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Epidemiology of diabetes in a well defined population in Sweden: the Skaraborg Diabetes Registry

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The Skaraborg Diabetes Registry

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Contents

Abbreviations

AUC	Area under the curve
GADA	Glutamic acid decarboxylase 65 antibodies
HLA	Human leukocyte antigen
IAA	Insulin autoantibodies
IA-2A	Protein tyrosine phosphatase-like protein IA-2 antibodies
ICA	Islet cell antibodies
JDF	Juvenile Diabetes Foundation
LADA	Latent autoimmune diabetes mellitus in adults
M	Molar concentration (= mol/l)
ROC	Receiver operating characteristic

List of papers

I.   Berger B, Stenström G, Chang Y-F, Sundkvist G
     The prevalence of diabetes mellitus in a Swedish population of 280 411
     inhabitants. A report from the Skaraborg Diabetes Registry
     Diabetes Care 1998;**21**:546-8

II. Berger B, Stenström G, Sundkvist G
     Incidence, prevalence, and mortality of diabetes in a large population. A
     report from the Skaraborg Diabetes Registry
     Diabetes Care 1999;**22**:773-7

III. Berger B, Stenström G, Sundkvist G
     Random C-peptide in the classification of diabetes
     Scand J Clin Lab Invest 2000;**60**:115-20

IV. Berger B, Borg H, Fernlund P, Stenström G, Sundkvist G
     Islet antibodies associated with beta-cell dysfunction at and three years
     after diagnosis of diabetes among 35-64 years old: degree of impairment
     less severe than among 0-34 years old
     Diabet Med, in press

Background

Diabetes mellitus was described already in 1550 BC as a chronic disease with high concentration of sugar in the body-fluids, but not until 1979, criteria for diagnosis and classification of diabetes were more generally accepted [National Diabetes Data Group 1979] [World Health Organisation Technical report series 646, 1980]. These recommendations have thereafter been revised repeatedly [World Health Organisation Technical report series 727, 1985] [The Expert Committee on the diagnosis and classification of diabetes mellitus, 1997] [Alberti *et al.* 1998].

Subtypes of diabetes were described already in 600 AD [Zimmet *et al.* 2002]. Historically the classification was purely clinical with attributes like juvenile, adult, obese, non-obese, insulin dependent, non-insulin dependent, ketosis prone, non-ketotic etc. [Lister *et al.* 1951]. After the development of insulin assays in 1951, the classification was based on the presence or absence of insulin, and after the identification of autoimmunity towards the islet components the classification has been changed towards the presence or absence of islet autoantibodies [Bottazzo *et al.* 1974]. Most cases of diabetes are now defined as one of the sub-types type 1 or type 2 diabetes.

Type 1 diabetes

The etiology of type 1 diabetes is suggested to be a non-mendelian polygenic inheritance associated with certain HLA-types that either increase or decrease the risk of developing the disease. Environmental factors have also been suggested, because genetic disposition seems neither necessary nor sufficient [Kumar *et al.* 1993]. The pathophysiology is thought to be a T-cell mediated autoimmune inflammatory destruction of the insulin-producing pancreatic beta-cell [Gepts *et al.* 1965] [Wegmann *et al.* 1994]. Most young patients with clinically diagnosed type 1 diabetes have autoantibodies directed towards the beta-cell [Mustonen *et al.* 1984]. The beta-cell destruction is often rapid in children. Hence, in children the symptoms of type 1 diabetes are often acute, uniform, and easily recognized with malaise, thirst, polyuria, weight loss, and eventually ketoacidosis. In adults, the symptoms of type 1 diabetes are more inconsistent and insidious with sometimes only modest and intermittent increase in blood glucose for several years, and the diagnosis then is much more dependent on laboratory findings [The Expert Committee on the diagnosis and classification of diabetes mellitus, 2003]. Type 1 diabetes is common in Scandinavia affecting about 0.5 % of the population and comprise about 15 % of all diabetes in the developed countries [Zimmet *et al.* 1997] [Pociot *et al.* 2001]. In other parts of the world, less than 5 % of all diabetes is type 1 diabetes [Di Cianni *et al.* 1994].

Type 2 diabetes

About 85 % of all diabetes in the developed countries is type 2 diabetes [Zimmet *et al.* 1997]. A strong non-mendelian polygenic inheritance with a 3-4 fold increased risk in siblings to patients with type 2 diabetes is recognized [Turner *et al.* 1995]. A defective action of insulin (i.e. insulin insensitivity or insulin resistance) is fundamental. The patients are often obese, and obesity is a risk factor for insulin insensitivity [Eriksson *et al.* 1992]. The risk of developing type 2 diabetes is increased with age, because aging is associated with decreased insulin sensitivity and decreased insulin secretion capacity. There is also a strong association between type 2 diabetes, arterial hypertension, and hyperlipidemia.

There are indications that an insulin secretion defects is of importance also in type 2 diabetes. Individuals with extreme insulin insensitivity do not develop diabetes, provided they succeed in compensating the insensitivity with increased secretion of insulin [Polonsky *et al.* 1996]. An insufficient acute insulin response to the elevation of blood glucose is fundamental in patients developing type 2 diabetes [Polonsky *et al.* 1988]. The cause of this secretion defect, however, could be the insulin insensitivity, leading to a persistent hyperinsulinemia and in susceptible persons to a down-regulation of the insulin receptors, creating a vicious circle with accelerating insulin insensitivity and eventually beta-cell failure [Zimmet 1982]. The onset of type 2 diabetes is often insidious and the disease can go undiagnosed with disturbed insulin response for several years. Sometimes late complications from blood vessels and nerves are the first symptoms noticed [The Expert Committee on the diagnosis and classification of diabetes mellitus, 2003]. After diagnosis the insulin secretion often continues to deteriorate, so that within 10 years a considerable part of the patients with type 2 diabetes has an absolute insulin deficit similar to patients with type 1 diabetes [Rudenski *et al.* 1988] [Clausson *et al.* 1994].

Other types of diabetes

Other types of diabetes have been defined by the American Diabetes Association and the Word Health Organisation and comprise about 1 % of all diabetes in Sweden.

Gestational diabetes, of course, requires pregnancy, but is otherwise a conglomerate of heterogeneous diseases with everything from a subtle elevation of blood glucose after challenge, to severe insulin-requiring ketoacidosis. One special feature of gestational diabetes is the remission after delivery and the high frequency of type 2 diabetes later in life. Gestational diabetes is not registered or considered in the Skaraborg Diabetes Registry.

Monogenetic defects of beta-cell function is rarely identified in young patients, often misdiagnosed as type 1 diabetes but with a milder forms of hyperglycemia and less hyperglycemic complications [Cammidge *et al.* 1928] [Tattersall *et al.* 1974]. These heterogeneous clinical entities are considered under the eponym MODY (Maturity Onset Diabetes in Young ages) [Hattersley *et al.* 1998]. A few patients have point mutations in the insulin gene with a dysfunctional insulin molecule or mutations in the insulin receptor with resulting hyperinsulinemia and hyperglycemia.

Mitochondrial gene lesions are rare cause for diabetes and have the unique property of being inherited only from the mother, as the paternal mitochondrion is discarded when the sperm penetrates the ovum. This form of diabetes is often presented together with hearing loss [Gerbitz *et al.* 1995]. Diabetes secondary to pancreatic disorders, cystic fibrosis, haemochromatosis and other metabolic diseases or secondary to pharmacotherapy can mimic type 1 or type 2 diabetes depending on beta-cell function and compromised insulin action.

Latent autoimmune diabetes mellitus in adults (LADA) [Groop *et al.* 1986] is an eponym for diabetes with islet autoantibodies and slowly progressive destruction of the beta-cells and preserved insulin secretion for several years. Due to genetic likeness, LADA is included in the group with autoimmune type 1 diabetes [Tuomi 1993] [Zimmet et *al.* 1999] [Stenström *et al.* 2002] [Fourlanos *et al.* 2005]. Attempts to identify genetic defects, secondary diabetes, or LADA have not been done in the Skaraborg Diabetes Registry.

Epidemiology

The first estimation of diabetes prevalence was published in US 1935-1936 [US Public Health Service, 1938] and in Sweden 1947 [Dahlberg *et al.* 1947]. After 1950 epidemiological research activities expanded all over the world. One of the first screenings of a population with oral glucose tolerance tests was published 1965 [Hayner *et al.* 1965]. In 1965, the European Diabetes Epidemiology Study Group (EDESG) was organized and the first international report comparing diabetes prevalence between countries and using standardized criteria for diagnosis was published 1966 [West *et al.* 1966].

Diabetes mellitus has been referred to as the epidemiologist's nightmare [Zimmet 1982]. Studies from before 1985 used diagnostic criteria, which are not representative of diabetic patients defined by current Word Health Organisation criteria [Heyden *et al.* 1980]. The prevalence varies from country to country, between different ethnic groups in the same country, and in the same ethnic group undergoing migration between continents or from rural to urban areas. Comparisons are confounded by different methodologies,

ascertainment rates, and diagnostic procedures. Collection and analyze of epidemiological data in a standardized manor for insulin-dependent diabetes started around 1986 by the Diabetes Epidemiology Research International Study Group (DERI) [Rewers *et al.* 1988]. They stated seven criteria that should be fulfilled for registries eligible for comparison of diabetes epidemiology. The criteria were initially outlined for insulin-dependent diabetes, but are valid for registries of all types of diabetes.

- The registry should be population-based and ascertain all cases of diabetes in a geographically defined population. Registries of patients attending a clinic or a hospital could give biased data concerning epidemiology due to difficulties to assess the background population.

- The registry should ascertain all incident cases and not only prevalence. Prevalence is dependent not only on incidence but also on survival in the diseased group and hence on the quality of health care.

- The registry should use standardized criteria for diagnosis and classification. A change in diagnostic criteria could dramatically change the incidence and prevalence.

- The registry should cover all age groups because the incidence and prevalence of diabetes vary 20-fold in different age groups.

- The registry should contain individual records of sex, residence, date of birth and diagnosis so that duplets can be identified and age- and time-related prevalence and incidence can be calculated.

- High quality denominator data must be available from the target population in order to calculate incidence and prevalence.

- The registry should be ascertained by at least two independent sources. Registries that report prevalence data without estimation of ascertainment actually claim that they have zero missing patients without any grounds for that claim. At best such reports provide a lower boundary of prevalence.

Few reports in the world, however, come from registries fulfilling all these criteria, but despite all confounding factors, a general acceptance has developed, that the prevalence of diabetes is increasing in the world [Zimmet *et al.* 1997] [Alberti *et al.* 2004].

There was, however, in the 1980th a widespread uncertainty, which of several possible factors caused the increasing prevalence [Laakso *et al.* 1985] [Gregg *et al.* 2004] [Colagiuri *et al.* 2005]:

- Was the increase in prevalence a result of changed diagnostic criteria and an earlier diagnosis?

- Was the increase in prevalence a result of an increase in incidence in the past with protracted imbalance between incidence and mortality?

- Was there an increase in the total incidence of diabetes?

- Was there an increase in the incidence of type 1 or type 2 diabetes?

- Was there an increase restricted to certain age groups?

- Was there an increase in incidence caused by an increasing age of the population?

- Was there a general shift towards onset in younger age groups?

- Was there an increase in incidence caused by a generally increase in obesity?

- Was the increase in diabetes prevalence a result of increasing life expectancy among diabetic patients?

The prevalence of diabetes by 1990 varied from less than 1 % in Alaskan Eskimos [Mouratoff *et al.* 1967] to over 50 % in Pima Indians above 35 years of age from Arizona [Bennet 1971]. Earlier reports of diabetes prevalence did not distinguish between type 1 and type 2 diabetes. Type 1 diabetes is, however, uncommon in most populations and the prevalence of type 2 diabetes in general reflects 85-90 % of the total prevalence of diabetes [Zimmet 1982].

Reports of diabetes incidence in entire populations varied from 13.3/100 000/year in 0-29 year olds in Denmark [Christau *et al.* 1979] to over 3 % per year in adults from certain populations in Brazil [Gimeno *et al.* 2002] and Taiwan [Tseng *et al.* 2000].

A seasonal variation of diabetes incidence has been observed in young type 1 diabetic patients, with a peak in the winter and low incidence in the summer months [Reunanen *et al.* 1982] [Dahlquist *et al.* 1985] [Siemiatycki *et al.* 1986] [Hamman *et al.* 1990] [Joner *et al.* 1991], but had not been reported in adults with type 1 or type 2 diabetes in the 1990th.

Previous reports of mortality in diabetic patients from Europe [Królewski *et al.* 1977] [Reunanen 1983] [Panzram 1984], US [Garcia et al. 1974] [Palumbo *et al.* 1976], and Asia [Sasaki *et al.* 1983] suggested an 1.3-4.5 times higher overall mortality rate for diabetic patients compared with the healthy background population [Panzram *et al.* 1987].

Islet autoimmunity

Antibodies against the islet cells of the pancreas (ICA) were described in 1974 [MacCuish *et al.* 1974]. The ICA reactivity consists of a conglomerate of antibodies directed against the surface of the beta-cells and other islet cells, giving indirect immunofluorescence to human pancreatic islets [Genovese *et al.* 1992] [Månsson *et al.* 2003]. The first antigen-specific autoantibody identified, was directed against insulin (IAA) [Palmer *et al.* 1983]. The significance of this antibody disappears after introduction of insulin therapy, because exogenous insulin induces IAA in many patients. Antibodies towards specific components of the insulin-producing beta-cell have later on been identified as contributors to the ICA reactivity.

The antigen-specific antibodies most frequently identified in patients with type 1 diabetes are GADA and IA-2A [Leslie *et al.* 1999]. Some of the ICA reactivity has been identified as GADA, present in 70-85 % of young patients with newly diagnosed type 1 diabetes [Christie *et al.* 1988]. The antigen is an enzyme converting glutamate to gamma amino butyric acid, present in beta-cells but also in the central nervous system, liver, kidney, and other endocrine organs [Bækkeskov *et al.* 1990]. The popularity of GADA-analyses has increased with time, because GADA in diabetic patients is more consistent over time than ICA [Christie *et al.* 1990] and the analyses is much easier to perform than the immunofluorescence analysis of ICA, that needs fresh human cadaver pancreata.

IA-2A has been characterized more recently as an antibody contributing to ICA reactivity and directed against a protein tyrosine phosphatase-like protein found in pancreatic alfa- and beta-cells and in neuroendocrine cells of the central nervous system, pituitary gland, and adrenals [Pietropaolo *et al.* 1997]. The protein tyrosine phosphatase seems to be involved in the transport of insulin and other neuroendocrine peptides over the membranes of the endoplasmic reticulum, golgi-network, and secretory granules.

Other antibodies directed against components of the islet cell have been isolated but with low prevalence in diabetic patients. All signs of autoimmunity (ICA, IAA, GADA, IA-2A etc.) directed against the pancreatic cells or against insulin have been interpreted as diagnostic for type 1 diabetes. The absence of these autoantibodies, however, has not excluded the possibility of a type 1 diabetes diagnosis. Nevertheless, some reports have presented figures on islet autoantibodies also in patients with type 2 diabetes [Pietropaolo *et al.* 2000] [Batstra *et al.* 2001].

In this thesis, ICA, GADA and IA-2A have been considered and their potential to differentiate type 1 from type 2 diabetes has been evaluated.

Beta-cell function

Another way to discriminate between type 1 and type 2 diabetes is to estimate the capacity to secret insulin. Insulin is synthesized and stored in the beta-cell in the pancreatic islands of Langerhaan. Before secretion the insulin molecule is bound to a connecting peptide (C-peptide) and stored in granules in the beta-cells as proinsulin [Clark 1999]. When the beta-cell is stimulated by increased blood-glucose concentration, the insulin is cleaved from the C-peptide and both are secreted in equimolar concentrations [Hoekstra et al. 1982]. Insulin and C-peptide are excreted in two phases: the first phase consists of pre-fabricated insulin and begins within seconds after the increase in blood glucose concentration and lasts for a few minutes [Horwitz et al. 1975]. The second phase consists of insulin fabricated after the stimulation has begun, a few minutes later, and lasts for at least an hour. In healthy persons the beta-cell action and insulin secretion are brisk and pulsatile. The first sign of dysfunction, observed both in early type 1 and type 2 diabetes, is less frequent pulsatility with a partial loss of the first phase and a compensatory prolongation of the second slower phase [Leahy et al. 1990].

Determination of the plasma-insulin concentration as an indication of beta-cell function has several drawbacks. Insulin concentration varies 10-fold in plasma depending on blood-glucose concentration and fasting state; a variable proportion of the excreted insulin is extracted by the liver before entering the extrahepatic circulation; the half-life of insulin in plasma is only 3-5 minutes [Polonsky et al. 1984]; and insulin is unstable in the presence of haemolysis due to insulin degrading enzymes in the erythrocytes. Another drawback of plasma insulin determination is the inability to differ endogenous from exogenous insulin. Hence, a single estimation of plasma insulin concentration gives little information of the beta-cell function.

C-peptide, on the other hand, has low hepatic and tissue clearance, the removal of C-peptide from blood is fairly constant with a half-life of 33 minutes, and there is no analytical interference with exogenous insulin [Hoekstra et al. 1982] [Gottsäter et al. 1992]. C-peptide concentration as a marker of endogenous insulin secretion in diabetic patients has been studied in urine [Blix et al. 1982] [Bantle et al. 1984] [Koskinen et al. 1986] and plasma during fasting conditions [Poulsen et al. 1985] [Webb et al. 1991] [Clauson et al. 1994], after stimulation by standardized meals [Faber et al. in Diabetes 1977] [Koskinen et al. 1988] [Escobar-Jimenes et al. 1990], after challenges with glucose [Heding et al. 1980] [Gottsäter et al. 1992], and after challenge with glucagon [Madsbad et al. 1981] [Hother-Nielsen et al. 1988] [Gjessing et al. 1989]. C-peptide levels before and after stimulation with glucagon have shown high consistency in repeated tests in diabetic patients and healthy controls [Horwitz et al. 1975]. Hence, assessment of C-peptide is generally accepted as an index of beta-cell function.

Glucagon-stimulated C-peptide has been the golden standard for determination of beta-cell function since the 1990th. Fasting C-peptide were introduced as an attractive alternative, because there was need for a simple test for insulin-dependency that could be used without the need to have all patients traveling to the health centers early in the morning, without breakfast. There were, however, theoretical doubts concerning fasting C-peptide. The secretory capacity of hormones is usually tested in connection with some kind of stimulation, but fasting C-peptide is a test of secretory capacity in connection with maximal inhibition of the beta-cell. Hence, C-peptide measurements without fasting or glucagon stimulation have been recommended as an adequate test for routine clinical use [Rönnemaa et *al.* 1986].

