

Adjusted Limited Dependent Variable Mixture Models of Health State Utilities in R

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1 Introduction

Health-related quality of life is a key outcome in health technology assessments because it is patient-relevant and it is needed to calculate quality-adjusted life years. Quality of life instruments typically measure health problems in multiple domains using ordinal Likert scales. Value sets or valuation functions convert these profiles of ordinal measures into cardinal health-related utilities between 1 (perfect health) and minus infinity, where 0 represents death, and negative values represent health states worse than death. Because 100% quality of life represents perfect health, health state utilities are limited at 1. The lowest possible utility in a local value set further defines a lower limit of health state utilities in a local population. Thus, health state utilities are limited dependent variables. In addition, health state utilities often show gaps between 1 and the next smaller utility in the value set. These gaps occur more frequently in quality of life instruments with few levels in the Likert scales such as the EQ-5D-3L (Mulhern et al. 2018). A last but important particularity of health state utilities is that they can be the consequence of multiple latent classes, or they can exhibit multi-modal marginal densities (Hernández Alava et al. 2014).

Adjusted limited dependent variable mixture models are finite mixtures of normal distributions that account for limits, gaps between 1 and the next smaller utility value and multi-modality (Hernández Alava, Wailoo, and Ara 2012; Hernández Alava et al. 2013, 2014; Hernández Alava and Wailoo 2015; Mukuria et al. 2019). These features can improve empirical fit, parameter identification and predictive accuracy compared to standard regression models. Thus, adjusted limited dependent variable mixture models are particularly useful for mapping studies (Gray, Wailoo, and Hernández Alava 2018; Gray, Hernández Alava, and Wailoo 2018; Dixon, Hollingworth, and Sparrow 2020; Yang et al. 2019; Xu et al. 2020; Fuller et al. 2017; Pennington et al. 2020).

The R ‘aldvmm’ package is an implementation of the adjusted limited dependent variable model mixture model proposed by Hernández Alava and Wailoo (2015) using normal component distributions and a multinomial logit model of probabilities of component membership.

The objectives of this vignette are to demonstrate the usage of the ‘aldvmm’ package, show important challenges of fitting adjusted limited dependent variable mixture models and validate the R implementation against the STATA[®] package (Hernández Alava and Wailoo 2015) using publicly available data.

2 Methods

Adjusted limited dependent variable mixture models are finite mixtures of normal distributions in K components c with conditional expectations $E[y|X, c] = X\beta^c$ and standard deviations σ^c . The probabilities of component membership are estimated using a multinomial logit model as $P[c|X] = \exp(X\delta^c) / \sum_{k=1}^K \exp(X\delta^k)$. The model accumulates the density mass of the finite mixture below a minimum value Ψ_1 at the value Ψ_1 ,

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and the density mass above a maximum value Ψ_2 at 1. If the maximum value Ψ_2 is smaller than 1, the model emulates a value set with a gap between 1 and the next smaller value.

$$y_i|c = \begin{cases} 1 & \text{if } y_i|c > \Psi_2 \\ \Psi_1 & \text{if } y_i|c \leq \Psi_1 \\ y_i|c & \text{if } \Psi_1 < y_i|c \leq \Psi_2 \end{cases} \quad (1)$$

In this vignette, we estimate the same models of post-operative EQ-5D-3L utilities as Hernández Alava and Wailoo (2015) and include post-operative Oxford Hip Scores (divided by 10) as the only explanatory variable x .

$$\begin{aligned} \text{Model 1: } E[y|c, X] &= \beta_0^c + \beta_1^c x \\ P[c|X] &= \text{mlogit}(\delta_0^c) \\ \text{Model 2: } E[y|c, X] &= \beta_0^c + \beta_1^c x \\ P[c|X] &= \text{mlogit}(\delta_0^c + \delta_1^c x) \end{aligned} \quad (2)$$

The `aldvmm()` function fits an adjusted limited dependent variable mixture model using the likelihood function from Hernández Alava and Wailoo (2015). The function calls `optimr::optimr` to minimize the negative log-likelihood using numerical gradients from `numDeriv::grad()`. The `aldvmm()` function accepts all optimization methods available in `optimr::optimr()` except for “nlm,” which requires a different implementation of the likelihood function.

