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Disease concurrence in diabetes mellitus: a study of concurrent morbidity over 12 months using diabetes mellitus as an example

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Abstract

***Study objective*—The aim was to examine disease concurrence, using diabetes mellitus as an illustrative example.**

***Design*—The study involved a general practice morbidity survey, conducted over 12 months in 1981–82. All patients who consulted their general practitioners with a diagnosis of diabetes mellitus (type 1 or type 2) were identified and the number of these who consulted with additional morbidities were counted for each rubric of the Royal College of General Practitioners' modification of the International Classification of Disease. These observed numbers were then compared with expected numbers calculated from the total non-diabetic population after standardisation by age. Standardised person consulting ratios (SPCR) were derived and the 99% confidence intervals (CI) surrounding these values calculated.**

***Setting*—This was a national survey involving the whole of England and Wales.**

***Patients*—The study involved 280 000 patients from selected general practices, of whom 953 males and 1035 females consulted their general practitioners with diabetes.**

***Measurements and main results*—In an examination of 80 disease rubrics in the diabetic population in which there were at least 20 observed or expected cases, there were 34 among males and 28 among females in which there were increased values of the SPCR, and none in which the SPCR was decreased. SPCRs were high for infections generally (bacterial, fungal, and viral) and particularly so for cardiovascular disorders and for hypothyroidism in males. Though SPCRs for upper respiratory infections were increased, those for asthma and hay fever were not. SPCRs for neoplasms as a group were not raised.**

***Conclusion*—By confirming other work and widely held clinical opinion, this study has shown the potential of this data base for the examination of disease concurrence.**

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The study reported here is concerned with diseases occurring together within a 12 month period and therefore we have described this as a study of disease concurrence. In this exercise, there will be some people newly diagnosed with the index disease during the 12 months and others who have had the condition for several years. Other words used in epidemiological studies of this type include: "association", which does not imply any temporal quality; "coincidence", implying incidence at the same time; and "coexistence", which implies an association at a single point in time.

Studies of any form of association are helpful towards: (1) identifying common aetiological factors; (2) providing an epidemiological perspective to confirm (or otherwise) clinical impressions; (3) identifying risk factors for preventive medical care; and (4) measuring commercial risk for employment and insurance, etc. These studies usually involve intensive investigation of a particular group of patients identified primarily by the morbidity but secondarily by such factors as attendance at a specialist clinic. It can be very difficult to obtain a representative sample of persons with a specific disease.

In the third national (England and Wales) morbidity study, based on general practice, doctors recorded in a diagnostic index[1] the morbidity considered at every consultation during a 12 month period (1981–82). Recorded information included a coded patient identifier, the relevant morbid problem(s), and the episode type, whereby new episodes of illness are distinguished from recurrences. The patient identifier facilitated linkage between different morbidities.

The study population, though not randomly selected, was representative of the national population by age and sex.[2] The practices participating may not have been representative of practices throughout the country and therefore are potentially biased in the extent to which illnesses are identified. For some illnesses (eg, mental illness), the potential must be recognised in the interpretation of the data; for others, where diagnostic criteria are firmer or where consensus exists, it is less relevant.

In this study, we illustrate the use of national morbidity study data by examining disease concurrence with diabetes. The extensive knowledge available about the prevalence of diabetes and its associations with other diseases provide an opportunity to assess the potential of the data base. Both type 1 and type 2 diabetes mellitus are associated with increased mortality.[3] In patients developing diabetes beyond the age of 40, 70% die from cardiovascular disease, the risk for the diabetic being two or three times that for non-diabetics. Renal failure is an important cause of death, especially in young diabetics, and some die from diabetic ketoacidosis.

Methods

Approximately 330 000 persons were included in

the third general practice morbidity study. Of these, 280 000 were present in the study for the entire 12 month period and they constituted the study population. There were 1988 persons (953 male and 1035 female) who consulted their general practitioners with diabetes mellitus (index cases); ie, a person consulting rate of 7·5 per 1000 at risk. Counts were made among them of persons with concurrent morbidity in each of the other rubrics of the disease classification (Royal College of General Practitioners' modification of the International Classification of Disease). Expected numbers of cases for each rubric were calculated from the age composition of index cases (10 year age bands) and the age specific person consulting rates of each condition in the remaining study population (ie, all non-diabetics). The ratio of observed to expected (indexed to 100) provided the standardised person consulting ratio (SPCR). For each standardised person consulting ratio, the 99% confidence interval (CI) was calculated assuming an underlying Poisson distribution of observed values. We chose the 99% level because of the large number of comparisons made in this study.