In this thesis, different methods of measuring C-peptide have been considered and their potential to differentiate type 1 from type 2 diabetes has been evaluated.

Aims

The initial purpose with the Skaraborg Diabetes Registry was to determine the prevalence of diabetes in the region and to estimate the resources needed in health centers and hospital facilities. Rather soon, a need appeared to validate the estimations, to be able to interpret time-trends in incidence, prevalence, and mortality. Type 1 was separated from type 2 diabetes in the analyses, due to a suspicion that they could have different prognosis. In the classification work, it was necessary to evaluate how the classification tools could be used most efficient in an entire diabetic population. To clarify these items the Skaraborg Diabetes Registry was created and the following aims were formulated:

- to estimate the capture rate of the Skaraborg Diabetes Registry [Paper I]
- to estimate the prevalence and incidence of diabetes [Paper II]
- to estimate the mortality risk in diabetic patients [Paper II]
- to look for time-trends in prevalence, incidence, and mortality [Paper II]
- to find a way to separate type 1 from type 2 diabetes [Paper III and IV]
- to compare the prognosis for type 1 and type 2 diabetes [Unpublished]
- to look for factors associated with the prognosis of diabetes [Unpublished]

Methods

Patients

Skaraborg in 1990 was a rural county in southern Sweden with a health care organization administrating one central hospital, three local hospitals, and 30 health centers. The population was stable with about 280 000 inhabitants, of whom 67 % were born in Skaraborg and 94 % in Sweden. The age, gender distribution, and morbidity were similar to the general Swedish population [Spek *et al.* 1994] [Pellmer *et al.* 1994].

After 1996 Skaraborg has ceased to be a separate county and the care facilities have been integrated in Västra Götalands-regionen. The inhabitants of the Skaraborg care district are now 254 000 after the loss of two communities. Two hospitals have reduced their capacity and seven health centers have closed, merged, been transferred, or reduced their capacity. These confounding factors have been adjusted for as far as possible.

All diagnosed cases of diabetes present at Jan. 1, 1991 and all new cases of diabetes thereafter diagnosed were registered by physicians at the hospitals, by general practitioners, private practitioners, and by specialized diabetes nurses at the local health centers. Patients with gestational diabetes (i.e. who normalized their blood glucose value after delivery) were not registered. The patients were divided into two age groups for comparison with other studies in Sweden: young (0-34 years) and adults (35-64 years).

The validity of the registered data (civic number, home address, county of residence and deaths) were checked with Population Statistics Sweden [SCB Befolkningsstatistik] each year and the local health centers were contacted regularly for control and updating of registration, social and clinical data. Three complementary sources were used to find diabetic patients in Skaraborg:

- An administrative hospital registry at the Department of Medicine, Kärnsjukhuset Skövde comprising civil number and diagnoses of all patients cared for in the hospital and at the out-patient wards. This registry was scrutinized for unregistered cases of diabetes in 1994, 1996, 1998, 2000, and 2002.

- The Skaraborg Retinopathy Screening Program comprising all patients diagnosed before 60 years (after year 2000 changed to: *before 70 years*) of age and with diabetes duration of more than 5 years (after year 2000 changed to: *diabetes of any duration*). This registry was scrutinized for unregistered cases of diabetes in 1994, 1997, 2000, and 2003.

- A prescription inventory of expedized insulin and antidiabetic drugs, conducted at 10 different pharmacies in Skaraborg during three months during the period 1992–94.

In the study of islet autoantibodies, the patients diagnosed during a two-year period (Sep. 1996 - Aug. 1998) were registered together with clinical symptoms at diagnosis. The presence of typical symptoms of type 1 diabetes (low age, high blood glucose, severe clinical symptoms of thirst, polyuria, weight loss, fatigue, ketoacidosis [pH < 7.3, bicarbonate < 15 mM]) and of type 2 diabetes (high age, high body-mass index, and blood pressure) were registered.

Diagnosis

At the establishment of the Skaraborg Diabetes Registry in 1991, diabetes was diagnosed in accordance with international recommendations [World Health Organisation Technical report series 727, 1985], by chronic elevation of blood glucose. In the presence of typical symptoms a single glucose value of at least 12.2 mM in capillary plasma, 11.1 mM in venous plasma or capillary whole blood, or 10.0 mM in venous whole blood was diagnostic. In the absence of typical symptoms at least two consecutive tests for glucose on two different days had to be at least 6.7 mM in whole blood or 7.8 mM in plasma after fasting; 10.0 mM in venous whole blood, 11.1 mM in capillary whole blood or in venous plasma, or 12.2 mM in capillary plasma 2 hours after a 75 g glucose load.

This definition was later changed [The Expert Committee on the diagnosis and classification of diabetes mellitus, 1997] [Alberti *et al.* 1998]. The main changes were a lowering of the diagnostic glucose value to 6.1 mM in whole blood and to 7.0 mM in plasma after fasting. All care personnel in Skaraborg were continuously informed and upgraded concerning diagnostic criteria and classification by local and regional meetings and by postgraduate courses for the specialized diabetes nurses in the region.

Calculation of prevalence

In the determination of capture rate, the Skaraborg Diabetes Registry was compared with the three pre-existing registries mentioned above. Due to the difficulty to classify the type of diabetes on clinical signs [Tuomi *et al.* 1993] [Arnqvist *et al.* 1993], the first objective was to ascertain the prevalence of diagnosed diabetes without considering the type. The prevalence was related to age and year of diagnosis to elucidate time trends and changes in age at onset.

Calculation of incidence

A varying delay between diagnosis and registration could confound the estimation of yearly incidence. Hence, in the study of incidence, the number of diagnosed but still unregistered cases each year had to be appreciated. We determined how many of the patients diagnosed in 1991, were registered in 1991 and how many who were registered each of the following years between 1992 and 1998. A similar determination was done for patients diagnosed each following year between 1992 and 1998. We could then determine how many patients had been registered with 1-7 years delay after diagnose during the study period. The number of patients diagnosed with diabetes was determined as the calculated number of undiagnosed patients added to the number of registered patients each year. After 1998 the estimation of unregistered patients were verified as the patients with onset of diabetes between 1991 and 1998 successively were registered. Incidence rates were calculated as the estimated number of new cases in 5-years age groups each year, divided by the number of persons at risk in each age group in the background population of Skaraborg, according to Population Statistics Sweden [SCB Befolkningsstatistik]. The fact that a small proportion of the background population already was diagnosed with diabetes and the denominator hence might bee positively biased was ignored.

Calculation of mortality

In the determination of mortality, standard mortality rate was calculated as the death rate for diabetic patients in 5-years age groups, divided by the death rate for the corresponding age group of the background population according to Population Statistics Sweden [SCB Befolkningsstatistik 1991-1995]. The fact that the diabetic patients is not separated from the background population in Population Statistics Sweden and therefore contribute to a positively biased mortality in the background population has not been adjusted.

All patients with the onset of diabetes between the age of 25 and 34 years and alive sometime between 1991 and 2004 were explored whether mortality risk was related to the type of diabetes rather than to the age at onset. The age interval 25-34 years was chosen for two reasons.

- In age group 25-34 years the number of patients diagnosed with type 1 and type 2 diabetes was similar.

- A broader age interval made the median age different for type 1 and type 2 diabetes. This could lead to a biased mortality by more patients with type 2 diabetes in the upper part of the age interval. A more narrow age interval would give to few patients to explore.

The correlation between mortality and complicating factors, such as BMI, systolic and diastolic blood pressure, and HbA1c, was investigated. All diabetic patients diagnosed after 1991 were checked for BMI, blood pressure, or HbA1c at registration. Survival for the next ten years was related to the different parameters and survival graphs were constructed.

Tests for autoimmunity

In the study of type 1 and type 2 diabetes classification, islet cell antibodies (ICA) were determined by a prolonged two-color immunofluorescence assay [Landin-Olsson et al. 1987]. ICA > 0 JDF was considered abnormal. Glutamic acid decarboxylase 65 antibodies (GADA) and protein tyrosine phosphatase like protein IA-2 antibodies (IA-2A) were determined by radioligand binding assays [Borg, Clin Chem;43:779-85, 1997] [Borg, Clin Chem;43:2358-63, 1997].

A GADA-index > 6.51 and an IA-2A-index > 1.06 were considered abnormal (97.5 percentile of 299 healthy controls 7-70 years of age). In the Diabetes Autoantibody Proficiency Program no. 13, the ICA assay performed with 100 % sensitivity and specificity. In the Diabetes Autoantibody Standardization Program (DASP), the GADA assay performed with 80 % sensitivity and 96 % specificity, and the IA-2A assay with 58 % sensitivity and 100 % specificity.

Tests for beta-cell function

To evaluate the correlation between type of diabetes and C-peptide concentration, all inhabitants of Skaraborg with a well-defined type of diabetes who had a C-peptide assessment done at Nova Medical Laboratories, KSS Skövde between 1995-1998 were retrospectively analyzed. The clinical classification was done by the reporting physician. All samples were measured with commercial kits [C-PEP-CT2 1994] [Nova Medical 1997] [DPC Immulite 1995]. Patients considered having well defined types of diabetes fulfilled the following criteria:

- The patient was registered with type of diabetes in the Skaraborg Diabetes Registry prior to the C-peptide assessment.
- Patients with type 1 diabetes had started insulin treatment within a year after diagnosis.
- Patients with type 2 diabetes had been managed without insulin for more than a year after diagnosis.

There were three options for the C-peptide determination:

- Fasting C-peptide: Blood was sampled in the morning after at least 10 hours of fasting.
- Glucagon stimulated C-peptide: After at least 10 hours of fasting over night, a blood sample was drawn 6 minutes after the intravenous injection of 1 mg glucagon. A fasting C-peptide was assessed before the injection of glucagon.
- Random C-peptide: Blood was sampled at an ordinary visit to the clinic, without considering time of the day or the relation to previous food intake. Blood glucose was measured at the same time and random C-peptide was analyzed only if blood glucose exceeded 8 mM to avoid suppressed beta-cells [Nosari et al. 1992]. Traveling time, waiting time at the health centers, and normal mealtimes made it unlikely that the blood was sampled within an hour or more than 4 hours after previous meal.

In order to check for possible selection bias, a subgroup analysis was done on 168 patients in whom all three C-peptide protocols had been determined.

Statistical analyses

Between groups, nonparametric Kruskal Wallis and Mann Whitney tests were used to evaluate differences between groups with continuous variables. Fishers test was used to determine differences in frequencies of categorical variables. Spearman's log rank test was used to analyze correlation. Wilcoxon paired test was used in intra group comparisons.

Conventional formula for capture-recapture calculations was used in the determination of prevalence, [Wittes et al. 1968] [LaPorte et al. 1993] and graphs for assessment of potential dependencies between the three registries were constructed [Bruno et al. 1994] [LaPorte et al. 1995].

The temporal trend in incidence was analyzed with a test for linear trends [Armitage 1995] and the difference between male and female incidence was tested with a chi-square test. The significance of seasonal trends was tested with Roger's test [Roger 1977].

The 95 % confidence interval around the standardized mortality risk was calculated as $1.96 * SD * n^{-\frac{1}{2}}$, assuming a Poisson distribution of deaths. The time trend in median age at death was tested with a chi-square test for trend.

Receiver Operating Characteristic (ROC) curves [Beck *et al.* 1986] were constructed to compare the power of the different C-peptide protocols in the classification of diabetes and to find the optimal cut-off value to discriminate type 1 from type 2 diabetes. ROC curves illustrate the relationship between the specificity and the sensitivity of diagnostic tests considering all possible cut-off values. The areas under the ROC-curves (AUC) were calculated. The AUC can take values between zero and one and represents the probability that a randomly chosen type 1 diabetic patient has a lower C-peptide value than a randomly chosen type 2 diabetic patient does. An AUC of 0.5 indicates no discriminating value by the test. An AUC exceeding 0.7 indicates a discriminating strength of statistically importance. An area exceeding 0.8 indicates good discriminating power by the test [Forsström *et al.* 1995].

Calculations and analyses were done in Abacus Stat View 4.5 (Berkeley, Ca). $P < 0.05$ was considered significant. Data in figures and tables are presented as median (inter-quartile range) if not otherwise stated.

Results

Prevalence

The Skaraborg Diabetes Registry had a total capture rate of 88.4 ± 1.3 %. The capture rate was 97 % of those with pharmacological treatment, 80 % of those with only diet, 93 % of those below 60 years of age, and 90 % of those above 60 years of age. A diabetic population of 8 960 ± 133 was obtained, indicating a total diabetes prevalence of 3.20 ± 0.08 % in Skaraborg 1995. The prevalence varied according to age and gender (Figure 1). In 0-5 year olds the prevalence was < 0.1 % for both boys and girls. The highest prevalence was found in 75 years old men (10.5 %) and in 76 years old women (9.5 %).

Figure 1. The prevalence of diabetes in Skaraborg 1994 (arrow), and the variation in prevalence according to age and gender.
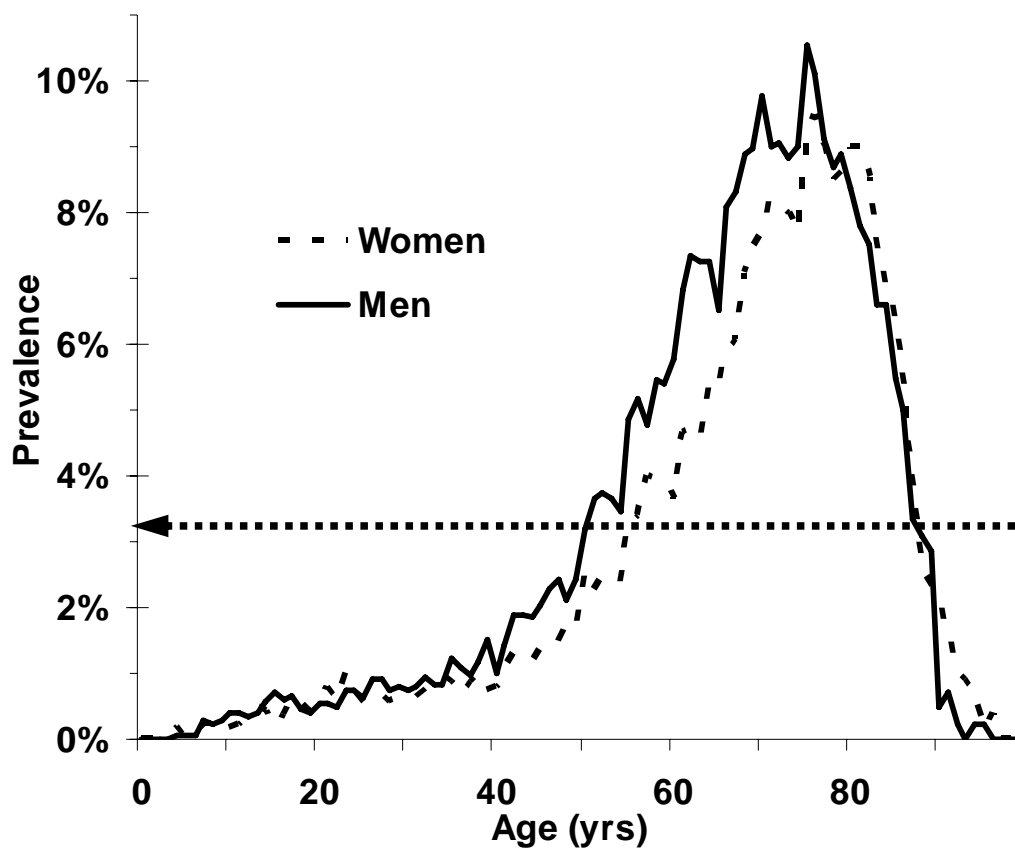
There was a significant 11 % male preponderance of diabetes in Skaraborg. The preponderance was seen in all age groups except in < 5, 20-24, and > 80 year olds. The male preponderance was rather stable around 11 % in type 2 diabetes during 1991-2005, but in type 1 diabetes the male preponderance increased from insignificant 4 % to 11 % between 1991 and 2005.

A temporal change in the prevalence of diabetes was observed. The prevalence increased with about 6 % per year between 1991 and 1995. The following ten years the increase in prevalence was slower with about 4 % increase per year, corresponding to a yearly 0.1 % net increase of diabetes in the population (Figure 2). At the end of 2004 the prevalence of diabetes in Skaraborg had increased to 4.23 %.

Figure 2. The prevalence of diabetes increased with about 0.1 % per year between 1993 and 2004
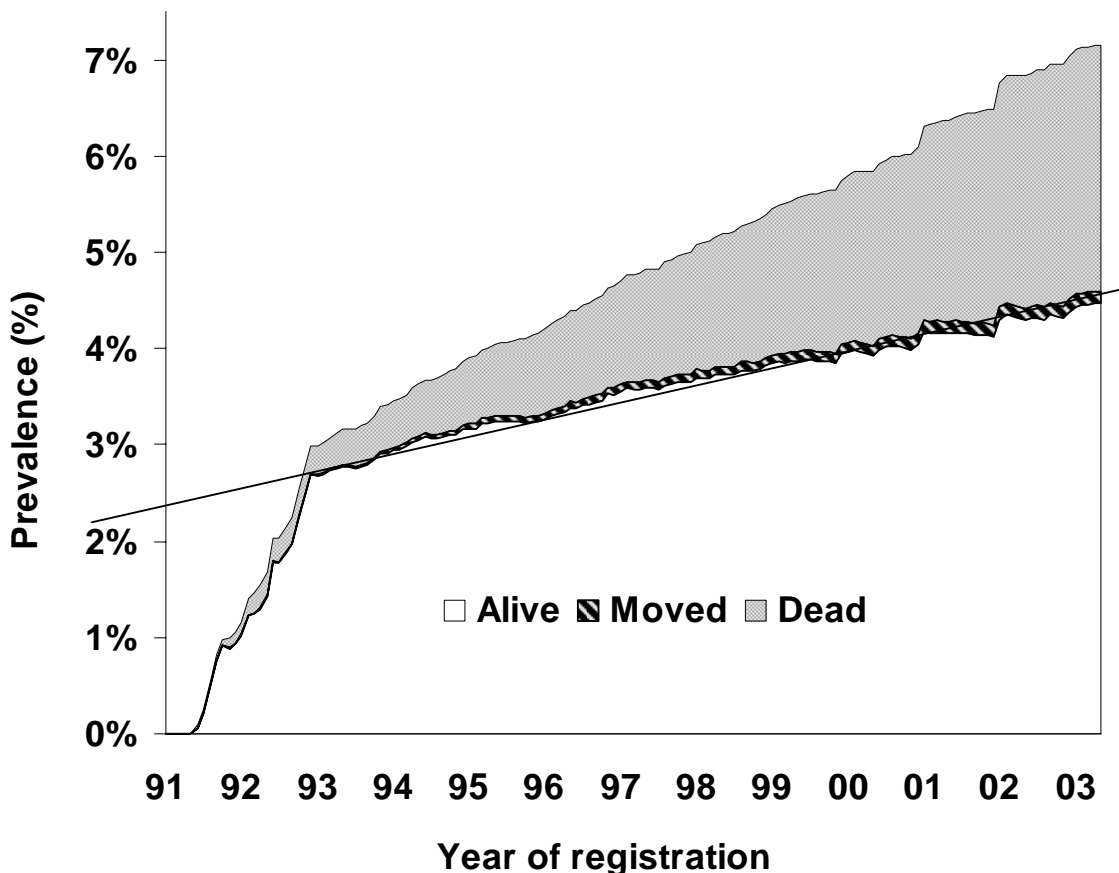
Incidence

It took about two years to inform all participating departments and health centers about the Skaraborg Diabetes Registry. Hence, between 1991 and 1993 the registrations increased successively. After 1993 the rate of registrations, movements, and deaths was more stable (Figure 2).