The model formula in `aldvmm()` is an object of class “formula” with two parts on the right-hand side of \sim . The first part on the left of the `|` delimiter represents the model of expected values of K normal distributions. The second part on the right of the `|` delimiter represents the model of probabilities of component membership from a multinomial logit model.

The ‘aldvmm’ package provides four options for the generation of starting values of the optimization algorithm.

1. “zero”: A vector of zeroes (default).
2. “random”: A vector of standard normal random values.
3. “constant”: Parameter estimates of a constant-only model as starting values for intercepts and standard deviations, and zeroes for all other parameters.¹
4. “sann”: Parameter estimates of a simulated annealing algorithm.

The ‘aldvmm’ package obtains fitted values using the expected value function from Hernández Alava and Wailoo (2015). Covariance matrices and standard errors of parameters are obtained from a numerical approximation of the hessian matrix using `numDeriv::hessian()`. Standard errors of fitted values in the estimation data SE_i^{fit} and standard errors of predicted values in new data SE_i^{pred} are calculated using the delta method (Dowd, Greene, and Norton 2014; Whitmore 1986). G_i denotes the gradient of a fitted value with respect to changes in parameter estimates, Σ denotes the covariance matrix of parameters, and MSE denotes the mean squared error of fitted versus observed values in the estimation data.

$$SE_i^{fit} = \sqrt{G_i' \Sigma G_i} \quad (3)$$

$$SE_i^{pred} = \sqrt{MSE + G_i' \Sigma G_i} \quad (4)$$

The `aldvmm()` function returns an object of S3 class “aldvmm” for which methods for generic functions `summary()` and `predict()` are available.

¹The auxiliary models for obtaining starting values are fitted using zero starting values.

3 Installation

The ‘aldvmm’ package can be installed from cran.

```
install.packages("aldvmm")
```

4 Data

We analyze the same publicly available EQ-5D-3L utility data from English patients after hip replacement in 2011 and 2012 (NHS Digital 2013) as Hernández Alava and Wailoo (2015) in their description of the STATA® ALDVMM package.

```
temp <- tempfile()

url <- paste0("https://files.digital.nhs.uk/publicationimport/pub11xxx/",
             "pub11359/final-proms-eng-apr11-mar12-data-pack-csv.zip")

download.file(url, temp)
rm(url)

df <- read.table(unz(description = temp,
                    filename = "Hip Replacement 1112.csv"),
                sep = ",",
                header = TRUE)

unlink(temp)
rm(temp)

df <- df[, c("AGEBAND", "SEX", "Q2_EQ5D_INDEX", "HR_Q2_SCORE")]
df <- df[df$AGEBAND != "*" & df$SEX != "*", ]

df$eq5d <- df$Q2_EQ5D_INDEX
df$hr <- df$HR_Q2_SCORE/10

df <- df[stats::complete.cases(df), ]

set.seed(101010101)
df <- df[sample(1:nrow(df), size = nrow(df)*0.3), ]
```

The data includes 35'166 observations with complete information on patients' post-operative utilities, Oxford Hip Scores, age and sex. Like Hernández Alava and Wailoo (2015), we draw a 30% sub-sample of 10'549 observations from the population of complete observations of these variables. Although we follow a similar approach in data preparation preparation as Hernández Alava and Wailoo (2015), our random sample is not identical to the data used in their study. Post-operative EQ-5D-3L utilities from English value sets (Dolan 1997) show a bimodal distribution, limits at -0.594 and 1 and a gap between 1 and 0.883 (figure 1).

