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Epidemiological studies on complications in type 1 diabetes

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To my family and in the memory of my beloved mother

with love and gratitude

ABSTRACT

The main threat to the health of patients with type 1 diabetes (T1DM) is its complications. This thesis aimed to assess the risks of hip fracture, non-trauma lower extremity amputation (LEA) and myocardial infarction in patients with T1DM as well as the fertility in women with T1DM.

In the Swedish Inpatient Register, we identified a population-based cohort of T1DM patients who were first hospitalized for diabetes before age 31. Follow-up for outcomes of interest was done through cross-linkage of the Inpatient Register or linkage to the Causes of Death, Multi-Generation or Medical Birth Register. Standardized Hospitalization / Incidence / Fertility Ratios (SHRs, SIRs and SFRs) with 95% Confidence Interval (CI), were used to estimate relative rates. Poisson Regression modeling was used to compare the relative effects of the SHRs/SIRs/SFRs and the risk of LEAs in different calendar periods. The Kaplan-Meier method was used to estimate the cumulative probability of the outcome of interest.

Compared with the general population, more than 7-fold and 9-fold excess risks for hip fracture were observed in men and women, respectively. The cumulative probability of hip fracture was 6.58% until age 65. The risk of LEAs had decreased by 40% in the most recent calendar period (2000-2004) compared to the previous period. However, these patients still had an extremely high risk compared with the general population. By the age of 65, the cumulative probability of a LEA was 11.0% for women, and 20.7% for men. The SIRs for myocardial infarction among T1DM patients decreased from 32.3 for the period 1975-1984 to 15.3 for 1985-1994, and then decreased further to 9.7 for 1995-2004. The relative risk during the follow-up period 1995-2004 decreased by 50% compared to 1975-1984. Similar trends were observed for men and women, non-fatal and fatal myocardial infarction, although excess risks were notable for fatal myocardial infarction in women. No excess risk of myocardial infarction was observed for their non-DM brothers, while a modest excess risk was noted for their non-DM sisters. At age 65 the cumulative probability of a myocardial infarction was 28% for T1DM patients, while the corresponding figure for their non-T1DM siblings was 6%. The presence of diabetes complications conferred much higher risks for hip fracture, non-trauma LEAs and myocardial infarction. Reduced fertility was confined to women first hospitalized before 1985 and a normalization of fertility was observed in women who were first hospitalized after 1985. The presence of diabetes complications was associated with subfertility in all calendar-year strata. The proportions of newborns with congenital malformations decreased from 11.7% during 1973–1984 to 6.9% during 1995–2004, but were still higher compared to that of the women in the general Swedish population.

In conclusion, although relative risks for myocardial infarction, non-trauma LEAs decreased markedly with time and also fertility normalized in recent period, T1DM patients are still at increased risk for these complications, especially among those with diabetes complications. Better treatment of hyper-glycemia and hyper-lipidemia as well as hypertension are most probably the cause of the reduced risks. Effective early preventive programs should be further designed and implemented.

LIST OF PUBLICATIONS

I. Miao J, Brismar K, Nyrén O, Ugarph-Morawski A, Ye W: Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. *Diabetes Care* 28:2850-2855, 2005

II. Jonasson JM, Ye W, Sparén P, Apelqvist J, Nyrén O, Brismar K: Risk of lower extremity amputation in patients with type 1 diabetes – a population-based cohort study in Sweden. Submitted for publication

III. Jonasson JM, Brismar K, Östenson CG, Hergens MP, Gu HF, Nyrén O, Ye W: Falling risk of myocardial infarction in type 1 diabetes mellitus patients: Secular trends in a Swedish population-based cohort. Submitted for publication

IV. Jonasson JM, Brismar K, Sparén P, Lambe M, Nyrén O, Östenson CG, Ye W: Fertility in women with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care* 30:2271-2276, 2007

CONTENTS

LIST OF ABBREVIATIONS

CI	Confidence Interval
CVD	Cardiovascular Disease
ICD	International Classification of Diseases
IDF	International Diabetes Federation
LEA	Lower Extremity Amputation
NRN	National Registration Number
SIR	Standardized Incidence Ratio
SFR	Standardized Fertility Ratio
SHR	Standardized Hospitalization Ratio
T1DM	Type 1 Diabetes Mellitus
WHO	World Health Organization

1 INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a common chronic disease among children. It accounts for about 10% of all diabetes (1). The incidence is highest among Caucasian populations, particular in Finland and Sweden (2; 3). The incidence and prevalence of T1DM is increasing worldwide (4).

With tight metabolic control, improved preventive treatment, and life-style modifications, the long-term survival of T1DM patients has improved. At the diagnosis of T1DM, the presence of its complications is rare. Even with tighter glucose control, improved treatment of hypertension and hyperlipidemia, diabetic complications occur frequently with time (5). Poor blood glucose control and duration are well recognized risk factors (6-8). The fact that diabetic nephropathy and retinopathy cluster in families suggests that genetic factors also contribute to the development of diabetic complications (9; 10). These complications often result in clinical problems, which affect patients' quality of life and even the length of life. In 1989, the St. Vincent Declaration highlights the importance of the issues related to diabetes and set the general goals and 5-year targets for the treatment and health care of people with diabetes. The 5-year targets included reducing the occurrence limb amputation and coronary heart disease, and achieving normal pregnancy outcome for women with diabetes (11). Accordingly, Sweden made efforts to improve the diabetes care and the improvement in the glycemic and blood pressure controls has been reported (12; 13). Studies on long-term complicated health problems in T1DM patients and the trends over time which estimate the efficacy of the preventive programs are very important.

2 BACKGROUND

2.1 EPIDEMIOLOGY OF T1DM

Diabetes mellitus is caused by inherited and/or acquired deficiency in insulin production by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency or ineffectiveness result in increased concentrations of blood glucose, which in turn damage many of the body's system, in particular the blood vessels and nerves. Type 1 and type 2 diabetes are the main forms of diabetes.

As one of the most common non-communicable diseases worldwide, diabetes is one of the most challenging health problems in the 21st century (14). In most developed countries, diabetes is the fourth or fifth leading cause of death. Substantial evidence shows that it is also epidemic in many developing countries. The incidence of diabetes is increasing greatly worldwide (4). And this trend is likely to keep going in the future decades (15). Figures 1 and 2 show the estimated worldwide increasing prevalence of diabetes (16).

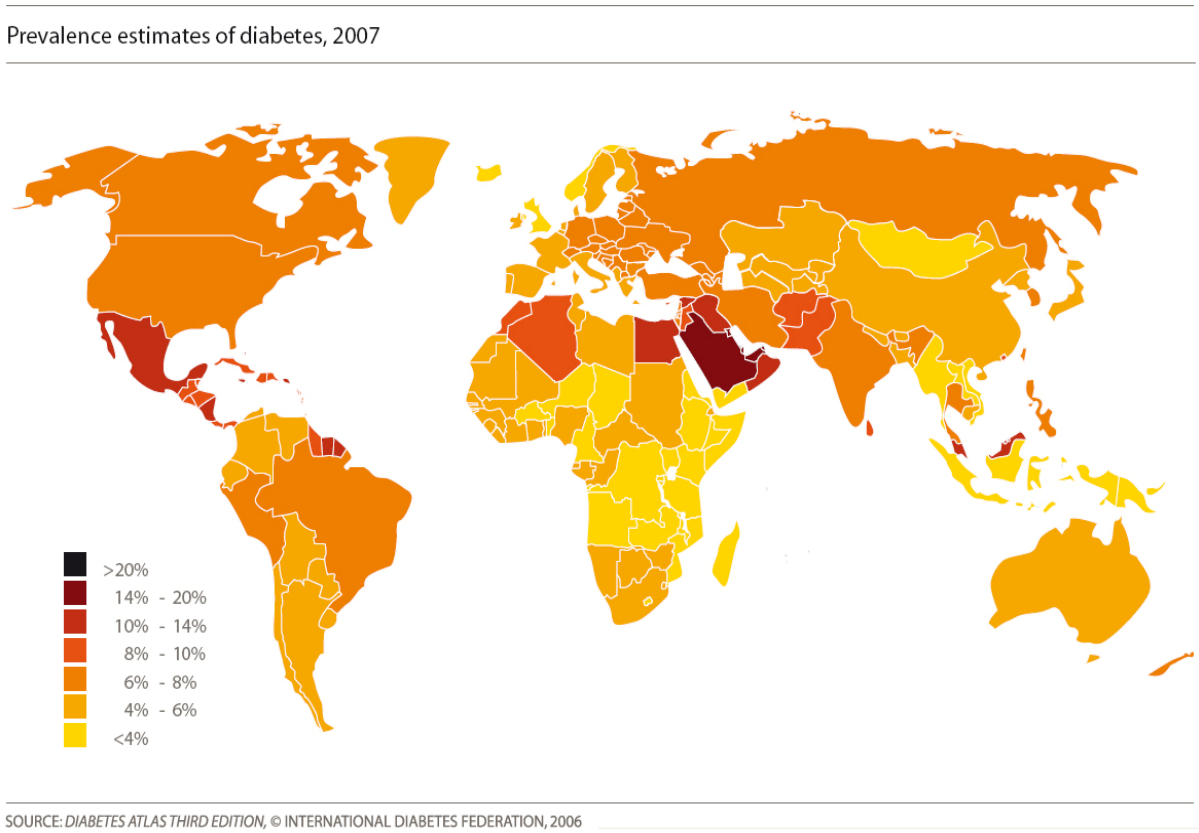


Figure 1. The global prevalence estimates of diabetes in 2007.

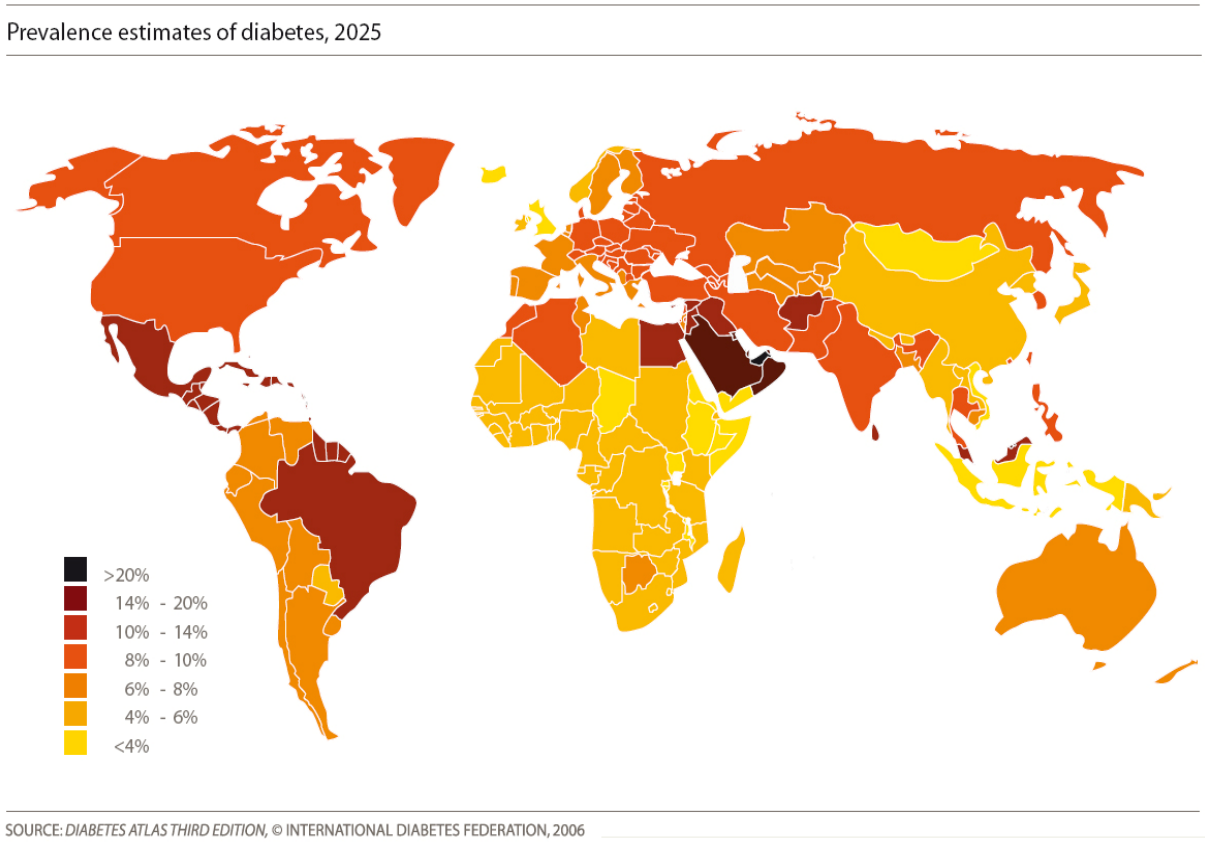


Figure 2. The global prevalence estimates of diabetes in 2025.

