Estimating utility values for health states of type 2 diabetic patients using the EQ5D

Philip Clarke and Alastair Gray

Health Economic Research Centre
University of Oxford
Institute of Health Sciences
Old Road
Oxford OX3 7LF

PRESENTED AT HESG CONFERENCE, NOTTINGHAM, JULY 2000
***

Abstract

An important step in evaluating therapies for type 2 diabetes is to measure their impact on quality of life. Since a major objective of therapy is prevention of the complications associated with diabetes, it would be useful to have utility values for the most common diabetes-related complications. This study explores how these can be obtained using quality of life data from a large trial of exceptional duration. The EuroQoL EQ-5D instrument was administered cross-sectionally in 1996 to 3,667 patients participating in the UK Prospective Diabetes Study. These patients were between 4 and 20 years from entry to the study, and a full clinical history was available for each patient. Regression equations were used to estimate the impact of six conditions (myocardial infarction, ischaemic heart disease, stroke, heart failure, amputation and blindness) on the EuroQol thermometer and tariff values. The resulting quality of life equation was used to estimate the effect experiencing each of these conditions had on these values.

Introduction

The increasing use of quality-adjusted life years as a measure of outcome in cost-effectiveness studies has been accompanied by a growing reliance on secondary data sources to provide estimates of quality of life in various health states. Such reference values for health state qualities of life are of particular value in modelling studies, which often explicitly require quality of life valuations to be attached to specified health states. Typical sources of information are population surveys providing normative data on usual quality of life levels, [1] community surveys providing quality of life scores in groups reporting a range of disease conditions and disabilities, [2] and disease specific studies reporting utilities associated with, for example, different prostate cancer health states. [3] Here we add to this literature by reporting quality of life reference values for major complications of Type 2 diabetes, using data from a landmark trial of diabetes therapies, the United Kingdom Prospective Diabetes Study (UKPDS). [4]

A number of previous studies have reported quality of life amongst patients with diabetes. These can be divided into studies showing no relation between therapies to control blood glucose and quality of life, [5, 6, 7, 8] studies showing a significant relation between therapies and quality of life, [9, 10, 11] and studies showing that the occurrence of a complication affects quality of life. [12, 9, 10, 11, 13] However, these studies have generally used instruments or questionnaires that are not directly useful as measures of utility. The Diabetes Control and Complications Trial, for example, reported the impact of intensive versus conventional treatment on quality of life of Type 1 diabetic patients as assessed by the Diabetes Quality of Life Measure, the Symptom Checklist-90R, and the SF-36.[5] Lacking a direct measure of utility, the subsequent economic evaluation from this trial confined its outcome measurement to life years gained. [14]

Previously reported results from the UKPDS have shown no detectable difference in quality of life between patients allocated to different therapies, and have demonstrated that the recent occurrence of a complication significantly

reduced quality of life. [15] Here we focus exclusively on the impact of complications on utility, consider complications occurring recently or at any other time from diagnosis of diabetes, and report results for specific categories of complication.

Methods

The clinical trial

The United Kingdom Prospective Diabetes Study (UKPDS) was conducted from 1977 to 1991 in 23 participating UKPDS hospitals. A total of 5,102 newly diagnosed diabetic patients were recruited to the study. Of these 3,867 patients with fasting plasma glucose concentrations of 6.1-15.0 mmol/L were randomly assigned to an intensive policy with sulphonylurea or with insulin or a conventional policy of diet alone. A further 342 overweight patients (>120% ideal bodyweight) were treated with metformin. The median duration of follow-up was 11.1 years in the main trial and 10.7 years for the group on a policy of metformin. [16, 17]

Assessment of Quality of Life

Quality of life in the UKPDS was measured in two ways: a specially designed questionnaire examined specific quality of life domains in terms of cognitive mistakes, mood disturbances, symptoms, and work satisfaction, [15] and the EuroQol EQ-5D instrument examined generic health-related quality of life.[18] Both instruments were administered cross-sectionally to all patients in the study, the specific questionnaire to 3121 patients when they been in the study for a mean of 8 years, and the EQ-5D to 3667 patients when they had been in the study for a mean of 10.7 years. Here we are concerned only with the EQ-5D.

