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The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65)

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Abstract

Aims To develop a model for estimating the immediate and long-term healthcare costs associated with seven diabetes-related complications in patients with Type 2 diabetes participating in the UK Prospective Diabetes Study (UKPDS).

Methods The costs associated with some major complications were estimated using data on 5102 UKPDS patients (mean age 52.4 years at diagnosis). In-patient and out-patient costs were estimated using multiple regression analysis based on costs calculated from the length of admission multiplied by the average specialty cost and a survey of 3488 UKPDS patients' healthcare usage conducted in 1996–1997.

Results Using the model, the estimate of the cost of first complications were as follows: amputation £8459 (95% confidence interval £5295, £13 200); non-fatal myocardial infarction £4070 (£3580, £4722); fatal myocardial infarction £1152 (£941, £1396); fatal stroke £3383 (£1935, £5431); non-fatal stroke £2367 (£1599, £3274); ischaemic heart disease £1959 (£1467, £2541); heart failure £2221 (£1690, £2896); cataract extraction £1553 (£1320, £1855); and blindness in one eye £872 (£526, £1299). The annual average in-patient cost of events in subsequent years ranged from £631 (£403, £896) for heart failure to £105 (£80, £142) for cataract extraction. Non-in-patient costs for macrovascular complications were £315 (£247, £394) and for microvascular complications were £273 (£215, £343) in the year of the event. In each subsequent year the costs were, respectively, £258 (£228, £297) and £204 (£181, £255).

Conclusions These results provide estimates of the immediate and long-term healthcare costs associated with seven diabetes-related complications.

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Keywords Type 2 diabetes mellitus, UKPDS, healthcare costs, diabetes-related complications

Abbreviations GLM, generalized linear models; UKPDS, UK Prospective Diabetes Study; MI, myocardial infarction; IHD, ischaemic heart disease; ICD, International Classification of Disease

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Introduction

The range of therapies to prevent, delay or treat Type 2 diabetes-related complications is rapidly expanding, and it is increasingly expected that their costs and benefits should be properly evaluated before they are widely adopted. Recent economic evaluations of policies for the management of Type 2 diabetes mellitus have shown that the increased costs of implementing more intensive blood glucose and blood pressure control policies are partly offset by substantial savings associated with treating fewer diabetes-related complications [1,2]. As future savings from reducing or preventing diabetes complications may have a large effect on the overall costs of other diabetes therapies, it is important to have accurate estimates of the medical costs of diabetes-related complications.

Many costing studies have documented the total burden of diabetes to the health system and society, with varying focus on the impact of diabetes-related complications [3]. While these aggregate cost of illness studies quantify the scale of the problem, they convey no information on the cost-effectiveness of existing or alternative interventions. Such analyses require patient-level data collected prospectively in a well-designed clinical trial, or the use of models that simulate the impact of alternative interventions on the probability and cost of experiencing diabetes-related complications [4,5]. A small number of studies have reported cost estimates for a limited range of complications [6–9], but a recent review of the literature concluded there are '… no recent papers that provide comprehensive patient-level cost estimates for the majority of relevant diabetic complications' [7].

This scarcity of cost data is a serious handicap for researchers intending to evaluate alternative interventions for the management of Type 2 diabetes. The purpose of this study is to address this deficiency using prospectively collected data from the United Kingdom Prospective Diabetes Study (UKPDS), a large trial of therapies for diabetes. A regression-based approach is employed to estimate the short-term and long-term annual hospital and non-hospital costs associated with seven major diabetes-related complications: myocardial infarction (MI); stroke, angina or ischaemic heart disease (IHD); heart failure; blindness in one eye; amputation and cataract extraction.

Subjects and methods

Research setting and study population

The UKPDS was conducted from 1977 to 1997 in 23 participating centres in England, Scotland and Northern Ireland. A total of 5102 patients with newly diagnosed Type 2 diabetes were recruited to the study, with a mean age at entry of 52.4 years (SD 8.8 years). Of the study population, 58% were men, and in regard to ethnic composition 81% were Caucasian, 10% were Indian/Asian, 8% were Afro-Caribbean, and 1% were from other ethnic groups. From this total, eligible patients were then randomized into blood glucose control and blood pressure control studies. The median duration of follow-up in the study was 10.3 years, and this generated 55 942 patient years of data. Details of the study design and the main clinical results have been published elsewhere [10].

