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A Comparison of Methods to Handle Skew Distributed Cost Variables in the Analysis of the Resource Consumption in Schizophrenia Treatment

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Abstract

Background: Transformation of the dependent cost variable is often used to solve the problems of heteroscedasticity and skewness in linear ordinary least square regression of health service cost data. However, transformation may cause difficulties in the interpretation of regression coefficients and the retransformation of predicted values.
Aims of the Study: The study compares the advantages and disadvantages of different methods to estimate regression based cost functions using data on the annual costs of schizophrenia treatment.
Methods: Annual costs of psychiatric service use and clinical and socio-demographic characteristics of the patients were assessed for a sample of 254 patients with a diagnosis of schizophrenia (ICD-10 F 20.0) living in Leipzig. The clinical characteristics of the participants were assessed by means of the BPRS 4.0, the GAF, and the CAN for service needs. Quality of life was measured by WHOQOL-BREF. A linear OLS regression model with non-parametric standard errors, a log-transformed OLS model and a generalized linear model with a log-link and a gamma distribution were used to estimate service costs. For the estimation of robust non-parametric standard errors, the variance estimator by White and a bootstrap estimator based on 2000 replications were employed. Models were evaluated by the comparison of the R^2 and the root mean squared error (RMSE). RMSE of the log-transformed OLS model was computed with three different methods of bias-correction. The 95% confidence intervals for the differences between the RMSE were computed by means of bootstrapping. A split-sample-cross-validation procedure was used to forecast the costs for the one half of the sample on the basis of a regression equation computed for the other half of the sample.
Results: All three methods showed significant positive influences of psychiatric symptoms and met psychiatric service needs on service costs. Only the log- transformed OLS model showed a significant negative impact of age, and only the GLM shows a significant negative influences of employment status and partnership on costs. All three models provided a R^2 of about .31. The Residuals of the linear OLS model revealed significant deviances from normality and homoscedasticity. The residuals of the log-transformed model are normally distributed but still heteroscedastic. The linear OLS model provided the lowest prediction error and the best forecast of the dependent cost variable. The log-transformed model provided the lowest RMSE if the heteroscedastic bias correction was used. The RMSE of the GLM with a log link and a gamma distribution was higher than those of the linear OLS model and the log-transformed OLS model. The difference between the RMSE of the linear OLS model and that of the log-transformed OLS model without bias correction was significant at the 95% level. As result of the cross-validation procedure, the linear OLS model provided the lowest RMSE followed by the log-transformed OLS model with a heteroscedastic bias correction. The GLM showed the weakest model fit again. None of the differences between the RMSE resulting form the cross-validation procedure were found to be significant.
Discussion: The comparison of the fit indices of the different regression models revealed that the linear OLS model provided a better fit than the log-transformed model and the GLM, but the differences between the models' RMSE were not significant. Due to the small number of cases in the study the lack of significance does not sufficiently proof that the differences between the RSME for the different models are zero and the superiority of the linear OLS model can not be generalized. The lack of significant differences among the alternative estimators may reflect a lack of sample size adequate to detect important differences among the estimators employed. Further studies with larger case number are necessary to confirm the results.
Implications: Specification of an adequate regression models requires a careful examination of the characteristics of the data. Estimation of standard errors and confidence intervals by nonparametric methods which are robust against deviations from the normal distribution and the homoscedasticity of residuals are suitable alternatives to the transformation of the skew distributed dependent variable. Further studies with more adequate case numbers are needed to confirm the results.

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Introduction

Multivariate regression analysis is being used in a growing number of studies to explain the variation in individual mental health service use and resource consumption.[1-24] The two purposes of the regression based cost function are the analysis of the causes of the cost variance and the forecast of costs for

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populations or for time periods where empirical cost data are not available.[8] For the first purpose, the regression coefficients and their standard errors must be efficient and unbiased and for the second purpose, an unbiased forecast of the mean costs in the original metric of the cost variable must be provided by the regression model. Unfortunately, due to the usual distributional characteristics of mental health service cost data, it is difficult to meet both of this criteria at the same time.

However, a critical review of existing studies makes obvious that the well known methodological problems associated with the application of ordinary least square regression on health service cost data[25-30] will either be ignored or managed inadequately in a majority of the existing studies. In most of the older but also in some recent studies, simple OLS regression with parametric standard errors has been used,[1,2,4-7,13,14;21] ignoring the potential problems from the non normality and heteroscedasticity of the residuals due to distributional characteristics of the dependent cost variable. In most of the more recent studies, the distributional characteristics of the dependent cost variable have been handled by a log transformation,[8-11,15-17,20] overlooking that the normalization of the dependent variable by a log transformation does not inevitably eliminate all of the skewness and heteroscedasticity of the residuals of the OLS regression. Furthermore the problem of the retransformation of the predicted costs after a log transformation has often been disregarded in these studies. Only some of the recently published studies on costing in mental health employ a methodology which takes into account the full range of problems attended with using regression analysis on skew distributed dependent variables.[18,19,22-24]

