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Mortality during 25 Years of Follow-Up of a Cohort with Diabetes

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Background. Diabetes is one of the most common chronic diseases in Western populations. There have been few large published cohort studies of people with diabetes that have had more than 10 years of follow-up, and none other than the present one are in the UK. Such studies are important to understand the long-term fatal consequences of diabetes and their variation over time and between countries.

Methods. Cause-specific mortality was analysed in follow-up from 1966–1970 to December 1992 of 5783 members of the British Diabetic Association living in England and Wales during 1966–1970. Comparison was made with age-, sex- and calendar year-specific mortality by cause in the general population of England and Wales.

Results. During the follow-up 3399 (58.8%) subjects died. The relative risk of all-cause mortality in the cohort compared to the general population was 2.31 in women and 1.58 in men (both $P < 0.001$). Relative risks were greater for women than men at almost all ages and for each major diabetes-related cause of death. Absolute excess ('attributable') mortality rates were also greater in women than men, except at ages <50. Half the deaths in each sex were from circulatory diseases and only 3.4% were from renal disease. The relative risks of mortality for all-causes and circulatory diseases were particularly great at younger ages, but changed little with duration of follow-up. At ages <40 the relative risks for all-causes were 3.79 in men and 5.51 in women and for ischaemic heart disease were 10.44 and 25.25 respectively (all $P < 0.001$). At these ages one-third of deaths were due to acute complications of diabetes, suicides and accidents, whereas at older ages these accounted for only 4% of deaths.

Conclusions. The mortality rates at young ages in the cohort were around twice those in Sweden, Norway and Israel, suggesting that many of the deaths in England and Wales are preventable. The results also indicate a particular need for investigation and amelioration of cardiovascular risk factors in English and Welsh patients, especially women.

Keywords: diabetes mellitus, cohort, mortality, England and Wales

Diabetes is exceptional among chronic diseases in being a major cause of morbidity at virtually all ages. In childhood it is the second most prevalent chronic disease after asthma. By the age of 20 its cumulative incidence is the same as that for all cancers combined. It is important in young adulthood, and at older ages is one of the most common causes of death. Overall, the lifetime incidence in the UK is about 10%.[1]

Before the introduction of insulin in 1922, people with insulin-dependent diabetes (IDDM) had a life expectancy of 2–3 years. Since then, and with subsequent improvements in treatment, there have been large improvements in survival both for IDDM and for non insulin dependent diabetes (NIDDM). Diabetes is often not stated as the underlying cause of death on the death certificates of people with the disease, and in a substantial proportion is not mentioned at all on the death certificate.[2,3] Therefore, mortality of people with diabetes can only satisfactorily be assessed by cohort studies.

There have been relatively few large, long-term cohort studies examining mortality of people with diabetes by cause. For all ages, sizeable studies with about 10 years of follow-up have been conducted in Poland[4] and East Germany,[5] and there have been studies with longer follow-up than this in Japan[6] and the US.[7,8] For children with IDDM there have been studies with long-term follow-up in Denmark,[9] Norway,[10] the US,[11–13] Japan, Israel and Finland.[12,13] In Britain there have been no studies with follow-up appreciably beyond 10 years, and the only studies based on more than a few hundred subjects have been that by Shenfield *et al.*[14] in Edinburgh following 3113 subjects from 1968 to 1975, and the present cohort followed to mid-1973 by Armstrong *et al.*[15] and briefly reported with follow-up to 1979 by Fuller *et al.*[2] Since mortality in people with diabetes varies greatly by country and is changing over time,[12,13,16] there is a need for more recent UK data on a large enough cohort to enable examination of risks by

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cause, age and sex, and hence to draw implications for clinical care. We present here data on the mortality of nearly 6000 people with diabetes in England and Wales identified in the late 1960s, who have now been followed for up to 26 years during which over 3000 deaths have occurred.

SUBJECTS AND METHODS

The cohort was identified during 1 January 1966 to 1 January 1970 by A J Lea, now deceased. It consisted of all new members during that period, and some old members, of the British Diabetic Association (BDA) then resident in England and Wales. At the time of inauguration of the study, 25 years ago, identifying details on each subject were sent to the National Health Service Central Register (NHSCR), where they were 'flagged'. The NHSCR is a virtually complete population register of all residents of England and Wales, on which are recorded all deaths and emigrations since 1939. The flagging enabled notification of all deaths and emigrations that occurred in the study cohort since its inception, and also provided for future notification of these events. Of the subjects, 5928 were satisfactorily identified and flagged on the NHSCR, constituting approximately 95% of the original people with diabetes delineated by Dr Lea. The records of those not identified at the NHSCR are no longer available, and their exact number is not known. For the analysis we excluded a further 22 individuals because they were ≥85 years at the start of the follow-up period (see below), and 125 individuals because they had dates of death or emigration before their date of identification into the cohort. These latter apparent incongruities were possible because the BDA membership list was not immediately updated if a member died or left the country. There remained 5781 subjects who formed the cohort that was analysed.