5 Results

5.1 Model 1

5.1.1 BFGS optimization method with zero-only starting values

We first fit model 1 with the “BFGS” optimization method and “zero” initial values. The values 0.883 and -0.594 in the argument ‘psi’ represent the maximum and minimum values smaller than 1 in the English value

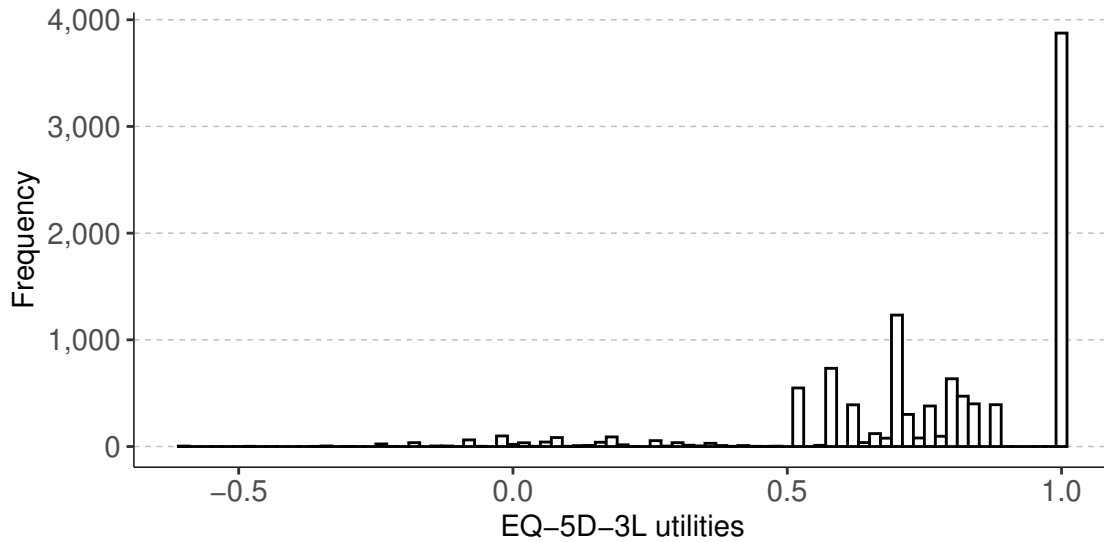


Figure 1: Frequency distribution of observed EQ-5D-3L utilities

set (Dolan 1997). As the data showed a bi-modal distribution (figure 1), we estimate a mixture of 2 normal distributions (`ncmp` = 2). `aldvmm()` returns an object of class “aldvmm.”

```
library("aldvmm")

fit <- aldvmm::aldvmm(eq5d ~ hr | 1,
  data = df,
  psi = c(0.883, -0.594),
  ncmp = 2,
  init.method = "zero",
  optim.method = "BFGS")

summary(fit)

pred <- predict(fit,
  newdata = df,
  se.fit = TRUE,
  type = "fit")
```

We obtain a summary table of regression results using the generic function `summary()`. The model converges at a log-likelihood of 706.32 and an Akaike information criterion value of -1'398.65 (table 1).

The coefficients of the intercept and covariates for the expected values $E[y|c, X]$ of the normal distributions can be interpreted as marginal effects on component means. ‘`lnsigma`’ denotes the natural logarithm of the estimated standard deviation σ^c . The coefficients of covariates in the multinomial logit model of probabilities of component membership are log-transformed relative probabilities. Our model only includes two components, and the multinomial logit model collapses to a binomial logit model. The intercept of 0.728 means that the average probability of an observation in the data to belong to component 1 is $\exp(0.728)$ or 2.0709346 times the probability to belong to component 2.

We obtain expected values of observations in the estimation data using the generic function `predict()`. Standard errors of fitted (estimation data) or predicted (new data) values are calculated using the delta method. Expected values exhibit a smoother distribution than observed values and do not show a gap between 1 and 0.883, because they are weighted averages of component distributions and 1.