The mean incidence of diabetes between 1991 and 2005 was 261/100 000/year. For type 1 diabetes the incidence was 15.6/100 000/year and the incidence rate peaked at 44.4/100 000/year in 10-14 year olds (Figure 3).

Figure 3. Incidence of diabetes in realtion to gender and age
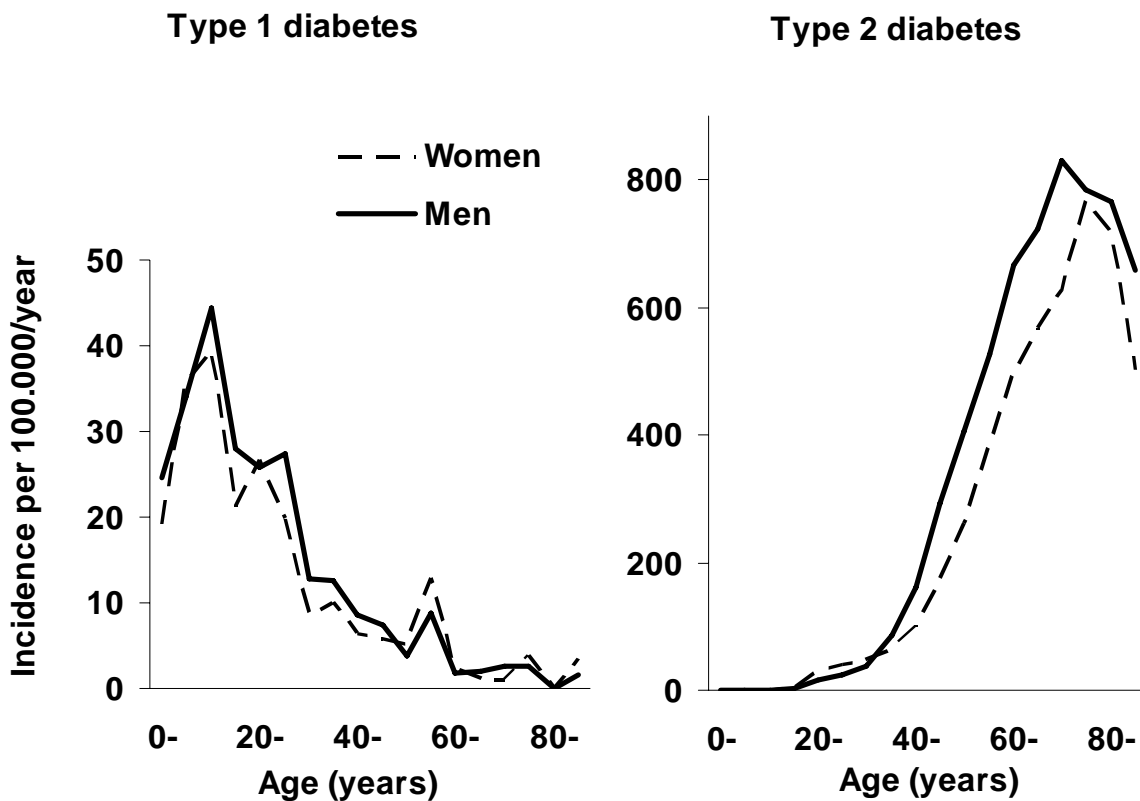
For type 2 diabetes the mean incidence was 246/100 000/year and the incidence peaked at 829/100 000/year in 70-75 year olds. There were no consistent trends in the incidence of diabetes over the years, neither for type 1 nor for type 2 diabetes (Figure 4).

Figure 4. Time trends in diabetes incidence 1991 - 2004

Type 1 diabetes

Type 2 diabetes

— Men
− − Women
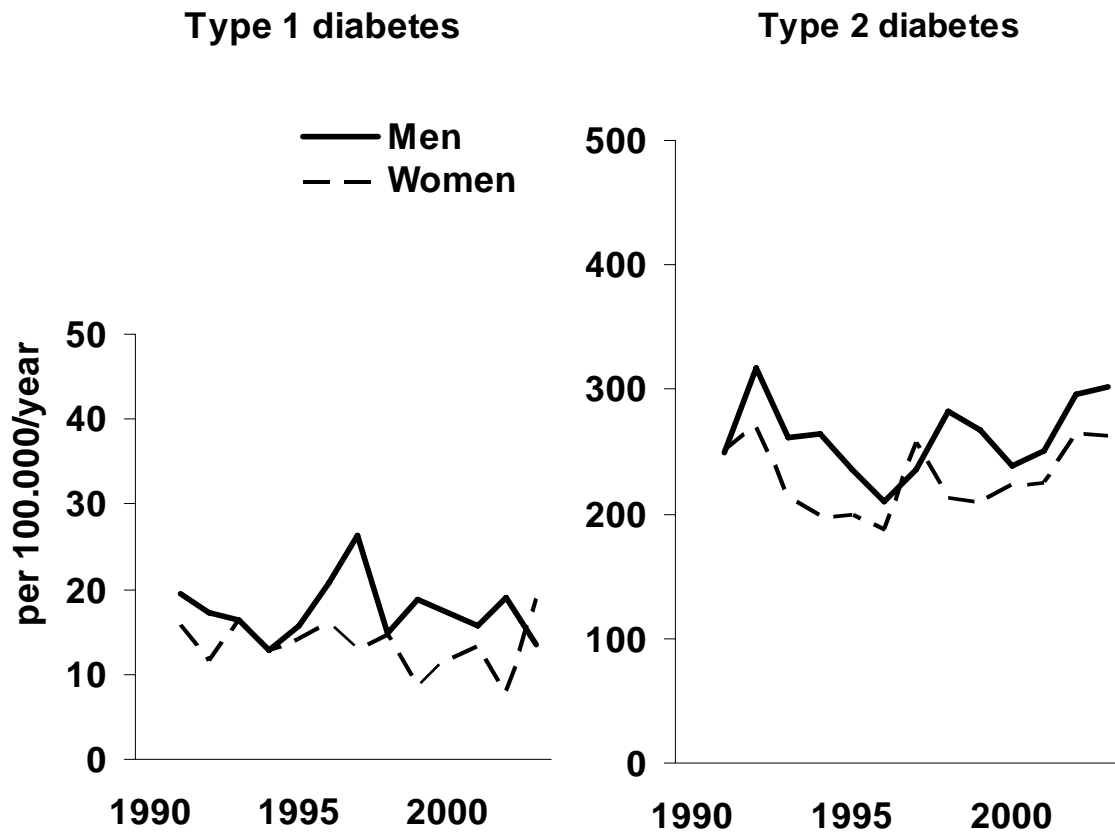
There was a significant gender difference in incidence of type 2 diabetes (men: 262.5, women: 228.6/100 000/year, $P = 0.04$). The gender difference in incidence of type 1 diabetes was not significant in 1999 (men: 14.9, women: 13.7/100 000/year, $P = 0.06$), but the difference reached significance in 2003 (men: 17.5, women: 13.4/100 000/year, $P = 0.04$). Hence, men had 30 % excess in incidence of type 1 diabetes and 15 % excess in incidence of type 2 diabetes.

The mean age at diagnosis was 22.3 years for type 1 diabetes (23.2 years for women and 21.4 years for men) and varied between 13.6 and 32.4 years between 1991 and 2003. In type 2 diabetes the mean age at diagnosis was 64.6 years (66.2 years for women and 63.0 years for men) and varied between 60.9 and 68.9 years between 1991 and 2003. There was no consistent change of age at diagnosis, neither for type 1 nor for type 2 diabetes over time (figure 5).

Figure 5. Time trends in age at diagnosis for men and women with type 1 and type 2 diabetes.
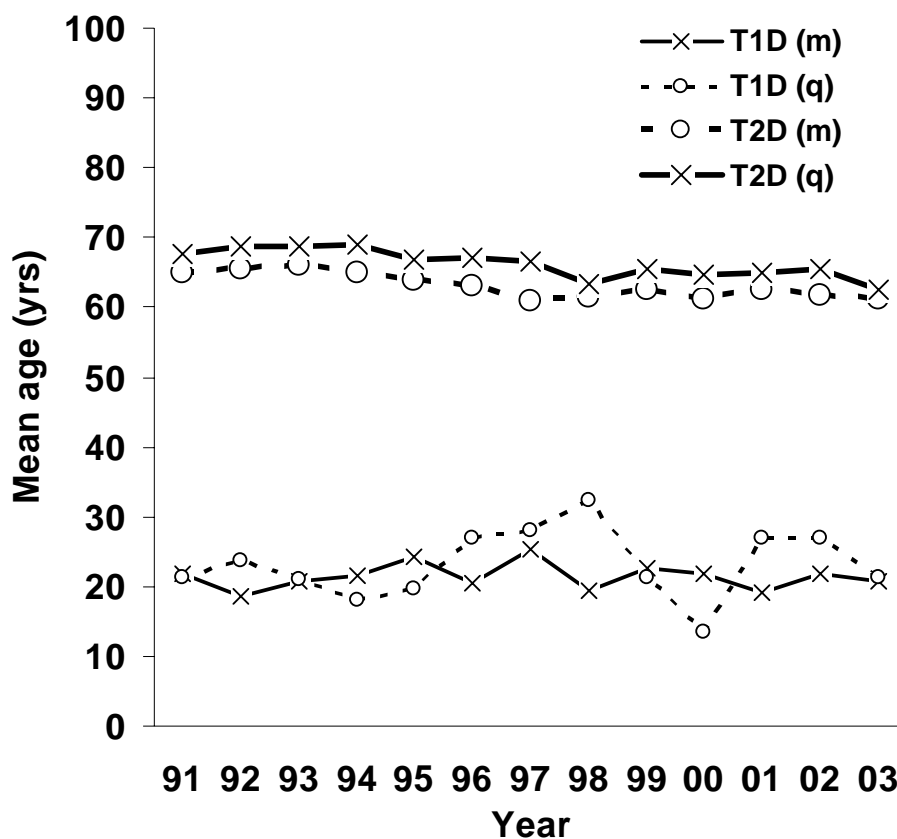
There was a significant seasonal variation in the incidence of diabetes (Figure 6). Most patients were diagnosed in the winter months and fewer in the summer. This seasonal variation was most pronounced in 10-19 year olds and 50-59 year olds but was present in all age groups, in both men and women, and in both type 1 and type 2 diabetes.

Figure 6. Relative incidence of diabetes each month of the year
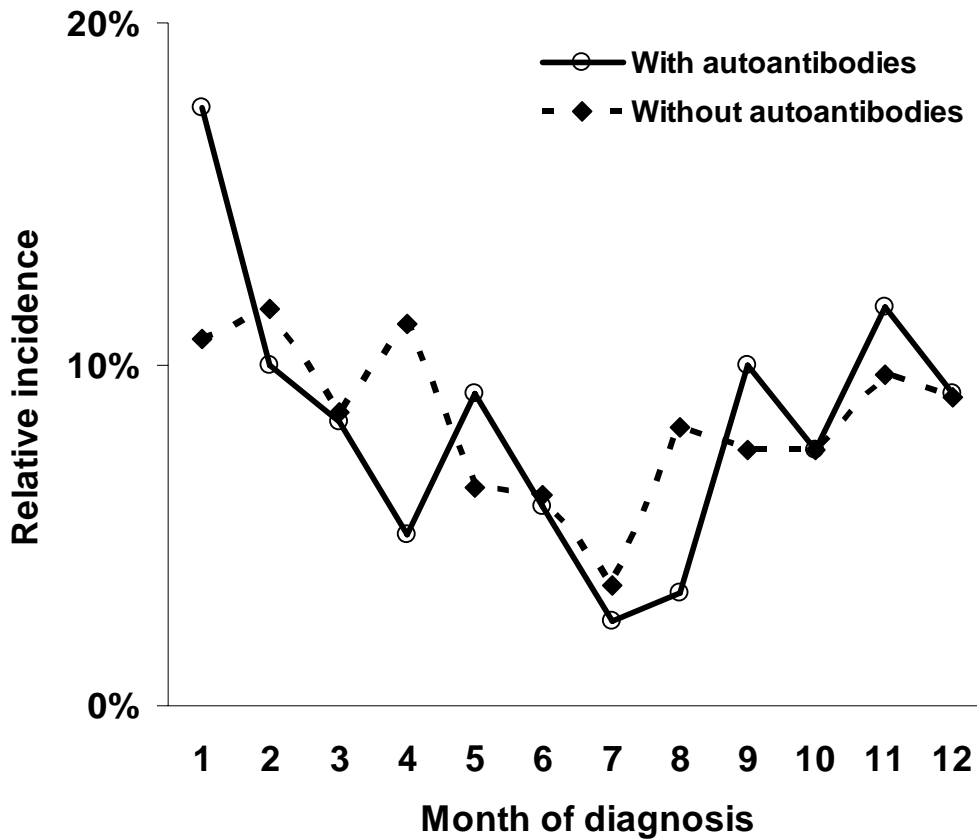
Mortality

Diabetic patients had an overall 3.8 times increased mortality risk compared with the background population. The mortality risk was age dependent. Patients 0-19 years of age at diagnosis had a 6 times increased mortality risk, whereas patients above 80 years of age at diagnosis had no increased mortality risk at all compared to the background population (Table 1).

Table 1. Mortality risk (standardized mortality ratio) in diabetic patients, by gender, age at diagnosis, and actual age. Means and (95 % confidence interval)

| Actual Age (yr) sex	Age at diagnosis (yr) 0-19		20-39		40-59		60-79		80-99		All ages	
0-19	**7.1**	**(2.2-22.1)**									**7.1**	**(2.2-22.1)**
men	3.6	(0.5-26.2)									3.6	(0.5-26.2)
women	12.7	(3.1-52.0)									12.7	(3.1-52.0)
20-39	**5.6**	**(2.6-11.9)**	**5.7**	**(2.3-13.8)**							**5.6**	**(3.2-10.1)**
men	3.4	(1.1-10.8)	3.3	(0.8-13.4)							3.4	(1.4-8.3)
women	10.4	(3.8-28.5)	10.8	(3.4-34.3)							10.6	(4.9-23.0)
40-59	**7.8**	**(5.2-11.7)**	**3.1**	**(2.0-4.7)**	**3.5**	**(2.7-4.6)**					**3.9**	**(3.2-4.8)**
men	7.3	(4.3-12.2)	3.2	(1.9-5.2)	3.3	(2.4-4.5)					3.7	(2.9-4.7)
women	8.3	(4.3-16.2)	2.6	(1.2-5.8)	3.6	(2.2-5.9)					4.0	(2.8-5.7)
60-79	**3.4**	**(1.9-6.1)**	**2.8**	**(2.0-3.8)**	**1.7**	**(1.5-1.9)**	**1.6**	**(1.5-1.8)**			**1.7**	**(1.6-1.8)**
men	3.3	(1.6-6.8)	2.5	(1.7-3.7)	1.4	(1.2-1.6)	1.5	(1.3-1.7)			1.5	(1.4-1.6)
women	3.3	(1.2-9.0)	3.0	(1.8-4.9)	2.0	(1.7-2.4)	1.8	(1.3-2.1)			1.9	(1.7-2.1)
80 +			**0.7**	**(0.2-3.0)**	**1.2**	**(0.9-1.6)**	**0.9**	**(0.8-0.9)**	**1.1**	**(0.9-1.2)**	**0.9**	**(0.9-1.0)**
men			1.0	(0.7-1.5)	1.0	(0.7-1.5)	0.8	(0.7-0.9)	1.0	(0.8-1.1)	0.8	(0.8-0.9)
women			1.3	(0.2-10.8)	1.4	(0.9-2.0)	0.9	(0.8-1.0)	1.1	(1.0-1.3)	1.0	(0.9-1.1)
Mean	**6.0**	**(4.5-8.0)**	**3.1**	**(2.4-3.9)**	**2.1**	**(1.9-2.4)**	**1.2**	**(1.2-1.3)**	**1.1**	**(0.9-1.2)**	**3.8**	**(3.7-4.0)**
men	4.4	(3.0-6.5)	2.4	(1.8-3.1)	1.9	(1.7-2.1)	1.1	(1.0-1.2)	1.0	(0.8-1.1)	2.6	(2.4-2.8)
women	8.7	(5.5-13.6)	4.4	(3.0-6.5)	2.3	(2.0-2.7)	1.4	(1.2-1.5)	1.1	(1.0-1.3)	6.0	(5.6-6.5)

The mortality risk showed a significant gender dependency. Women had a 6 times increased mortality risk, whereas men had a 2.6 times increased mortality risk compared to the background population. The relative mortality risk was highest (12.7 times increased) in young women 0-19 years of age. The gender difference was largest in age group 0-19 years with a 3.5 times higher mortality risk for women.