Kilian *et al.,*[23] as well as Byford *et al.,*[22] compute OLS regression models without transformation, despite the skewness of the dependent cost variable but employ a bootstrap procedure for getting standard errors which are robust against the violation of normality and heteroscedasticity of the residuals. Byford *et al.,*[22] compute an alternative generalized linear model (GLM) to confirm the adequacy of the linear OLS model. Unfortunately, the authors do not provide any information about the type of the GLM they computed, nor the results of the GLM and the criteria for the comparison with the OLS model. Knapp et al.[24] compare a linear OLS model with a log transformed OLS model and a GLM with a log link and a gamma distribution.The retransformation of the predicted costs of the log transformed OLS model were corrected by a smearing procedure.[31] As criteria for the comparison of regression models, the authors present the mean squared error and the mean absolute error for the log transformed OLS model and for the GLM. The authors find that the log transformed OLS model was the most appropriate for their data. The disadvantage of the approach employed by Knapp *et al.,* is that they do not test the homoscedasticity of the residuals of the log transformed OLS model. If the residuals are still heteroscedastic after a log transformation, the use of the simple smearing estimator to correct the prediction bias seems not to be adequate.[28] By contrast, Ettner *et al.,*[18] and Ettner and Hermann[19] employ a smearing algorithm taking into account the violation of non normality and heteroscedasticity of the residuals. Furthermore, Ettner *et al.,*[18] found that a square root transformation of the dependent variable was more adequate than the usually applied log transformation.

Methodological Problems of Regression with Health Service Cost Data

The main problems related to regression-based health service cost data analysis result from the extremely skewed distribution of the dependent variable. In most kind of health services, only few persons induce very high costs whereas the resource consumption of the majority of service users is low.[10,23,26] If health service costs of non clinical populations will be analysed, an additional complication results from the great proportion of people with zero health service costs.[30,32] Due to this common pattern of service utilization the distribution of mental health service cost data for clinical populations shows its peak on the left and a long tail on the right. For non clinical populations the peak of the distribution is at the zero point of the cost axis. As a consequence of this typical distribution of the dependent variable, the residuals of the regression model are frequently non-normal and heteroscedastic.[26,33-34] Though the violation of the assumption of normal and homoscedastic residuals has no consequences on the bias in parameter estimators, it may cause misestimation of standard errors and the calculation of wrong confidence intervals which could lead to biased conclusions about the significance of effects.[34] In particular when the influence patterns of equal sets of independent variables will be compared between different data sets such as in multi-centre studies, it becomes difficult to assess whether differences have a fundamental meaning or if they are only methodological artefacts. To deal with skewness, the dependent variable is often transformed to approximate the Gaussian normal curve. Additionally in the case of zero inflated cost data, it may be necessary to employ a two step estimation approach combining a logistic and a linear or non linear regression model.[30,32,35] However, because analysis of mental health service costs are often limited to clinical populations, the two step regression models will not be discussed further here. In the case of a positively skewed distribution with no zeros and a long right tail, the log-transformation of the form

$$\ln(y) = \alpha + \beta x + e$$

is often employed to obtain approximately normal and homoscedastic residuals. If the log transformation fails to provide a normal and homooscedastic error distribution other power transformations or the more general transformation of the Box-Cox[36] form

$$\frac{y^{\lambda} - 1}{\lambda} = \alpha + \beta x + e$$

might be applied.[18] Unfortunately, though normality of the residuals will be achieved by a power transformation, heteroscedasticity often still exists. Furthermore, when using a log or any other exponential transformation of the raw data regression parameters and predicted values are much more difficult to interpret than that of a regression with the original cost variable. For example, the regression parameter resulting from a log-transformed cost model reflects the change of the logarithm of service costs resulting from a one unit change of the independent variable. However, in most cases the researcher needs information on the impact of a change of an independent variable (e.g. psychopathological symptoms) on the services costs in pecuniary units. The calculation of effect ratios through the exponentiation of the regression parameter given by $\exp(b) \equiv e^{b}$, results in values which indicate the proportional change of the original cost variable due to an unit change of the independent variable.[26] More complicated than the interpretation of the regression parameter is the interpretation of the predicted values resulting from a regression with a log-transformed dependent variable. Originally the values predicted from a log-transformed regression model are log-costs. The exponentiation of the predicted values given by

$$\exp\left(\ln(y)\right) \equiv e^{x\hat{\beta}}$$

would result in the prediction of the median instead of the arithmetic mean of the costs. The simple exponentiation of the predicted values could result in a systematic positive or negative bias of the predicted costs depending on the distribution of the original variable, because the difference between the geometric mean (median) and the arithmetic mean of a variable increases with the variance on the log-scale, and the deviation of the distribution from log-normality.[26-28] Therefore the simple retransformation requires a bias correction. The type of the bias correction which must be used depends on the type of transformation, the distributional characteristics and the heteroscedasticity of the residuals.[26,28,29,31,37]