Cause of death was coded to the revision of the International Classification of Diseases (ICD)[17] in force at the time of death registration—ICD-7 for deaths up to 1967, ICD-8 for deaths 1968–1979, and ICD-9 for deaths from 1979 onwards. For analysis, bridge coding of ICD revisions was conducted to give the ICD-9 categories shown in Table 2.

Since deaths coded to the underlying cause 'diabetes' might reflect a range of different short-term metabolic events or long-term degenerative complications, we examined the full statements on causes written on the death certificates of all deaths certified to diabetes at ages <40, and an age- and sex-stratified random sample (for logistic reasons in obtaining the certificates) of such deaths at ages ≥40.

For each cohort member, person-years at risk were calculated by age, sex, and calendar year, starting from the date during 1966 to 1970 when the individual had been identified for the study, and finishing at the date of death, emigration, loss to follow-up, 85th birthday, or 31 December 1992, whichever was earliest. Follow-up was truncated at age 85 because the quality of data on cause of death after this age is poor, national data to give expected death rates are not available by 5-year age group, and any failure to identify deaths by flagging would disproportionately dilute the apparent mortality rates over this age. Expected deaths by cause in the cohort were calculated by multiplying the age-, sex-, and year-specific person-years at risk within the cohort by corresponding national cause-specific mortality rates, using the computer program PYRS.[18] Standardized mortality ratios (SMR) were then calculated, as the ratio of observed to expected deaths. Confidence intervals of the SMR were calculated based on the Poisson distribution, and linear trends in risk tested as in Breslow and Day.[19] Comparisons of SMR between the sexes are complicated because the SMR are standardized to different (sex-specific) age distributions, although the effect of this in the present study is small because the age distributions of the two sexes are in fact similar. Nevertheless, for those analyses where comparisons between the sexes were of interest, we calculated comparative mortality factors (CMF), using as the common standard for both sexes, the total population of England and Wales in 1981. These CMF are referred to in the text, but not presented in the Tables since in practice they give sex comparisons similar to those of the SMR. Absolute excess mortality rates (sometimes called 'attributable' risks) were calculated by subtracting the expected from the observed number of deaths, and dividing by the person-years at risk.

Direct details about diabetes in the cohort members were only available to the extent that they had been collected at the inception of the cohort and published by Armstrong *et al.*[15] and Fuller *et al.*[2] but further information to infer likely characteristics and socioeconomic status was obtained from a survey in 1994 of 1302 current BDA members and certain statistics kept on BDA members overall (Murphy M, personal communication).

RESULTS

The age and sex distribution of the cohort, and the person-years at risk by age at entry, are shown in Table 1. Of the subjects, 1953 were aged <40 at entry to the cohort and 3828 were aged 40–84. The cohort members were followed for a total of 90 715 person-years, an

TABLE 1 *Cohort by sex and age at entry*

Age at entry (years)	Males (N)	Females (N)	Person-years of follow-up[a]	
			males	females
0–19	506	487	12 204.9	11 655.3
20–39	560	400	12 484.8	9068.7
40–59	896	707	14 952.8	12 343.1
60–84	945	1281	7235.3	10 688.7
Total 0–84	2907	2874	46 877.7	43 755.8

[a] Follow-up truncated at age 85.

average of 15.7 years per subject, with 22–26 years of follow-up for subjects surviving to the end of the study period. During the follow-up period 3090 deaths occurred at ages <85, 1517 in males and 1573 in females, 86 subjects are known to have emigrated, and 309 were censored from risk at age 85, leaving 2296 (40%) alive and under follow-up at the end of the study period. All of the subjects censored at age 85 (116 males and 193 females) died during follow-up. These deaths, which were not included in the risk analyses, were mainly certified to circulatory diseases (146 [47%]), diabetes (57 [18%]), and respiratory diseases (51 [17%]).