For patients of the same age, the mortality risk was higher for those with an early onset of diabetes (Figure 7). With the onset of diabetes at 0-19 years of age the patient had 21 years shorter median life-span; with the onset of diabetes at 20-39 years of age the patient had 14 years shorter median life-span, with the onset of diabetes at 40-59 years of age the patient had 7 years shorter median life-span, and with the onset of diabetes at 60-79 years of age the patient had 3 years shorter median life-span. Patients with onset of diabetes after the age of 80 years had a survival indistinguishable from the background population.

Figure 7. Survival in relation to age at diagnosis
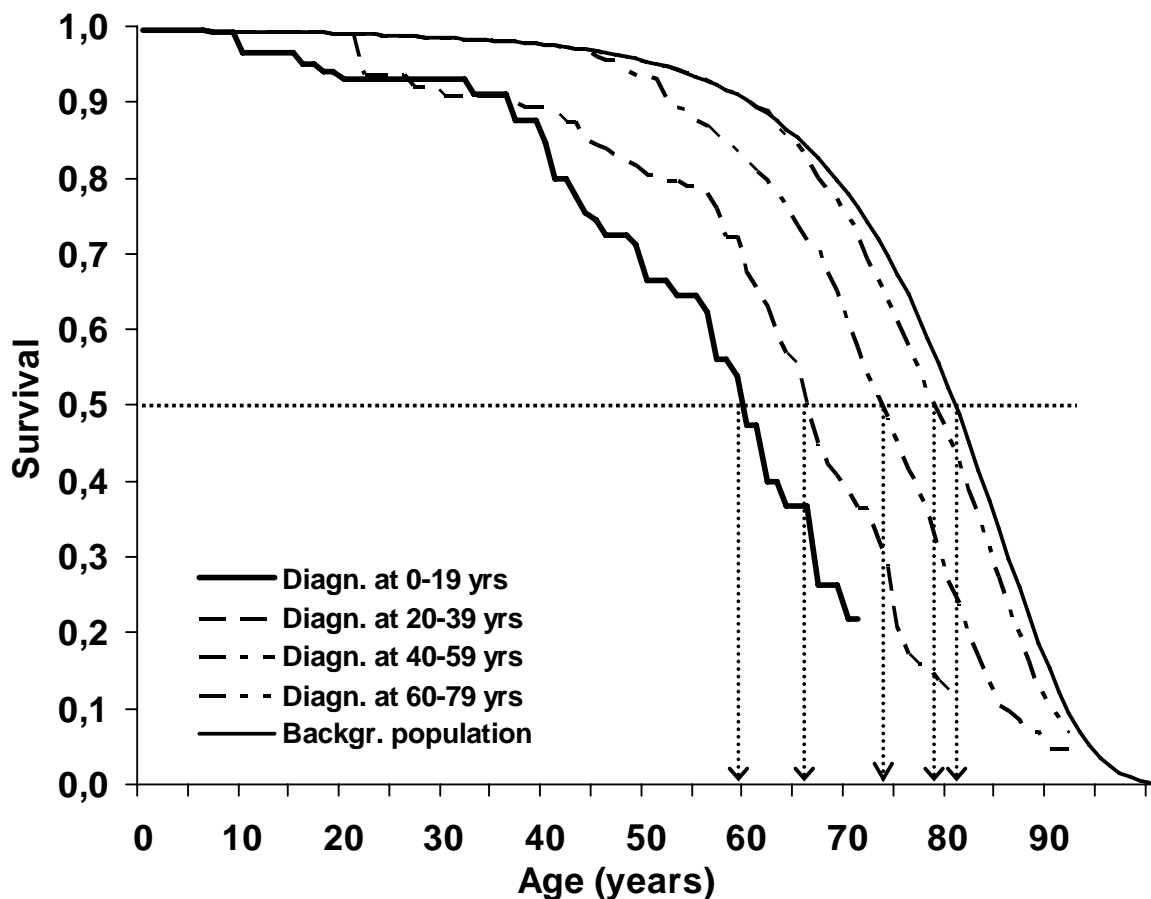
The survival for diabetic patients improved significantly from a median life span of 75.6 years in 1991 to 79.1 years in 2004 (Figure 8). No patient diagnosed with diabetes before the age of 15 was alive after the age of 65 before 1999. Between 1999 and 2005, 25 patients with onset of diabetes before 15 years of age have reached and passed 65 years of age.

In the age group 25-34 years there were 284 patients with type 1 diabetes and 259 patients with type 2 diabetes in the Skaraborg Diabetes Registry. The mean age at diagnosis was 28.7 years and 30.7 years, respectively, and the mean age of those who were alive in 2004 was 50.5 years and 51 years respectively, for type 1 and type 2 diabetes. The mean age at death were 60.4 years for those with type 1 diabetes and 59.8 years for those with type 2 diabetes. Among patients with type 1 diabetes 42 had died and among those with type 2 diabetes 46 had died. The mortality rates were 6.78 and 8.75 deaths/1000 patients/year, respectively, for type 1 and type 2 diabetes.

Figure 8. Lifespan for diabetic patients.
(Doted line = Life-span of back-ground population)
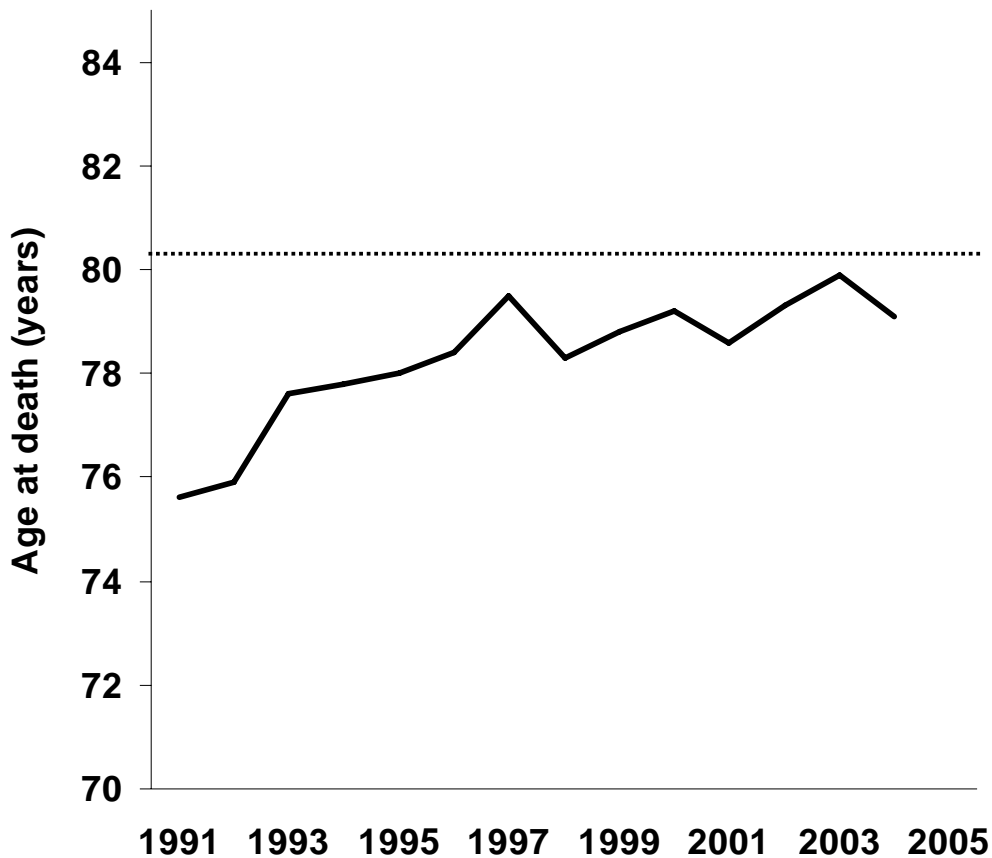
The relation between 10-years survival versus HbA1c, body-mass index, and blood pressure were studied. The 10-years survival was closely correlated to HbA1c in the range 3-13 % (Figure 9).

Figure 9. HbA1c and 10-year survival
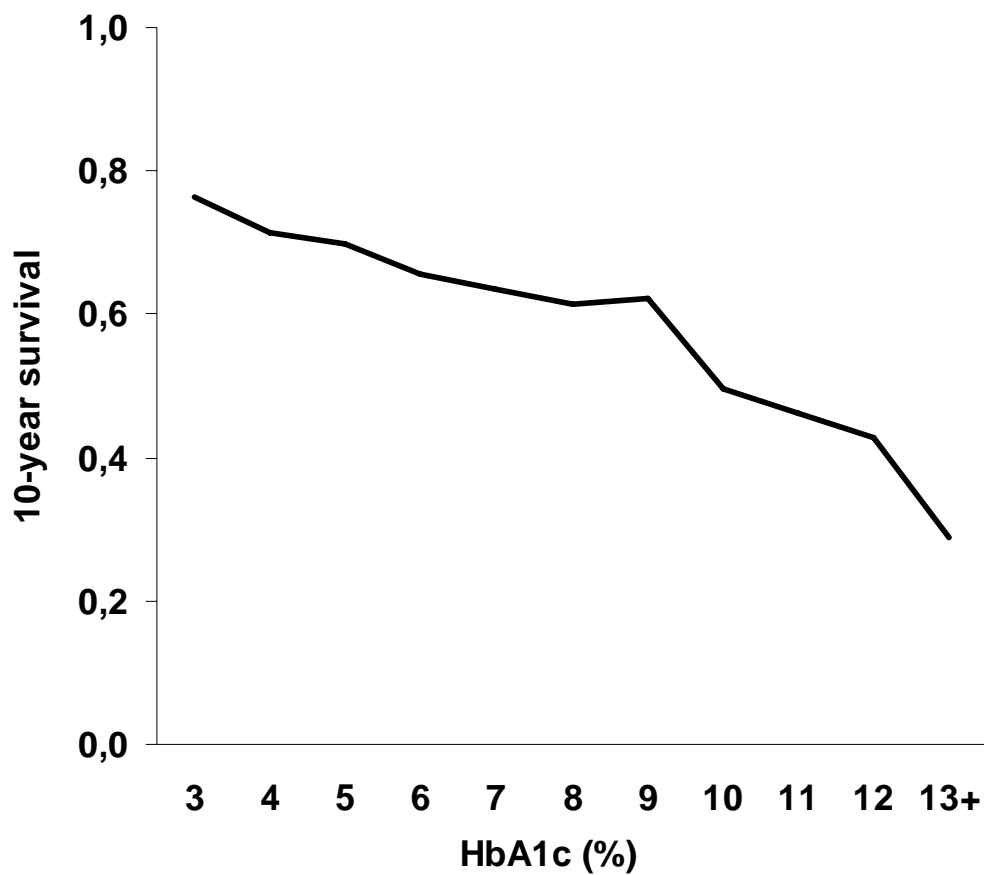
The 10-years survival in diabetic patients was not negatively correlated to body-mass index in the range 19-41 kg/m^2. Actually, the 10-years survival was 50 % for those with body-mass index 19 kg/m^2 and gradually improving to 65 % for those with body-mass index 40 kg/m^2 (Figure 10).

Figure 10. Body-mass index and 10-year survival
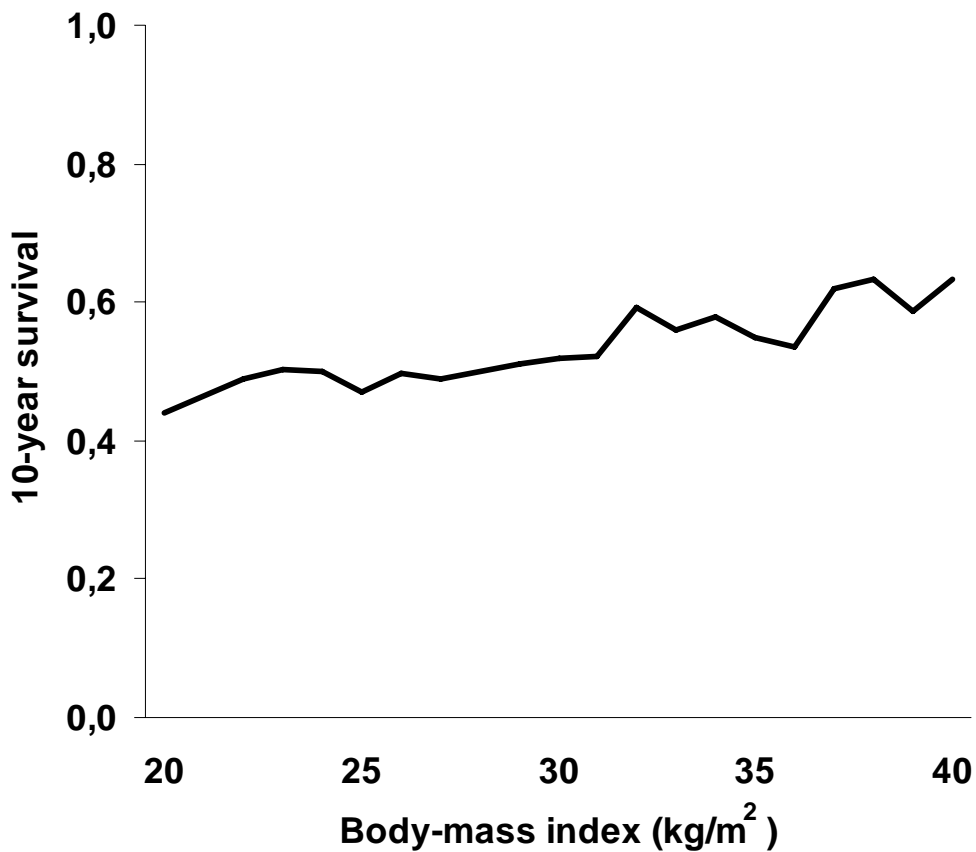
The 10-years survival was not correlated to the diastolic blood pressure in the range 40-130 mmHg (high blood pressure was, however, treated after detection), but had a close inverse correlation to systolic blood pressure (Figure 11). Patients with 100 mmHg systolic blood pressure had 75 % 10-years survival, whereas patients with 230 mmHg systolic pressure had 20 % 10-years survival.

Figure 11. Blood pressure and 10-year survival
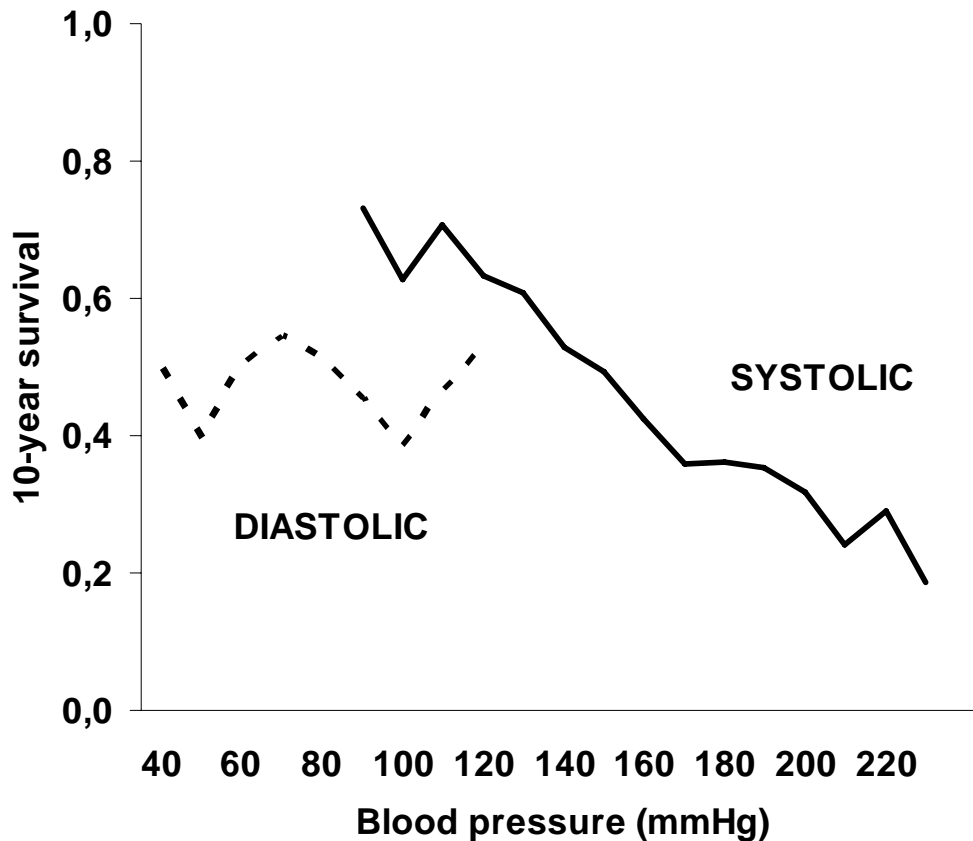
Tests for islet autoimmunity

There were different results in young versus adult patients concerning islet autoantibody findings. Among young patients (0-34 years old), 80 % had islet autoantibodies at diagnosis. ICA (61 %), GADA (63 %), and IA-2A (59 %) were equally common and most of the patients (70 %) had several islet autoantibodies. Among adult patients (35-64 years old), only 11 % had islet autoantibodies at diagnosis and only 5 % had more than one single antibody. The prevalence of ICA (6.2 %) and GADA (9.0 %) were similar, whereas the prevalence of IA-2A was significantly lower (4 %, $P < 0.0041$). Among young patients ICA was more frequently together with IA-2A than with GADA, whereas in adult patients, ICA together with GADA was the only combination of two antibodies found.

At follow-up, the median concentration of IA-2A had decreased among both young and adult IA-2A-positive patients. A similar decrease was found for ICA (significant only in young patients), whereas the median concentration of GADA remained unchanged in both young and adult GADA-positive patients.

In young antibody-positive patients, 38 % had lost one or more antibody at follow-up, and 14 % had become antibody negative. During the same time 13 % of the young antibody-negative patients had developed antibodies and 33 % had converted to antibody positive. Among adult antibody-positive patients 37 % had lost an antibody at follow-up and 23 % had become antibody negative. On the other hand, at follow-up 3 % of the adult antibody-negative patients had developed an antibody and converted to antibody positive. Multiple antibodies did not, however, develop in patients without antibodies at diagnosis, and patients with multiple antibodies did not become antibody negative.

