Increased Utilization of Primary Care 5 Years Before Diagnosis of Type 2 Diabetes

A matched cohort study

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OBJECTIVE — To determine whether case subjects who were later diagnosed with type 2 diabetes utilized primary care differently from control subjects who remained free from diabetes.

RESEARCH DESIGN AND METHODS — We conducted a matched cohort study using the U.K. General Practice Research Database. Case subjects were aged 30–89 years, diagnosed with diabetes, and later prescribed oral hypoglycemic drugs between 1997 and 2000. Control subjects, who were matched for age, sex, and general practice, were not diagnosed with diabetes and not treated with oral hypoglycemic drugs or insulin.

RESULTS — Data were analyzed for 5,158 case subjects (2,492 women and 2,666 men) and their matched control subjects with a mean age of 63 years. Five years before the date of diagnosis, case subjects consulted more frequently than control subjects (rate ratio [RR] 1.26 [95% CI 1.20–1.33]) and received more prescription items (1.44 [1.36–1.53]). Consultations were increased for a wide range of conditions. The cumulative 5-year prevalence of diagnoses of hypertension or treatment, hyperlipidemia or treatment, obesity, or coronary heart disease or stroke was 66.1% in case subjects and 45.9% in control subjects (1.44 [1.40–1.49]). A medical diagnosis of hyperglycemia or impaired glucose tolerance was highly (>99%) specific for later diagnosis of diabetes.

CONCLUSIONS — Primary care consultations and drug utilization are increased from 5 years before diagnosis of diabetes. Diagnoses of hypertension, hyperlipidemia, obesity, or coronary heart disease or stroke have moderate sensitivity for subsequent diabetes but are nonspecific. A diagnosis of hyperglycemia has a high specificity for later detection of diabetes.

Diabetes Care **28:47–52, 2005**

Type 2 diabetes is an increasing concern for public health and health services in many countries. In the U.S., 14.4% of adults had either diagnosed or undiagnosed diabetes or impaired glucose tolerance in 1999–2000 (1). A rapid increase in obesity is expected to lead to an increase in diabetes over the coming decades, and this may lead to a decline in life expectancy (2).

The clinical diagnosis of diabetes represents a step in the development of a progressive condition leading from normal glucose tolerance, first to impaired fasting glucose or impaired glucose tolerance, and then to diabetes, with the degree of hyperglycemia increasing over time. In population studies (1), ~29% of prevalent cases of diabetes are undiagnosed, and up to 35% of subjects with newly diagnosed type 2 diabetes may already show signs of diabetic retinopathy (3). These observations suggest that by the time a diagnosis is made, metabolic abnormalities may have been present for several years (4). This preclinical stage is important because intervention at this time has the potential to reduce progression to diabetes and possibly reduce subsequent morbidity or mortality.

Clinical trials have shown that in subjects with known type 2 diabetes, treatment of elevated blood glucose (5), blood pressure (6), or cholesterol (7) levels may delay the onset and progression of complications or reduce mortality. These findings have prompted calls for screening for type 2 diabetes. However, opinion is divided between those who argue for more equitable access to effective diabetes care and those who caution that the costs are high, appropriate screening tests are uncertain, and the effectiveness of early intervention is unproven. More recent studies (8) have demonstrated the feasibility of preventing or delaying the onset of diabetes in subjects with impaired glucose tolerance through the promotion of healthy dietary and physical exercise habits or additional pharmacological intervention. These results have redirected attention toward possible screening for "pre-diabetes," including impaired glucose tolerance or impaired fasting glucose. The American Diabetes Association (9) recommended that adults aged 45 years or older should be screened for prediabetes, and that in younger subjects, screening should be undertaken if risk markers such as hypertension or hyperlipidemia are present.