Bias problems caused by retransformation of OLS results can be avoided by using a non-linear link function in a generalized linear model (GLM) instead of the transformation of the dependent variable.[26-28,30,32,38,39] One can fit a regression equation of the general form:

$$g(E(y|x)) = \alpha + \beta x, \qquad y \sim F$$

where g is the link function, E(y) is the expected value of the dependent variable, and F is the distributional family of the dependent variable. The GLM can be estimated by iteratively re-weighted least square (IRLS) or the maximum likelihood method (ML). As shown in recent simulation studies the overall fit of the generalized linear model depends to a high degree on the adequate combination of the link function and the distributional family; see Blough *et al.*,[32] Blough and Ramsey[39] and Manning and Mullahy.[29] The correct specification of a GLM requires the precise knowledge of the mean function E(y|x) and of the variance function v(y|x) of the dependent cost variable *y* conditional to the independent variables *x*.[29,32,39] As an alternative to the specification of non-linear models robust standard errors and confidence intervals can be computed. While hitherto the so called sandwich estimator developed by White[40] predominantly has been used for that purpose, during the last years the application of bootstrapping techniques for the estimation of standard errors and confidence intervals became more popular.[41-45] Mechanically, bootstrapping is a Monte Carlo technique that draws *k* samples of the size *n* from the original sample with replacement. The distribution of the so called bootstrap samples provides an estimate of the "true" empirical distribution which can be used to compute standard errors and confidence intervals based on an empirical instead of a theoretical distribution.[44] The advantage of the bootstrapping method results from the possibility to get standard errors and confidence intervals which are robust against heteroscedasticity without the transformation of the original data and without the interpretation problems resulting from transformation.[25,27,45] However, they run the risk that the response is not linear on the original raw-scale, as well as being less efficient estimators. Given several regression-based methods for handling the problem of skew distributions of service cost data criteria are needed for the choice of the most appropriate method. In this paper we examine the results of four methods of managing the problems of positively skewed cost data for schizophrenia treatment over a twelve month period. We develop a strategy for choosing among the models and compare the performances of the alternatives.

Methods

Sampling Procedure and Sample Characteristics

The study sample consists of 254 patients with a diagnosis of schizophrenia (ICD-10 F 20.0) aged 18-64 years, who were treated by psychiatric services in Leipzig.[46] Participants where recruited from outpatient clinics, community mental health centers and private practitioners, psychiatric hospitals, and psychiatric day hospitals. Participants from every type of service were consecutively recruited until the stratification of patients to services in the sample was equivalent to the stratification of the population of persons with schizophrenia which were treated in Leipzig at the time of the study. Participants were asked to sign a written consent before they were included in the sample.

Data Collection and Instruments

Data were obtained by face-to-face interviews conducted by clinical psychologists who were trained in the application of the study instruments. Information on service use was collected with the German version of the Client Sociodemographic and Service Receipt Interview (CSSRI)[47,48] for a retrospective period of six months: the information for each patient was collected twice between September 1998 and September 1999.

Table 1. Summary statistics of continuous variables

Variable	Mean	SD	Skewness	Kurtosis
Cost	6278.82	10114.02	2.054	6.509
Log-cost	7.59	1.515	0.470	2.207
$Cost^{0.5}$	60.41	51.38	1.375	3.706
$-(Cost^{-0.5})$	-0.03	0.02	-1.001	4..795
Age	43.715	11.01	-.006	2.099
Years of education	9.74	1.64	-.278	3.176
General Assessment of Functioning	54.90	15.47	.178	2.516
BPRS 4.0 mean global score	1.39	0.32	1.169	4.366
Number of met service needs	2.51	2.51	1.141	4.009
Number of unmet needs	0.97	1.49	1.704	5.334
Global quality of life score	57.67	19.13	-.129	2.591

The clinical characteristics of the participants were assessed by means of the Brief Psychiatric Rating Scale (BPRS 4.0) for psychopathology,[49] the General Assessment of Functioning (GAF) for functional disability[50] and the German version of the Camberwell Assessment of Needs (CAN) for service needs. [51,52] For subjective quality of life we used to assess the short form of the World Health Organization Quality of Life questionnaire (WHOQOL-BREF)[53,54] was used.

Calculation of Service Costs

The service costs were calculated on the basis of the actual fees and charges for the period of the study paid by the German sickness funds. Costs were calculated for the following types of services: Psychiatric inpatient treatment, psychiatric day hospital treatment, sheltered accommodation, psychiatric outpatient treatment provided by outpatient clinics, community mental health centers, and office based psychiatrists, psychiatric medication prescribed in outpatient treatment, work rehabilitation, legal supervision, ambulant occupational therapy, and ambulant psychotherapy. Costs calculated for the two six-month periods were summed up to annual costs. Annual costs were converted into Euro at the exchange rate of € 1.00 = DM 1.95583.

Data analysis

Specification of the Linear OLS Model

All statistical analysis were done using STATA 7.0.[55] 24 cases with missing values at one of the model variables were excluded from the analysis. No significant differences in the means of the dependent or independent variables were found between included and excluded cases. The following linear regression model with ordinary least square estimation was computed as the basic model by the STATA procedure *regress.*

$$y = c+b_1x_1+b_2x_2+b_3x_3+b_4x_4+b_5x_5+b_6x_6 + b_7x_7+b_8x_8+b_9x_9+b_{10}x_{10}+b_{11}x_{11}+e$$

where

y = Annual cost of psychiatric treatment.
c = Constant.
$b_1 - b_{12}$ = Unstandardized regression coefficients of the independent variables $x_1 - x_{12}$.
e = Error term.
x_1 = Age in years.
x_2 = Gender: 0 = female, 1 = male.
x_3 = Employment status: 0 = unemployed, 1 = employed.
x_4 = Living situation: 0 = living alone, 1 = living with others.
x_5 = Years of education
x_6 = Partnership: 0 = having no partner, 1 = having a partner.
x_7 = General assessment of functioning GAF score (range = 0 – 100).
x_8 = BPRS 4.0 mean global score (range = 1.00 – 2.80).
x_9 = Number of met service needs (range = 0 – 12).
x_{10} = Number of unmet service needs (range = 0 – 7).
x_{11} = Global quality of life score(WHOQOL-BREF) (range = 0 – 100).