Table 2 shows mortality at ages <85 by cause. All-cause mortality in the cohort was significantly raised in each sex, but the relative risk was considerably greater in females (CMF = 2.45; 95% confidence interval [CI]: 2.29-2.62) than males (CMF = 1.68; 95% CI : 1.55–1.81) (the ratio of these CMF, 1.46, is the same as the ratio of the SMR for the two sexes [in Table 2, also 1.46]). About half of the deaths in each sex were from circulatory diseases, and again the CMF was appreciably higher in females (CMF = 2.45; 95% CI : 2.23–2.69) than males (CMF = 1.66; 95% CI : 1.51–1.81) (again similar ratio of CMF, 1.48, to that of SMR, 1.38). Since the sex ratio of the CMF proved in practice to be similar to that of the SMR, the CMF are not shown separately in the text hereafter. There were significantly raised SMR (at least $P < 0.05$) in each sex for deaths certified to diabetes, other disorders of pancreatic internal secretion, ischaemic heart disease, cerebrovascular disease, and pneumonia; in males for non-pancreatic endocrine and metabolic disorders; and in females for hypertensive heart disease, heart disease other than hypertensive or ischaemic, vascular disease other than of the cardiac or cerebral vasculature, digestive diseases, diseases of the urinary system (for which risk was also raised, but not significantly, in males), and injury and poisoning, especially accidental falls. Within the urinary system deaths, risks were raised similarly for nephritis (SMR = 1.75; 95% CI : 0.80–3.33 for males and SMR = 1.98; 95% CI : 0.86–3.90 for females) and other urinary system deaths (SMR = 1.43; 95% CI : 0.53–3.12 for males and SMR = 2.51; 95% CI : 1.30–4.38 for females). The raised mortality from non-pancreatic endocrine and metabolic disorders reflected three deaths from haemachromatosis, one from cystic fibrosis, one from thyrotoxicosis and one from cortico-adrenal insufficiency in men, and two from myxoedema, one from pituitary disease, and one from adrenal disease in women. The deaths coded to 'other disorders of pancreatic internal secretion' were all certified as hypoglycaemia. The borderline significantly raised risk of digestive system mortality in women ($P = 0.044$) reflected deaths from a wide range of causes with no obvious common factor. There were significant deficits of mortality (at least $P < 0.05$) in males from neoplasms, bronchitis, and respiratory diseases other than pneumonia and bronchitis. (The latter deficit was mainly due to a diminished number of cases of chronic airways obstruction, not further specified.) Site-specific analyses of cancer mortality will be reported elsewhere.

Deaths coded by the ICD rules to diabetes or hypoglycaemia (ICD 250, 251.0, 251.2) accounted for 38% of deaths under age 40 and 21% of deaths over this age. From examination of samples of the death certificates we estimate that at ages <40 these deaths were mainly due to acute hypo- or hyperglycaemia (29.7%), diabetes unspecified (21.6%), renal failure (27.0%), myocardial infarction (10.8%), and cerebrovascular accident (5.4%), whereas at ages ≥40 27.3% were due to myocardial infarction, 11.5% to cerebrovascular accident, and 12.6% to renal failure, with relatively few due to acute complications of diabetes (8.3%) or diabetes unspecified (0.5%). If one were to re-analyse all deaths using these recategorized causes for those initially certified to diabetes or hypoglycaemia, then at ages <40 myocardial infarction would account for 21.7% of deaths rather than the 17.6% on the basis of underlying cause, cerebrovascular accident for 6.4% rather than 4.6%, and renal failure for 12.1% rather than 1.9%. Deaths due to acute hypo- or hyperglycaemia (or certified to diabetes with no other cause mentioned, and therefore likely to be acute complications of diabetes) would account for 19.5% of deaths at this age, and suicide and accidents for 13.0%. At ages ≥40 years the impact of recategorizing deaths coded to diabetes would be smaller: adding these deaths to those certified by underlying cause would give 40.7% of all deaths due to myocardial infarction (rather than 35.1% based on underlying

TABLE 2 *Mortality of the cohort by cause*

ICD-9 code	Cause of death	Males			Females		
		No.	SMR[a]	(95% CI)	No.	SMR	(95% CI)
001–139	Infectious and parasitic	4	0.90	(0.24–2.29)	2	0.82	(0.10–2.94)
140–239	Neoplasms	198	0.83	(0.72–0.96)**	161	1.02	(0.87–1.19)
250	Diabetes mellitus	297	38.44	(34.31–43.07)***	355	39.77	(35.84–44.13)***
251	Other disorders of pancreatic internal secretion	3	96.46	(19.89–281.85)***	2	86.08	(10.43–310.92)**
240–246, 252–279	Other endocrine and metabolic diseases	6	3.31	(1.21–7.20)*	4	1.40	(0.38–3.57)
401–405	Hypertensive heart disease	9	0.81	(0.37–1.54)	23	2.13	(1.35–3.20)**
410–414	Ischaemic heart disease	567	1.90	(1.75–2.06)***	500	3.00	(2.75–3.27)***
420–429	Other non-pulmonary heart disease	32	1.02	(0.70–1.44)	58	1.83	(1.41–2.36)***
430–438	Cerebrovascular disease	141	1.43	(1.21–1.69)***	173	1.58	(1.36–1.84)***
390–398, 415–417, 440–459	Other vascular disease	44	1.03	(0.75–1.38)	53	1.37	(1.05–1.79)*
480–486	Pneumonia	73	1.33	(1.06–1.68)*	104	2.16	(1.79–2.62)***
450–466, 490–493	Bronchitis	27	0.44	(0.29–0.64)***	15	0.82	(0.46–1.36)
470–478, 487–489, 494–519	Other respiratory diseases	12	0.54	(0.28–0.94)*	12	1.55	(0.62–2.08)
571	Chronic liver disease and cirrhosis	5	1.43	(0.47–3.34)	4	1.57	(0.43–4.03)
577	Diseases of pancreas	1	0.87	(0.02–4.86)	2	1.89	(0.23–6.84)
520–570, 572–576, 578–579	Other digestive system diseases	17	0.92	(0.54–1.48)	26	1.55	(1.01–2.26)*
580–629	Diseases of genitourinary system	19	1.52	(0.92–2.38)	20	2.19	(1.34–3.38)**
580–599	diseases of urinary system	15	1.61	(0.90–2.66)	20	2.27	(1.38–3.50)**
E800–999	External causes of injury and poisoning	39	1.38	(0.98–1.89)	32	1.72	(1.18–2.43)**
E810–825	motor vehicle accidents	8	0.93	(0.40–1.83)	2	0.50	(0.06–1.81)
E880–888	accidental falls	4	0.89	(0.24–2.28)	14	2.29	(1.25–3.85)**
E950–959	suicide	10	1.46	(0.70–2.69)	7	1.95	(0.78–4.01)
001–999	All causes	1517	1.58	(1.50–1.66)***	1573	2.31	(2.20–2.43)***