Among young patients with immeasurable C-peptide at follow-up, 75 % were ICA-positive, 69 % were GADA-positive, 69 % were IA-2A-positive, and 7 % lacked islet autoantibodies. Among old patients with immeasurable C-peptide at follow-up, 75 % were ICA-positive, 75 % were GADA-positive, 42 % were IA-2A-positive, and 25 % lacked islet autoantibodies. Among young patients with persistent C-peptide > 0.1 nM at follow-up, 35 % were ICA-positive, 53 % were GADA-positive, 41 % were IA-2A-positive, and 41 % lacked islet autoantibodies. Among old patients with persistent C-peptide > 0.1 nM at follow-up, 4 % were ICA-positive, 6 % were GADA-positive, 3 % were IA-2A-positive, and 92 % lacked islet autoantibodies.

Tests for beta-cell function

All together 3115 C-peptide samples from 2243 patients (22 % of the entire diabetic population in Skaraborg 1995-1998) were assessed. The random C-peptide closely correlated both with fasting C-peptide (rs = 0.78, $P < 0.01$), and glucagon stimulated C-peptide (rs = 0.77, $P < 0.02$). There were also clear associations between the C-peptide level and the clinical type of diabetes with significant differences between type 1 versus type 2 diabetes for random C-peptide (median 0.10 versus 1.30 nM), for fasting C-peptide (median 0.15 versus 0.85 nM), and for glucagon stimulated C-peptide (median 0.30 versus 1.25 nM), respectively.

The ROC-curves visualized that random C-peptide in the study population was superior to fasting C-peptide and glucagon stimulated C-peptide in discriminating type 1 from type 2 diabetes with an area under the ROC-curve significantly higher (AUC = 0.98) for random C-peptide than for fasting C-peptide (AUC = 0.91) and glucagon stimulated C-peptide (AUC = 0.92) (Figure 12).

Figure 12. ROC-curves comparing random, fasting, and glucagone-stimulated C-peptide.
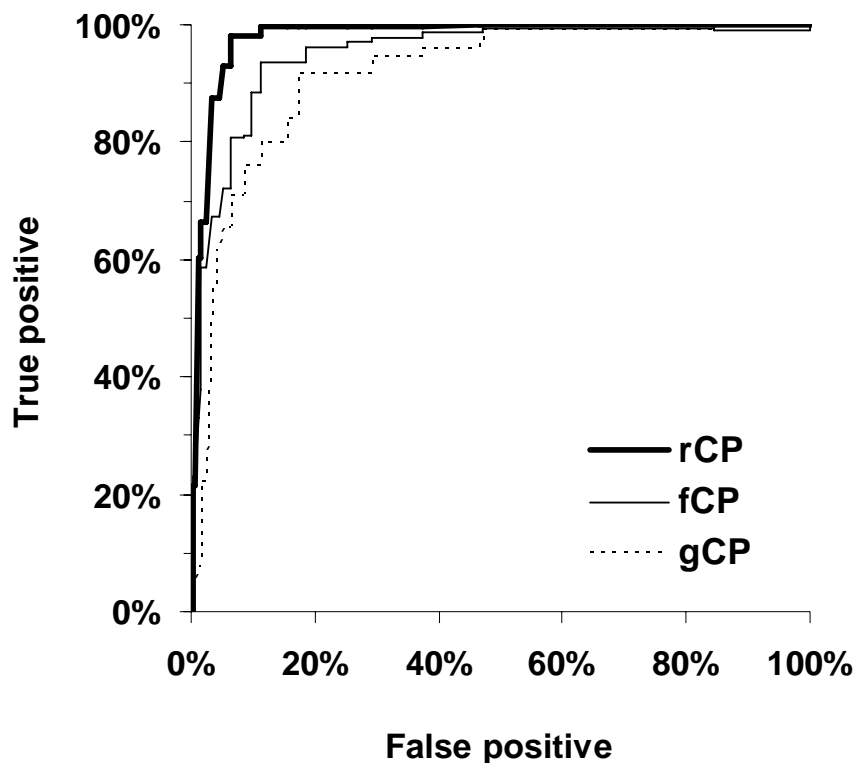
There was significantly less overlap in the values between type 1 versus type 2 diabetic patients for random C-peptide than for both fasting C-peptide (6 % versus 12 % [$P = 0.0002$]) and glucagon stimulated C-peptide (6 % versus 20 % [$P < 0.0001$]) (Figure 13).

Figure 13. C-peptide. Comparison between different protocols
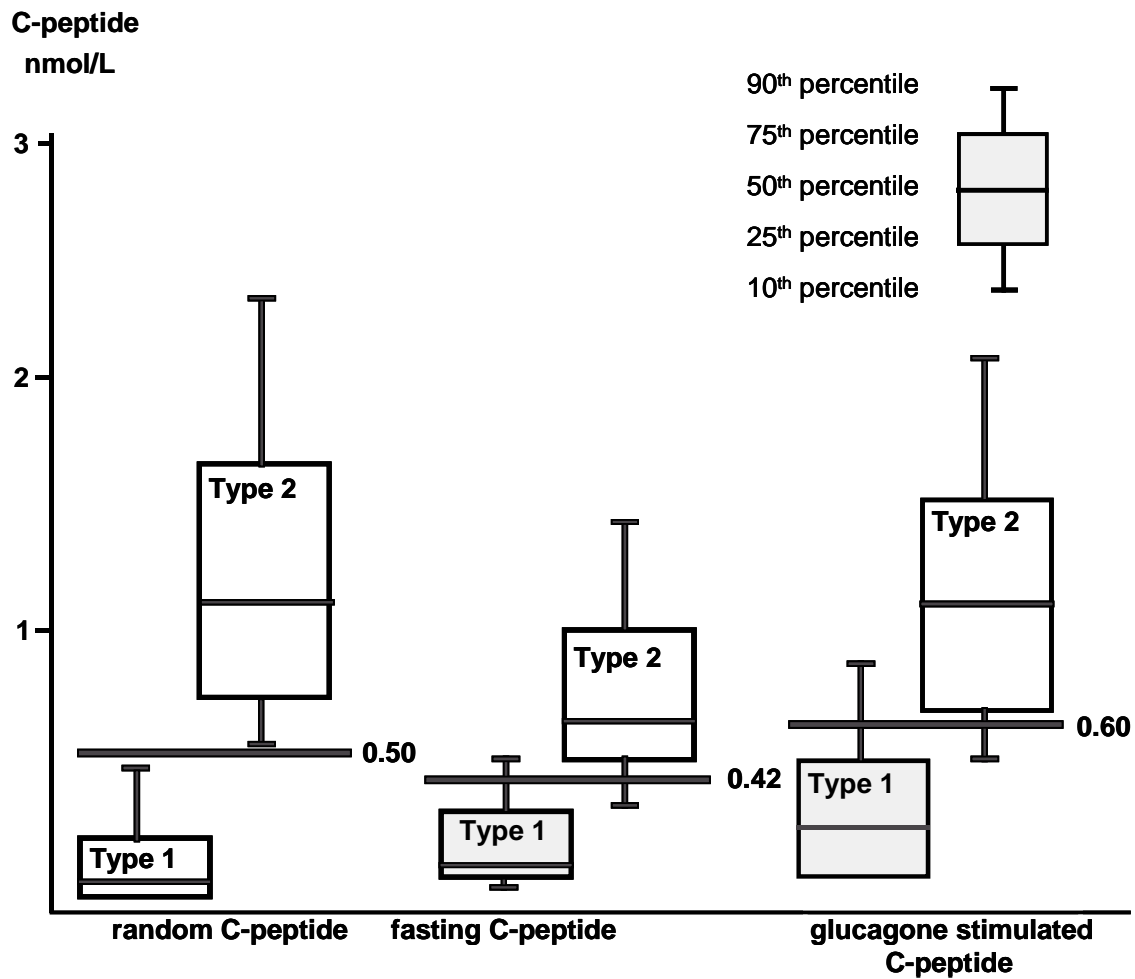
Among young antibody-positive patients, fasting C-peptide was as low at diagnosis as was found three years later, in agreement with a diagnosis of type 1 diabetes (Figure 14). Indeed, C-peptide was undetectable in plasma at diagnosis in 57 % of the young antibody-positive patients but only in 11 % of the young antibody-negative patient ($P = 0.0233$). At follow-up, fasting C-peptide was undetectable in plasma in all but one young antibody-positive patient who had fasting C-peptide 0.13 nM.

Nine young patients had no islet autoantibodies and five of them had fasting C-peptide $\geq$ 0.42 nM, in agreement with a type 2 diabetes diagnosis, and despite the young age. All still had high plasma concentrations of fasting C-peptide (median 1.32 nM, range 0.52-2.81) at follow-up but two had developed islet autoantibodies (ICA-positive and GADA-positive). Among the four patients with fasting C-peptide < 0.42 nM, three still were without islet autoantibodies and had fasting C-peptide < 0.42 nM at follow-up. Three of these patients had been started on insulin, but one patient with fasting C-peptide 0.17 nM was managed with oral glucose-lowering drugs. She had increased her fasting C-peptide to 0.55 nM despite her conversion to GADA-positive at follow-up after 3 years.

Figure 14. C-peptide concentrations at diagnosis (Y^0) and at follow-up after three years (Y^3) in patients with 0-3 islet autoantibodies (Ab^0, Ab^+, Ab^{++}, and Ab^{+++}).

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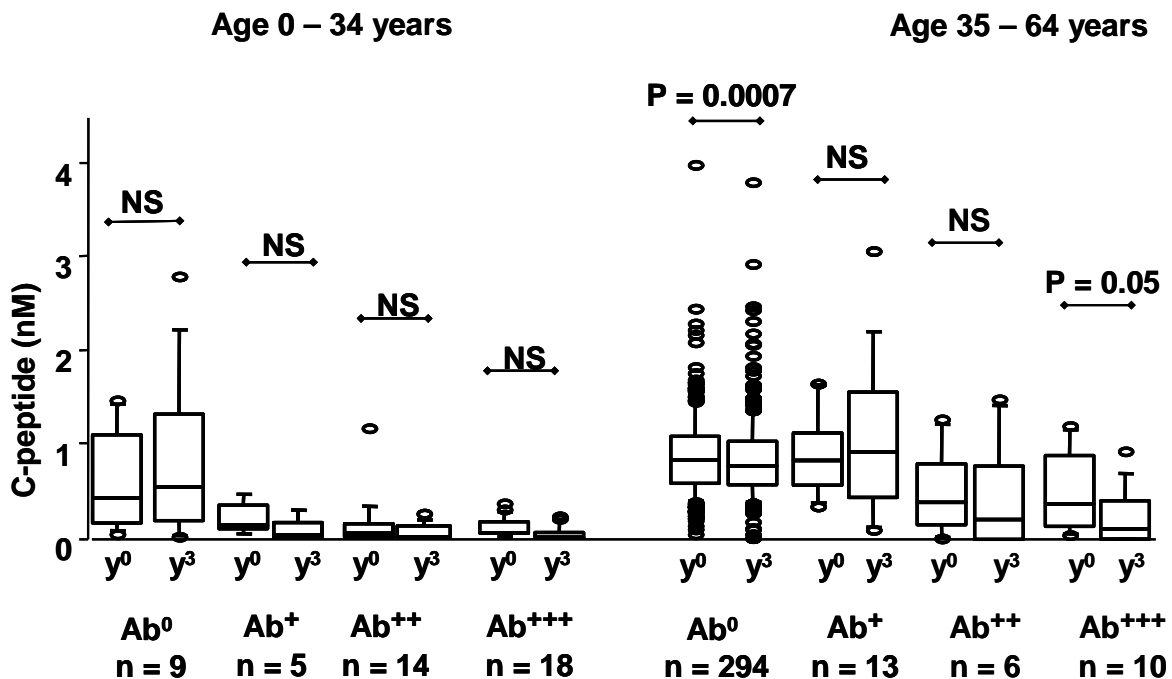
Most of the adult patients (89 %) had no islet autoantibodies and had high plasma concentrations of fasting C-peptide (80 %), in agreement with a diagnosis of type 2 diabetes. Thirty-five (11 %) of the adult patients had islet autoantibodies and 17 (5 %) of them had low C-peptide, in agreement with a diagnosis of type 1 diabetes. Among antibody-positive patients 35-64 years, 18 (51 %) had C-peptide > 0.42 nM both at diagnosis and at follow-up.

Among adult patients, those with 2-3 antibodies at diagnosis had significantly lower fasting C-peptide at diagnosis compared to those with 0-1 antibody (median 0.35 nM, IQR 0.63 nM versus 0.85 nM, IQR 0.49 nM; $P = 0.0004$). At follow-up, adult patients with 3 antibodies showed a further decrease in fasting C-peptide ($P = 0.05$). Thirteen out of 18 adult antibody-positive patients with high C-peptide had only one islet autoantibody and 12 patients were GADA-positive.

None of the 288 patients 35-64 years of age without islet autoantibodies had immeasurable C-peptide at diagnosis but 28 (10 %) had fasting C-peptide < 0.42 nM. Fourteen (50 %) had normal or even high fasting C-peptide at follow-up, in agreement with a type 2 diabetes diagnosis with transient beta-cell insufficiency, but 50 % still had low fasting C-peptide at follow-up and one of them had developed GADA-positive. Seven of the patients with fasting C-peptide < 0.42 nM both at diagnosis and at follow-up could be managed without insulin with acceptable HbA1c during the three first years.

Clinical presentation

Antibody-positive patients below 35 years of age had normal body-mass index, insulin treatment, and were considered as having type 1 diabetes by the reporting physician. Ketoacidosis was not a common finding, not even in young patients with type 1 diabetes. Only 16 % presented with this commonly mentioned finding. Thirst, polyuria, fatigue, and weight loss, were common symptoms present in 100 %, 100 %, 86 %, and 70 %, respectively. Antibody-positive patients above 35 years of age had different clinical appearance. Only 46 % were considered as having type 1 and only 43 % were treated with insulin, whereas 23 % were treated with glucose-lowering drugs and 32 % had diet treatment. Only 6 % presented with ketoacidosis. More than half of these patients (51 %) were obese with body-mass index over 30 kg/m^2. Thirst, polyuria, fatigue, and weight loss were present in 71 %, 65 %, 65 %, 60 %, and 40 %, respectively.

There were only nine antibody-negative patients below 35 years of age. Seven of them (78 %) were men and had a mean age of 26.9 years. Two (22 %) presented with ketoacidosis and none were asymptomatic at diagnosis. They had a mean body-mass index of 28.8 kg/m^2 and 6 (67 %) were classified

as having type 2 diabetes. Four (44 %) were started on insulin, but two could later be changed to diet treatment. Antibody-negative patients above 35 years of age had clinical appearances different from the other patients. Only 2 % were considered having type 1 diabetes and only 11 % were started on insulin treatment. Four patients (however only 1.3 %) presented with ketoacidosis. They had a mean body-mass index of 31.2 kg/m^2 and 52 % had body-mass index over 30 kg/m^2.

The body-mass index at onset of diabetes increased with about 0.07 kg/m^2 per year from 28 kg/m^2 in 1991 to 29 kg/m^2 in 2004 for the entire diabetic population. However, the body-mass index increased in a similar way but at a lower level in the background population in Sweden from 24.7 kg/m^2 to 25.0 kg/m^2 between 1991 and 1996 and in Västra Götaland from 24.9 kg/m^2 to 25.6 kg/m^2 between 1991-2000, according to "Undersökning av levnadsförhållanden (ULF)" at the Swedish Central Bureau of Statistics (SCB) (Figure 14).

Figure 13. Body-mass index at onset of diabetes
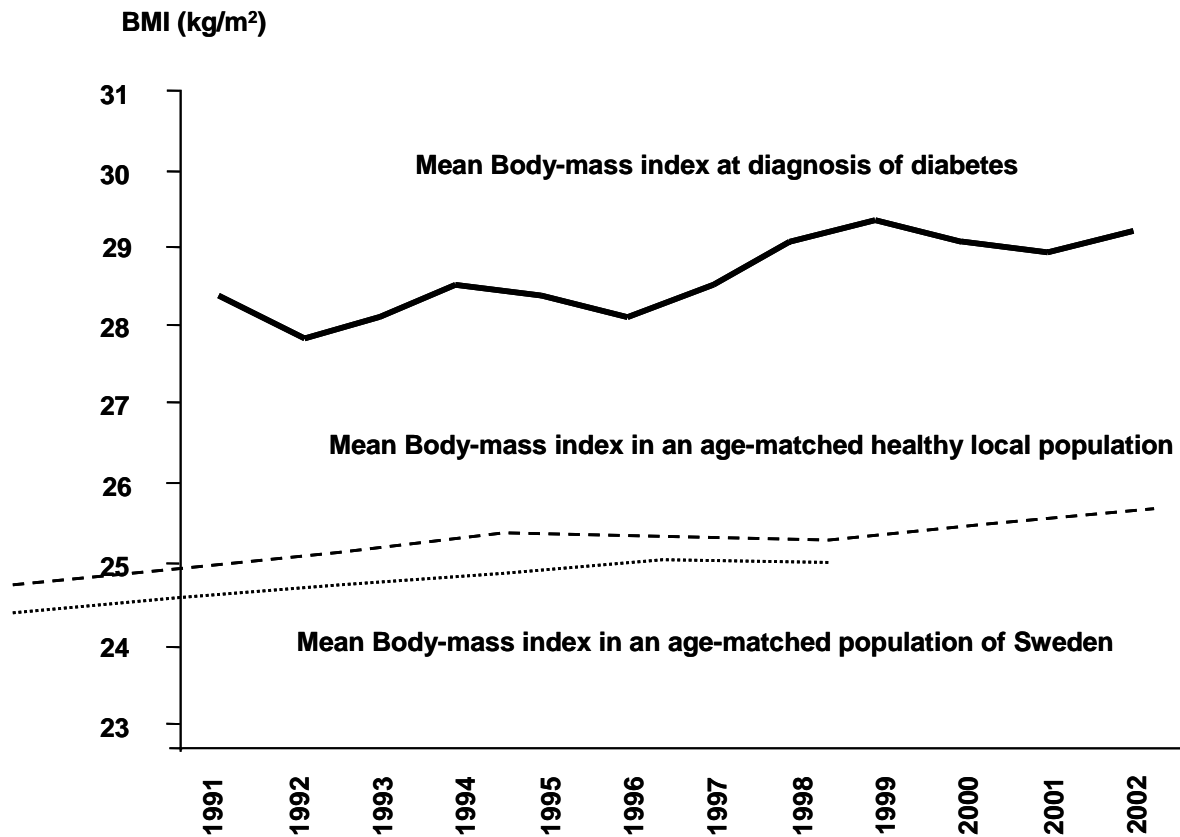
Although the incidence of type 1 diabetes did not increase with time, the ratio of newly diagnosed patients with body-mass index 25-27 kg/m^2 increased slightly (4.0 %) whereas the ratio of patients with higher and lower body-mass index decreased. The incidence of type 2 diabetes was also unchanged with time. Among patients with type 2 diabetes the ratio of patients with body-mass index below 25 kg/m^2 decreased (10 %) and the ratio of patients with body mass index above 25 kg/m^2 increased.