Patients were given the EQ-5D and asked to complete it during routine visits to UKPDS clinics, in a quiet room with no help from nursing staff, family or friends. Patients who did not attend clinics during the survey period were sent the questionnaire at home, and those who did not return the questionnaire were sent

up to two reminders. Both the 5 question descriptive health state part and the Visual Analogue Scale part of the EQ-5D were administered; health states were subsequently allocated tariff scores based on population-base time trade off valuations, ranging from 1 for full health to 0.594 for severe problems in all five dimensions; [19] the Visual Analogue Scale was scored from 100 indicating best state of health to 0 indicating worst state of health.[20]

Clinical events

All patients had an annual assessment to determine whether they had experienced any clinical events within the previous year. Information on each event was recorded on data sheets and the notifying UKPDS centre was requested to provide full information on the event. This information was then presented to two clinical assessors who independently classified the event into predefined categories based on the 9th revision of the International Classification of Diseases (ICD9) codes. If there was disagreement on the assessment, the information was submitted to two further independent assessors for a final decision (UKPDS 8). There were a total of ten non-fatal clinical event categories in the UKPDS. In this study we examine how quality of life is affected by six of these: myocardial infarction (MI), ischaemic heart disease (IHD), stroke, heart failure, amputation and blindness. The remaining four events were excluded from this study, because they were either primarily treatment related (i.e. retinal photocoagulation), or because there were insufficient numbers of events for reliable analysis.

Subjects

3,192 EQ-5D questionnaires were returned, a response rate of 87%. Here we report on an analysis of responses from 2,747 patients participating in the main trial and the metformin randomisation. (The remaining questionnaires will be added to the analysis shortly). 42 respondents had not completed at least one the five EuroQol questions or did not respond to the VAS and so were excluded from further analysis, leaving 2,705 in the sample. The patients were between 4 and 20 years from entry to the UKPDS (and from diagnosis of diabetes), with a

mean of 10.7 years from randomisation and a mean age of 62 at the time of the questionnaire. Given the trial exclusion criteria, no patients at entry to the trial had had a myocardial infarction in the previous year, angina or heart failure, more than one major vascular event or a concurrent illness that would limit life

Data analysis

We use regression analysis to model the relationship between tariff and VAS values and clinical events after adjusting for age, sex and duration in the trial. Dolan has noted that time-trade off valuations that form the basis of the tariff values for the EuroQol states are bounded by one (the score for full health).[21] In EuroQol surveys it is common for a significant fraction of respondents to rate themselves in full health (i.e. 11111 on EQ-5D survey): for example, population data from the 1996 Health Survey for England showed that 52% of all respondents gave this response. While all of these patients are assigned the same tariff value, there are still likely to be variations in quality of life between patients and hence there is a qualitative difference between those at this limit value and those at other tariff values.[1] In these circumstances conventional linear regression analysis is inappropriate and so a tobit model [22] with upper censoring at one is employed:

$$q_i^* = x_i \boldsymbol{b} + e_i$$

$$q_i = \begin{cases} q_i^* & q_i^* < 1 \\ 1 & q_i^* \geq 1 \end{cases}$$

Where q_i* is a latent quality of life variable that is observed for values less than or equal one; x_i a vector of K independent variables influencing quality of life; $\boldsymbol{b}$ coefficients on the independent variables; an error term $\varepsilon_i \sim N(0,\sigma^2)$; and q_i the

[1] Although this is also true of other states (i.e. 11112) the proportion of the sample in these states is often lower and so censoring is less of a problem. However a possible extension would be to estimate a model that takes into account the grouping of the tariff values (for an example of such a model see Stewart 1983).[27].

observed quality of life value. For consistency we also use a tobit model in the analysis of the VAS values.

To determine the impact various clinical events have on quality of life we analyse the relationship between the tariff and VAS values and the six non-fatal clinical events (see above). To ensure comparability between tariff values and the VAS we divide the VAS score by 100 to generate a one-zero index. Our initial model includes a dummy variable for each clinical event to indicate whether patients have experienced one or more of the events at any time while participating in the UKPDS trial. The dummy therefore indicates whether the patient has a history of that clinical event since diagnosis of diabetes.

In addition, the impact of these clinical events on quality of life may vary over time. For example, if the underlying disease has an acute phase then the event may only have a transient impact on quality of life. In a secondary analysis, we examine how events occurring at different points in time in relation EuroQol questionnaire affect the EuroQol scores. In this sub-analysis the models include two separate dummy variables for each clinical event. The first variable indicates whether the event occurred in the year prior to the survey and the second whether it occurred prior to the previous year.

