

Referral Bias in Diabetes Research

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Of all the known diabetic individuals residing in the community of Rochester, Minnesota, only about one-half would have been recognized through a review of the medical records of 1 yr. Only one-fifth of the diabetic residents were hospitalized during the index year and a similarly small proportion were attended in a diabetes clinic. This selective process produced distortion in the apparent clinical spectrum of diabetes observed at different levels in the medical care system. Notable was overestimation of the relative importance of insulin-dependent diabetes and of the vascular complications of diabetes among hospital and diabetes clinic patients. Referral bias should be taken into account when differences are noted in the epidemiologic features of diabetes as reported from different types of medical care settings.

DIABETES CARE 7: 12-18, JANUARY-FEBRUARY 1984.

The clinical characteristics of diabetic patients seen in different settings may vary substantially. For example, 10.5% of adult diabetic residents of Rochester, Minnesota, had peripheral vascular disease on a specified prevalence date, as indicated by the presence of arteriosclerosis obliterans or gangrene.¹ Figures from other community studies are similar.² In contrast to these population-based data, the prevalence of arteriosclerosis obliterans in a clinical series, measured in a comparable fashion, was 25%.³ Other clinical studies have provided similar high estimates.⁴⁻⁶ Such differences commonly result from selective referral of the more severe or complicated cases from the community to secondary or tertiary care centers, thus distorting the clinical spectrum of the disease as judged by practitioners in the latter settings.

It is important to be able to distinguish the discrepancies in diabetes epidemiology that are the result of studying selected subpopulations of patients from those that may reflect real biologic differences, but the potential impact of referral bias has received little attention in the literature. Using data from the population-based study of diabetes mellitus in Rochester, Minnesota, we identified the prevalence cases living in the community on 1 January 1970. By reviewing the medical records for each patient for the preceding year, we were able to specify those patients who would have been found had a survey been done of (1) hospitalized patients, (2) those seen in a diabetes clinic or by an endocrinologist, or (3) those recognized in any fashion that year by the medical care

system. We then assessed the clinical spectrum of diabetes in each group and compared each one with the spectrum for all prevalence cases. Situations where referral bias did or did not seem to produce a potentially serious effect were identified.

METHODS

Rochester, Minnesota, is well suited for a study such as this because comprehensive unit medical records for the residents are available and because these records are accessible through a central index of diagnoses made by essentially all medical care providers whose services are used by the local population. This index includes the diagnoses made among outpatients seen in clinic consultations, emergency room visits, house calls, or nursing home care, as well as diagnoses recorded among hospital inpatients or at death. The potential of this data system for population-based studies has been described previously.⁷ The original medical records of the patients identified through the index were retrieved and reviewed for an initial diagnosis of diabetes in the 25-yr period, 1945-69. The diagnostic criteria for diabetes mellitus required fasting hyperglycemia on two consecutive determinations over 120 mg/dl (Folin-Wu method) for 1945-58 or over 110 mg/dl (AutoAnalyzer ferrocyanide reductase technique) for 1959-70 on whole venous blood for Mayo patients. Fasting blood glucose values from other institutions where Rochester patients sought medical care were interpreted in

TABLE 1
Diagnostic criteria for oral glucose tolerance tests among Rochester, Minnesota, residents, 1945-70

Age (yr)	Blood glucose value (mg/dl)			
	1945-58*		1959-70†	
	1 h	2 h	1 h	2 h
<50	>170	>130	>150	>110
50-59	>180	>140	>160	>120
60-69	>190	>150	>170	>130
70+	>200	>160	>180	>140

*Determined by Folin-Wu method on venous whole blood.

