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REGISTER-BASED STUDIES OF EPIDEMIOLOGY AND HEALTH CARE COSTS IN TYPE 2 DIABETES

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ABSTRACT

Type 2 diabetes is a public health problem of great magnitude. Globally, prevalence of the disease is increasing, mainly as a result of population ageing and increased rates of obesity. The overall aim of this thesis was to study the epidemiology and health care costs of type 2 diabetes and its complications in Uppsala county, Sweden using register data from clinical practice. A total of 11 856 patients with type 2 diabetes were retrospectively identified in computerised records from 26 primary care centers kept between years 1993 and 2004.

Within Paper I, we estimated the prevalence and incidence of type 2 diabetes and its complications during years 1996-2003. Crude population prevalence of type 2 diabetes was found to increase from 2.2% to 3.5% but diabetes incidence did not exhibit any increase. Instead, increasing prevalence was a product of the number of patients diagnosed with type 2 diabetes each year being higher than the number of deaths among type 2 diabetic patients, as well as of declining mortality.

Within Paper II, we examined trends in control of glycemia, total cholesterol and blood pressure among type 2 diabetic study patients during years 1996-2005. Over the observation period, the proportion of patients with adequate control increased from 38% to 56% for glycemia, from 8% to 27% for total cholesterol, and from 8% to 11% for blood pressure. Despite this increase, a substantial proportion of patients did not achieve adequate control, in particular with regard to blood pressure.

Within Paper III, we examined medical resource use of study patients and estimated annual costs of health care. The average type 2 diabetic patient made 2 GP visits and 2 outpatient hospital visits per year. The mean (SD) total health care costs incurred by study patients were estimated at €3 602 (€9 537) in year 2004. Though a minority (16%) of patients were hospitalised during the year, inpatient care was the major contributor to costs, accounting for 57% of total health care costs.

Within Paper IV, we determined the immediate and long-term impact of acute myocardial infarction (AMI) and stroke on health care costs in patients with type 2 diabetes. Suffering an AMI was associated with a 4.1-fold increase in total health care costs during the year of a first AMI and a 6.5-fold increase in total health care costs during the year of a first stroke. For both AMI and stroke, the increase in costs was largely accounted for by inpatient care.

This thesis has contributed to increased knowledge of the epidemiology of type 2 diabetes in Sweden and has provided estimates of health care costs which may be used to inform capacity planning and as input into economic evaluations. This thesis also illustrates how computerised medical records from real-life clinical practice can be used to retrospectively identify cohorts of patients with a specific disease, how record linkage to can be used to retrieve information from complementary health care registers, and how epidemiological and health economical research questions can be studied through analysis of the resulting datasets.

Key words: type 2 diabetes, epidemiology, costs, economic, register studies, primary care

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I. **Ringborg A**, Lindgren P, Martinell M, Yin DD, Schön S, Stålhammar J. Prevalence and incidence of Type 2 diabetes and its complications 1996-2003 - estimates from a Swedish population-based study. Diabet Med 2008;25:1178-86.

II. **Ringborg A**, Martinell M, Yin DD, Lindgren P, Stålhammar J. Trends in control of glycemia, cholesterol and blood pressure in a large cohort of Swedish patients with type 2 diabetes 1996-2005. (Submitted manuscript)

III. **Ringborg A**, Martinell M, Stålhammar J, Yin DD, Lindgren P. Resource use and costs of type 2 diabetes in Sweden - estimates from population-based register data. Int J Clin Pract 2008;62:708-16.

IV. **Ringborg A**, Yin DD, Martinell M, Stålhammar J, Lindgren P. The impact of myocardial infarction and stroke on health care costs in patients with type 2 diabetes in Sweden. Eur J Cardiovasc Prev Rehabil 2009; 16:576-582.

LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AMI	Acute myocardial infarction
ATC	Anatomical Therapeutic Chemical
CABG	Coronary artery bypass grafting
CI	Confidence interval
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DDD	Defined daily doses
DR	Diabetic retinopathy
EASD	European Association for the Study of Diabetes
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
GP	General Practitioner
HbA1c	Glycosylated haemoglobin / Haemoglobin A1c
HDL	High-density lipoprotein
ICER	Incremental cost-effectiveness ratio
ICD	International classification of diseases
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IHD	Ischemic heart disease
LDL	Low-density lipoprotein
LYG	Life-years gained
MI	Myocardial infarction
NDR	National Diabetes Register
OAD	Oral antidiabetic drug
OR	Odds ratio
PCI	Percutaneous coronary intervention
QALY	Quality-adjusted life year
SD	Standard deviation
SEK	Swedish kronor
SRAU	Swedish Registry for Active Treatment of Uraemia
WHO	World Health Organization

CONTENTS

1. INTRODUCTION

Type 2 diabetes is a public health problem of great magnitude. The World Health Organisation (WHO) estimated the global prevalence of diabetes to be 2.8% in the year 2000 and projected an increase to 4.8% in 2030 (1). Although it has a strong genetic component, lifestyle factors such as obesity and physical inactivity are pivotal in triggering development of the disease (2;3). Given current rates of obesity and physical inactivity, a significant proportion of the Swedish population is at risk of developing type 2 diabetes (4). Since the disease is more prevalent in higher age-groups, population ageing will also contribute to higher numbers of individuals suffering from type 2 diabetes.

Management of type 2 diabetes is aimed at preventing disease-related complications such as neuropathy, nephropathy, retinopathy and cardiovascular disease (CVD) (5;6). Apart from having a large impact on patients' quality of life, these complications are associated with significant morbidity and often require frequent contacts with health care providers. Accurate measures of the prevalence of type 2 diabetes and the costs associated with the disease are critical for health care planning and allocation of resources. Also, since resources are limited, interventions aimed at treating type 2 diabetes or preventing diabetes-related complications should be subjected to cost-effectiveness analysis in order to determine if they provide value for money.

The present thesis has studied aspects of the epidemiology and health care costs of type 2 diabetes and its complications within the Swedish Real-Life Effectiveness and Care Patterns in Diabetes Management (RECAP-DM) study. This was a retrospective register-based open cohort study of patients with type 2 diabetes residing in Uppsala county, Sweden. The following sections provide a background on type 2 diabetes as well as an overview of health care registers in Sweden and cost of illness studies.

1.1   Type 2 diabetes

1.1.1 Definition and diagnosis

Type 2 diabetes is a metabolic disorder characterized by chronic high blood glucose values, also referred to as hyperglycemia, and insulin resistance. Type 2 diabetes has previously been referred to as adult-onset diabetes, but today onset of the disease is seen also in younger age groups. Disease symptoms include increased thirst and urine volume, recurrent infections, unexplained weight loss and, in severe cases, drowsiness and coma. However, it is not uncommon for asymptomatic patients presenting with signs of the metabolic syndrome to be diagnosed with type 2 diabetes when seeking health care for other reasons.

Clinical diagnosis of diabetes is made upon measurement of blood glucose levels and is defined by the WHO as (7):

1. Fasting blood glucose (FBG) >= 6.1 mmol/l

and/or

2. Fasting plasma glucose (FPG) >= 7.0 mmol/l

Additionally, in its Standards of Medical Care from year 2010, the American Diabetes Association (ADA) recently endorsed the use of glycosylated haemoglobin (HbA1c) as an option for diagnosing diabetes, with a cut-off of >=6.5% (5).

Unless a patient presents with obvious symptoms of hyperglycemia, the diagnosis of diabetes should not be made on the basis of a single abnormal blood glucose value but should be confirmed by a test result in the diabetic range taken on another day (7). Though more complicated than a blood test, diabetes can also be tested for through a 75-g oral glucose tolerance test (OGTT), in which case diagnosis can be made if the 2-hour glucose concentration in plasma or capillary whole blood is >=11.1 mmol/l.

When glucose levels are higher than normal but not in the diabetic range, individuals are categorized as having Impaired Fasting Glucose (IFG) [FPG 5.6 mmol/l to 6.9 mmol/l] and/or Impaired Glucose Tolerance (IGT) [2-hour OGTT glucose values of 7.8 mmol/l to 11.0 mmol/l]. These states are sometimes referred to as pre-diabetes as their presence is often a precursor of future development of diabetes (8;9). For example, European patients with IGT and IGF have been reported to have an annual progression rate to type 2 diabetes of 17% and 12%, respectively (10).

The differentiation of type 2 diabetes from type 1 diabetes is based on a number of key clinical and laboratory factors. Type 1 diabetes is caused by destruction of the β-cells of the pancreas leading to an absolute deficiency of insulin secretion and has a typical age of onset between 10-14 years of age, while type 2 diabetes is defined by insulin resistance and degeneration of pancreatic β-cells and typically affects obese individuals above the age of 40 years. Other types of diabetes, such as drug-induced diabetes and gestational diabetes, should also be ruled out before diagnosis of type 2 diabetes is confirmed (11).

1.1.2 Pathophysiology

The underlying cause of type 2 diabetes is fundamentally unknown but insulin resistance as well as degeneration of the pancreatic β-cells leading to decreased insulin secretion are both significant in the development of the disease (12;13).

In a non-diabetic individual, the β-cells of the pancreas respond to intake of carbohydrates by secreting insulin, which signals to skeletal muscle and other insulin-sensitive tissues in the body to absorb glucose and suppresses endogenous glucose production from the liver (gluconeogenesis). As blood glucose levels fall, the β-cells

reduce their insulin output and the glucose production from the liver is upregulated. The balance between insulin secretion, gluconeogenesis and glucose uptake ensures that blood glucose is maintained within a narrow range at approximately 5 mmol/l (14). In the diabetic individual this balance is disrupted and blood glucose levels are increased.

Insulin resistance is a typical early feature of type 2 diabetes and implies that insulin-sensitive tissue in the muscle, fat and liver does not respond adequately to increased insulin levels (15). This entails decreased transportation of glucose to the muscles, increased gluconeogenesis and breakdown of fat, resulting in higher levels of glucose in the blood. In the early stages of the disease, the pancreas produces more insulin in order to compensate for the high glucose levels. But as glucose levels continue to rise, the increased stress on the pancreatic functions will eventually lead to degeneration of the secretory capacity of the β-cells resulting in decreased secretion of insulin. Over time, a patient developing type 2 diabetes will experience a progressive deterioration of the β-cells, reduced β-cell mass and, if left untreated, worsening hyperglycemia (16;17). The onset of type 2 diabetes is gradual and insulin sensitivity and β-cell function have generally deteriorated over several years before overt type 2 diabetes develops (18). During the progression of type 2 diabetes, patients typically not only develop hyperglycemia, but also increased and abnormal quantities of lipoproteins in the blood, referred to as dyslipidemia, and hypertension. These disturbances will increase the risk for diabetes-related complications.

1.1.3 Risk factors for type 2 diabetes

There is a strong genetic component involved in the development of type 2 diabetes. Genetic factors may influence both the defect of insufficient secretory capacity of the β-cells and that of insulin resistance (13). Additionally however, genetic factors interact with environmental factors in the development of type 2 diabetes. The relative contribution of genes and environment can differ considerably across individuals and certain ethnic groups e.g. indigenous American Indians and Australian Aborigines are genetically more susceptible to type 2 diabetes (19).

Numerous environmental factors have been proposed as risk factors for type 2 diabetes. Those listed by the International Diabetes Federation (IDF) in their consensus statement on type 2 diabetes prevention are illustrated in Figure 1. Among them, obesity is singled out as the most important risk factor (2). It is highly associated with the development of type 2 diabetes and the majority of individuals diagnosed with the disease are overweight or obese. Obesity appears to aggravate insulin resistance and it is also a risk factor for CVD, thus further increasing the risk for one of the most important diabetes-related complications (20-22).

The most common measure of rating the degree of overweight or obesity is the Body Mass Index (BMI) defined as body weight (kg) divided by height squared (m^2). The WHO has defined a normal weight body as BMI between 18.5 and 25, whereas a BMI above 25 is defined as overweight and BMI over 30 as obese (23). Different associations between BMI, percentage of body fat and health risks have been found for Asian populations compared to European populations which has led the IDF to advocate

public health action for prevention of type 2 diabetes at BMI >23 kg/m² in Asian populations (2).