Table 1: Regression results from model1 with "BFGS" optimization method and "zero" starting values

		Estimate	Std. Err.	z	P> z	[95% Conf. Interval]
E[y X, c]						
Comp1	(Intercept)	0.236	0.007	34.179	0.000	0.222 0.249
	hr	0.146	0.002	76.362	0.000	0.142 0.150
	lnsigma	-2.462	0.018	-138.131	0.000	-2.497 -2.427
Comp2	(Intercept)	-0.431	0.022	-19.231	0.000	-0.475 -0.387
	hr	0.313	0.007	47.942	0.000	0.301 0.326
	lnsigma	-1.248	0.022	-57.989	0.000	-1.290 -1.206
P[c X]						
Comp1	(Intercept)	0.728	0.061	12.006	0.000	0.609 0.847
N = 10549		ll = 706.32	AIC = -1398.65	BIC = -1347.80		

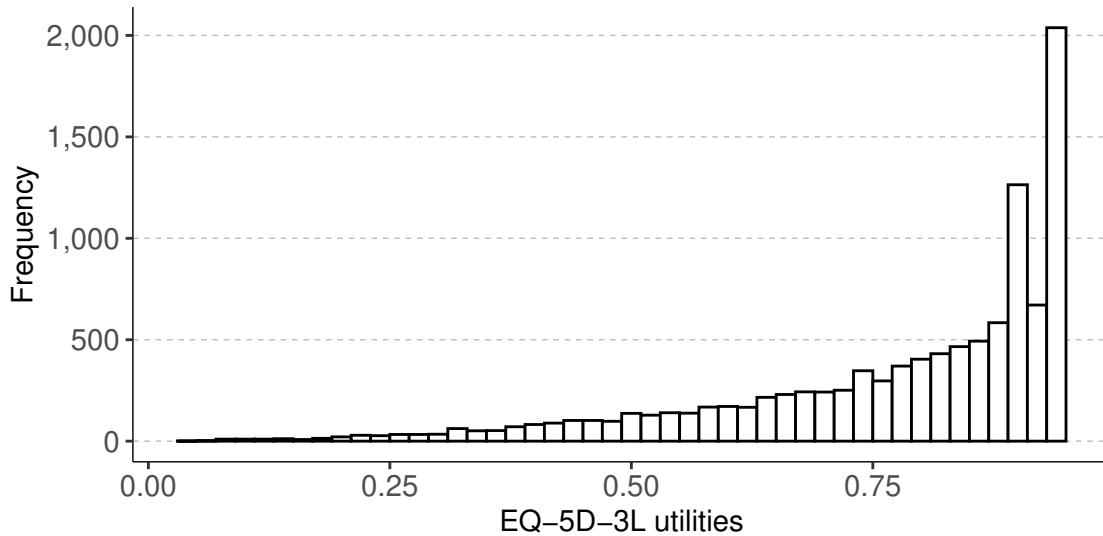


Figure 2: Expected values from base case model

Expected values of observations in the estimation data can also be used to calculate average incremental effects or average treatment effects on the treated. Average treatment effects on the treated compare predictions for treated individuals to predictions for the same individuals without the effect of the treatment indicator. Standard errors of average treatment effects on the treated can be calculated using the delta meethod (see example code in the appendix).

5.1.2 Comparison of optimization methods

Hernández Alava and Wailoo (2015) suggested that the likelihood function of the adjusted limited dependent variable mixture model with the English EQ-5D-3L data might have multiple local optima, and that the estimation is sensitive to initial values. We thus fit model 1 with all optimization algorithms and methods for generating initial values available in `aldvmm()` to assess the sensitivity of the model to optimization settings and to find the maximum likelihood estimates.

```

init.method <- c("zero", "random", "constant", "sann")

optim.method <- c("Nelder-Mead", "BFGS", "CG", "L-BFGS-B", "nllminb", "Rcgmin",
                 "Rvmmmin", "hjn")

fit1_all <- list()