†Determined by AutoAnalyzer ferrocyanide reductase method on venous whole blood.

light of the method being employed. An oral glucose tolerance test was generally carried out when an equivocal fasting or postprandial blood glucose determination was obtained. At Mayo Clinic, the oral glucose tolerance test was performed by administering 1 g of glucose per kilogram of body weight and determining blood glucose concentrations at 0, 1, 2, and 3 h after the loading dose. Only the 1- and

2-h values were used for the interpretation of the test, and both values had to be elevated in comparison to age-specific standards (Table 1) for the diagnosis of diabetes mellitus to be made. While the criteria used here were somewhat more generous than those proposed by the National Diabetes Data Group,⁸ we have shown that the differences have little practical effect on the resulting clinical spectrum of diabetes.⁹

There were 810 diabetic patients who had met our diagnostic criteria residing in Rochester on 1 January 1970. This was more than the number originally reported,¹⁰ as additional cases were found when the initial study was updated to 1974. While these individuals represented "known" diabetic patients only, the completeness of case ascertainment was enhanced by surveillance of the local population for clinically diagnosed incidence, prevalence, and mortality cases for the entire 30-yr period, 1945-74. Included in this data set were patients who developed clinically evident diabetes, or whose blood glucose levels deteriorated in conjunction with an acute illness, or who had hyperglycemia noted on blood samples obtained in the course of inpatient or outpatient care for unrelated disease or for routine health evaluations. Individuals with asymptomatic abnormalities of glucose tolerance undoubtedly remain undetected in the population; we are unable to estimate the size of this group but believe it to be small.

TABLE 2
Sources of care during calendar year 1969 for the 810 Rochester, Minnesota, residents known to have diabetes mellitus (DM) on 1 January 1970, by patient group*

	Hospital cases (N = 148)		Diabetes clinic cases (N = 166)		All medical system cases (N = 428)		Total community cases (N = 810)	
	N	%†	N	%†	N	%†	N	%†
Hospitalized								
Yes	148	100.0	61	36.7	162	37.9	186	23.0
% of "yes" with mention of DM		100.0		90.2		91.4		79.6
No	0	0.0	105	63.3	266	62.1	624	77.0
Attended in diabetes clinic								
Yes	55	37.2	166	100.0	166	38.8	166	20.5
% of "yes" with mention of DM		100.0		100.0		100.0		100.0
No	93	62.8	0	0	262	61.2	644	79.5
Attended by other physician								
Yes	135	91.2	159	95.8	410	95.8	567	70.0
% of "yes" with mention of DM		74.1		80.5		86.6		62.6
No	13	8.8	7	4.2	18	4.2	243	30.0
Attended by non-M.D. provider								
Yes	67	45.3	103	62.0	195	45.6	262	32.3
% of "yes" with mention of DM		34.3		65.0		37.4		27.9
No	81	54.7	63	38.0	233	54.4	548	67.7

*Individuals can be counted in more than one group.

†Percentage figures refer to the proportion with "yes" or "no" responses within each category of provider noted in the left column.

The 810 prevalence cases were divided into four groups (not mutually exclusive) based on whether or not they could have been found through review of specific classes of medical records for calendar year 1969. These groups were defined as follows: (1) hospital cases were those patients who were hospitalized during 1969 and had diabetes mentioned at least once in a hospital record. If the diagnosis of diabetes was not recorded anywhere, the patient was not counted (hospitalized without mention of diabetes); (2) diabetes clinic cases were those patients seen in a formal diabetes clinic or who were attended outside the hospital by a board-certified or board-eligible endocrinologist; (3) all medical system cases included all patients attended anywhere in the medical care system with a mention of the diagnosis of diabetes. This included care delivered by dentists, nurse educators, dietitians, social workers, etc., as well as by physicians; (4) unattended cases were patients who were not seen by any medical care provider in calendar year 1969 or who were seen but the diagnosis of diabetes was never recorded anytime during the index year; and (5) total community cases were the total 810 known diabetic Rochester residents residing in the community on the prevalence day.