By using only the data concerning persons registered for the entire year, there was a theoretical danger that there could be a bias involving a loss of index cases due to withdrawal from the practice, especially because of death. As a check therefore, withdrawals among the index cases were counted (75 male and 78 female) and shown to be similar to the expected numbers calculated from total study withdrawals and the age and sex composition of index cases (74 and 79 respectively).

Results

Table I gives the 99% CI for the standardised person consulting ratio for diseases aggregated by Chapter of the International Classification of Disease. No data are presented for Chapter III—*Endocrine disorders*—because it includes diabetes, and the chapters concerned with complications of pregnancy, congenital malformations, and perinatal conditions have been excluded because of the very small numbers involved. High values of the standardised person consulting ratio for index cases were found in both sexes and in all chapters, with the exception of neoplasms (both sexes) and blood disorders (females). Ratios for the sexes were broadly similar, but there was considerable variation between chapters.

In table II data are presented for the 80 (out of a total of 330) morbidity rubrics in which there were 20 or more observed or expected cases. The data given include the number of cases of each sex, the standardised person consulting ratios, and the confidence intervals. No diagnosis by site within Chapter II—*Neoplasms*—met the above criterion.

The tables are self explanatory and comment is restricted to diseases of special interest; mention is made of some involving less than 20 cases. Using the data for Chapter I as an example, the confidence intervals for males do not include 100 (excepting dermatophytosis) and therefore the standardised person consulting ratios are significant at the 1% level. Among females, the consulting ratios for two conditions were significant at this level. In the case of non-urogenital monilia infection, the consulting ratio was significantly increased at this level for males (n = 8, SPCR = 485, CI = 156–1127) but not for females (n = 8, SPCR = 250, CI = 80–581).

In Chapter V—*Mental disorders*—there is an interesting contrast between the results for anxiety state (SPCR 91) and those for depressive disorder (SPCRs 231 and 169). There were eight males with psychogenic disorders of sexual function, SPCR 471 (CI 151–1094). For Chapter VII—*Diseases of the circulatory system*—standardised person consulting ratios are uniformly high (excluding varicose veins). For *Respiratory diseases* (Chapter VIII), high consulting ratios only occurred for upper respiratory tract infections (febrile and male non-febrile) and for acute bronchitis.

In Chapter XII—*Skin disorders*—consulting ratios were especially high for infective conditions and for chronic ulcer of skin. For *Musculoskeletal disorders* (Chapter XIII), consulting ratios were in general not significantly high at the 1% level, the exception being non-specific limb pains for both males and females and non-specific arthritis for females. In Chapter XVII—*Accidents, injuries etc*—it is noteworthy that the consulting ratios were significantly increased for the adverse effects of medication.

Discussion

The examination of disease concurrence requires unique patient identification for linkage and entry of every relevant event referable to a substantial population. The general practice based morbidity studies for England and Wales are almost unique in achieving this comprehensive ideal over the total range of morbidity and most especially in a nationally representative population.

Table I Standardised person consulting ratios (SPCR) by chapter of International Classification of Disease

Chapter		Males			Females		
		Cases	SPCR	(CI)	Cases	SPCR	(CI)
I	Infections	118	222	(173–281)	146	201	(161–248)
II	Neoplasms	21	112	(59–192)	22	100	(54–170)
IV	Blood disorders	14	232	(103–445)	24	146	(81–242)
V	Mental disorders	91	140	(105–183)	179	129	(105–156)
VI	Disorders of nervous system	167	135	(110–165)	203	137	(113–164)
VII	Cardiovascular disease	309	188	(162–218)	352	179	(155–205)
VIII	Respiratory disease	271	136	(115–158)	315	140	(120–161)
IX	Gastrointestinal disease	125	149	(117–187)	139	145	(115–180)
X	Genitourinary disease	72	197	(143–266)	166	158	(128–192)
XII	Skin disease	187	217	(178–261)	203	182	(151–217)
XIII	Musculoskeletal disease	217	138	(115–164)	299	131	(112–152)
XVI	Symptoms, signs, etc	211	161	(134–192)	295	153	(131–177)
XVII	Accidents, etc	129	145	(115–182)	176	146	(119–176)