Discussion

Prevalence

The use of capture-recapture methods to ascertain the prevalence of diabetes has limitations. The underlying assumptions that the population is stable, that the registries (often designed for other purposes) are independent of each other, and that the individuals have equal catchability are often not fulfilled. Some of the problems with biased registries can be compensated for by utilizing multiple sources, and three different sources has been suggested as the optimal number to reduce bias by dependent lists and unequal catchability [Bruno *et al.* 1994]. Accordingly, the capture rate was ascertained by two other care-registries and by an unassociated prescription registry. The Skaraborg Diabetes Registry can therefore be considered as a valid tool to follow the epidemiology of diabetes.

The Skaraborg Diabetes Registry achieved a high capture rate of 88.4 % for all types of diabetes in all ages. The completeness was similar to the Swedish Childhood Diabetes Registry (99 % of all 0-14 year olds with insulin-dependent diabetes) [Dahlquist *et al.* 1985], and the Diabetes Incidence Study in Sweden registry (79 % of all 15–34 year olds with any type of diabetes) [Blohmé *et al.* 1992] [Littorin *et al.* 1996].

The prevalence of diabetes in Skaraborg 1995 was 3.20 %. The prevalence was in accordance with previous results from Sweden and Europe at that time. Swedish reports from before 1990 found lower prevalence; 2.05 % of type 2 diabetes [Grönberg *et al.* 1967], 2.7 % total diabetes-prevalence [Hallqvist *et al.* 1981], 2.01 % of type 2 diabetes [Sartor *et al.* 1984], and 2.02 % total diabetes-prevalence [Forrest 1990]. More recent Swedish reports have found 3.3 % total diabetes-prevalence [Falkenberg 1987], 5.7 % in women and 4.7 % men 25-64 years of age [Eliasson *et al.* 2003], and 4.3 % total diabetes-prevalence when screening with fasting blood-glucose was applied [Andersson *et al.* 1991]. The prevalence was also in agreement with reports from Finland (2.54 %) [Eriksson *et al.* 1992], Iceland (2.9 % for men and 2.1 % for women 30-79 years of age) [Vilbergsson *et al.* 1997], Italy (2.2-3.3 %) [Bruno *et al.* 1992] [Di Cianni *et al.* 1994] [Bruno *et al.* 1994] [Muggeo *et al.* 1995] [Garancini *et al.* 1995]. Lower prevalence of diabetes (2.2-3.1 %) has been reported from US (1.6 %) [Palumbo *et al.* 1976] and the Netherlands in 2003 [Ubink-Veltmaat *et al.* 2003]. Higher prevalence has been reported among ethnic minorities in US and in the Pacific region [King *et al.* 1993], and among adults above 25 years of age in Australia (7.4 %) when screening with an oral glucose load was applied [Dunstan *et al.* 2002].

It must be emphasized that the observed prevalence (3.20 %) in Skaraborg was found without any general screening procedure, because the

basic purpose of the registry was to estimate the burden of diabetes on the care system. With general screening of the population 20-50 % of undiagnosed diabetic patients have been found [King *et al.* 1993] [Eliasson *et al.* 2003]. However, in Laxå, adjacent to Skaraborg, the undiagnosed patients found by a period of screening with fasting blood glucose, were only about 10 %. Compared with Laxå, the discrepancy in prevalence of diabetes (Skaraborg 3.20 % versus Laxå 4.3 %) was mainly found in diet treated patients above 60 years of age [Andersson 1991, and personal communication]. In agreement with the capture-recapture result, the unregistered patients were old and without pharmacological treatment. Patients not known by general practitioners, specialized diabetes nurses or by hospital departments, and who do not take any glucose-lowering drugs, pose a negligible burden on the care system.

The epidemiologic results derived from hospital and clinic populations are error-prone due to referral bias [Melton *et al.* 1984]. It is often difficult to identify the background population from which the patients are recruited. Most reliable are prospective studies of defined cohorts recruited from general population surveys, and the prevalence figures can be very confusing if not the entire age panorama of the population is included (Figure 1). Studies including all ages are few [Garcia *et al.* 1974] [Palumbo *et al.* 1976] [Heyden *et al.* 1980].

In Skaraborg, most patients were diagnosed by fasting blood-glucose. Different methods for screening, diagnosis, and classification confound comparisons of prevalence figures with other studies. OGTT, random glucose and fasting glucose from urine, blood, and plasma has been used in different frequencies to screen for, and to diagnose diabetes. The tests catch somewhat different patients [Alberti 1993], and the cut-offs for the assays have varied [McCance *et al.* 1997]. During the studied period the cut-off for diagnosis of diabetes has been changed from blood glucose 6.7 mM [National Diabetes Data Group (NDDG) 1979] [WHO technical report 646, 1980] [WHO technical report 727, 1985] to 6.1 mM [The Expert Committee on the diagnosis and classification of diabetes mellitus, 1997] [Alberti *et al.* 1998]. A consequence of the lowered diagnostic criteria is an increased prevalence of diabetes. Another result might be an earlier detection of patients with fewer complications and thereby better prognosis. Hence, a probable consequence of the downwards sliding of the diagnostic criteria would be an epidemic increase of prevalence together with improved prognosis for diabetic patients, similar to what we actually have been seen the last decade.

Apart from all these confounding factors, the prevalence of diabetes depends on the age specific incidence, the number of individuals at risk in the background population, and the age-specific mortality among the diabetic patients [Alberti 1993]. A diabetes incidence of 100/100000/year and a 25 years life expectancy after diagnosis, results in a prevalence of 2.5 %. The same incidence, but 5 years life expectancy after diagnosis, results in a prevalence

of only 0.5 %, and a slightly reduced mortality, due to improvement in diabetes care or changed diagnostic criteria, results in a steadily increasing prevalence for several years or even decades until the patients will be so numerous, that their mortality equals the incidence [Green *et al.* 1996] [Green *et al.* 2005]. Hence, comparison of prevalence data from different studies with different design is difficult to interpret.

There was a significant male preponderance of diabetes in the Skaraborg Diabetes Registry. This was seen in patients with both types of diabetes and in all ages. Among patients with type 2 diabetes the male preponderance was rather stable around 11 % during the studied years, whereas among patients with type 1 diabetes there was an increasing male preponderance from 4 % to 11 % between 1991 and 2005. This could indicate that the observed male preponderance is a rather new phenomenon that has not yet resulted in a stable prevalence. Another possible explanation is an improving mortality among men compared to women with type 1 diabetes.

A male preponderance in prevalence has previously been reported in children with type 1 diabetes in Sweden (1.65/1) [Dahlquist *et al.* 1985], in most other countries [Kyvik *et al.* 2004], and also in adults with type 2 diabetes [Sartor *et al.* 1984] [Welborn *et al.* 1989]. In some historical reports from other regions of Sweden, on the other hand, a female preponderance of diabetes was found (1.2/1) [Hallqvist *et al.* 1981]. In Italy a female preponderance was observed in all ages except above 70 year olds (1.2/1) [Bruno *et al.* 1992] [Di Cianni *et al.* 1994]. Globally, the gender imbalance varies from a marked male preponderance, most prominent in Caucasians and Hispanics with high socio-economic status, to a marked female preponderance, most prominent in rural areas of developing countries and in the Pacific region [King *et al.* 1993].

The Skaraborg Diabetes Registry revealed an increase in prevalence of diabetes with up to 6 % per year, corresponding to an increase of diabetes in the population with 0.2 % per year. After the first 5 years of registration, the increase waned off; suggesting that the initially steep increase was caused by an increasing capture rate. The 4 % increase in prevalence per year, seen the last ten years, is more in accordance with other reports. The Swedish Childhood Diabetes Registry comprising patients 0-14 year old [Dahlquist *et al.* 1982] and the Diabetes Incidence Study in Sweden comprising patients 15-34 year old [Östman *et al.* 1986] [Nyström *et al.* 1990] [Andersson *et al.* 1991] [Green *et al.* 1996] [Ramachandran *et al.* 1999] support an increasing prevalence, and the worldwide prevalence in 20-79 year olds has been estimated to 5.1 % in year 2003 and is expected to reach 6.3 % by year 2025 [International Diabetes Federation, 2003] [Wild *et al.* 2004]. A high prevalence of diabetes, however, does not necessarily imply a high incidence and an increasing prevalence does not imply an increasing incidence.

Incidence

The incidence of diabetes in Skaraborg (261/100 000/year) was within the interval reported from other parts of Sweden. From Malmö lower incidence of 53/100 000/year [Landin-Olsson *et al.* 1990] and of 106/100 000/year in 40-75 year olds was reported [Wroblewski *et al.* 1998], and from Laxå a higher incidence of 346/100 000/year was reported [Andersson *et al.* 1991]. The Diabetes Incidence Study in Sweden found an incidence of 12.7/100 000/year for women and 20.5/100 000/year for men in 15-34 year olds [Blohmé *et al.* 1992]. This was considerably lower than in Skaraborg (47.2 and 49.2/100 000/year, respectively, in women and men of the corresponding age group). A somewhat lower incidence was found in women and men 30-79 years old with type 2 diabetes in Iceland (266 and 377/100 000/year, respectively, compared to 405/100 000/year in the same age group and type of diabetes in Skaraborg) [Vilbergsson *et al.* 1997]. A lower incidence was also found in 30-49 year olds in Italia (58/100 000/year, compared to 131/100 000/year in the corresponding age group in Skaraborg) [Bruno *et al.* 2005], and in 17-94 year olds in US (153/100 000/year, compared to 370/100 000/year in the corresponding age group in Skaraborg) [Maty *et al.* 2005]. A similar incidence was found in The Netherlands (222-231/100 000/year) [Ubink-Veltmaat *et al.* 2003]. A higher incidence was reported from US 1970-1990, where an increase in incidence was seen from 2 % to 3.7 % per 8 year corresponding to about 250/100 000/year in 1970 and 462/100 000/year in 1990.

Accurate estimation of incidence is dependent of a constant and intensive search for diabetic patients, with control of capture rate and diagnostic delay. A change in the search intensity will result in an immediate change in incidence, because the majority of patients with type 2 diabetes (making up 85 % of total diabetes prevalence) are asymptomatic for long periods after onset, and does not hurry to the nearest health centre at onset. Reports from entire populations of all ages have shown more than a 5 fold difference in incidence of diabetes between regions in Sweden [Landin-Olsson *et al.* 1990] [Andersson *et al.* 1991]. Even greater differences have been found within rather close geographic areas. In Spanish adults above 14 years of age, an incidence of 379/100 000/year (6.5 times higher than in Italy) was reported [Mata-Cases *et al.* 2006].

Some report hardly any new cases of type 1 diabetes after 55 year of age [Laakso *et al.* 1985], whereas other report almost the same incidence of type 1 diabetes in 50-70 year olds as in children [Scott *et al.* 1991] [Bruno *et al.* 2005]. Although this could suggest different risk related to geography and ethnicity, different selections of patients, different criteria for diagnosis and classification, and uncertain diagnostic delay are more probable causes. These confounding factors together with a variety of age groups and a wide range of

capture rates, make comparison of diabetes incidence between previous studies almost pointless [Zimmet 1982] [Bruno *et al.* 2005] [Melton 1983].

There was an overall male excess in diabetes incidence in Skaraborg, both for type 1 and for type 2 diabetes and in all age groups except 5-9 and 20-34 year olds. The strong male preponderance of type 1 diabetes could explain the increasing male preponderance in type 1 diabetes prevalence seen in Skaraborg between 1991 and 2005. A male preponderance was reported from Sweden (2.16/1 in 40-75 year olds [Wroblewski *et al.* 1998], 1.8/1 in type 1 and 1.3/1 in type 2 diabetes for 15-34 year olds [Blohmé *et al.* 1992]) and from other countries [Palumbo *et al.* 1976] [Ubink-Veltmaat *et al.* 2003] [Bruno *et al.* 2005]. In most studied populations the male predominance seems to affect both type 1 and type 2 diabetes in all age groups [Vandewalle *et al.* 1997], but there are a few reports of female preponderance [Tseng *et al.* 2006], and without gender difference [Mata-Cases *et al.* 2006] [Landin-Olsson *et al.* 1990]. In one of the longest and most complete registries in Sweden, there was no significant gender difference in incidence, for neither type 1 or type 2 diabetes [Andersson *et al.* 1991]. A male preponderance in type 2 diabetes is easily accepted in the light of the male association with abdominal obesity, hypertension, and the metabolic syndrome. A male preponderance in type 1 diabetes is more unanticipated in the light that most other autoimmune diseases have a female preponderance. Obviously, some other pathophysiologic factor, active in both type 1 and type 2 diabetes, such as testosterone, growth hormone, or abdominal obesity, counterbalance the female autoimmune disposition.

No significant change in diabetes incidence over time was detected in Skaraborg. This was in agreement with other studies from Sweden [Andersson *et al.* 1991] [Pundziūtè-Lyckå *et al.* 2002], Scandinavia [Ustvedt *et al.* 1977] [Vilbergsson *et al.* 1997], Europe [Mata-Cases *et al.* 2006], and US [Hamman *et al.* 1990] [Kostraba *et al.* 1992] [Palumbo *et al.* 1976]. Historical data from US, however, indicate a 5 times increase in total incidence of diabetes between 1936 and 1973 [Zimmet 1982]. One report from Taiwan suggests a rapidly increasing incidence (up to 2.8 fold increase in age group below 35 years) between 1992 and 1996 [Tseng *et al.* 2006]. Reports from Europe have suggested an increasing incidence of type 1 diabetes [Reunanen *et al.* 1982] [Dahlquist *et al.* 1985] [Bingley *et al.* 1989] [Green *et al.* 1996] [Onkamo *et al.* 1999]. This controversy between the present study from Skaraborg and previous studies could arise from an increase in incidence that has happened between 1940 and 1970 in the western hemisphere and that now happens 20-50 years later in Asia and Africa. A mathematical compilation of data from industrialized and developing countries concludes that there has to be an ongoing increase in incidence to be able to explain the increasing prevalence of diabetes [Colagiuri *et al.* 2005]. In this compilation a larger increase in prevalence than in Skaraborg

has been used, which implicates a need for an increasing incidence to satisfy the equation.

In type 1 diabetes the mean age at diagnosis was 22.3 and in type 2 diabetes the mean age at diagnosis was 64.6 years. There were no signs of decreasing age at onset of diabetes between 1991 and 2005 in Skaraborg. This was in contrast to Swedish studies of type 1 diabetes in children [Pundziūtè-Lyckå et al. 2002]. A lowering of the mean age at onset of diabetes has been suggested as a reason for the increasing prevalence of diabetes [Nyström et al. 1990]. The reason for the lack of change in age at diagnosis among children in Skaraborg could be the small sample size. However, no tendency for a change in age at diagnosis was detected in adults or type 2 diabetic patients in Skaraborg between 1991 and 2005.

The incidence of diabetes in Skaraborg showed a seasonal variation, with an increase in the winter and a decrease in the summer. Previous studies have shown a seasonal variability in children and in patients up to 29 years of age [Christau et al. 1977] [Dahlquist et al. 1982] [Vandrager et al. 1984] [Ludvigsson et al. 1989] [Kostraba et al. 1992], but seasonality in adults and in type 2 diabetes has hardly been investigated. In UK no seasonality was found in a hospitality material of 833 type 2 diabetic patients diagnosed 1987-90 [Muzulu et al. 1995] but in Hungary a seasonality similar to that in Skaraborg was seen among 26 695 patients started on oral glucose-lowering medication in 1999-2004   [Doro et al. 2006]. Indeed, the Skaraborg Diabetes Registry showed that the seasonal variability was present also in type 2 diabetes and most pronounced in 30-49 year olds.

The seasonal variability in incidence for type 1 diabetes has been suggested to reflect the seasonal infection panorama or the influence by the school year on distributing infections. The observation that middle-aged people in Skaraborg had a more pronounced seasonal variation may suggest an infectious stimulus also in the initiation of type 2 diabetes. Seasonal variation in insulin sensitivity and in diet and physical activity (more physical activity, more ingestion of vegetables, and less fat consumption during summer months) are other, perhaps more plausible explanations to the decrease in incidence of type 2 diabetes during the summer months. If the seasonal fluctuation in observed incidence was a result of less available consultations and screening for diabetes during the summer holidays, then there would be an accumulated peak in incidence closely after the summer months. This was not observed, but the peak of incidence appeared in late winter and early spring.

An increasing body-mass index in the population as underlying cause for an increasing incidence of diabetes could not be confirmed. In Skaraborg, the body-mass index increased over the years without any increase in diabetes incidence. The body-mass index increased similarly in the patients at onset of

diabetes (0.07 kg/m^2/year), in the background population in Skaraborg (0.06 kg/m^2/year), and in Sweden (0.077 kg/m^2/year). The major increase in body-mass index at diagnosis was found among patients with type 2 diabetes, whereas the incident cases of type 1 diabetes had unchanged body-mass index over the years. Hence, our results suggest a lack of importance of body-mass index for the incidence of diabetes. Actually the people in Skaraborg nowadays reach a higher body-mass index before the onset of diabetes than was needed 14 years ago. The lack of correlation between increasing body-mass index and diabetes prevalence is noted in reports from Sweden [Eliasson *et al.* 2003] where increasing body-mass index did not increase the prevalence of diabetes, and from India [Ramachandran *et al.* 1999], where diabetes in adults increased despite an unchanged body-mass index in the population. Already in 1990th the roll of obesity as cause of diabetes was questioned. The role of obesity in the pathogenesis of Type 2 diabetes have been considered as "innocent bystander", "partner in crime", or "culprit" from studies in diverse populations around the world [Zimmet 1992]. A major limitation in all these studies, however, is the use of body-mass index as an index of obesity and excess of fat. "Normal" body-mass index varies with ethnicity and does not recognize large muscle mass or less harmful peripheral fat deposits.