Since the dependent variable was found to be positively skewed with a long right tail robust standard errors and confidence intervals were computed using the sandwich estimator by White[39] with the *robust* option of STATA. In addition a nonparametric bootstrap technique with 2000 re-samples was used to estimate the standard errors

$$\hat{se}_i = \left\{ \frac{1}{k-1} \sum_{i=1}^{k} \left(b_i^* - \overline{b^*} \right)^2 \right\}^{1/2}$$

where i represent the 1,2,…k bootstrap samples, b_i^* are the

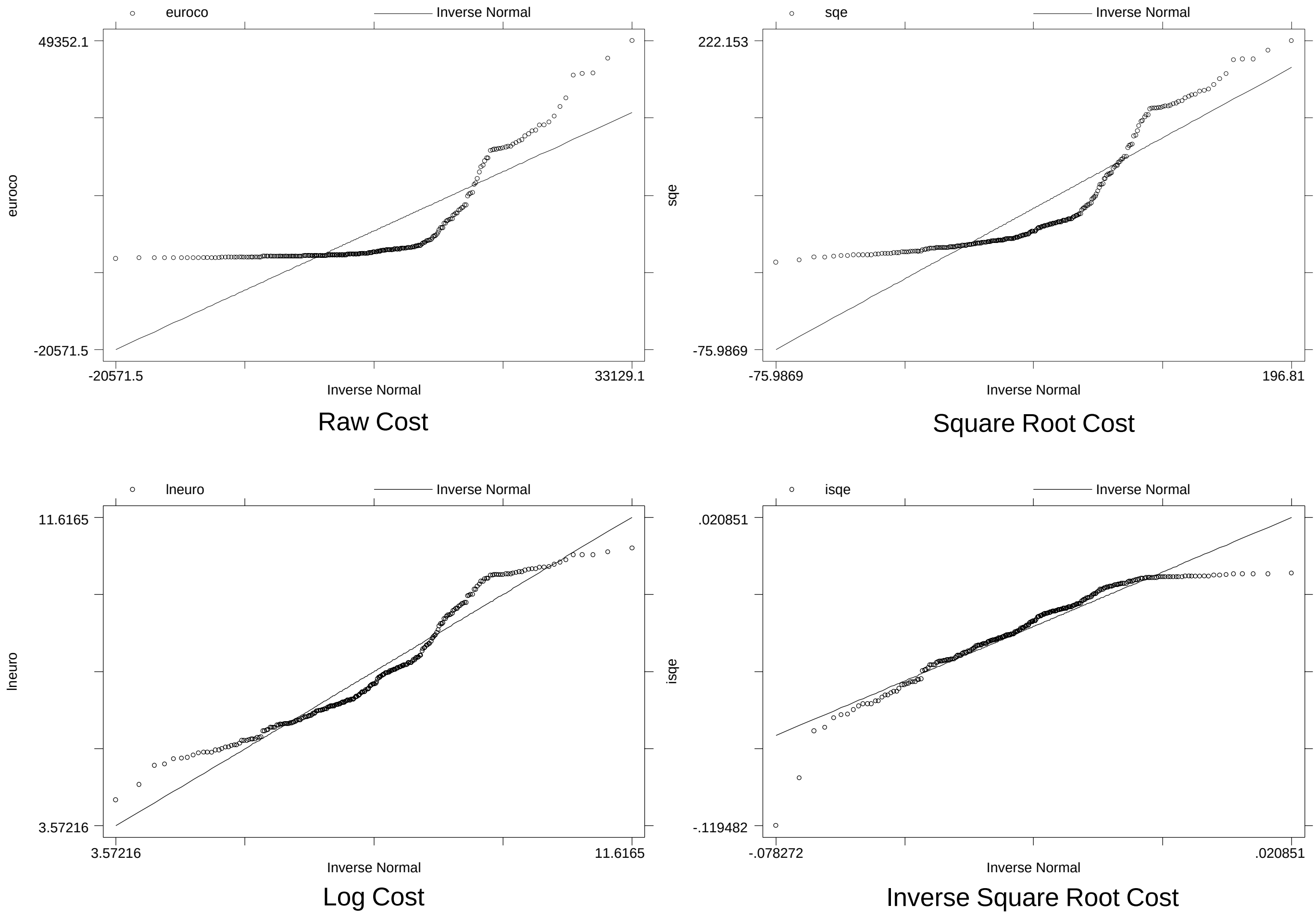

Figure 1. Quantile-normal plots for power-ladder transformations of the dependent cost variable

regression coefficients computed from each sample and $\overline{b^*}$ is the arithmetic mean of b_i^*. Confidence intervals were computed by means of the of the percentile method.[41-45] If the estimation bias defined as $(\hat{b}^* - \overline{b^*})$ was greater than 25% of the standard error, we used bias corrected confidence intervals.[55] Normality of the residuals were tested by the Shapiro-Wilk test[56] and heteroscedasticity of the residuals were tested by the Cook-Weisberg test.[33]