CI = 99% confidence interval

Table II Standardised person consulting ratios (SPCR) for selected diagnoses

	Males			*Females*		
	Cases	*SPCR*	*(CI)*	*Cases*	*SPCR*	*(CI)*
CHAPTER I *Infections*						
Intestinal inf disease	33	181	(110–279)	35	138	(86–211)
Herpes zoster	14	261	(116–500)	10	129	(48–275)
Viral inf, not specified	24	317	(175–525)	24	260	(144–431)
Dermatophytosis	13	170	(73–334)	12	219	(90–441)
Monilia, urogenital	10	751	(279–1607)	48	517	(345–741)
CHAPTER III *Endocrine and metabolic disorders*						
Hypothyroidism	9	660	(230–1467)	22	188	(101–319)
Obesity	24	387	(214–640)	69	372	(266–503)
CHAPTER IV *Diseases of the blood and blood forming organs*						
Iron deficiency anaemia	9	312	(109–694)	19	165	(84–289)
CHAPTER V *Mental disorders*						
Anxiety state	17	91	(44–165)	41	91	(58–134)
Depressive disorder	41	231	(149–341)	82	169	(125–223)
Insomnia and sleep disorders	9	116	(40–258)	20	121	(62–209)
Transient situational disorders	13	201	(86–394)	28	144	(83–230)
CHAPTER VI *Discorders of the nervous system and sense organs*						
Dis of nervous system NEC[a]	17	306	(149–555)	16	188	(89–347)
Cataracts	12	305	(125–613)	15	191	(88–358)
Conjunctivitis	18	117	(58–209)	29	118	(69–187)
Other diseases of eye	16	195	(92–359)	21	202	(106–345)
Otitis externa	11	98	(38–203)	13	129	(56–254)
Wax in ear	40	105	(67–156)	38	131	(83–196)
CHAPTER VII *Diseases of the circulatory system*						
Myocardial infarction	30	264	(157–416)	17	279	(135–505)
Angina	36	182	(114–276)	36	252	(157–382)
Other chronic isch heart disease	26	174	(98–282)	30	260	(154–409)
Congestive cardiac failure	26	189	(107–308)	52	260	(177–368)
Left heart failure	14	231	(103–442)	10	210	(78–450)
Uncomplicated hypertension	160	226	(183–277)	191	197	(162–236)
Other cerebrovasc disorders	20	215	(111–373)	19	198	(100–348)
Peripheral vasc disorders	25	352	(197–578)	13	250	(107–490)
Varicose veins	18	169	(84–301)	22	105	(56–178)
CHAPTER VIII *Diseases of the respiratory system*						
URTI non-febrile	60	144	(101–199)	101	167	(127–214)
URTI febrile	44	203	(133–295)	33	137	(83–211)
Acute sinusitis	11	135	(53–280)	20	139	(72–242)
Tonsillitis	13	133	(57–261)	17	117	(57–212)
Tracheitis	12	121	(50–243)	17	98	(48–178)
Acute bronchitis	103	148	(113–190)	122	163	(128–205)
Catarrh	17	122	(59–220)	15	87	(40–163)
Hay fever	12	139	(57–279)	16	161	(76–296)
Influenza	22	151	(81–256)	19	133	(67–234)
Chronic bronchitis	24	117	(65–194)	10	111	(41–238)
Asthma	20	129	(67–223)	21	129	(68–220)
CHAPTER IX *Diseases of the digestive system*						
Diseases of teeth, etc	11	215	(84–444)	14	211	(94–405)
Diseases of the mouth, etc	9	166	(58–370)	14	146	(65–280)
Disorders of gastric function	22	124	(67–211)	29	156	(92–248)
Irritable bowel syndrome	11	143	(56–295)	20	138	(72–240)
Constipation	29	284	(167–451)	27	183	(105–295)
CHAPTER X *Diseases of the genitourinary systems*						
Urinary tract infection	30	244	(144–383)	68	173	(124–234)
Haematuria NEC	12	350	(144–705)	9	574	(200–1275)
CHAPTER XII *Diseases of the skin*						
Carbuncle and furuncle	14	355	(158–680)	11	330	(130–684)
Cellulitis and abscess of digits	27	566	(325–912)	29	414	(243–657)
Other cellulitis	33	312	(190–481)	34	271	(166–416)
Miscellaneous skin infections	12	503	(207–1013)	10	380	(141–812)
Contact dermatitis	32	160	(97–249)	34	144	(88–220)
Pruritus	9	142	(50–316)	18	162	(80–288)
Corns	14	755	(336–1448)	7	249	(72–609)
Chronic ulcer of skin	23	614	(334–1027)	23	345	(188–578)
Other diseases of skin	16	230	(109–423)	18	154	(77–275)
CHAPTER XIII *Diseases of the musculoskeletal system*						
Rheumatoid arthritis	12	191	(79–384)	11	70	(27–145)
Osteoarthritis	52	146	(99–207)	97	121	(92–156)
Non-specific arthritis	18	136	(67–242)	35	182	(112–277)
Shoulder syndrome	14	148	(66–284)	19	161	(82–282)
Other bursitis, etc	15	113	(52–212)	12	105	(43–210)
Other non-articular rheumatic disorders	19	132	(67–232)	23	125	(68–210)
Non-specific limb pain	30	179	(106–281)	45	186	(122–270)
Low back pain	44	138	(90–201)	43	117	(76–171)
Osteoarthritis of spine	10	153	(53–327)	19	177	(90–310)
Cervical spine problem	13	98	(42–192)	17	96	(46–173)
Intervertebral disc syndrome	25	173	(97–284)	19	138	(70–242)
Other back pain	7	163	(48–400)	12	209	(86–420)
CHAPTER XVI *Symptoms, signs and ill-defined conditions*						
Dizziness	19	143	(73–252)	39	160	(102–239)
Headache	9	111	(39–247)	17	114	(55–207)
Odema—localised or dependent	14	213	(95–409)	28	141	(82–226)
Chest pain	21	131	(69–224)	19	137	(70–242)
Cough	18	111	(55–198)	33	162	(98–249)
Nausea and/or vomiting	16	326	(154–601)	23	231	(126–387)
Abdominal pain	29	151	(89–239)	36	128	(80–195)
Malaise NEC	11	125	(49–259)	30	148	(88–234)
Rash NEC	6	92	(24–240)	16	166	(78–305)
Signs, symptoms NEC	17	230	(112–416)	16	206	(97–380)
CHAPTER XVII *Accidents, injury, poisoning and violence*						
Lacerations	14	127	(57–244)	11	88	(35–182)
Abrasions	10	248	(92–532)	12	228	(94–459)
Bruises and contusions	20	134	(70–233)	39	150	(95–224)
Adverse effects of medication	19	287	(146–504)	28	228	(132–364)