All models were estimated using LIMDEP 7.0 and tests undertaken to determine the significance (at a 5% level) of the independent variables. The time invariant tariff and VAS models were compared with their time varying counterparts using likelihood ratio tests. The marginal effect on the tariff and VAS values from any of the significant clinical events were then calculated using the partial derivative with respect to x_k for k=1..K : [22]

$$\frac{\partial E(q \mid \bar{x})}{\partial x_K} = \Phi(-d)b_k + f(d)\frac{b_k}{s}$$

Where δ=($\bar{x}$ $\boldsymbol{b}$-1)/σ and the $\bar{x}$ mean of the independent variables. To understand the two sources of the change in the censored outcome we apply the decomposition of ¶$E(q)$/¶x_k suggested by McDonald and Moffitt (1980) that highlights the change in the censored outcome: [23]

$$\frac{\partial E(q \mid \bar{x})}{\partial x_k} = \Pr(U \mid \bar{x}) \frac{\partial E(q \mid q < 1, \bar{x})}{\partial x_k} + [E(q \mid q < 1, \bar{x} \quad \frac{\partial \Pr(U \mid \bar{x})}{\partial x_k}$$

Where $\Pr(U \mid \bar{x})$ is the probability of an observation being censored at the mean of the independent variables. The intuitive explanation of this decomposition at $\bar{x}$ is that the total change in q for a change in x_k can be separated into two parts. The first part is the change in q of those below the limit (i.e. those who are not in full health) weighed by the probability of being not being in full health. The second part is the change in probability of not being in full health, weighted by the expected value of q if they are not in full health.

Results

Descriptive values and definitions of the variables used in the regression analysis are shown in Table 1. The mean tariff value based on responses to the five EQ-5D questions was 0.76 (SD 0.27) and the mean scores on the VAS was 0.74 (SD 0.19). Diabetic patients rate their quality of life lower on the VAS and their scores are less dispersed than the tariff values. When the quality of life survey was conduced the mean age of patients was 63.7 years (SD 8.7 years). The proportion of patients that had experienced the six diabetes related clinical events is also reported in Table 1. The most commonly diagnosed clinical event was an MI, which was reported for 7.3% of patients. In contrast, the least common was amputation that affected only 0.8% patients. To provide an indication of when these events occurred we have separated events diagnosed in the year prior to the survey from those diagnosed prior to the previous year.

The relationship between quality of life and clinical events

Table 2 reports the results of the Tobit regression analyses of the relationship between the tariff/ VAS scores and experiencing clinical events at any point in time (i.e. a single dummy variable is included for each clinical event to indicate whether a patient has ever been diagnosed as having this event while participating in the trial). These regression analyses are based on 2,705 observations. In regard to patient characteristics, the tariff and VAS values were constant with age and the duration of time since a patient had been randomised to a therapy group in the trial. Gender had an effect, with males having significantly (at the 5% level) higher tariff and VAS values. Being diagnosed with any of the clinical events also had a significant negative impact on the quality of life scores. Given their lack of significance *age* and *time in trial* were dropped and reduced form models estimated (see Table 2).

The relationship between the quality of life and clinical events overtime

Table 3 reports the results of the tobit regression analyses of the relationship between the tariff values/ VAS scores and experiencing one or more clinical events within two different time intervals: within the previous year (i.e. at any time within the year prior to the survey); and prior to the previous year. Again gender is shown to have an influence with men having higher tariff and VAS values. In regard to the impact of clinical events that occurred within the previous year, those that had been diagnosed with an MI, or IHD reported a significantly lower tariff value. The tariff value was also significantly lower for heart failure. The rest of the clinical events occurring during this period had no significant effect on either the tariff or VAS values. Prior to the previous year, macro vascular events (MI, IHD, stroke, heart failure) had a negative effect on both the tariff and VAS values, while amputation and blindness had a significant and negative effect only on the tariff values. To determine if the coefficients on each clinical event were stable over time we estimated a further model for each clinical event in which the coefficient on the variables *previous year* and *prior to the previous year* was restricted to be equal. Comparisons with the unrestricted model were then

undertaken using likelihood ratio tests. The test statistics ranged from 0.62 (p=0.43) for MI to 2.94 (p=0.09) for stroke in the tariff model and from 0.00 (p=0.98) for stroke to 2.52 (p=0.11) for MI in the VAS model. Thus events occurring more than one year ago did not have a significantly different impact on the tariff or VAS values than events occurring within the previous year.

