Register-based studies of diabetes

BENDIX CARSTENSEN[1,2] & KNUT BORCH-JOHNSEN[3]

[1]*Steno Diabetes Center, Gentofte, Denmark,* [2]*Department of Biostatistics, University of Copenhagen, Copenhagen, Denmark, and* [3]*Research Center for Quality in Health Care, Institute of Public Health, University of Southern Denmark, Odense, Denmark*

Abstract

Introduction: During the last decade, a number of population-based diabetes registers have emerged which have enhanced the population-based epidemiology of diabetes. The aim of this paper is to review research based on Danish diabetes registers and to compare with similar research in Finland, Sweden, Scotland, and Canada. *Research topics:* The pattern with the highest prevalences in ages around 75 years is consistent between studies based on different registers, and so is the finding that incidence rates of diabetes are higher among females than males only in ages 20–40. Diabetes registers have been and is increasingly being used to study and particularly quantify links with cardiovascular disease and with cancer. Recently, available medication profiles of diabetes patients have been used as well to further elucidate these links. **Conclusion: Diabetes registers are valuable sources of data for description of the trends in occurrence, development, and mortality of diabetes. However, it requires careful application of modern statistical methods since effects of calendar time, age, and duration of diabetes all have to be taken into account when reporting results.**

Key Words: *Demography, diabetes, epidemiology, incidence, mortality, prevalence*

Introduction

Registration of diabetes patients at a population level is relatively recent, as opposed to cancer registration, which dates back to the middle of the 20th century. The reason for this is the relative uncertainty of a diabetes diagnosis. The diagnosis of diabetes has always been based on some form of glucose measurement and the diagnostic criteria have varied over time and does vary across the world. Moreover, far from all persons meeting the diagnostic criteria have any clinical symptoms, and a substantial fraction of patients therefore remain undiagnosed.

In this paper we will briefly describe Danish and international research based on population-based diabetes registration, but mostly concentrate on a couple of Danish studies based on registered diabetes, albeit not all based on the newly established National Diabetes Register [1].

Research topics

Registers

Nordic countries The Nordic countries have unique opportunities for long-term population-based epidemiological studies due to the unique personal identification number which is in use for all major health events and administrative purposes in general.

Denmark, Sweden, and Finland have registers of diabetes patients, but in somewhat different form and shape. To our knowledge, there are no population-wide diabetes registers in Norway or Iceland.

Denmark has a regularly updated register of diabetes patients, based on existing registers [1,2]. This is a population-based register where all diabetes patients (according to the definition) are recorded with date of birth, date of diabetes, and date of death, as well as sex and the entry criteria met.

The National Indicator Project (NIP) for diabetes [3] is another register, attempting to collect clinical information for all diabetes patients on a regular basis (at least annually). The purpose is to monitor the treatment of diabetes patients. This register however only covers less than 20% of all diabetes patients; the coverage for patients in outpatient clinics is high, generally over 80%, but the coverage from general practice is very poor – only some 7% of general practices currently report the NIP register.

Sweden has a National Diabetes Register, which only covers about 50–60% of the diabetes patients [4,5]. It is primarily collecting clinical information on patients, but the exact coverage is not known, so it is not suitable for epidemiological and demographic studies in diabetes occurrence and mortality. It is a valuable source for quality assurance in diabetes treatment, as well as a tool for studies *internally* in the diabetes population, that is studies where comparisons are only made between diabetes patients with different clinical characteristics, and not with the non-diabetic part of the population.

The Swedish National Diabetes Register is thus comparable to the Danish National Indicator Project, but currently the Swedish register has a far better coverage.

The National Institute for Health and Welfare in Finland has linked various databases to produce a database, which resembles a register. This is not at present in a formal frame as a proper register as it is a one-time compilation of linked data [6,7].

Non-Nordic countries Outside the Nordic countries, diabetes registration exist in Scotland [8,9] and in Canada [10,11].

The Scottish system covers the entire population as of 2000 and is virtually complete, collecting information from several administrative databases to form the register; however the system is recently established, so no official publications for the total of Scotland exist, only from the pioneering region Tayside [8].

The Canadian system is based in the National Diabetes Surveillance System (NDSS) that collects data from all states of Canada and issues reports annually [11].

Apart from these registers there is a large number of childhood diabetes registers, some of them with associated biobanks [12]. These are not discussed further here, since they only cover the youngest part of the population, typically the range 0–14 which is covered by the pediatric wards.