The fasting blood glucose value used in this report for prevalence cases was the value recorded closest to 1 January 1970. The fasting blood glucose levels were divided into three categories as recommended by West:¹¹ ≤ 199 mg/dl of whole venous blood, 200–299 mg/dl, and ≥ 300 mg/dl. Relative weight was calculated using recommended height/weight tables,¹² and patients were considered obese whose relative weight was 1.2 or greater. Therapeutic regimens were classified as insulin (with or without other therapy), oral agent (with or without diet but without insulin), or diet alone (no insulin or oral agents) as of prevalence day. The characterization of specific clinical types of diabetes generally followed National Diabetes Data Group recommendations, although, as explained in detail in a separate report, some modifications were required in the context of a retrospective study using existing medical records.¹³ Diabetic "complications" were classified as macrovascular (angina pectoris, myocardial infarction, sudden unexpected death, stroke, transient ischemic attack, or peripheral vascular disease) or microvascular (retinopathy or diabetic renal disease). Complications on prevalence day included a history of any one or more of these. Accurate assessment of complications and other clinical features as of prevalence day was assured by reviewing each patient's entire medical history in the community up to 1974.

Relative survival was determined with actuarial methods¹⁴ using death rates for West North Central whites (1970) as the standard. For the calculation of prevalence rates, the entire population of Rochester was considered to be at risk, and the age- and sex-specific denominators were derived from decennial census figures for 1970. We calculated 95% confidence intervals around the rates using a method similar to that outlined by Bailar and Ederer.¹⁵ Statistical testing was not performed on the distribution of specific characteristics in one group compared with another since the same indi-

viduals could be in two or more of the patient groups being evaluated.

RESULTS

Of the 810 known diabetic individuals residing in Rochester on 1 January 1970, 18% (148) would have been identified through a review of 1969 hospitalizations; 20% (166) could have been found through the records of diabetic clinics or individual endocrinologists for that year; and 53% (428) might have been identified through a canvas of the entire medical care system in the community for 1 yr. However, 47% (382) of the prevalence cases would have been missed in a review of the medical records of 1 yr.

As shown in Table 2, 23% of the total prevalence cases were hospitalized during calendar year 1969, although only 18% of these (79.6% of 23.0%) had a hospitalization during which diabetes was mentioned. This compares with a hospitalization rate of 37.9% for all of the patients recorded as having diabetes by the medical care system in that year and a nearly identical rate of 36.7% for the patients also attended in a diabetes clinic. About 90% of the hospitalized patients from these latter two groups had at least one hospitalization in which the diagnosis of diabetes was specifically noted. By definition, all of the patients in the hospital group had been hospitalized with some mention of diabetes. Only 20.5% of all prevalence patients in the community were attended in diabetes clinics or by an endocrinologist, but this proportion was much greater among all medically attended patients (38.8%) as well as for the patient group defined by hospitalization (37.2%). Seventy percent of all community patients were seen on an outpatient basis by nonendocrinologist physicians compared with 95.8% of all medically attended patients, 95.8% of diabetes clinic patients, and 91.2% of hospitalized individuals. However, diabetes was not mentioned in the records of a substantial minority of the patients in each group during the study year. Likewise, diabetes was not mentioned in most contacts with nonphysician providers during calendar year 1969. The exception was for patients attended in a diabetes clinic in that year, where 65% of the nonphysician contacts did involve diabetes. Of interest is the observation that of the 382 patients ("unattended cases") who would not have been recognized as diabetic by review of the 1969 medical records, two-fifths (157) were actually seen by a physician and 18% were seen by a nonphysician provider, even though diabetes was not mentioned, and 24 (6%) were hospitalized during the index year (data not shown in Table 2).