Specification of the Power Transformed OLS Model

The distribution of the dependent cost variable shows a positive coefficient of skewness of 2.05, which suggests the application of a power transformation to prevent non normal and heteroscedastic residuals. The power ladder approach[58] was used to find the most appropriate power transformation for the dependent cost variable. A square root transformation ($y^{.5}$), a log transformation (ln(y)) and an inverse square root transformation ($-(y^{-.5}$) were applied to the dependent variable and the distributional characteristics resulting from these transformations were compared.

Following this approach we found that the square root transformation provides a distribution with a coefficient of skewness of 1.37, the log transformation provides a distribution with a coefficient of skewness of .47 and the inverse square root transformation with provides a distribution with a coefficient of skewness of –1.00 (see **Table 1**). Additionally, quantile-normal plots of the raw cost and the power transformed cost were compared (see **Figure 1**).

As shown in **Figure 1**, the log transformation of the cost variable provides the best approximation to normal distribution. Therefore an OLS model was computed with the natural log of the annual service costs as dependent variable

$$\ln(\text{costs}) = c + b_1 x_{i,1} + b_2 x_{i,2} + \ldots + b_{11} x_{i,11} + e$$

and the same set of independent variables. The linearity of the model was confirmed by Pregibon's goodness-of-link-test using the STATA 7.0 procedure *linktest.*[55] For predicting the mean costs on the original scale of *y*, the predicted values of a power transformed regression model must be retransformed. Retransformation needs the use of a bias correction depending on the type of power transformation and the distributional characteristics of the residuals.[28,31,37] In the case of a log model with normally distributed and homoscedastic residuals, the expectation of y on the raw scale with respect to the independent variables *x* is

$$E(y \mid x) = e^{(\hat{z} + 0.5\hat{v})}$$

Table 2. Linear ordinary least square regression with nonparametric standard errors for the explanation of the variance of the annual costs in € for the treatment of schizophrenia.

	Robust "sandwich" standard errors and 95% confidence intervals				Bootstrap ‡ standard errors and 95% confidence intervals		
	b	se	95 % ci		se	95 % ci	
Age	-81.38	60.61	(-200.83	38.07)	59.54	(-198.14	35.38)
Gender*	-456.60	1157.89	(-2738.69	1825.50)	1156.67	(-2724.99	1811.80)
Employment status**	-1347.97	1160.97	(-3636.12	940.183)	1225.56	(-3751.47	1055.53)
Living situation†	325.51	1653.27	(-2932.93	3583.94)	1647.94	(-2906.36	3557.37)
Education	-49.44	355.24	(-749.58	650.71)	371.15	(-777.32	678.45)
Having a partner††	-2197.30	1600.64	(-5352.01	957.41)	1610.60	(-5355.94	961.33)
GAF	-40.27	57.39	(-153.38	72.83)	55.44	(-148.99	68.45)
BPRS 4.0 mean global score	6896.53	3439.53	(117.53	3675.52)	3314.59	(396.12	13396.93)
Met service needs	1446.13	315.20	(824.90	067.36)	317.66	(823.15	2069.12)
Unmet service needs	435.10	529.61	(-608.72	8.91)	526.53	(-597.50	1467.70)
Global quality of life	20.90	34.80	(-47.68	89.48)	35.00	(-47.75	89.55)
constant	-1447.16	8804.74	(-18800	15906.16)	8550.53	(-18216.04	15321.71)

R^2	.31
RSME (95% CI)[5)]	8317.50 (7349.54-9747.27)
F/Sig.	8.99/0.000
Cook-Weisberg heteroscedasticity tests	chi^2 = 97.32;p < = 0.000
Shapiro-Wilk Test for normality of residuals	V = 18.07/p =.000
N	230

***** 1 = male; ****** 1 = having a job; 0 = not having a job; **†** 1 = living with others; 0 = living alone **††** 1 = having a partner; 0 = having no partner
‡ 2000 replications.
Note: Bias corrected CI were presented if estimation bias was greater than 25% of the standard error.

where is the $E(y)$ expectation of *y* on the raw scale with respect to the independent variables *x*, z_i is the log of cost, $\hat{z}$ is the predicted log cost, and *v* is the variance of the residuals. In the case of non normal homoscedastic residuals, Duan[31] suggests

$$E(y \mid x)_i = e^{\hat{z}_i}\left(\frac{1}{n}\sum_{i=1}^{n} e^{z_i - \hat{z}_i}\right)$$

as a nonparametric bias correction. In the case of normal but heteroscedastic residuals, Manning[28] and Manning and Mullahy[29] suggest the replacement of the constant variance *v* by a log scale variance function *v*(x) leading to

$$\mathrm{E(y \mid x)} = \mathrm{e}^{(\hat{z}+0.5\mathrm{v(x)})}$$

where *v*(*x*) is the variance of the log-scale as a function of the x; one method to obtain v(x) is to regress the squared residual***** on the covariates.