Figure 1. Environmental risk factors for type 2 diabetes
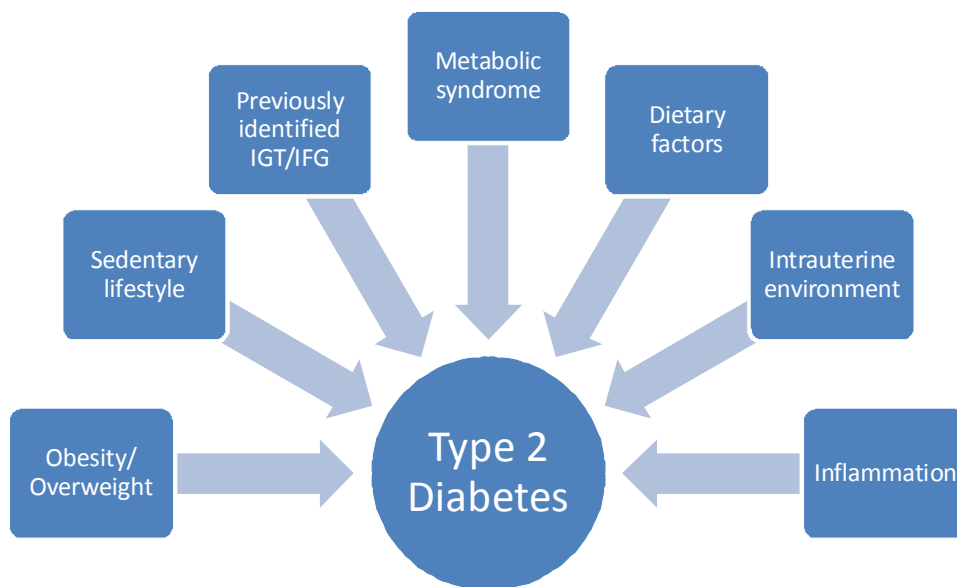
Source: International Diabetes Federation Consensus on type 2 diabetes prevention (2). IGT, Impaired Glucose Tolerance. IFG, Impaired Fasting Glucose.

There is general agreement in the scientific community that BMI is not an optimal tool to classify obesity as it does not accurately represent fat mass or distribution. Also, concentrated adipose tissue in the abdominal region entails an increased risk of developing type 2 diabetes, which might no be reflected by BMI. Therefore, waist circumference or waist-to-hip ratio may be more appropriate indicators of the risk of developing type 2 diabetes (20).

In addition to obesity, a sedentary lifestyle is a key risk factor for type 2 diabetes. Numerous studies have demonstrated the preventive effect of physical activity on the risk of developing type 2 diabetes. Amongst other, physical activity aids to increase insulin-mediated and non-insulin-mediated glucose metabolism (24;25).

1.1.4 Micro- and macrovascular complications

Patients with type 2 diabetes are at risk of developing numerous complications related to the disease. These are typically classified into microvascular complications and macrovascular complications.

Microvascular complications are complications of the small blood vessels of the body and include neuropathy, retinopathy and nephropathy, which may lead to foot ulcers, limb amputation, blindness and renal failure. Among patients enrolled in the United Kingdom Prospective Diabetes Study (UKPDS) which followed more than 5,000 newly diagnosed type 2 diabetic patients, the prevalence of microalbuminuria, which is an early marker of nephropathy, was 24.9% ten years following diagnosis of diabetes (26).

Macrovascular complications are complications of the large blood vessels of the body, including the coronary arteries, the aorta, and the sizable arteries in the brain and in the limbs. The most important macrovascular complication is CVD including stroke and myocardial infarction (MI). Compared to non-diabetic individuals, patients with type 2 diabetes have a two- to four-fold higher risk of developing CVD and it is the most common cause of death (27-31). It also appears as if CVD in diabetic individuals has a more severe course with greater prevalence of multiple-vessel coronary artery disease than in non-diabetic individuals (32). Patients with type 2 diabetes often present with a cluster of cardiovascular risk factors such as obesity, hypertension and dyslipidemia but hyperglycemia appears to have an independent effect on cardiovascular risk (33). Analysis of populations that included patients with IGT and IFG suggest that the pathogenic role of hyperglycemia on the blood vessel wall exists already in early stages of glucose intolerance (32).

In addition to the humanistic burden, the presence of micro- and macrovascular complications is strongly associated with costs in patients with type 2 diabetes (34-36). Within the Cost of Diabetes in Europe – Type 2 (CODE-2) study, late-stage complications were found to be the single factor with the largest impact on costs (37) and a US estimate from year 2007 attributed 50% of diabetes-related medical expenditures to hospital inpatient care (38). Micro- and macrovascular complications have also been seen to significantly reduce patients' quality of life (39).

1.1.5 Management of type 2 diabetes

The ultimate goal of type 2 diabetes management is to prevent or delay the onset of diabetes-related micro- and macrovascular complications. The main focus of treatment lies in controlling HbA1c, but control of other cardiovascular risk factors such as obesity, hypertension and dyslipidemia are also highly important. Tight control of glycemia, blood pressure and cholesterol have independently been shown to reduce the risk of complications in patients with type 2 diabetes (40-43). Additionally, lipid-lowering treatment with simvastatin has been shown to be cost-effective and in overweight patients, glucose-lowering treatment with metformin has been shown to be cost saving (44;45).

Within the Steno-2 study, multifactorial treatment involving a combination of professional lifestyle counseling, tight glucose regulation and the use of renin-angiotensin system blockers, aspirin and lipid-lowering agents was associated with a 50% reduction in the risk of cardiovascular and microvascular events (46). Recently however, there has been some debate on just how intensive treatment of hyperglycemia should be following reports of very low HbA1c being associated with raised mortality rates (47;48).

According to the consensus statement on medical management of hyperglycemia in type 2 diabetes issued by the ADA and the European Association for the Study of Diabetes (EASD), HbA1c levels should be maintained at <7%. At diagnosis of type 2 diabetes, it is recommended that a lifestyle intervention program to promote weight loss and increase activity levels as well as pharmacological treatment with metformin be initiated. Additional antidiabetic medications should be added when the target glycemic level of HbA1c <7% is not achieved or sustained, with insulin or a sulfonylurea designated as preferred second-line agents (49).

In Sweden, the National Board of Health and Welfare issued an updated set of guidelines for diabetes care in 2010 (50). The recommended general treatment targets are reported in Table 1.

Table 1. Treatment targets for diabetes care in Sweden

Risk factor	Target value
HbA1c	<6%*
Blood pressure	<130/80 mmHg
LDL cholesterol	<2.5 mmol/l

LDL, Low-density lipoprotein
*According to Mono-S measurement method, equivalent to 6.9% in DCCT terms.

It should be noted that HbA1c in Sweden is measured using the Mono-S method, which is a technique that differs from the Diabetes Control and Complications Trial (DCCT) measurement method used in the United States and elsewhere in Europe. An HbA1c value of 6% according to the Mono-S method is equivalent to 6.9% in DCCT terms, according to an established conversion formula (51). No Swedish target was stated for total cholesterol but in European guidelines, the recommended treatment target for total cholesterol in diabetic patients is <4.5 mmol/l for primary prevention of CVD (52).

Apart from the target risk factor values, the guidelines of the National Board of Health and Welfare include several general health care components recommended to be undertaken for patients with type 2 diabetes in Sweden, including the following:

- Advice and support for increased physical activity.

- Counselling on smoking cessation for patients who smoke.

- Group-based educational programs held by trained health care professionals.

- In patients needing medical treatment of hyperglycemia:

- prescription of metformin as first-line agent unless it is contraindicated or not tolerated.
- preferred prescription of sulfonylurea or insulin as second-line treatment.

- In patients with hypertension:
  - prescription of one or more agents from the classes ACE inhibitors, beta-blockers, calcium channel blockers and/or thiazide diuretics.

- In patients with increased levels of cholesterol:
  - prescription of generic statins for primary prevention.

- In patients free from eye disease:
  - retinal photography every third year.

- Targeted self-measurement of glucose as a pedagogical tool or to patients in specific situations such as those receiving treatment with insulin, those switching treatment and those experiencing acute variability in blood glucose.

1.2 Sources of electronic health care data in Sweden

1.2.1 National registers

Sweden is internationally renowned for its national registers, which offer an exceptional source of patient-level data for medical research. Compared to prospective data collection, registers provide an efficient means of obtaining health care data at a relatively low cost. Most registers are nationwide in coverage and the unique personal identification number which is assigned to all Swedish citizens enables tracking of individuals over time and record linkage for merging of data from different sources.

To date, there are 89 so-called national quality registers, which are designed to document diagnoses, treatment and outcomes within different medical specialties in order to improve the quality of care. The national quality registers cover a selection of specialties and include registers for patients with acute coronary syndromes (SWEDEHEART), stroke, asthma, multiple sclerosis and various forms of cancer. There is also a national register for diabetes, NDR, which was launched in 1996. Medical professionals within the different specialties are often the ones who have initiated establishment of a register and are highly involved in the subsequent development. Since participation in the national quality registers is voluntary with reporting on an annual basis, there is continuous work on maintaining/improving the completeness of the data reported for each patient as well as the coverage in terms of the number of participating centers.

In addition to the national quality registers, there are five so-called national health care registers which are maintained by the National Board of Health and Welfare. Details of these are reported in Table 2.

Table 2. National health care registers in Sweden

Register	Start year	Content
The Cancer Register	1958	Data on malignant cases of cancer
The Patient Register	1964 for hospitalisations; 2001 for outpatient care	Data on all hospitalisations and visits to specialised outpatient care
The Medical Birth Register	1973	Data on all births (characteristics of mothers and infants)
The Prescription Register	2005	Data on all prescriptions
The Dental Health Register	2008	Data on dental care

The transfer of hospitalisation records from the county councils' administrative systems to the national health care registers is compulsory and the registers therefore have good coverage and quality. According to a report on the quality and content of the Patient Register during years 1964-2007, about 1.5 million hospitalisations were reported in 2007 and data on diagnosis was missing in only 1% of cases (53). The National Board of Health and Welfare additionally maintains the Causes of Death Register, which contains data on the date and cause of death of all deceased Swedish citizens since 1961.

1.2.2 Computerised primary care records

The one main area in Sweden in which register data is still largely lacking is primary care. Since medical records these days are computerised it is however possible to extract data from individual primary care centers using specific data extraction programs. In recent years, several county councils have also created databases based on computerised routine administrative data and medical records from primary care. For example, the county council of Skaraborg have created the Skaraborg Primary Care Database which includes computerised medical records from 23 public primary care centers in the county, including diagnoses, prescriptions, caregiver contacts and laboratory values. There are also administrative databases in the counties of Östergötland, Västra Götaland and Skåne in which diagnoses and health care provision by providers in primary care are recorded.

There is general agreement that a national register for primary care would enable valuable tracking of outcomes and quality of care. Implementation of such a register is largely complicated by differences in administrative practices and computer systems between regions but a recent assessment led by the director the Swedish Council on Health Technology Assessment suggested creation of a national health care register for primary care as well as uniformly designed regional databases (54).

The health care data which is recorded in primary care and in the various national registers described above constitutes personal and potentially highly sensitive information. By law it is only available for research upon approval from an ethics committee. Research is also always conducted using anonymous study identification numbers in place of the personal identification numbers.

1.3   Health economics

1.3.1 Cost of illness

Studies of the patterns of resource use and costs of patients suffering from different diseases can provide useful information on the economic burden of disease and on the distribution of total costs across different resource categories. The principal objective of a cost of illness study is to estimate the costs related to a specific disease and the following steps should be undertaken: 1) identification of the relevant resources used; 2) quantification of these resources; 3) valuation (55).

According to economic theory, resources should be valued at their opportunity cost, which for a given resource is defined as the value of the resource put to its best alternative use (56). In practice, market prices are typically used for valuation. For resource items not on the market such as informal care by family members or friends, several methods have been proposed including the human capital method, the replacement cost method and contingent valuation (57).

The classical approach in cost of illness studies is rooted in welfare economics and involves adoption of a societal perspective. This implies that all costs are taken into account, irrespective of where in society they are incurred. Consequently, direct costs arising from the disease or its treatment as well as indirect costs arising from disease-related production foregone should be included. Within the narrower "health care payer" perspective, only costs incurred by the payer are included; thus, indirect costs are omitted.

Cost of illness studies can be conducted using a "bottom-up" or "top-down" approach. The former involves observational assessment of the costs incurred by individual patients from a representative sample with a given disease and estimation of mean per patient costs; the latter involves breaking down aggregate estimates obtained from e.g. national accounts into total costs attributable to different diseases. Moreover, cost of illness studies can be conducted using a prevalence-based or an incidence-based approach. In the prevalence-based approach, costs incurred during a specific time period (typically one year) by a cohort of individuals suffering from a given disease are estimated. In the incidence-based approach, longitudinal costs from diagnosis to cure or death are estimated.

Cost of illness studies are often a powerful means of drawing attention to a disease and raising awareness of its economic impact. The burden a given disease imposes on society may also be contrasted with amounts being invested in research to find treatments. But on their own, cost of illness studies offer little guidance as to how resources should be allocated. The burden of a disease can be ever so large but if there are no prospects of treatment or cure, investment in research may not be meaningful.

For guidance on how to allocate resources, economic evaluation of alternative courses of action in terms of both costs and consequences is necessary. These evaluations typically use modeling to simulate the costs and health outcomes associated with competing interventions and are increasingly called for by health care payers and reimbursement agencies. Cost estimates obtained through cost of illness studies play an

important role as inputs into economic evaluation. In type 2 diabetes, estimates of the costs associated with complications are fundamental since the key driver of economic models of type 2 diabetes is the risk of complications (58).