T1DM, previously defined as insulin-dependent or juvenile diabetes mellitus, is caused by β cell destruction, often immune mediated, that leads to loss of insulin secretion and absolute insulin deficiency. It accounts for about 10% of all diabetes (1). The incidence is highest among Caucasian populations, especially in Scandinavian countries, and is lowest in Asia and South America (2; 3). Sweden has the second highest incidence of the T1DM in children of the world (figure 3) (16). The incidence of T1DM is increasing worldwide (2; 4). A report in 1999 based on data of published incidence trends showed that the incidence of T1DM is increasing globally by 3.0% per year (17). However, studies from Sweden found no increase in the incidence of T1DM (18; 19), but shifted to a younger age at diagnosis (19). With the improvement in the metabolic control and diabetic care, life expectancy among patients with T1DM is gradually increasing. Consequently, the prevalence of T1DM is growing.

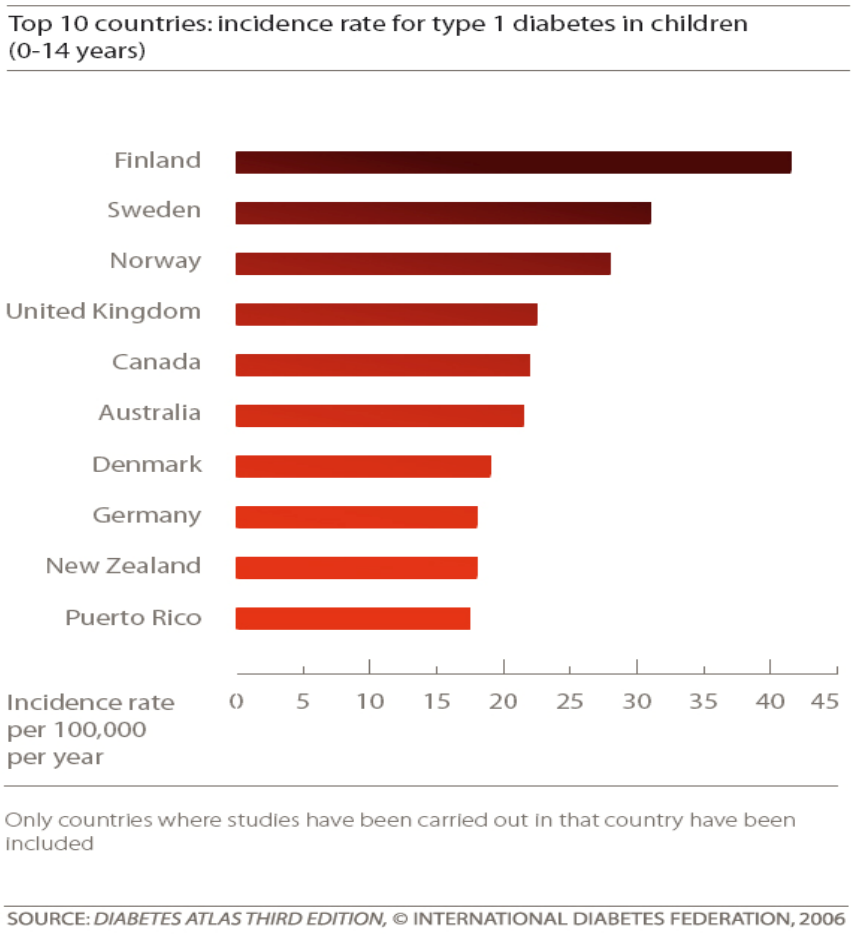


Figure 3. The top 10 countries with highest incidence rate for type 1 diabetes in children (0-14 years).

2.2 COMPLICATIONS OF DIABETES

The main threat to the health and quality of life of patients with T1DM is its complications which often lead to increasing disability, shortened life expectancy and enormous burdens to society. Even with tighter control and improvement in the treatment, diabetes often leads to complications which could be contributed by the

metabolic and haemodynamic abnormalities of diabetes (20). The development of the long-term diabetic complications is multi-factorial. One important risk factor is glycemic exposure which consists of hyperglycemia and the time. Genetic, environmental risk factors and gene-environment interactions of these factors are involved also (5).

The major types of diabetic complications are macrovascular and microvascular complications and neuropathy (figure 4). The macrovascular complications include cerebrovascular disease, coronary heart disease and peripheral arterial disease. The microvascular complications consist of diabetic retinopathy and nephropathy. In addition, the presence of diabetes is associated with many different health problems, such as hip fracture (21-31), subfertility and negative pregnancy outcomes (32-37), psychological problems (38-45) and cancers (46-59).

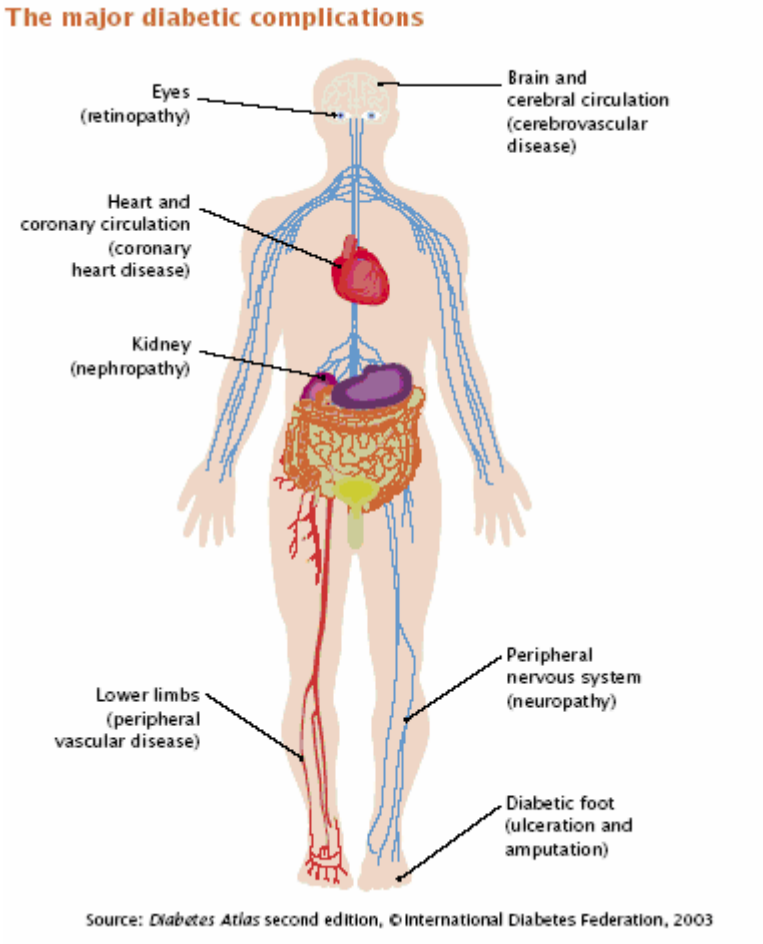


Figure 4. The major diabetic complications.

There have been few large scale population-based epidemiological studies on complications in type 1 diabetes, especially the complications included in this thesis which mainly focused on the risks of hip fracture, non-trauma lower extremity amputations (LEAs), myocardial infarction in patients with T1DM as well as fertility in

women with T1DM (figure 5). These complications are the end-stage of tissue and organ dysfunction developed due to metabolic disturbances.

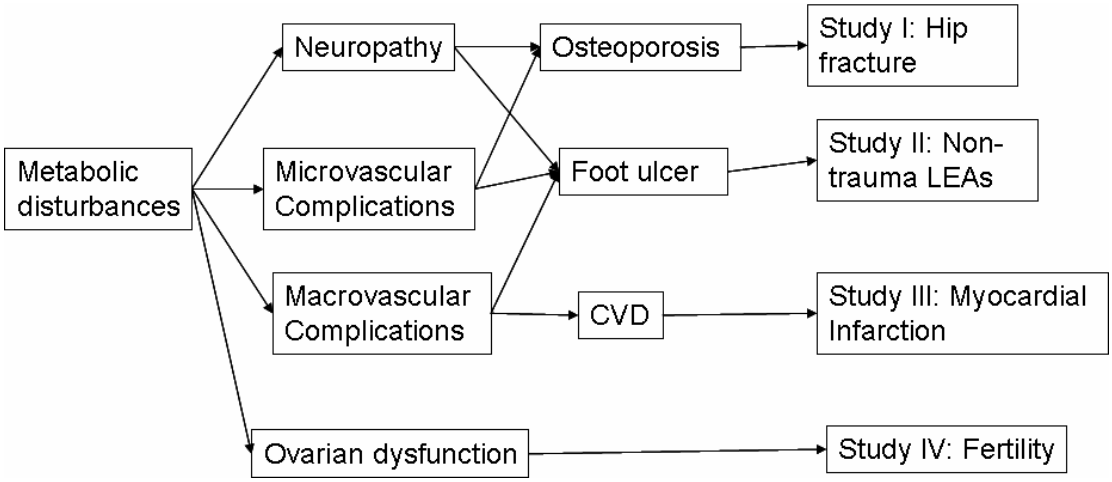


Figure 5. The studies included in this thesis.

2.3 HIP FRACTURE IN PATIENTS WITH T1DM

Hip fracture is a break near the top of the thighbone (femur) where it angles into the hip socket. It is associated with considerable morbidity and long-term mortality (60), posing a major and growing burden on health care. Old age, low bone mineral density, low body mass index, weight loss, tall stature, sedentary life style, cigarette smoking, moderate to heavy alcohol consumption, vitamin D deficiency and propensity for falls are proposed as risk factors for hip fracture (61). Both men and women with T1DM have been reported to have lower bone mineral density, one important risk factor for hip fracture (21-23; 62).

However, previous epidemiological studies on the risk of hip fracture among patients with T1DM have usually been of limited sample size, and their results are inconsistent. An increased hip fracture risk among post-menopausal women with T1DM was reported in some (29; 31), but not all (63; 64), previous investigations. The sparse data that existed regarding men with T1DM have been insufficient to confirm any significant excess risks (29; 64).