Identification of clinical events

All patients attended UKPDS clinics every 3 or 4 months for the duration of the study. At each visit they were assessed to determine the occurrence of any clinical events or hospital episodes since the previous visit. Full clinical information on the event was obtained, and this was presented to the UKPDS Endpoint Adjudication Committee where two clinical assessors independently classified the event into predefined categories based on the 9th revision of the International Classification of Diseases (ICD9) codes. If any disagreements could not be resolved by arbitration, the information was submitted to a further panel of assessors for a final decision.

Resource use data

Information on hospital in-patient stays was collated by each clinic based on patient interviews at every clinic visit, death records and hospital records. Where an in-patient stay had occurred, details were obtained from the relevant hospital of dates of admission and discharge, reasons for admission, and any major procedures undertaken. All hospital episodes were subsequently allocated to one of 40 national specialty codes [11] using information from the hospital or assessment by a panel of two clinicians based on reason for admission, ICD code and/or the procedures undertaken. In approximately 16% of cases (predominantly in the earliest years of the study) the length of stay was not recorded and so multiple imputation methods were applied to replace the missing data [12]. The variance was increased according to standard rules [13] to reflect the uncertainty surrounding the missing data. The cost of each episode of hospitalization was estimated by multiplying the length of stay by the average cost of the respective specialty, based on an average (after adjusting for inflation) of the Department of Health's NHS Trust Financial Returns (TFR2) for 1997/8 and 1998/9 [14]. The average cost per day of the 10 specialties most frequently allocated to the hospital episodes of UKPDS patients, and the mean length of stay of recorded episodes in each specialty, are reported in Table 1. These specialties accounted for just over 80% of all episodes of UKPDS patients over the duration of the study. The average cost per patient day ranged from £165 in the specialty Other Medicine to £534 in Ophthalmology and the average length of stay ranged from 13.6 days in Neurosurgery to 3.6 days in Ophthalmology. After multiplying the cost per patient day by the length of stay for each episode the costs were then aggregated into annual costs for each patient relative to their entry into the study (which coincides with diagnosis of diabetes).

Information on non-in-patient health care resources was obtained using a different method. A cross-sectional survey of 3488 UKPDS patients was conducted between January 1996 and September 1997, using a questionnaire distributed at clinic visits or by post to patients who did not attend clinics during the

Table 1 Cost per day of the 10 specialties that were most frequently allocated to the hospital episodes of UKPDS patients

Specialty	Proportion of all episodes, %	Cost per patient day*	Mean length of stay (days) of recorded episodes
Cardiology	20	£408	7.7
Other medicine	11	£165	6.4
General surgery	9	£266	8.6
Urology	8	£256	5.6
Orthopaedics	8	£266	11.6
Gastroenterology	6	£224	6.7
Ophthalmology	6	£534	3.6
Gynaecology	4	£318	6.8
Neurosurgery	4	£421	13.6
Oncology	4	£340	9.4
Total	80		

*Source: Annual financial returns of NHS trusts (TFR2 return), 1997/98 and 1998/99 [14].

Table 2 Diabetes-related complications included in the regression analysis, with diagnostic definitions and number of first events in each category

Category	Predefined diagnostic definitions	Number of first events
Myocardial infarction	ICD9 Code 410	828
Stroke	Major stroke with symptoms that persist more than 1 month (ICD9 Codes 430 to 434.9 and 436)	271
Ischaemic heart disease	ICD9 Code 411 to 414.9	319
Heart failure	ICD9 Codes 428 to 428.1	166
Blindness in one eye	ICD9 Code 369 to 369.9	163
Amputation	Major limb complications requiring amputation of digit or limb for any reason (ICD9 Codes 5.845 to 5.848)	67
Cataract extraction	ICD9 Codes 5.143 to 5.146	297

survey period. This survey recorded information on all home, clinic, and telephone contacts with general practitioners, nurses, podiatrists, opticians, and dieticians, and with eye and other hospital out-patient clinics over the 4 months prior to the survey. The total costs over this period were estimated by multiplying the number of contacts by unit costs for each type of contact, derived from UKPDS clinics and from published sources [15], and the resulting total cost was then annualized.

Methods of analysis

We examine the relationship between healthcare costs and seven clinical event categories defined in Table 2 [16]. The number of first events in each category experienced by patients during the study is also reported. These ranged from 828 first non-fatal MIs to 67 first amputations.