[a] Standardized mortality ratio.
*$P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

cause), 12.7% to cerebrovascular accident (compared with 10.4% without recording) and 3.2% to renal failure (compared with 0.6% based on underlying cause), with 1.8% due to acute complications of diabetes and 1.9% to suicide and accidents.

All-cause SMR were greatest for those who were youngest at entry to the study, and diminished significantly ($P < 0.001$) with increasing age at entry (Table 3). For each age at entry, the relative risk was considerably greater for females than for males. Decreasing SMR with increasing age at entry were present for diabetes and ischaemic heart disease, and less uniformly for cerebrovascular disease, pneumonia, and diseases of the genitourinary system.

There was a steeper gradient of all-cause SMR in relation to attained age (Table 4) than to age at entry, and again the relative risks were greater for females than males at each age. Further subdivision of the youngest age group in the Table, which has the highest relative risks, leads to small numbers, but for all-causes high risks appeared to be present at each age (not shown in Table). The effects of age and sex were particularly striking for ischaemic heart disease: in the youngest age group in the Table, 0–49, women had an over 10-fold relative risk, and indeed further subdividing by age, the SMR for those <40 were 10.44 (95% CI : 5.71–17.52) in men and 25.25 (95% CI : 8.20–58.93) in women, based on 14 and five deaths

TABLE 3 *Mortality by age at entry to cohort, selected causes*

ICD-9 Code	Cause		Age at entry (years)						χ^2_1 trend
			0–39		40–59		60–84		
			No.	SMR[a]	No.	SMR	No.	SMR	
140–208	All malignant neoplasms	males	15	1.02	74	0.72**	103	0.87	
		females	15	1.34	50	0.85	92	1.06	
250	Diabetes mellitus	males	43	83.81***	124	39.86***	130	31.68***	***
		females	35	137.98***	116	48.78***	204	32.41***	***
410–414	Ischaemic heart disease	males	43	2.65***	252	2.04***	272	1.71***	**
		females	15	6.51***	150	3.60***	335	2.73***	***
430–438	Cerebrovascular disease	males	6	2.32	37	1.29	98	1.46**	
		females	6	3.89*	41	1.96***	126	1.45***	*
480–486	Pneumonia	males	4	4.11*	13	1.25	56	1.29	
		females	2	4.17	20	3.17***	82	1.99***	
580–629	Disease of genitourinary system	males	1	2.30	5	1.45	13	1.51	
		females	3	9.42**	7	3.18*	10	1.51	*
E800–999	Injury and poisoning	males	19	1.68*	9	1.05	11	1.31	
		females	5	1.55	11	2.42*	16	1.48	
E950–959	suicide	males	6	2.07	3	1.25	1	0.65	
		females	2	2.13	3	2.27	2	1.50	
001–999	All causes	males	147	2.57***	573	1.62***	797	1.45***	***
		females	96	3.84***	446	2.55***	1031	2.15***	***

[a] Standardized mortality ratio.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

respectively. There were also gradients of decreasing mortality risk with increasing age, although less consistently, for deaths certified to diabetes (not shown in Table) and cerebrovascular disease. For cerebrovascular disease the sex comparison was inconsistent by age, resulting in all-age relative risk that was only slightly greater for women than men. For non-cardiovascular disease mortality overall, relative risks were substantially greater for women than men at virtually every age, with, for instance, SMR of 6.14 for women and 2.36 for men at ages 0–19, and 1.78 for women and 1.10 for men at ages 80–84 years.