2.4 NON-TRAUMA LEAS IN PATIENTS WITH T1DM

Diabetic foot complications result in significant costs for society and individual patients (65). Approximately 20% of the total expenditure on diabetes care can be attributed to diabetic foot problems (66). Foot ulcers are the most common precursor of diabetes-related LEAs. The negative consequences of diabetic foot ulcers and especially amputation include reduced quality of life, increased morbidity, disability and premature mortality (67; 68). It has been claimed that a LEAs occurs every 30 seconds worldwide due to diabetes since 50% to 70% of all LEAs are related to diabetes (66).

Lower extremity amputation in patients with diabetes is related to increased postoperative mortality (69).

Diabetes-related lower extremity amputation rate has been considered an indicator of quality of diabetic foot care (70). In 1991, The World Health Organization (WHO) and International Diabetes Federation (IDF) initiated a program for improved diabetes care – the Saint Vincent Declaration (11). Certain goals were set up to reduce the incidence of diabetes related complications. One of these goals is to achieve a reduction of more than 50% in major LEAs caused by diabetes. In Sweden, the Medical Research Council (MFR) and the Development Institute for the Health and Social Services (Spri) launched a consensus (71) followed by the international consensus of the diabetic foot (WHO/IDF) (72). These consensus stated that a multidisciplinary approach including a preventative strategy, patient and staff education and multifactorial treatment which has been reported to be effective in reducing amputation rate (73).

A decreasing trend in the risk for LEAs was reported from the UK, the Netherlands and Finland (74-80). The implementation of preventive guidelines (78; 81) and better organized diabetes care (74) were reported to be associated with improved diabetic foot care, and in turn reduced LEAs. However, there was no large-scale epidemiological study on the change of non-trauma LEAs risk in patients with T1DM after 1999 when the national preventive consensus was introduced in Sweden.

2.5 MYOCARDIAL INFARCTION IN PATIENTS WITH T1DM

Myocardial infarction is related to a great burden of suffering and premature mortality (82). With the improvement in preventive intervention and medical treatment during the recent period, in general, the incidence and mortality of myocardial infarction has been reported to decrease over time in Sweden (82-84). In northern Sweden during 1989-2000, this decline in the incidence and mortality of myocardial infarction in people without diabetes but no such favorable trend in people with diabetes has been reported (85).

The prevalence of cardiovascular disease in T1DM (15 to 59 years age group) patients in Europe was around 10% in 1996 (86). For T1DM diagnosed in childhood, relative risks for cardiovascular disease and total mortality are 10-fold higher than those in the general population (87; 88). A recent cohort study in the UK reported that men aged 45-55 years with T1DM had an absolute risk for cardiovascular diseases similar to that of men 10-15 years older in the general population, with a higher difference in women (89). With the improvement of medical care for T1DM patients in recent years, the long-term survival of T1DM patients has improved (88). However, the type of morbidity or mortality that has been prevented remains essentially unknown, and it is unclear if the improvement can be attributed to the reduction of cardiovascular disease.

Epidemiological studies have shown that diabetes is an important risk factor for cardiovascular morbidity and mortality (90-92). Already adolescent type 1 diabetic patients have mildly disturbed cardiovascular risk profiles, such as lipid disorders, largely independent of blood glucose control and health-related behavior (25). Another study of individuals younger than 21 years of age with T1DM found that 25% had elevated non-high-density lipoprotein cholesterol (93). In addition, changes in vascular structure and function, such as the significant coronary intimal thickening and endothelial dysfunction, occur early in the course of T1DM (94) .

Family members, such as siblings of T1DM patients might share some common genetic background and early life environmental exposures. It is not clear how much these factors contribute to the observed high risk of cardiovascular disease among T1DM patients. Comparison of cardiovascular disease incidence between T1DM patients and their non-T1DM siblings might give a hint on the pure effect of T1DM on cardiovascular disease risk among these patients. However, few data are available about the risk of cardiovascular disease among siblings of T1DM patients.

2.6 FERTILITY IN WOMEN WITH T1DM

Reproductive abnormalities, such as delayed menarche and increased incidence of menstrual cycle irregularities and delayed ovulation, were reported in previous small-scale studies of women with diabetes (33; 34). Insufficient metabolic control affects the homeostasis of the hypothalamus-pituitary-ovary (HPO) axis (95), which in turn could result in delayed menarche (88; 96), and menstrual disturbances (34; 88; 96). Patients with diabetic complications have shown a higher incidence of menstrual disorders compared to those without (34). Delayed menarche and early onset of menopause might shorten the reproductive years by 17% (35). Poorly controlled T1DM disease status is associated with abnormal concentrations of insulin-like growth factors (IGF) (97) and insulin-like growth factor-binding proteins (IGFBP) (98-101). The concentration of IGF-I decreases (97) while that of IGFBP-1 increases (98-101). Animal models with lower IGF-I and higher IGFBP-1 levels showed reduced fertility with impaired ovulation or decreased levels of progesterone and reduced capacity to maintain pregnancy (102-105). Both hyperglycemia and low IGF-1 can explain the development of micro- and macro-complications as well as impaired fertility. Psycho-social mechanisms may also contribute; as a chronic disease, T1DM could negatively affect the patients' attitude to having children (106).

It is fairly well established that adverse pregnancy outcomes, including spontaneous abortion (36; 107; 108) and stillbirths (37; 109-111), are more common among women with T1DM (36; 107; 108) than among women without this disease. The presence of T1DM mellitus in pregnant women has been associated with adverse effects on the fetal outcomes of pregnancy, such as congenital malformations (86). A four to ten-fold increased risk of congenital malformations among diabetic women has been reported (37; 109; 112; 113). The teratogenic mechanism in infants of diabetic mothers is still unknown. A number of potential factors, such as ketosis and hyperglycemia, as well as other factors in the diabetic process may play different roles (114; 115). On the basis of animal (116) and human studies (117; 118), the susceptibility to teratogenic factors occurs mainly during the period of organogenesis, which corresponds to the first 8 weeks of gestation. Both clinical and experimental studies have shown that poor metabolic control at the time of conception and organogenesis is an important teratogenic factor (117-120). Animal studies showed that the cause of dysmorphogenesis in embryos by high blood glucose is through an interaction of oxidative stress and inositol depletion (121).

With prolonged life expectancy following the refinement of insulin therapy, improved fertility might be expected, although fertility among type 1 diabetic women reportedly remained below that in the non-diabetic population in the 1980s (122). To our knowledge, there is no recent population-based epidemiological study on fertility rates over time among women with T1DM. In 1989, the St. Vincent declaration set treatment

goals for T1DM patients (11), one of which was to achieve equal pregnancy outcomes among women with diabetes compared to those without.

3 AIMS

The overall objective of this thesis was to study the risks of complications in T1DM. Our hope was that the findings from this thesis would provide information and contribute to improve the health care for T1DM patients. The specific aims were:

- To quantify the cumulative and relative risk of hip fracture in both men and women with T1DM (Study I)

- To estimate the risk of non-trauma LEAs in patients with T1DM and its changes after the introduction of a national program for diabetic foot care (Study II)

- To investigate the secular trend of myocardial infarction incidence in patients with T1DM, and the risk of myocardial infarction among their siblings (Study III)

- To assess the fertility in women with T1DM (study IV)

4 SUBJECTS AND METHODS

4.1 ETHICAL CONSIDERATIONS

All the four studies included in this thesis were approved by the Regional Ethics Committee of Karolinska Institutet.

4.2 SETTINGS

The studies included in this thesis were all based on Swedish population-based registers. Sweden has high-quality population-based registers which provide unique opportunities to conduct population-based nation-wide epidemiological studies. The study cohort – patients with T1DM who were first hospitalized for diabetes before age 31 were identified from the Swedish Inpatient Register. The follow-up of the study cohort was accomplished through linkage to the Inpatient, Causes of Death, Migration, Multi-Generation and Medical Birth Registers depending on the study outcome. The National Registration Number (NRN) is the unique identification number assigned to each resident in Sweden. From 1947, each resident in Sweden has been assigned a unique NRN immediately after birth, or after immigration, which contains the date of birth and additional 4 digits. The 9^{th} digit can be used for gender identification. The 10^{th} digit is a check sum that protects against incorrect data entries in computerized registers. The NRN has been used extensively and it is a unique identifier which allows linkage between different registers (123).

4.2.1 The Swedish Inpatient Register

The Swedish Inpatient Register was established by the National Board of Health and Welfare in 1964-65, but most counties joined the Register later in different years, the latest one in 1987, when the Register became nationwide (124). Figure 6 (124) shows the year of partial or complete coverage for each county in Sweden. With minor exceptions, in-hospital medical services in Sweden have been exclusively public, organized by the community. Since patients have been obliged to use the hospitals in their county of residence, the Inpatient Register is, in practice, population-based and referable to the county where the patient lives. Each record in the Register corresponds to one hospital admission and contains, in addition to the patient's NRN, the dates of admission and discharge, codes for all surgical procedures, and discharge diagnoses.

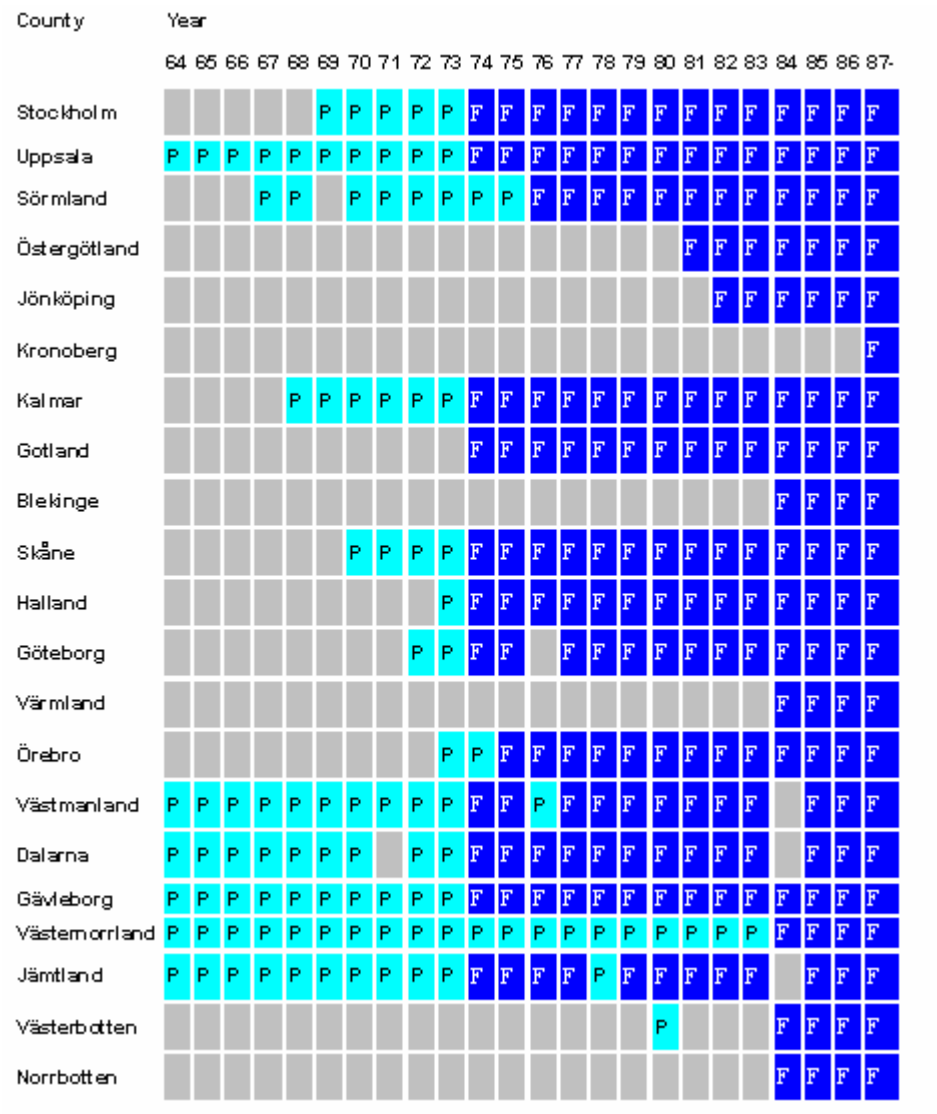


Figure 6. The coverage of Inpatient Registers in different counties in Sweden.
(F: full coverage. P: partial coverage)

4.2.2 The Swedish Multi-Generation Register

In the early 1990s, Statistics Sweden created the Multi-generation Register by linking data from several different population-based registers. The register provides information on all first-degree relatives for residents born in 1932 or later (index person). To be included in the register, the index person had to be alive in 1960 or born thereafter. Adoptions and other non-biological relations are flagged. Siblings are identified indirectly through common linkages to parents. Familial information for about 40 percent of those who died between 1968 and 1990 were missing, however (125). In the register of 2004, over 95% of parents could be identified for those who were born in Sweden in 1950 or later, around 70% for those who were born in Sweden and deceased during 1961-2004 (110). The Multi-Generation Register is unique in an international perspective.