While the total crude prevalence rate was 15.4 per 1000 on 1 January 1970 (95% confidence interval 14.3–16.5), the prevalence of patients who had been hospitalized with some mention of diabetes was only 2.8 per 1000 (95% confidence interval 2.3–3.3) and of diabetes clinic patients was 3.2 per 1000 (95% confidence interval 2.7–3.7). Even if all patients recognized by the medical care system in that year were included, the 8.1 per 1000 figure (95% confidence interval

7.3–8.9) would have underestimated the actual situation by nearly one-half. Prevalence rates for these four groups, directly sex- and age-adjusted to the demographic distribution of 1970 white population of the United States were 17.4, 3.0, 3.5, and 9.0, respectively. In addition to underestimating prevalence rates in the community, use of the hospital cases or the diabetes clinic cases would have produced a very different pattern of apparent prevalence by age and sex (Figure 1).

While the relatively low proportion of diabetic patients identified in a cross-section through several major components of the medical care system is of concern, differences in the clinical spectrum of cases are more worrisome. The sex ratio (female/male) of cases, which in the community was 1.2/1, was exaggerated to 1.4/1 for all medical system cases and 1.6/1 among the hospital and the diabetes clinic patients. The age distribution of patients also varied quite substantially, with overrepresentation of young people in the diabetes clinic and overrepresentation of elderly patients among those hospitalized during the index year (Figure 2). The median age for the hospitalized group was 68 yr, compared with only 62 yr for the diabetes clinic patients. The median ages of the medically attended patients, the unattended patients, and of all prevalence cases were each 66 yr.

Differences in the clinical characteristics of patients in each group were also apparent (Table 3). The prevalence of insulin-dependent diabetes was much overestimated in the diabetes clinic population compared with the actual situation in the community, as was the proportion of patients using insulin or with severely elevated fasting blood glucose levels. Most of these same characteristics were overrepresented, albeit to a lesser degree, among hospital patients and among all patients identified as diabetic in provider records during 1969. The patients who were not noted by the medical system to have diabetes in 1969 (unattended cases) were generally less likely to have these characteristics. Few patients in any group had one or more of the classic triad of diabetes symp-

Prevalence per 1000 population on January 1, 1970

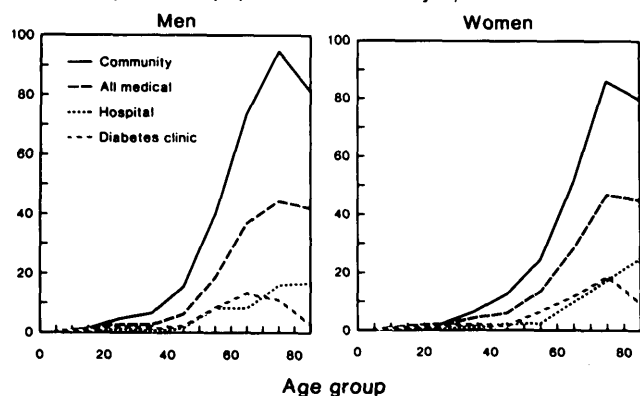


FIG. 1. Age- and sex-specific prevalence of diabetes mellitus among Rochester, Minnesota, residents on 1 January 1970, using cases ascertained from different sources.

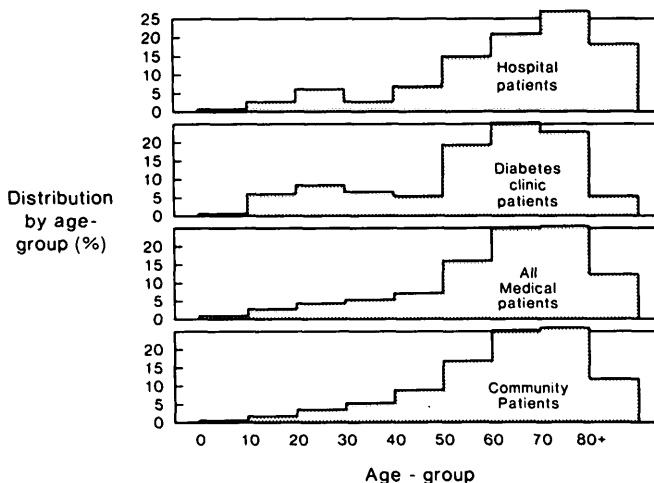


FIG. 2. Distribution by age of Rochester, Minnesota, residents with diabetes on 1 January 1970, using cases ascertained from different sources.

