Height	If ever measured	If ever measured	-	If ever measured
Weight	12 months	**15 months**	-	15 months
Microvascular screening				
Albuminuria test	12 months	12 months	15 months	-
Monofilament test	12 months	**15 months**	15 months	-
Eye examination	2 years + referrals last 2 years	2 years + referrals last **30 months**	30 months	-
Others				
Smoking habits	3 years	**5 years**	5 years	5 years
Medication	Not specified	**15 months**	15 months	-
Complications	If ever registered	If ever registered	If ever registered	If ever registered

ROSA 3 (2005):
12 months (Jan. 1st to Dec. 31st 2005)
2 years (Jan 1st 2004 to Dec. 31st 2005)
3 years (Jan. 1st 2003 to Dec.31st 2005)

ROSA 4 (2014):
12 months (Jan. 1st to Dec. 31st 2014)
15 months (Oct. 1st 2013 to Dec. 31st 2014)
2 years (Jan. 1st 2013 to Dec. 31st 2014)
30 months (July 1st 2012 to Dec. 31st 2014)

*Table 4. Variable inclusion periods in papers 1-3. * 92.2% of HbA1c values and 81.9% of LDL-c values were within the last 15 months.*

GP characteristics

GP characteristics were included as explanatory variables in papers 2 and 3, and the small differences in variable selections are shown in Table 5.

GP characteristics	Paper 2	Paper 3
Gender	m/w	m/w
Age	Per 10-year	**5-cat**
Country of birth, Norway	y/n	y/n
Country of medical education, Norway	y/n	y/n
≤ 5 years as a GP in Norway	y/n	y/n
Specialist in general practice	y/n	y/n
Clinical days per week > 3	y/n	y/n
No. of type 2 diabetes patients per GP	3-cat	3-cat
No. of list patients per clinical day/week	3-cat	**4-cat**
User of a structured diabetes form	y/n	y/n

Table 5. GP characteristics included as explanatory variables in papers 2 and 3.

Demographics included GP gender, age, country of birth, and country of medical education (Norway vs. others, where Norway was reference in paper 2, and others were reference in paper 3).

Experience. We used proxies for GP experience that included specialist status (specialist in general practice vs. no specialist), years as a GP in Norway (≤ 5 years vs. > 5years), and no. of type 2 diabetes patients (< 25, 25-49, ≥ 50).

Work load. Proxys for workload were defined as clinical days per week (> 3 vs. ≤ 3 days), total no. of patients on GP's list per clinical day worked each week, categorized as < 250, 250-350, > 350 patients in paper 2, and as <225, 225-300, 301-375, >375 patients per clinical day in paper 3.

Routines. GP usage of a structured diabetes form (the Noklus diabetes form, Figure 7) was a proxy for GP routines. The GP was defined as a user of the form if the form was

more than 50% completed in ten or more people, or in more than 50% of their patients with type 2 diabetes.

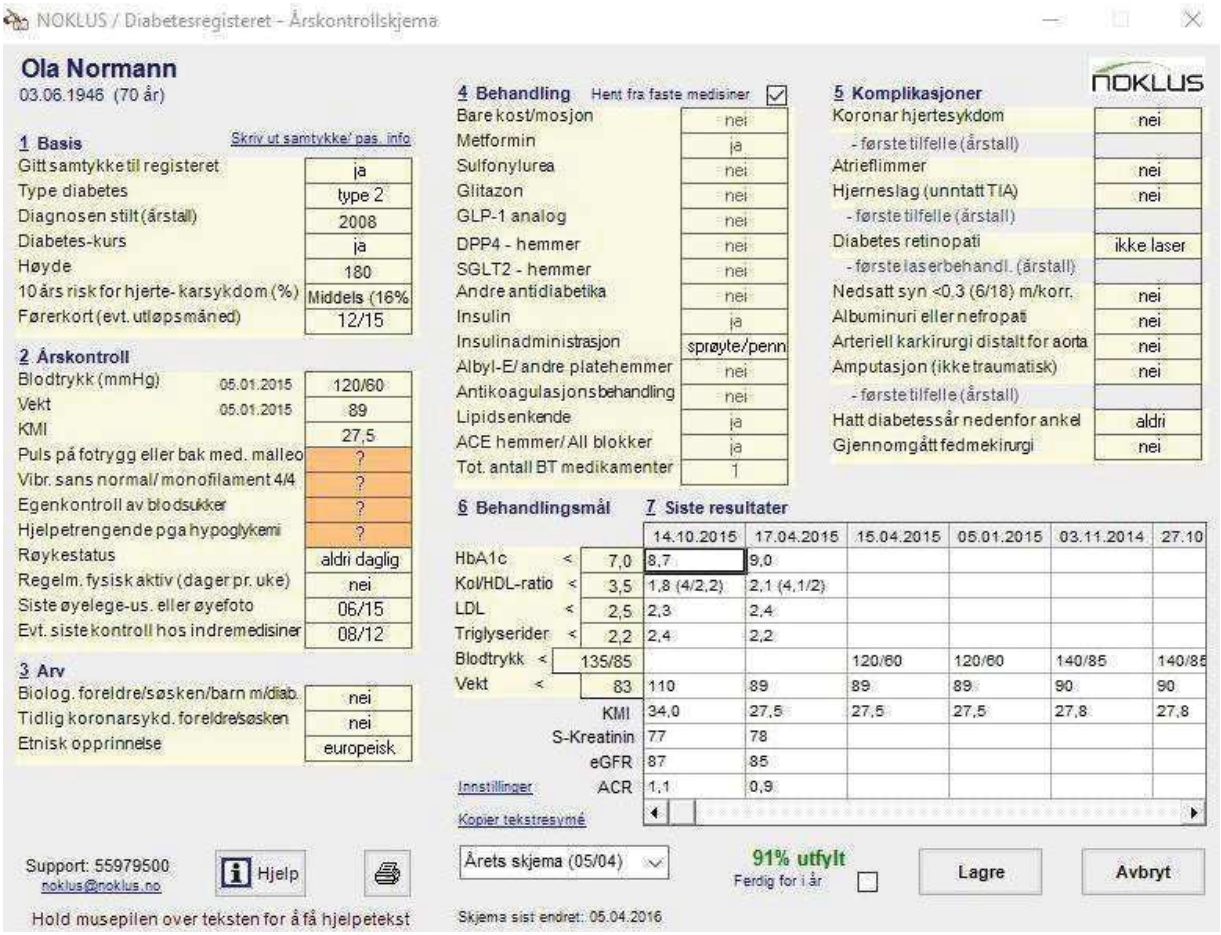


Figure 7. The Noklus diabetes form, - a structured electronic diabetes form in Norway. Printed with permission.

Practice characteristics

Practice characteristics were included as explanatory variables in papers 2 and 3, and differences in variable selections are shown in Table 6.

Practice characteristics	Paper 2	Paper 3
County	5-cat	5-cat
Urban location	y/n	-
No. of GPs per office	Cont.	Cont.
No. of list patients per full-time staff	Cont.	**3-cat**
Staff with duties related to microvascular complication screening	y/n	-
Diabetes competency	y/n	-
Routines of annual follow-up	y/n	y/n

Table 6. Practice characteristics included as explanatory variables in papers 2 and 3.

Location. Practices were located within counties, and accounted for in the analysis (Oslo, Akershus, Hordaland, Rogaland, and Nordland). Further, the variable urban vs. rural location was used in paper 2, where urban location was defined as municipalities with > 80% of the population living in densely populated areas according to Statistics Norway.

Practice size. The variables no. of GPs per practice, and total no. of people on list per full-time employed staff (categorized as < 1250, 1250-1750, > 1750 patients in paper 3), were used as proxies for practice size. Two composite variables regarding diabetes related tasks were included in paper 2; one variable called diabetes competency included employment of a diabetes nurse, or ancillary staff attending a diabetes course within the past three years (yes/no), and another variable named "duties related to microvascular complication screening" included ancillary staff with responsibility for at least one of the three microvascular procedures albuminuria, monofilament test or eye examination (yes/no).

Routines of annual-follow up, included practices with a reminder system for the annual diabetes care review.

4.6 Statistics

4.6.1 Multiple regression modelling

In this thesis we have used linear and logistic regression modeling. Linear regression models estimate the expected value of a continuous outcome variable for given values of a set of explanatory variables:

$$Y_i = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_P x_{Pi} + \varepsilon_i \quad , \qquad (1)$$

where Y_i is the outcome variable (also called dependent variable, response) for a patient i, and $x_{1i}, x_{2i}, \ldots, x_{Pi}$ are observed values of P explanatory variables (also called independent variables, predictors, covariates) for patient i. The βs are the regression coefficients describing the relationship between each x_p and Y. β_p gives the expected increase in Y for a one unit increase in x_p, when all other x are held constant. β_0 is the expected value of Y when all $x_p = 0$ (i.e. the intercept). ε_i is the residual, i.e. the difference between the outcome variable that is predicted by the regression model for patient i and what is actually observed for this patient (133). It is assumed that the residuals follow a normal distribution with an expected mean of zero and a constant variance σ^2 (the assumption of homoscedasticity), and that they are independent of each other, i.e. $\varepsilon_i \sim N(0, \sigma^2)$. Thus, the expected value of Y_i is given as a linear combination of the explanatory variables;

$$E(Y_i | x_{1i}, x_{2i}, \ldots, x_{pi}) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots + \beta_p x_{pi} \quad . \qquad (2)$$

A linear model is usually fitted either via the method of least squares or via maximum likelihood estimation (MLE). Inferences from a regression analysis typically concerns the coefficients β_p, including point estimates, confidence intervals (CI), and tests of null effects; which in linear regression are based on the assumptions mentioned above. Evaluations of the model fit are also often reported (see 4.6.1, p. 53, Assessment of model fit).

When the outcome variable Y is not continuous, but rather a binary variable (values 1 or 0) reflecting the presence or not of some condition, e.g. a disease, being married, etc., linear regression is unsuitable. A binary logistic regression model gives the conditional probability that the outcome condition is present (i.e. $Y = 1$ as opposed to $Y = 0$) given the values of a set of explanatory variables:

$$P(Y_i=1|\, x_{1i},\, x_{2i},\, \ldots,\, x_{Pi}\,) = \frac{\exp(\beta_0 + \beta_1\, x_{1i} + \beta_2\, x_{2i} + \cdots + \beta_P\, x_{Pi})}{1+\exp(\beta_0 + \beta_1\, x_{1i} + \beta_2\, x_{2i} + \cdots + \beta_P\, x_{Pi})}\,, \qquad (3)$$

where $\exp(a) = e^a$ denotes the exponential function. Equation 3 may be rewritten using the logit transformation:

$$\begin{aligned} \text{logit}(x_{1i},\, x_{2i},\, \ldots,\, x_{Pi}) &= \ln\left(\frac{P(Yi=1|\, x1i,x2i,\ldots,xPi\,)}{1 - P(Yi=1|\, x1i,x2i,\ldots,xPi\,)}\right) \\ &= \beta_0 + \beta_1\, x_{1i} + \beta_2\, x_{2i} + \ldots + \beta_P\, x_{Pi}\,, \qquad (4) \end{aligned}$$

where ln is the natural logarithm, for which ln(e) = 1. The logit, or the log odds of $Y = 1$, is given as a linear combination of the explanatory variables. The effect estimates of a logistic regression are usually presented as $e^{\beta p}$, which has the interpretation of an odds ratio (OR), that is, the proportional change in the odds of $Y = 1$ for a one unit increase in x_p. The intercept, β_0, the constant term, is the log odds of $Y = 1$ when all $x_p = 0$.

Logistic regression models are usually fitted using MLE. Confidence intervals for ORs are estimated via a normality assumption for the estimates of β_p. Significance testing of individual parameters β_p can be performed as likelihood ratio tests or Wald tests, the latter assuming normality of the sampling distribution of β_p. From a fitted logistic regression model one can obtain predicted probabilities and predicted outcomes.

Assessment of model fit

The goodness of fit of a linear regression model is often summarized using the coefficient of determination R^2, which estimates the proportion of variance in the outcome variable Y that is explained by the explanatory variables (134). R^2 ranges from 0 to 1, i.e. 0 to 100% of the variation in Y can be explained:

$$R^2 = \frac{Explained\ variation}{Total\ variation} \qquad (5)$$

As opposed to linear regression where the error variance is assumed to be the same for all values of Y (i.e. the assumption of homoscedasticity), the error variances in logistic regression are different for each value of Y (1/0), and we cannot use the same approach to calculate R^2. However, several pseudo-R^2 have been developed to evaluate the goodness of fit in logistic regression (135).

Multicollinearity

Estimation of individual effects will become problematic if there is high correlation among the independent variables in a regression model, so-called multicollinearity. The variance inflation factor (VIF) quantifies how much the variance of a regression coefficient is affected due to multicollinearity. The VIF for a given independent variable is estimated by regressing it against all the other independent variables in the model, i.e. independently of the outcome. The VIF can take a value of 1 and upwards. A VIF of 1 means no correlation, a VIF between 1 and 5 shows moderate correlation, and above 5 shows high correlation (134).

4.6.2 Multilevel regression modelling

Regular regression modeling as described above, is based on an assumption of independent observations. In situations where this assumption is not met, i.e. if there is correlation in the data, we need to use other methods to get correct inference (133). In quality of care research there is usually a hierarchical structure in the data, in that patients (level 1) are clustered or nested within clinics (level 2), and where patients treated by the same clinic tend to be more alike than patients treated at different clinics, i.e. there is intra-cluster correlation. Correspondingly, there will be heterogeneity among the clinics, and in mixed regression models we allow for this heterogeneity by introducing cluster-specific random effects (133). For example, a linear random intercept model can be formulated as:

$$Y_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \ldots + \beta_P x_{Pij} + u_j + \varepsilon_{ij} \quad , \qquad (6)$$

where x_{pij} denotes the observed value of x_p for patient i within clinic j, $\beta_0 + u_j$ denotes the cluster-specific intercept, and ε_{ij} the residual for patient i in clinic j. We assume normal distribution for the random intercept term $u_j \sim N(0, \sigma^2)$, and for the error $\varepsilon_{ij} \sim N(0, \sigma^2)$. Equation *(6)* is illustrated in Figure 8.

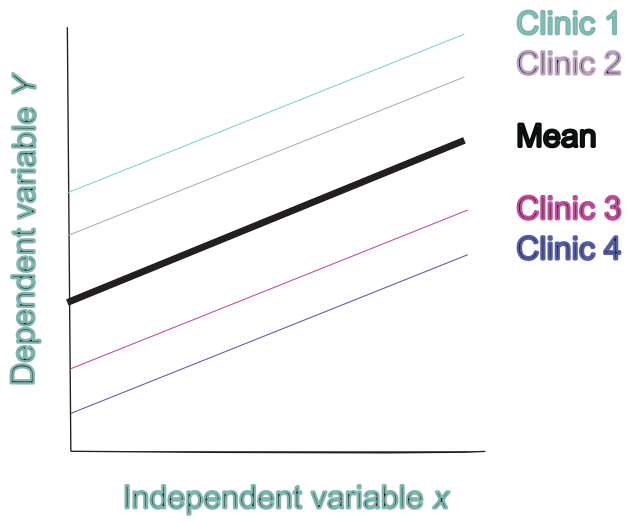


Figure 8. Illustration of a linear random intercept model with one independent variable. We have random between-cluster variation in the overall level of the outcome Y, and a fixed effect of the independent variable x (i.e. same slope for all clinics).