4.2.3 The Swedish Medical Birth Register

The Medical Birth Register has received standardized information on all hospital births since 1973, including maternal demographic data, maternal reproductive and medical history, complications and treatments provided during pregnancy, delivery and neonatal period, and neonatal medical conditions. Antenatal, obstetric, and neonatal data are recorded on standardized records starting with the first antenatal visit and collected until the mother and child are discharged from hospital after delivery. This Register includes more than 99% of all births in Sweden (126).

4.2.4 Causes of Death Register

The Causes of Death Register contains information on the date of death, underlying and contributory causes of death of all deceased Swedish residents from 1952. The causes of death are classified according to ICD-7 before 1969, ICD-8 from 1969 through 1986, ICD-9 from 1987 to 1996, and ICD-10 from 1997 and thereafter. This register has more than 99% overall completeness (127).

4.3 RESEARCH DESIGN AND METHODS

4.3.1 Study I, II and III

4.3.1.1 T1DM cohort

The ICD code before the 10th revision which was introduced in 1997 did not allow us to separate type 1 from type 2 diabetes. Even after this date, some patients coded as having type 1 diabetes actually had advanced type 2 diabetes that had developed into insulin dependency. Therefore, we used age less than 31 years at first hospitalization for diabetes as the obligatory criterion. In an analysis confined to patients hospitalized from 1998 to 2004, when the ICD-10 code was used exclusively in Sweden and allowed differentiation between T1DM and other diabetes, of 28,480 records of diabetes diagnosed younger than age 31, 26,959 had a diagnosis of T1DM. Thus, our age algorithm had a positive predictive value for insulin-dependent diabetes of 95%.

Based on figure 6, we could see that different counties had full coverage of the Inpatient Register from different years. Thus, cohort accrual started on different dates in different counties but was always at least 2 years after the Register had attained full coverage without interruption in that county. The earliest starting date was January 1st , 1975 (Uppsala and Gävleborg counties); the latest was January 1st, 1989 (Kronoberg county). We used the information available in the Inpatient Register even before it became complete in each county. For example, in Study II and III, we first identified 35,316 unique NRNs who were first hospitalized for T1DM from all available material in the Inpatient Register in each county. Among them, 31,950 could be found in 1975 or later, when Inpatient Register became complete in each county, and thus were included in our further record linkage.

For study I, we initially identified 25,221 records with a discharge diagnosis of T1DM from 1975 to 1998. These records were further linked to the Register of Total Population, the Migration Register and the Causes of Death Register. These linkages

resulted in the exclusion of 171 records with NRNs that could not be found in any of the registers, i.e., without a link to any currently or previously existing person. As the NRNs could not be linked to any currently or previously existing person, they were deemed to be erroneous and the records were excluded. Further excluded were 376 patients with a date of emigration before the index hospitalization, 43 patients who died on the index hospitalization, and 26 patients who already had hip fractures before or on the index hospitalization. Hence, our final T1DM cohort included 24,605 patients.

For study II, we first identified 31,950 unique national registration numbers with at least one discharge diagnosis of T1DM from 1975-2004. The corresponding records were linked to the Register of Total Population, the Emigration Register, and the Causes of Death Register. During these linkages we identified 42 records whose NRNs could not be found in any of the registers. Further excluded were 58 patients with non-trauma LEAs before the index hospitalization, and 496 records with other inconsistencies found upon the record linkages. Hence the final T1DM cohort included 31,354 patients from 1975 to 2004.

Similarly, for study III, we first identified 31,950 unique national registration numbers with at least one discharge diagnosis of T1DM from 1975-2004. The corresponding records were linked to the Register of Total Population, the Emigration Register, and the Causes of Death Register. During these linkages we identified 42 records whose NRNs could not be found in any of the registers. Further excluded were 118 patients with prevalent myocardial infarction at baseline, and 494 patients with other inconsistencies found during the linkages. Hence, our final T1DM cohort included 31,296 patients.

4.3.1.2 Siblings of patients with T1DM

In Study III, 59,466 records were identified through linking our T1DM cohort to the Multi-Generation Register. These records were linked to the Total Population Register to identify their county of residence on January 1st, 1969, or their county at birth if they were born after January 1st, 1969. We further linked this cohort to the Register of Domestic Migration, and cohort entry dates for siblings were set to the date when the Inpatient Register in their county of residence had reached complete coverage.

Thereafter, following similar data cleaning procedure as in the T1DM cohort, 110 records with invalid NRNs were excluded. Further excluded were 11 persons with prevalent myocardial infarction at baseline, 872 persons who were not biological siblings, as well as 1,160 with inconsistencies found upon the record linkages. Linkage with T1DM cohort further identified 2,380 persons who had T1DM, and these subjects were also excluded. Thus, the final cohort of non-T1DM siblings consisted of 54,933 subjects.

4.3.1.3 Follow-up of the cohort

Cohort members were followed from immediately after the index hospitalization for T1DM or the designated entry date for their siblings until occurrence of a first hospitalization for outcomes of interest, i.e., hip fracture (study I), non-trauma LEA (study II) or myocardial infarction (study III), emigration, migration to a county without or with incomplete Inpatient Register coverage, death, or the end of follow-up (31 December, 1998 [study I] or 2004 [study II and III]), whichever occurred first. The

first hospitalization for hip fracture or non-trauma LEA, if any, was identified through cross-linkage within the Inpatient Register. In Study III, the first occurrence of the myocardial infarction was identified through linkage to the combination of the Inpatient Register and Causes of Death Register. The non-fatal myocardial cases were defined as those who survived at least 28 days after first hospitalization for myocardial infarction, while fatal cases as those who died without hospitalization, or died within 28 days after the first hospitalization for myocardial infarction. Vital status and coverage by the Inpatient Register was ascertained by linkage to the Register of Causes of Death. Migration to a county without or with an incomplete coverage of the Inpatient Register was ascertained through the Domestic Migration Register which records all the between county movements. Emigration out of Sweden was ascertained through the Foreign Migration Register.

4.3.2 Study IV

4.3.2.1 Women with T1DM in their childbearing age

Women in Sweden who were first hospitalized for diabetes at age 16 years or younger (thus deemed to almost exclusively have T1DM) were identified from the Inpatient Register. From Figure 7, we could see that the fertility rate of Swedish women before age of 16 years and after age 48 years were very low in 1965, 1975, 1985, 1995 and 2004. So the study cohort was followed from the age of 16 years until age of 48 years.

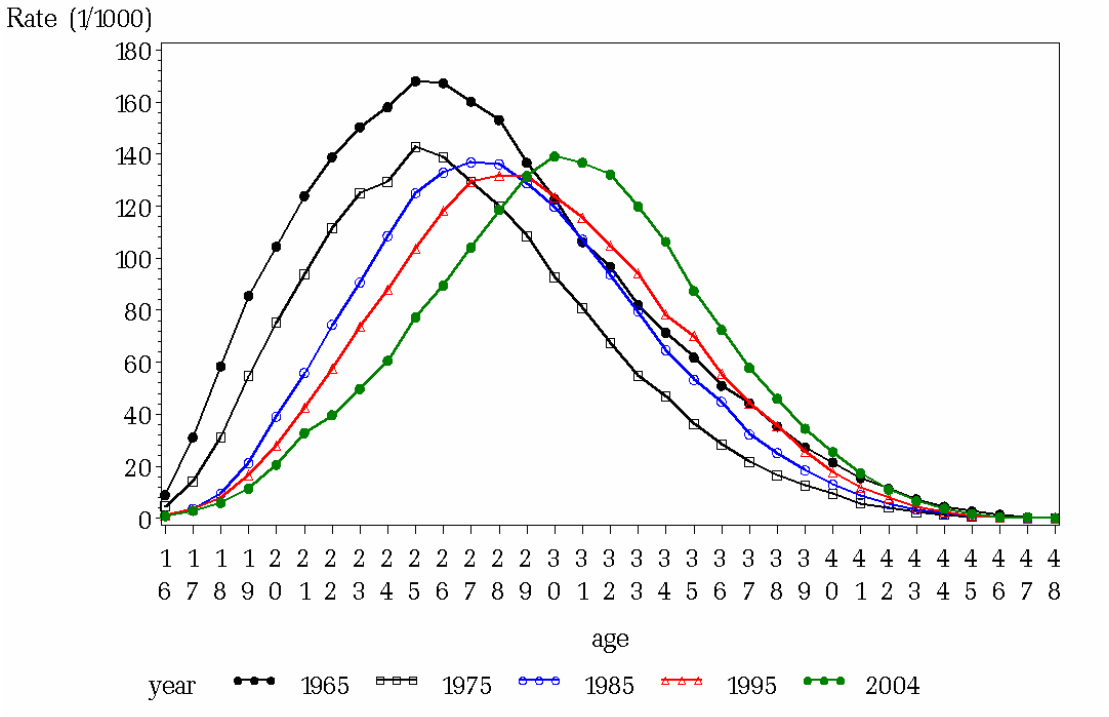


Figure 7. Fertility rate of Swedish women by age (16-48 year) and calendar year.

4.3.2.2 Follow-up of the cohort

Cohort members were followed from age 16 until age 48 years, emigration, death, or the end of follow-up (31 December 2004), whichever occurred first. Information on the

number of live births was obtained through linkage to the Swedish Multi-Generation Register. Through linkage to the Swedish Medical Birth Register, information on congenital malformations of the live newborns was obtained.

4.4 STATISTICAL ANALYSIS

All statistical analysis were performed by using SAS statistical software (SAS Institute, Cary, NC, USA)

4.4.1 Study I, II and III

By using the Kaplan-Meier method, we calculated lifetime cumulative probability of developing hip fracture, myocardial infarction and non-trauma LEA by attained age. The log-rank test was used to test the significance of any differences between groups.