Hospital in-patient costs are estimated for each of these seven complications. Previous studies of diabetes-related complications have shown that their costs have a distinct profile over time [17]. To address this, we estimate both the immediate or acute impact of the first diabetes-related complication (i.e. the effect in the year the complication occurs) and the long-term impact (i.e. the effect in all subsequent years) on in-patient costs.

The occurrence of complications also has an impact on non-in-patient costs, as many patients will require subsequent care and rehabilitation. However, because data on these costs were obtained from a single cross-sectional study, there is insufficient information to distinguish between each type of diabetes-related complication. Consequently, in the analysis of non-in-patient costs we combine complications into two major groupings: macrovascular complications (MI, stroke, IHD, heart failure) and microvascular and eye-related complications (blindness in one eye, amputation and cataract extraction).

Statistical analysis

Healthcare cost data often have several characteristics that must be addressed through the careful selection of appropriate statistical analyses. Typically, within a defined period (e.g. 1 year) a significant proportion of individuals have no contact with some types of healthcare providers and so incur no costs. However, amongst the individuals who do make use of health services, the distribution of costs is frequently highly skewed due to the presence of relatively few individuals incurring very high healthcare costs [18–20].

To estimate the cost of various complications we employ a two-part model in our analysis. In the first part, logistic regression is used to model the probability of incurring some hospital costs within a single patient-year time period. The dependent variable is set equal to 1 in any patient year an individual incurs costs. To determine the impact of various clinical events on the probability of attending hospital we include an indicator variable for each event and variables to adjust for age (centred by deducting 55 from current age) and sex. In the second part the total hospital costs incurred, conditional on incurring any costs, is estimated. As the events amputation and cataract extraction are treatments requiring hospitalization, we exclude them from the first-stage equation (i.e. the probability of attending hospital is set equal to 1).

When modelling the second part of the model it is important to recognize that the positive component of hospital costs is skewed and hence some episodes with extremely high costs can overly influence the model's parameters. To model these data we employ a generalized linear model (GLM) [21], which assumes patient characteristics and complications have a multiplicative effect on costs (see Statistical Appendix for further discussion). Estimates of the probability of incurring costs, the costs conditional on a cost being incurred and the expected cost (the product of probability and conditional cost) can be calculated using the model. Similar methods were used to estimate the likelihood that non-hospital costs were incurred within a single time period of 4 months (the period covered by the survey) and the total non-hospital costs incurred conditional on incurring any costs. These costs were then annualized.

Results

Hospital in-patient costs

Table 3 reports the coefficients and standard errors for the two-part model that can be used to predict hospital in-patient costs. The first part is a logistic regression equation to model the annual probability of incurring some hospital in-patient cost. In the second, a GLM is used to model cost of hospitalization conditional on at least one event occurring and the multiplicative effect of each coefficient is also reported to assist in interpretation.

All equations include variables representing the patients' age and sex, and sets of indicator variables for the occurrence of diabetes-related complications in the year in question, or in any previous year. These equations can be used to estimate the annual hospital costs based on the patient's characteristics and history of complications (the Statistical Appendix below contains a worked example).

Table 4 reports predictions from the logistic regression equations for an individual with characteristics set to reflect the average values for the UKPDS study population (i.e. a male aged 58.6 years) for the first complication of any type. The second column of the table shows the annual probability of this individual incurring any hospital in-patient costs. Patients who had no complications had a probability of incurring any hospital in-patient costs in any single year of 0.06; that is, approximately 6% of patients who did not have any diabetes-related complications in a given year nevertheless were admitted to hospital as an in-patient and consequently incurred some hospital costs. Table 4 also reports the annual probability of incurring any hospital costs for each type of event for

Table 3 Regression equations to derive annual probability of incurring hospital costs, and costs of hospital care conditional on incurring a cost (5102 patients and 55 942 patient years)