2. AIMS OF THE THESIS

The overall aim of this thesis was to study the epidemiology and health care costs of type 2 diabetes and its complications in Uppsala county using retrospective register data from clinical practice. Based on these data, the four papers included in the thesis have the following specific aims:

- To estimate the prevalence and incidence of type 2 diabetes and its complications during years 1996-2003 and to investigate trends over time (Paper I)

- To examine trends in control of glycemia, total cholesterol and blood pressure among patients with type 2 diabetes during years 1996-2005 (Paper II)

- To examine medical resource use of patients with type 2 diabetes and to estimate annual costs of health care (Paper III)

- To determine the immediate and long-term impact of acute myocardial infarction (AMI) and stroke on health care costs in patients with type 2 diabetes (Paper IV)

3. REVIEW OF LITERATURE

In order to obtain an overview of previous research in the field, a literature review focusing on Swedish studies of epidemiology and health care costs in type 2 diabetes was conducted. The review was divided into studies of the prevalence and incidence of type 2 diabetes, studies of trends in risk factors for CVD among patients with type 2 diabetes, and studies related to the economic burden of type 2 diabetes. The search was performed in the PubMed/MedLine database. Studies published before year 1995 were not considered.

3.1 Prevalence and incidence of type 2 diabetes in Sweden

A total of 12 studies reporting estimates of the prevalence of type 2 diabetes in Swedish populations were identified (Table 3). Five of the identified studies retrospectively estimated the prevalence of type 2 diabetes for the total population of a specific county or community using medical records and/or health care register data. The remaining seven studies estimated prevalence based on samples of patients invited to participate in various health surveys. As for diabetes incidence, only two Swedish studies were identified which reported it. Both belonged to the category of population-based studies based on register data.

3.1.1 Register-based studies

Among the register-based studies, the largest and most recent was conducted by Wiréhn et al. in the county of Östergötland (59). The authors made use of an administrative health care register in which details of all visits within primary care, outpatient hospital care and inpatient care are recorded to retrospectively identify patients with diabetes (types 1 and 2). All residents of Östergötland alive on December 31 2003 and with one or more health care contacts between January 1 1999 and December 31 2003 at which a diagnosis of diabetes (International Classification of Diseases (ICD) 10th revision codes E10–14) was recorded were classified as cases and the population prevalence of diabetes on December 31 2003 was thus estimated at 4.4%.

In the county of Skaraborg, the prevalence of diabetes was estimated at 3.2% in 1995 (60). Four sources were used to retrospectively identify patients with diabetes: 1) the Skaraborg Diabetes Registry 2) an administrative hospital registry, 3) a registry for the retinopathy screening program, and 4) a pharmacy prescription inventory.

In the small community of Laxå, a registry in which all prevalent and incident cases of patients diagnosed with diabetes are listed was created already in 1972. In 2001, the prevalence of type 2 diabetes in the population of Laxå was estimated to be 3.9% in men and 4.1% in women (61). To ensure inclusion of all patients diagnosed with diabetes in the community, patient record files at nearby primary care centers, private

practitioners and hospitals were checked in addition to records at the local primary care center.

3.1.2 Survey-based studies

While the register-based studies report estimates of diagnosed diabetes, the identified survey-based studies provided estimates of the prevalence of known diabetes as reported by patients taking part in the survey, or estimates of previously undiagnosed diabetes as demonstrated by blood glucose levels measured within the survey.

The two surveys carried out repeatedly over the longest periods of time were those conducted in the counties of Västerbotten and Norrbotten as part of the WHO multinational MONItoring of trends and determinants in CArdiovascular disease (MONICA) project and those conducted among middle-aged men and women in the city of Göteborg.

In 2009, the prevalence of known diabetes in the random population sample aged 25-64 years participating in the WHO MONICA survey in Västerbotten and Norrbotten was estimated at 2.7% in men and 2.4% in women (62). In the Göteborg city cohorts, the prevalence of known diabetes was estimated at 4% in 50-year old men and 2% in 50-year old women in 2003. Additionally, among males, the prevalence of previously undiagnosed diabetes as revealed by a blood glucose test was estimated at 2.6% (63;64).

The study in 64-year old women residing in Göteborg by Brohall et al. is interesting as the prevalence of previously undiagnosed diabetes of 4.8% was comparable with the prevalence of known diabetes of 4.7% (63). In this study, all 64-year-old women living in Göteborg were invited to take part in a screening examination including OGTT. The authors found that repeated OGTTs were needed to identify and not misclassify a considerable proportion of patients.

3.1.3 Incidence and trends

The two studies reporting estimates of diabetes incidence were carried out in Laxå and in Skaraborg (61;64). Interestingly, neither of these two studies found diabetes incidence to be increasing during years 1972-2001 and years 1991-1995, respectively.

As for trends in diabetes prevalence, results of the identified studies are somewhat contradictory. In Skaraborg county, prevalence was found to increase by 6% annually between years 1991 and 1995 (64). Prevalence was also found to increase between 1990-1995 and 2002-2007 among individuals participating in the Västerbotten Intervention Program (65). In contrast, the prevalence of known diabetes was not seen to increase in individuals aged 25-74 during years 1986-2009 in the WHO-MONICA surveys conducted in Västerbotten and Norrbotten (62;66), or during years 1980-2003 in middle-aged male and women participating in the Göteborg city health surveys (67;68).

Table 3. Studies of prevalence and incidence of diabetes in Sweden

Author, year	Geographical area	Population size	Source of data	Study year(s)	Crude diabetes* prevalence	Crude diabetes* incidence	Trend
Berger et al., 1998 (60)	Skaraborg county	280 411 (total county population)	Register	1995	3.2%	-	-
Lundman et al., 1998 (69)	Medelpad county	125 521 (total county population)	Register	1992	3.3%	-	-
Berger et al., 1999 (64)	Skaraborg county	Approximately 275 000 (total county population)	Register	1991-1995	3.2% (year 1995)	266/100 000 inhabitants (mean for the 5 years; type 2 diabetes only)	6% annual increase in prevalence; No significant trend in incidence
Eliasson et al., 2002 (66)	Västerbotten and Norrbotten county	6 167 (4 independent random samples; individuals aged 25-64 years)	Survey	1986, 1990, 1994, 1999	Known: 2.7% in men; 2.2% in women (year 1999). Previously undiagnosed: 3.3% in men; 3.1% in women (year 1994)	-	No increase in prevalence
Brohall et al., 2006 (63)	City of Göteborg	2 595 (64-year old females participating in population-based survey)	Survey	2001-2004	Known: 4.7%; Previously undiagnosed: 4.8%	-	-
Jansson et al., 2007 (61)	Laxå municipality	6 577 (total county population)	Register	1972-2001	Type 2 diabetes: 3.9% in men; 4.1% in women (year 2001)	Type 2 diabetes: 3.6/1 000 in men; 3.0/1 000 in women (year 2001)	No increase in prevalence or incidence
Wiréhn et al., 2007 (59)	Östergötland county	415 000 (total county population)	Register	2003	4.4%	-	-

Author, year	Geographical area	Population size	Source of data	Study year(s)	Crude diabetes* prevalence	Crude diabetes* incidence	Trend
Wändell et al., 2007 (70)	Stockholm county	4 106 (random sample of males and females aged 60 years)	Survey	1997-1999	9.7% in men; 5.1% in women	-	-
Rosengren et al., 2009 (68)	City of Göteborg	3 251 (5 independent random samples of men aged 50 years)	Survey	1963, 1973, 1983, 1993, 2003	Known: 4.0%; previously undiagnosed: 2.6% (year 2003)	-	No increase in prevalence of known diabetes. Increase from 3.6% to 6.6% in diabetes defined as known or previously undiagnosed
Johansson et al., 2009 (67)	City of Göteborg	1 951 (5 independent random samples of females aged 50 years)	Survey	1980, 1985, 1990, 1995, 2003	Known: 2% (year 2003)	-	No increase in prevalence
Lindahl et al., 2010 (65)	Västerbotten county	102 822 (40-60-year old participants of the population-based Västerbotten Intervention Programme)	Survey	1990-2007	6.8% in men; 4.3% in women (years 2002-2007)	-	44% increase in men and 17% increase in women between 1990-1995 and 2002-2007
Eriksson et al., 2010 (62)	Västerbotten and Norrbotten county	10 586 (6 independent random samples; individuals aged 25-74 years)	Survey	1986, 1990, 1994, 1999, 2004, 2009	Ages 25-64 years: 2.7% in men and 2.4% in women. Ages 65-74 years: 15.3% in men and 7.8% in women (year 2009)	-	No increase in prevalence

* types 1 and 2 unless otherwise indicated.

3.2 Trends in risk factors for cardiovascular disease

A total of three studies of trends in cardiovascular risk factor control in Swedish patients with type 2 diabetes were identified in the literature. All were based on the Swedish National Diabetes Register (NDR). This register was launched in 1996 with the goal of monitoring and improving the quality of diabetes care. The register includes patients with type 1 as well as type 2 diabetes and is based on voluntary annual reporting of data for individual patients by primary care centers and hospital outpatient diabetes clinics. In 2009, an estimated 70% of all patients with diabetes in Sweden were registered in the NDR but the coverage varied considerably between counties. The estimated proportion of patients with diabetes reported to the NDR was the highest in Kronoberg county (90%) and the lowest in Uppsala county (39%) (71).

All three studies of trends in risk factor control based on the NDR reported improvements in control of glycemia and blood pressure for patients with type 2 diabetes:

- Gudbjörnsdottir et al. reported decreases in mean HbA1c and blood pressure values from 7.0% and 151/82 mmHg to 6.7% and 147/80 mmHg, respectively, between years 1996 and 1999. Mean BMI was however increasing over the period (72).

- Eliasson et al. evaluated risk factor control in relation to national and international targets during years 1996-2003 and found increasing proportions of NDR patients with type 2 diabetes achieving national targets for HbA1c and blood pressure recommended at the time. In contrast, the proportion of patients with BMI <25 appeared to be decreasing (Figure 2). Also, the majority of patients did not achieve the updated international treatment targets, which were issued in 2003. Blood pressure <130/80 mmHg was achieved by only 13% of all patients in 2003 and despite a dramatic increase in the use of lipid-lowering drugs (from 9% in 1996 to 38% in 2003), the proportion of patients achieving total cholesterol <4.5 mmol/l in 2003 was only 28% (total n=45,091) (73).

- Gudbjörnsdottir et al. studied cardiovascular risk factor control among NDR patients with type 2 diabetes and coronary heart disease (CHD). In 1 612 patients with first incidence of CHD 1-2 years before 2002, the proportions of patients achieving HbA1c <7%, blood pressure <=130/80 mmHg, total cholesterol <4.5 mmol/l and low-density lipoprotein (LDL) cholesterol <2.5 mmol/l were 47%, 31%, 47% and 49%, respectively, in 2002. In 4 570 patients with first incidence of CHD 1-2 years before 2005, corresponding proportions were 54%, 40%, 60% and 65% in 2005. Use of antihypertensives in the two patient samples increased from 90% to 94% while use of lipid-lowering drugs increased from 75% to 86% (74).

Looking at studies conducted in the general Swedish population, not just in patients with type 2 diabetes, the overall trend of improved risk factor control with respect to blood pressure and cholesterol levels and deteriorated control with respect to weight is confirmed. Within the WHO MONICA survey in northern Sweden, there were

important decreases in the prevalence of hypertension, smoking and hypercholesterolemia between years 1986 and 2009, which could be explained by a higher education level, changing dietary patterns, and increasing use of more effective antihypertensive and lipid-lowering treatment. Obesity (BMI>30) was however increasing; one in five individuals aged 25–64 years was obese in 2009, which was twice as many as in 1986 (62).

Similarly, Rosengren et al. observed favorable trends with respect to smoking, blood pressure and cholesterol levels between 1963 and 2003 in random samples of 50-year old men living in the city of Göteborg, but the prevalence of obesity in these men increased from 6.0% to 13.8% over the period (68).

Figure 2. Proportion of patients in the Swedish National Diabetes Register achieving national targets for HbA1c, blood pressure and BMI, years 1996-2003
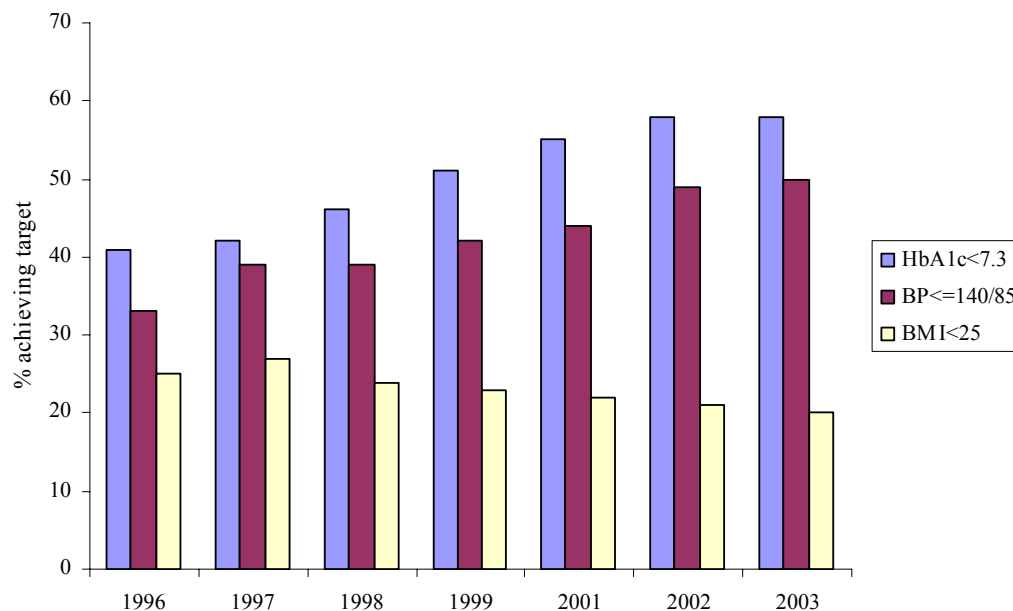
Source: Adapted from article by Eliasson et al. (73). Data for year 2000 were not given.