```

```

for (i in init.method) {
  for (j in optim.method) {
    set.seed(101010101) # Seed for random starting values
    fit1_all[[i]][[j]] <- aldvmm::aldvmm(eq5d ~ hr | 1,
                                       data      = df,
                                       psi       = c(0.883, -0.594),
                                       ncmp     = 2,
                                       init.method = i,
                                       optim.method = j)
  }
}

```

The maximum likelihood varies considerably across optimization methods and initial values which confirms the sensitivity of the model to changes in these settings (table 2). The most frequent log-likelihood is 706.32, but the Hooke and Jeeves Pattern Search Optimization (“hjn”) with “zero” initial values converges at a log-likelihood 33’057.43.

The optimization methods “Nelder-Mead,” “CG,” “L-BFGS-B,” and “Rvmmmin” are particularly sensitive to starting values. The method “BFGS” coversges at a log-likelihood of 706.32 with three of four sets of initial values, and the method “hjn” with two of four sets of initial values. The methods “nlminb” and “Rcgmin” converge at a log-likelihood of 706.32 regardless of initial values.

Table 2: Log-likelihood by optimization method

	Nelder-Mead	BFGS	CG	L-BFGS-B	nlminb	Rcgmin	Rvmmmin	hjn
zero	-259.21	706.32	223.96	-4513.33	706.32	706.32	-8393.14	33057.43
random	-434.21	-623.98	65.03	-2830.18	706.32	706.32	-11074.58	-627.78
constant	354.36	706.32	-601.52	-634.81	706.32	706.32	-10867.67	706.32
sann	706.19	706.32	576.51	706.32	706.32	706.32	706.32	706.32

The computation times of optimization routines vary considerably across methods (table 3). The optimization methods “Nelder-Mead,” “BFGS,” “L-BFGS-B” and “Rvmmmin” are the fastest methods, but this speed comes at the cost of a higher risk of convergence at local optima. Naturally, the generation of initial values using simulated annealing (“sann”) is the slowest method for generating initial values which results in long overall computation times of aldvmm(). The Hooke and Jeeves Pattern Search Optimization (“hjn”) with “zero” starting values that converges at the largest log-likelihood is the slowest approach with a computation time of 15.16 minutes.

Table 3: Estimation time [minutes] by optimization method

	Nelder-Mead	BFGS	CG	L-BFGS-B	nlminb	Rcgmin	Rvmmmin	hjn
zero	0.14	0.30	1.01	0.10	0.54	4.20	0.05	15.16
random	0.13	0.39	1.07	0.20	0.54	4.16	0.05	0.41
constant	0.20	0.48	1.35	0.31	0.83	2.96	0.05	1.00
sann	2.13	2.06	3.00	3.07	2.33	5.38	2.04	4.06

Parameter estimates differ considerably across the three optimization algorithms (table 4). The solution of the “hjn” method is rather extreme with no effect of the Oxford Hip Score and a standard deviation of almost 0 in component 1 and a very low probability of membership of component 1.

To get a better understanding of the differences between the results of the “Nelder-Mead,” “nlminb” and “hjn” algorithms we plot the densities of each component weighted by the probability of component membership.

```

nsim <- 100
hr <- 3.825244 # Population average Oxford Hip Score

```

Table 4: Regression results of model1 with zero starting values in "Nelder-Mead", "nlminb" and "hjn" algorithms