Standardized hospitalization/incidence ratios (SHRs or SIRs; the ratios of the observed to the expected numbers of first hospitalizations for hip fractures, non-trauma LEA or incidence of myocardial infarction) were used as measurement of relative risk. To calculate the background hospitalization or incidence rates, we used the entire Inpatient Register or in combination with Causes of Death Register and counted the number of first event of interest in the general population by age (in 5-year groups), sex and calendar periods (every 1 year, 2 years or 5 years depending on the rarity of the outcome). Since the occurrence of the non-trauma LEAs in the general population is rare in those without diabetes, especially in the younger age groups, the stratum-specific number of the first hospitalization was calculated by subtracting the respective stratum-specific number from the study cohort. Stratum-specific hospitalization/incidence rates were computed by dividing the number of outcomes by the corresponding number of general population at risk. The expected number of outcome of interest in the cohorts was derived by multiplying the observed number of person-years in age, sex and calendar period strata by the corresponding stratum-specific hospitalization or incidence rate. The SHRs or SIRs are inherently adjusted for age, gender and calendar period. Ninety-five percent Confidence Intervals (CIs) were calculated by assuming that the number of observed events followed Poisson distribution (128). Additional analyses were stratified according to follow-up duration, and a χ^2 test for linear trend was used to evaluate the time-risk relationship (129). We further performed stratified analysis by presence/absence of diabetes complications. Complications of diabetes were identified through cross-linkage within the Inpatient Register. Person-time experienced before the onset of complications was allocated to the complication negative strata.

The multiplicative Poisson regression model is fitted as log-linear regression model, in which number of outcome is a dependent variable with logarithm of person-time or expected number of events as offset. When the expected number of event is used as the offset, the model provides estimates of the relative effects of the SHR/SIR. This applies when the stratum-specific rates of exposed and unexposed groups are both proportional to the reference rates from the general population (129). To isolate the independent effects of explanatory variables in study I and III, we estimated relative effects on the standardized hospitalization/incidence ratios using a multivariate Poisson regression method with the logarithm of expected number as the offset, assuming multiplicative effects between outcome and explanatory variables. The occurrence of the non-trauma LEAs is usually diabetes-related, particularly in the younger groups. Although we

subtracted T1DM-related non-trauma LEAs in calculating background rates, SIRs might be differentially underestimated in different calendar periods. Thus making internal comparison is more appropriate. In study II, Poisson regression was fitted with the logarithm of observed person-years as the offset to compare the risk of non-trauma LEAs in different calendar periods of follow-up while adjusting for gender and attained age at follow-up. The Pearson's χ^2 test was used to check the degree of fit of the model (129). A scale parameter, the square root of Pearson's χ^2 divided by the degrees of freedom, was used to correct standard errors where there is overdispersion.

4.4.2 Study IV

Standardized fertility ratios (SFRs, the ratio of the observed to the expected numbers of live births) were used as measure of relative fertility, using age- and calendar-year-matched Swedish women as reference. Confidence intervals (95%) were calculated by assuming that the number of observed events followed a Poisson distribution (129; 130). The expected number of births was calculated by multiplying the person-years experienced among the diabetic women in strata of age (one year) and calendar year (one year) by the stratum-specific fertility rates in the Swedish female population. The latter rates were calculated through dividing the number of live births in each stratum by the corresponding female mid-year populations. Stratified analyses were done by presence of diabetic complications, calendar period or age at index hospitalization for T1DM, and calendar period or age at follow-up.

To isolate the independent effects of explanatory variables, we estimated relative effects on the standardized fertility ratios using a multivariable Poisson regression model with the expected number as the offset, assuming multiplicative effects between outcome and explanatory variables. The Pearson's χ^2 test was used to check the degree of fit of the model (129). A scale parameter, the square root of the Pearson's χ^2 divided by the degrees of freedom, was thus used to correct standard errors where there is overdispersion.

5 RESULTS

5.1 HIP FRACTURE IN PATIENTS WITH T1DM

There were 24,605 patients (12,551 men and 12,054 women) in this study. The mean age at entry was 20.7 years. The cohort members were followed for an average of 9.9 years, yielding 242,428 accumulated person-years at risk. During follow-up, a total of 121 incident cases of hip fracture were recorded (51 among women, 70 among men). The mean age at diagnosis of first hip fracture was 43.1 years for women and 41.3 years for men.

Figure 8 showed Kaplan-Meier estimates of the cumulative risk of hip fracture among patients with T1DM stratified by sex. The incidence of hip fractures before age 30 was almost negligible, but increased quickly thereafter. The cumulative probability of having a hip fracture was similar in both sexes before age 40, but thereafter, it increased more rapidly among men.

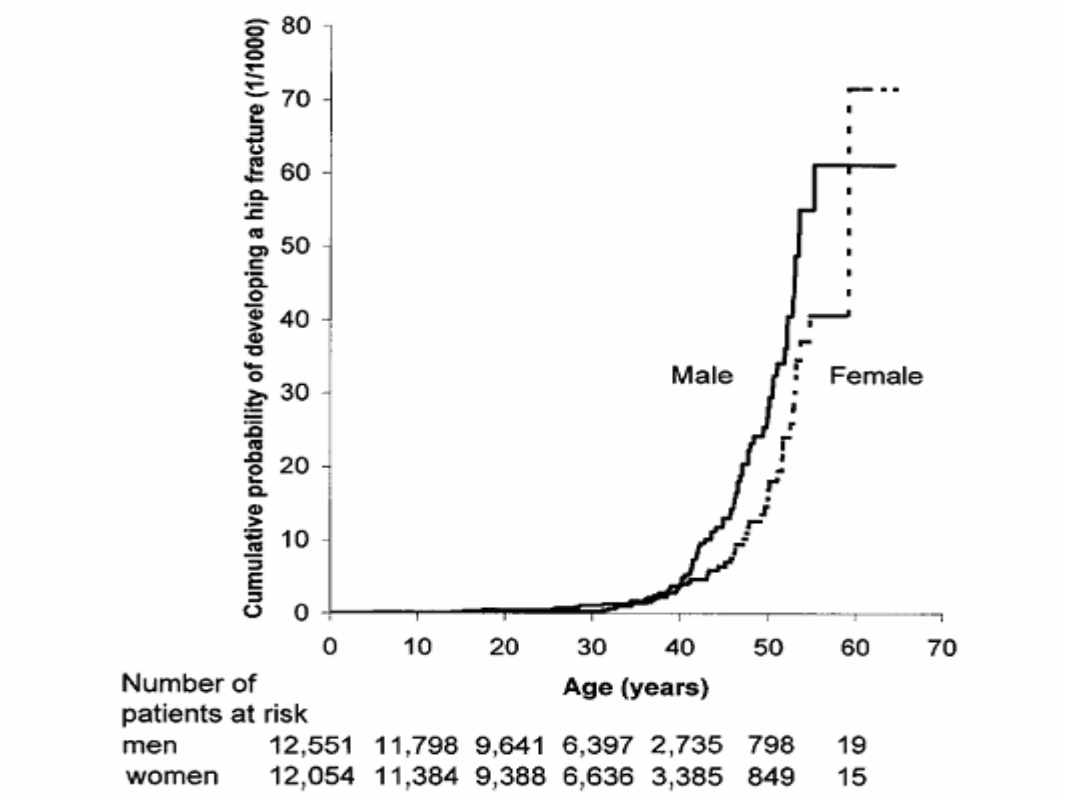


Figure 8. Cumulative probability (per 1,000) of having hip fracture before the age of 65 years among patients with T1DM, estimated by the Kaplan-Meier method.

Significantly increased risks for hip fractures were observed in both men and women with T1DM (SHR=7.6, 95% CI 5.9-9.6 and SHR=9.8, 95% CI 7.3-12.9, respectively). The excess risks increased with follow-up duration among women (p value for trend=0.02). The excess risks were evident across different durations of follow-up but

without a clear trend in men. The presence of diabetic ophthalmic, nephropathic, neurologic and cardiovascular complications conferred especially higher risks for hip fractures (table 1).

Table 1. Standardized hospitalization ratios* (SHRs) and 95% CI for hip fracture among men and women hospitalized at least once for T1DM, stratified by presence of ophthalmic, nephropathic or neurological complications, 1975-98, Sweden.

	Men		Women	
	Obs	SHR (95% CI)	Obs	SHR (95% CI)
Total	70	7.6 (5.9-9.6)	51	9. 8 (7.3-12.9)
Duration of follow-up				
0-4 years	15	4.3 (2.4-7.1)	9	5.6 (2.6-10.6)
5-9 years	31	10.5 (7.2-15.0)	15	9.7 (5.4-16.0)
10-14 years	17	9.3 (5.4-14.9)	15	12.3 (6.9-20.3)
≥ 15 years	7	7.3 (2.9-15.1)	12	14.5 (7.5-25.3)
P value for trend		0.09		0.02
Ophthalmic complications				
No	28	4.1 (2.7-6.0)	14	4.1 (2.3-6.9)
Yes	42	17.4 (12.5-23.5)	37	20.5 (14.5-28.3)
Nephropathic complications				
No	37	4.5 (3.2-6.3)	29	6.4 (4.3-9.2)
Yes	33	31.6 (21.7-44.3)	22	32.6 (20.4-49.4)
Neurologic complications				
No	38	4.6 (3.3-6.4)	26	5.7 (3.7-8.3)
Yes	32	32.6 (22.3-46.0)	25	41.6 (26.9-61.4)
Cardiovascular complications				
No	57	6.6 (5.0-8.5)	39	8.1 (5.8-11.0)
Yes	13	28.6 (15.2-48.8)	12	29.2 (15.1-51.1)

* The Swedish general population was used as reference population. The SHRs are inherently adjusted for age, sex and calendar period.
Obs: number of observed first hip fracture.

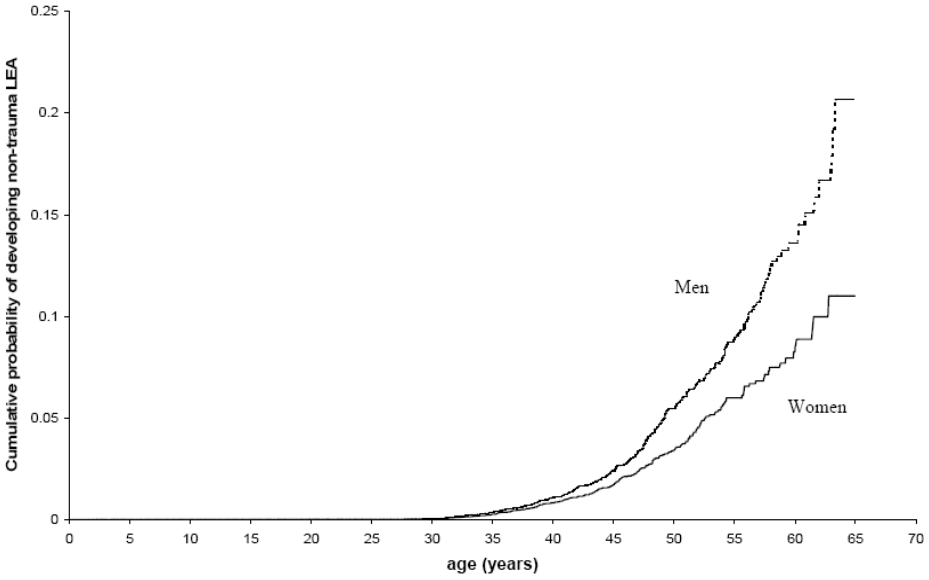
There was no obvious difference of SHRs for hip fracture between men and women, either in the univariate or multivariate analysis. After controlling for effects of the other explanatory variables, patients with diabetic complications had generally higher relative risks, particularly among those with nephropathic or neuropathic complications (RR=2.0, 95% CI 1.0-3.8 and RR=2.4, 95% CI 1.3-4.6, respectively).