3.3   Economic burden of type 2 diabetes in Sweden

A total of 11 studies related to the economic burden of type 2 diabetes or both types of diabetes in Sweden were identified in the scientific literature. Seven of these were general cost of illness studies (Table 4). The remaining four investigated the impact of different diabetes-related complications on costs (Table 5).

3.3.1 Cost of illness

The only cost of illness study that focussed specifically on type 2 diabetes rather than both types of diabetes was conducted by Henriksson et al. (75) as part of a larger European cost of illness study for type 2 diabetes (CODE-2) (37). Based on resource use data collected for 777 patients recruited from 9 primary care centers in Sweden, Henriksson et al. estimated the mean annual direct costs incurred by patients with type 2 diabetes at 24 983 SEK (1998 prices). The authors additionally assumed that the sample was representative and multiplied the mean cost by the estimated total number of patients with type 2 diabetes in Sweden, thus obtaining an estimate of the total direct costs incurred by type 2 diabetic patients in Sweden of 7 billion SEK, or 6% of total national health care expenditures. In the survey which was used to collect data on resource use, patients were asked to indicate whether use of a given resource was related to diabetes, to its complications, or unrelated to diabetes. The authors were thus able to report that 27% of the total cost was due to management of diabetes per se, 34% to diabetes-related complications and 39% was unrelated to diabetes. Norlund et al. (76) confirmed that complications account for a substantial part of costs in patients with diabetes.

The study by Wiréhn et al. (77) is interesting as it estimated the excess health care costs incurred by patients with diabetes (types 1 and 2) as compared to non-diabetic individuals. The authors used an administrative health care register in which all visits within primary care, outpatient hospital care and inpatient care in the county of Östergötland are recorded to calculate costs and explore age-specific differences between the diabetic and the non-diabetic population. Complementary data on the use of prescription pharmaceuticals was obtained from the National Prescription Register. The mean cost per person and year was estimated at €4 474 for the diabetic population and €2 504 for the non-diabetic population. The diabetes/non-diabetes cost ratio decreased with age, being 3.5 in individuals aged 45-54 years, 2.3 in individuals aged 55-64 years, 1.8 in individuals aged 65-74 years, and 1.4 in individuals aged 75 years and above.

A study by Jonsson et al. (78) also studied excess costs of care of patients with diabetes but was excluded from the present review due to fact that included patients predominantly represented cases of type 1 diabetes.

A very different approach was applied by Bolin et al. (79), who used a top-down methodology to estimate the total cost attributable to diabetes and its complications in years 1987 and 2005, respectively. Apart from health care costs, this study also included costs of lost productivity and lost life-years due to diabetes. This study found that the total cost attributable to diabetes increased from €439 million to €920 million between

Table 4. Cost of illness studies for diabetes in Sweden

Author, year	Type of costs	Methodology	Sample size	Source of data	Price year	Perspective	Main result
Bolin et al, 2009 (79)	Health care costs and productivity losses resulting from diabetes and its complications in 1987 and 2005.	Top-down		Registers and aggregate data	2005	Societal	Estimated total costs of diabetes were €439 million in 1987 and €920 million in 2005, corresponding to €2 927 and €3 622 per person diagnosed with diabetes.
Wiréhn et al, 2008 (77)	Additional health care costs for patients with diabetes compared to non-diabetic individuals.	Bottom-up	20 876	Register	2005	Health care system	The annual cost per person was 1.8 times or €1 971 higher for patients with diabetes compared to non-diabetic individuals.
Ostgren et al, 2006 (80)	Costs of primary care resources consumed by patients with diabetes compared to all patients.	Bottom-up	277	Patient records	2001	Primary care	The mean annual cost of primary care incurred by patients with diabetes was €841.
Norlund et al, 2001 (76)	Direct and indirect costs of patients with diabetes aged 25 years and older.	Bottom-up	1 677	Patient survey and records	1993	Societal	The mean annual direct and indirect costs incurred by patients with diabetes were 61 700 SEK.
Henriksson et al, 2000 (75)	Direct medical costs incurred by patients with type 2 diabetes.	Bottom-up	777	Patient survey	1998	Health care system	The mean annual cost incurred by patients with type 2 diabetes was 24 983 SEK.
Henriksson & Jönsson, 1998 (81)	Total cost due to diabetes in Sweden.	Top-down	-	Registers and aggregate data	1994	Societal	The estimated cost due to diabetes was 5.7 billion SEK in 1994.
Persson, 1995 (82)	Excess costs of production losses arising from morbidity in patients with diabetes.	Bottom-up	285	Patient records	1994	Societal	The mean annual excess cost of production losses as a result of morbidity in people aged 20-64 years with type 2 diabetes was approximately SEK 40 000.

Table 5. Studies of the impact of diabetes complications on costs in Sweden

Author, year	Type of complication(s)	Methodology	Sample size	Source of data	Price year	Perspective	Main result
Heintz et al, 2010 (83)	Diabetic retinopathy	Bottom-up	3 124 with T2DM and DR	Registers	2008	Health care system	Mean health care costs attributable to DR (any kind) were €68 per year for patients with type 2 diabetes.
Gerdtham et al, 2009 (84)	Diabetic coma, heart failure, non-fatal stroke, peripheral circulatory complications, non-fatal MI, IHD, renal failure and amputation	Bottom-up; Panel data regression	179 749	Registers	2003	Hospital	The average annual inpatient costs for a 60-year-old male in the year an event first occurred were €6 488 for diabetic coma; €6 850 for heart failure; €7 853 for non-fatal stroke; €8 121 for peripheral circulatory complications; €8 736 for non-fatal MI; €10 360 for IHD; €11 411 for renal failure; and €14 949 for amputation.
Jönsson et al, 2006 (85)	Hypoglycemia	Top-down	-	Scientific literature	2005	Societal	Annual costs attributable to hypoglycemia were estimated at €14 per patient with type 2 diabetes.
Tennvall et al, 2000 (86)	Deep foot infections	Bottom-up	220	Patient records	1997	Health care system	Total per patient costs for healing were 136 600 SEK without amputation, 260 000 SEK with minor amputation and 234 500 SEK with major amputation.

Abbreviations: DR, diabetic retinopathy; IHD, ischemic heart disease; MI, myocardial infarction.

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1987 and 2005, mainly as a result of increased diabetes prevalence. Henriksson and Jönsson also applied a top-down approach in their cost of illness study from 1994 and found that indirect costs arising from diabetes-related short-term illness, early retirements and premature death accounted for as much as 57% of total costs (81).

3.3.2 Impact of complications on costs

Details of the studies identified as dealing with the economic impact of diabetes-related complications are reported in Table 5. The study with the broadest scope was the one by Gerdtham et al. (84). Using a methodology very similar to that used within a previous study based on data from the UKPDS (87), the authors estimated the short- and long-term costs of inpatient admissions for major diabetes-related complications.

Patients with diabetes aged 35-94 years were retrospectively identified in the year 1998 Swedish National Diabetes Register (NDR). Using record linkage, this dataset was linked to the National Patient and Causes of Death Registers to obtain information on hospital episodes and mortality for the period 1998-2003. Annual short- and long-term hospitalisation costs in patients suffering the following diabetes-related complications were subsequently estimated: diabetic coma, heart failure, non-fatal stroke, fatal stroke, peripheral circulatory complications, non-fatal MI, fatal MI, IHD, renal failure and amputation. This was done through use of two-part models, in which the first estimated the probability of hospitalisation using logistic regression, and the second estimated hospitalization costs conditional on hospitalization occurring using panel data regression. Since the occurrence of events was ascertained using hospital records, it should be noted that the probability of hospitalisation was equal to one in the year the event occurred. The average annual inpatient costs for a 60-year-old male in the year an event first occurred were estimated at €6 488 for diabetic coma, €6 850 for heart failure, €7 853 for non-fatal stroke, €8 121 for peripheral circulatory complications, €8 736 for non-fatal MI, €10 360 for IHD, €11 411 for renal failure and €14 949 for amputation.

4. MATERIALS AND METHODS

4.1 The Swedish RECAP-DM study

The present thesis is based on data collected within the Swedish Real-Life Effectiveness and Care Patterns in Diabetes Management (RECAP-DM) study. This was a retrospective register-based open cohort study of patients with type 2 diabetes residing in Uppsala county, located just north of Stockholm. On December 31 2010, Uppsala county had 335 882 inhabitants (88). The mean age of the population was 39.8 years, which is only slightly lower than the national average of 41.1 years. The proportion of females was 50.2%, which is identical to the national level. Uppsala county comprises urban (city of Uppsala) as well as rural (municipality of Tierp) districts.

Figure 3. Map of Uppsala county

The RECAP-DM study was approved by the Regional Ethics Committee of Uppsala. The following sections provide an account of the data sources used within the study, inclusion and exclusion criteria, as well as techniques used to create the study database.

4.1.1 Primary care data

The main source of data for the RECAP-DM study consisted of computerised patient-level medical records from the 26 primary care centers in Uppsala county participating in the study. These computerised records were a complete account of demographic characteristics (gender and year of birth), diagnoses, drug prescriptions, caregiver contacts, referrals to other caregivers, laboratory results and blood pressure measurements recorded for patients in association with day-to-day caregiver contacts at the centers. The records did not include systematic data on medical history, diabetes duration or initial date of diagnosis.

The Pygargus CxP system (Pygargus AB, Stockholm, Sweden) allowed for identification of patients with type 2 diabetes in the computerised medical records and extraction of data for these patients. At the time of the study, the Pygargus CxP system was however dependant on the ProfDoc administrative system for medical records being installed (CompuGroup Medical Sweden AB, Stockholm, Sweden). As this installation occurred on different dates at the different centers, the initial date on which computerised data were accessible for extraction varied between centers. Table 6 reports the first date on which medical records were accessible at each participating center. This date approximately coincides with installation of the ProfDoc system and delineates the start of the observation period within the RECAP-DM study. Table 6 also reports the number of patients with type 2 diabetes included in the study by center, as well as the mean age of these patients at inclusion.

Table 6. Initial observation date, number of included patients and mean age by center

Primary care center	Initial observation date	N*	Mean age at inclusion (min-max)
Alunda	1994-05-30	221	68 (31-96)
Årsta	1994-03-23	973	68 (30-95)
Bålsta	1994-08-24	574	62 (30-89)
Enköping	1994-02-10	844	68 (31-95)
Eriksberg	1993-09-30	464	70 (31-94)
Fjärdhundra	1994-03-14	343	67 (34-93)
Flogsta	1998-09-30	277	64 (33-93)
Gimo	1994-06-30	254	63 (31-93)
Gottsunda	1995-11-12	475	63 (30-98)
Knivsta	1994-05-24	383	63 (31-98)
Knutby	1997-10-16	82	67 (38-91)
Kungsgärdet	1993-08-27	204	63 (33-93)
Liljeforstorg	1993-11-02	328	68 (31-98)
Luthagen	1994-03-22	268	73 (33-97)
Möllan	1995-01-20	209	71 (34-95)
Nyby	1994-05-03	384	67 (33-94)
Öregrund	1994-06-15	122	66 (30-94)
Örsundsbro	1993-06-14	205	67 (35-96)

Österbybruk	1994-07-25	155	70 (42-92)
Östhammar	1994-06-20	327	65 (31-94)
Samariterhemmet	1994-02-16	268	67 (30-94)
Sävja	1994-12-30	303	62 (33-93)
Skutskär	1994-05-16	711	66 (31-93)
Storvreta	1993-12-02	181	64 (30-97)
Svartbäcken	1994-10-07	691	69 (34-99)
Tierp	1994-04-20	1 455	67 (30-101)

*A total of 11 856 patients with type 2 diabetes were included in all. 1 155 patients were identified in medical records at more than one center.

It is clear from Table 6 that the observation period began during year 1993-1994 at the majority of study centers (23 out of 26). There were 3 centers which were late to computerise (Gottsunda in November 1995; Knutby in October 1997; Flogsta in October 1998) whose period of observation consequently began later.