	Part 1: Equation to derive annual probability of incurring hospital costs		Part 2: Equation to derive annual cost of hospital care, conditional on costs being incurred		
Variable	Coefficient	Standard error	Coefficient	Standard error	Multiplicative effect
Constant	–2.674**	0.036	7.902**	0.043	
Current age –55 (years)	0.017**	0.002	0.013**	0.002	1.01
Male (= 1)	–0.108**	0.041	–0.106*	0.052	0.90
Event during year indicator					
Fatal MI	3.743**	0.137	–0.485**	0.107	0.62
Non-fatal MI	4.091**	0.148	0.696**	0.067	2.01
Fatal stroke	4.108**	0.356	0.508	0.279	1.66
Non-fatal stroke	2.087**	0.172	0.987**	0.136	2.68
Ischaemic heart disease	2.363**	0.133	0.627**	0.128	1.87
Heart failure	2.822**	0.191	0.508**	0.115	1.66
Blindness in one eye	1.330**	0.198	0.541**	0.204	1.72
Amputation	—	—	1.202**	0.253	3.33
Cataract extraction	—	—	–0.493**	0.134	0.61
History of event†					
Non-fatal MI	0.809**	0.083	0.348**	0.076	1.42
Non-fatal stroke	0.328*	0.134	0.155	0.141	1.17
Ischaemic heart disease	0.812**	0.083	0.405**	0.077	1.50
Heart failure	1.016**	0.135	0.477**	0.146	1.61
Blindness in one eye	0.471**	0.135	0.147	0.136	1.16
Amputation	0.309	0.216	0.358	0.207	1.42
Cataract extraction	–0.093	0.105	–0.316**	0.142	1.17

*$P < 0.05$; **$P < 0.01$.
†Refers to events that occurred in previous patient years.
Part 1 is derived using a logistic regression model, part 2 is derived using a generalized linear model. MI, Myocardial infarction.

Table 4 Estimated probability of incurring some hospital in-patient costs, estimated annual hospital in-patient costs conditional on cost being incurred, and expected mean cost, for a representative individual by first diabetes-related complication, during year of complication and in subsequent years*

Complication	Mean (95% CI) probability of incurring some hospital in-patient costs	Estimated annual hospital in-patient costs (95% CI) conditional on cost being incurred	Expected mean (95% CI) hospital in-patient cost of complication†
Column 1	Column 2	Column 3	Column 4
No complications	0.06 (0.06, 0.07)	£2543 (2406, 2697)	£157 (145, 170)
Estimates for the year in which the event occurred			
Fatal MI	0.74 (0.68, 0.78)	£1567 (1279, 1919)	£1152 (941, 1396)
Non-fatal MI	0.80 (0.75, 0.84)	£5104 (4486, 5806)	£4070 (3580, 4722)
Fatal stroke	0.80 (0.67, 0.89)	£4227 (2454, 7280)	£3383 (1935, 5431)
Non-fatal stroke	0.35 (0.27, 0.43)	£6822 (5255, 8858)	£2367 (1599, 3274)
Ischaemic heart disease	0.41 (0.35, 0.48)	£4760 (3736, 6064)	£1959 (1476, 2541)
Heart failure	0.53 (0.43, 0.62)	£4227 (3431, 5208)	£2221 (1690, 2896)
Blindness in one eye	0.20 (0.14, 0.27)	£4370 (3219, 5933)	£872 (526, 1299)
Amputation	1	£8459 (5220, 13706)	£8459 (5295, 13200)
Cataract extraction	1	£1553 (1278, 1888)	£1553 (1320, 1855)
Estimates for each year subsequent to the year in which the event occurred			
Non-fatal MI	0.13 (0.11, 0.15)	£3603 (3134, 4142)	£464 (377, 578)
Non-fatal stroke	0.08 (0.07, 0.11)	£2970 (2278, 3872)	£249 (166, 357)
Ischaemic heart disease	0.13 (0.11, 0.15)	£3814 (3291, 4420)	£493 (392, 606)
Heart failure	0.15 (0.12, 0.19)	£4097 (3148, 5331)	£631 (403, 896)
Blindness in one eye	0.10 (0.07, 0.12)	£2945 (2349, 3692)	£281 (189, 401)
Amputation	0.08 (0.06, 0.12)	£3639 (2445, 5416)	£300 (154, 531)
Cataract extraction	0.06 (0.05, 0.07)	£1854 (1464, 2349)	£105 (80, 142)

*The characteristics of the representative individual were set to the UKPDS mean population values, i.e. a male who is 58.63 years of age.
†Product of probability and conditional cost. MI, Myocardial infarction.

someone who has not previously had any of these complications. The immediate impact of complications such as a MI is to increase greatly the probability of incurring some hospital in-patient costs (e.g. a 74% probability of incurring hospital costs for a fatal MI and 80% for a non-fatal MI). These data suggest that approximately one-fifth of all non-fatal MIs do not incur any hospital in-patient costs in the year in which they occur, and this may be due to patients not being diagnosed as having had an MI until a subsequent investigation. Similarly, a proportion of non-fatal strokes and instances of heart failure are not associated with in-patient costs in the year in which they occur, while IHD and blindness in one eye are primarily treated in a non-in-patient setting.