		Nelder-Mead	nlminb	hjn
<hr/>				
E[y X, c]				
Comp1	(Intercept)	-0.057	-0.431	0.691
	hr	0.223	0.313	0.000
	lnsigma	-1.838	-1.248	-36.737
Comp2	(Intercept)	4.402	0.236	-0.149
	hr	-0.997	0.146	0.250
	lnsigma	0.125	-2.462	-1.589
<hr/>				
P[c X]				
Comp1	(Intercept)	3.849	-0.728	-2.190
N = 10549		ll = -259.21	AIC = 532.42	AIC = -1398.65
				AIC = -66100.87

```
# Nelder-Mead parameter estimates
n1 <- nsim*exp(3.8489)/(1 + exp(3.8489))
mean1 <- -0.0575 + 0.2233 * hr
sd1 <- exp(-1.8381)
n2 <- nsim*(1 - exp(3.8489)/(1 + exp(3.8489)))
mean2 <- 4.4022 + -0.9974 * hr
sd2 <- exp(0.1250)

# Make plot
ggplot2::ggplot(data = data.frame(x = c(-1, 1)), aes(x)) +
  ggplot2::stat_function(fun = dnorm,
                        n = n1,
                        args = list(mean = mean1, sd = sd1)) +
  ggplot2::stat_function(fun = dnorm,
                        n = n2,
                        args = list(mean = mean2, sd = sd2))
```

The densities in the solution of the “Nelder-Mead” method resemble the bi-model distribution observed in the data (figure 3). The densities in the solution of the “nlminb” method include two distributions with similar means but different standard deviations (figure 4). The densities in the solution of the “hjn” method include two distributions with similar means, but component 1 shows an extremely small standard deviation and a low probability of group membership (figure 5). The density plots also suggest that the model fit benefits more from improving the modeling of the more frequently observed higher utilities rather than replicating the bi-modal distribution observed in the data. Overall, the differences between optimization methods show that it is very difficult to fit a two-component model to the data. We suspect that a simple one-component model would be more likely to converge towards a global optimum and would fit the data similarly well as the two-component model.

The differences in parameter estimates from different optimization methods show that the choice of the optimization algorithm and initial values is very important for parameter identification. As adjusted limited dependent variable mixture models are frequently used for tasks that rely on predictions, we also compare expected values from the “Nelder-Mead” and “hjn” methods to expected values from the “nlminb” method. Expected values from the “Nelder-Mead” and “hjn” methods differed from expected values from the “nlminb” method among observations with lower expected values (figure 6).

An visual inspection of mean residuals over deciles of expected values shows that model 1 fits the data poorly regardless of the optimization method, and that the patterns of over- and under-predictions of observed values are similar across optimization methods despite different log-likelihoods (figure 9, figure 10 and figure 11 in the appendix).

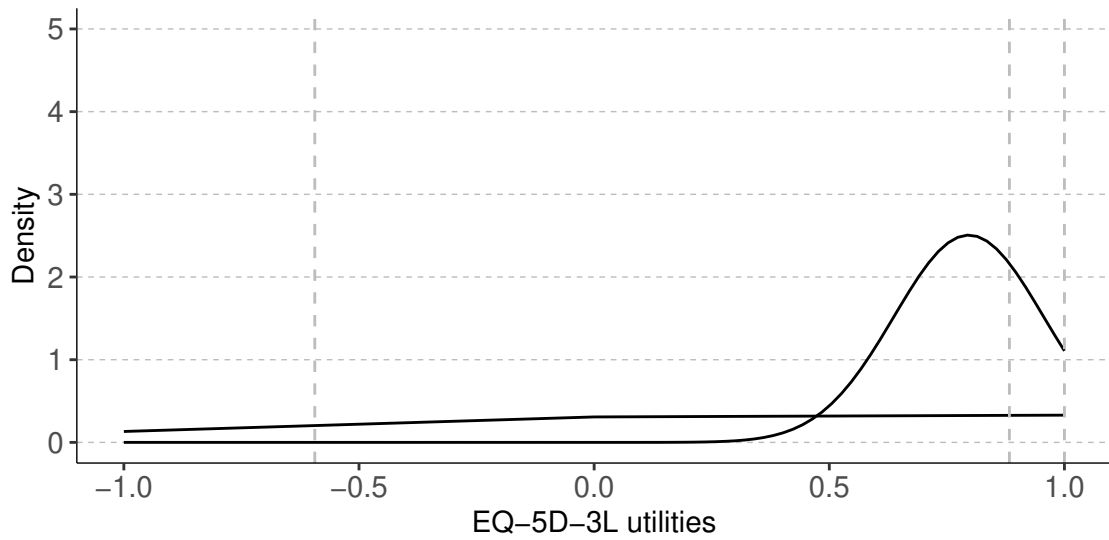


Figure 3: Densities in components based on “Nelder-Mead” parameter estimates (observation with population average Oxford Hip Score 3.8489)