According to county council capitation lists from year 2004, participating centers served 77% of the Uppsala county population. These capitation lists detail the number of residents served by each primary care practice (public as well as private) and are the basis of the per capita remuneration for primary care applied by the county council. The remaining 23% of the population were served by private general practitioners (15%) and by the 5 public primary care centers not able to participate in the study due to use of a computer system that did not permit extraction of medical records (8%; Enköpings vårdcentral, Håbo, Vaksala-Rasbo, Länna and Uppsalahälsan) (Monica Carlsson and Linn Malmer; personal communication; March 2007).

4.1.2 Inclusion and exclusion criteria

The computerised medical records at each participating center were electronically searched from the start of the observation period onwards in order to identify patients with type 2 diabetes. Patients were included in the study upon meeting at least one of the following three criteria:

1) ICD diagnostic code for type 2 diabetes
   o ICD-10 codes E11-E14
   or
   o ICD-9 code 250

2) Prescription of an oral antidiabetic drug (OAD), i.e. a drug with an Anatomical Therapeutic Chemical (ATC) code starting with A10B

3) Fasting blood or plasma glucose value indicative of diabetes as defined in Swedish guidelines (89):
   o Prior to 1998: FBG >=6.7 mmol/l
   o As of 1998: FBG >=6.1 mmol/l or FPG >=7.0 mmol/l

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Patients with a single FBG or FPG value over cut-off and no diagnosis of type 2 diabetes at any time during the study period were excluded as were patients under 30 years of age, patients under 40 years of age who were prescribed insulin but not OAD treatment and patients ever diagnosed with type 1 diabetes (ICD-10 code E10; ICD-9 codes 250.x1, 250.x3), diabetes due to underlying condition (ICD-10 code E08), drug or chemical induced diabetes (ICD-10 code E09), gestational diabetes (ICD-10 code O24.4; ICD-9 code 648.8) or non-clinical diabetes (ICD-9 code 790.2).

Data were extracted on October 7 2005 but patients whose initial date of meeting study inclusion criteria lay after December 31 2004 were excluded due to insufficient follow-up.

4.1.3 Construction of the RECAP-DM study database

Extensive data management and cleaning were required before the primary care data obtained within the RECAP-DM study could be analysed. Since three different inclusion criteria were applied, three different sets of data were obtained for each of the 26 participating centers, one for patients included according to the diagnosis criteria, one for patients included according to the OAD prescription criteria, and one for patients included according to FBG/FPG criteria. Patients could clearly be present in more than one of these datasets, as is depicted in Figure 4. A relational database based on standard query language (SQL) programming was used to create an ultimate dataset including unique patients and to identify their study inclusion date, defined as the earliest date of meeting any of the three study inclusion criteria. This final dataset included 11 856 patients.

Figure 4. Venn diagram of RECAP-DM inclusion criteria
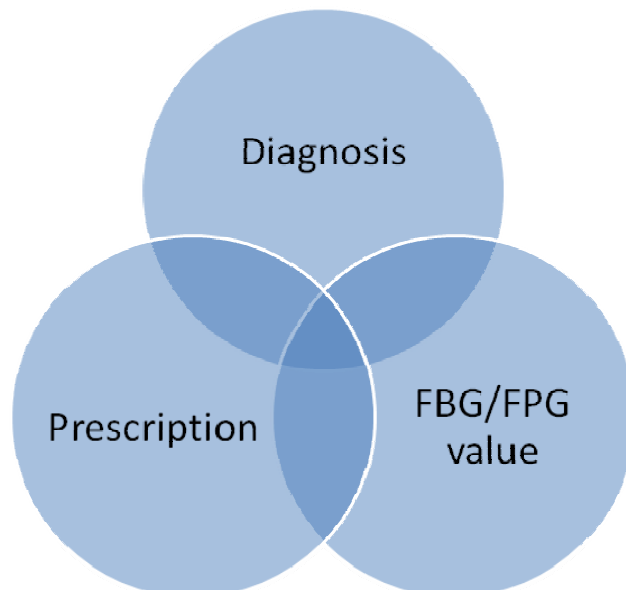
The Pygargus CxP system assigned an anonymous 10 digit study-ID to each patient seeking care at a given primary care center, the first 5 digits of which were a center-specific prefix. If a patient sought care at several primary care centers, he or she received a study-ID for each center. In order to be able to base the analyses on individuals, a new anonymous variable with a one-to-one relationship to each patient's unique personal identification number was generated. All analyses were carried out using this anonymous study identification number.

Data from the 26 centers were merged in the SQL database and separate tables were generated for patient characteristics, diagnoses, prescriptions, caregiver contacts, laboratory measurements (FBG, FPG, HbA1c, total cholesterol, LDL cholesterol and HDL cholesterol), BMI and blood pressure measurements. Records of caregiver contacts and blood pressure measurements did not commence until mid-1999 while all other data were available for the entire study period. Since data were direct extracts from medical records, in particular the laboratory data needed cleaning from free text entered alongside numerical test results.

4.1.4 Data obtained through record linkage

Once the study cohort had been defined, register data from four additional sources were obtained via linkage to the personal identification numbers of included patients:

- The National Patient Register provided patient, medical and administrative data on all hospitalisations in Sweden for years 1987-2004.

- The National Causes of Death Register ran until December 31 2003 at the time of the study and provided data on mortality including date and cause of death.

- The Swedish Registry for Active Treatment of Uraemia (SRAU) keeps records of patients undergoing treatment for renal failure and provided data for years 1988-2005.

- Uppsala Akademiska Hospital, the main county hospital, provided data on outpatient clinic visits (number of visits by type of clinic) for years 1993-2004.

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5. SUMMMARY OF PAPERS

5.1 Prevalence and incidence of type 2 diabetes and its complications (Paper I)

5.1.1 Objective

The objective of Paper I was to estimate the prevalence and incidence of type 2 diabetes and its complications in Uppsala county during years 1996-2003.

Though patients were included in the RECAP-DM study up until December 31 2004, the necessary mortality data was only available until December 31 2003. As for the start year of 1996, this was set due to the fact that a certain diabetes-free observation period was required before patients could be categorized as incident cases of type 2 diabetes.

5.1.2 Prevalence, incidence and mortality

Annual prevalence rates of type 2 diabetes were estimated for age-groups 30-39, 40-49, 50-59, 60-69, 70-79 and >=80 years by dividing the number of prevalent cases of type 2 diabetes identified at the 26 participating centers by the number of residents they served according to county council capitation lists. Study patients were counted as prevalent cases of type 2 diabetes from the year they were included in the study cohort until the year of their last record of any kind in the extracted primary care data, which lasted up until October 7 2005. This assignment of prevalence status is illustrated for three hypothetical patients in Table 7.

Table 7. Assignment of status as prevalent case of type 2 diabetes

Patient-ID	Study inclusion date	Date of last primary care record	Years as prevalent case
101	1996-12-01	2000-04-14	1996, 1997, 1998, 1999, 2000
102	1999-05-01	2005-06-12	1999, 2000, 2001, 2002, 2003, 2004, 2005
103	2001-06-01	2003-10-10	2001, 2002, 2003

Data on the initial date of type 2 diagnosis was not available in the primary care records. Instead, annual incidence rates of type 2 diabetes for each age-group were estimated as the annual number of individuals included in the study cohort per 1 000 residents of the source population. The incidence date of type 2 diabetes was thus defined as the date of study inclusion.

For the 23 centers whose observation period began during years 1993-1994 (see Table 6), more than one full year of observation had passed in 1996. Assuming that patients with type 2 diabetes make at least one visit to their primary care center every year, this period of at least one year was judged sufficient to categorize patients included in the study from 1996 onwards as incident cases. For the three centers late to computerise (Gottsunda, Knutby and Flogsta), the observation period was required to have lasted at least one year before individuals included in the study were counted as incident cases.

Annual mortality rates among patients with type 2 diabetes were calculated as the number of deaths documented in the National Causes of Death Register per 1 000 type 2 diabetic patients included in the study.

5.1.3 Prevalence and incidence of complications

Annual prevalence rates of CVD (defined as a record of an AMI, stroke, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)), and renal failure were calculated as the proportion of prevalent cases of type 2 diabetes with records of the complication documented in the National Patient Register or, in the case of renal failure, in SRAU on any previous occasion. Complications were tracked using appropriate ICD-9 and ICD-10 codes and rates were estimated for December 31 of each year between 1996 and 2003.

Incidence rates were calculated for AMI, stroke and amputation as the number of patients experiencing first events as recorded in the Patient Register, divided by the number of patients included in the study cohort who were alive and without history of the event on January 1 of the studied year.

5.1.4 Statistical analysis

Using county population statistics for 1996-2003, a dataset listing all residents aged >=30 years in the source population by age, sex, diabetes prevalence status (case=1; non-case=0) and study year was created. A similar dataset listing residents by age, sex, diabetes incidence status and study year was created.

Multiple logistic regression was then used to analyse trends in prevalence and incidence over time while controlling for changes in the underlying age and sex distribution of the studied population. In separate versions of the models, interaction effects between age-group and time were added as covariates in order to investigate whether rates of change in prevalence/incidence differed across age-groups.

Trends in mortality among type 2 diabetic study patients were similarly analysed through logistic regression with age-group, sex and a continuous variable for time as covariates.

5.1.5 Results

The crude population prevalence of type 2 diabetes increased by 55% (from 2.2% to 3.5%) between years 1996 and 2003. The age- and sex-adjusted rate of increase was 6% per year. Increased type 2 diabetes prevalence was apparent in all age-groups (Figure 5).

Figure 5. Prevalence of type 2 diabetes in Uppsala county by age-group, 1996-2003
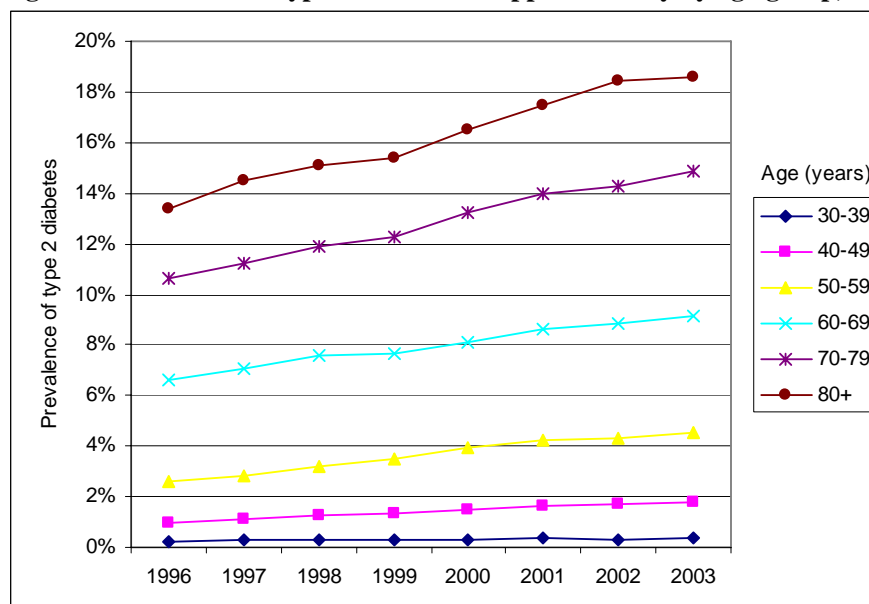
Crude diabetes incidence did not exhibit any increase between 1997 and 2003 and was thus not the source of increasing prevalence. Instead, increasing prevalence was a product of the gap between incidence and mortality: the number of incident cases of type 2 diabetes greatly outnumbered deaths among type 2 diabetic patients each and every year, leading to larger and larger prevalence cohorts. The overall trend in mortality over the study period was declining, which also contributed to increased prevalence. Between years 1996-2003, the annual decrease in age- and sex-adjusted mortality among the studied type 2 diabetic patients was 4% (OR 0.96, 95% CI 0.94-0.97).

Prevalence rates of CVD among type 2 diabetic patients were essentially stable, affecting 13.8% of females and 18.0% of males in 2003. Nor was any trend detected for prevalence of renal failure or incidence of AMI, stroke and amputation.

5.2 Trends in control of risk factors among patients with type 2 diabetes (Paper II)

5.2.1 Objective and methods

The objective of Paper II was to examine trends in control of glycemia, total cholesterol and blood pressure among patients included in the RECAP-DM study. Data on all measurements of HbA1c, total cholesterol and blood pressure recorded from year 1996 until the end of the observation period (October 2005) were extracted from the study database, though in the case of blood pressure, records were only available from year 2000 onwards.

Glycemic control was defined as HbA1c <7% in terms of the DCCT measurement method. Control of cholesterol was defined as total cholesterol <4.5 mmol/L and control of blood pressure as systolic blood pressure <130 mmHg and diastolic blood pressure < 80 mmHg. These targets are in line with current international guidelines as well as the national health care guidelines for diabetes issued by the Swedish National Board of Health and Welfare (50;52).