The effect of clinical events on tariff and vas values

Table 4 reports the marginal effect of each clinical event computed at the sample mean. Given the absence of significant differences in the impact of clinical events over time these marginal effects are based on the reduced form of the time invariant models reported in Table 2. The greatest impact on the tariff was associated with the event *amputation,* this reduced the tariff value by 0.17 and the VAS value by 0.091. It is important to bear in mind these events have an additive impact on quality of life scores. Hence, for a patient who has experienced an MI and has a history of IHD the tariff will be reduced by –0.143.

To provide insight into the nature of the change, we report two further statistics. The proportion of the sample not in full health and the faction of the mean effect due to the response below the limit value obtained from McDonald and Moffitt's decomposition. In the VAS model 90% of the observations are below the limit value. For any of the clinical events, we can say that 72% of the total change in VAS values would be generated by marginal changes in thermometer values. The remaining 28% would be generated by changes in the probability of moving away from the limit value (full health). Decomposition of the tariff model reveals quite a different story. In this model a much lower proportion of observations are below the limit value (65%). Decomposition shows that only 45% of the tariff values are due to marginal changes in tariff values of states below full health. The majority of the change is due the reduction in the probability of being in full health.

Discussion

This paper reports preliminary estimates of utility values associated with major complications of Type 2 diabetes. Because it draws on information collected within a large long-term clinical trial, accurate and validated information on the clinical history of all patients is available from diagnosis of diabetes onwards, and this greatly enhances the confidence with which quality of life estimates can be linked to precisely recorded complications..

Comparison of the characteristics of patients who returned EQ-5D questionnaires with the entire UKPDS population produced no evidence of sample bias. However, patients entering the study were newly diagnosed with Type 2 diabetes, and even after a mean of 11 years follow-up the older, sicker patients with the longest durations of Type 2 diabetes are under-represented in comparison with the entire population of people with Type 2 diabetes. Moreover, because the survey was conducted cross-sectionally towards the end of the study, the possibility of a healthy survivor effect cannot be ruled out: all patients who had had a previous fatal diabetes-related complication were by definition excluded. This may partly explain why age or duration of diabetes were not independently associated with quality of life in our analysis, in which the impact of disease progression on quality of life seems to be captured entirely by the occurrence of diabetes-related endpoints. However, the overall quality of life of respondents in this study does appear to be slightly lower than population norms: the mean EQ-5D tariff value in the sample is 0.76 (mean age 62.2), compared with a mean tariff of 0.79 for the age-group 55-64 in the 1996 Health Survey of England. [1]

A striking feature of the analysis is the strong influence on the results of changes in the proportion of patients on the limit value of the EQ-5D - that is, patients initially indicating they are in a state of full health. As Table 4 showed, more than half of the recorded changes in mean quality of life scores following a clinical event can be attributed to patients initially recording a state of full health moving

away from that state. The inability to record relatively small changes in quality of life using the EQ-5D instrument has previously been noted:[24] at the full health state (11111) the minimum possible health change - from 1 to 2 in one dimension - corresponds to a reduction in utility of between 0.12 and 0.2. This may not be a particular problem in the present context, as all the complications considered are relatively serious in nature; however, the inability to express a state of health between 0.88 and 1 may compromise the ability of the instrument to detect quality of life changes associated with less serious complications or over time, and may also raise issues of appropriate estimation.

This analysis is incomplete: additional responses will be added, increasing statistical power; some patients were issued with the EQ-5D on sequential clinic visits, allowing an opportunity for test-retest analysis; and experimentation is under way on different cut-off points to delineate recent from more distant events. However, once analysis is finished the results obtained should be of value for future cost-effectiveness analyses in the area of Type 2 diabetes. The major published economic evaluations to date from the UKPDS have focused on life years lost and endpoint-free time as the main measures of outcome, [25, 26] as do publications in process on metformin therapy and ace inhibitors versus beta blockers. However, the estimation of the quality of life impact of complications, coupled to development of a lifetime model of risk, will allow the cost-utility of all these comparisons to be calculated. Other analysts should also find the results of use in estimating the cost-utility of different current and future interventions.