Despite the absence of increase in incidence and the absence of decreasing age at diagnosis, the prevalence of diabetes increased with 4 % per year, suggesting that the life span for people with diabetes increases. This was in agreement with reports from Denmark which showed that the major driving force behind the increasing prevalence of diabetes is not increasing incidence, but mortality slightly lower than the incidence with onset before the period of observation [Green *et al.* 2005].

Mortality

The mortality rate in diabetic patients in Skaraborg was 3.8 times higher than the background population and varied with age at diagnosis and with the duration of diabetes. The mortality was in accordance with other studies [Palumbo *et al.* 1976] [Królewski *et al.* 1977] [Panzram *et al.* 1981] [Jarrett *et al.* 1982] [Green *et al.* 1985] [Panzram *et al.* 1987] [Sasaki *et al.* 1989] [Head *et al.* 1990] [Schneider *et al.* 1993] [Muggeo *et al.* 1995] [Swerdlow *et al.* 1996] [Morgan *et al.* 2000] [Morrish 2001] [Ubink-Veltmaat *et al.* 2003] which found the mortality risk increased 1.4 - 6 times in different age groups.

The standardized mortality ratio in Skaraborg indicated that diabetes is a particularly serious disease when it is diagnosed in early age. Most diabetic patients, however, are diagnosed after 60 years of age and the prognosis is much better among these patients. Patients diagnosed before 20 years of age had a six-fold increased mortality risk. In contrast, no increased mortality risk at all was noticed among diabetic patients diagnosed after 80 years of age. The survival figures in the Skaraborg Diabetes Registry fit an algorithm predicting that an early onset of diabetes cause a loss of 25 year. If the onset of diabetes could be postponed 1 year, the life-span for the patients would be in average 4 months longer. Another way to express the same thing is to state that a diagnosis of diabetes takes away 30 % of the remaining expected lifetime. The high incidence of diabetes in adults, together with few symptoms and no increased mortality, indicate that the diagnostic criteria for diabetes in adults maybe should be different from diagnostic criteria in younger persons.

There was a significant gender difference in mortality risk. Men increased their mortality risk 2.6 times, whereas women increased their mortality risk 6.0 times when diagnosed with diabetes. The difference in mortality risk between women and men was highest in age group 0-19 years and disappeared in the oldest age groups. The excess mortality risk for women was in agreement with previous studies [Jarrett *et al.* 1982] [Sasaki *et al.*1989]. There appears to be some unknown factor that increases the incidence of diabetes (both type 1 and type 2) in men above the incidence in women. On the other hand there appear to be some unknown factor that protects men more than women from premature death from diabetes. Whether these factors are genetic, endocrine, metabolic, or environmental is not possible to conclude from this study. One conclusion that can be drawn from these results, however, is that women should have a lower cut-of for diagnosis of diabetes than men, if similar incidence, prevalence, and prognosis are desirable for the two genders.

The survival of diabetic patients (both type 1 and type 2) improved during the studied years. The prognosis improved remarkably for the younger diabetic patients in Skaraborg. The prognosis to reach 65 years of age for

patients diagnosed with diabetes before 15 years of age increased from zero 1991 to 32 % in 2005.This was in agreement with studies from Scandinavia [Green *et al.* 1985] [Borch-Johnsen *et al.* 1986]. In contrast, studies from Japan revealed a remarkable increase in mortality in diabetic patients above 75 years of age [Sasaki *et al.* 1994]. One possible explanation for the difference in prognosis for the oldest diabetic patients could be the high prevalence of type 2 diabetes in Scandinavia making geriatric personnel more familiar with diabetes care.

There is a general opinion that type 1 diabetes is a more severe disease than type 2 diabetes. This idea is based on the observation that many patients with type 1 diabetes are young and contract many complications before a premature death [Swerdlow *et al.* 1996]. Nowadays, however, it is apparent that type 1 diabetes also affects persons in middle and old age. These patients contract fewer complications and have a prognosis more like what is expected in type 2 diabetes. On the other hand, patients with onset of type 2 diabetes in young age, contract complications similar to those associated with type 1 diabetes. Therefore we tried to analyze if there was any difference in prognosis between type 1 and type 2 diabetes, apart from the age at diagnosis. In 25-34 year olds the incidence of type 1 and type 2 diabetes are similar. There was no difference in mortality for type 1 versus type 2 diabetes in this age group. Both types of diabetes had a high standardized mortality rate of 6.78-8.75 times above the background population. In agreement, an equal or lower mortality risk for type 1 diabetes was reported from Sweden [Nyström *et al.* 1992] and U.K. [Roper *et al.* 2002]. Patients with type 2 diabetes have higher blood pressure and higher body-mass index and more dyslipidemia that could elevate the mortality risk in type 2 diabetes and counterbalance the hazard by the more dysregulated blood glucose of type 1 diabetes.

In accordance with the Stockholm Diabetes Intervention Study [Reichard *et al.* 1996] and the U.K. Prospective Diabetes Study [UK Prospective Diabetes Study (UKPDS) Group, 1998], which linked several types of complications to HbA1c, the Skaraborg Diabetes Registry could link HbA1c to survival. About 70 % of the patients with normal HbA1c, but only 35 % of those with the highest HbA1c survived for ten years.

There was a lack of correlation between body-mass index and survival. The comparison of body-mass index and survival is confounded by the fact that lower body-mass index is found in patients with type 1 diabetes and high body-mass index is found in patients with type 2 diabetes. This implies that slim patients with type 1 diabetes have an equal mortality risk as obese patients with type 2 diabetes which strengthens the findings that type 2 diabetes is not a "light" form of diabetes but has a similar prognosis as type 1 diabetes.

A strong inverse correlation between systolic, but not diastolic blood pressure and survival was found. A high systolic blood pressure is correlated to high age and vascular stiffness, which can explain why systolic blood pressure and 10-year survival are inversely correlated.

Clinical findings as classification tools

Children with type 1 diabetes are few, adults with type 1 diabetes are more numerous, and adults with type 2 diabetes are the most numerous. This imbalance distorts sensitivity and specificity of symptoms, diagnostic for type 1 diabetes in children, when they are applied on an adult population [Wilson *et al.* 1985]. Typical signs of type 1 diabetes in children, such as weight loss, ketoacidosis, islet autoantibodies, and low concentration of C-peptide are often found in patients with type 2 diabetes, not because they are common in type 2 diabetes, but because patients with type 2 diabetes are so numerous. If we state that all diabetic patients have type 2 diabetes, we would be true in 85 % of the cases. If we improve our classification by stating that all diabetic patients below 40 years of age have type 1 and the rest have type 2 diabetes, we would be true in about 90 % of the cases. Hence, any sign or test used for classification of diabetes in an entire population should have at least 90 % predictive value (sensitivity * specificity) to improve classification compared to just determine the age of the patients [Eriksson *et al.* 1992].

Another problem with classification of diabetes based on clinical findings is the weakening of symptoms in adults compared to children. Some of the typical findings of type 1 diabetes in children (i.e. ketoacidosis, weight loss, thirst, polyuria, and fatigue) are less common and less intense in adults. The diagnosis of type 2 diabetes is mainly based on absence of signs associated with type 1 diabetes. This has created a quagmire of conflicting symptoms, laboratory tests, and vague criteria which are utilized to characterize patients in between typical children with type 1 diabetes and typical obese, elderly patients with type 2 diabetes [Alberti 1993].

Young patients in Skaraborg with type 1 diabetes were accurately classified by clinical findings at diagnosis such as thirst, polyuria, fatigue, and weight loss, and there were concordant autoimmune markers and beta-cell function. Young patients with type 2 diabetes were more difficult to classify based on clinical findings. Six young patients were classified with type 2 diabetes based on high body-mass index (4 patients) and treatment without insulin (4 patients). Three of these patients became antibody positive and only 3 patients continued to have preserved beta-cell function, absence of antibodies, no insulin treatment, and probable type 2 diabetes. One of these patients, however, had normal body-mass index and presented with ketoacidosis, but could later be changed from insulin to diet.

The clinical classification of type 1 diabetes in adults above 35 years of age in Skaraborg was often in disagreement with the biochemical and the immunological classification. More than 50 % of the adult antibody-positive patients were clinically classified as having type 2 diabetes, based on high

body-mass index (51 %) and treatment without insulin (57 %). The adult patients with type 2 diabetes, finally, were often correctly classified (98 %) by clinical findings. More than 50 % were obese and only 11 % were insulin treated, but four of them had ketoacidosis at diagnosis. Hence, 30 % of all patients presenting with ketoacidosis left the hospital with type 2 diabetes diagnoses. Ketoacidosis appears to be an unreliable tool for identifying type 1 diabetes. Between 16 % [Pitteloud *et al.* 2000] and 40 % [Balasubramanyam *et al.* 1999] of diabetic ketoacidosis has been reported in adults with type 2 diabetes and C-peptide > 1 nM. In the Diabetes Incidence Study in Sweden in 0-34 year olds, there was no difference in prevalence of islet autoantibodies in patients presenting with ketoacidosis versus patients without [Östman *et al.* 2000]. Also the weaker symptom ketonuria without acidosis has limited value in the classification of diabetes [Hoter-Nielsen *et al.* 1988].

Obesity was a week discriminator between type 1 and type 2 diabetes. In Skaraborg 12 % of the patients with type 1 diabetes (antibody positive and fasting C-peptide < 0.42 nM) had a body-mass index above 25 kg/m^2 and 6 % of the patients had body-mass index above 27 kg/m^2, whereas 19 % of the adults with type 2 diabetes (antibody-negative and fasting C-peptide > 0.42 nM) had body-mass index below 27 kg/m^2 and 10 % had body-mass index below 25 kg/m^2. These figures are similar to figures from patients 15-34 years of age in the Diabetes Incidence Study in Sweden from the early 1990th. About 12 % of the type 1 diabetic patients had body-mass index above 25 kg/m^2 [Blohmé *et al.* 1992]. Half a decade later, almost 50 % of the patients had body-mass index above 25 kg/m^2 and were considered as having overweight [Wroblewski *et al.* 1998]. However, the body-mass index in type 2 diabetic patients have also increased from the early 1990th when about 35 % of the patients with type 2 diabetes had body-mass index below 25 kg/m^2 [Blohmé *et al.* 1992] [Di Cianni *et al.* 1994].

There is a well-established covariation between age and body-mass index, most pronounced in young persons, who have the highest incidence of type 1 diabetes. Hence, it is not surprising that young patients with type 1 diabetes in general are leaner than adults with mainly type 2 diabetes are. The week correlation between body-mass index and type of diabetes was noticed in a report that overweight at 25 years of age and weight gain in 40-55 year olds had little impact on the risk of developing diabetes. Only those with a weight gain between 25 and 40 years of age had a 25 % increased risk to develop type 2 diabetes [Schienkiewitz *et al.* 2006].

Independency of insulin treatment is a somewhat arbitrary attribute to type 2 diabetes. In Skaraborg, adult insulin-treated patients without autoantibodies (n = 23) outnumbered those with antibodies (n = 13). The tendency to give insulin to type 2 diabetic patients has increased over the

years [Gale 2005], and the possibility to detect an absolute need for insulin is, of course, reduced if insulin therapy is started for other reasons.

The age at diagnosis finally, was an inappropriate classification tool. In Skaraborg 35 % of the patients with type 1 diabetes were above 30 years of age, and 23 % were above 40 years of age at diagnosis. In previous studies, up to 37 % of patients with insulin-dependent diabetes were diagnosed after 19 years of age and 6 % of these patients could be managed without insulin [Laakso *et al.* 1985] [Mølbak *et al.* 1994].

Classification based on synthesis of clinical requirements (ketoacidosis, body-mass index, treatment, and age at diagnosis) has been tried [Hother-Nielsen *et al.* 1988] [Irvin *et al.* 1997] but not surprisingly, the misclassifications concerning autoimmunity were as common as in Skaraborg [Wilson *et al.* 1985] [Notkons *et al.* 2001]. Nevertheless, a clinical algorithm in the screening for autoimmune diabetes was recently suggested [Fourlanos *et al.* 2006], and other modern studies identify type 1 and type 2 diabetes by one or more of the somewhat arbitrary clinical criteria mentioned [Fajardo *et al.* 2001] [Bruno *et al.* 1992] [Balasubramanyam *et al.* 1999].

Islet autoantibodies as classification tools

Among 0-34 year olds in Skaraborg 80 % had islet autoantibodies and 70 % had multiple antibodies. One or more islet autoautoantibody has previously been reported in 80-90 % of young patients with type 1 diabetes (ICA 50-90 %, GADA 52-85 %, and IA-2A 48-80 %) [Borg *et al.* 2000] [Batstra *et al.* 2001] [Fajardo *et al.* 2001] [Mustonen *et al.* 1984]. In agreement with previous studies the three antibodies studied were equally common and had equal strength to diagnose type 1 diabetes and beta-cell insufficiency. [Zimmet *et al.* 1994] [Littorin *et al.* 1999] [Juneja *et al.* 2001] [Borg *et al.* 2001]. Twelve years after diagnosis 80 % of the patients with islet autoantibodies had lost their beta-cell function, whilst those without antibodies had preserved beta-cell function [Borg, Gottsäter *et al.* 2002]. As most of the young patients had multiple islet autoantibodies, one single antibody test was enough to find children with autoimmune diabetes. ICA has largely fallen into disuse, because the assay is labor-intensive, operator-dependent, and has never really been mastered by more than a handful of laboratories [Gale 2005]. In the choice of GADA or IA-2A, GADA has shown to be a more significant predictor of insulin treatment in a young population with unclassifiable diabetes in whom 59 % had islet autoantibodies [Törn *et al.* 2000].

Due to the definition of type 1 diabetes as diabetes with autoimmune markers, [The Expert Committee on the diagnosis and classification of diabetes mellitus, 1997], it is not surprising that most patients with type 1 diabetes have islet autoantibodies. It is more surprising that up to 30 % of the patients with clinical signs of type 1 diabetes lack all signs of immunological attack on the beta-cell. Biopsies have revealed that 31 % of the patients with type 1 diabetes lack all signs of inflammatory affection of the pancreatic islets. Moreover, 20 % of those with insulitis lacked islet autoantibodies and 32 % of those without islet autoantibodies had insulitis [Imagawa *et al.* 2001]. Furthermore, only 60-93 % of the young patients with clinically diagnosed type 1 diabetes and insulin deficiency had islet autoantibodies [Hagopian *et al.* 1995] [Batstra *et al.* 2001] and 5.8 % of the patients with total beta-cell failure lacked islet autoantibodies both at diagnosis and at follow-up [Schölin, Björklund *et al.* 2004].

In adult patients in Skaraborg, 11 % had islet autoantibodies (ICA 6.2 %, GADA 9.0 %, and IA-2A 4.0 %). The prevalence of islet autoantibodies in adults was in agreement with others studies with 16 % antibody-positive, 8-12 % ICA-positive, 4-11 % GADA-positive, and 2 % IA-2A-positive [Wroblewski *et al.* 1998] [Takeda *et al.* 2002] [Lohman *et al.* 2001]. The results from the Skaraborg Diabetes Registry indicate that the detection of low titers of islet autoantibodies, and one single islet autoantibody in adults are features associated with clinical signs of type 2 diabetes, whereas the combination of ICA and GADA is characteristic for patients with clinical signs of type 1 diabetes. The assessment of IA-2A did not add any discriminating power.

Other studies have shown that few (1-2 versus 3-4) of the islet autoantibodies ICA, IAA, GADA, IA-2A are associated with a preserved beta-cell function [Turner et al. 1997] [Valdez et al. 2001] [Schölin, Törn et al. 2004] [Stenström et al. 2005] [Genovese et al. 2006].

ICA has been reported as an excellent discriminator between insulin-dependent and non-insulin-dependent diabetes [Landin-Olsson et al. 1990]. GADA and IA-2A have been suggested to replace the troublesome ICA assay [Bonifacio et al. 1995] [Borg et al. in Clin Chem 2358-63, 1997] [Wiest-Ladenburger et al. 1997] [Batstra et al. 2001]. Both GADA and ICA was equally effective predictors of insulin treatment within 6 years in patients above 35 years of age [Turner et al. 1997] and GADA was present in 73 % of the insulin-dependent patients above 30 years of age [Zimmet et al. 1994]. On the other hand, the concentration of GADA has been shown to have no correlation to the rate of beta-cell destruction [Batstra et al. 1997], and GADA has been shown least useful in patients above 45 years of age, where the majority of diabetic patients with uncertain classification are found [Irvin et al. 1997] [Schernthaner et al. 2001]. ICA has been shown to be a better predictor of insulin-dependent diabetes than GADA or IA-2A in relatives to diabetic patients [Pietropaulo et al. 2005]. In agreement with the findings in Skaraborg, IA-2A has been reported significantly less common and without value in the differential diagnosis of type 1 versus type 2 diabetes in adult patients [Fajardo et al. 2001] [Lohman et al. 2001]. Islet autoantibodies has been reported in 3.5-25 % of patients with clinical type 2 diabetes [Landin-Olsson et al. 1982] [Tuomi et al. 1993] [Turner et al. 1997] [Pietropaolo et al. 2000] [Batstra et al. 2001] [Borg et al. 2003] and only 38 % of GADA-positive adults were considered insulin-deficient [Takeda et al. 2002].

One problem with islet autoantibodies as classification tools is the instability of the antibodies. In Skaraborg 37 % of the patients lost an antibody after diagnosis and 18 % became antibody negative after diagnosis. In the same time, 4 % gained an islet autoantibody and became antibody positive. The instability of the islet autoantibodies have been revealed by others [Ludvigsson et al. 1997] [Bastra et al. 1997] [Savola et al. 1998] [Landin et al. 1999]. Six percent of type 1 diabetic patients converted to antibody negative within four years after diagnosis [Decochez et al. 2000]. Nine percent lost ICA, 12 % lost GADA, and 28-29 % lost IA-2A after diagnosis in another follow-up [Nakamoto et al. 2000]. After a period of 4 months to 6 years, 10-14 % of the antibody-negative, 24 % of the GADA-negative, and 9 % of the IA-2A-negative patients gained an islet autoantibody and converted to positive [Nakamoto et al. 2000] [Decochez et al. 2000] [Borg et al. 2003] and only 41 % of 15-34 year olds had unchanged antibody status after 8 years [Schölin, Björklund et al. 2004]. Others, on the other hand, have found that islet autoantibodies, at least GADA and IA-2A, often are persistent for long time and can be used to detect autoimmune diabetes long after diagnosis [Borg et al. 2002].