Excess mortality rates for all-causes (Table 4) were also greater in females than males, except at the youngest ages, but absolute death rates were slightly greater in males than females. For ischaemic heart disease, excess mortality rates were greater for males than females at ages <65 and the reverse at ages older than this, whereas absolute mortality rates were greater for males than females at each age group, although to a smaller extent at older than at younger ages. For cerebrovascular disease, in contrast, both excess and absolute mortality rates were greater in females than males at every age group except 75–84 years.

When all-cause SMR were considered in relation to both age at entry and age at death (Table 5), a large reduction in SMR with attained age was observed in each stratum by age at entry, whereas there was no significant or consistent independent effect of age at entry when stratified by attained age ($P = 0.16$). Similar analyses of the age relationships for specific causes of death were limited by small numbers, but for ischaemic heart disease, cerebrovascular disease, other cardiovascular disease, and all non-cardiovascular disease, broadly the same pattern occurred of a large decrease in SMR with attained age and little independent effect of age at entry.

Table 6 shows all-cause SMR by time since entry to the cohort for those entering aged <15 years, for whom cohort entry is likely to have been soon after diagnosis (Murphy M, personal communication). There was some indication of an increase in SMR with duration, although it was not significant, in males, and no trend in females or for both sexes combined. Analyses by

TABLE 4 *Comparison of relative risks, excess risks and absolute risks of mortality from ischaemic heart disease, cerebrovascular disease, and all causes, by attained age and sex*

		Males					Females				
		0–49	50–64	65–74	75–84	Total 0–84	0–49	50–64	65–74	75–84	Total 0–84
Ischaemic heart disease	No. of deaths	35	154	229	149	567	13	72	203	212	500
	SMR[a]	3.47	2.23	2.01	1.42***	1.90	11.27	4.67	3.33	2.38***	3.00
	Excess rate in cohort[b]	104	703	1591	1253	573	59	590	1607	2412	762
	Absolute rate in cohort[b]	146	1272	3173	4253	1210	64	751	2297	4161	1143
	Expected rate[b,c]	42	569	1582	3000	637	5	161	690	1749	381
Cerebrovascular disease	No. of deaths	5	13	55	68	141	5	13	74	81	173
	SMR[a]	2.79	1.07	1.57	1.37	1.43	4.01	1.66	2.16	1.23**	1.58
	Excess rate in cohort[b]	13	7	277	523	90	19	54	450	296	146
	Absolute rate in cohort[b]	21	107	762	1941	301	25	136	837	1590	395
	Expected rate[b,c]	8	100	485	1418	211	6	82	387	1294	249
All causes	No. of deaths	131	349	535	502	1517	82	233	574	684	1573
	SMR[a]	3.15	1.87	1.52	1.32***	1.58	4.20	2.83	2.48	1.97***	2.31
	Excess rate in cohort[b]	372	1345	2530	3479	1187	309	1571	3879	6606	2040
	Absolute rate in cohort[b]	545	2883	7414	14 330	3236	405	2430	6494	13 426	3595
	Expected rate[b,c]	173	1538	4884	10 851	2049	96	859	2615	6820	1555

[a] Trend in SMR with age significant at * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
[b] Rate per 100 000 person-years.
[c] Rate that would be expected in the cohort if general population rates applied.

TABLE 5 *Relative risks[a] of all-cause mortality by age at entry to study and attained age*

Sex	Age at entry (years)	Attained age (years)								
		0–19	20–29	30–39	40–49	50–59	60–69	70–79	80–84	All ages
Males										
	0–19	3.10	1.89	5.70	2.99	—	—	—	—	3.46
	20–39	—	4.77	4.17	2.74	1.94	0.56	—	—	2.36
	40–59	—	—	—	2.67	1.95	1.69	1.30	0.89	1.62
	60–84	—	—	—	—	—	1.77	1.45	1.25	1.45
	All ages	3.10	2.54	4.80	2.72	1.95	1.69	1.42	1.21	1.58
Females										
	0–19	6.01	5.85	5.00	0.00	—	—	—	—	5.15
	20–39	—	10.06	4.58	3.49	3.14	1.20	—	—	3.47
	40–59	—	—	—	3.14	2.67	2.69	2.50	0.68	2.55
	60–84	—	—	—	—	—	2.42	2.33	1.75	2.15
	All ages	6.01	6.73	4.76	3.25	2.77	2.56	2.36	1.70	2.31

[a] Standardized mortality ratios.