Table 4 also shows the probability of incurring hospital in-patient costs in subsequent years. This indicates that the rate of hospitalization continues to be significantly higher than the 6% rate experienced by individuals who have not had any complications. For example, patients who have experienced a heart failure are predicted to have a 15% probability of incurring hospital in-patient costs for all subsequent years.

Column 3 of Table 4 shows the estimated mean hospital in-patient costs associated with each complication, conditional on some hospital in-patient costs being incurred calculated using the GLM equation reported in Table 3. Thus, if the patient incurred hospital in-patient costs in the year in which they had a non-fatal MI, these costs averaged £5104 (£4486, £5806), while patients who experienced an amputation on average incurred hospital in-patient costs of £8459 (£5220, £13 706) in that year. For all complications except fatal MI and cataract extraction, these hospital in-patient costs are substantially higher than the £2543 (£2406, £2697) incurred on average by the 6% of patients with no complication who nevertheless were admitted to hospital as in-patients.

Finally, column 4 of Table 4 shows the product of columns 2 and 3: i.e. the expected hospital in-patient costs associated with each complication. For example, someone who experiences a non-fatal stroke has a 35% probability of incurring hospital in-patient costs in the year the event occurred, the cost for these 35% of patients was £6822 (£5255, £8858) and so the expected or unconditional hospital in-patient costs associated with a non-fatal stroke are the product of these, or £2367 (£1599, £3274). Note that the 95% confidence intervals around these estimates are not symmetrical, due to the effects of retransformation.

Non-in-patient costs

Table 5 reports the coefficients and standard errors for the comparable regression equations relating to non-in-patient costs. These can also be used to calculate the annual non-in-patient costs for an individual based on their age and sex and history of macrovascular and microvascular and eye-related

Table 5 Regression equations to derive annual probability of incurring non-in-patient costs, and costs of non-in-patient care conditional on incurring a cost (3460 patients)

	Part 1: Equation to derive annual probability of incurring non-in-patient costs		Part 2: Equation to derive non-in-patient costs, conditional on costs being incurred		
Variable	Coefficient	Standard error	Coefficient	Standard error	Multiplicative effect
Constant	1.658	0.086	4.475	0.044	
Current age –55 (years)	0.023**	0.005	0.003	0.003	1.00
Male (= 1)	–0.604**	0.098	–0.229	0.049**	0.80
Event during year indicator					
Macrovascular event	1.142**	0.468	0.501	0.156**	1.65
Microvascular event	2.181*	1.014	0.291	0.193	1.33
History of event					
Macrovascular event	0.720**	0.170	0.358	0.072**	1.43
Microvascular event	0.456*	0.229	0.204	0.096*	1.22

*$P < 0.05$; **$P < 0.01$. Part 1 equation derived from logistic regression, Part 2 equations derived from generalized linear model.

Table 6 Estimated probability of incurring some non-in-patient costs, estimated non-in-patient costs conditional on cost being incurred, and expected mean cost*

Complication	Mean (95% CI) probability of incurring some non-in-patient cost†	Estimated non-in-patient costs (95% CI) conditional on cost being incurred†	Expected mean (95% CI) annualized non-in-patient cost
Column 1	Column 2	Column 3	Column 4
No complication	0.76 (0.74, 0.78)	£70 (66, 76)	£159 (149, 173)
Estimates for the year in which the event occurred			
Macrovascular	0.91 (0.83, 0.98)	£116 (94, 142)	£315 (247, 394)
Microvascular	0.97 (0.88, 1.00)	£94 (75, 118)	£273 (215, 343)
Estimates for each year subsequent to the year in which the event occurred			
Macrovascular	0.86 (0.83, 0.90)	£101 (88, 114)	£258 (228, 297)
Microvascular	0.83 (0.77, 0.89)	£82 (74, 99)	£204 (181, 255)

*All costs are for a representative individual (set to the UKPDS mean population values, i.e. a 58.63-year-old male) by first diabetes-related complication, during year of complication and in subsequent years.
†Costs for a 4-month period only. All costs in 1999 UK pounds sterling.

complications. Table 6 reports for the cost of a first complication for an individual with characteristics set to the average values for the UKPDS study population (i.e. a male aged 58.6 years). For patients with no complications the probability of incurring some non-in-patient costs in any year is 76%. For patients with macrovascular complications this probability increases to 91% in the year the event occurs and 86% in subsequent years and patients with microvascular complications 97% and 83%, respectively.