The fixed effects β_p represent the usual effects of explanatory variables, which can be related to level 1 units or level 2 units. Notice that we do not estimate a fixed effect of any specific cluster (e.g. clinic 1 vs. clinic 2), only the random variation σ_u^2 in the mean outcome among clusters.

In a logistic random intercept model, σ_u^2 will incorporate the variation between clusters in the log odds of $Y = 1$ given all $x = 0$.

Empirical Bayes estimates

Prediction from a mixed regression model needs to incorporate the random effects, which is usually done by Empirical Bayes (EB) estimation (133). In essence, each cluster's level is estimated as a weighted average between the total mean and the observed cluster mean. Big clusters will have EB estimates close to their mean, whereas small clusters will be adjusted closer to the a priori assumed value, i.e. the total mean. This shrinkage will provide an unbiased estimate of the between-cluster variation as opposed to using observed cluster means directly.

Measures of cluster heterogeneity

The intraclass correlation coefficient (ICC): The ICC represents between-cluster variance as a proportion of the total variance, i.e. "quantifies the proportion of observed variance in the outcome that is attributable to the effect of clustering" (136). Given a multilevel linear model with a continuous outcome the ICC would be:

$$\text{ICC} = \frac{between\text{-}cluster\ variance}{total\ variance} = \frac{\sigma_u^2}{\sigma_u^2 + \sigma^2} \quad . \qquad (7)$$

The larger between-cluster variance relative to the between-subject variance, the greater the degree of clustering. The ICCs range from 0 to 1 (0 to 100%).Values close to one indicate high homogeneity in the outcome between individuals in the same

cluster. Values close to zero indicate that subjects within a cluster are no more similar than subjects from different clusters.

The ICC estimated for an empty model, i.e. one without fixed effects, is called an unconditional ICC, which reflects a decomposition of all the variance in the outcome variable. ICCs for models with fixed effects are conditional on these effects, i.e. the ICC decomposes the residual (unexplained) variance. By including subject-level explanatory variables, it is expected that the level 1 variance be reduced and also that the higher-level variance to be affected due to adjustment for case-mix. Inclusion of higher-level variables which explain some of the between-cluster variance, is expected to give a reduction in the ICC.

For a logistic multilevel model, the definition and estimation of an ICC is not as straight-forward. The problem is that the residual variance at level 1 cannot be summarized as a single value like in linear regression, and furthermore that the variances at different levels are measured on different scales. One possible solution is to consider the binary response at level 1 to be a result of the dichotomization of an underlying continuous variable following a logistic distribution, in which case the variance is defined as a constant $\frac{\pi^2}{3}$ (136). Thus, the ICC can then be estimated as:

$$\text{ICC} = \frac{\sigma_u^2}{\sigma_u^2 + \frac{\pi^2}{3}} \quad . \qquad (8)$$

Having the level 1 variance fixed at a constant value of $\frac{\pi^2}{3}$ complicates the comparison of models with and without subject-level variables, and can give illogical changes to the ICC. Inclusion of higher-level variables is however expected to affect the ICC as in linear regression.

Median odds ratio (MOR): In logistic regression, the median odds ratio is another measure of heterogeneity between clusters, obtained by transforming the random intercept variance into a more familiar scale, i.e. into an OR (136). MORs range from 1 to infinity. If we randomly and repeatedly sampled two individuals with identical covariates from different clusters, the MOR is the median of all pairwise odds ratios between the individual with the higher probability of a binary outcome and the individual (with identical covariates) with the lower probability (136). For example, if all subject level variables affecting the outcome were accounted for, it would be the median increase in odds of the outcome one would experience by changing to a better performing clinic.

Assessment of model fit

In multilevel modelling there are different approaches to estimate the coefficient of determination, R^2. We used the approach outlined in Reference (135). In general, we distinguish between so called marginal and conditional R^2. R^2 for fixed effects (marginal R^2) shows how much the independent variables explain of the total variance in the outcome. R^2 for fixed effects and random effects together (conditional R^2) shows how much the total model explain of the total variation. In multilevel logistic modelling the R^2 is based on the same latent variable assumption as the ICC; i.e. that subject level variance equals $\frac{\pi^2}{3}$. R^2 is expected to be lower in logistic regression than in linear regression, and will never become 1 (135).

Clustering at multiple levels

In our data, we have patients (level 1) clustered within GPs (level 2), and GPs clustered within practices (level 3) (Figure 9).

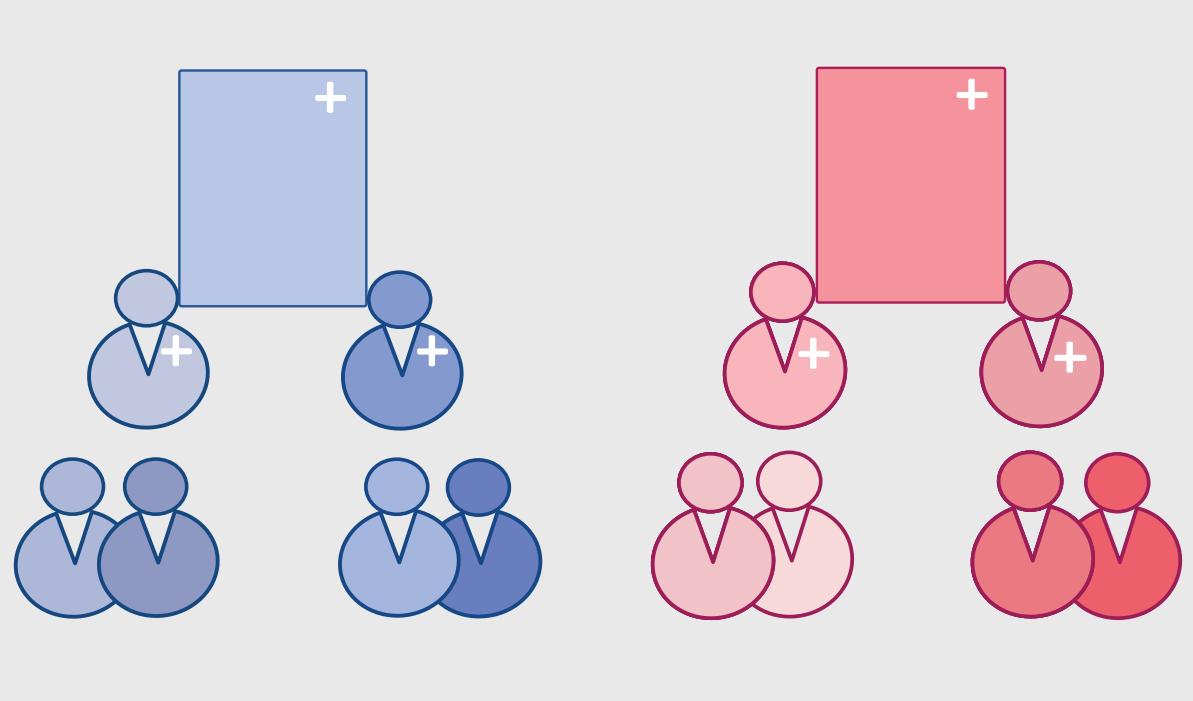


Figure 9. Clustering of GPs within practices, and patients within GPs. The highest cluster in the hierarchical model represents level 3 (practices), whereas the lower levels represent level 2 (GPs) and level 1 ((patients). GPs within one practice are more similar than they are to GPs at another practice, and patients treated by one GP are more alike than patients treated by another GP. This means that there is intra-cluster correlation.

With three-level data, we can expand the linear model with another random intercept term, $v_{k:}$

$$Y_{ijk} = \beta_0 + \beta_1 x_{1ijk} + \beta_2 x_{2ijk} + \ldots + \beta_P x_{Pijk} + u_j + v_k + \varepsilon_{ijk} \quad , \qquad (9)$$

where x_{pijk} denotes observation of variable x_p for patient i treated by GP j at practice k, and ε_{ikj} is the independent residual variance at level 1. We assume normal distribution for the random intercepts, $u_j \sim N(0, \sigma_u^2)$, and $v_k \sim N(0, \sigma_v^2)$, and for the residual $\varepsilon_{ijk} \sim N(0, \sigma^2)$. Thus, the unexplained variance can be decomposed into variance σ_u^2 between GPs and variation σ_v^2 between practices and residual variance σ^2.

For a three-level *logistic* regression model, the expansion with an extra random intercept term is done quite similarly.

Alternative way of accounting for clustering

If the decomposition of variance is not of interest in itself, instead of estimating a mixed regression model including random effects, one can simply estimate the standard errors of effect estimates by methods that account for the correlation due to clustering. The preferred method for doing so, is to use so called cluster-robust sandwich estimates of standard error (137). In some applications of this method (e.g. in Stata), it is, however, not possible to specify clustering at more than one level with this approach, for which case it is recommended to allow for clustering at the highest level (138).

4.6.3 Handling of missing data

Missing data can be missing completely at random, missing at random or missing not at random. Missing completely at random occurs when the missing data is not related to the observed value nor to the unobserved values (139), i.e. the observed data can be interpreted as a random sample of the complete data. Missing at random refers to the situation where the missing value is related to some of the observed data, but independent of the unobserved values. Missing not at random is when the missingness is dependent on the unobserved data.

There are several approaches to handle missing data in cross-sectional studies; 1) to omit cases with missing data, and analyse the remaining data (complete case analysis), 2) to only eliminate information when the specific data-point is needed (available cases analysis), and 3) to replace missing data with estimated values, so called imputation (139).

Imputation

Single imputation is when a missing value for one variable is replaced with a probable value, e.g. the mean of all observed values or a predicted value from a regression model involving other observed variables. Single imputation underestimates the variance in the data since estimated values are treated like any other measured value, i.e. the uncertainty in the imputation is not allowed for.

With multiple imputation, the main idea is similar to regression-based single imputation. However, by repeatedly drawing from an estimated probability distribution for the missing data point, it allows for the estimation and incorporation of increased variance due to the imputation.

We used multiple imputation by chained equations (MICE) with predictive mean matching (140), where we used information from the explanatory variables in the model, from the outcome variables, and any other (auxiliary) variables that could be predictive of the missingness of the explanatory variables in the main model. In addition, we allowed for the clustering structure of the data (140). Without going into further details, the entire process was repeated *m* times, resulting in *m* complete datasets. Each complete dataset was then analysed by standard methods, i.e. with the planned outcome variable and explanatory variables. Finally, all the *m* analysis results were averaged or pooled by applying Rubin's rule (Figure 10) (140).

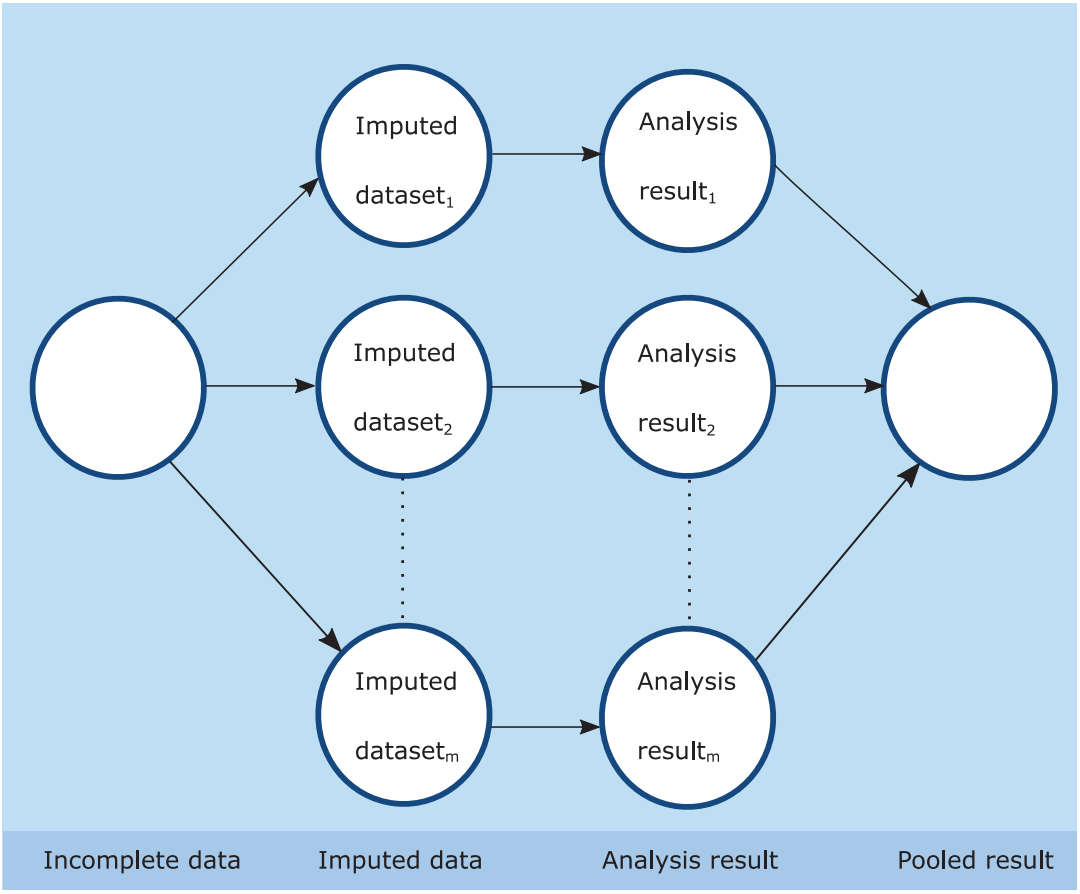


Figure 10. Multiple imputation.

4.6.4 Statistical methods in the papers

Paper 1: Main methods were linear and logistic regression models accounting for clustering with the sandwich method, and with Wald tests for significance testing of effects of individual explanatory variables. Mean values and percentages were calculated from valid cases.

Papers 2 and 3: We used multilevel regression models including fixed effects and random intercepts for GPs and practices. Wald tests were applied for significance testing of individual effects. Continuous explanatory variables were roughly checked for linearity of effects by categorizing them, and in case of obvious non-linearity we categorized the variables. VIFs were applied to check for multicollinearity. ICCs were calculated for unadjusted and adjusted models. In paper 3 we supplied with EB estimates, unconditional and adjusted MORs and R^2. The variable "years practicing as a GP in Norway" was missing for 11 GPs, and the variable was single imputed

based on the year of Norwegian authorization which was known for all GPs. Otherwise, missing data were handled differently in papers 2 and 3:

In paper 2, missing care processes were considered as not performed, and 705 patients were excluded in the regression models due to missing data on diabetes duration, ethnicity, and education. Further, we defined some variables as "registered with risk factor", e.g. we included people with high HbA1c ≥ 8.0% (≥ 64 mmol/mol) and missing observations were defined as "not registered with risk factor". We chose to omit BMI in the analysis as close to 50% of the population did not have a calculation of this the last 15 months.

In paper 3, missing information on patient characteristics (7.4%) was imputed by MICE. One hundred imputed datasets with predictive mean matching were produced, while accounting for the hierarchical structure of the data (140).