* As suggested by Manning and Mullahy[29] for small samples, we used $\varepsilon/1\text{-hii}^{0.5}$ - where ε is the residual and hii is the diagonal element of the hat matrix - instead of the raw residuals as basis of the heteroscedasticity test and the heteroscedastic retransformation.

Specification of the Generalized Linear Model

Given the earlier evidence on the adequacy of the log transformation for the Leipzig data we estimated a log link function for the generalized linear model (GLM) leading to

$$\ln(E(costs)) = c + b_1 x_{i,1} + b_2 x_{i,2} + \dots + b_{12} x_{i,11} + e$$

Following the proposal of Manning and Mullahy[29] we estimated the variance function *v*(*y*/*x*) by regressing the log of the squared residuals $\ln(y-\hat{y})^2$ on the log of the predictions of the linear OLS regression model $\ln(\hat{y})$. The sloop of b_1= 1.88 resulting from this estimation indicates the variance of y(given x) is proportional to the square of the mean function, this suggests the choice of the gamma distribution as the distributional family of the GLM.[29, 32] The GLM provides predicted values in the original metric, therefore no exponentiation and consequently no correction of predicted values are necessary. Generally the overall fit of a GLM is estimated by the deviance and by the log-likelihood statistic. For a GLM with a gamma distribution the deviance D^2 is defined as

$$D^2 = \sum -2\left(\ln \frac{y_i}{\hat{\mu}_i}\right) - \left(\frac{y_i - \hat{\mu}_i}{\hat{\mu}_i}\right)$$

where $\hat{\mu}_i$ is the predicted mean of y for the i^{th} observation. A smaller value of D^2 indicates a better overall fit of the GLM. Unfortunately this statistics can not be used for comparisons between a GLM and a linear or nonlinear OLS regression. Zheng and Agresti[60] suggest calculating the R^2 of a GLM by computing $cor(y,\hat{y})^2$ which is the squared zero order correlation between the actual and the predicted values of y. Additionally the root mean square error (RSME) can be calculated for a GLM in the same way as for a OLS regression. The generalized linear model with a log link and a gamma distribution was estimated using the STATA 7.0 procedure *glm*.[55]

Comparison of Models

For the comparison of the predictive power of the three regression models the R^2 = $cor(y,\hat{y})^2$ and the root mean square error (RMSE)

$$rmse = \sqrt{\frac{1}{n}\sum(\hat{y}-y)^2}$$

were computed for each model.[60] Additionally, a split-sample-cross-validation approach suggested by Diehr *et al*.[26] was used for the comparison of the predictive power of the models. Regression models were computed for a 50% random sample of the original sample and annual costs were forecasted for the other 50% of the sample. Standard errors and 95% confidence intervals for the RMSE and for the difference between the RMSE of the linear OLS model and the RMSE of the other models were estimated by a bootstrap with 2000 replications using the *bstrap* procedure of STATA 7.0.[55]

Results

Table 2 shows the regression coefficients of the linear OLS regression with robust standard errors and confidence intervals estimated by White correction and by bootstrapping. The regression coefficients of the linear OLS model indicate the change of the annual costs in Euro (€) caused by a change of the independent variable by one unit. The robust confidence intervals show that the BPRS global score (b = 6896.53) and the number of met service needs (*b* = 1446.13) have a significant impact on the annual treatment costs. With each change of the mean BPRS symptom score by one unit, the annual treatment costs increase by € 6896.53. With each met service need, the annual costs increase by € 1446.13. As indicated by the R^2 the model explains 31% of the variance in cost. The RMSE is € 8317.50 with a 95% CI of € 7080 - € 9554.24. A comparison of the standard errors and 95% confidence intervals estimated by sandwich and by bootstrap method reveals only very small differences, in no case was the significance level of a variable changed due to the estimation method.

The results of the Shapiro-Wilks test reveal that the distribution of the residuals deviates significantly from normality. The results of the Cook-Weisberg test indicate that the residuals are heteroscedastic too.