Discussion

In this study we have reported the results of a regression analysis on a large patient-specific dataset to obtain empirical estimates of the hospital in-patient costs and non-in-patient healthcare costs associated with a set of diabetes-related complications. It is important to stress that these are not simply the healthcare costs that are administratively allocated to events (e.g. the average cost of an in-patient admission for a non-fatal stroke). Instead they represent an estimate of the increase in all healthcare costs in the year in which the complication occurs. Thus, the hospital in-patient costs reported here for a non-fatal stroke will capture any in-patient stays directly associated with the stroke, but also the potential indirect impact of the stroke, e.g. on lengths of in-patient stay for other conditions.

Our results indicate the substantial impact of many diabetes-related complications on hospital costs, not only in the year in which the event occurs, but in permanently raising the average level of hospital costs in all subsequent years. This could be due either to subsequent occurrences of the same complication, or because patients with a history of diabetes-related complications have a greater propensity to require more hospitalizations of longer duration due to increased frailty compared with those free of complications.

The estimates we have reported are based on first events for a patient with average characteristics. These models can also be used to calculate estimates of costs for patients with other characteristics and for various combinations of complications. To facilitate use of these models we have written a program that can be used to calculate hospital and non-hospital costs which can be downloaded from the Health Economics Research Centre website (www.ihs.ox.ac.uk/herc).

It is interesting to compare our estimates with results from other sources such as specific costing studies or English Department of Health reference costs. For example, our estimates indicate that the annual hospital costs for a fatal MI are £1567 (£1279, £1919) and for a non-fatal MI are £5104 (£4486, £5806). These are significantly higher than the Department of Health reference cost for a finished consultant episode for a MI with complications of £1479 in the general population [22], and support previous research suggesting that cost analyses based on utilization labelled to particular complications significantly underestimate the true incremental costs of complications of diabetes [17].

We have not reported results for patients with end-stage renal disease, due to the small numbers of patients (25 in the main UKPDS randomization) with this complication at the end of the trial follow-up period. Fortunately, this is an area in which many bottom-up costing studies have been performed: data from one such large UK study suggest that the annual cost per patient (with and without diabetes) for all hospital costs associated with renal dialysis averaged £20 902 in 1996 prices, and also suggest that the presence of diabetes does not lead to a significant difference in treatment-specific costs compared with non-diabetic patients [23], although it may lead to a lower probability of renal transplantation [24].

The results relating to in-patient costs are based on clinical practice in the UK from 1977 to 1997—the period covered by the study. While there are significant advantages in using long-term follow-up data in order to quantify fully the cost of complications, several important factors should be considered if these results are used to estimate the cost of complications in other populations or time periods. First, UKPDS patients were newly diagnosed and tended to be relatively younger than people with Type 2 diabetes in the general population, and so the costs reported here may not reflect the resource use associated with complications of some older patients in the general population. Second, the treatment protocols for some complications are changing over time, for example, coronary stents are increasingly used in the treatment of patients with IHD and this will impact on the future costs associated with this complication. Finally, the probability of hospitalization and cost of each complication conditional on being hospitalized reported here are likely to differ in other countries, particularly the USA. In the absence of other data, one option for the analyst wanting to employ these costs on other populations and healthcare settings would be to regard the results reported here as a form of relative risk in relation to individuals not experiencing complications. Thus, a macrovascular complication could be considered to double non-hospital costs in the year it occurs relative to someone not experiencing a complication, and in subsequent years leaves them elevated by approximately 60% compared with the no complication group (Table 6), but further investigation of the validity of this approach would be very useful.

Although the randomized phase of the UKPDS finished in 1997, follow-up continued beyond that date and substantial additional information on complications and hospital in-patient costs of UKPDS patients will become available in the future. This will permit re-estimation and validation of the results reported here, as well as facilitate an examination of how recent changes in treatment protocols impact on costs. Meanwhile, the results reported here provide evidence of the healthcare cost impact of specific diabetes-related complications that has hitherto been unavailable. They should be of interest to other economists and health service researchers, particularly those wishing to assess within a modelling framework the cost-effectiveness of interventions for Type 2 diabetes that prevent complications.

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References

1 UKPDS Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. *Br Med J* 1998; **317**: 720–726.

2 UKPDS Group. Cost effectiveness of an intensive blood glucose control policy in patients with type 2 diabetes: economic analysis alongside a randomised controlled trial. UKPDS 41. UK Prospective Diabetes Study Group. *Br Med J* 2000; **320**: 1373–1378.