TABLE 6 *Relative risks of all-cause mortality by duration since entry to cohort by sex, for those under age 15 years at entry*

	Duration since entry (years)											
	0–4		5–9		10–14		15–19		⩾20		All durations	
	No.	SMR[a]	No.	SMR	No.	SMR	No.	SMR	No.	SMR	No.	SMR
Males	2	2.06	5	3.89*	2	1.40	5	3.51*	11	6.33***	25	3.65***
Females	3	5.98*	2	3.51	2	3.19	4	5.80*	3	3.19	14	4.20***
Both sexes	5	3.39*	7	3.78**	4	1.95	9	4.26***	14	5.23***	39	3.83***

[a] Standardized mortality ratio.
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.
χ^2_1 test for trend with duration males: $P = 0.08$ (+ve trend)
females: $P = 0.68$ (−ve trend)
both sexes: $P = 0.26$ (+ve trend)

calendar period (not shown) gave results similar to those by duration.

DISCUSSION

The study cohort provides much the largest published follow-up of people with diabetes in Britain, but certain points should be noted in interpretation of it.

The study population was defined by membership of the BDA, rather than direct evidence of diabetes. Of the members, 99% were in fact individuals with the disease,[2] however, so the degree of dilution by non-diabetic subjects will have been negligible.

We estimate that the subjects constituted about 5% of all people aged <85 with diabetes in England and Wales at the time of entry to the study, based on contemporary prevalence rates of diabetes.[20] The BDA members are a self-selected group who might be more health-conscious and careful in their diabetes control, diet, and clinic attendance, than non-members, and therefore their mortality might also be less. Although we do not have direct information on this for the study cohort, 27% of current BDA members are from social grades A and B (professional and managerial) compared to 16% of the national population (Murphy M, personal communication), implying that their experience

may indeed be somewhat better than average. Potential for selection applies particularly to those with NIDDM, for whom a smaller proportion of all affected people in the country are members (currently estimated at 12%) and less to people with IDDM (of whom it is currently estimated 38% are members). The proportion of insulin-treated people who are members does not diminish with age, but because diabetes at older but not younger ages is mainly NIDDM, the current membership forms a larger proportion of all people with diabetes at young ages (currently 40% of those aged <20 years) than at older ages (19% of those aged ≥60). This also appears to be true of the cohort members at entry to the study, with 34% aged <40 years compared to, we estimate, 13% nationally based on prevalence rates at the time.[20] There is no appreciable geographical selection in BDA membership, however, with substantial proportions of members coming from each NHS region. The problem of potential selection, in different form, has also occurred with other published studies with ≥20 years of follow-up, where the subjects have come from centres of excellence in diabetes care, for instance the Joslin Clinic[8] and the Steno Memorial Hospital.[9]

We did not have information on the treatment of cases. In previous British population-based data, however, almost all patients with diabetes aged <40 years had IDDM,[14] and among current BDA members, 96% of individuals with diabetes aged <40 are insulin-treated (Murphy M, personal communication). At these ages almost all insulin-treated patients are insulin-dependent,[21] so it is likely that almost all of the cohort entering the study at ages <40 were insulin-dependent, and in that sense were representative of people with diabetes in general in England and Wales. In previous British data the great majority of people with diabetes aged ≥50 had NIDDM,[14] whereas among current BDA members this is less striking: 34% of those aged 40–59 and 58% at ages ≥60 have NIDDM, so our cohort entering at these ages may be similarly mixed, and hence less representative of prognosis in those with diabetes in general. This is particularly so because the date of entry to risk in the study was based on a date of membership of the BDA, not the date of incidence of diabetes, and therefore in some subjects (mainly older ones, see below) diabetes will have been incident several years before entry. In a sample of 62 subjects from the present cohort who had survived to 1975, 51% had diabetes for <5 years at entry to the study, 15% for 5–9 years, and 34% for ≥10 years.[15] Further complicating interpretation, at older ages most insulin-treated patients are not insulin-dependent.[21]

Causes of death in the analysis were taken from those stated on death certificates, which is appropriate for comparison of the cohort mortality with that in the general population, but care is needed in comparing the results with those from analyses where the cause was classified on the basis of case-note information.[14,22] The deaths coded to the underlying cause diabetes were correctly categorized according to ICD coding rules, but these rules give a misleading result if the purpose of the analysis is to determine the contribution of chronic and acute complications to mortality in patients with diabetes. We therefore examined the effect of re-coding these deaths according to the complication of diabetes responsible for the death: the effect of this is taken into account when discussing individual causes below.

As in other large cohort studies of people with diabetes, the general population mortality rates used as the comparison will have included people in the general population with diabetes, and hence the SMR for diseases associated with diabetes will be slight underestimates of the values that would have been obtained with the ideal comparison group of the general population minus people with diabetes. This inevitably occurs in all studies using population comparisons, since data on rates in the general population excluding people with diabetes do not exist. The effect is small for causes other than diabetes, but it should be noted that the relative risks for the ICD category diabetes, itself, are substantially a reflection of the proportion of people with diabetes in the general population compared to the study cohort.