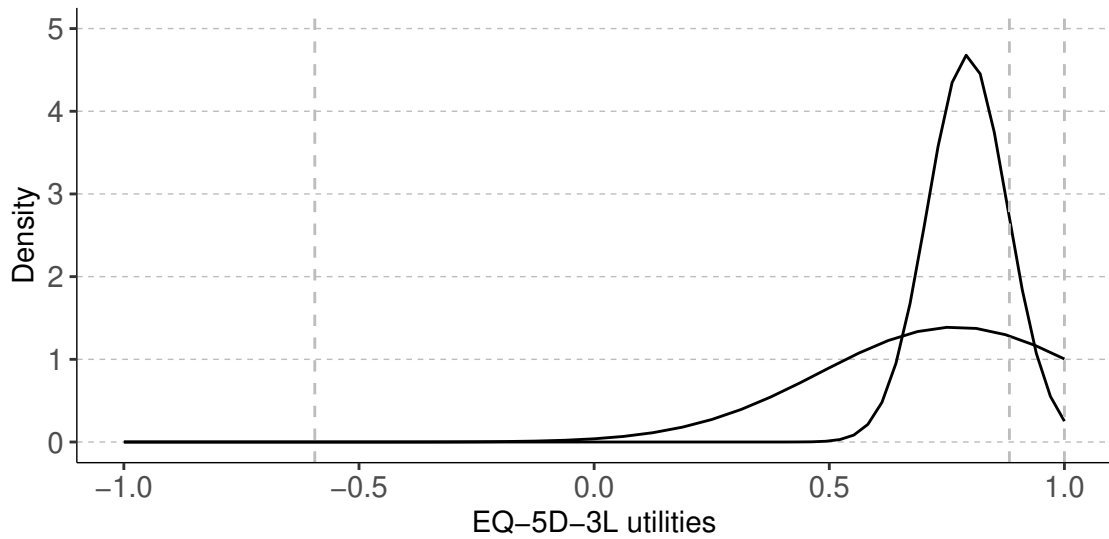


Figure 4: Densities in components based on “nlnmb” parameter estimates (observation with population average Oxford Hip Score 3.8489)