3 Pagano E, Brunetti M, Tediosi F, Garattini L. Costs of diabetes. A methodological analysis of the literature. *Pharmacoeconomics* 1999; **15**: 583–595.
4 Dixon S, Currie CJ, Peters JR. The cost of diabetes: time for a different approach? *Diabet Med* 2000; **17**: 820–822.
5 Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Zbrozek AS, Dong F *et al*. Model of complications of NIDDM. I. Model construction and assumptions. *Diabetes Care* 1997; **20**: 725–734.
6 Brown JB, Nichols GA, Glauber HS, Bakst AW. Type 2 diabetes: incremental medical care costs during the first 8 years after diagnosis. *Diabetes Care* 1999; **22**: 1116–1124.
7 O'Brien JA, Shomphe LA, Kavanagh PL, Raggio G, Caro JJ. Direct medical costs of complications resulting from type 2 diabetes in the US. *Diabetes Care* 1998; **21**: 1122–1128.
8 Ramsay SD, Newton K, Blough D, McCulloch DK, Sandhu N, Wagner EH. Patient-level estimates of the cost of complications in diabetes in a managed care population. *Pharmacoeconomics* 1999; **16**: 285–295.
9 Culler SD, Weintraub WS, Shaw LJ, Becker ER. Hospital resource consumption in patients with diabetes and multivessel coronary disease undergoing revascularization. *Am J Manag Care* 2000; **6**: 217–229.
10 UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; **352**: 837–853.
11 Department of Health. *Hospital Episodes Statistics*, Vol. 1, *Finished Consultant Episodes by Diagnosis, Operation and Specialty. England: Financial Year 1994–95*. London: Department of Health, 2000.
12 Schafer JL. *Analysis of Incomplete Multivariate Data*. London: Chapman & Hall, 1997.
13 Little RJ, Rubin DB. *Statistical Analysis with Missing Data*. New York: John Wiley and Sons, 1987.
14 Department of Health. *NHS Trust Financial Returns (TFR2) for 1997/8 and 1998/9*. London: Department of Health, 2000.
15 Netten A, Dennett J, Knight J. *Unit Costs of Health and Social Care 1999*. University of Kent at Canterbury: Personal Social Services Research Unit, 1999.
16 UKPDS Group. UK Prospective Diabetes Study VIII: study design, progress and performance. *Diabetologia* 1991; **34**: 877–890.
17 Brown JB, Pedula KL, Bakst AW. The progressive cost of complications in type 2 diabetes mellitus. *Arch Intern Med* 1999; **159**: 1873–1880.
18 Mullahy J. Much ado about two: reconsidering retransformation and the two-part model in health econometrics. *J Health Economics* 1998; **17**: 247–281.
19 Blough DK, Madden CW, Hornbrook MC. Modeling risk using generalized linear models. *J Health Economics* 1999; **18**: 153–171.
20 Jones AM. Health econometrics. In Culyer AJ, Newhouse JP eds. *Handbook of Health Economics*. Amsterdam: Elsevier, 2000; 265–344.
21 Manning WG, Mullahy J. Estimating log models: to transform or not to transform? *J Health Economics* 2001; **20**: 461–494.
22 Department of Health. *Reference Costs 1999/2000*. London: Department of Health, 2001.
23 Lamping DL, Constantinovici N, Roderick P, Normand C, Henderson L, Harris S *et al.* Clinical outcomes, quality of life, and costs in the North Thames Dialysis Study of elderly people on dialysis: a prospective cohort study. *Lancet* 2000; **356**: 1543–1550.
24 UK Renal Registry. *Third Annual Report*. Bristol: Southmead Hospital, 2000.

Statistical appendix

Separate statistical analyses were employed in modelling the inpatient and non-in-patient costs. In the case of in-patient cost, the data was characterized by repeated observations on each patient for the years they participated in the UKPDS. Given the structure of the data we used a random effects panel data model for both stages of the two-part model. In particular:

$$C_{it} = \delta X_{it}^{j} + \mu_i + \upsilon_{it}$$

where C_{it} are the total hospital costs for the *i*th patient ($i = 1 \dots n$) in year t of the study ($t = 1, \dots, T$) and X_{it}^{j} are variables ($j = 1 \dots J$) that influence costs including age, sex, indicator variables representing the occurrence of diabetes-related complications. To estimate the immediate impact of complications we include an indicator variable that is set to 1 in the year that the event occurs. A second indicator variable is included to estimate the long-term effect that is set equal to 1 for all subsequent years while the patient is participating in the study. In the random effects model the error term is divided into two parts, μ_i an unobservable individual specific effect independently identically distributed with zero mean and variance of σ_μ^2 (i.e. μ_i IID$(0, \sigma_\mu^2)$) and υ_{it} which denotes the remaining error term (μ_i IID$(0, \sigma_\upsilon^2)$). In the first part a logistic regression is applied to the panel data and the predicted probability of incurring hospital costs for each event is calculated:

$$\Pr(C_{it} > 0 \mid X_{it}^{j}) = \{\exp(\alpha^{j} X_{it}^{j}) / [1 + \exp(\alpha^{j} X_{it}^{j})]\} \quad (1)$$

where α^j is the estimated coefficient for the *j*th variable. In the second stage of the two-part model we use a GLM with a log link function on the assumption that:

$$E(C_{it} \mid C_{it} > 0, X_{it}) = \exp(\beta^{j} X_{it}^{j}) \quad (2)$$

where β^j is the coefficient on the *j*th variable in the GLM equation. Diagnostic tests [20] indicate that the gamma family should be used to specify the mean–variance relationship. Expected or mean costs were calculated for each complication conditional on having positive hospital costs. The overall estimate of hospital costs is then $\Pr(C_{it} > 0 \mid X_{it}^{j}) \times \exp(\beta^{j} X_{it}^{j})$.

It is important to note that a GLM with a log link function assumes that complications have a multiplicative effect on overall costs and so patients with several complications will incur much higher costs than if the costs of complications were assumed to be additive (as in traditional linear regression). Only a limited number of patients in the UKPDS experienced more than two complications and so the validity of predicting costs using a GLM in this context needs to be determined when the follow-up data are available. We have therefore also estimated a model using ordinary least squares (OLS) regression that could be used to provide alternative estimates (particularly for patients with multiple complications) and these along with GLM estimates can be downloaded from our website (www.ihs.ox.ac.uk/herc).

The coefficients for β^j and α^j reported in Tables 3 and 5 can be used to calculate the cost of different complications, for example, to calculate the annual hospital costs of a male who is 58.63 years of age without a previous history of complications who has a non-fatal MI. First the annual probability of a hospitalization must be calculated. Using the values for the relevant coefficients α^{Constant}, α^{age}, α^{male} and $\alpha^{\text{non-fatal MI}}$ of –2.674, 0.017, –0.108 and 4.091 in Equation 1 the probability of this individual incurring hospital costs in year 1 is:

$$\Pr(C_{i1} > 0 \mid X_{i1}^{j}) = \frac{\exp(-2.674 + 0.017 \times (58.63 - 55) - 0.108 \times 1 + 4.091 \times 1)}{(1 + \exp(-2.674 + 0.017 \times (58.63 - 55) - 0.108 \times 1 + 4.091 \times 1))} = 0.80$$

The total hospital costs conditional on the patient attending hospital during the year can then be calculated using the GLM equation, which is also reported in Table 3. The relevant values for the coefficients β^{Constant}, β^{age}, β^{male} and $\beta^{\text{non-fatal MI}}$ are 7.902, 0.013, –0.106 and 0.696 and so using Equation 2 the hospital cost are:

$$E(C_{i1} \mid C_{i1} > 0, X_{i1}) = \exp(7.902 + 0.013 \times (58.63 - 55) - 0.106 \times 1 + 0.696 \times 1) = 5111$$

which is slightly greater than £5104 reported in Table 4 which was calculated using coefficients accurate to a greater number of decimal places. The estimate of expected hospital costs is the product of estimates from parts 1 and 2.

The 95% CI for estimates of the cost for complications reported in Tables 4 and 6 are obtained through non-parametric bootstrapping involving 1000 replications. This was done by randomly re-sampling individuals with replacement and re-estimating the equations. Costs were then calculated and rank-ordered, and the 25th and 975th estimates were taken as the confidence limits.

The analysis of non-in-patient costs is based on a similar approach, but was based on data from a cross-sectional survey conducted towards the end of the trial. For methodological consistency we assign non-in-patient costs to the patient year in which the survey is conducted (denoted as year s) and employ the same two-part approach but with $t = s$. The coefficients of the equations reported in Table 5 can be used to calculate non-in-patient costs based on the patients' characteristics and history of complications.