The relation between the appearance of islet autoantibodies and autoimmune beta-cell destruction as detected by low or decreasing C-peptide is not always obvious [Zimmet et al. 1999]. There are several indications that islet autoantibodies are not pathogenic. They can develop after the onset of diabetes and they can be totally absent even in cases with obvious immunologic attack to the beta-cell [Ludvigsson et al. 1997] [Landin et al. 1999]. Most likely the islet autoantibodies are signs of beta-cell injury. Intensive destruction of beta-cells as in children with type 1 diabetes releases large quantities of cellular antigens and evokes islet autoantibodies in high titers, whereas a slow and mild degradation of beta-cells, as in adult type 1 diabetes, LADA, and even in some forms of type 2 diabetes, only few cellular antigens are exposed to the antigen-presenting cells and only few islet autoantibodies in low titers will be the result. Hence, in agreement with others, the results from the Skaraborg Diabetes Registry suggest that the number of islet autoantibodies and their titer could be a result rather than a cause of the beta-cell destruction [Notkons et al. 2001]. Nevertheless, islet autoantibodies are of value to diagnose beta-cell destruction and predict insulin dependency. According to the WHO definition of diabetes [World Health Organization report 727, 1985], type 1 diabetes does not have to be insulin-dependent, at least not from start. Maybe, awareness of islet autoantibodies in non-insulin-dependent patients would enable earlier start of treatment and prevent development of hyperglycemia and long term complications. In patients with low C-peptide and in insulin treated patients, detection of islet autoantibodies, however, add very little clinically useful information at present. Not until the pathogenesis of type 1 and type 2 diabetes is revealed, the value of the different islet autoantibodies will be clarified.

C-peptide as classification tool

In the Skaraborg Diabetes Registry, ROC-curves were used for the first time to find the optimal cut-off values for classification of type 1 and type 2 diabetes and to compare the power of random C-peptide, fasting C-peptide, and glucagon-stimulated C-peptide to differentiate type 1 from type 2 diabetes.

The cut-off value for glucagon-stimulated C-peptide at 0.60 nM corresponded to previous studies. Plasma C-peptide concentration > 0.6 nM 6 minutes after a challenge with 1 mg of intravenous glucagon gave a high ratio of a probably correct classification of type 1 and type 2 diabetes and was a reliable cut-off for the choice of therapy [Welborn *et al.* 1981] [Madsbad *et al.* 1981] [Poulsen *et al.* 1985] [Koskinen *et al.* 1985] [Rönnemaa *et al.* 1986] [Cravarezza *et al.* 1986] [Sarlund, Siitonen *et al.* 1987] [Hother-Nielsen *et al.* 1988].

The cut-off value for fasting C-peptide at 0.42 nM in Skaraborg was higher than in some of the previous studies. Fasting plasma C-peptide < 0.16 nM [Webb *et al.* 1981] [Welborn *et al.* 1981], < 0.17 nM [Service *et al.* 1997], < 0.20 nM [Gjessing *et al.* 1989], or < 0.30 nM [Hother-Nielsen *et al.* 1988] indicated beta-cell dysfunction, type 1 diabetes, and need for insulin treatment. Patients with fasting C-peptide 0.24-0.32 nM had high frequency of islet autoantibodies [Gjessing *et al.* 1989] [Gottsäter *et al.* 1993]. Application of classification algorithms that do not recognize type 1 diabetes at high ages or in obese patients may have contributed to lower cut-off values for fasting C-peptide in some of the previous reports. On the other hand, one study found fasting plasma C-peptide < 0.42 nM in all their insulin-dependent patients [Madsbad *et al.* 1981] and most patients with fasting C-peptide > 0.32 nM [Webb *et al.* 1981], > 0.4 nM [Koskinen *et al.* 1985] had clinical features of type 2 diabetes and could be treated without insulin.

In agreement with the results from the Skaraborg Diabetes Registry, others have found that glucagon-stimulated C-peptide correlate closely to fasting C-peptide and that a glucagon-stimulated C-peptide value of 0.6 nM corresponds to a fasting C-peptide value of 0.4 nM [Madsbad *et al.* 1981] [Koskinen *et al.* 1985]. In some studies fasting C-peptide and glucagon-stimulated C-peptide had similar discriminating power [Hother-Nielsen *et al.* 1988], but some studies support the findings from the Skaraborg Diabetes Registry, that glucagon-stimulated C-peptide gives more overlapping results than fasting C-peptide between patients requiring insulin therapy versus patients managed without [Törn 2003] [Grant *et al.* 1984].

A cut-off value of 0.50 nM was found most appropriate for random C-peptide. Previous studies suggested cut-off values for random C-peptide at 0.33 nM [Zimmet *et al.* 1994], at 0.6 nM [Arnqvist *et al.* 1993], or at 1 nM [Bell *et al.* 2004] as

useful in the diagnosis of beta-cell failure and insulin-dependency but none of these studies tested alternative cut-points. The close correlations between random C-peptide versus both fasting C-peptide and glucagon-stimulated C-peptide and the cut-points for fasting C-peptide and glucagon-stimulated C-peptide in agreement with previous reports, indicate that the cut-off for random C-peptide at 0.50 nM is relevant. An explanation for our good results with random C-peptide could be the requirement of blood glucose > 8 mM at testing. Others have found that high blood glucose is more important than the fasting state, when testing for C-peptide [Rönnemaa et al. 1986].

A 24-hours collection of urinary C-peptide has been suggested as discriminator between type 1 and type 2 diabetes, however unreliable in patients with renal insufficiency and dependent on high compliance in urine collection [Sjöberg et al. 1983] [Katzeff et al. 1985].

In general, patients with absolute need for insulin have lower C-peptide than what is found in patients without absolute need for insulin [Faber et al. in Diabetologia, 1977] [Hoekstra et al. 1982] [Gottsäter et al. 1992]. At diagnosis of type 1 diabetes about 50 % of normal beta-cell capacity is found. After diagnosis the beta-cell function generally continues to decline with 0.75 nM per month and levels off after about two years at 0.028 nM in 7–30 year olds [Steele et al. 2004]. Hence, generally adults with islet autoantibodies feature obvious beta-cell failure within 3 years after onset [Gottsäter et al. 1993], although sometimes it takes up to 12 years until obvious decrease in C-peptide appear [Borg, Gottsäter et al. 2002]. A decline in C-peptide could be expected also in type 2 diabetes [Polonsky et al. 1988] [Eriksson et al. 1992]. Increased apoptosis of pancreatic beta-cells have been shown [Butler et al. 2003], but obvious beta-cell impairment in type 2 diabetes is rare before 10 years duration [Eriksson et al. 1992] [Clauson et al. 1994].

The measuring of C-peptide is relevant from several aspects. Clearly the measurement of C-peptide is the most direct measurement of beta-cell function. Insufficient beta-cell function is the sole pathophysiological process that renders a normal person diabetic, and in trials to preserve the beta-cell function there were few indications that islet autoimmunity correlated with the change of the beta-cell function [Ludvigsson et al. 1997] [Palmer et al. 2004]. The C-peptide is a relevant indicator, and may be a better tool than islet autoantibodies to find adult patients in need for insulin therapy [Service et al. 1997] [Törn 2003] [Bell et al. 2004]. The C-peptide could be relevant also for the prognosis. In several studies, patients with preserved C-peptide secretion had a better metabolic control [Faber et al. in Diabetologia, 1977] and experienced a reduced prevalence of complications both in the group with intensive treatment and in the conventional treated group and hence irrespective of HbA1c [The Diabetes Control and Complications Trial Research Group, 1998] [Steffes et al. 2003] [Palmer et al. 2004].

Nevertheless, some have suggested that islet autoantibodies have a

higher predictive value for future need for insulin and long-time prognosis. This might seem like a contradiction to the pathophysiologic hypothesis with a successive loss of beta-cell function until insulin-dependency appears. However, insulin sensitivity varies widely among patients in risk of developing insulin-dependency. Hence, an obese, inactive patient can experience insulin-deficiency with fasting plasma C-peptide above 1.0 nM, whereas a slim active patient can manage without insulin despite a fasting plasma C-peptide < 0.5 nM [Batstra *et al.* 2001]. Even though a low C-peptide at diagnosis can be reversed when glucose-toxicity has been cured by treatment, low C-peptide in connection with high blood glucose always indicate a need for extra insulin for a shorter or longer period. A high C-peptide, on the other hand, indicates that there is a therapeutic window for diet, physical activities, and oral antidiabetic drugs. If these means does not suffice, the patient has to expect large insulin dosages to overcome the insulin insensitivity, and thereby increased risk of weight gain and perpetuating increase in blood glucose and insulin dosage.

It has been shown that patients with clinical type 1 diabetes but no islet autoantibodies have several high-risk HLA alleles [Pietropaolo *et al.* 2002] and that healthy relatives with these HLA-types have lower C-peptide titer than healthy relatives without these HLA-types [Li *et al.* 2001] [Weets *et al.* 2002]. This suggests that the genetic background decides the capacity for beta-cell secretion, proliferation, and regeneration and hence, the probability to withstand an attack towards the beta-cells from what ever cause (inflammatory, infectious, toxic, or just an increased need due to diet or obesity). This puts focus on the interaction between insulin sensitivity and insulin secretion capacity in the pathogenesis of diabetes and links type 1 and type 2 diabetes together as different shades of insufficient insulin processing.

Conclusions

This study showed that, despite a stable incidence and an unchanged age at diagnosis, Skaraborg has an increasing prevalence of diabetes due to an improved survival for diabetic patients between 1991 and 2005.

The mortality risk is significantly increased, especially for women diagnosed with diabetes in young age. The survival for diabetic patients, however, improved considerably during the studied years. The increased survival could be a success story for all personnel involved in the management of diabetes, but could partly be an artifact due to sliding criteria for diagnosis leading to detection of borderline cases.

The most relevant clinical finding separating type 1 from type 2 diabetes is age. The three islet autoantibodies have almost equal sensitivity and specificity to diagnose autoimmune diabetes in children. Hence, one single islet autoantibody (preferably GADA) can be recommended to screen for autoimmune diabetes in children. In adults, on the other hand, one single islet autoantibody is not enough for detecting autoimmune destruction of the beta-cell. Only in the presence of two or more antibodies, there is an increased risk of impaired beta-cell function. In this context, GADA and ICA is more sensitive and specific than other combinations of islet autoantibodies and the value of analyzing IA-2A in adults is low.

The classification of diabetes into type 1 and type 2 ought to be modified or discarded. The conflicting clinical findings underline that nature has developed a spectrum of clinical and laboratory findings associated with hyperglycemia and not two separate diseases. The struggle to divide diabetic patients into separate classes will not be successful unless the purpose with the classification first is defined. A classification based on C-peptide, lipids, HbA1c, blood pressure, body-mass index etc. may be helpful in the choice of therapy. An immunological classification based on islet autoantibodies is essential in the search for patients suitable for immune-modulating research. A genetic classification based on HLA-types could be of value for risk evaluation in relatives. A description of the patients in terms of genetic susceptibility, autoimmune markers, beta-cell function, and insulin sensitivity would be most appropriate for identifying homogenous groups of patients for studies of epidemiology, therapeutic alternatives, and prognosis.

Random C-peptide, analyzed without considering relation to previous meals, is simpler and more powerful than fasting C-peptide or glucagon-stimulated C-peptide in distinguishing type 1 from type 2 diabetes. Random C-peptide is also more effective than any combination of islet autoantibody assessments, in identifying patients with beta-cell dysfunction and need for

insulin treatment. Therefore, without the need for fasting or injecting glucagon, random C-peptide is recommended for determination of beta-cell function and need for insulin treatment in all age groups.

There could be a therapeutic value in repeated measurements of C-peptide in diabetic patients and in persons with high risk to develop diabetes. A high insulin requirement (expressed as high plasma C-peptide concentration), increases the risk of developing overt diabetes and therapies that lower plasma C-peptide retard the onset of diabetes and improves the survival prognosis. The future cure for diabetes should be looked for in therapies that can improve both insulin sensitivity and beta-cell function. Strategies for improvement of insulin sensitivity are already well known. Physical activity, weight reduction, stress reduction, and diet are easily prescribed but hard to swallow. The mechanism behind the augmented beta-cell function observed in obese persons without diabetes, might give clues to therapies for those unfortunate diabetic brothers and sisters whose beta-cells do not meet their requirements.

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Svensk populärvetenskaplig sammanfattning

I Skaraborg med 280 000 invånare har alla fall av diabetes, oavsett ålder och diabetestyp, registrerats i Skaraborgs Diabetesregister sedan 1991. Patienterna har följts med avseende på behandling och utveckling av komplikationer. Registret innehåller uppgifter från drygt 15 000 patienter.

3,20 % av Skaraborgs befolkning hade diabetes 1995 och 88,4 % av alla diabetespatienter i Skaraborg var registrerade i Skaraborgs Diabetesregister. Av 100 000 invånare insjuknade varje år 15 nya patienter med typ 1 diabetes och 266 nya patienter med typ 2 diabetes. Bland de nya fallen var något fler män än kvinnor. Detta var oväntat då andra autoimmuna sjukdomar oftast har en kvinnlig överrepresentation.

Antalet diabetespatienter i Skaraborg ökade med ca 400 patienter per år. Antalet nya fall av diabetes ökade däremot inte alls mellan åren 1991-2005. Inte heller sjönk medelåldern för dem som insjuknade. Det ökande antalet patienter med diabetes berodde i stället på att dödligheten minskade.

Patienter med diabetes hade fyra gånger högre dödlighet jämfört med normalbefolkningen. Riskökningen var högst för unga kvinnor som hade 12 gånger högre dödlighet än unga kvinnor utan diabetes. Kvinnor och män som insjuknade i diabetes efter 80 års ålder hade däremot ingen ökad dödlighet alls jämfört med normalbefolkningen. En person som får diabetes förlorar i genomsnitt 30 % av sin återstående livslängd. För unga patienter innebär det ca 25 förlorade år, medan patienter som insjuknar senare lever 4 månader längre för varje år som diabetesinsjuknandet kan fördröjas. Dödligheten i diabetes har emellertid minskat sedan 1991. Livslängden för patienter med diabetes var i genomsnitt 75,6 år 1991 och 79,1 år 2004. Chansen att uppnå pensionsålder för barn som fick diabetes före 15 års ålder ökade från 0 % 1991 till 32 % 2005. Orsaken till den ökade överlevnaden är inte bara bättre sjukvård, utan en viss betydelse har också sänkningen av blodsockervärdet för diabetesdiagnos mot värden som ligger närmare friska människors värden. Genom denna ändring 1998 kom en stor grupp tidigare friska människor med marginellt förhöjda blodsockervärden och en bättre överlevnad att klassificeras som diabetessjuka.

Diabetessjukdomen har sedan lång tid tillbaka delats in i två olika typer. Typ 1 diabetes utmärks av att den drabbar unga människor, medför relativt akut insjuknande, att bukspottkörtelns insulinproducerande betaceller blir inflammerade och att insulinproduktionen upphör. Typ 2 diabetes utmärks av att den drabbar äldre och överviktiga, insjuknandet är smygande och symptomfattigt, att betacellerna inte blir inflammerade och att insulinproduktionen finns kvar.

Bland unga patienter var de tre autoantikropparna (ICA, GADA, IA-2A) lika vanligt förekommande och de hade likvärdig förmåga att särskilja type 1 diabetes (med antikroppar) från type 2 (utan antikroppar). Även utan laboratorieanalys kunde typiska symptom vid debuten ge god vägledning för att särskilja typ 1 och typ 2 diabetes. Bland äldre patienter fanns ofta lägre halter av autoantikroppar och oftare endast en eller två typer av autoantikroppar. Därför gav analys av autoantikroppar sämre vägledning i klassificeringen av typ 1 och typ 2 diabetes hos äldre. Inte heller symptomen vid debuten var till lika stor hjälp för att särskilja typ 1 från typ 2 diabetes hos äldre.

Tre olika sätt att analysera C-peptid (ett mått på förmågan att utsöndra insulin) jämfördes. Alla tre analysmetoderna (utan förberedelse, fastande, och med föregående injektion av glucagon) uppvisade god överensstämmelse med den kliniska klassifikationen av typ 1 (utan insulinutsöndring) och typ 2 diabetes (med insulinutsöndring). Slump-C-peptid (dvs. C-peptidbestämning utan förberedelse) överensstämde bäst med den kliniska klassifikationen av diabetestyp. Slump-C-peptid var dessutom den enklaste analysmetoden som inte krävde att patienten kom till mottagningen fastande på morgonen. Inte heller behövdes injektion av glukagon som är kostsamt, arbetskrävande och obehagligt för patienten. För rutinbruk rekommenderas därför slump-C-peptid när patientens insulinproduktion ska värderas.

I framtiden bör begreppen typ 1 och typ 2 diabetes emellertid avskaffas eftersom de saknar relevans när diabetessjukdomens olika förlopp ska beskrivas. Skaraborgs Diabetesregister visar att ålder vid insjuknandet, kroppskonstitution, symptom vid insjuknandet, autoantikroppar och insulinproduktion inte duger för att entydigt särskilja type 1 från typ 2 diabetes. I stället bör diabetessjukdomen beskrivas i termer av ärftlig risk, autoimmunitet, insulinproduktion och insulinkänslighet. Med dessa parametrar är det lättare att hitta patientgrupper med mer enhetliga former av sjukdom vilket underlättar tolkningen av forskningsresultat.

Det kan vara av värde att mäta C-peptid upprepade gånger både på patienter med diabetes och på personer med stor risk att få diabetes. Höga nivåer av C-peptid talar för en ökad risk att få diabetes och behandlingar som sänker C-peptidnivån kan fördröja insjuknandet i diabetes och därigenom minska komplikationsrisken och förbättra överlevnaden. Framtida effektivare behandling av diabetes kommer antagligen att kräva strategier som förbättrar såväl insulinkänsligheten som insulinproduktionen. Välutvecklade metoder för att mäta dessa parametrar är en grundförutsättning för att kunna utvärdera sådana behandlingsstrategier. Redan idag känner vi till effektiva behandlingsstrategier för att förbättra insulinkänsligheten. Fysisk aktivitet, viktminskning, minskad stress och en lämplig kost är lätt att ordinera men

svårare att svälja. Mekanismerna bakom den ökade insulinproduktionen som ses hos överviktiga utan diabetes, kan förhoppningsvis ge ledtrådar till behandlingar för de diabetespatienterna vars betaceller förlorat förmågan att anpassa sig till ökande krav på insulinproduktion.

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