Mean values of HbA1c, total cholesterol and blood pressure and the proportions of patients achieving target values for control were computed by year. Logistic regression was applied to infer annual rates of change in the proportion of patients achieving control of each risk factor over time, controlling for gender, current age and medical treatment. The time component was captured through addition of a continuous variable defined as the number of years since the beginning of the observation period. To determine whether rates of change in control differed by age and gender, multiplicative interaction variables for time by gender and time by age were added.

5.2.2 Results

Over the observation period, the proportion of patients with adequate control increased from 38% to 56% for glycemia, from 8% to 27% for total cholesterol, and from 8% to 11% for blood pressure. Despite this increase, a substantial proportion of patients did not achieve adequate control, in particular with regard to blood pressure. Additionally, a considerable proportion of patients did not appear to undergo regular monitoring of risk factors.

Results of the logistic regression indicated that the odds of control of glycemia, cholesterol and blood pressure increased at a rate of 8%, 15% and 11% per year, respectively, for the reference group of male patients aged 50-64 years, controlling for prescription of medical treatment (see Table 8). Glycemic control improved slightly more in females than males over the observation period (OR 1.02 for time by gender interaction, 95% CI 1.00-1.04). As for the interaction of time with age, the rate of improvement in control of cholesterol was higher among patients aged >=65 years compared to patients aged 50-64 years (OR 1.06, 95% CI 1.02-1.09). In contrast, for patients aged <50 years, the rate of improvement in control of glycemia was lower

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compared to patients aged 50-64 years (OR 0.96, 95% CI 0.92-1.00) and the odds of control of blood pressure among patients aged <50 years actually deteriorated by a factor of 0.98.

Table 8. Results of logistic regression models for control of glycemia and total cholesterol years 1996-2005 and blood pressure years 2000-2005

Variable	Control of glycemia		Control of total cholesterol		Control of blood pressure	
	OR	95% CI	OR	95% CI	OR	95% CI
Female	0.87	(0.78-0.98)	0.61	(0.48-0.76)	0.90	(0.77-1.07)
Age < 50 years	1.23	(0.97-1.56)	1.07	(0.72-1.59)	2.37	(1.83-3.07)
Age ≥ 65 years	0.97	(0.85-1.11)	0.98	(0.78-1.24)	0.81	(0.67-0.98)
Treatment [a]	0.2	(0.19-0.21)	2.01	(1.83-2.20)	0.43	(0.39-0.47)
Time (years) [b]	1.08	(1.06-1.10)	1.15	(1.12-1.18)	1.11	(1.06-1.15)
Time by gender interaction	1.02	(1.00-1.04)	1.00	(0.97-1.03)	1.00	(0.95-1.04)
Time by age < 50 interaction	0.96	(0.92-1.00)	0.99	(0.93-1.05)	0.88	(0.82-0.95)
Time by age ≥ 65 interaction	1.00	(0.98-1.02)	1.06	(1.02-1.09)	0.99	(0.94-1.05)

[a] Prescription of oral antidiabetic agent or insulin in glycemia model; prescription of lipid-lowering drug in cholesterol model; prescription of antihypertensive drug in blood pressure model.
[b] Continuous variable defined as current year minus 1996 for glycemia and cholesterol models, and current year minus 2000 for blood pressure model.

5.3 Annual health care costs of patients with type 2 diabetes (Paper III)

5.3.1 Objective and methods

The objective of Paper III was to examine medical resource use of RECAP-DM study patients and to estimate annual costs of health care. Annual quantities of medical resource use were estimated for years 2000-2004. Years prior to 2000 were not considered due to the fact that records of care-giver contacts in primary care were not available before mid-1999. Nor was year 2005 considered since the observation period ended in October 2005 and estimation of annual quantities required data on resource use for a full year. Annual health care costs were estimated for year 2004 alone.

Quantities of resource use were estimated at the per-patient level using a prevalence-based approach, with study patients counted as prevalent cases of type 2 diabetes as described in section 5.1.1, i.e. from the year they were included in the study cohort until the year of their last record of any kind in the extracted primary care data. The resource items for which data was available were: care-giver contacts within primary care; outpatient hospital visits at Uppsala Akademiska Hospital; inpatient care; cardiac surgical procedures; dialysis; antidiabetic, lipid-lowering and antihypertensive drugs; and prescription devices for glucose monitoring and injection of insulin.

Health care costs incurred by each patient were estimated by multiplying annual quantities of resource use for 2004 by the relevant unit costs (in 2007 prices).

5.3.2 Results

Type 2 diabetic patients included in the RECAP-DM study required steady annual amounts of outpatient care and slightly increasing amounts of inpatient care during years 2000-2004 (Table 9). Higher rates of hospitalisation (12% in 2000 compared with 16% in 2004) led to an increase in the mean (SD) number of inpatient days from 2.3 (11.8) to 2.7 (11.9) between years 2000 and 2004 (p=0.04 for difference). In the field of outpatient care and considering all patients, the mean (SD) number of visits to a general practitioner (GP) was 2(2) and the mean (SD) number of outpatient hospital visits was 2(4) during all studied years.
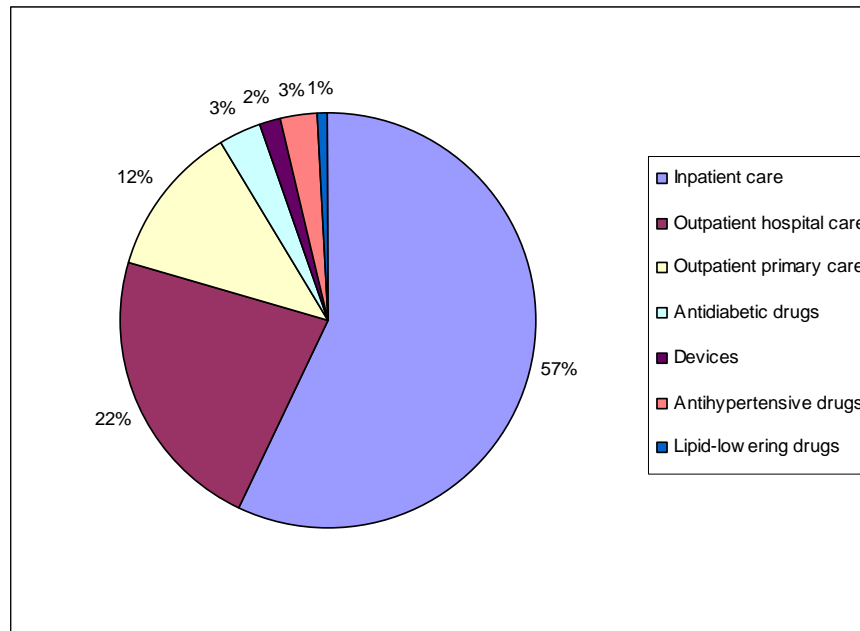
Table 9. Annual resource use of prevalent cases of type 2 diabetes, 2000-2004

	2000	2001	2002	2003	2004
N	6 711	7 256	7 598	7 961	8 230
Hospitalised during the year	837 (12)	962 (13)	1 120 (15)	1 233 (15)	1 307 (16)
Mean (SD) no of inpatient days, hospitalised pts	19 (29)	18 (25)	18 (28)	18 (28)	17 (26)
Mean (SD) no of inpatient days, all pts	2 (12)	2 (11)	3 (13)	3 (13)	3 (12)
PCI performed	62 (1)	66 (1)	67 (1)	83 (1)	91 (1)
CABG performed	26 (0.4)	18 (0.2)	24 (0.3)	28 (0.4)	26 (0.3)
Visited outpatient hospital facility	3 389 (50)	3 749 (52)	3 954 (52)	4 082 (51)	4 198 (51)
Mean (SD) no of visits, pts using services	4 (5)	4 (5)	4 (5)	4 (5)	4 (5)
Mean (SD) no of visits, all pts	2 (4)	2 (4)	2 (4)	2 (4)	2 (4)
Contacted outpatient primary care	6 084 (91)	6 558 (90)	6 909 (91)	7 349 (92)	7 708 (94)
Mean (SD) no of GP visits, all pts	2 (2)	2 (2)	2 (2)	2 (2)	2 (2)

Note: Data are reported as number (%) of patients unless otherwise indicated.

Based on resource quantities consumed in 2004, the mean (SD) total health care cost incurred by study patients was estimated at €3 602 (€9 537). Though a minority of patients were hospitalised during the year, inpatient care was the major contributor to costs, accounting for 57% (€2 051) of mean total health care costs (Figure 6). At €810, outpatient hospital care was the second most important resource component, accounting for 22% of total health care costs. Costs of antidiabetic, antihypertensive and lipid-lowering drugs accounted for 7% of total health care costs.

Figure 6. Distribution of annual health care costs of RECAP-DM study patients, year 2004

Pie chart legend:
- Inpatient care
- Outpatient hospital care
- Outpatient primary care
- Antidiabetic drugs
- Devices
- Antihypertensive drugs
- Lipid-lowering drugs

Values shown: 57%, 22%, 12%, 3%, 2%, 3%, 1%

No distinction was made between diabetes-related and non-diabetes-related resource use, thus the estimates of Paper III should be interpreted as resource use and costs incurred by patients with type 2 diabetes rather than resource use and costs attributable to type 2 diabetes.

5.4 The impact of myocardial infarction and stroke on health care costs (Paper IV)

5.4.1 Objective and methods

The objective of Paper IV was to determine the immediate and long-term impact of acute myocardial infarction (AMI) and stroke on health care costs in patients with type 2 diabetes.

While Paper III estimated health care costs incurred in year 2004, we now similarly estimated health care costs incurred by prevalent study cases during all five years 2000-2004 by multiplying annual quantities of resource use (from Paper III) by the relevant unit costs (in 2007 prices). All observations were subsequently merged to create a panel dataset covering years 2000-2004, in which patients thus had a minimum of 1 and a maximum of 5 observations on health care costs, each pertaining to one calendar year between 2000-2004.

For each year between 2000 and 2004, patients suffering an AMI or stroke were identified in the National Patient Register according to the relevant ICD-10 codes, with first events distinguished from recurrent events. Additionally, patients having suffered a prior AMI or stroke were identified for each of years 2000-2004, using ICD-9 and ICD-10 codes applied to the Patient Register data from 1987-2004.

A population-averaged panel data regression model which accommodated the within-patient correlation between outcomes was used to estimate the immediate and long-term impact of AMI and stroke on health care costs, while controlling for age, gender, amputation and presence of renal failure, heart failure and diabetic eye disease.

5.4.2 Results

Suffering an AMI was associated with a 4.1-fold increase in total health care costs during the year of the event, irrespective of whether the AMI was a first or recurrent event. Suffering a stroke was associated with a 6.5-fold increase in total health care costs if the stroke was a first-time event (95% CI 4.9-8.5) and with a slightly lower 6.4-fold increase in total costs when all events were considered (95% CI 5.0-8.1). For both AMI and stroke, the increase in costs was largely accounted for by inpatient care.

As for the economic impact of these events in subsequent years, annual health care costs of patients having suffered a first AMI were 1.1 times higher than those of event-free patients (95% CI 1.0-1.3) while annual health care costs of patients having suffered a first stroke were 1.4 times higher (95% CI 1.2-1.6) if recurrent events were not controlled for. However, in the models which incorporated all events, expected annual costs of patients with a history of an AMI or stroke were not found to be higher than patients without a history of these events. It thus appears as if the increased costs in years following a first AMI or stroke were accounted for by recurrent events. Expected values of health care costs associated with an AMI or stroke (first or recurrent) during the year of the event as well as during subsequent years for the average study patient are reported in Table 10.

Table 10. Expected values of annual health care costs (2007 euros) [a]

Complication	Total costs	Inpatient costs	Non-inpatient costs
All events			
AMI	€ 10 107	€ 7 438	€ 1 807
Post-AMI	NS	NS	NS
Stroke	€ 15 782	€ 12 445	€ 1 758
Post-stroke	NS	NS	€ 1 196
No complications	€ 2 466	€ 1 146	€ 1 316

[a] For average study patient (69-year old male) without amputation, renal failure, heart failure and diabetic eye disease. NS, non-significant compared to patient with no complications.

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6. DISCUSSION

6.1 Using medical records from clinical practice

This thesis illustrates how computerised medical records from real-life clinical practice can be used to retrospectively identify cohorts of patients with a specific disease, how record linkage can be used to retrieve information from complementary health care registers, and how epidemiological and health economical research questions can be studied through analysis of the resulting datasets.

Compared to prospective data collection, computerised medical records and registers provide an efficient means of obtaining health care data for large numbers of patients at a fraction of the cost. Sweden has several high quality national health care registers which are accessible for research upon ethical approval and though primary care data is currently not collected at the national level, data from individual counties or primary care centers may be extracted as was done within the RECAP-DM study. The primary care data on lab values and blood pressure which are available for each measurement occasion constitutes a particularly valuable asset for outcomes research. In comparison, lab values and blood pressure among patients enrolled in the Swedish NDR are only reported once yearly.