Table 1: Descriptive statistics and definitions of variables used in regression analyses

Variable	Mean	Description
Quality of life measure		
EQ-5D social tariff	0.764 (± 0.269 SD)	Social tariff value
EQ-5D VAS	0.735 (± 0.190 SD)	Visual analog score divided by 100
Characteristics		
Age	63.7 (± 8.792 SD)	Patients age at time of survey (years)
Male	0.597	Equals one if patient is male, zero otherwise
Time in trial	11.211 (2.939 SD)	Duration in years the patient the patient has been participating in the UKPDS trial
Previous events		
Myocardial infarction(MI) Previous year Prior to previous year	0.073 0.012 0.061	Diagnosed with a myocardial infarction (ICD9 Code 410)
Ischaemic heart disease (IHD) Previous year Prior to previous year	0.068 0.012 0.056	Diagnosed with ischaemic heart disease (ICD9 Code 411-414.9).
Stroke Previous year Prior to previous year	0.023 0.008 0.015	Diagnosed with a major stroke with symptoms that persist more than one month (ICD9 Codes 430 to 434.9 and 436)
Heart failure Previous year Prior to previous year	0.021 0.007 0.014	Diagnosed with heart failure (ICD9 Codes 428 to 428.1)
Amputation: Previous year Prior to previous year	0.008 0.003 0.005	Diagnosed with major limb complications requiring amputation of digit or limb for any reason (ICD9 Codes 5.845 to 5.848)
Blindness Previous year Prior to previous year	0.031 0.006 0.025	Diagnosed as having blindness in one eye (ICD9 Code 369 to 369.9)

Table 2: Results of a tobit regression analysis of the relationship between Quality of life scores (EQ-5D tariff values and VAS) and clinical events and patient characteristics (n=2,705).

	EQ-5D Tariff (Model 1)		VAS (Model 2)	
	Full model β(SE)	Reduced model β(SE)	Full model β(SE)	Reduced model β(SE)
Constant	0.847(0.059)*	0.802(0.012)**	0.715(0.006)**	0.715(0.006)
Age	-0.0003(0.001)	---	0.000(0.005)	---
Male	0.142(0.015)**	0.143(0.016)**	0.064(0.008)**	0.064(0.008)**
Time in Trial	-0.002(0.003)	---	-0.001(0.001)	---
Previous events				
MI	-0.086(0.027)**	-0.089(0.027)**	-0.053(0.014)**	-0.053(0.014)**
IHD	-0.127(0.029)**	-0.130(0.029)**	-0.049(0.015)**	-0.050(0.015)**
Stroke	-0.174(0.044)	-0.176(0.044)**	-0.063(0.020)*	-0.062(0.020)*
Heart Failure	-0.177(0.050)**	-0.179(0.050)**	-0.091(0.026)**	-0.091(0.026)**
Amputation	-0.260(0.071)**	-0.261(0.071)**	-0.101(0.038)**	-0.101(0.038)**
Blindness	-0.104(0.041)*	-0.108(0.041)**	-0.045(0.211)*	-0.045(0.210)*
σ	0.372	0.372	0.196	0.196

*p<0.05; **p<0.01

Table 3: Results of a tobit regression analysis of the relationship between Quality of life scores (EQ-5D tariff and VAS values) and clinical events occurring in the previous year and prior to the previous year (n=2,705)

	Eq-5D Tariff (Model 3) β(SE)	**VAS (Model 4)** β(SE)
Constant	0.801(0.001)**	0.715(0.006)**
Male	0.143(0.015)**	0.065(0.008)**
Previous events		
MI		
Previous year	-0.137(0.065)**	-0.102(0.033)**
Prior to previous year	-0.080(0.030)**	-0.043(0.015)**
IHD		
Previous year	-0.180(0.067)**	-0.088(0.034)**
Prior to previous year	-0.120(0.032)**	-0.042(0.016)*
Stroke		
Previous year	-0.051(0.085)	-0.062(0.043)
Prior to previous year	-0.260(0.084)**	-0.063(0.044)**
Heart Failure		
Previous year	-0.205(0.085)*	-0.086(0.045)
Prior to previous year	-0.168(0.062)**	-0.093(0.032)**
Amputation		
Previous year	-0.131(0.136)	-0.136(0.071)
Prior to previous year	-0.329(0.096)**	-0.082(0.050)
Blindness		
Previous year	-0.035(0.092)	-0.051(0.047)
Prior to previous year	-0.126(0.046)**	-0.041(0.027)
σ	0.372	.196