Statistical packages

For the statistical analysis in paper 1 we used STATA/SE V.14.0 with functions logit, mlogit and regress, with allowance for clustering via the vce (cluster clustvar) option, and with margins and test post estimation procedures. For paper 2 we used STATA/SE V.15.0 with functions xtmelogit and post estimation procedure estat icc. The imputations for paper 3 were performed in R version 3.4 with packages mice and miceadds. Furthermore, STATA/SE V.15.0 was used with functions mi estimate, melogit, mixed, and mimrgns post estimation procedure for multiply imputed data. CIs of ICCs were estimated using the logit transform described in Reference (141). EB estimation was performed with original data using post estimation procedure predict. The Venn diagrams of papers 2 and 3 were created in Python version 3.7 with package matplotlib.

5. Results

5.1 Paper 1

The objective was to present status of type 2 diabetes care in 2014 (ROSA 4) and assess time trends 2005-2014 (ROSA 3 to ROSA 4). Data from n = 5463 vs. n = 9464 people were available for analysis (2005 vs. 2014). The presented results are given as percentages, adjusted for age, gender, and county, and clustering within practices.

5.1.1 Processes of care

Most people had measured laboratory tests and BP in both study years (Figure 11).

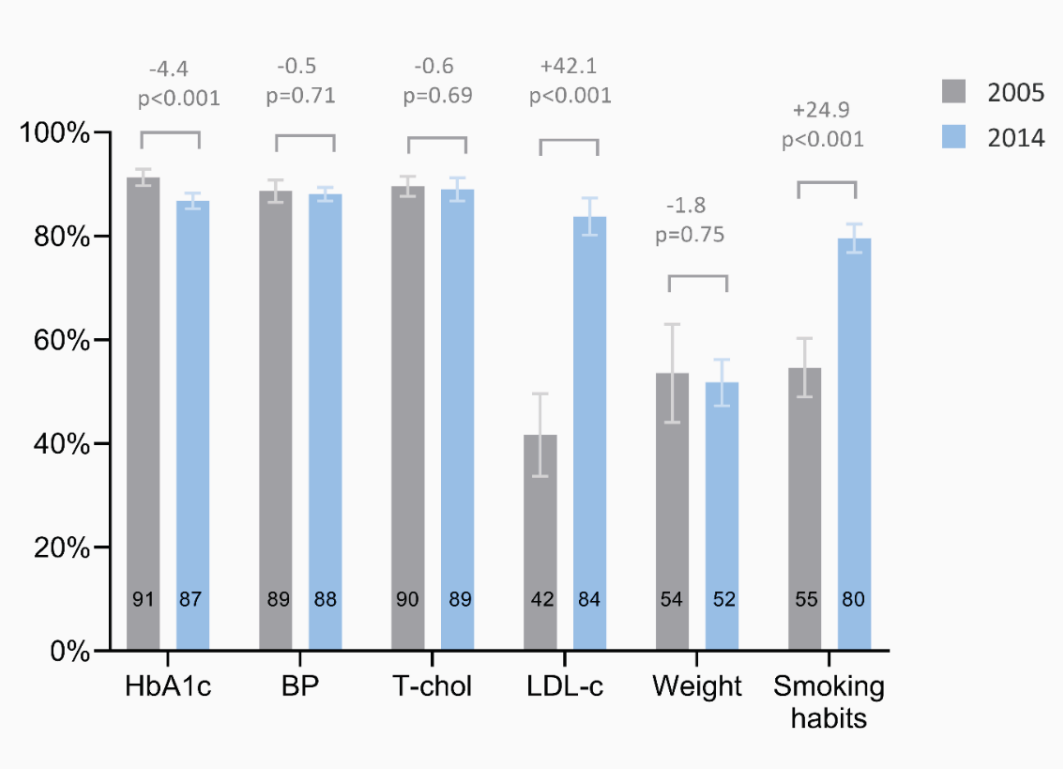


Figure 11. Predicted percentages of type 2 diabetes patients with a measurement, stratified by study year, n = 5463 (2005) and 9464 (2014). Error bars represent 95% confidence intervals. Adjusted for gender, age, counties, and clustering within practices.

We observed a substantial increase in LDL-c tests. Only half had recorded weight, with no improvements during the nine years. On the other hand, smoking habits were registered more frequently in 2014.

The recordings of screening procedures to detect microvascular complications were low in both 2005 and 2014 (Figure 12), and only 9.6% vs. 13.4% had performed all three microvascular screening procedures as recommended.

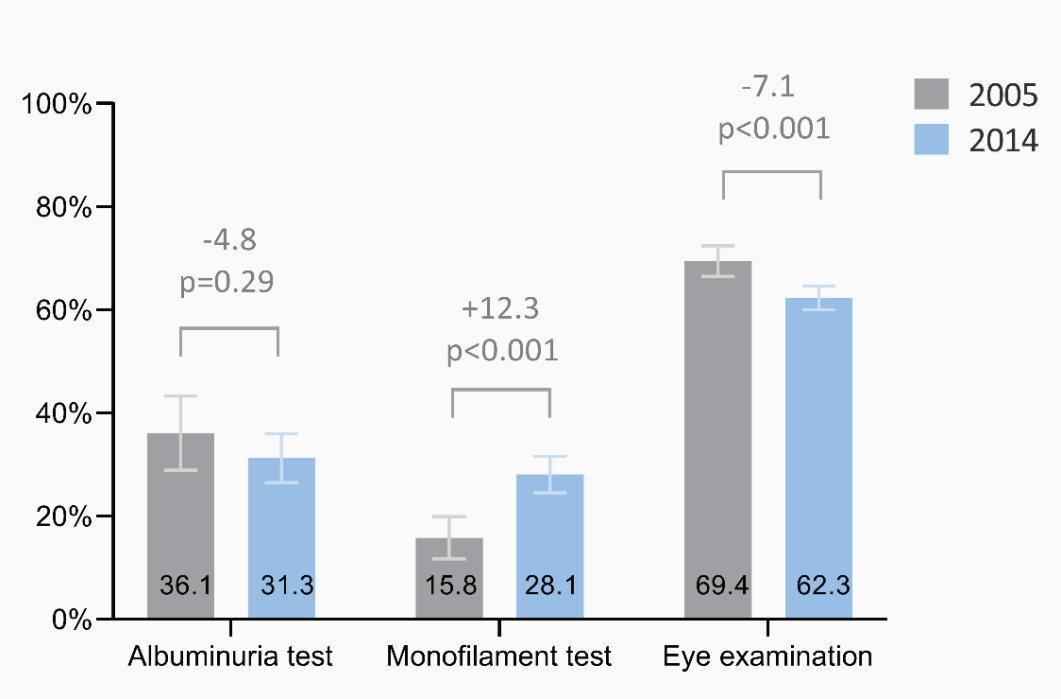


Figure 12. Predicted percentages of type 2 diabetes patients with a recorded microvascular screening procedure, stratified by study year, n=5463 (2005) and n=9464 (2014). Error bars represent 95% confidence intervals. Adjusted for gender, age, counties and clustering within practices.

5.1.2 Medication

The use of antihyperglycaemic medication changed substantially as new agents appeared and combination therapy increased. In 2014, 13.9% used dipeptidyl peptidase-4 inhibitors (DPP4i), 2.6% glucagon-like peptide-1 agonist (GLP-1 analogues), and 3.4% sodium-glucose co-transporter-2 inhibitors (SGLT2i), with none registered users in 2005. More people used combination therapy with three or more antihyperglycaemic agents, 2.1% vs. 9.0%. Metformin use increased, while use of sulfonylureas and insulin declined in the total population (Figure 13).

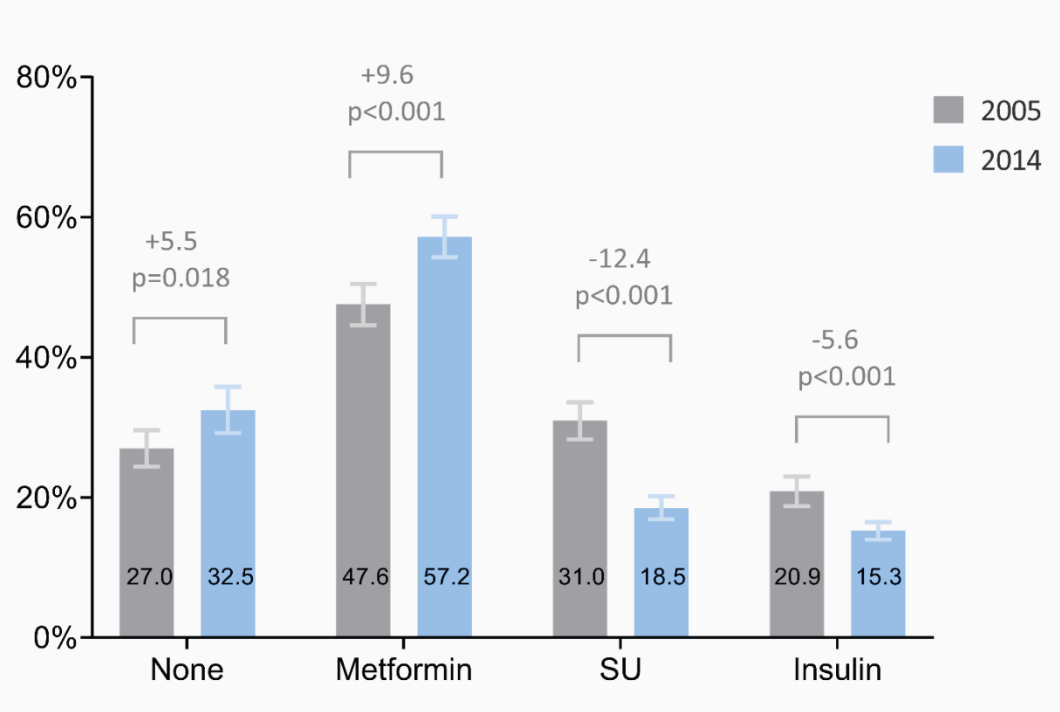


Figure 13. Predicted percentages of all type 2 diabetes patients with categories of antihyperglycaemic therapy, stratified by study year, n=5463 (2005) and n=9464 (2014). Error bars represent 95% confidence intervals. SU, sulfonylureas. Adjusted for gender, age, counties and clustering within practices.

The proportion of people on antihypertensives did not change; 66% of the study population were on medication in 2005, and in 2014. However, more people were on ACE inhibitors or ARBs. Lipid-lowering therapy increased in the general type 2 diabetes population from 43.4 to 54.7%, and from 68.5 to 77.3% in people with a history of coronary heart disease.

5.1.3 Cardiovascular risk factors

There was no significant decline in current smokers, and the percentage of current smokers was high: 25.0% in 2005 and 22.8% in 2014. Further, we observed no differences in BMI levels, with mean BMI 29.8 kg/m^2 in 2005 and 30.1 kg/m^2 in 2014. Mean values for HbA1c, systolic BP and total cholesterol all improved significantly between 2005 and 2014; HbA1c levels were reduced from 7.1 to 7.0% (54 to 53 mmol/mol) with a mean change of -0.2% (-1.6 mmol/mol), systolic BP declined from 139 to 135 mmHg with a mean change of -3.3 mmHg, and total cholesterol was reduced from 5.1 to 4.7 mmol/L, mean change -0.4 mmol/L. More people achieved recommended targets (Figure 14). However, there was no significant reduction in people with HbA1c > 9% (> 75 mmol/mol); 6.9% in 2005 vs. 5.6% in 2014.

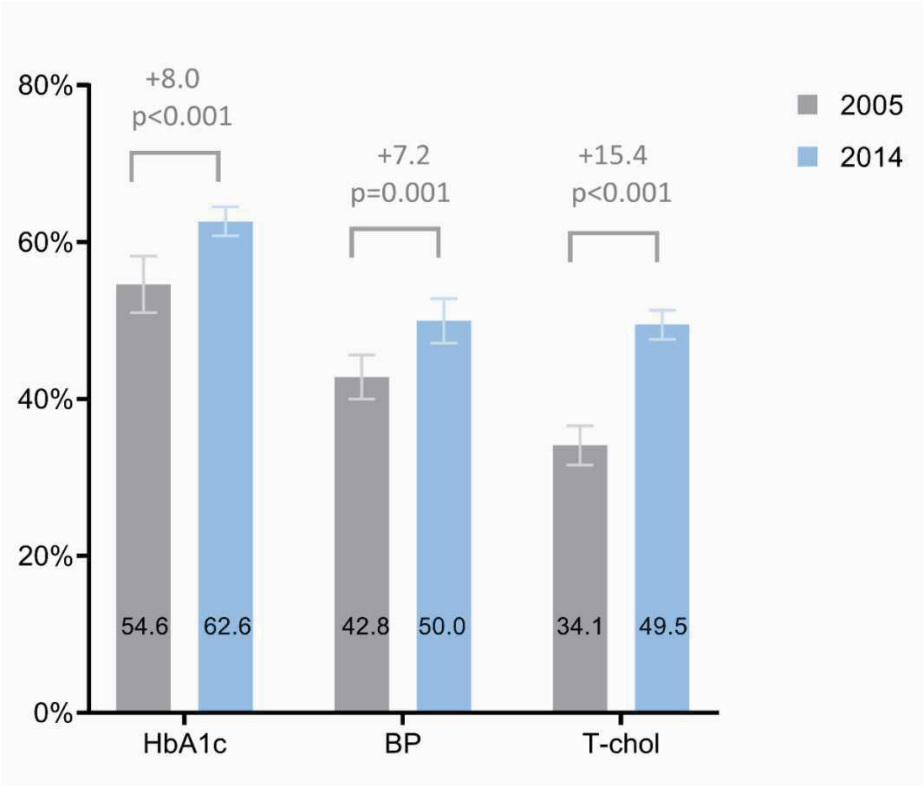


Figure 14. Predicted percentages of patients at treatment target, stratified by study year, 2005 and 2014. Error bars represent 95% confidence intervals. Adjusted for gender, age, counties and clustering within practices.

5.2 Paper 2

The objective was to assess factors associated with the performance of screening for microvascular complications. Data from *n* = 8246 people with type 2 diabetes, *n* = 281 GPs, and *n* = 77 practices in 2014 were included in the analysis.

Approximately one third, 31.5%, had a test for albuminuria performed, and 27.5% a monofilament test within the last 15 months, while 60.0% had records of an eye examination within the last 30 months (Figure 15). Thirty-five percent had two or more microvascular screening procedures performed, while 12.3% were tested for all three procedures. About one in four, 28.3%, had not had any of the recommended procedures performed.