toms; the distribution by relative weight was not dramatically different either, although diabetes clinic patients seemed more likely to be thin. However, hospitalized patients were much more likely to have one of the macrovascular complications of diabetes, while diabetes clinic patients were slightly less likely to have one of these than members of the diabetes population at large. This reflects differences in the age distribution of the various groups, in part, although it is also obvious that macrovascular complications are a frequent reason for hospitalization. Microvascular complications of diabetes were more prevalent among both hospital and diabetes clinic patients than in diabetic residents of the community in general.

Short-term survival also varied from group to group as shown in Figure 3. Relative survival to 4 yr after prevalence day was 90.4% for the entire cohort of prevalence cases. Survival relative to that expected for a group of like age and sex from the general population was only 77.2% after 4 yr for the patients hospitalized during calendar year 1969. For the patients attended in a diabetes clinic or by any provider during 1969, the 4-yr relative survival rates were practically identical, that is, 85.5% and 85.1%, respectively. Survival among patients not recognized as diabetic using only the 1969 records (unattended cases) was a much higher 95.9% of that expected.

DISCUSSION

It was not our intent to evaluate the adequacy of any particular data source, such as the accuracy and completeness of hospital discharge diagnoses, because the specific characteristics might vary from one institution to another. Rather, we wanted to study inherent differences in the clinical spectrum of diabetes mellitus as viewed from several settings in the medical care system. Consequently, we reviewed the complete medical records of the known prevalence cases to determine who would have been recog-

TABLE 3

Clinical characteristics of Rochester, Minnesota, residents known to have diabetes mellitus on 1 January 1970, using cases ascertained from different sources

	Hospital cases (N = 148)	Diabetes clinic cases (N = 166)	All medical system cases (N = 428)	Unattended cases (N = 382)	Total community cases (N = 810)
Clinical type (%)					
Insulin-dependent	10.1	15.2	10.5	5.0	7.9
Obese, non-insulin-dependent	56.8	46.7	57.1	59.7	58.4
Nonobese, non-insulin-dependent	29.7	36.9	30.7	32.4	31.5
Secondary diabetes	3.4	1.2	1.6	2.9	2.2
Treatment (%)					
Insulin	35.1	45.8	30.8	13.9	23.5
Oral agents	28.4	28.3	30.1	17.5	24.2
Diet alone	36.5	25.9	39.0	68.6	52.3
Fasting blood glucose					
Median value (mg/dl)	118	128	120	109	116
≤199 mg/dl (%)	83.0	80.7	84.7	87.5	86.0
200–299 mg/dl (%)	15.0	15.1	12.0	8.9	10.6
≥300 mg/dl (%)	2.0	4.2	3.3	3.5	3.4
Classic symptoms					
One or more (%)	2.0	1.8	2.1	0.8	1.5
Relative weight (%)					
<1.0	14.9	17.5	13.6	10.5	12.1
1.0–1.19	27.7	36.1	29.4	29.7	29.6
≥1.2	57.4	46.4	57.0	59.7	58.3
Complications present					
Macrovascular (%)	46.6	27.7	37.4	23.0	30.6
Microvascular (%)	39.9	34.3	29.9	20.7	25.6

nized, and by what part of the medical care system, if only the data from calendar year 1969 had been used. This may seem to be an artificial situation because investigators would generally use all of the previous medical history available;