The raised risks of cardiovascular and cerebrovascular disease mortality in the cohort accord with numerous previous reports.[4,6,8,23] The small proportion of deaths from renal disease, however, contrasts with certain cohorts in other countries, notably cohorts with IDDM in Denmark,[24] Japan[22] and the US,[11] where 29% or more of deaths were from renal disease, and subjects with NIDDM in Japan,[6] 13% of whom died of renal disease. Even if deaths coded to diabetes were re-coded to renal disease if this appeared to be the actual cause of death in that individual, renal disease still constituted only 12.1% of deaths at ages <40 and 3.2% at ages older than this in the present cohort.

Cirrhosis mortality has been found to be excessive in cohorts of Scottish men[14] and French and Japanese subjects of both sexes[6,25] with diabetes, but was not raised in the present data. To the extent that the previous association may have been due to alcoholism leading to diabetes,[25] the absence of association in the present study might have been because people with alcoholism who develop secondary diabetes might be less likely to join the BDA than other people with diabetes.

The significantly low SMR for bronchitis in men implies that they smoked substantially less than the general population, and their low SMR for malignancies, mainly due to a significant reduction in lung cancer (Swerdlow & Jones, unpublished), supports this. The lack of reduction in these SMR for women, however, implies that their smoking habits have not been curtailed as successfully. Given the large relative risks of ischaemic heart disease mortality in women, this is of concern, and an area where greater preventive efforts are needed.

The raised relative risk for bronchopneumonia is difficult to interpret, and may be at least in part an artefact: until 1984 this cause was often coded as the underlying cause of death on death certificates in England and Wales when it was probably in fact a 'terminal event' incorrectly assigned as underlying.[26] It seems likely that this occurred more for diabetes-related deaths than for other causes[26] and hence it could have inflated the apparent SMR for bronchopneumonia in cohort members.

The substantial mortality at young ages from acute complications of diabetes, suicide and accidents in our data is seen also in several other countries,[10,22] and indicates a large proportion of deaths that are potentially preventable.

One of the most striking features of the results was the markedly greater relative risks of mortality in women than men in many of the analyses. In cohort studies of adults with diabetes the greater all-cause relative risks in females than males is a usual[8,14,23,27] but not universal[28] finding. At younger ages, and for subjects with IDDM, however, while some studies have found greater relative risks in females,[8,14,23,29] as we did, several have not.[10,11,30–32] Greater relative risks of ischaemic heart disease mortality or incidence in females than males with diabetes have again been found in several studies[8,23,27,33,34] but not all.[6,23,28] The absolute rate of IHD was greater in men than women in our data (although only slightly so in the oldest age group), but the larger relative risks, and for all ages larger excess rate, in women indicate a likely greater potential for prevention of the diabetes-related excess in women. For women the raised risks of ischaemic heart disease in subjects with diabetes have not been explicable by known risk factors for ischaemic heart disease, other than diabetes itself, but for men studies have differed on whether there is an independent effect of diabetes.[28,34] A specific diabetic cardiomyopathy has been hypothesized to explain the risk,[33] but endothelial injury caused by high glucose levels, or other mechanisms, might be responsible.[35] The greater relative effect of diabetes on ischaemic heart disease mortality for women than men has not been explained. In our population the difference may in part relate to smoking, since our data on bronchitis and lung cancer imply that this has been reduced for men but not women with diabetes compared to the general population in England and Wales. It would seem worthwhile also, however, to investigate the possible role of oestrogens in ischaemic heart disease aetiology in diabetic and non-diabetic women.

For cerebrovascular disease, relative risks of mortality were slightly greater in women than men, reflecting greater female than male relative risks at ages <75, and the reverse at ages 75–84. At all but the oldest ages, the excess rates and absolute rates of mortality were also greater in women than men, unlike the small male excess in the general population, again implying the particular potential for prevention of diabetes-related mortality in women. The previous literature has mainly[8,14,23] but not entirely[4,6] found greater cerebrovascular disease relative risks in females than males, but has not provided substantial analyses of this by age. There is evidence from most but not all studies that there is an independent effect of diabetes on risk of stroke incidence or severity, and hence on stroke mortality.[36]

In our data as in previous studies,[3,8,14] the all-cause SMR decreased with attained age beyond about age 40. This finding is not simply a reflection of the greater relative risk of death for people with IDDM (generally young) than NIDDM (generally older), since it occurred steadily throughout the age range, and has been found separately in insulin-treated and non-insulin treated subjects.[14,37] There is limited previous information on cause-specific SMR by age, but the available data generally accord with the present results that ischaemic heart disease[3,4,6] and cerebrovascular disease[4] SMR decrease with age, although one study did not find this for ischaemic heart disease after adjusting for other risk factors.[28] In one analysis a decline in the cardiovascular disease SMR with age was shown in insulin-treated subjects considered separately.[37] The steeply increasing excess mortality rates with age for ischaemic heart disease and cerebrovascular disease in our data, however, indicate that although the cardiovascular risks of diabetes are less than multiplicative with age, they are much more than additive.