On the left side **Table 3** contains results for the log transformed OLS model. Results of the Shapiro-Wilk test confirm that the distribution of the residuals are approximately normal. However, the homoscedasticity tests indicated that the log-scale residuals were still heteroscedastic. Therefore the sandwich estimator was used to get robust standard errors and confidence intervals. In contrast to the linear model the coefficients of the log-transformed model are not interpretable as changes of the annual costs but as changes of the log annual costs. The exponentiated coefficient e^b provides a more comprehensible interpretation as the proportional change of the annual costs resulting from a one unit change of the independent variable. As indicated by the 95% confidence intervals the log-transformed annual costs are negatively influenced by age and positively influenced by symptoms and number of met service needs. The exponentiated coefficients attest that an increase of the age by one year causes a decrease of the costs by approximately 2% (e^b = .978), that an increase of the mean symptom score by one unit causes more than a threefold increase of the annual costs (e^b= 3.068), and that with each additional met service need the annual costs increase by nearly 23% (e^b=1.226). The R^2 of .32 implies that the log-transformed model explains 32% of the variance of the log-transformed costs. For the assessment of the predictive power of the log-transformed model we computed the RMSE without bias correction and with the three bias correction procedures described above: (i) the simple smearing correction; (ii) the nonparametric bias correction proposed by Duan;[31] and (iii) the heteroscedastic bias correction proposed by Manning[28] and Manning and Mullahy.[29] As shown in **Table 3**, the raw RSME denotes a mean prediction error of € 9387,14 with a 95% CI of € 8044.80 - € 11359.36, the RSME calculated from predicted values corrected with simple smearing indicates a slightly higher mean prediction error of 9642, the same is true for the RMSE calculated from the nonparametric smearing correction of € 9467.49 with a 95% CI of € 5963.65 - € 12989.34. The smallest RMSE of € 9173.69 with a 95% CI of € 7021.96 - € 11325.41 was provided by the retransformation with the heteroscedastic bias correction. The 95% confidence intervals of the differences between the RSME of the linear OLS model and the log-transformed OLS model shows a significant difference when the retransformation was performed without bias correction.

The right column of **Table 3** contains the results form a generalized linear model (GLM) with a log-link and a gamma distribution are shown. The regression coefficients of the GLM were estimated by the maximum likelihood method, and the standard errors were estimated by using the sandwich estimator. The regression coefficients and the exponentiated coefficients can be interpreted analogous to those of the

Table 3. Log-transformed OLS regression model and generalized linear model for the explanation of the variance of the annual costs in € for the treatment of schizophrenia

	Log-transformed OLS model					GLM (maximum likelihood) with log link and gamma distribution $v(\mu) = \mu^2$				
	b	se ‡	95 % ci ‡		exp (b)	b	se ‡	95 % ci ‡		exp (b)
Age	-.022	.008	(-.038	-.005)	.978	-.006	.009	(-.024	.0124)	.994
Gender *	-.036	.170	(-.371	.298)	.964	-.115	.172	(-.452	.222)	.891
Employment status **	-.480	.245	(-.963	.003)	.618	-.813	.267	(-1.332	-.2892)	.443
Living situation †	-.347	.234	(-.808	.114)	.707	-.149	.214	(-.570	.271)	.861
Education	.022	.051	(-.078	.123)	1.022	-.050	.053	(-.155	.054)	.951
Having a partner ††	-.093	.239	(-.564	.379)	.911	-.651	.234	(-1.109	-.193)	.522
GAF	-.006	.007	(-.021	.009)	.994	-.002	.008	(-.017	.0142)	.998
BPRS 4.0 mean global score	1.121	.367	(.398	1.84)	3. 068	1.323	.316	(.703	1.943)	3.753
Met service needs	.204	.045	(.116	.292)	1.226	.200	.039	(.124	.276)	1.221
Unmet service needs	.008	.073	(-.136	.152)	1.008	.085	.062	(-.036	.207)	1.090
Global quality of life	-.001	.005	(-.011	.009)	.999	-.001	.005	(-.011	.009)	.998
constant	6.940	1.080	(4.810	9.070)	.978	7.184	1.140	(4.949	9.419)	.994
R^2	32					31				
RMSE (95% CI)/ Difference between RMSE and RMSE of linear OLS model (95% CI)	9387.14 (8044.80-11359.36) / 1069.64 (277.04 – 1862.24) • 9642.47 (5785.80-13499.15) / 1324.98 (-52.78 – 6878.82) •• 9476.49 (5963.65-12989.34) / 1158.99 (-60.36 – 6466.08) ••• 9173.69 (7021.96-11325.41) / 856.19 (-839.48 – 2551.86) ••••					11533.38 (4899.27 – 18167.50) / 3215.88 (304.98 – 16090.97				
F/sig.(df)	9.66/0.000 (11/218)					Deviance = 322.57				
Cook-Weisberg heteroscedasticity tests	$chi^2 = 13.68$;p < = 0.002									
Shapiro-Wilk Test for normality of residuals	V = 2.455/p =.0.869					V = 5.769/ p = 0.000				
N	230									

* 1 = male; ** 1 = having a job; 0 = not having a job; † 1 = living with others; 0 = living alone; †† 1 = having a partner; 0 = having no partner; ‡ sandwich estimator

• no bias correction; •• simple bias correction; ••• nonparametric "smearing" bias correction; •••• heteroscedastic bias correction

Table 4. Split-sample-cross-validation comparison of the forecast power of linear and non-linear cost functions with 95% CI.*

Model	RMSE(95% CI) $\sqrt{\frac{1}{n}\sum(\hat{y}-y)^2}$	Difference RMSE - RMSE (linear OLS) (95%CI)
Linear OLS	8898.87 (6725.28-10545.52)	-
Log-transformed OLS without bias correction	9725.27 (6883.61 - 12866.67)	826.41 (-3576.46 - 5229.28)
Log-transformed OLS with simple bias correction	10376.81 (6780.91 - 18834.83)	1477.94(-1013.29 - 19383.57)
Log-transformed OLS with nonparametric "smearing" bias correction	10608.24 (6802.91 - 20167.38)	1709.38 (-976.62 – 21916.60)
Log-transformed OLS with heteroscedastic bias correction	9624.58 (6487.72 - 12794.71)	725.72 (-7643.91 – 9095.35)
GLM (maximum likelihood) with log-link and gamma distribution	11645.46 (7486.00 – 32236.41)	2746.60 (-711.95 – 33679.98)