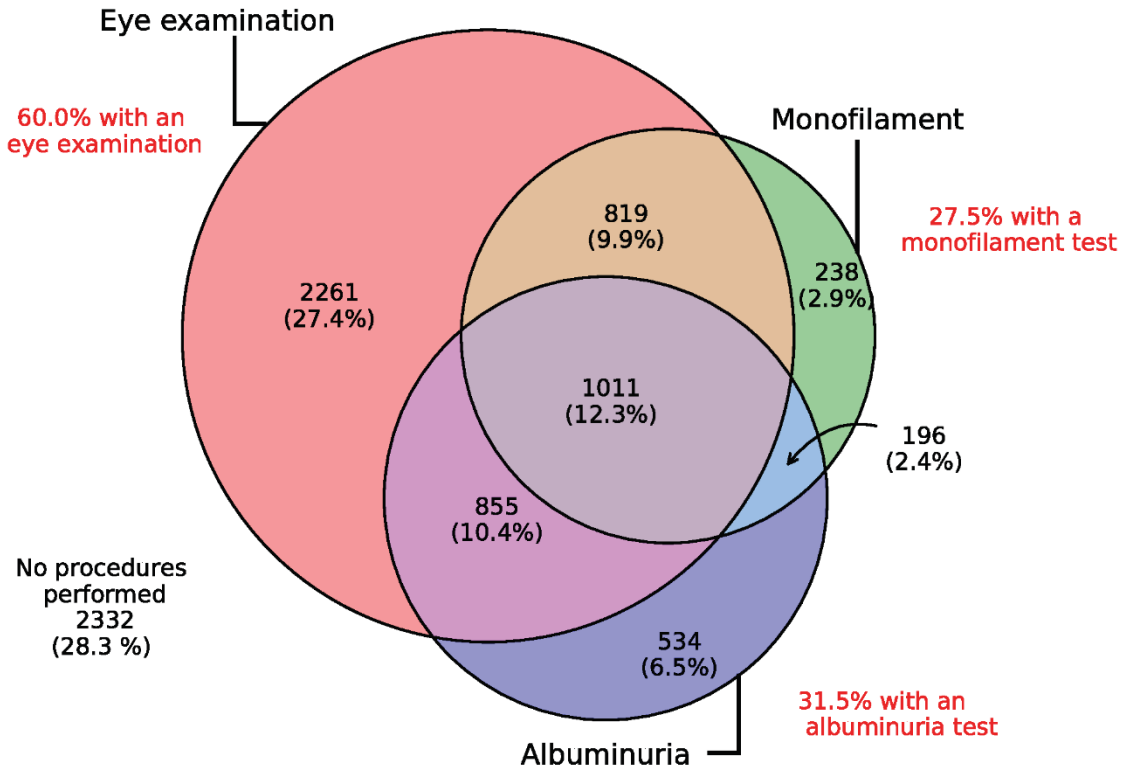


Figure 15. Percentage of 8246 people with type 2 diabetes and a recorded eye examination, albuminuria test and monofilament test. Bakke et al.(142). Reprinted with permission.

5.2.1 Factors associated with the performance of microvascular screening procedures

Factors associated with the performance of the albuminuria test

People < 50 years had 25% lower odds of being checked for albuminuria, compared with 60-69 year olds, OR 0.75. Further, people with macrovascular complications had low odds of being tested, OR 0.69. On the other hand, it was more likely that people registered with hypertension (OR 1.34), and people treated with antihyperglycaemic agents (OR 1.72), antihypertensives (OR 1.31) and lipid-lowering therapy (1.54) had increased odds of having an albuminuria test.

Increasing GP age was associated with reduced odds of performing an albuminuria test; per 10 year increase in GP age, the odds of performing the procedure were reduced with 24%, OR 0.76, although specialists in general practice had higher odds of screening for albuminuria, OR 1.73. Several GPs per office were also associated with more testing for albuminuria; for each GP at the practice, the odds increased with 35%, OR 1.35. Finally, practices with a reminder system for annual review, had almost three times higher odds of performing an albuminuria test, OR 2.57.

Factors associated with the performance of the monofilament test

People ≥ 80 years were less likely to be examined with a monofilament test, OR 0.63, as were people registered with macrovascular complications, OR 0.72. Furthermore, people on antihyperglycaemic medication were two to three times more likely to be tested for neuropathy than those with lifestyle modification only.

Increasing GP age was associated with low odds of performing the monofilament test. Per 10 year increase in GP age, the odds for testing monofilaments were reduced with 16%, OR 0.84. High workload was associated with low performance of the monofilament test, e.g. GPs who had 250 or more vs. less than 250 listed patients per clinical day worked each week had 48% lower odds of testing monofilaments, OR 0.52. The strongest GP association with a monofilament examination, was GPs who

regularly used the Noklus diabetes form. They had almost five times higher odds of performing the procedure, OR 4.51. Additionally, practices with routines for annual follow-up, had 75% higher odds of screening for diabetic peripheral neuropathy, OR 1.75.

Factors associated with the performance of eye examinations

People <50 years had 21% lower odds of having an eye examination performed, compared with 60-69 year olds, OR 0.79. People with known macrovascular complications (OR 0.82) and known eGFR < 45 ml/min/1.73 m^2 (OR 0.74) were less likely to have their eyes checked. On the other hand, per five-year increase in diabetes duration, the odds of having a recording of an eye examination increased with 26%, OR 1.26. Insulin users had more than two times higher odds of having an eye examination performed compared with people on lifestyle-modification only, OR 2.40.

Specialists in general practice had higher odds of recording eye examinations, OR 1.29. GPs with more type 2 diabetes patients on their list (25-49 or ≥ 50, compared with < 25) were more likely to record eye screening, OR 1.49 and OR 1.38, respectively. GPs who were regular users of the Noklus diabetes form had also 38% higher odds of recording an eye examination, OR 1.38. Furthermore, practices with ancillary staff with duties related to microvascular screening were more likely to record an eye examination, OR 1.58.

Factors associated with the performance of ≥ 2 microvascular screening

People aged 80 years or older were less likely to have two or more microvascular screening procedures performed, OR 0.57. People with macrovascular complications had also lower odds of the composite outcome, OR 0.68. However, insulin users had more than two times higher odds of being checked for more than one vascular complication compared with people on lifestyle modification only, OR 2.40.

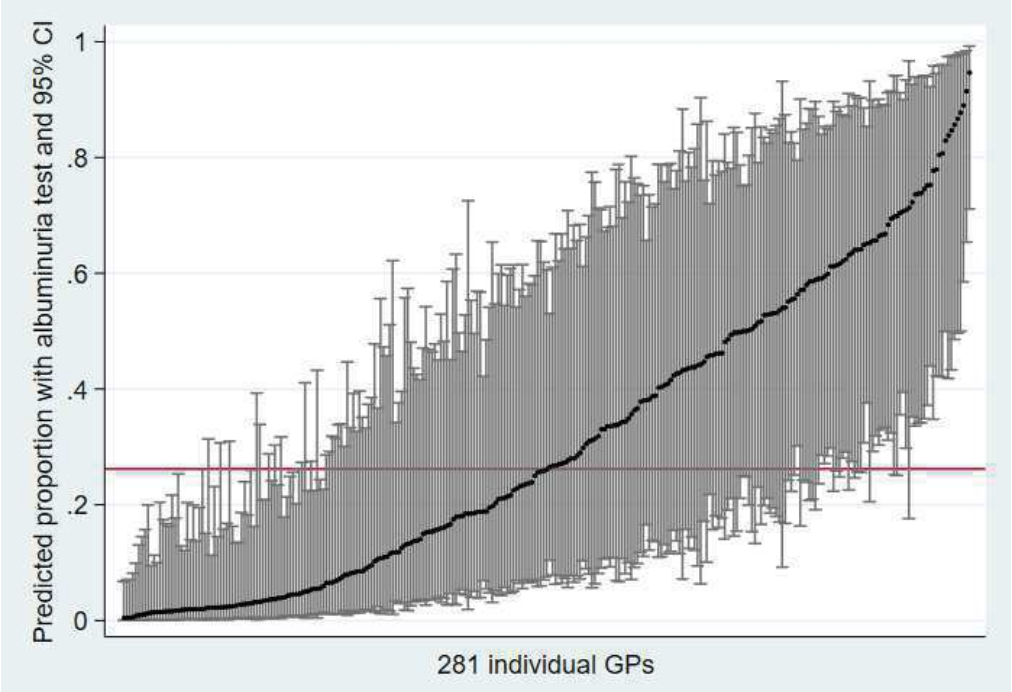
Per 10 year increase in GP age, the odds of having ≥ 2 microvascular screening procedures performed decreased with 21%, OR 0.79. High workload, with responsibility for 250-350 or > 350 patients on GPs list per day worked each week compared with < 250 listed patients, was associated with lower odds of performing the procedure, OR 0.59 or OR 0.55, respectively. Specialists in general practice performed the recommended procedures more often, OR 1.50. In particular, GP users of a structured diabetes form had almost three times higher odds of performing the procedures than non-users, OR 2.65. Practices with routines for annual diabetes review, had also high odds of screening for microvascular complications, OR 1.92.

5.2.2 Variation in the performance of microvascular screening procedures

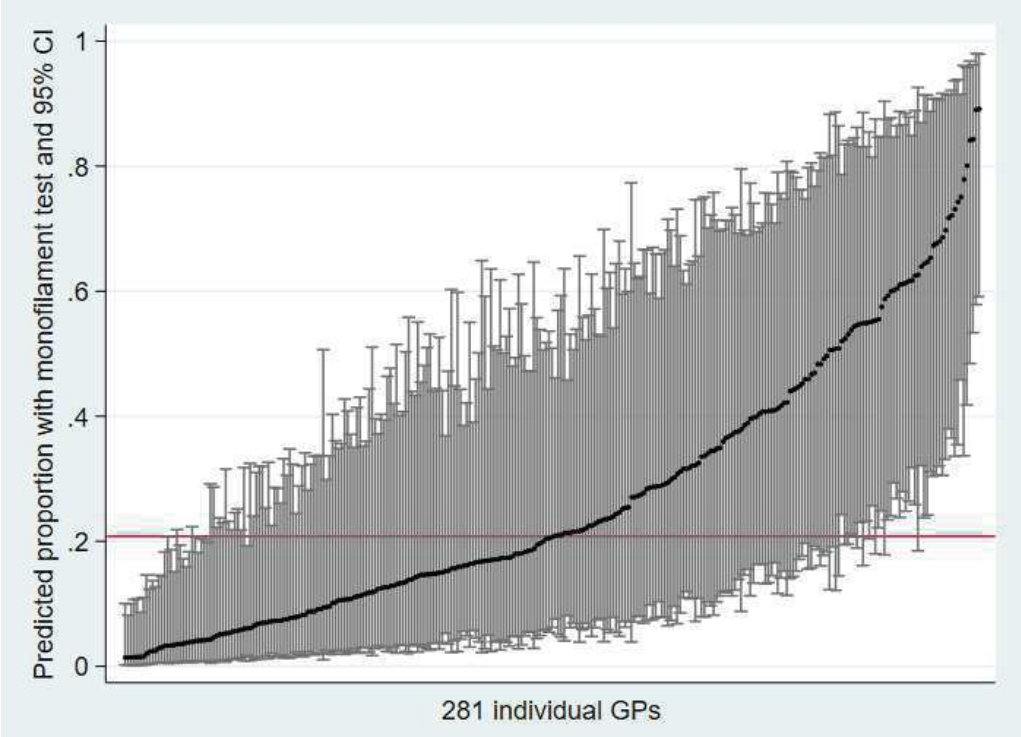
We observed substantial heterogeneity in the performance of all three procedures between GPs and between practices. The estimated proportions of a GPs' diabetes patients with a recorded microvascular screening procedure are shown for 281 individual GPs in Figure 16 a-d (data not published). Eighty percent of the estimated recordings was between 2.2-68.1% for the albuminuria test, 4.3-60.4% for the monofilament test, 36.6-80.5% for eye examination, and 6.7-67.4% for ≥ 2 microvascular screening procedures (data not previously published).

Figure 16. Estimated proportions of GPs within practices' diabetes patients with a) the albuminuria test, b) the monofilament test, c) a recorded eye examination, and d) ≥ 2 recorded microvascular screening procedures. Empirical Bayes estimates from three-level models with no covariate adjustments. The red line represents the 50th percentile of the estimated proportions

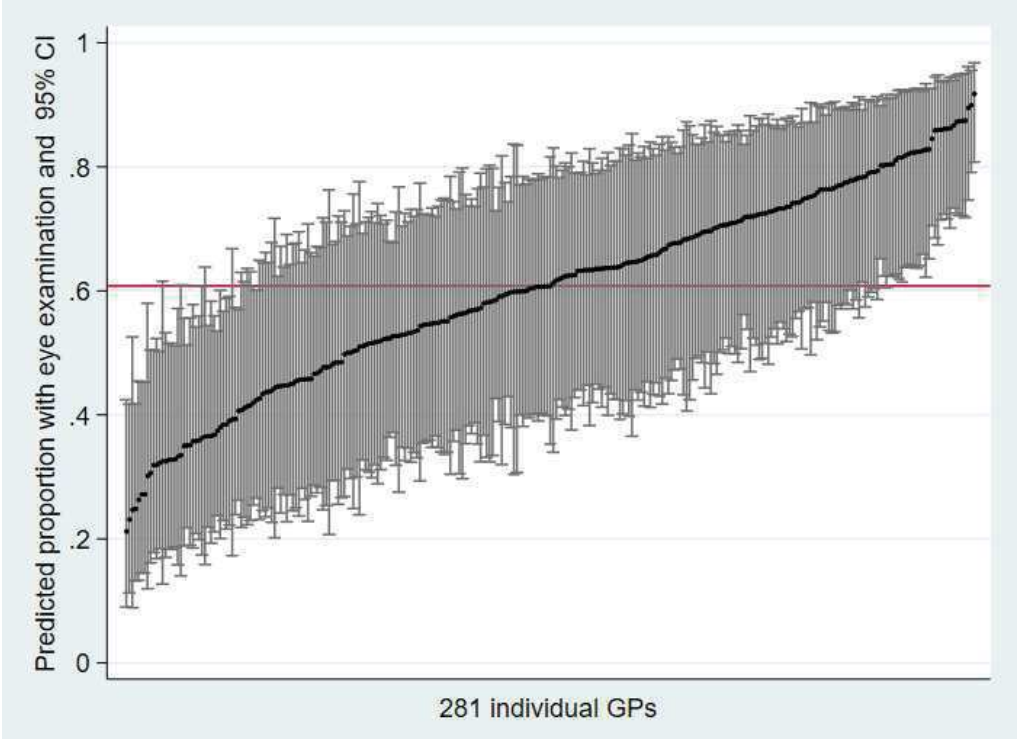
a) GPs' estimated proportions of patients tested for albuminuria



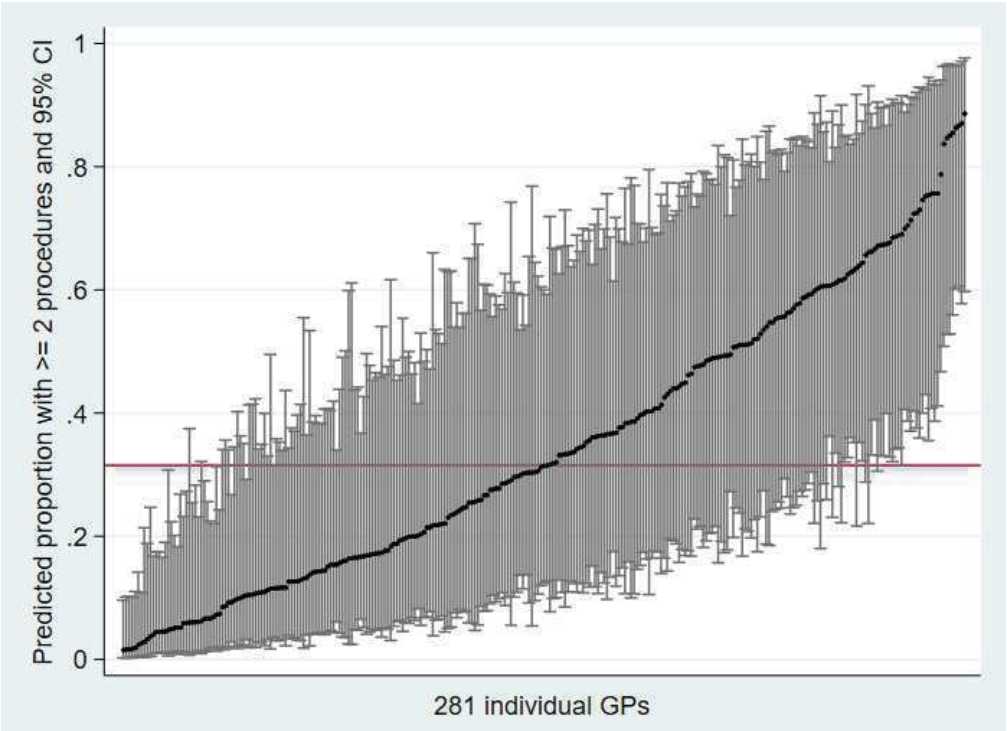
b) GPs' estimated proportions of patients tested with monofilament



c) GPs' estimated proportions of patients with recorded eye examination



d) GPs' estimated proportions of patients with ≥ 2 procedures



The unconditional ICCs for GPs within practices were 52% for the albuminuria test, 38% for the monofilament test, and 17% for eye examination, and 37% for the performance of ≥ 2 microvascular screening procedures (Supplementary Table S1, Paper 2). E.g., for the monofilament test, 38% of the total variation among patients, in the log odds of having a monofilament test done, was due to differences among GPs within practices. The heterogeneity was larger for the albuminuria test and smaller for eye examination.