Contacts with primary care occurring before the diagnosis of diabetes offer opportunities for prevention or early detection of pre-diabetes or diabetes, but little is known about the nature of these contacts. One report (10) found that primary care physicians had little awareness of the clinical significance of impaired glucose

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Received for publication 15 September 2004 and accepted in revised form 11 October 2004.
Abbreviations: GPRD, General Practice Research Database; UTS, up to standard.
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tolerance as a precursor of diabetes. In the present study, we aimed to evaluate whether the utilization of primary care services by subjects who were later diagnosed with diabetes was different from that of age- and sex-matched control subjects who did not develop diabetes. We specifically aimed to determine how frequently these subjects consulted their physicians and for what reasons when compared with control subjects.

RESEARCH DESIGN AND METHODS

— Data were obtained from the General Practice Research Database (GPRD). This is a large database including data from general practices in the U.K. The database includes records of all patients who were registered with practices as well as medical diagnostic codes for consultations and referrals and details of all prescriptions issued through the general practice computer. Data in the GPRD are subject to quality checks, and when the data are judged to be of a high enough quality to be used in research, they are said to be up to standard (UTS). The quality of UTS data has been shown to be good (11). The Scientific and Ethical Advisory Group of the GPRD approved the study protocol.

Practice and patient selection

We initially selected all 255 practices that provided UTS data continuously between 1 January 1992 and 31 December 2000. Two practices were excluded because medical consultation data were missing, leaving 253 practices. We identified all patients who were registered with these practices between 1 January 1992 and 31 December 1992, and, from these, we identified patients who were prescribed oral hypoglycemic drugs, including sulfonylurea drugs, metformin, and other oral hypoglycemic drugs, for the first time after 1 January 1993. For each of these incident cases, we identified the date of the first recorded diagnostic code for diabetes, and this was identified as the date of diagnosis of diabetes. When the first diagnostic code was recorded after the first prescription of oral hypoglycemic drugs, the date of the first prescription was used as the date of diagnosis. A small number of cases in which the first diagnostic code was recorded >12 months after the first oral hypoglycemic prescription were excluded. The first year before diagnosis was defined as ending on the day before the date of diagnosis. The age at the date of diagnosis was calculated for each patient as the diagnosis year minus the year of birth. Subjects aged <30 or >89 years were excluded. To ensure that a 5-year record before the date of diagnosis was available for each patient, we kept only those patients whose date of diagnosis was after 1 January 1997. This gave a total of 7,135 case subjects.

Control subjects were randomly selected from all patients who were never prescribed insulin or oral hypoglycemic drugs and were never diagnosed with diabetes. Control subjects were matched for practice, sex, and age, and we also ensured that the control subject had at least a 5-year record before the diagnosis date of the matched case subject. Four case subjects for which control subjects could not be identified were excluded, as were 281 case-control pairs with missing medical records. In the early years of the GPRD, Oxmis medical codes were used, while Read codes were used exclusively in the later years. Oxmis codes are not hierarchically organized and cannot be readily mapped to equivalent Read codes. We therefore excluded all 1,692 case-control pairs from 72 practices whose 5-year record before the date of diagnosis included Oxmis codes.

Analysis

We grouped consultations into a broad group of cause using the first character from the Read code classification (12). This provided a classification that is comparable to the ICD chapter heading. Diagnostic codes for hypertension, coronary heart disease, and stroke were those described by the U.K. Office for National Statistics (13). Antihypertensive drugs and lipid-lowering drugs were classified using appropriate headings from the British National Formulary (14). Hyperglycemia or impaired glucose tolerance was recorded if an appropriate Read code was recorded in the medical code field of the medical file.

In a matched cohort study, when there are no missing data as in our study, then the rate ratio (RR) is the same as that calculated for an unmatched study (15). Accounting for matching in the analysis permits a modest gain in precision. We obtained RRs by using Poisson regression for count data and binomial regression using the "binreg" command in Stata version 7 (16) for analysis of proportions. We accounted for matching by estimating robust SEs with clustering for pair identifier. This approach gave slightly more conservative estimates than an analysis using conditional Poisson regression but allowed the same method to be used to adjust for matching in both types of regression models.