CI = 99% confidence interval
[a]NEC = not elsewhere classified

Many illnesses are self limiting and minor in nature. For these, detailed investigation is unwarranted and diagnosis often imprecise. Though this is a legitimate criticism of general practice based studies, it does not apply to the diagnosis of serious illnesses nor does it influence the results of this study, in which any bias in diagnostic quality is equal in index and control populations.

In using diabetes as an example of morbidity, we acknowledge the potential for some loss of information about insulin dependent diabetics, who sometimes receive care in hospital outpatient departments for other conditions when attending for review of diabetes. Nevertheless, most conditions so treated are brought back to the general practitioner, who is invariably responsible for any prescribed medication. An additional problem specific to diabetes concerns the two types of the disease, which may have differing aetiologies.[4] The study included approximately 18% of patients who were aged under 44 but the age at diagnosis, which might have provided a proxy for estimating the number of type 1 diabetics, is not known. In spite of the aetiological differences between type 1 and type 2 diabetes, there is an inference from this study that the pattern of concurrent disease is similar in both. The large number of significant findings are unlikely to have occurred if referable only to a portion of the index cases. A study of disease concurrence allows for making only limited conclusions about cause and effect. The vast majority of the diabetics were diagnosed before the study began, as were patients with many of the concurrent diagnoses. Self limiting illnesses of short duration (such as virus disorders) can be assumed to have occurred in established diabetics.

The method involves calculating an expected number of cases from a control population after standardising for age. By excluding persons present for only part of the study year, we have minimised the risk of underestimating prevalence in the control population (and therefore of overestimating relative prevalence in the index population), which might be attributed to inflation of practice patient registers. Another possibility of overestimating relative prevalence in index cases arises from the need for diabetics to consult more frequently (because of the danger of destabilising the diabetes), and once the person consults he may be more likely to report a secondary problem—a general practice equivalent of the Berkson bias. The extent of this bias is difficult to quantify since it can only be estimated in those morbidity rubrics for which we could be convinced from independent evidence that there is no association (positive or negative). Nevertheless, there were 153 male and 95 female diabetics who did not consult for any other condition during the year.