The conditional ICCs from the fully adjusted models, showed that the residual variation for GPs within practices was moderately affected. E.g. the residual variance in the patients' probability of having an albuminuria test done that is attributable to differences between GPs within practices was reduced from 54% to 44% after accounting for GP and practice level variables. For the monofilament test, the corresponding reduction was from 41% to 23%, for eye examination from 21% to 8%, and for ≥ 2 microvascular screening procedures, from 42% to 25%. I.e. the included GP- and practice variables explained some of the cluster heterogeneity, but not all.

Similarly, patients treated by a well-performing GP at a well-performing practice had a median six times higher odds of having an albuminuria test done compared with a patient (with identical covariates) treated by a poorer-performing GP at a poorer-performing practice, MOR 6.1 (data not previously published, Table 7). The corresponding MORs for the monofilament test were 3.9, for eye examination 2.2, and for ≥ 2 microvascular screening procedures the MOR was 3.8. After adjusting for patient, GP and practice factors, the MORs were moderately reduced; for the albuminuria test the MOR declined from 6.5 to 4.6, for the monofilament test 4.3 to 2.6, for eye examination 2.4 to 1.7, and for ≥ 2 microvascular screening procedures the MOR declined from 4.3 to 2.7.

Outcome/explanatory variables	Median odds ratio (MOR)		
	Different GP, different practice	Same GP, different practice	Different GP, same practice
>=2 procedures			
Null model	3.8	2.8	2.3
Model with patient factors	4.3	3.1	2.5
Model with patient and GP factors	3.2	2.3	2.2
Full model	2.7	1.8	2.2
Albuminuria test			
Null model	6.1	4.5	2.7
Model with patient factors	6.5	4.8	2.8
Model with patient and GP factors	5.6	4.0	2.7
Full model	4.6	3.1	2.7
Monofilament test			
Null model	3.9	2.6	2.6
Model with patient factors	4.3	2.8	2.8
Model with patient and GP factors	2.9	1.9	2.3
Full model	2.6	1.5	2.3
Eye examination			
Null model	2.2	1.9	1.6
Model with patient factors	2.4	2.1	1.6
Model with patient and GP factors	2.1	1.7	1.6
Full model	1.7	1	1.7

Table 7. Median odds ratios (MORs) among general practitioners (n=281) and practices (n=77) in the performance of albuminuria, monofilament test, eye examination, and ≥ 2 recorded microvascular screening procedures in 8951 people with type 2 diabetes. Data unpublished.

In summary, we were able to explain the least of the variance due to GPs within practices for the albuminuria test, whereas we were able to explain more of the differences between GPs within practices for the monofilament test, and most of the differences for eye examination.

All the independent variables included in our full model (fixed effects) explained 20% of the variation in the performance of the albuminuria test ($R^2 = 0.20$), while fixed and random effects together accounted for 55% of the variation. Corresponding results for the monofilament test were 29% and 45%, for eye examination 20% and 27%, and for ≥ 2 microvascular screening procedures 26% and 45%.

5.3 Paper 3

The objective was to describe variation in the achievement of HbA1c, BP, and LDL-c targets, and assess factors associated with target achievement. Data from *n* = 9342 people with type 2 diabetes, *n* = 281 GPs, and *n* = 77 practices in 2014 were included in the analysis.

Among patients where HbA1c, BP and LDL-c were available for all (*n* = 7086), 64.1% achieved the HbA1c target, 50.0% the BP target, 52.2% the LDL-c target, while 17.4% met all three targets (Figure 17).

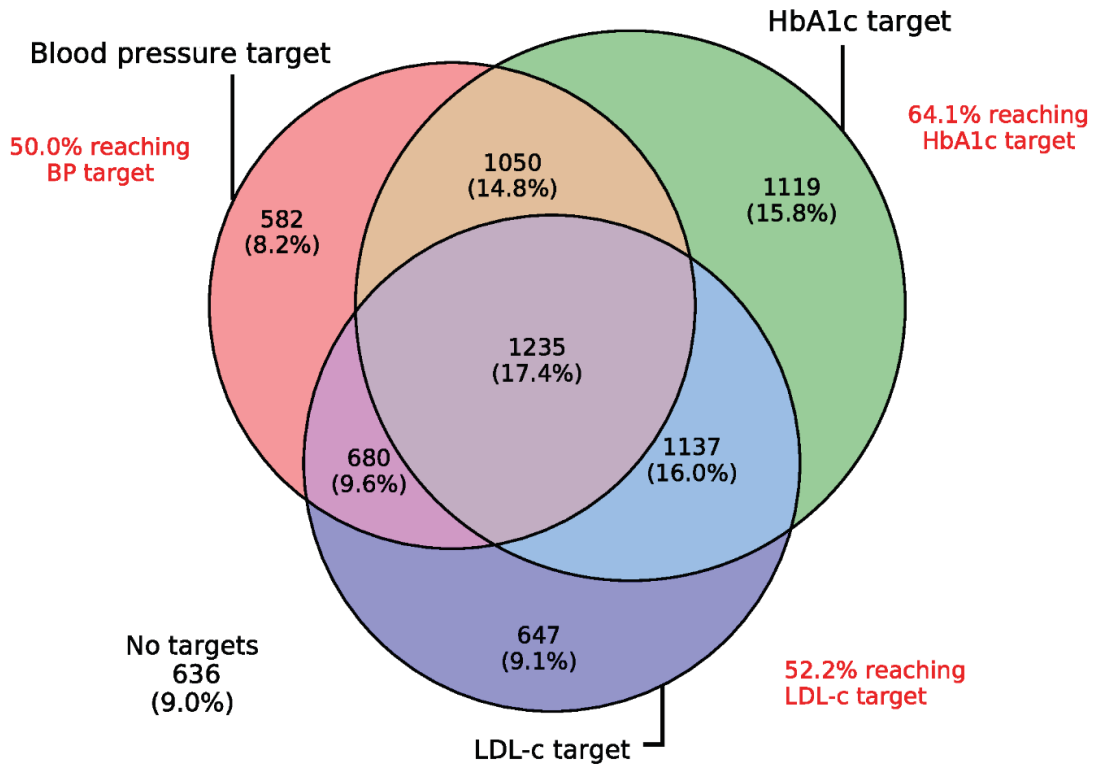


Figure 17. Percentage of 7086 people with type 2 diabetes achieving HbA1c, blood pressure and LDL-c targets. Bakke et al. (143). Reprinted with permission.

5.3.1 Factors associated with the achievement of treatment targets

Factors associated with the achievement of HbA1c target

People < 50 years were less likely to achieve the HbA1c target, compared with 60-69 year olds, OR 0.60. However, people 70-79 years, and those aged 80 years or older had higher odds of achieving the target, OR 1.36 and OR 1.26, respectively. Ethnic differences were observed, as South Asians had 34% lower odds of achieving the HbA1c target compared with Western Europeans, OR 0.66. Per 5 year increase in diabetes duration, the odds of being at target declined with 35%, OR 0.65. Further, obesity was associated with higher HbA1c-levels: People with BMI ≥ 30 kg/m^2 had 22% lower odds of achieving target, compared with BMI 25-29.9 kg/m^2, OR 0.78. On the other hand, those with a history of bariatric surgery vs. no surgery, had almost three times higher odds of achieving the HbA1c goal, OR 2.78. The only GP variable included in our study that was found to be associated with achievement of the HbA1c target was GP usage of a structured diabetes form. Patients attending GPs who were regular users of the Noklus diabetes form were more likely to being at HbA1c target, OR 1.23.

Factors associated with the achievement of blood pressure target

People ≥ 80 years, had 31% lower odds of achieving the BP target compared with 60-69 year olds, OR 0.69, while those under 50 years had higher odds of being at BP target, OR 1.49. There existed ethnic differences in target achievement: South Asians vs. Western Europeans had two times higher odds of achieving the BP target, OR 1.99. Further, obesity was associated with poor blood pressure control: People with BMI ≥ 30 kg/m^2 were less likely to achieve the target compared to those with BMI 25-29.9 kg/m^2, OR 0.76, while people with BMI < 25 kg/m^2 were more likely to achieve the target, OR 1.40.

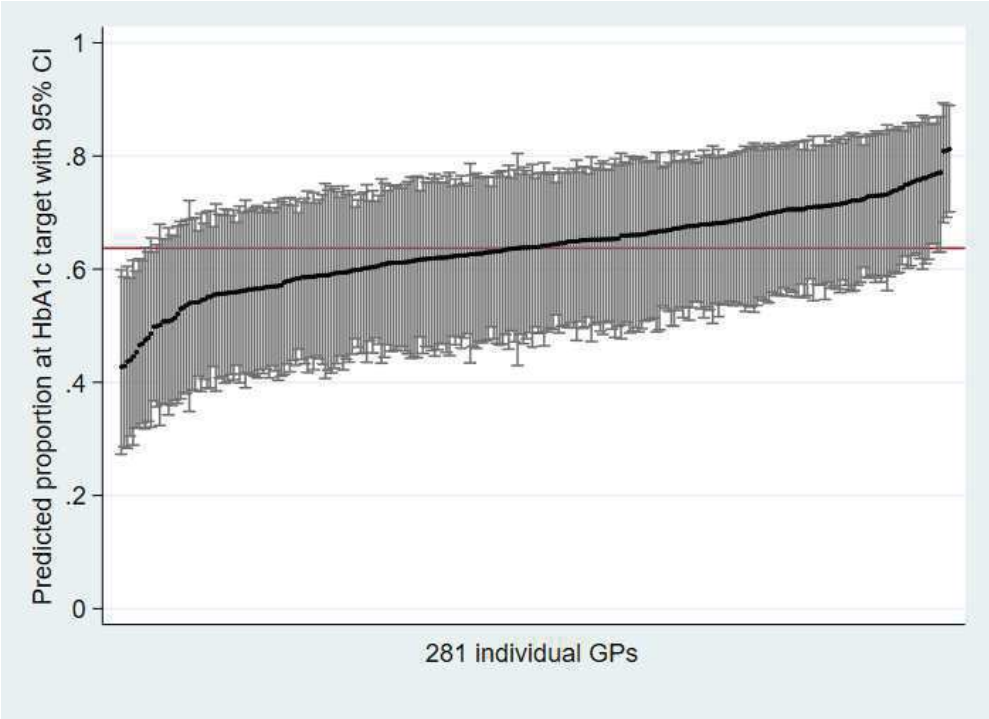
Factors associated with the achievement of LDL-cholesterol target

People with macrovascular disease had very low odds of achieving the LDL-c target, OR 0.20. Additionally, men were more likely to achieve the LDL-c target than women, OR 1.51. Per 5 year increase in diabetes duration, the odds increased by 18% of being at target, OR 1.18. The only GP factor in our study that was significantly associated with better lipid control was GP usage of the Noklus diabetes form. Patients treated by GPs who were regular users of the form had higher odds of being at target, OR 1.17.

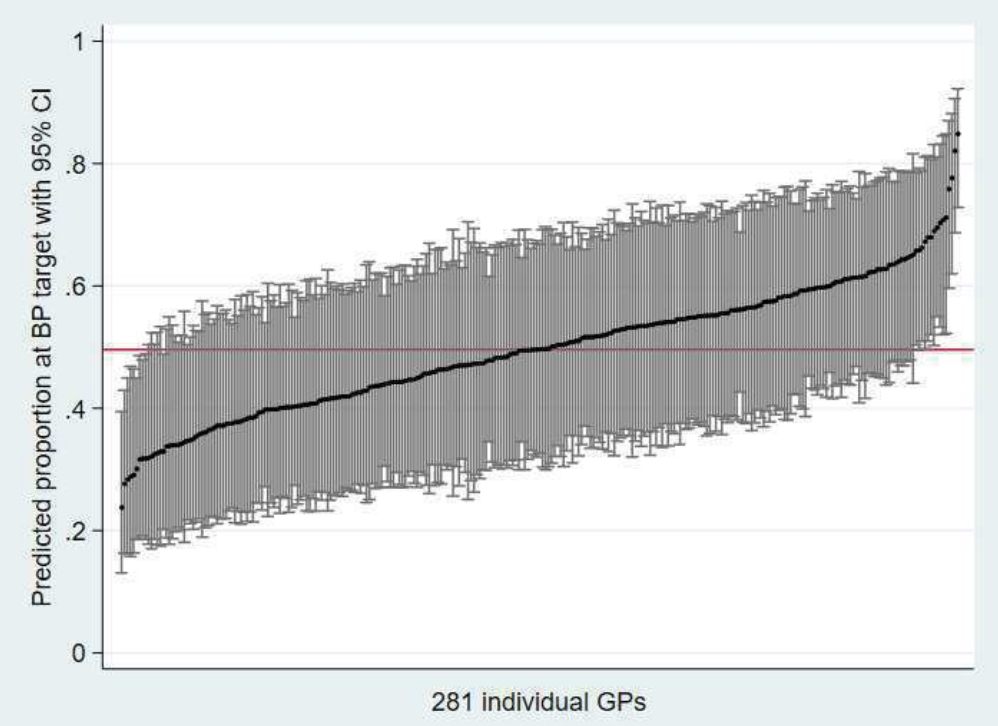
5.3.2 Variation in the achievement of treatment targets

We observed heterogeneity in the achievement of targets among GPs and among practices. Eighty percent of GPs within practices' patients were estimated to lie between 54.6 and 72.9% for the HbA1c target, 36.0-62.7% for the BP target, and 47.2-56.7% for the LDL-c target. The estimated proportions of GPs within practices' patients at target are shown in Figure 18 a-c. The variation was biggest for the BP target, and smallest for the LDL-c target.