RESULTS

— Data were analyzed for 5,158 case subjects drawn from 181 practices with an equal number of control subjects that were individually matched for age, sex, and practice. There were 2,492 (48%) women and 2,666 (52%) men with a mean age of 63 years. There were 1,376 case subjects diagnosed in 1997, 1,340 in 1998, 1,285 in 1999, and 1,157 in 2000.

Table 1 shows the frequency of consultations and prescriptions by study year for case and control subjects. The data were skewed but are summarized as means (interquartile range) because comparison of means provides the RRs. From 5 years before diagnosis of diabetes, case subjects had rates of consultation that were ~25% higher than control subjects. The RRs remained approximately constant until the year before diagnosis, when the rate of consultations was ~50% higher. From 5 years before diagnosis onwards, the number of pharmaceutical items prescribed per year was between 40 and 60% higher for case compared with control subjects. Women made slightly more consultations and received more prescriptions than men, but the difference between case and control subjects was similar for men and women.

Table 2 shows the proportion of patients who consulted for broad groups of cause during the 5 years before diagnosis. Case subjects were more likely to consult with endocrine, metabolic, and nutritional disorders. The most frequently recorded diagnoses in these categories were for hypothyroidism, gout, obesity, hyperlipidemia, or hypercholesterolemia. Case subjects were also more likely to consult with circulatory disorders. For case subjects, the proportion consulting with infectious and parasitic diseases, mental disorders and disorders of the nervous system and sense organ, respiratory system, digestive system, genitourinary system, skin and subcutaneous tissues, musculoskeletal system, undefined symptoms, and injuries were also modestly increased. RRs were generally con-

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Table 1—*Numbers of consultations or prescription items per subject by the year before diagnosis for case and control subjects*

Year before diagnosis	Number per patient per year [mean (interquartile range)]		RR (95% CI)	*P*
	Case subjects	Control subjects		
Consultations				
Year 1	8.98 (3–12)	5.93 (1–8)	1.51 (1.46–1.57)	<0.001
Year 2	7.08 (1–10)	5.74 (1–8)	1.23 (1.17–1.30)	<0.001
Year 3	6.94 (1–9)	5.51 (1–8)	1.26 (1.21–1.31)	<0.001
Year 4	6.76 (1–9)	5.33 (1–7)	1.27 (1.21–1.33)	<0.001
Year 5	6.51 (1–9)	5.15 (1–7)	1.26 (1.20–1.33)	<0.001
Prescription items				
Year 1	25.76 (4–37)	16.31 (1–23)	1.58 (1.50–1.66)	<0.001
Year 2	22.57 (2–32)	14.99 (1–20)	1.51 (1.42–1.60)	<0.001
Year 3	20.48 (2–29)	13.67 (1–18)	1.50 (1.42–1.58)	<0.001
Year 4	18.38 (2–26)	12.56 (1–16)	1.46 (1.39–1.55)	<0.001
Year 5	16.54 (2–23)	11.45 (1–14)	1.44 (1.36–1.53)	<0.001

sistent with a 10–20% increase in the proportion that consulted with these conditions. High RRs were obtained for congenital anomalies and external causes of injury, but these were based on small numbers of subjects.

Table 3 shows the cumulative prevalence of recorded diagnoses of hypertension or prescription of antihypertensive drugs, coronary heart disease, stroke, hyperlipidemia or prescription of lipid-lowering drugs, obesity, or any of these conditions during the study period for case and control subjects. Over 5 years, the cumulative proportion of case subjects who were diagnosed with any of these outcomes was 66.1% compared with 45.9% in control subjects (RR 1.44 [95% CI 1.40–1.49]). These proportions may be interpreted as sensitivity (percentage) and 100-specificity (percentage), respectively. Over 5 years, only 33 (0.6%) of case subjects were diagnosed with impaired glucose tolerance, and 259 (5.0%) received a medical diagnosis of hyperglycemia or impaired glucose tolerance. However, only three (0.06%) control subjects were diagnosed with impaired glucose tolerance, and six (0.12%) were diagnosed with hyperglycemia or impaired glucose tolerance.