5.2 NON-TRAUMA LEA IN PATIENTS WITH T1DM

There were 15,001 women and 16,353 men enrolled in this study. Mean age at entry was 19.7 years. The cohort members were followed for 12.5 years on average, yielding 393,134 accumulated person-years at risk. In total, 465 cohort members underwent non-trauma LEA; 29 with amputation above the knee, 193 below the knee but above the ankle, and 243 below the ankle. Mean age at LEA was 45.4 years.

T1DM patients had a 40% lower risk of non-trauma LEA during the most recent calendar period of follow-up (2000-2004), as compared to the previous calendar period. Women had a lower risk of non-trauma LEA than men (RR=0.7, 95% CI 0.5-0.8). There was a clear increasing trend of relative risks with increasing attained age at follow-up (p-value for trend <0.0001). Compared to the age-, gender- and calendar-period matched general population, T1DM patients had notably high excess risks for LEAs. The SIR for the most recent calendar period of follow-up was 85.8 for all LEA (95% CI 72.9-100.3). Similar results were observed in analyses by subsite of amputations.

Figure 9 showed the cumulative probability of non-trauma LEA among T1DM patients, estimated by the Kaplan-Meier method. This probability was almost negligible before the age of 30 in both men and women. Before the age of 40, the cumulative probability increased similarly in both genders, however, it increased more quickly in men thereafter. By the age of 65, the cumulative probability of LEA was 11.0% for women, and 20.7% for men ($P_{log\text{-}rank}<0.01$).



No. of patients at risk														
Men	16179	15565	14135	12497	10821	8880	6739	4637	2864	1618	770	208	26	1
Women	14880	14294	12975	11501	10126	8643	6933	5205	3599	1987	947	301	29	0

Figure 9. Cumulative probability of non-trauma LEAs in patients with T1DM, estimated by the Kaplan-Meier method.

5.3 MYOCARIDAL INFARCTION IN PATIENTS WITH T1DM

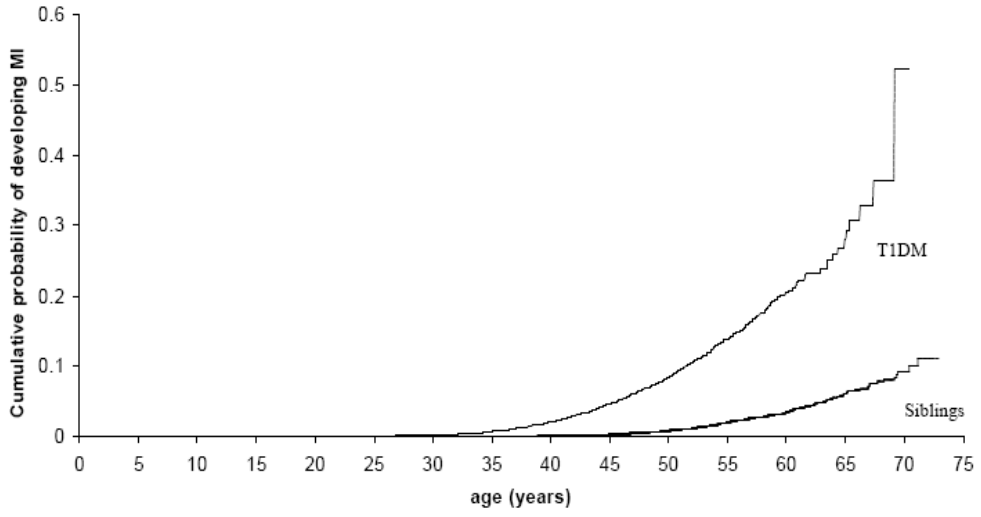
The mean age at entry for the 31,296 T1DM patients was 19.7 years. They were followed for up to 30 years (mean = 12.5 years), yielding 391,390 accumulated person-years of follow-up. In total in the T1DM cohort, we observed, 938 cases of myocardial infarction, including 727 non-fatal cases and 211 fatal cases, which, compared with the general population, rendered SIRs of 11.4 (95% CI 10.6-12.1), 10.7 (95% CI 9.9-11.5), and 14.7 (95% CI 12.7-16.8), respectively. SIRs for any myocardial infarction

decreased significantly from 32.3 during the earliest period of follow-up (1975-1984) to 9.7 during the most recent period (1995-2004).

In order to disentangle the effects of calendar period of follow-up (which is most likely to reflect changes in management practices) from other effects, notably attained age at follow-up, follow-up duration, and sex, we did a multivariable Poisson regression of SIRs for both sexes combined. SIRs for the more recent calendar periods of follow-up were 40% and 50% lower than that for the earliest period of 1975-1984 (RR=0.6, 95% CI 0.5-0.9; RR=0.5, 95% CI 0.3-0.7, for period 1985-1994 and 1995-2004, respectively).

Non-T1DM sisters and brothers had similar mean age at entry (around 14 years) and mean follow-up duration (around 19 years). Compared with the general population, there was only a modest excess risk of myocardial infarction among sisters (SIR=1.3, 95% CI 1.1-1.6), while no obvious excess risk was noted for brothers (SIR=1.1, 95% CI 0.9-1.2).

Figure 10 showed the cumulative probability of developing a myocardial infarction among T1DM patients and their non-T1DM siblings, estimated by the Kaplan-Meier method. Myocardial infarction was rare before age 45 for non-T1DM siblings, while occurrence of myocardial infarction started as early as age 30 in T1DM patients, indicating an about 15 years left shift.



No. of subjects at risk														
T1DM	31296	31001	29801	27052	23940	20880	17446	13583	9738	6331	3518	1662	482	59	1
Siblings	54933	53205	50652	46131	40798	35297	29946	24404	18622	13388	9188	5422	2509	874	150

Figure 10. Cumulative probability of developing myocardial infarction in patient with T1DM and their non-T1DM siblings, estimated by the Kaplan-Meier method.

5.4 FERTILITY IN WOMEN WITH T1DM

On average, the 5978 cohort members were followed for 13.3 years, yielding 79,774 person-years. During follow-up, 4013 live births were noted. The mean age at first live

birth during the entire observation period was 25.8 years. The overall observed number of live births was smaller than expected (SFR=0.80, 95% CI 0.77-0.82). Relative fertility increased monotonically with calendar year of first hospitalization (p for trend <0.01) and was close to the expected rate among women with a first hospitalization after 1984 (table 2). The SFRs for those who were ever hospitalized for retinopathy, nephropathy, neuropathy and cardiovascular complications were 0.63 (95% CI 0.58-0.68), 0.54 (95% CI 0.47-0.62), 0.50 (95% CI 0.41-0.61) and 0.34 (95% CI 0.22-0.51), respectively.

Table 2. Standardized fertility ratios* (SFRs) and corresponding 95% CIs among women first hospitalized for T1DM at age 16 or younger, 1965-2004, Sweden

	Live births		SFR (95% CI)
	Expected	Observed	
Total	5,040	4,013	0.80 (0.77-0.82)
Calendar period at first hospitalization for T1DM			
1965-69	408	237	0.58 (0.51-0.66)
1970-74	1,001	686	0.69 (0.63-0.74)
1975-79	1,486	1,114	0.75 (0.71-0.80)
1980-84	1,253	1,087	0.87 (0.82-0.92)
1985-89	694	671	0.97 (0.89-1.04)
1990-94	166	189	1.14 (0.98-1.31)
1995-2004	31	29	0.92 (0.62-1.32)
p-value for trend			<0.01

*The age- and calendar-year-matched Swedish women were used as reference population. The SFRs are thus inherently adjusted for attained age and calendar year.

Moreover, we grouped our cohort into women who were first hospitalized before 1985 and those who were hospitalized in 1985 and thereafter and then further stratified by calendar year at follow-up, attained age and presence of diabetic complications. This analysis showed that the subfertility observed in the group hospitalized before 1985 remained through all calendar years of follow-up. With the exception of a significant deficit in fertility among the oldest, women who were first hospitalized in 1985 or later exhibited essentially normal fertility rates in virtually all substrata. Presence of diabetic complications was associated with a substantially decreased fertility (SFR=0.77, 95% CI 0.60-0.98) also in the subcohort included in 1985 or later (table 3).

Table 3. Standardized fertility ratios* (SFRs) and corresponding 95% CIs stratified by calendar period at follow-up, attained age at follow-up, and presence of any diabetic complication†, among women first hospitalized for T1DM at age 16 or younger, grouped by calendar period at first hospitalization before 1985 or in 1985 and thereafter, 1965-2004, Sweden

	Calendar year at first hospitalization <1985		Calendar year at first hospitalization ≥1985	
	Live births	SFR (95% CI)	Live births	SFR (95% CI)
Calendar period at follow-up				
1965-79	158	0.75 (0.63-0.87)	-	-
1980-89	679	0.67 (0.62-0.73)	9	1.93 (0.88-3.67)
1990-99	1,594	0.78 (0.74-0.81)	322	1.03 (0.92-1.15)
2000-04	693	0.80 (0.74-0.86)	558	0.97 (0.89-1.05)
Attained age at follow-up				
16-19	114	0.82 (0.68-0.99)	70	1.06 (0.83-1.34)
20-24	799	0.81 (0.76-0.87)	359	1.04 (0.94-1.16)
25-29	1,208	0.77 (0.73-0.82)	361	1.00 (0.90-1.11)
30-34	775	0.71 (0.66-0.76)	98	0.82 (0.67-1.00)
35-39	208	0.63 (0.55-0.72)	1	0.54 (0.01-2.99)
40-48	20	0.57 (0.35-0.88)	-	-
Presence of diabetic complications				
No	2,440	0.79 (0.76-0.83)	822	1.02 (0.95-1.09)
Yes	684	0.64 (0.59-0.68)	67	0.77 (0.60-0.98)

* The age- and calendar-year-matched Swedish women were used as reference. The SFRs are thus inherently adjusted for attained age and calendar year.
† Including ophthalmic complication, diabetic nephropathy, neurological complications and cardiovascular complications.

In a Poisson regression model with mutual adjustments for calendar year and age at first hospitalization for diabetes, presence/absence of diabetic complications, as well as duration of T1DM, the relative fertility was significantly lower for those who were first hospitalized for T1DM before 1985, as compared with those hospitalized in 1985 and thereafter. Hence, this effect was independent of the presence or absence of recorded diabetic complications. Presence of such complications was associated with a markedly reduced relative fertility, independent of calendar year at first hospitalization for diabetes.

We identified 3,979 live births during the period 1973-2004, and among them 3,815 were found also in the Medical Birth Register. The overall proportion of live newborns with congenital malformations was 7.4% (95% CI 6.6-8.3), which was significantly higher than the corresponding proportion of 4.2% observed in the general population. For T1DM cohort, the proportion was highest during 1973-1984 (11.7%), and after then it dropped to 7.3% and 6.9% for calendar periods 1985-1994 and 1995-2004, respectively. However, in all 3 calendar periods, the proportions were consistently higher than the corresponding figures in the general population (figure 11).