A major strength of computerised medical records as a source of data for research is that they reflect actual practice patterns and are free from the recall bias potentially seen in data collected through patient surveys. Within this thesis, the absence of recall bias is particularly relevant to the analysis of resource use and costs conducted in Paper III. Also, compared to survey-based studies in which patients are invited to participate, or the NDR which is based on voluntary participation, the risk of selection bias is small.

Since computerised medical records can be obtained from geographically defined populations, they may also be used to answer research questions which require population-based settings, for example studies of prevalence and incidence of disease, as was done in Paper I.

6.2 Data source limitations

The fact that computerised medical records reflect clinical practice may also be viewed as a weakness. Clearly, nothing but was has been recorded by the treating physicians or nurses can be analysed. Parameters which are of high importance in type 2 diabetes such as levels of physical activity, smoking status, BMI and waist-to-hip ratio are highly underreported. Furthermore, since the computerised medical records reflect day-to-day clinical practice they do not include systematic information on medical history. Diabetes duration or initial date of diagnosis was a parameter that we repeatedly lacked. Notably, in the calculation of type 2 diabetes incidence within Paper I, operational definitions of incidence had to be used.

Since data is not recorded for research purposes or according to any protocol, values for variables such as HbA1c and cholesterol were only available whenever these tests were conducted in clinical practice and not at regular intervals as in a clinical trial. Data availability therefore varied between variables and between patients. In Paper II, a substantial proportion of patients lacked measurements of HbA1c, total cholesterol and blood pressure and there is therefore somewhat of a risk of biased results stemming from potential differences in characteristics of patients with and without measurements. It is however interesting to note that values of the studied risk factors among type 2 diabetic patients enrolled in the NDR and patients included in the RECAP-DM study followed each other very closely. In 2003, mean values were 7.24% and 7.20% for HbA1c, 5.08 mmol/l alike for total cholesterol, and 146.2 mmHg and 145.8 mmHg for systolic blood pressure among NDR and RECAP-DM patients, respectively (73).

Computerised medical records do not constitute a register in the traditional sense and we did not conduct any formal evaluation of completeness or quality, as is typically done for the Swedish national health care registers. The study inclusion criteria related to OAD prescription and FBG/FPG in the diabetic range which we applied in addition to the inclusion criterion of type 2 diabetes diagnosis were in fact added due to uncertainty regarding the completeness of data on diagnosis. It is for example uncertain whether GPs record the ICD-code for type 2 diabetes at contacts with patients who are known cases or are seeking care for an issue unrelated to their diabetes.

The accuracy of the extracted primary care data was validated against individual patient files at the primary care center of Eriksberg to certify the performance of the data extraction program but further assessments of completeness and quality will be important, particularly since computerised medical records are likely to be used increasingly for epidemiological research in coming years.

6.3   Identification of patients with type 2 diabetes

Retrospective identification of individuals with type 2 diabetes in computerised medical records clearly implies that only diagnosed cases can be studied. In contrast, survey-based studies have the possibility of identifying cases of known diabetes as well as previously undiagnosed diabetes in samples of the general population, e.g. through administration of OGTTs.

Since the onset of diabetes is gradual, symptoms may go unnoticed and it is well-known that many patients with type 2 diabetes remain undiagnosed. A recent US study found that crude prevalence of diabetes (types 1 and 2) in people aged >=20 years was 12.9%, of which approximately 40% was undiagnosed (90). Within Swedish survey-based studies conducted in recent years, the ratio of diagnosed to undiagnosed cases of diabetes was approximately 1:1 in the study conducted by Brohall et al. among 64-year old women in Göteborg (63) and 3:2 in the study by Rosengren et al. among 50-year old men in Göteborg (68). In Uppsala county, type 2 diabetes is not systematically screened for but guidelines for diabetes care issued by the county council in 2004 recommend opportunistic screening among individuals presenting with the metabolic syndrome,

coronary heart disease, foot wounds, family history of diabetes or history of gestational diabetes.

We used computerised medical records from primary care to identify patients with type 2 diabetes. While the great majority of Swedish patients with type 2 diabetes are cared for by GPs and diabetes nurses in primary care, some may be cared for at outpatient hospital clinics and will not have been captured. Elderly patients staying at nursing homes in Uppsala county are in contrast visited by GPs and diabetes nurses and are included in the computerised medical records we obtained. A previous study in the municipality of Tierp found that 79% of patients with diabetes (types 1 and 2) could be identified in primary care (91), but type 1 patients which constitute 10-15% of cases are typically cared for in the outpatient hospital setting; the corresponding figure in the county of Medelpad was 92% (type 2 only) (92).

A case-finding algorithm encompassing the three inclusion criteria was applied to the medical records of the participating primary care centers with the aim of including all patients with type 2 diabetes. Additional exclusion criteria were applied to avoid the inclusion of patients with type 1 diabetes or other types of diabetes. Nevertheless, certain patients may have been unduly excluded (e.g. type 2 diabetic patients <40 years prescribed insulin but no OAD) while other may have been mistakenly included (e.g. patients prescribed metformin off-label).

Since the numbers of patients mistakenly excluded or included are likely to be very small, the effect on the results of this thesis should be minor. But what does it mean for the results that we have captured diagnosed cases but not undiagnosed cases and patients cared for in primary care but not patients cared for in other settings?

- For Paper I, it is clear that true prevalence of type 2 diabetes is significantly underestimated. Assuming that the ratio of diagnosed to undiagnosed cases is 3:2, and that 8% of diagnosed cases are not captured in primary care, crude prevalence in 2003 would be 5.7% instead of 3.5%.

- For Paper II, if undiagnosed cases of type 2 diabetes are so because they have fewer symptoms and have not yet developed diabetes-related complications, true control of risk factors may be better than what is reported. On the other hand, patients cared for in specialist settings are likely to have worse control of risk factors. Changes over time in the ratio of diagnosed to undiagnosed cases and in the proportion of patients cared for in settings other than primary care will in this case also affect observed trends in control.

- For Papers III and IV, patterns of resource use are clearly likely to be different for undiagnosed cases of type 2 diabetes (lower levels) and for cases cared for in specialist settings (higher levels). It should be kept in mind that our results pertain to the typical diagnosed type 2 diabetic patient identified in primary care.

6.4   Prevalence counts

Papers I, III and IV all rely on the categorisation of patients as "prevalent cases" of type 2 diabetes. In Paper I, the number of prevalent cases was divided by the number of residents in the source population to obtain the prevalence rate of type 2 diabetes in a given year; in Papers III and IV, resource use and costs were similarly estimated for prevalent cases of type 2 diabetes. The concept of a prevalent case has been defined as a subject with a given disease or condition, who is alive in a defined population at a given time (93). As illustrated by Table 7, we counted study patients as prevalent cases of type 2 diabetes from the year they were included in the RECAP-DM study cohort until the year of their last record of any kind in the Uppsala county primary care data.

An alternative way of assigning prevalence status would have been to count patients as prevalent cases as of the year of their inclusion in the study and each year thereafter until the end of the observation period, with no consideration of the year of their last record in the primary care data, but with right-censoring at death. The reason we did not choose this approach was that we did not want to risk including patients who had moved to other counties in the prevalence counts. It is however clear from Table 11 that prevalence counts are higher if right-censoring is applied at death instead of at the last primary care record. This table reports prevalence counts for years 1999-2003 as well as crude prevalence rates of type 2 diabetes using both methods.

Table 11. Alternate ways of assigning prevalence status within the RECAP-DM study

	1999	2000	2001	2002	2003
Prevalent cases, right censoring at last primary care record*	6 161	6 711	7 256	7 598	7 961
Source population	224 575	225 943	227 810	229 367	230 750
Crude prevalence of type 2 diabetes	2.7%	3.0%	3.2%	3.3%	3.5%
Prevalent cases, right censoring at death	6 493	7 079	7 695	8 135	8 637
Source population	224 575	225 943	227 810	229 367	230 750
Crude prevalence of type 2 diabetes	2.9%	3.1%	3.4%	3.5%	3.7%

*as in Papers I, III and IV

It is unlikely that migration accounts for the full difference in prevalence counts between the two methods and it therefore appears as if the number of prevalent cases of type 2 diabetes has been underestimated by applying right censoring at the last primary care record. Since patients missed out through this method are those who have not sought regular primary care, one would expect that they represent either severe cases who are cared for in specialist settings, or mild cases that do not require renewal of drug prescriptions or see the need for regular care.

In retrospect, it would have been better to apply right-censoring of prevalence status at death and to request data from Statistics Sweden on the residential address of study patients, in order to be able to subtract those who had moved from Uppsala county. For the results of Paper I, the resulting higher prevalence counts would imply slightly higher prevalence rates of type 2 diabetes (approximately 0.2% in absolute terms, see Table 10) and possibly an impact on the prevalence of complications, depending on the

characteristics of presently "uncounted" patients. For the results of Papers III and IV, mean quantities of resource use and costs could also be affected, for example if uncounted patients represent mild cases.

In Paper I, prevalent cases should also have been subtracted from the source population denominator when calculating annual incidence rates of type 2 diabetes. This was not done and though it leads to incidence rates which are only marginally higher (approximately 0.1/1 000 each year), it constitutes a methodological error since the denominator of the incidence rate should be the population at risk of disease.

6.5   The source population

A population-based study has been defined as a study of properties of "a well-defined population, such as individuals residing in a defined geographic region in a given time period" (93). Within the papers of this thesis, the RECAP-DM study is referred to as a population-based study of type 2 diabetic patients in Uppsala county. This is not entirely accurate since the true source population was that served by the 26 participating primary care centers. The RECAP-DM study was population-based in the sense that it covered the population served by the 26 participating centers of Uppsala county; it is strictly speaking a question of external validity whether results are applicable to Uppsala county as a whole.

All citizens of Uppsala county are automatically listed at a public primary care center according to their residential address so the population uptake of the 26 centers was geographically defined. This area listing can however be superseded through active listing of an individual at a public primary care center or private GP of his or her choice. The county council keeps track of the numbers of area-listed individuals and the numbers who have actively listed themselves with alternative caregivers. For the analysis of prevalence and incidence described in Paper 1, a list for year 2004 was provided, enabling calculation of the proportion of the total county population that was listed at the 26 study centers (= 77%).

What we do not know is if the remaining 23% (individuals listed at the five public centers not participating in the study and individuals actively listing themselves with private GPs) differed from the rest in terms of age, gender and other risk factors for type 2 diabetes. Data on demographic characteristics of residents served by individual primary care practices was not available and we therefore assumed that the population listed with the 26 centers participating in the study had the same age and sex distribution as the total population of Uppsala. There is however a possibility of some variation between the population served by the study centers and that of the county as a whole. A greater proportion of health-conscious, younger individuals may for example have actively listed themselves with private GPs in which case prevalence and incidence of type 2 diabetes reported in Paper I would be underestimated for the lower age-groups and overestimated for the higher age-groups.

Among the three study centers late to computerise, whose observation period consequently began later, Flogsta served a relatively young and Gottsunda a relatively

socioeconomically weak population so the fact that they were excluded from estimations of prevalence/incidence during the first few years of the study may have inflicted a slight bias on estimates.

Furthermore, since we were only provided with the capitation list for 2004, it was assumed that the population coverage proportion of 77% was applicable to all years. It could be that the population served by the 26 centers fluctuated somewhat over time if rates of active listing increased or decreased, which would affect estimates of prevalence and incidence.

6.6   The "epidemic" of diabetes

There is a widespread notion that a diabetes epidemic is underway (94). The term 'epidemic' is typically used within infectious diseases to characterise an unusually high occurrence of a disease (95). If "unusually high occurrence of disease" is interpreted as a higher than usual proportion of individuals carrying a disease, it seems incontestable, albeit somewhat sensationalistic, to speak of a diabetes epidemic. The number of individuals with type 2 diabetes is increasing rapidly worldwide and, as previously mentioned, the WHO has projected an increase in the global prevalence of diabetes from 2.8% in the year 2000 to 4.8% in 2030 (1).

If, however, "unusually high occurrence of disease" is interpreted as a higher than usual number of new cases of disease, matters are somewhat different. Internationally, there have been several studies reporting increased incidence of type 2 diabetes. For example, analyses of health care databases conducted by Lipscombe and Hux (96) showed a 31% increase in annual incidence of diabetes (from 6.6/1 000 to 8.2/1 000) between years 1997 and 2003 in the province of Ontario, Canada. In the UK, Gonzalez et al. (97) observed an increase in type 2 diabetes incidence from 2.6/1 000 in year 1996 to 4.3/1 000 in 2005. In Sweden however, we are yet to see a study reporting increased diabetes incidence, as neither the results of Paper I, nor previous studies of trends in Skaraborg county and Laxå municipality show evidence of this (61;64). Paper I grants support to the notion of a diabetes epidemic in the sense of increasing prevalence of disease but not in the sense of increasing incidence.