(a) GPs' estimated proportions of patients achieving HbA1c target



(b) GPs' estimated proportions of patients achieving blood pressure target



(c) GPs' estimated proportions of patients achieving LDL-c target

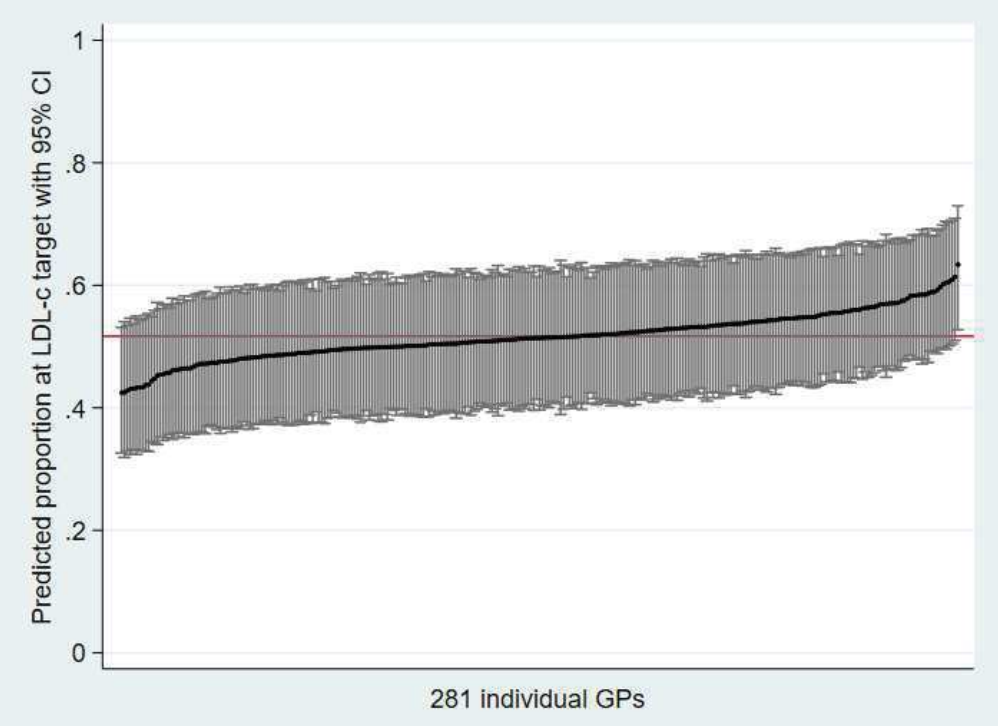


Figure 18. Estimated proportions of GPs within practices' diabetes patients at a) HbA1c target, and b) BP target c) LDL-c target. Empirical Bayes estimates from three-level models with no covariate adjustments. The red line represents the 50th percentile of the estimated proportions. Bakke et al.(143). Reprinted with permission.

The unconditional ICCs for GPs within practices were 5.3% for the achievement of HbA1c target, 7.0% for BP target, and 2.3% for the LDL-c target (Supplementary Table S3, Paper 3). E.g., for the HbA1c target, 5.3% of the variation between patients, in the probability of achieving HbA1c ≤ 7.0% (≤ 53 mmol/mol), was due to differences among GPs within practices. The heterogeneity was larger for the BP target and smaller for the LDL-c target.

The conditional ICCs from the fully adjusted models, showed that the included GP and practice variables explained little of the cluster heterogeneity.

Similarly, patients treated by a well-performing GP at a well-performing practice had a median 50% higher odds of achieving HbA1c target, MOR 1.50 compared with a patient (with identical covariates) treated by a poorer-performing GP at a poorer-performing practice. The corresponding MORs for the BP target were 1.61, and for the LDL-c target 1.28. After adjusting for patient, GP and practice factors, the MORs changed only slightly.

The coefficient of determination, R^2, was estimated for each final model in paper 3, and was fairly small. All the independent variables included in our full model (fixed effects) explained 11% of the variation in the achievement of HbA1c target ($R^2 = 0.11$), while fixed and random effects together explained 16% of the variation. Corresponding results for the BP target were 5% and 11%, and for LDL-c target 14% and 16%.

In summary, most of the variation in target achievement was between patients. We were able to explain little of the total variation.

6. General discussion

6.1 Methodological considerations

The main strengths of the studies are the size of the cross-sectional data, the thorough data collection by nurses with few missing variables, the possibility to adjust for socioeconomic factors by linkage with Statistics Norway, and the fact that we have available information on patient-, GP- and practice levels. This enabled us to assess the quality of care at GP- and practice levels in multilevel regression models.

To address the strength of our research methods, it is important to evaluate the validity of the study. Validity is to what extent the estimated associations are generalizable and unbiased, i.e. neither over- or underestimated (144). We usually distinguish between internal and external validity. Internal validity refers to the trustworthiness of the results in the included study population (the enrolled individuals) (144). External validity refers to how well the findings can be applied to other populations and other settings; i.e. are the findings representative for Norway, and are they generalizable to other countries, and other healthcare systems. The internal validity is a prerequisite for the external validity (144).

Several potential sources of bias might influence the internal validity of a study; selection bias, information bias, and confounding. Selection bias is present when the selection of individuals differs systematically from the population intended to be analysed, leading to a systematic error in an association. Information bias is also called measurement bias or misclassification bias (134). It occurs when key information is measured, collected, interpreted or classified inaccurately. Confounding bias occurs when the effect of confounders, i.e. variables that can influence both the dependent and independent variables, are not accounted for (134).

In the following we will address several methodological considerations regarding sampling, measurements and misclassifications, variable selection, treatment of missings, and modelling issues.

6.1.1 Sampling

There is always a possibility for misclassification of diabetes type. However, in ROSA 3 and 4, the type 2 diabetes diagnosis was based on the GPs' ICPC-code, and in case of ambiguity the research nurses could check the EHRs for supplementary information and sometimes specialist reports. Thus, the type 2 diabetes diagnosis has high reliability in our study. Further, the nurses followed a protocol for data collection so that data sampling should be consistent between the four nurses, i.e. reducing the chance of systematic differences in the registration of care processes, measurements and complications.

Residents at nursing homes, and people with main follow-up by diabetes specialists at outpatient clinics were excluded from the analyses as our intention was to study people with main follow-up in general practice. Thus, we may have excluded the most multimorbid people and those with the poorest glycaemic control. Consequently, our results cannot be generalized to these settings.

Whether or not the ROSA 3 and 4 samples are representative for Norway is debatable as the counties were not randomly selected and consist of less than 10% of the diabetes population and GPs in Norway. However, a variety of practices from urban and rural areas, and from districts with a high proportion of ethnic minorities and low socio-economic status were included. The location of practices spanned from the South to the North of Norway. Therefore, our study presents data from a "real-life setting".

On the other hand, 26% of the GPs included in ROSA 4 were defined as users of the Noklus diabetes form, which is a higher proportion than among GPs in Norway in general. The reason for this is probably that the use of the diabetes form has been campaigned by healthcare workers located in Hordaland, Nordland, and Rogaland. As we have found GP usage of the diabetes form to be associated with the performance of microvascular screening procedures, care processes might have been overestimated in our sample due to this selection.

To what extent the inferences can be generalized to other countries is restricted due to different healthcare systems and incentives. However, the achievement of treatment targets are similar to what has been found in other countries like Sweden, Scotland, and the UK (129, 130, 145), and some associations with care processes and treatment targets have also been observed in other settings, e.g. that young people are less likely to perform care processes and achieve targets (128), and poor achievement of the LDL-c targets among people with macrovascular complications (146).

Studies with insufficient sample sizes have increased risk of type II error (false negative findings) due to low power (147). In multilevel modelling, the number of clusters have been found to be more important than the number of observations per cluster (147). In our study we had 281 GPs at level 2 and 77 practices at level 3; which should be beyond sufficient for estimation of regression coefficients, variance components, and standard errors in linear multilevel models (148), while also ensuring good estimation properties in most settings in logistic modelling (149). With our large number of patients (at level 1), we were able to use a smaller significance level of 1% for level 1 fixed effects, while still having high power for detection of these effects (149).

6.1.2 Measurement errors and misclassifications

Misclassification is a form of information bias. By misclassifications we here mean either errors in classification of categorical variables or in measurements of continuous variables. There are two types of misclassifications; non-differential misclassification and differential misclassification (134). Non-differential misclassification occurs when the information is incorrect, but misclassified equally across groups so that bias goes toward the null (134). Differential misclassification occurs when the error in classifications differ between groups, so that associations might be over- or underestimated. Misclassification may occur both in outcome and explanatory variables, and be systematic or random.

Care processes: The time frame for data inclusion differed slightly between 2005 and 2014 for some variables (Paper 1, Table 4). Most of these differences in data inclusion were small, but the observed increase in monofilament test and recordings of smoking status observed, might be due to a longer inclusion period in 2014. Further, the definition of stroke differed, where TIA was included in ROSA 3, but excluded in ROSA 4. These differences must be taken into account when drawing conclusions regarding time trends.

Screening procedures for microvascular complications stood out as the processes of care with the biggest room for improvement (papers 1 and 2). However, we cannot be certain if the lack of recordings were true omissions of performance. It is likely that all laboratory results (including the albuminuria test) were registered. On the other hand, performance of the monofilament test was only registered if the GP had recorded it, or if the research nurses found results of a monofilament test in specialist reports from the last 15 months. However, it is unlikely that GPs have performed the monofilament test without recording it. For eye examination, a bias is more probable, as not all GPs may have received reports from the ophthalmologists, thus the performance of eye examinations may have been underestimated. How this bias might have influenced estimated associations is uncertain. Furthermore, if GP users of the diabetes form were more likely to register information in the EHR, the associations between GP usage of the form and the performance of care processes would be overestimated.

Medication: Data on the GPs' prescriptions were transferred electronically from the EHR to our data base. If specialists in hospitals prescribed some of the medication this may not have been registered in the EHR, in which case medication use would be underestimated in paper 1. In addition, we do not have information on the patients' compliance. If patients were non-compliant with registered medication, our estimates of use will be biased upwards. If receiving prescriptions from other than the GP, or compliance, is associated with other patient characteristics (e.g. poor health or

education), estimated associations with the outcomes in paper 2 may be biased due to differential misclassification.

Due to the rise in use of new antihyperglycaemic agents the recent years, our findings regarding medication are not generalizable to the current antihyperglycaemic therapy used by people with type 2 diabetes today.

Laboratory tests: Measurement errors might have occurred due to the use of different measurement methods, i.e. different lab-based and point-of-care systems. However, benchmarking by HbA1c results was rarely affected by measurement bias in Norwegian hospital clinics, regardless of the use of results from hospital laboratories or point-of-care devices, e.g. corrected HbA1c values were within ± 0.2% (2 mmol/mol) (150). In our study, measurements were based on the latest registered value. One single measurement may not be representative of a persons' true level. It could be argued that using a mean of several values would give a more precise measure of a person's true level, however, only the last registered measurement was available in our dataset. Furthermore, it is likely that the level for some measurements will change with time and thus the last value would serve better as an outcome.

Target achievement: In paper 3 we used the dichotomized outcomes for HbA1c, BP, and LDL-c rather than of a continuous outcome. Each measurement has its own variability, and the mentioned measurement error in e.g. HbA1c will transfer to misclassification of the dichotomized version. However, measurement bias had little effect on the proportion of patients achieving glycaemic targets in hospital clinics (150). Given small measurement errors in continuous outcomes, we assume that there will be little misclassification in the dichotomized outcomes, and consequently minor changes in effect estimates.

Demographics: Measurement errors in patient- or GP demographics are unlikely, as age and gender were known due to a personal identification number, and information

on education and ethnicity was accessed by linkage to Statistics Norway. Country of birth, country of medical education, and specialist status were self-reported for GPs, and we consider this information to reliable.

Practice related variables: The self-reported questionnaires were mainly completed by GPs and health care personnel in 2015, but some even in 2016. The few GPs who were included in 2016 have probably reported one additional year as a GP in Norway. The composite variable "ancillary staff with duties related to microvascular complication screening" might have been under reported for some practices, as the questionnaire only included specific questions regarding foot examinations, and a more open question if they had other responsibilities (not related to the albuminuria test or eye examination in particular). The open question could have been answered differently depending on the health personnel's memory, and time to complete the form, thus leading to misclassification. However, it is unknown how this could have affected the effect estimates.

6.1.3 Variable definitions

We had detailed information on country of birth on almost all participants. However, the ethnicity variable differed in papers 1-3. In papers 1 and 2 we dichotomized ethnicity as another peer planned to explore differences in ethnicity in ROSA 4 in another subproject. However, she found no ethnic differences in care processes (data not published). In paper 3 we found it necessary to divide ethnicity into three categories and adjust for this variable as previous research has shown that in particular South Asians have different age at diabetes diagnosis, glycaemic control, and risk of CVD (151). If we had not adjusted for being South Asians in paper 3, it could have led to confounding bias in the effect estimates of the other explanatory variables for HbA1c, and BP.

Medication variables at the patient level were introduced as explanatory variables in paper 2, but excluded in paper 3. Medication is probably one of the strongest mediators for the achievement of treatment targets in individual patients. GPs play an important role in the achievement of targets, as they prescribe the medication. Thus, a GP variable describing a "good prescriber" would be of great value in the regression model in paper 3. However, it is challenging to define a good GP prescriber, not the least based on cross-sectional data, as prescription patterns are best studied with longitudinal data. When we studied factors associated with the achievement of targets, the HbA1c-, BP-, and LDL-c measurements could be both a reason for prescriptions and an effect of prescriptions, and therefore we excluded medication from the analysis. However, the inclusion of such a variable would probably have led to higher R^2.

The use of the Noklus form was set as a GP level variable. A GP was defined as a user if the form was more than 50% completed in ten or more people, or more than 50% of their patients with type 2 diabetes. This is not a strict criteria for being a user of the form. The associations with a GP user and the outcomes could possibly be stronger if we had used a stricter criteria for GP usage of the form.

In paper 2 we classified "total no. of persons on GPs list per day worked each week" into three categories. In paper 3, we chose to add another category that included the official mean number of list patients in Norwegian general practice, and used this category as a reference. This classification is probably easier relatable for the Norwegian general practitioners, but does not necessarily influence the results. Further, "the number of list patients per full-time ancillary staff" was used on a linear scale in paper 2, but categorized in paper 3 as the effects on target achievement were non-linear.

Multicollinearity is problematic as it underestimates the statistical significance of explanatory variables (see 4.6.1, p. 53, Multicollinearity) (134). To avoid multicollinearity we checked the VIFs for the explanatory variables. As years as a GP in Norway naturally is correlated to GP age, we chose to dichotomize the former variable to evaluate the effect of being a less experienced GP. Both variables then had an acceptable VIF below 3.5. Similarly, a correlation between the GPs' country of birth and country of education is likely, however the VIFs were below two probably because a proportion of Norwegians are educated abroad, and thus we decided to keep both variables. The majority of rural inhabitants and diabetes nurses were located in the Nordland County. The VIFs for urban/rural and diabetes nurse present/not were about three, and the VIF for Nordland County was about four, indicating moderate multicollinearity. We chose to omit urban/rural and diabetes nurse present/not in paper 3 while keeping the adjustments for counties.