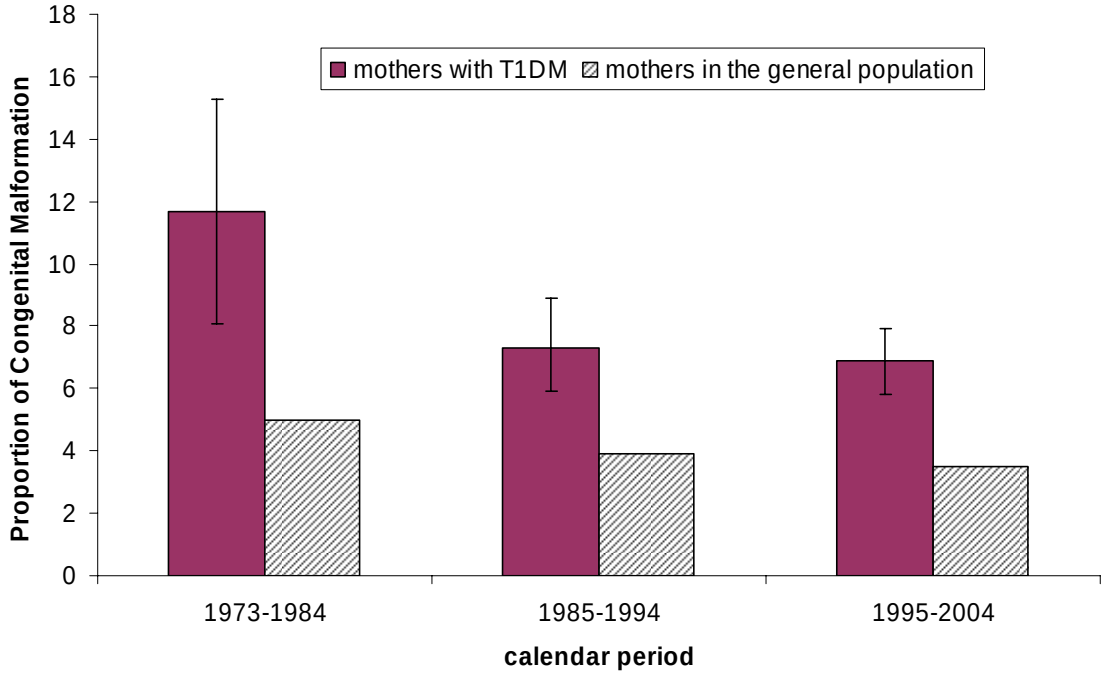


Figure 11. Proportion of congenital malformation in live newborns of mothers with T1DM and that in mothers in the general Swedish population.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Design of the studies

All the studies included in this thesis were retrospective cohort studies based on Swedish nation-wide registers. In the analytical epidemiology, case-control and cohort study are two main study designs. Cohort study is a follow-up study of a cohort group defined on the basis of their exposure status until the occurrence of the outcome of interest or the end of follow-up. There are two main types of cohort study: prospective and retrospective cohort studies. They both define subjects on the basis of their exposure status. The difference is where the investigator is at the beginning of the follow-up. In the prospective study, the investigator records the exposure status of the cohort and follows them through until the outcome occurs. It usually has the relevant and comprehensive information on the exposure. However, it is time-consuming and expensive for diseases with long latent period. At the beginning of the retrospective cohort study, the outcome of interest already occurred. The information on the exposure was obtained through the recorded information. The time at risk for the outcome of interest had already occurred. This type of study is cheap, quick and efficient for the long-latent disease. However, due to the retrospective characteristic, the quality of the exposure information might be questionable and it might have limited and/or missing information (131). However, in Sweden, the health-care system is well-organized and the registers are comprehensive and with high quality. With the NRN assigned to each resident in Sweden, we could conduct efficient and high quality retrospective studies.

6.1.2 Validity

An epidemiological study will be considered valid after exclusion of bias, confounding and random error as alternative explanations.

6.1.2.1 Bias

Bias is a systematic error that leads to incorrect estimates of the association between the exposure and disease. It could occur in any type of epidemiological study and any stage of the study. It can be introduced during the study design, data collection and data analysis.

6.1.2.1.1 Selection bias

Selection bias might occur in the process of selecting participants if there are systematic differences in characteristics between those who are selected and those who are eligible but not selected into the study (132). Case-control and retrospective cohort study designs are more susceptible to selection bias because both the exposure and outcome of interest have occurred at the time of subject selection. It is introduced in a retrospective cohort study if selection of exposed and non-exposed subjects is related to developing the outcome of interest.

All our studies were based on hospitalized patients identified from the Inpatient Register based on the ICD-coding. We were unable to identify patients whose diabetes was managed entirely on an outpatient basis. However, because of the often dramatic onset, the need for careful evaluation and insulin treatment education on the diabetes control (133; 134), it has been consistently recommended in Sweden that all pediatric patients with newly onset T1DM be hospitalized at least once in their early course. Thus, the proportion of missed cases is negligible. Selection bias might occur if the hospitalization for T1DM was related to the probability of detecting the outcomes of interest. In study I-III, follow-up started for some subjects when they were re-hospitalized after Inpatient Register was complete in their county of residence. This might introduce selection bias if their re-hospitalization was related to severity of diabetes or outcomes of interest. However, we could identify more than 90% of patients by using all available material. Further, sensitivity analysis revealed similar results when restricting to patients first hospitalized after the Inpatient Register had reached completeness in each county, or after excluding the first year of follow-up. In study IV, left truncation before the start of registration probably led to misses of the true first hospitalization in some of the earlier patients. Hence, the second (or third or higher) hospitalization might then have been misinterpreted as the first. If it is assumed that the number of hospitalizations during childhood and adolescence is related to severity of the diabetes, we may to some extent have inadvertently selected patients with more severe forms of the disease in the early part of the study. This selection could have contributed to a spuriously strong finding toward improvement over time.

In cohort studies, the loss of follow-up might lead to selection bias when it is related to the exposure and outcome of interest. Since all studies are based on linkage of Swedish registers, our studies had virtually complete follow-up. In addition, the outcomes in our studies were actually all covered in the registers. Thus, the selection bias caused by loss of follow-up in our studies should be considered minimum.

6.1.2.1.2 Information bias

Information bias could be introduced during the collection or measurement of information on the exposure or outcome. The measurement error often leads to the misclassification which means errors in the classification of the exposure or the disease. There are two types of misclassification, differential and non-differential. Differential misclassification means that the error on one variable (exposure or disease) depends on the actual value of another variable (exposure or disease). For example, an error in the classification of exposure is more likely to happen for the diseased subjects than non-diseased subjects. It could lead to either overestimated or underestimated results. Non-differential misclassification refers to the error on one variable (exposure or disease) independent on the actual value of the other. For example, an error in the classification of exposure occurs equally for the diseased subjects and non-diseased subjects. In most situations, it biases the results toward the null. However, non-differential disease misclassification with perfect specificity does not affect the risk-ratio estimate (135).

Differential misclassification might not be a big concern in all studies included in this thesis because of the register-based cohort design. The outcomes in Study I and II were identified through cross-linkage to the Inpatient Register. In study III, we used the combination of the Inpatient Register and Causes of Death Register to identify the cases of myocardial infarction which had high specificity (136). The Swedish Inpatients register has high quality. Hip fractures and non-trauma LEAs are virtually always

treated on an inpatient basis and should therefore appear in the Inpatient Register. The underreporting of hip fractures was found less than 2% in the Inpatient Register (137). Any underascertainment of the outcome is likely to be due to technical errors and is thus probably non-differential. Such underascertainment in follow-up studies will not affect the rate ratio (132). The proportion of patients with diabetes complications in the cohort of T1DM was low. This could be due to the nonspecific reporting in the Inpatient Register. Thus, it is possible that the patients with mild diabetic complications were misclassified as without complications. This might lead to the overestimation of the risks of outcomes in the groups of patients without complications.

6.1.2.2 Confounding

Confounding is the mixing of effects between the exposure, the outcome and a third variable, i.e., confounder. A confounder has three necessary properties: 1) it is associated with the outcome independent of the exposure, 2) it is associated with the exposure independent of the outcome, 3) it is not an intermediate in the causal pathway between the exposure and the outcome. It distorts the estimate of the association between an exposure and outcome.

Confounding can be controlled either in the design phase, the analysis phase, or a combination of the two. If the information on the confounder is known and collected, the confounding could be controlled in the data analysis. Limitation for cohort studies based on the registers is that the information on potential confounders was not available.

In our studies, information on potential confounding factors such as weight change, smoking and body mass index was not available for adjustment. The degree to which an effect estimate is biased by the presence of a confounder is jointly determined by the prevalence of the confounder, the magnitude of the association between the outcome and the confounding variable, the association between exposure and the confounding variable, and the prevalence of exposure. It is however, unlikely that any confounding from these risk factors could produce relative risk elevations of the magnitude observed in our studies (138).

6.1.2.3 Random error

Epidemiological studies are based on sampling which is always related to random error. Random error, or chance, leads to lack of precision and is a main concern of epidemiological studies. Means to reduce random error and increase the precision include increasing the study sample size and study efficiency. The factors related to the study efficiency consists of proportion of exposed subjects, proportion of subjects with outcomes and the distribution of the subjects according to important factors (132). All the studies included in this thesis were based on one of the largest study sample size. However, the play of random error still could not be completely ruled out in the stratified analysis when sample sizes in some substrata were relatively small (study I-IV).

6.2 INTERPRETATION AND IMPLICATIONS

6.2.1 Hip fracture in patients with T1DM

In study I, increased hip fracture risks were observed among both men and women who had been hospitalized for T1DM. Presence of diabetic microvascular complications (ophthalmic or nephropathic), neurological, or cardiovascular complications indicated excess risks that range from 17- to 42-fold. After our study was published (139), there was similar finding reported from the Nurse Health study (24).

Putative mechanisms for the increased risks of hip fracture in patients with T1DM is an impaired bone quality due to the lower bone mineral density observed among patients with T1DM (21; 22; 140). Moreover, a link between microvascular complications of T1DM and long-term bone loss has been reported (141), notably between neuropathy and decreased bone mineral density (142). Another mechanism for the increased risk could be diabetes-related non-skeletal risk factors, such as a propensity for falls (143). Many factors could predispose patients to an increased frequency of falls. These include impaired proprioception, balance, and gait due to neuropathy and visual impairment from diabetic retinopathy and cataracts (144), and frequent nocturia (145).

Given that as many as 1 in 15 patients with T1DM may sustain a hip fracture before the age of 65, development of methods for primary prevention should be put high on the agenda. Although candidate treatments should ideally be evaluated in randomized intervention trials, our data provides some hints regarding the importance of tight metabolic control; the covariation with other diabetes complications and the considerably higher relative risk among patients born before 1950, who may have had a considerable part of their disease trajectory before the importance of meticulous metabolic control was clearly demonstrated, suggest that such control may also be a cornerstone in the prevention of diabetic hip fractures.

6.2.2 Non-trauma LEAs in patients with T1DM

Study II showed that patients with T1DM had substantial absolute and relative risk for non-trauma LEA. One out of ten women and one out of five men might have undergone a LEA by the age of 65 years. Poisson regression demonstrated obvious reductions in LEA incidence among T1DM patients in the most recent calendar period of follow-up, which might be due to the introduction of a national program for prevention and treatment of foot ulcers in diabetes patients (71). A longer period of follow-up is needed to confirm the observed time trend.

Our finding of a higher risk for LEA risk among male than among female T1DM patients is consistent with previous studies (75; 77; 146). The higher cumulative risk of amputations in men may be due to several factors, such as a higher prevalence of smoking among men (147), or better wound healing in women due to the presence of estrogen receptor beta (148; 149).