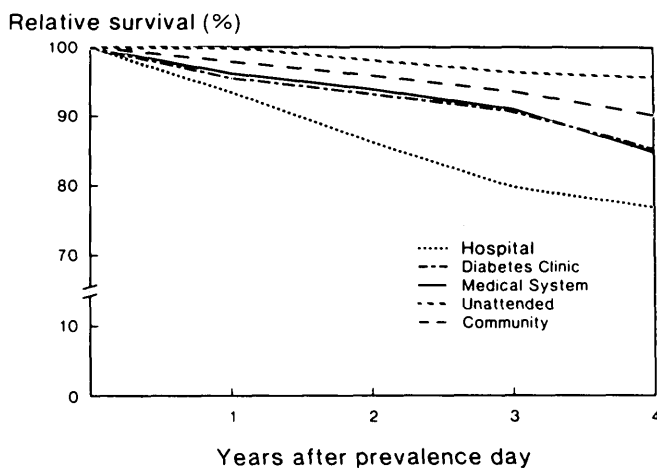


FIG. 3. Relative survival among Rochester, Minnesota, residents with diabetes mellitus on 1 January 1970, using cases ascertained from different sources.

however, recall that, in a substantial proportion of hospitalized cases, for example, diabetes was not mentioned anywhere in the record of the hospitalization. Admissions falling into this category were typically for minor elective surgical procedures, but they nonetheless represent a missed opportunity for identifying a diabetic patient. Others have shown that hospital records alone, even if reviewed for a number of consecutive years, will fail to detect over one-half of the diabetic patients in the community.¹⁶

Subtle biases may not be of particular concern, but it seems apparent that referral (or selection) bias is capable of introducing significant distortion into the epidemiologic picture of diabetes mellitus. This study assessed the effects of selection within one community. Where referral to a distant tertiary care center is involved, more intense selection probably takes place; and the clinical spectrum of cases may be distorted even more, as has been shown for other diseases.^{17,18} Even within this community, the potential for underascertainment of cases using only hospital or diabetes clinic data was striking. Hospitalized patients represented only about one-fifth of all diabetic residents of the community. This proportion was similar to the National Health Interview Survey finding that about 23% of diabetic individuals were admitted to a short-stay hospital in a 12-mo period (Dr. Maureen Harris, personal communication). Likewise, about 20%

of the Rochester patients were to be found in a diabetes clinic during the index year. Even if information from all medical records for a 1-yr period were used, only about one-half of the known Rochester diabetic patients would have been identified. Information from the Health Interview Survey indicates that about 80% of diabetic individuals see a physician in a 12-mo period (Dr. Maureen Harris, personal communication); however, the data presented here reveal that diabetes is not mentioned in the records of perhaps one-third of such encounters. Thus, the clinical records for any short period of time may be somewhat inadequate for diabetes case finding, even if the medical care actually delivered was satisfactory.

If only the numbers were affected by the selection process, it might be possible to suggest some sort of adjustment, but the clinical characteristics of the patients were biased as well. In general, the relative importance of insulin-dependent diabetes, along with elevated blood glucose levels and insulin use, was exaggerated among the patients medically attended in 1969, especially the diabetes clinic patients. The proportion of diabetes clinic patients on insulin in this study was quite similar to the 50% or so reported from a specialty practice in New York State.¹⁹ The proportion of cases with classic symptoms of diabetes was low in each patient group, in contrast to the situation among incidence cases where 29% were symptomatic.²⁰ Likewise, the distribution of relative weight was not particularly different from one group to the next. On the other hand, the impact of macrovascular complications of diabetes seemed to be seriously overestimated among the hospital patients, while microvascular complications were disproportionately frequent among both hospital and diabetes clinic patients. The figures were comparable to those reported from some referral practices^{21,22} but were greater than the proportion of diabetic patients so affected in the community. Both kinds of vascular complications were more common among prevalence cases than at the time of the initial diagnosis of diabetes, when only 6.3% of the patients had microvascular disease and only 21.5% had macrovascular complications.²⁰ The greater prevalence of vascular complications probably explains much of the poorer relative survival observed among the medically attended patients, especially those who were hospitalized.

ACKNOWLEDGMENTS: The authors wish to thank Lois Bartz for help in data collection and Janet R. King for assistance in preparing the manuscript. This study was supported in part by research grants from the American Diabetes Association and NIH (AM-30582).

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