Confounding is mainly a problem when studying causality. The cross-sectional design of our study prohibits any claims of causality. Even if the direction of an effect is given by logic, the true causal effect of any given variable may not be reflected in our estimates due to the concomitant inclusion of variables that may act as mediators or colliders for the variable, or due to the omission of confounders. To consider confounding variables, mediators and colliders, it is recommended to develop directed acyclic graphs for each explanatory variable, which would normally result in one and only one model being correct for the study of the effect of each explanatory variable; i.e. interest in the effects of q explanatory variables would require the analysis if q different adjusted regression models. As we have multiple explanatory variables on several levels, this would be far too comprehensive to do. Thus, we cannot exclude confounding bias in our analyses. In particular, we lack extensive information about socioeconomic status, which may have influence on compliance and thereby on the possibility of performing procedures and of reaching treatment targets, and at the same time may be related to explanatory variables like BMI, smoking status, and macrovascular complications. Furthermore, it is important to notice that some of the total effects of e.g. sex and age may be hidden due to the

inclusion of variables that mediate some of these effects. On the other hand, we have tried to avoid including explanatory variables that may be results of the outcomes (e.g. medication), thus colliding bias should not be a great concern.

6.1.4 Handling of missing data

The EHR for each patient was scrutinized by research nurses, thus the amount of missing data has been minimized. However, about half of the population lacked a measurement for height or weight, thus BMI could not be calculated. This might be due to selective measurement, i.e. if the patient does not appear overweight, BMI might be given no attention during the consultation. BMI is particularly important in people with type 2 diabetes, and by omitting this explanatory variable in paper 2, we could not measure the effect of BMI, and BMI could not be adjusted for in the analysis. We performed a sensitivity analysis (not published) for each of the three microvascular screening procedures (n = 8246 patients), with all the patient characteristics included in the full model in addition to a dichotomized variable "known with BMI >30 kg/m^2" assuming that the GPs would have recorded BMI if it was a problem. "Known with BMI > 30 kg/m^2" was significantly associated with the performance of microvascular screening procedures (albuminuria OR 1.37, monofilament test OR 2.26, and eye examination OR 1.30), but the effect estimates for the other explanatory variables did not change, except for one variable "born in Western Europe" that was no longer positively associated with the monofilament test. However, it is probably not correct to assume that all the people with missing BMI have a normal weight, and consequently we excluded "known with BMI > 30 kg/m^2" from the main analysis in paper 2.

Further, in paper 2 we excluded 705 patients in the regression models due to missing data on diabetes duration, ethnicity and education. We assume that at least some of these had a diabetes duration of less than one year and would have been excluded anyway. The missingness of the two latter variables was not suspected to be related to diabetes as they were gathered by linkage to Statistics Norway.

Due to missing observations, some variables in paper 2 were defined as “registered with risk factors”. This way of handling the missing data in the regression analysis, was done as the purpose was largely to study GP behaviour (i.e. performance of care processes, yes/no), and if some explanatory variables should have an influence on GP behaviour, they would probably be known to the GP, and registered. However, some of the people with missing observations may have been misclassified, leading to incorrect effect estimates.

In paper 3 it was not natural to use variables “known with risk factor”. Seven percent of the data regarding patients was missing, but a complete case analysis would have reduced the data set by 62-65%, i.e. with a risk of inducing bias. Thus we opted to impute the missing values by MICE. The model for each imputed variable included all variables in the final model and a range of auxiliary variables either predictive of the variable itself or of the missingness. Consequently, the imputation lowered the risk of bias due to data missing not at random. The 100 imputed data sets give good estimates of the uncertainty pertaining to the imputation process. Further, by imputing missing values for the outcome variables (HbA1c, BP and LDL-c targets) bias from outcome variables missing not at random might have been prevented (140).

6.1.5 Modeling issues

All analyses allowed for clustering. If we had ignored the correlation between patients within the same cluster, confidence intervals would be too narrow due to underestimated standard errors. Correspondingly, p-values would be too small.

Paper 1: The aim was to assess status of diabetes care in 2014 and time trends, and not to study the components of variance at different levels. Therefore, we simplified the regression analysis by merely accounting for clustering by using sandwich-estimates of standard errors (see 4.6.2. p. 59, Alternative way of accounting for clustering). It was only possible to specify one level of clustering, and we used the highest level as recommended.

Papers 2 and 3: A three-level analysis allows us to analyse patient heterogeneity in outcomes, while considering the contextual variance, i.e. differences between GPs and between practices (152). "The multilevel approach represents an improved method for evaluation healthcare provider performance" (152). The use of this analytical method is a strength of our study.

6.2 Discussion of the results

6.2.1 Time trends and status 2014

Healthcare systems and resources regarding diabetes care differ across Europe, and even between the Scandinavian and other neighbouring countries. The major discrepancy was care processes for weight, albuminuria, foot examination and eye examination that were considerably lower in Norway than in Sweden, Scotland and the UK (129, 130, 145). In paper 1 we discussed the performance of microvascular screening procedures with results from the 2014 annual report in the Swedish National Diabetes Register (130). After publication, we became aware that in this report missings were excluded, while we in our study defined missing cases as non-performers. By comparing our cases of performed procedures with 2014 results in "Knappen" in the Swedish National Diabetes Register where all patients including missings are reported (as opposed to the annual report), there were still considerable differences between Norway and Sweden; recording of weight 52 vs. 89% in Sweden, albuminuria 31 vs. 69%, foot examination, 28 vs. 71%, and eye examination, 62% last two years vs. 71% last three years. Fewer people in Norway (< 90 %) had measured HbA1c and BP as compared with Sweden (≥ 95%), and fewer had a record of smoking habits, 80% in Norway vs. 85% in Sweden. Differences in screening procedures between the countries are most likely due to the fact that we compare non-registry data with registry data. In Norway, the majority of GPs have no specific form to complete other than to report findings in "free text", with the exception of medication and laboratory examinations. In national diabetes registers health personnel fill in information in a form, and data are most often transferred directly

from the health record systems. Furthermore, unlike Norway, most GP practices in Sweden, Scotland and the UK have employed diabetic specialized nurses, and the incentives in diabetes care differ.

Although care processes were measured more frequently in the nationwide diabetes registers, risk factor control was fairly similar in Norway and Sweden, with mean HbA1c 7.0% (53 mmol/mol) vs. 7.1% (54 mmol/mol) in Sweden, BP 135/80 mmHg vs. 135/76 mmHg and LDL-c 2.8 mmol/L vs. 2.6 mmol/L, except that more people achieved LDL-c < 2.5 mmol/L in Sweden (52.6%) than in Norway (42.1%). However, in 2014 intervention threshold for LDL-c was 3.5 mmol/L in Norway, so it is not justifiable to compare the achievement of this target in ROSA 4. Nevertheless, we must keep in mind that the results in Norway are based on adjusted values for ~ 10 000 people in Norway with possible selection bias and unadjusted values for > 300 000 people in the NDR with almost 100% coverage of the type 2 diabetes population.

Between 2005 and 2014, the proportion with an HbA1c measurement declined while the proportion with an LDL-c measurement increased. Naturally, LDL-c measurements increased as LDL-c targets were incorporated in the national guidelines from 2009. Concurrently, only a small proportion were screened for diabetic kidney disease and diabetic peripheral neuropathy. The performance of the albuminuria test remained unchanged in 2014 compared with 2005, although the importance of screening has been emphasized through research (11, 22) and in evidence based guidelines (25, 54, 55, 153). Similar low rates have been observed in other European countries (154). GPs in Norway receive fees for the albuminuria test if it is analysed at the office, but apparently incentives are not enough. Our study showed that people attending practices with a reminder system for annual diabetes review had almost three times higher odds of having an albuminuria test performed. The performance of foot examinations seemed to increase the last decade, but the data inclusion period was three months longer in 2014 than in 2005, so the true rate of recordings is uncertain Nevertheless, there was a large gap between the proportion

with an annual monofilament test and national and international recommendations (25, 55, 153). Norwegian GPs do not receive additional fees for foot examinations. The introduction of a standardized foot screening program in general practice, together with administrative support, increased community podiatry staffing, hospital multidisciplinary foot clinics, and easier access to delivery of these foot care provisions, reduced the incidence of foot ulcers and lower limb amputations in South England (38, 39).

We observed a small reduction in mean HbA1c, a moderate reduction in BP and total cholesterol, with more people achieving targets in 2014 compared with 2005. However, still ~ 50% on antihyperglycaemic agents and ~ 60% on antihypertensive agents were not at HbA1c and BP targets. As much as 70% of people with a history of CHD had not achieved the recommended LDL-c target of 1.8 mmol/L. All in all, only 17% of the population achieved all three targets. With knowledge from the Steno-2, BARI 2D trials, and the comprehensive analyses from Sweden where the importance of multifactorial intervention are shown (71, 95, 101), further improvement in target achievement in Norway would be highly beneficial to reduce CVD and CV death. Furthermore, the introduction of novel antihyperglycaemic therapies with SGLT2i and GLPi will probably contribute to reductions in MACE in the future as shown in recent large cardiovascular outcome trials (72). Only 3% of the population used each of these drugs in ROSA 4.

Another issue regarding target achievement that we have not accounted for, is that of individualized medicine. National and international guidelines recommend tailored targets for HbA1c, BP, and LDL-c depending on personal preferences, age, diabetes duration, micro- and macrovascular complications, comorbidities, risk of polypharmacy, and life-expectancy (55, 153, 155, 156). GPs have probably used a personalized approach for years, and this can partly explain the apparent failure to achieve the given treatment targets. On the other hand, we found that people aged 80 years or more might be over treated, as they were twice as likely to achieve the

HbA1c target as those under 50 years old. The same age groups had similar odds of achieving the LDL-c target. Nevertheless, tailored targets are a challenge when assessing the quality of care in research. A personalized approach led to a higher proportion of patients considered to be cardio metabolic well-controlled in the Netherlands (115).

The percentage of daily smokers declined in the general population in Norway, from 25% in 2005 to 13% in 2014 (aged 16 to 74 years) (157). However, this trend was not seen in adults with type 2 diabetes in the ROSA-studies, where data showed 25% current smokers in 2005, and 23% in 2014, with the highest proportion of smokers < 60 years. The results may have been overestimated due to different registration periods in ROSA 3and 4 (registered as current smokers if recorded yes the last 3 vs. 5 years). The registration period may also differ from other countries, as the prevalence of smokers among people with type 2 diabetes in Sweden and Scotland in 2014, were 15% and 18%, respectively (130, 145). Smoking is an independent risk factor of CVD and CV death, and cessation should be strongly encouraged (71, 85).

The prevalence of CVD was similar to what has been found in other European countries (48). There were no significant reductions in people with a history of coronary heart disease between 2005 and 2014, and the percentages with cerebrovascular disease were not comparable in the study years due to different definitions of stroke. However, from Sweden we know that between 1998 and 2013 there was more than a 20% risk reduction in non-fatal cardiovascular events in people with type 2 diabetes compared with matched controls (158). Correspondingly, there was an improvement in risk factor control in Sweden (158), similar to findings from Norway in the much smaller ROSA-studies in the same period (110, 159).

6.2.2 Factors, care processes and treatment targets

Only one in eight had performed all three microvascular screening procedures, and only one in four had achieved treatment targets for HbA1c, BP and LDL-c. We wanted to assess factors associated with the performance of microvascular screening procedures, and with treatment targets.

Two factors were negatively associated with both care processes and target achievement; age < 50 years, and a history of macrovascular complications;

Young age < 50 years: The fact that screening procedures have been performed less frequently in young people, and that they are less likely to achieve the HbA1c target is not a new finding. In the annual report from the UK National Diabetes Audit 2014, those < 40 years received less annual care processes and were much less likely to achieve treatment targets for HbA1c, BP and cholesterol, and this continued to be the case in 2017-18 (128, 129). Another study showed that people with type 2 diabetes < 55 years of age have a doubled risk of all-cause-mortality and cardiovascular death compared with controls, even with HbA1c < 6.9% (52 mmol/mol) and normoalbuminuria (52). For each risk factor outside target (HbA1c, BP, LDL-c, albuminuria, smoking), the risk of CVD, death and hospitalization for heart failure increased, with the greatest excess risk in people with type 2 diabetes and age < 55 years compared with matched controls (71). Therefore, health authorities and health personnel must focus on the youngest age group with diabetes, and try to convince them of the importance of compliance to lifestyle changes, medication and annual review.

Macrovascular complications: Our analyses showed that people with a history of macrovascular complications were less likely to have all three microvascular screening procedures performed, and they were less likely to achieve the LDL-c target. A similar low proportion at LDL-c target was found in the NHANES and EUROASPIRE IV (28% in both studies) (146, 160). However, people with concomitant polyvascular disease (i.e. coronary, peripheral, or cerebrovascular

disease) and type 2 diabetes have a very high cardiovascular risk (84). Results from the IMPROVE-IT trial implied that LDL-c target in high-risk groups should be even stricter than the current target of 1.8 mmol/L to reduce myocardial infarction, stroke and cardiovascular death (83, 84). The most recent guideline from the European Society of Cardiology recommend an LDL-c target of < 1.4 mmol/L in people with type 2 diabetes at very high CV risk (54). Therefore, adequate treatment intensification to reduce LDL- c, especially among people with diabetes and macrovascular disease, should be advocated in Norwegian general practice.

Ethnicity: South Asians had lower odds of achieving glycaemic control, but higher odds of achieving BP and LDL-c targets compared with Western Europeans/North Americans. South Asians are known to have generally poorer glycaemic control than Westerners, with an increased risk of developing diabetic retinopathy and diabetic kidney disease (151). Thus, it is suggested that this ethnic group could benefit from a stricter blood pressure target of less than 130/80 mmHg (151).

Diabetes duration: People with long diabetes duration were less likely to have the albuminuria test performed. Even early studies such as UKPDS revealed that diabetes duration and progression to albuminuria was closely related (14). We found a strong and negatively association between disease duration and the achievement of HbA1c target which is also reported in other studies (56). On the other hand, the longer time since diagnosis, the higher the odds were of achieving the LDL-c target. The latter is probably due to the introduction of lipid-lowering therapy as years go by.

No antihyperglycaemic agents: People with lifestyle-modification only had low odds of being checked for possible microvascular diabetes complications compared with people on antihyperglycaemic therapy. GPs may not prioritise to screen people with a recent diabetes diagnosis and without antihyperglycaemic medication for microvascular complications. Nevertheless, microvascular complications can be

present in newly diagnosed people (13, 97, 161) , and guidelines advocate screening for microvascular complications at the time of type 2 diagnosis, and with annual follow-up (25, 54, 55, 153).

BMI: BMI calculations were not included in paper 2 due to a large amount of missing values. However, when we imputed missing patient-level characteristics in paper 3, we were able to study the effect of BMI levels on target achievement. We chose to use BMI 25-29.9 kg/m^2 as the reference group rather than "normal weight", as mean BMI in 2014 was 29.2 kg/m^2. People with obesity (BMI ≥ 30 kg/m^2) had lower odds of achieving the HbA1c- and BP targets. The relation between obesity, insulin resistance and hypertension is well-established (162). A study from the Swedish National Diabetes Register found that long-term mortality in people with type 2 diabetes increased stepwise from a BMI of ≥ 30 kg/m^2, with a doubled risk among people with BMI ≥ 40 kg/m^2 (163). On the other hand, initial weight loss within the first year of diabetes diagnosis was associated with reduced incidence of CVD in the ADDITION-Cambridge trial (89). Furthermore, bariatric surgery is an accepted treatment of obesity. We found that bariatric surgery was a strong predictor for good glycaemic outcome, and this is in line with a systematic review of RCTs looking at the effects of bariatric surgery vs. medical treatment in type 2 diabetes (164).