CONCLUSIONS — People who will later be diagnosed with type 2 diabetes may represent a heterogeneous group: some may have undiagnosed diabetes, some may have either diagnosed or undiagnosed impaired glucose tolerance or impaired fasting glucose, while some may have normal glucose tolerance. Overall such individuals consult with their primary care physician more frequently and receive more prescriptions than age- and sex-matched control subjects who remained free from diagnosed diabetes. The RRs were elevated from up to 5 years before diagnosis, and this raises a question concerning how long before diagnosis such differences exist or whether subjects who are later diagnosed with diabetes always experience worse health than subjects who will remain free from diabetes.

Consultations are increased for endocrine, metabolic or nutritional disorders

Table 2—*Proportion of subjects who had consultations for specified diagnostic categories in the 5 years before diagnosis*

Diagnostic category	Proportion who consulted in 5 years before diagnosis				RR (95% CI)	*P*
	Case subjects		Control subjects			
	Freq.	%	Freq.	%		
Infectious and parasitic diseases	1,499	29.1	1,244	24.1	1.20 (1.13–1.29)	<0.001
Neoplasms	386	7.5	403	7.8	0.96 (0.84–1.10)	0.533
Endocrine, nutrition, and metabolic	984	19.1	546	10.6	1.80 (1.63–1.99)	<0.001
Diseases of blood and blood-forming organs	206	4.0	203	3.9	1.01 (0.82–1.25)	0.891
Mental disorders	1,075	20.8	905	17.5	1.19 (1.10–1.28)	<0.001
Nervous system and sense organ diseases	2,453	47.6	2,311	44.8	1.06 (1.01–1.11)	0.016
Circulatory system diseases	2,412	46.8	1,735	33.6	1.39 (1.34–1.44)	<0.001
Respiratory system diseases	3,112	60.3	2,821	54.7	1.10 (1.07–1.14)	<0.001
Digestive system diseases	1,723	33.4	1,503	29.1	1.15 (1.08–1.22)	<0.001
Genitourinary system diseases	1,708	33.1	1,485	28.8	1.15 (1.09–1.21)	<0.001
Complications of pregnancy, childbirth, and puerperium	18	0.3	21	0.4	0.86 (0.53–1.39)	0.534
Skin and subcutaneous tissue diseases	2,437	47.2	2,071	40.2	1.18 (1.12–1.23)	<0.001
Musculoskeletal and connective tissue diseases	3,266	63.3	3,020	58.5	1.08 (1.05–1.12)	<0.001
Congenital anomalies	21	0.4	11	0.2	1.91 (0.96–3.80)	0.065
Perinatal conditions	2	0.0	3	0.1	0.67 (0.11–4.03)	0.659
Symptoms, signs, and ill-defined conditions	3,061	59.3	2,385	46.2	1.28 (1.23–1.34)	<0.001
Injury and poisoning	1,714	33.2	1,577	30.6	1.09 (1.03–1.15)	0.004
External causes of morbidity and mortality	20	0.4	8	0.2	2.50 (0.93–6.75)	0.071
Unspecified conditions	564	10.9	409	7.9	1.38 (1.25–1.52)	<0.001

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Table 3—*Cumulative proportion of subjects who consulted for specified conditions by the year before diagnosis*