Register results

Prevalence and incidence No detailed figures of age-specific rates or prevalences are published from the Swedish and Scottish registers, so only results from Denmark, Finland, and Canada are mentioned here.

Broadly speaking, the age-specific diabetes prevalences in Denmark, Finland, and Canada show the same pattern with a peak between age 75 and 85 years with prevalences from 13% in Finland in 2002 to 16% in Denmark in 2008 and 25% in Canada in 2008. Moreover, males have higher prevalences, most pronounced in the older ages (over 70). The specific results from the latest version of the Danish National Diabetes Register are shown in Figure 1.

Incidence rates are not available from Finland, but both Danish and Canadian figures show that female incidence rates are higher than male incidence rates in the fertile age range under 40, in Canada around 1 and 2 per 1000 person-years for males and females, respectively, and in Denmark about half of this. The peak incidence rates are seen in the late seventies, with rates in Canada around 16 and 12 per 1000 person-years for males and females, respectively, whereas the corresponding peak rates in Denmark are around 12 and 10 per 1000 person-years. Also there were indications that the increase in incidence rates has ceased after about 2004.

Mortality Carstensen et al. [2] showed that the mortality among diabetes patients is decreasing by calendar time and that standardised mortality ratio (SMR; i.e. the mortality rate-ratio relative to the non-diabetic part of the population) is decreasing by age as well as by calendar time. They showed that the decrease in mortality among diabetes patients was stronger than in the general population, leading to a decrease in SMR. Also the SMR was highest in younger ages, about 5 in age 50 decreasing to 1.5 in ages 80+, but quite similar for males and females.

A similar age-specific pattern of the SMR was seen in Canada [11]; however with a SMR of only 3 in ages around 50.

An important consequence of the decreasing SMR by age is that overall SMR values for a population will be strongly confounded by the age distribution in the population and thus is hardly comparable between populations.

Register-based studies in diabetes epidemiology

A comprehensive overview of the basic demographics of diabetes in Denmark (i.e. how incidence, prevalence, mortality, and SMR depend on sex, age, and calendar time) based on the diabetes register was
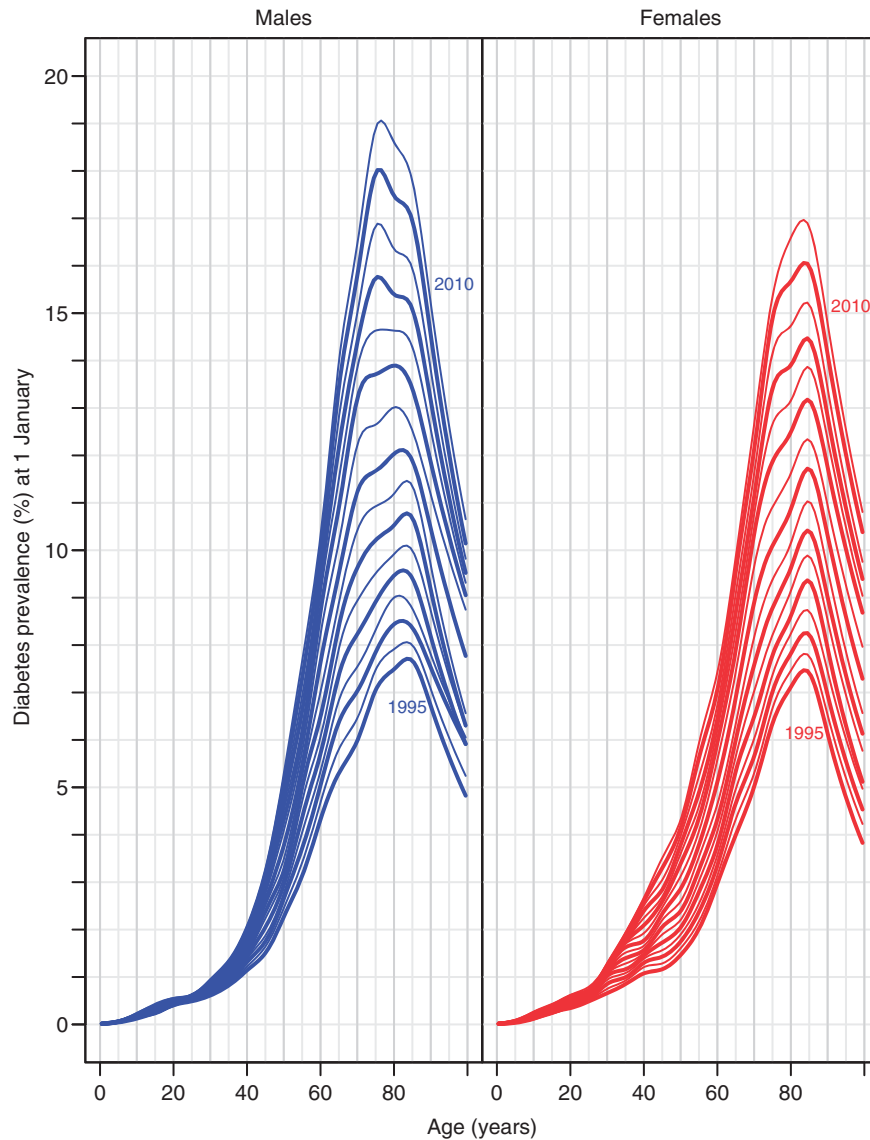
Figure 1. Age- and gender-specific diabetes prevalences in Denmark in 2010.