Kessler's[8] large study of patients with diabetes in Boston, which like the present study could not directly separate IDDM from NIDDM, found that in each sex SMR of patients with diabetes incident at any age <40 were generally greatest at ages 30–39. Studies of cohorts with IDDM suggest the same conclusion in each sex[11] or for both sexes combined.[9,32] Our data showed this pattern for males, but for females entering

TABLE 7 *Comparison of British Diabetic Association (BDA) cohort mortality rates with those in other recent cohort studies of young subjects with diabetes*

Authors	Country	Years of follow-up	Attained ages	Mortality rate[a] in published cohort, per 100 000 (no. of deaths)		Mortality rate[a] in BDA cohort at same ages, per 100 000 (no. of deaths)
Dorman *et al.*[11]	US	1950–1981	0–34	Males	877 (72)	373 (42)
				Females	911 (66)	203 (31)
DERI[13]	US	1965–1989	0–39		556 (58)	342 (108)
DERI[12]	Israel	1965–1984	0–37		185 (9)	332 (98)
DERI[12]	Japan	1970–1984	0–37		681[b] (48)	314[b] (98)
DERI[13]	Finland	1965–1989	0–39		279 (172)	342 (108)
Joner & Patrick[10]	Norway	1973–1988	0–29		108[b] (20)	230[b] (45)
Sartor *et al.*[30]	Sweden	1977–1985	0–24		75[b] (10	222[b] (29)
Nyström *et al.*[31]	Sweden	1983–1987	15–39		156[b] (6)	355[b] (103)

[a] Age-standardized when age-specific data published for the cohort, and sex-specific when such data published.
[b] Crude rate.

the study before age 40 the greatest relative risk was at youngest ages.

For diabetes at young ages, cohort studies from various countries have now published data on mortality, and the English and Welsh results do not compare favourably with several of them (Table 7). Although the absolute death rates in England and Wales were similar to or below those in the US[11,13] and Japan,[12] they were greater than those in Finland[13] and about twice or more those at the same ages in Israel,[12] Norway,[10] and Sweden,[30,31] indicating considerable potential for prevention. The Scandinavian and Israeli cohorts were population-based, unlike ours, but this is unlikely to be the reason for their better mortality than our cohort, and indeed might indicate that our data underestimate the difference between England and Wales and these countries, since, as discussed above, our cohort may have had if anything a better prognosis than people with diabetes overall in England and Wales. The Scandinavian and Israeli data also differ from ours in that they included all cases from the date of incidence, but our results by duration do not suggest that this is likely to explain the worse mortality in England and Wales.

For most age groups in the study, analyses of risk in relation to duration since entry to follow-up would be difficult to interpret because of possible large variation in the duration of diabetes before entry. For cases entering in childhood, however, this will be a much less marked problem: they cannot have had diabetes for longer than their age when they entered the cohort, and usually far less since incidence in childhood peaks around age 12. Furthermore, in practice most children join the BDA at incidence of the disease, often when their paediatrician gives them an information pack when they first attend hospital. The age distribution at cohort entry of cohort members entering aged <15 was very similar to the usual age distribution of age of onset of childhood diabetes. We therefore conducted the analyses of risk in relation to duration only in children. The analyses did not show any significant increase in relative risk with increasing duration of diabetes. It should be noted that since calendar period is highly confounded with length of follow-up in our data (and in most other studies), it is possible that improvements in treatment over time have improved prognosis, while increasing duration of diabetes has had an opposing effect.

There are few previous studies of childhood onset diabetes with similarly long follow-up, with which to compare the present results on the effects of duration of diabetes. Dorman *et al.*[11] in the US found little if any relation of age-specific death rates to duration, whereas in Norway[10] duration ($\leqslant 15$ years) was found to be negatively associated with mortality. In Finland[29] and in Kessler's study in the US,[8] SMR increased with duration of disease, and in Denmark[9,32] relative mortality was greatest at 15–30 years from diabetes incidence, but thereafter was less raised (although still above that in the general population). It was suggested that the pattern in Denmark represented high mortality from renal complications in a susceptible subset of the population at 15–30 years after onset, followed by lower mortality in the cohort survivors, because of selection, after the subset had deceased.[9] In our subjects, however, too few deaths occurred from renal failure for this to have an appreciable effect on the all-cause mortality patterns. Of more concern, and needing preventive measures, was the high proportion of

mortality in young British subjects from acute diabetic complications, suicide and accidents, and the high relative mortality from cardiovascular diseases in women at all ages.

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