GP factors: Several GP factors were associated with microvascular screening procedures. Increasing GP age was negatively associated with the performance of the albuminuria and the monofilament test. On the other hand, specialist in general practice were associated with higher performance of the albuminuria test, and of the recording of eye examinations. In addition, GPs with responsibility for ≥ 25 vs. < 25 patients with diabetes were associated with higher recordings of eye examinations. GPs with longer patient lists were less likely to perform the monofilament test. It is an ongoing debate in Norway that GPs in general have too many tasks and responsibilities, and too many working hours (105, 165). This is also an international challenge, as a qualitative systematic review, mainly from the USA and Europe,

stressed that GPs "struggle to meet evolving treatment targets within limited time and resources, and are frustrated with resulting compromises" (166). Furthermore, in qualitative interviews of 25 GPs in Norway, the GPs experienced negative consequences for themselves, and for their patients, when they felt obliged to apply a variety of single disease guidelines in multimorbid patients (167).

GP usage of the Noklus diabetes form was strongly associated with the performance of the monofilament test, and to a lesser extent to the recordings of eye examinations. Furthermore, people attending GP users of the form, had higher odds of achieving the HbA1c- and LDL-c target. Web-based diabetes forms have previously been shown to improve process indicators in previous studies (168, 169), without any effects on metabolic control (169). Our results strongly support the use of a structured diabetes form.

Practice factors: We found that good routines at the practice was a strong predictor for having the albuminuria test performed, and to a lesser extent the monofilament test. Therefore, the implementation of reminder systems for annual diabetes review at every practice in Norway is highly recommended.

6.2.3 Variation in diabetes care

Variation in care processes and target achievement between regions, with the largest variation in the performance of the albuminuria test, and moderate variation in the achievement of targets was observed in annual reports from Sweden and UK (12, 128-130). This is consistent with our findings illustrated in the caterpillar plots of EB estimates (see 5.2.2 and 5.3.2), although in our study both the albuminuria test and the monofilament test were associated with poorer performance, and greater variation.

In this thesis, we have investigated the variation in care processes and target achievement further, by assessing variance at GP- and practice levels in empty

models and in adjusted models expressed as ICCs, and heterogeneity between GPs within practices expressed as MORs.

Thirty-six percent of the variation (ICC = 36%) in a persons' predicted probability of having an albuminuria test performed was due to differences between practices, and 16% was due to differences between GPs. The unconditional ICC for the albuminuria test was 16.5% for hospitals in the Danish Adult Diabetes Database in a two-level logistic regression analysis in 2013, with a compliance rate of 96% (152).

Correspondingly, 38% of the variance in a persons' predicted probability of having a monofilament test performed was due to differences between GPs within practices, with an evenly distribution of the contextual effects of GPs and practices. For comparison, we have not found ICCs for the performance of foot- or eye examinations in other studies.

GPs act as gatekeepers for eye examinations to be performed, and the contextual clustering (i.e. differences between GPs and between practices) was lower than for the other microvascular screening procedures; 6% for GPs and 11% for practices. A two-level study from UK suggested that practice level factors play an important role in determining rates of eye examinations (170).

The high unconditional ICCs and MORs for the performance of microvascular complication screening, imply that GPs and practices with low performance rates should be targeted in quality intervention strategies. After adjusting for GP- and practice factors the ICCs and MORs for the performance of the albuminuria test and monofilament test were moderately reduced, while we were able to explain all the variance attributed to differences between practices for eye examinations.

The performance of the albuminuria test might increase with organizational changes at the practice, e.g. by introducing routines for annual testing at the practice. A retrospective study from USA demonstrated that testing for albuminuria was underutilized, and consequently the presence of CKD was substantially under-diagnosed among people with type 2 diabetes in general practice (171).

Implementation of a National Quality and Outcome Framework in the UK doubled the testing for albuminuria (172).

Both GPs and practices should be targeted to increase the rate of monofilament testing. In particular the use of a structured diabetes form reminds the providers to perform the recommended procedure. Whether or not the low rate of monofilament testing is associated with increased foot ulcers and amputation in our population remains unknown. However, improved diabetic foot services have been shown to reduce the incidence of foot ulcers and major amputations in South England (38, 39).

To enhance the recordings of eye examinations, ophthalmologists' reports should be available for all GPs, the use of the diabetes form should be increased, and ancillary staff could be more involved in checks of performance and need of referrals. Delayed eye examination has been shown to increase the rate of proliferative retinopathy (42).

Although the EB estimates showed that variation in the performance of microvascular screening procedures between GPs within practices was large (see 5.2.2), the variation in target achievement was smaller (see 5.3.2). Correspondingly, the unconditional ICCs and MORs for care processes ranged from ICC 17-52% and MOR 2.2-6.1, compared with much smaller ICCs 2-7% and MORs 1.3-1.6 for target achievement. HbA1c, BP and LDL-c are some of the main risk factors of CVD and premature mortality (71), and low provider variance "indicate a homogeneous clinical practice for a given level of care" (152). Similarly sized ICCs for the achievement of treatment targets have been found in two-level studies in UK, Sweden, and USA (173-175), and in one three-level study (176). Consequently, most of the variance in the probability of achieving targets are at the population level. However, the low variance at GP and practice levels should not lead to the assumption that GPs and practice factors are not important. The variance explained by GPs and practices, as quantified by the ICCs, is not quite the same as the effect of GPs and practices. Mercuri proposed that "the source of a small proportion of the total variation can be important if that variation is large enough or is related to a medication or procedure that is used by a large population of patients"(131). Recent large studies from the UK

have shown wide variation at the practice level in the prescriptions of newer vs. older antihyperglycaemic therapies with effect on HbA1c outcome (177), and management of hypertension (178). The latter study has a very direct title; “Variation in the diagnosis and control of hypertension is not explained by conventional variables”, and they conclude that a marked variability existed even after adjustments for age, gender, ethnicity, comorbidity, social deprivation, region and practice size (178). This is in line with our findings. The ICCs and MORs for all treatment targets barely changed after adjustments for patient-, GP- and practice level factors.

A systematic review on variation research showed that few studies focused on the cause of variation (179). A recent two-level observational study from 89 general practices in UK examined several practice characteristics possibly associated with care processes and target achievement (173). Only few practice variables had significant associations with the outcome, and after adjusting for these variables, there was still substantial heterogeneity between practices. We performed a detailed analysis with several patient, GP- and practice factors. Nevertheless, our models explained little of the total variation in the performance of microvascular screening procedures and achievements of targets. However, we explained much more of the total variation in care processes than in target achievement. Twenty percent of the total variation in a persons’ probability of an outcome was explained for the albuminuria test, 29% for the monofilament test, 20% for eye examinations, 11% for the HbA1c target, 5% for the BP target, and 14% for the LDL-c target.

6.2.4 What matters?

So what really matters in the quality of care? What have we not been able to measure in our papers? Let us go back to Donabedian's model of how quality of care can be assessed: Structure, process, and outcome. Quality of care depends on the health care system, practical and interpersonal performance of practitioners, and on patient contribution (111).

We observed that the greatest variation in both care processes and target achievement was at the patient level. Poor medication adherence is suggested to be responsible for 75% of the discrepancy between medication effectiveness in randomized trials and the real world (180). Another contributor is clinical inertia, where GPs fail to initiate or intensify medication when indicated (181, 182). Clinical inertia can explain variation both at the patient- and GP level, as people may bargain with their GP to delay therapy (183). Patient-reported barriers associated with poor HbA1c-, BP- and LDL-c control were low frequency of glucose monitoring, non-adherence to medical advice and prescriptions, perceived low therapy efficacy, low utilization of primary care (184), and lack of perceived support from family and their GPs (185). None of these factors were included in our models.

We have explored the performance of GPs regarding care processes, and in particular microvascular screening procedures. The GP specialist status, GP age, workload and the GP use of a structured form had an effect on the process outcomes, but only the latter was of some relevance in the achievement of treatment targets. Mercuri quotes some relevant statements regarding the physician being a source of variation (131); Citations of Wennberg, "medical service provided is often found to be as strongly influenced by subjective factors related to the attitudes of individual physicians as by science" (186) and "variations appears more likely to be associated with differences in beliefs among physicians concerning the indications for, and efficacy of, the procedure" (187). Further, Djulbegovic argues that "most variation in care is a result of the way physicians make their decisions" (188). Information on the interpersonal performance and the reasoning for decision making have not been accessible in our data. However, it is important to discriminate between unwanted variation, and

variations that exist for good reasons (131). Justified variation could be caused by comorbidities, short life expectancy, and personalized treatment according to individual preferences (115). A systematic review of qualitative studies identified the following GP barriers to effective diabetes management; limited time and resources, poor confidence in knowledge of guidelines and skills and in facilitating behavioural change in patients (166).

In this thesis, practice level variables represent the healthcare system. We found that practices with routines for annual review and a system for sending reminders to people who did not meet for scheduled appointment had higher odds of performing microvascular screening procedures. This is consistent with findings from a systematic review of qualitative studies where they suggest that "high-performing practices may be those with better structured management systems, access to specialist teams, and shared awareness of guideline recommendations" (166). Another author states that "the large variation in care processes emphasize the importance of structured diabetes follow-up programme in each practice" (189). In Scotland, Sweden and UK, diabetes related care processes were much higher than in Norway, and these countries have political and financial systems that enhance diabetes registries (129, 130, 145). Further, nurses play an important role in the diabetes care in these countries. Process indicators improved in diabetes teams with a nurse (190), and patients were more likely to complete an annual cycle of care (191). Some studies have also shown an improvement in outcome indicators with the involvement of a diabetes nurse (124, 125), while others have not found any associations (190, 191). A systematic review of RCTs showed that the glycaemic control in nurse-led clinics were comparable to those led by doctors (192). Willis et al. (173), suggested that much of the variation in diabetes related care processes and target achievement in GP practices was probably attributable to disparities in clinical and organisational behaviour that they had not been able to measure.

7. Conclusion

This doctoral thesis identified moderate improvements in the achievement of HbA1c, BP and LDL-c targets among people with type 2 diabetes in general practice between 2005 and 2014. However, there were major gaps between recommended and recorded screening procedures to detect microvascular complications. There was substantial variation in the performance of the processes of care between GPs and between practices, and to a lesser extent in the achievement of treatment targets. We found several factors associated with care processes and risk factor control. On the other hand, our models explained less than 30% of the total variation in microvascular screening, and less than 15% of the total variation in the achievement of targets.

In 2014, only one in eight had performed all three microvascular screening procedures (albuminuria, monofilament, and eye examination) as recommended in national guidelines, and only one in five achieved all three treatment targets for HbA1c, BP and LDL-c. Microvascular complication screening procedures were less often performed in people < 50 years of age, in people with short diabetes duration and/or no antihyperglycaemic agents, and in those with established CVD. Older GPs were associated with lower performance of the albuminuria test and monofilament test, and GPs with higher workload was negatively associated with monofilament testing. People treated by GPs who were regular users of the Noklus diabetes form had almost five times higher odds of having a monofilament test performed, and also higher odds of a recorded eye examination. Furthermore, patients attending practices with routines for annual follow-up had about three times higher odds of having an albuminuria test performed, and two times higher odds of having a monofilament test performed.

The HbA1c target was less likely achieved in people aged < 50 years, in people with long diabetes duration, and in those with obesity. The BP target was less often achieved in people with obesity, and the LDL-c target was less often achieved in those with known CVD. People attending GPs who were regular users of the Noklus diabetes form were more likely to achieve the HbA1c- and LDL-c target.

There was a substantial variation in the performance of microvascular screening procedures between GPs within practices, and also in the achievement of treatment targets. However, while 17-52% of a persons' probability of having a microvascular screening procedure performed was attributed to GPs within practices, only 2.3-7.0% of the variation in the achievement of treatment targets was due to substantial differences in GPs within practices. This means that even though GPs' guidance and prescriptions are very important, the GPs' contributions to the achievement of treatment targets are relatively homogeneous for the diabetes population. The greatest variation was for the albuminuria test and monofilament test, and for the BP target. Our independent variables explained a moderate part of the variation in care processes, but little of the variation in target achievement. Clearly, our models have not captured the behavioural attitudes in patients and GPs that probably could explain much of the observed variation in both microvascular complication screening and target achievement.

Implications

Our data supports what is already known: First that the youngest, people with obesity, and people with a history of macrovascular complications need to be given high priority. Secondly, that implementation of a structured diabetes form is associated with improved care processes and risk factor control, and should be encouraged. Thirdly, that practices with routines for annual review and with a system for sending reminders to people who do not show up for scheduled control, and practices with ancillary staff involved in the follow up are more likely to perform recommended procedures. Systems with the use of a structured diabetes form and routines for annual review have been implemented in other countries, and it is time to mandate this, or at least highly encourage the use of a diabetes form and an annual diabetes review in Norwegian general practice.

Our data brings new information about how much of the variation in care processes and target achievement that is attributable to differences between GPs within

practices. The greatest variation was in care processes, and GPs with the lowest compliance rates with guidelines should be targeted.

Finally, quality of care is much more than care processes and treatment targets. It is about interpersonal relations, attitudes, decision making and patient satisfaction that is beyond the scope of this thesis.

8. Future perspective

First, to come closer to an answer of the research questions in this thesis, it is necessary to perform qualitative studies, with interviews of patients, GPs and ancillary staff at the practices. Further, longitudinal data would give us important information, together with linkage to the Norwegian Prescription Database.

The thesis highlights the need to gather information into a comprehensive, and nationwide diabetes register in Norway. It is unsatisfactory in a country with government-funded healthcare services that the quality indicators are not monitored continuously, or at least on an annual basis. Only then it is possible to detect challenges in outpatient and inpatient clinics, assess time trends, and improve diabetes care for all inhabitants. A representative and comprehensive diabetes register is an important basis for future research with hard endpoints.

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10. Errata

Page 15 Incorrect number: Reference page “1431-1433” corrected to “1431-1443”.

Page 19 Missing word: “128 Hz tuning” corrected to “128 Hz tuning fork”.

Page 25 Repetition: The word “should” should not be repeated.

Page 27 Spelling: “Intensifyed” corrected to “intensified”.

Page 32 Spelling: “Implantation” corrected to “implementation”.

Page 40 Omission: “Two counties differed” corrected to “Some counties differed”, and “while Hordaland County was” corrected to “while Hordaland and Akershus Counties were”

Page 94 Incorrect proportion: “One in four” corrected to “one in six”.

Errata in published papers:

Paper 2 Incorrect proportion: A GP was defined as a user of the Noklus diabetes form if it was **more than** 50% completed in ten or more people, or in more than 50% of the GP’s patients with type 2 diabetes.

Paper 3 Misclassification, Supplementary Table S1a: Reference group < 50 corrected to 60-69 years, and hence the lines with given odds ratios for 50-59 years and 60-69 years should be moved one line above the previously published version.

Papers 2 & 3 Omission: Macrovascular complications are defined as coronary heart disease, stroke, **PTA** and/or peripheral artery surgery.

11. Appendix

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……		

12. Papers 1-3