published in 2008 [2], but so far most other published studies from Denmark have been based in ad-hoc definitions of diabetes, mainly based on prescription records [13–15].

The studies by Schramm et al.[14] and Nørgaard et al. [15] were based on data from the National Patient Register, and defined diabetes patients from prescription records.

In these studies follow-up is analysed as fixed cohorts ignoring actual changes in diabetes status or cardiovascular disease (CVD) status during follow-up. The first study [14] showed that prevalent diabetes patients carry the same CVD mortality risk as prevalent survivors of myocardial infarction. The study by Nørgaard et al. [15] showed a dramatically decreasing excess mortality after incident acute

myocardial infarction (AMI), and that the long-term CVD mortality of AMI patients is higher (primarily for women) than that of the incident diabetes patients, when taking time since diagnosis into account.

These are examples of studies that add to the understanding of the demographic components (such as age, sex, and duration) in the development of diabetes in relation to other disease outcomes, in this case in terms of mortality and how this relates to other medical events.

Diabetes as exposure

In 2009, several articles appeared in Diabetologia [5,9,16–18], comparing the cancer risk among

patients prescribed the insulin analogue glargine to that among patients using other insulins. These studies gave no clear result, partly because the follow-up time was very short due to the short market-life of glargine.

These studies were all based on register data, except the German study [18] which was based on insurance data. The study from UK [17] were based on a register which is not population-based. They are all examples of pharmacoepidemiological studies which doubtless will be more abundant in the future, particularly in the field of diabetes where patients live for a very long time and are mostly quite extensively medicated, and therefore it is of considerable interest to detect possible rare adverse effects of medication use.

The study of diabetes and cancer is not new, but has previously largely been confined to the cancer literature, since cancer would be the main endpoint and diabetes an exposure collected either through a patient register or via medication records [13,19]. The results from these studies point to a general increase in cancer incidence of about 10%, mainly confined to cancers of the liver, pancreas, and digestive system as well as the endometrium in women. A somewhat lower risk of prostate cancer has been shown consistently across studies too. With the advent of pharmacological data, cancer has become to be regarded as a potential side effect of diabetes treatment, because it has become possible to study it as a widely registered and hence available endpoint. By the same token, other chronic diseases are likely to be studied as determined by diabetes and the medication for the disease.

Methodological challenges

In studies of follow-up of diabetes patients based on register data, the major challenge is to take both current age and duration of disease into account, thus handle analysis and in particular reporting of effects on two or more timescales. To the extent that medication is involved, duration and dosage of medication should be considered too.

In studies based on cancer or CVD register data, where death is the major outcome of relevance, time since disease onset is the dominating time scale of interest, whereas studies involving follow-up among diabetes patients will generally be more complex.

In the future we may expect not only pharmacological data to be available but also, as electronic medical records evolve in hospitals and clinics, an increasing wealth of directly applicable clinical data. Since diabetes is a chronic disease which is extensively pharmacologically treated over long periods of time, it is essential that that this kind of data be analysed with methods that are able to take account of multiple timescales (age, calendar time, disease duration etc.) as well as disease and exposure states that vary over time. This also calls for interpretation of study results that go beyond mere reporting of rates and rate-ratios and that describe quantities such as the life-time lost as well as the economic costs under various scenarios.