Year before diagnosis	Cumulative proportion who consulted during the study period				
	Case subjects		Control subjects		RR
	Frequency	%*	Frequency	%†	(95% CI)
Hypertension or blood pressure–lowering drugs					
Year 1	2,959	57.4	1,990	38.6	1.49 (1.43–1.55)
Year 2	2,676	51.9	1,795	34.8	1.49 (1.44–1.54)
Year 3	2,460	47.7	1,621	31.4	1.52 (1.46–1.58)
Year 4	2,208	42.8	1,412	27.4	1.56 (1.48–1.65)
Year 5	1,930	37.4	1,189	23.1	1.62 (1.54–1.71)
Coronary heart disease					
Year 1	673	13.1	407	7.9	1.65 (1.50–1.83)
Year 2	542	10.5	335	6.5	1.62 (1.44–1.82)
Year 3	431	8.4	272	5.3	1.58 (1.39–1.81)
Year 4	324	6.3	208	4.0	1.56 (1.32–1.83)
Year 5	200	3.9	121	2.4	1.65 (1.34–2.04)
Stroke					
Year 1	183	3.6	78	1.5	2.35 (1.83–3.00)
Year 2	135	2.6	67	1.3	2.01 (1.56–2.60)
Year 3	113	2.2	51	1.0	2.22 (1.66–2.96)
Year 4	75	1.5	37	0.7	2.03 (1.44–2.86)
Year 5	32	0.6	21	0.4	1.52 (0.86–2.69)
Hyperlipidemia or lipid-lowering drugs					
Year 1	491	9.5	332	6.4	1.48 (1.32–1.66)
Year 2	371	7.2	253	4.9	1.47 (1.27–1.69)
Year 3	274	5.3	183	3.6	1.50 (1.27–1.77)
Year 4	202	3.9	129	2.5	1.57 (1.28–1.92)
Year 5	130	2.5	80	1.6	1.63 (1.25–2.12)
Obesity					
Year 1	1,110	21.5	644	12.5	1.72 (1.59–1.87)
Year 2	967	18.8	577	11.2	1.68 (1.54–1.82)
Year 3	842	16.3	483	9.4	1.74 (1.60–1.80)
Year 4	640	12.4	374	7.3	1.71 (1.55–1.88)
Year 5	382	7.4	194	3.8	1.97 (1.73–2.24)
Any of above‡					
Year 1	3,409	66.1	2,365	45.9	1.44 (1.40–1.49)
Year 2	3,094	60.0	2,155	41.8	1.44 (1.39–1.48)
Year 3	2,857	55.4	1,939	37.6	1.47 (1.42–1.60)
Year 4	2,544	49.3	1,662	32.2	1.53 (1.46–1.60)
Year 5	2,161	41.9	1,342	26.0	1.61 (1.54–1.69)
Medical diagnoses of impaired glucose tolerance or hyperglycemia					
Year 1	259	5.0	6	0.1	43.2 (19.9–93.9)
Year 2	59	1.1	4	0.1	14.8 (5.56–39.1)
Year 3	35	0.7	2	0.0	17.5 (4.34–70.6)
Year 4	23	0.5	0	0	—
Year 5	11	0.2	0	0	—

*Equivalent to sensitivity; †equivalent to 100-specificity; ‡including hypertension or antihypertensive therapy, hyperlipidemia or lipid-lowering therapy, obesity, coronary heart disease, or stroke.

(including gout, hypothyroidism, obesity, or hyperlipidemia), cardiovascular disorders (including hypertension, coronary heart disease, and stroke), and mental health problems (17), each of which may be associated with diabetes. Primary care consultations are also increased for a wide range of conditions not generally regarded as associated with diabetes. Several explanations might be advanced to account for this finding. First, diabetes may be the cause of more widespread systemic problems than has been previously recognized. Secondly, ongoing exposures to risk factors that cause diabetes, such as obesity, physical inactivity, or cigarette smoking (18), may account for some of these clinical associations. Thirdly, fre-

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quent contacts with medical care may increase the likelihood of diabetes being detected. These possible explanations are not mutually exclusive.