6.2.3 Myocardial Infarction in patients with T1DM

In study III, we found that the relative risks for myocardial infarction in T1DM patients have been continuously decreasing in the last 3 decades, and this decreasing trend was

still significant after multivariate adjustment for other explanatory variables. But even in the most recent period, 1995-2004, T1DM patients had a close to 10-fold higher risk of myocardial infarction as compared to the general population. Compared to their non-T1DM siblings, there was a 15-year left shift of incidence of myocardial infarction; at age 65, the cumulative probability of developing a myocardial infarction was 28% among T1DM patients, while the corresponding figure for their non-T1DM siblings was only 6%.

Previous studies on secular trend of cardiovascular disease risk among patients with diabetes have shown inconsistent results. Two studies did not show a declining trend in the incidence of cardiovascular disease in patients with diabetes (85; 150). These studies were, however, based on shorter follow-up periods. In contrast, the Framingham Heart Study showed a 50% reduction in the incidence of cardiovascular disease during the period of 1950-1995, but the risk of cardiovascular disease was still twice as high as for people without diabetes (151). The decreasing trend could be due to advances in the prevention and treatment of cardiovascular diseases among patients with diabetes (151-157). There has been a lack of studies on the secular trend of cardiovascular disease risk in T1DM patients, except a recent large UK study (89) which showed a similar decreasing trend as observed in our study.

In our study, women with T1DM had an over 20-fold greater risk for myocardial infarction compared to age- and calendar-year-matched women in the general population. Similar phenomena have been observed in previous studies (89; 158). The reason for this is not completely known yet. The presence of diabetic microvascular complications, especially nephropathy, is associated with much higher risks for myocardial infarction, which is consistent with previous reports (159; 160).

The unique setting of the Multi-Generation Register in Sweden enabled us to identify siblings of T1DM patients. Although siblings of T1DM patients have been reported to exhibit abnormal levels of lipoprotein metabolism, oxidative stress, and cellular fragility which are major biomarkers of risk factors for cardiovascular disease (161), we found no evidence of any important excess risk for myocardial infarction among non-T1DM brothers, and only a modest excess risk among sisters. This finding indicates that shared genetic predisposition and early environmental exposures might contribute little to the observed significant excess risk of myocardial infarction among T1DM patients, and the diabetes status is the dominant risk factor. Comparison of cumulative probabilities of developing a myocardial infarction among T1DM patients and their non-T1DM siblings revealed an about 15-year left shift of incidence of myocardial infarction. This might explain our finding of the astonishing excess risk among the substratum with attained age younger than 40, which is consistent with a previous report (158), as myocardial infarction is rare before age 40 in the general population. The observed decreasing trend of SIRs with increasing follow-up duration, as well as the increasing SIRs in successive birth cohorts might also be explained at least partly by attained age at follow-up.

6.2.4 Fertility in women with T1DM

Overall, the fertility among women with T1DM recorded between 1965 and 2004 was reduced by 20%. Importantly, the lowest SFRs were observed among women who had their first hospitalization for diabetes in the earliest years, and SFRs increased monotonically with calendar year of first hospitalization to become statistically

indistinguishable from 1.0 after 1984. Presence of diabetic microvascular or cardiovascular complications was associated with particularly low fertility, essentially regardless of year of first hospitalization. Although the proportions of live newborns with congenital malformations of mothers with T1DM has decreased for the last 30 years, it was still twice that of the general Swedish female population in most recent years.

Our analyses indicated that the improvement in fertility in the subcohort with calendar year of first hospitalization in 1985 or later was essentially independent of complication status, age at first hospitalization, and duration of diabetes. This suggests that this cohort effect is real and likely attributable to interventions that were increasingly employed across successive subcohorts defined by year of first recorded hospitalization for diabetes. The improvement in the intervention includes stricter metabolic control, better control of blood pressure and more frequent use of drugs active in blocking the renin-angiotensin system which may decrease the development and progression of diabetic nephropathy, possibly retinopathy as well as endothelial function that may contribute to the fertility. As the improvement was equally evident among women with and without recorded diabetic complications, this implies that the metabolic control was improved in patients independently of complications. However, women with manifest complications always had lower fertility than those without. Since the national program for treatment of diabetes launched in 1990 prescribed that all women who planned to become pregnant were to follow a stricter insulin treatment plan, this measure may have played a critical role (162).

Earlier findings show that women with T1DM more often are nulliparous or have fewer pregnancies than women without diabetes (106; 122). Before 1990, it was common practice to advise against pregnancy if the woman had simplex retinopathy or microalbuminuria. In the most recent decade, however, women with such complications have not been discouraged from becoming pregnant, but strict metabolic control has been zealously enforced.

It must also be emphasized that, due to early censoring in the substrata included in the cohort in more recent periods, the number of observed births in these substrata was limited. The trend towards improved fertility was less certain in these groups. Swedish women in general have tended to delay childbearing to higher ages for social reasons. The mean ages at first birth for period 1970-1979, 1980-1989, 1990-1999 and 2000-2004 were 24.5, 25.9, 27.2 and 28.6 years, respectively. The mean age of first birth has increased by no less than 3 years in the past 20 years (163), thus the fertility in the reference population has gone down. Although a similar trend in the average age of first live birth was observed in the diabetic cohort, the younger mean age before 1990 in women with T1DM may be due to the advice to the older women to avoid pregnancy if they have had some mild complications, which are increasing with the duration of diabetes.

7 CONCLUSIONS

- Both men and women with T1DM are at increased risk for hip fracture. Although optimal preventive measures still need to be defined, tighter metabolic control might reduce the risk.

- Although our data suggest a drop in LEA incidence in the most recent years, patients with T1DM diagnosed before the age of 31 still have striking absolute and relative risks. The falling rates suggest that recent preventive efforts are effective, but our results underscore the need for untiring preventive efforts early in the course of T1DM.

- Although the adjusted relative risks of myocardial infarction have decreased by 50% in the recent three decades, T1DM patients are still at high risk of myocardial infarction, measured by relative or absolute risk.

- Women with T1DM have reduced fertility, but it appears that normalization has occurred among women with uncomplicated disease and an onset in the past 20 years. Our results suggest that the stricter metabolic control exercised in the past 20 years may have helped prevent subfertility. However, although the risk of congenital malformations has decreased, it is still higher than that for the general population.

8 SAMMANFATTNING PÅ SVENSKA

Det största hälsoproblemet vid Typ 1 diabetes mellitus (T1DM) är sena komplikationer till sjukdomen. De mest studerade komplikationerna är mikroangiopati som drabbar njurar och ögon samt neuropati. Vi har undersökt risken för höftfrakturer, icke-traumatisik amputation av nedre extremiteter och hjärtinfarkt hos patienter med T1DM, samt fertilitet hos kvinnor med T1DM.

Kohorten med T1DM-patienter omfattar de som sjukhusvårdades första gången för diabetes mellitus före 31 års ålder. Dessa patienter identifierades med hjälp av det svenska slutenvårdsregistret. Utfallen identifierades genom att med hjälp av personnummer koppla studiekohorten med dödsorsaksregistret, flergenerationsregistret, medicinska födelseregistret, samt genom att söka förekomst av höftfrakturer, icke-traumatiska amputationer och hjärtinfarkt i slutenvårdsregistret. Risker är bedömda i jämförelse med normalbefolkningen, standardiserade för sjukhusvård (SHR), fertilitet (SFR) och incidens (SIR) och beräknade med 95% konfidensintervall. Log-linjära regressionsmodeller med antagande om Poisson-fördelning för den beroende variabeln användes för att beräkna relativa effekter av SHR, SFR och SIR, samt risken för icke-traumatisk amputation av nedre extremiteter under olika tidsperioder. Kaplan-Meier-metoden användes för att beräkna kumulativa sannolikheter för vissa av utfallen.

Jämfört med normalbefolkningen hade män en sjufaldig och kvinnor med T1DM en niofaldig ökad risk för höftfraktur. Den kumulativa risken för höftfraktur var 6,58% fram till 65 års ålder. Risken för icke-traumatisk amputation av nedre extremiteter minskade med 40% under perioden 2000-2004 jämfört med före år 2000. T1DM-patienterna hade dock fortfarande en mycket stor risk jämfört med normalbefolkningen. Vid 65 års ålder var den kumulativa risken för amputation 11,0% för kvinnorna och 20,7% för männen. SIR för hjärtinfarkt hos T1DM-patienterna minskade från 32,3 (1975-84) till 15,3 (1985-94), för att sedan minska till 9,7-faldig ökad risk under 1995-2004. Uttryckt som en relativ risk innebär detta en minskning med 50% under uppföljningsperioden. Trenderna för hjärtinfarkt med eller utan dödlig utgång var liknande för män och kvinnor. Risken för död i hjärtinfarkt var mer markant för kvinnor än för män. Studier av friska syskon till T1DM-patienter, visade en ökad risk för hjärtinfarkt enbart hos systrar till T1DM-patienter. Vid 65 års ålder var den kumulativa risken för hjärtinfarkt 28% vid T1DM, medan motsvarande siffra för deras syskon utan T1DM var 6%. Samtidig förekomst av andra sendiabetiska komplikationer innebar kraftigt förhöjd risk för höftfraktur, icke-traumatisk amputation och hjärtinfarkt. Lägre fertilitet observerades hos kvinnor som sjukhusvårdades första gången för T1DM före 1985 medan en normalisering av fertiliteten kunde ses hos dem som fått diagnosen efter 1985. Förekomst av diabeteskomplikationer innebar reducerad fertilitet under hela observationsperioden. Andelen nyfödda med missbildningar minskade från 11,7% under 1973-1984 till 6,9% under 1995-2004, men var högre vid T1DM än i normalbefolkningen.

Sammanfattningsvis har T1DM-patienter ökad risk för höftfrakturer, amputation av nedre extremiteter och hjärtinfarkt, samt hos kvinnorna en lägre fertilitet, jämfört med normalbefolkningen. Detta gäller särskilt patienter med sendiabetiska komplikationer.

En märkbar minskning av risken för hjärtinfarkt och icke-traumatisk amputation av nedre extremiteter, samt en normalisering av fertiliteten observerades under senare kalenderår. Likaså minskade risken för missbildningar över tiden. Bättre blodsocker-, lipid- och blodtryckskontroll är den mest sannolika förklaringen till dessa resultat.

9 FUTURE STUDIES

With the improvement of medical treatment in T1DM, its complications are becoming one important challenge since they affect the quality of life of these patients. They also bring a heavy burden on society. Although the studies presented in this thesis have investigated certain complications, other complications of T1DM remain to be studied.

T1DM is a typical chronic disease with a considerable psychological impact on the patients. Thus study on risk of psychological complications, such as the risk of suicide etc, could provide us important information to design better preventive programs and social support to prevent such psychological complications.

As discussed previously, non-trauma LEAs is common among patients with diabetes. Diabetic foot complications result in significant costs for society and individual patients (65). A preventive program on diabetic foot care was launched in 1999 (72). Further study to estimate the efficiency of this program is needed to confirm the decreasing trend of non-trauma LEAs observed in recent years. The risk factors for non-trauma LEAs should be further explored. Family studies could help us to explore the genetic as well as environmental risk factors.

Studies on the secular trend in the risk of diabetic nephropathy, especially the end stage renal disease should be performed.

Finally, translational studies on efficient prevention of all sorts of complications of diabetes are particularly necessary for T1DM patients. Health education program on the improvement of quality of life and prevention of complications should be provided not only to patients, but also to the health care providers and the public society.

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