In studies of incidence of diabetes based on register data, both age and calendar time must be considered, but this is nothing new, and the problems flowing from this are already extensively discussed in the epidemiological literature, particularly in relation to cancer incidence studies [20–22].

Conclusion

Diabetes is a disease with long survival time, during which patients are medicated and potentially suffer a number of serious complications. Therefore, already the currently available diabetes registers present substantial challenges, and as they grow larger and more clinical data becomes available, increasing opportunities for new insights in the actual clinical course of the disease will become available.

Funding

Acknowledgement

References

[1] Carstensen B, Christensen JK, Marcussen MM, Borch-Johnsen K. The National Diabetes Register. Scand J Public Health 2011;39(Suppl 7):58–61.

[2] Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K. The Danish National Diabetes Register: Trends in incidence, prevalence and mortality. Diabetologia 2008;51:2187–96.

[3] Det Nationale Indikatorprojekt. National Auditrapport 2009. Available from: https://www.sundhed.dk/Profil.aspx?id=66788.1 (accessed 15 March 2011).

[4] Cederholm J, Nilsson PM, Eliasson B, Eeg-Olofsson K, Zethelius B, Gudbjornsdottir S. Connections between risk factors and complications in diabetes. A report after 13 years with the National Diabetes Registry (NDR). Läkartidningen 2009;106:2684–9.

[5] Jonasson JM, Ljung R, Talbäck M, Haglund B, Gudbjörnsdòttir S, Steineck G. Insulin glargine use and short-term incidence of malignancies-a population-based follow-up study in Sweden. Diabetologia 2009;52:1745–54.

[6] Niemi M and Winell K. Diabetes in Finland, prevalence and variation in quality of care. Technical report, Finnish Diabetes Association, 2006. Available from: http://www.diabetes.fi/files/1105/Diabetes_in_Finland._Prevalence_and_Variation_in_Quality_of_Care.pdf (accessed 15 March 2011).

[7] Winell KM, Paakkonen R, Pietila A, Niemi MK, Reunanen AR, Salomaa VV. Case fatality rates after first acute coronary syndrome in persons treated for type 2 diabetes show an improving trend. Diabetologia 2010;53:472–80.

[8] Evans JMM, Barnett KN, Ogston SA, Morris AD. Increasing prevalence of type 2 diabetes in a Scottish population: effect of increasing incidence or decreasing mortality? Diabetologia 2007;50(4):729–32.

[9] Colhoun HM, the SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. Diabetologia 2009;52:1755–65.

[10] Public Health Agency of Canada. *Report from the National Diabetes Surveillance System: Diabetes in Canada, 2009.* Ottawa: Public Health Agency of Canada, 2009. Available from: http://www.phac-aspc.gc.ca/publicat/2009/ndssdic-snsddac-09/pdf/report-2009-eng.pdf (accessed 15 March 2011).

[11] Johnson J, Balko SU and Hugel G. Alberta Diabetes Atlas 2009. Technical report, 2009. Available from: http://www.albertadiabetes.com/atlas09.php (accessed 15 March 2011).

[12] Green A, Patterson CC. Trends in the incidence of childhood-onset diabetes in Europe 1989–1998. Diabetologia 2001;44 Suppl 3:3–8.

[13] Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst 1997;89:1360–5.

[14] Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54.

[15] Norgaard ML, Andersen SS, Schramm TK, Folke F, Jørgensen CH, Hansen ML, et al. Changes in short- and long-term cardiovascular risk of incident diabetes and incident myocardial infarction-a nationwide study. Diabetologia 2010;53:1612–19.

[16] Smith U, Gale EA. Does diabetes therapy influence the risk of cancer? Diabetologia 2009;52:1699–708.

[17] Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–77.

[18] Hemkens LG, Grouven U, Bender R, Günster C, Gutschmidt S, Selke GW, et al. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 2009;52:1732–44.

[19] Adami HO, McLaughlin J, Ekbom A, Berne C, Silverman D, Hacker D, et al. Cancer risk in patients with diabetes mellitus. Cancer Causes Control 1991;2:307–14.

[20] Clayton D, Schifflers E. Models for temporal variation in cancer rates. I: Age-period and age-cohort models. Statistics in Medicine 1987;6:449–67.

[21] Clayton D, Schifflers E. Models for temporal variation in cancer rates. II: Age-period-cohort models. Statistics in Medicine 1987;6:469–81.

[22] Carstensen B. Age-period-cohort models for the Lexis diagram. Statistics in Medicine 2007;26:3018–45.