*p<0.05; **p<0.01

Table 4: Marginal effect of clinical events on Quality of life scores (EQ-5D tariff values and VAS)

	Change in values	
	Tariff values	**VAS values**
MI	-0.058	-0.047
IHD	-0.085	-0.044
Stroke	-0.115	-0.056
Heart Failure	-0.116	-0.082
Amputation	-0.170	-0.091
Blindness	-0.070	-0.041
Decomposition:		
Fraction of the sample below the limit	0.64	0.90
Fraction of mean due to responses below the limit	0.45	0.72

*p<0.05; **p<0.01

Reference List

1. Health Survey. *Health Survey of England 1996*. London: The Stationery Office, 1998.

2. Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med.Decis.Making.* 1993;**13**:89-102.

3. Litwin MS, Hays RD, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. *JAMA* 1995;**273**:129-135.

4. UKPDS Group. UK Prospective Diabetes Study VIII: study design, progress and performance. *Diabetologia* 1991;**34**:877-890.

5. DCCT Group. Influence of intensive diabetes treatment on quality-of-life outcomes in the diabetes control and complications trial [see comments]. *Diabetes Care* 1996;**19**:195-203.

6. Johnson JA, Nowatzki TE, Coons SJ. Health-related quality of life of diabetic Pima Indians. *Med.Care* 1996;**34**:97-102.

7. Weinberger M, Kirkman MS, Samsa GP, et al. The relationship between glycemic control and health-related quality of life in patients with non-insulin-dependent diabetes mellitus. *Med.Care* 1994;**32**:1173-1181.

8. Weinberger M, Kirkman MS, Samsa GP, et al. A nurse-coordinated intervention for primary care patients with non-insulin-dependent diabetes mellitus: impact on glycemic control and health-related quality of life [see comments]. *J.Gen.Intern.Med.* 1995;**10**:59-66.

9. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L. Quality of life and associated characteristics in a large national sample of adults with diabetes. *Diabetes Care* 1997; **20**:562-567.

10. Jacobson AM, de-Groot M, Samson JA. The evaluation of two measures of quality of life in patients with type I and type II diabetes. *Diabetes Care* 1994;**17**:267-274.

11. Keinanen KS, Ohinmaa A, Pajunpaa H, Koivukangas P. Health related quality of life in diabetic patients measured by the Nottingham Health Profile. *Diabet.Med.* 1996;**13**:382-388.

12. Klein BE, Klein R, Moss SE. Self-rated health and diabetes of long duration. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Diabetes Care* 1998;**21**:236-240.

13. Peyrot M, Rubin RR. Levels and risks of depression and anxiety symptomatology among diabetic adults. *Diabetes Care* 1997;**20**:585-590.

14. DCCT. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. *JAMA* 1996;**276**:1409-1415.

15. UKPDS. Quality of life in type 2 diabetic patients is affected by complications but not by intensive policies to improve blood glucose or blood pressure control (UKPDS 37). U.K. Prospective Diabetes Study Group. *Diabetes Care* 1999;**22**:1125-1136.

16. 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.

17. UKPDS Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;**352**:854-865.

18. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199-208.

19. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. *Health Econ.* 1996;**5**:141-154.

20. Gudex C, Dolan P, Kind P, Williams A. Health state valuations from the general public using the visual analogue scale. *Qual.Life Res.* 1996;**5**:521-531.

21. Dolan P. Modeling valuations for EuroQol health states. *Med.Care* 1997;**35**:1095-1108.

22. Long JS. *Regression models for categorical and limited dependent variables.* London: Sage, 1997;

23. McDonald JF, Moffitt RA. The Uses of Tobit Analysis. *Review of Economics and Statistics* 1980;**62**:318-321.

24. Jenkinson C, Gray A, Doll H, Lawrence K, Keoghane S, Layte R. Evaluation of index and profile measures of health status in a randomized controlled trial. Comparison of the Medical Outcomes Study 36-Item Short Form Health Survey, EuroQol, and disease specific measures. *Med.Care* 1997;**35**:1109-1118.

25. UKPDS Group. Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes: UKPDS 40. UK Prospective Diabetes Study Group. *BMJ.* 1998;**317**:720-726.

26. 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. *BMJ.* 2000;**320**:1373-1378.

27. Stewart MB. On Least Squares Estimation When the Dependent Variable Is Grouped. *Review of Economic Studies* 1983;**50**:737-753.