* 95 % CI computed by means of a bootstrap procedure with 2000 replications. Bias corrected CI were presented if the estimation bias was greater than 25 % of the standard error.

log-transformed OLS model. As indicated by the 95% confidence intervals partnership, employment status, the global BPRS symptom score and the number of met service needs have a significant impact on annual service costs. The exponentiated coefficients denote that for patients who have a regular job the annual service costs are only 44% of the costs of patients who are unemployed or who get a disability pension (e^b = .443). Participants who have a spouse or partner have 52% of the service costs of participants who have not (e^b = .522). The effects of the global symptom score and the number of met service needs are similar to those of the untransformed OLS model and the log-transformed OLS model. A unit increase of the mean symptom score causes nearly a fourfold increase of costs (e^b = 3.753). Each additional met service need increases annual costs at 22% (e^b = 1.221). As shown in **Table 3**, the R^2 of the GLM is .31 and the RMSE is € 11533.38 with a 95% CI of € 4899.27 - € 18167.50 which is higher than that of the untransformed OLS model and those of the log-transformed OLS model. Significance tests of the RMSE differences show that only the difference between the RMSE of the GLM and the RMSE of the linear OLS model is significant a the 95% level.

As suggested by Diehr *et al*.[26] a split-sample-cross-validation approach was employed to validate the comparison of the predictive power of the three regression based cost functions. For the purpose of getting standard errors and 95% confidence intervals, this procedure was replicated with 2000 bootstrap samples.

Results of the split-sample-cross-validation procedure are presented in **Table 4**. A comparison of the RMSE indicates that the untransformed OLS model produces the lowest forecast error indicated by a RMSE of € 8898.87 with a 95% CI of € 6725.28 -€ 10545.52, followed by the log-transformed OLS model with heteroscedastic bias correction, with a RMSE of € 9624.58 and a 95% CI of € 6487.72 - € 12794.71 and by the log-transformed model without bias correction with a RMSE of € 9725.27 and a 95% CI of € 6883.61 - € 12866.67. The 95% confidence intervals of the differences between the log-scale models and the linear OLS model in the right column of table 4 indicate that none of the differences is significant.

Discussion

The different methods for the estimation of costs functions were found to provide similar but not identical results. On the one hand each of the presented models implies that annual service costs are significantly influenced by psychiatric symptoms and by the number of met service needs. On the other hand, a significant negative effect of age on service costs was found only in the log-transformed OLS model and significant negative effects of employment status and partnership were only found in the GLM. That means, each of these models would lead to a slightly different interpretation of the influence structure. The comparison of the fit indices of the different models suggest that all models explain a similar proportion of the variance of annual mental health service costs but the linear OLS model shows the lowest prediction error and the lowest forecast error. The differences of the fit indices between the models are not statistically significant. The results of the application of the different methods for the correction of the retransformation bias confirm that in the case of residuals which remain heteroscedastic after a linear transformation of the dependent variable the method proposed by Manning and Mullahy[29] provides better results than the simple or the nonparametric smearing procedure. Since no single model dominated the others by a statistical significant amount, we decided that the easiest to interpret model with a non parametric estimation of standard errors was adequate for our data. However, it may be that for other data with different distributional characteristics log-transformed or other power transformed models may be run more appropriate. It is necessary to base the choice of the regression method for the analysis of health care cost data on an intensive examination of the data and not only on general recommendations. Furthermore, the generalizability of our findings is limited by the lack of statistical power due to the small sample size of our study.

Implications

According to the rationale for the application of regression analysis in the analysis of mental health service costs, the method used should provide regression coefficients, which are interpretable as changes of costs in the original metric, explain a substantial amount of variance, and provide forecast of the dependent variable in the original metric which are as precise as possible. Obviously, the fulfilment of this demands is mainly a question of adequate theory, measurement, and statistical analysis As demonstrated above, the same set of variables assessed by the same instruments in the same population may lead to different results, depending on the regression method used.

From the results presented above, we concluded that the application of linear OLS regression with non-parametric standard errors which are robust against non normality and heteroscedasticity of the residuals might be an appropriate method for the regression-based analysis of cost data in some cases. In comparison to transformed regression models the results from the untransformed OLS method were found to be more stable and provided an insignificantly better prediction and forecast of the dependent variable in its original metric than the log-transformed OLS model and the GLM with a log link and a Gamma distribution. However, that does not mean that linear OLS regression will be the best method for skew distributed health service cost data in general. On the contrary it means that the choice of the adequate method should be based on a careful screening of the characteristics of the data. Furthermore publications based on regression models of health service cost data should make the process of model selection fully transparent to the reader.

Limitations of the study result from the lack of statistical power due to the small sample size, particularly in the cross-validation samples. The non significance of the RMSE differences is therefore no sufficient proof that these differences are zero.

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