Limitations of the study

Our study has the strengths of a large sample size, with subjects drawn from a large number of practices throughout the U.K. and data collected prospectively over a number of years. Practices that volunteer to participate in the GPRD may differ from practices that do not participate, but case and control subjects were matched for practice, so confounding by practice characteristics, such as area-level deprivation score, should have been eliminated. We only included subjects who were eventually treated with oral hypoglycemic drugs. Subjects who were treated with insulin only were excluded because they might have type 1 diabetes. We also excluded subjects who were never treated with oral hypoglycemic drugs because a recorded clinical diagnosis of diabetes might be less secure for these subjects. Metformin may be prescribed for patients with polycystic ovary syndrome or for pre-diabetes, but we excluded subjects who were not diagnosed with diabetes within 12 months of the first prescription. Case and control subjects were matched for age and sex, but unmeasured confounders could explain some of the differences observed. Individual-level socioeconomic differences between case and control subjects might have also accounted for differences between case and control subjects. Lower socioeconomic status is associated with an increased frequency of diabetes and, in some studies, with greater utilization of primary care services (19). However, these associations might be explained by confounding with risk factors for diabetes, such as obesity and cigarette smoking, which also show pronounced socioeconomic gradients (20). In the GPRD, records of lifestyle risk factors, measurements of height and weight, and test results are included in the GPRD "prevention" file, which is not UTS. These data were therefore considered unsuitable for analysis. Another feature of clinical data is that use of diagnostic categories may vary between practitioners, and significant clinical information may not always be recorded in the form of a diagnostic category. The low frequency of recording of diagnostic codes for hyperglycemia or impaired glucose tolerance may not reflect the true level of clinical awareness of these problems. Nevertheless, the findings are consistent with those of Wylie et al. (10), who found that primary care physicians underestimated the significance of impaired glucose tolerance.

Comparison with other studies

The findings support the suggestion that health care costs for people who develop diabetes are increased for several years before diagnosis (21). Our results suggest that there are gradations in the risk of developing diabetes, which may be associated with graduated increments in the use of primary care services. In the population of subjects at increased risk of diabetes, continuing exposure to risk factors for diabetes may be associated with increased consultations for a range of conditions and symptoms that perhaps may not be specifically associated with diabetes. A higher-risk group of subjects may be identified in whom consultations are made for conditions associated with insulin resistance, including lipid abnormalities or hypertension, leading to increasingly frequent diagnoses of cardiovascular disease. In epidemiological studies (22), subjects who became diabetic had higher blood pressure and blood glucose levels with high triglycerides and lower HDL concentrations than subjects who did not convert to diabetes (22). In the Nurses Health Study (23), women who later developed type 2 diabetes had an age-adjusted relative risk of myocardial infarction of 3.75 (95% CI 3.10–4.53) when compared with subjects who remained free of diabetes. The age-adjusted relative risk of stroke was 2.53 (1.94–3.31).

These data show that there are patients who consult with increased frequency in primary care; they may have a range of clinical problems, possibly in association with obesity or a positive family history. In these subjects, efforts to prevent diabetes through lifestyle change will be especially relevant but may be more difficult because of comorbidity. Surveillance for hyperglycemia may be most relevant in patients who develop conditions associated with insulin resistance (24). However, our findings and those of other studies (25) suggest that differences in associated clinical diagnoses before the onset of diabetes are nonspecific and only give moderate sensitivity for later diagnoses of diabetes. By contrast, clinical diagnoses of impaired glucose tolerance and hyperglycemia or the results of tests for hyperlycemia (25) are highly specific, but the proportion of cases detected is determined by the coverage of the population at risk by appropriate tests that may not be sufficient at present.

Acknowledgments— This work was supported by the Charitable Foundation of Guy's and St Thomas' Hospitals.

Contributorship: M.C.G. thought of the idea; R.L. and M.C.G. designed the study; R.L. extracted and prepared the datafiles for analysis; J.C. analyzed the data; M.C.G. drafted the article, which was discussed and approved by R.L.; and J.C., M.C.G., and R.L. are joint guarantors.

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