Set against these causes of overestimating relative prevalence in index cases, the control population inevitably includes all undiagnosed diabetics whose concurrent illnesses will inflate the prevalence in controls and potentially underestimate the relative prevalence in index cases. In this study we observed a diabetic person consulting rate of 7 per 1000 over the 12 month period, which is compatible with other contemporary studies,[5] though some would argue that there are at least as many people in the community with undetected diabetes and many more with impaired glucose tolerance.[6]

The main analysis reported in this study is based on 160 comparisons (80 morbidity rubrics in each sex). With multiple testing of this number and using the 99% confidence interval, we might expect one or two to be significantly higher or lower by chance if there were no real differences. For 62 of them (34 male and 28 female), the lower limit of the confidence interval exceeded 100 and there was no example of the upper limit below 100.

The study has shown associations between several infectious disorders and diabetes, providing a response to the comments of Tofte and Sabath that "although it is a frequently stated clinical axiom that diabetics are more susceptible to bacterial and fungal infections than non diabetics of similar age/sex and social economic backgrounds, there is a paucity of supporting evidence in the literature".[7] Mumps and rubella and some other viruses have been incriminated as aetiological factors for diabetes,[8] but the associations described here are concerned with virus disorders in existing diabetics. Vaginal thrush is widely recognised as a presenting symptom of diabetes and the strong associations between diabetes and fungal infections shown here are hardly surprising. In this study, the increased prevalence of skin infections suggests an increased susceptibility for diabetics to bacterial infection, though other published evidence is not so conclusive.[9]

The results for neoplasms provide a contrast to those for all other chapters in the disease classification. Pancreatic carcinoma and diabetes has been studied,[10] but otherwise the relationship between malignancy and diabetes is not well documented. This one year general practice based study involving nearly 2000 diabetics clearly has not the statistical power to detect associations of uncommonly occurring individual malignancies.

The concurrence of diabetes and hypothryroidism confirms widely held clinical opinion. There is good evidence of association between diabetes type 1 and the presence of thyroid autoantibodies and also gastric parietal cell autoantibodies,[11] and further supportive evidence of association with biochemical hypothyroidism.[12] There is no evidence of any such association among type 2 diabetics. Our study, however, includes diabetics of both types and it is unlikely that there were sufficient type 1 cases to account for this association by themselves.

Blindness is a well known problem for diabetics. Diabetic retinopathy is responsible for 10% of new cases of blindness, and diabetes is the leading cause of blindness in middle age.[13] Neovascular glaucoma is a particular complication of diabetic retinopathy, and chronic simple glaucoma and cataracts are more frequent in patients with diabetes.[13] The findings in this study are consistent with these observations.

The associations between diabetes and cardiovascular disease are the best documented and, in their total impact on the diabetic, the most serious. The nature of the association is uncertain

but there are predisposing risk factors common to diabetes and to cardiovascular disease generally. The findings of the study largely conform to other data.[3 5] The standardised person consulting ratios for myocardial infarction, and similar values for other ischaemic heart disease, accord with the observation that the risk of cardiovascular death in diabetics is at least twice that of non-diabetics.[5] The greater values of standardised person consulting ratios for females than for males (due to the reduced expected values in female controls) also accord with other data.[3]

Increased severity of periodontal disease amongst diabetics has been reported.[14] Standardised person consulting ratios for disorders of the teeth, though increased at the 5% level, did not achieve the 1% level used throughout this paper.

Emphysematous cholecystitits is a particular complication of cholecystitis in diabetics.[15] In this study, there were 12 females compared with five expected (SPCR 254, 99% CI 105–511) who were reported as having gall bladder disease.

Urinary tract infections and haematuria were both more likely in diabetics. A higher incidence of urinary tract infection in females though often asymptomatic has been reported before.[16]

This analysis of disease concurrence illustrated by diabetes has shown the usefulness of data gathered routinely in a general practice based morbidity study. It has provided, in a large cohort of diabetics, considerable support for widely held opinions about diabetes and in general accords with the findings of other epidemiological studies. In addition, areas of disease have been identified in which there are no materially relevant associations, including cancer and disorders in which allergy plays an important part. This morbidity study, which was concerned with nearly 300 000 persons, provides opportunities to examine data relevant to other index diseases.

The most appropriate acknowledgement in all studies involving several general practices is to all those involved in the considerable exercise of data capture, including both the general practitioners and the practice ancillary staff. In the preparation of this paper we are pleased to acknowledge the assistance of the Office of Population Censuses and Surveys, in particular the staff involved in the extensive programming exercises required. In addition, the observations of Dr Anna McCormick of the OPCS have been particularly helpful in both the design and execution of this study.

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