The fact that we did not find evidence of increasing type 2 diabetes incidence is somewhat surprising given the increased rates of overweight and obesity seen in several Swedish studies (98). This inconsistency is comparable to the well-documented decrease in CVD incidence and mortality seen over the past decades despite increasing rates of overweight and obesity (99-101). Improvements in other risk factors such as blood pressure, smoking and cholesterol appear to explain the decline in CVD (102;103) and may play a role in the absence of trend observed for type 2 diabetes incidence. Interestingly, it has for example been shown that obese Swedish men in their fifties today have much lower levels of other CVD risk factors compared with obese men in their fifties 40 years ago (68).

If increasing type 2 diabetes prevalence is not explained by increasing incidence, what is driving it? Colagiuri et al. (104) have proposed a simple epidemiological model which illustrates five factors directly affecting the prevalence of diabetes (Figure 7).

Figure 7. Factors affecting diabetes prevalence
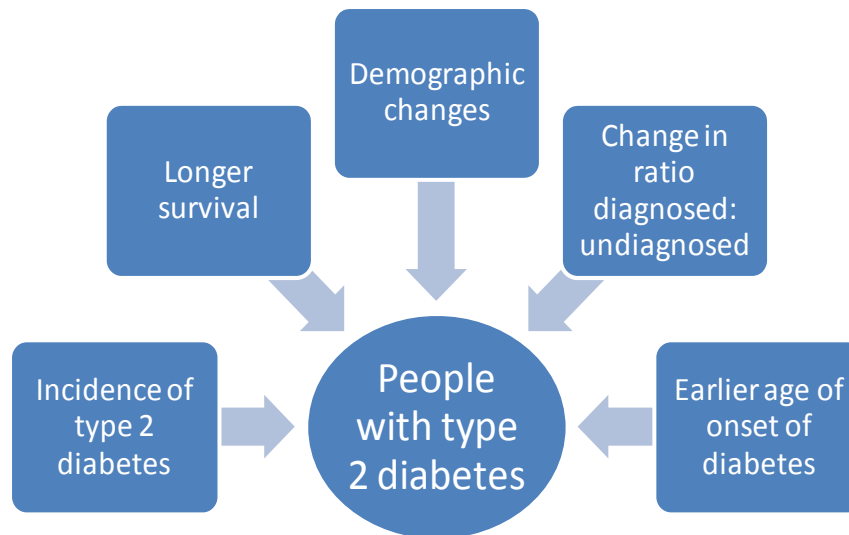
Note: Adapted from article by Colagiuri et al. (104)

However, none of these five factors appear to explain the full increase in prevalence seen in Paper I:

- **Incidence of type 2 diabetes:** As discussed above, we did not find evidence of increasing type 2 diabetes incidence within any age stratum. In the older age-groups incidence was even declining. However, since our study was restricted to diagnosed cases, the possibility remains that true type 2 diabetes incidence is increasing but that the **ratio of diagnosed to undiagnosed cases** is falling. Since we observed a relatively stable total incidence of diagnosed cases, a true increase in diabetes incidence would however require the ratio of diagnosed to undiagnosed cases to have been decreasing steadily each study year, which seems unlikely.

- **Longer survival:** Age- and sex-adjusted mortality among type 2 diabetic patients included in the RECAP-DM study was found to decrease by 4% per year between 1996 and 2003. Although clearly contributing to increased prevalence, this decline in mortality accounts for only a small part of the period increase in diabetes prevalence.

- **Demographic changes:** Population demographics can not explain increasing prevalence over the period since changes in the age and sex distribution of the underlying population were controlled for in the logistic regression model, and there was still a 6% annual increase in prevalence. Immigration rates to Uppsala were fairly constant during the study period (0.4-0.5% in the population >=30 years) giving little reason to believe that changes in the ethnic distribution of the underlying population impacted on prevalence estimates (88).

- **Earlier age of onset of diabetes:** What can be studied in register-based analyses such as the present is whether diabetes is being detected earlier. A recent study of diabetes prevalence in a large region in the UK concluded that prevalence was increasing predominantly as a result of increased detection prior to development of vascular complications (105). In the RECAP-DM study cohort, the decreasing mean age of incident cases of type 2 diabetes during years 1996-2003 appears to reflect somewhat decreased rates of type 2 diabetes incidence/detection among the older age-groups rather than increased incidence/detection among the younger age-groups.

Indeed, in addition to the five factors depicted above, Colagiuri et al. point out that an imbalance between incidence and mortality, with higher numbers of incident cases than deaths among the diseased, will lead to a non-steady-state situation and to increasing prevalence. In an interesting projection model based on data from Scotland, it has been shown that the prevalence of type 2 diabetes in the region of Tayside would increase by 20% between years 2003 and 2013 even if incidence and mortality remained constant at year 2003 levels, simply because the number of patients diagnosed with type 2 diabetes each year is greater than the number of type 2 diabetic patients who die (106).

Within Paper I, we found increased type 2 diabetes prevalence to be driven by such a gap between incidence and mortality. Each of the studied years, the number of incident cases of type 2 diabetes greatly outnumbered the deaths among type 2 diabetic patients, leading to larger and larger prevalence cohorts. For example, 936 incident cases of type 2 diabetes were identified in 2001 while 330 patients with type 2 diabetes died the same year. Similar findings in a Danish study using data from a pharmaco-epidemiological database led the authors to label the diabetes epidemic a "statistical artefact" (107;108).

Whether the gap between incident cases of type 2 diabetes and deaths among diabetic patients we have observed in Uppsala county is a result of a previous rise in incidence which has reached a plateau, a previous rise in the rate of detection following from increased disease awareness, or of declining mortality is not possible to say with the data at hand. We are however inclined to believe that this gap has widened as a result of the decline in cardiovascular mortality observed in Sweden over previous decades. For example, using data on all individuals (diabetic and non-diabetic) discharged from hospitals or deceased with a diagnosis of AMI in Sweden, Rosén et al. found that the age-standardized attack rate of AMI declined by 11% for men and 10% for women between 1987 and 1995. Mortality from AMI decreased by 14% for both sexes over the period (101). Though the 4% annual age- and sex-adjusted decline in mortality we observed over the study period of 1996-2003 only explains a small part of the period increase in diabetes prevalence, if this decline has been in effect for a longer period of time, it may explain the current gap between incidence and mortality. As an example, if

mortality were to decline by 4% annually over a period of 30 years, this would amount to a 70% reduction in the number of deaths (0.96^30).

6.7 Perspectives in cost of illness studies

The case for a societal perspective in the economic evaluation of medical innovations is strong in Sweden (109). In the guidelines for economic evaluation issued by the Swedish Dental and Pharmaceutical Benefits Agency, it is stated that "all relevant costs associated with treatment and disease should be identified, quantified and valued." This includes costs of production foregone, which should be estimated using the human capital method (110).

To be useful for economic evaluations, Swedish cost of illness studies should thus produce estimates which encompass all relevant costs. In practice however, conducting a cost of illness study is the art of the possible. The data on resource use available for the analyses of Papers III and IV implied a restricted county council perspective. The following costs should have been included for the county council perspective to have been complete:

- **Costs of private health care providers.** In particular, most of diabetic foot care and a significant part of all screening for diabetic retinopathy are provided by private health care providers, who are subsequently reimbursed by the county council.

- **Costs of outpatient hospital visits at Enköpings lasarett.** Enköpings lasarett is the second hospital in Uppsala county but we only obtained data on visits from Akademiska, the largest county hospital. In 2010, there were a total of 4,759 episodes of inpatient or outpatient care at Enköpings lasarett and a total of 74,868 at Akademiska hospital (111).

- **Costs of aids.** The county council reimburses aids such as diabetic footwear and low vision aids which are of importance to patients with type 2 diabetes.

The omission of these costs implies that, even from a county council perspective, the costs of patients with type 2 diabetes reported in Papers III and IV are underestimated. For a societal perspective, the following are important items which should additionally have been quantified and valued:

- **Indirect costs.** As reported in section 3.3.1, the study by Henriksson et al. from 1994 found that indirect costs arising from diabetes-related short-term illness, early retirements and premature death accounted for 57% of total costs among patients with diabetes (81).

- **Costs of community care services and institutionalised care.** These services are provided by the municipalities, of which there are 8 in Uppsala county (Enköping, Heby, Håbo, Knivsta, Tierp, Uppsala, Älvkarleby, Östhammar).

These costs are clearly substantial and are important to include in future studies to the greatest possible extent.

As previously mentioned, no distinction was made between diabetes-related and non-diabetes-related resource use in the analyses of Papers III and IV. Thus the estimates should be interpreted as resource use and costs incurred by patients with type 2 diabetes rather than resource use and costs attributable to type 2 diabetes. It is a clear limitation that we did not have access to data on resource use from a control group of individuals without type 2 diabetes identified at the participating centers in order to determine the excess cost of the disease. In comparison, Wiréhn et al. (77) obtained data on health care costs for all residents of the county of Östergötland during year 2005 and could thereby estimate costs incurred by the diabetic and non-diabetic populations (at €4 474 and €2 504, respectively).

6.8   Health policy implications

Though not attributable to increasing incidence, the increasing prevalence of type 2 diabetes we observed in Uppsala county is clearly a phenomenon that the health care system has to accommodate. Unless there has been an outright decline in incidence since year 2003, the gap between the number of incident cases of type 2 diabetes and deaths among diabetic patients is likely to have persisted since our study ended, or even to have widened due to a further decline in mortality. Assuming that prevalence has continued to increase by an annual 6%, which was the age- and sex-adjusted rate of increase over the study period 1996-2003, type 2 diabetes prevalence in the present year 2011 would be 5.6%. This imposes a considerable burden. In particular, Paper I showed that 14% of female patients and 18% of male patients with type 2 diabetes suffered from CVD which had led to hospitalisation.

Since we have not had access to data on resource use for a control group of non-diabetic patients, we can not say what excess burden the increased prevalence of type 2 diabetes imposes on the health care system. Nor does a cost of illness study such as the one we have conducted in Paper III offer guidance on how resources should be allocated. Instead the estimates of Paper III offer a descriptive picture of the resource use and costs being incurred by type 2 diabetes patients in clinical practice. Hopefully, these estimates can be used to inform budget and capacity planning.

As for the estimates of Paper IV, we hope they will be used as input into economic evaluations of treatments for type 2 diabetes. The market for antidiabetic drugs is growing in response to the increasing global prevalence of type 2 diabetes and the pipelines of nearly all large pharmaceutical companies contain antidiabetic agents. There will be an increased need to evaluate the extent to which these new treatments provide value for money.

The positive trend in control of risk factors which we observed in Paper II is a credit to the management of type 2 diabetes in Uppsala county over the study period. Notably,

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the proportion of patients with HbA1c <7% increased from 38% in 1996 to 56% in 2005 even though rates of prescription of antidiabetic drugs were constant. This is a signal of more effective drug treatment and/or improved general management. Indeed, in 1996 the county council of Uppsala assigned funding for the creation of "diabetes teams" at each primary care center which involved training of diabetes nurses, designation of a physician responsible for keeping staff up to date on diabetes care, and organised cooperation with dieticians and foot therapists. Nevertheless, further improvements in education, lifestyle management and pharmacological treatment could increase the number of patients reaching treatment goals for cardiovascular risk factor control.

7. CONCLUSIONS

This thesis has contributed to increased knowledge of the epidemiology of type 2 diabetes in Sweden and has provided estimates of health care costs which may be used to inform capacity planning and as input into economic evaluations. This thesis has also shown that computerised medical records from geographically defined populations offer ample possibilities of conducting epidemiological and health economical research reflecting real-life clinical practice. This is particularly the case in Sweden where record linkage can be used to retrieve complementary health care data from national registers.

The specific studies of this thesis concluded that:

- In the population served by the 26 primary care centers of Uppsala county participating in the RECAP-DM study, crude type 2 diabetes prevalence increased from 2.2% to 3.5% between years 1996 and 2003 but no increase was observed for type 2 diabetes incidence. Instead, increasing prevalence was a product of the number of patients diagnosed with type 2 diabetes each year being higher than the number of deaths among type 2 diabetic patients, as well as of declining mortality.

- There was a clear overall improvement in control of glycemia, total cholesterol and blood pressure between years 1996-2005 among type 2 diabetic patients included in the study. Nevertheless, a substantial proportion of patients did not achieve adequate control of these risk factors for cardiovascular disease, in particular with regard to blood pressure.

- Mean annual health care costs incurred by type 2 diabetic patients in Uppsala county during year 2004 were estimated at €3 602. This figure included primary care, outpatient hospital care, inpatient care, dialysis, drugs (antidiabetic, antihypertensive and lipid-lowering) and devices for glucose-monitoring and injection of insulin. Inpatient care was the major contributor to costs, accounting for 57% of total costs.

- Total health care costs of type 2 diabetic patients in Uppsala county who suffered a first AMI/stroke increased by 4.1/6.5 during the year of the event and by 1.1/1.4 during subsequent years, controlling for age, gender, the event of amputation and presence of renal failure, heart failure and diabetic eye disease. The increased health care costs in years subsequent to an AMI/stroke appeared to be explained by recurrent events of AMI/stroke.

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