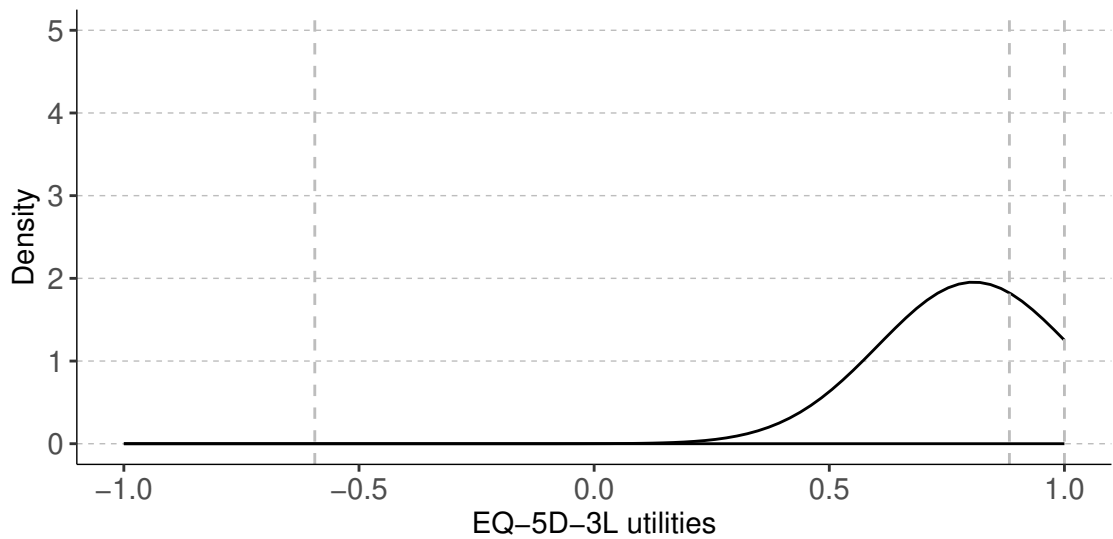


Figure 5: Densities in components based on “hjn” parameter estimates (observation with population average Oxford Hip Score 3.8489)

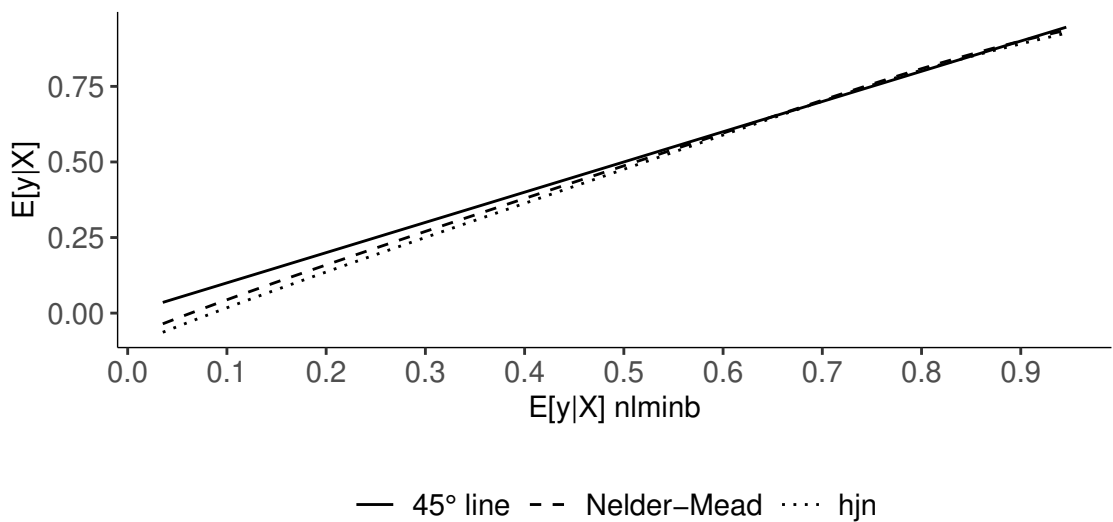


Figure 6: Expected values from model 1, “Nelder-Mead” and “hjn” versus “nlminb” with zero starting values

5.1.3 Constrained optimization with user-defined initial values

We can also fit model 1 with user-defined starting values and box constraints. When constraints are imposed, the `aldvmm()` function uses the optimization method “L-BFGS-B,” which shows very sensitive to starting values. We use zero initial values for all parameters except for the intercept in the multinomial logit which we set to the estimate from the “nlminb” optimization method with “zero” starting values (0.7283) (table 4). We impose a lower limit of -3 to the log-standard deviations in both components. The `aldvmm()` function returns a warning that the covariance matrix included negative values on the diagonal. We see that these values are the variances of the intercept and the log-standard deviation in component 2 (table 5). The log-likelihood amounts to -627.78, which is even lower than the log-likelihood in the solution of the “Nelder-Mead” optimization method with “zero” starting values. The parameter estimates do not resemble any of the solutions of the unconstrained “Nelder-Mead,” “nlminb” or “hjn” optimization methods with “zero” values (table 4), which further emphasizes the difficulties in finding a global optimum of the likelihood with English EQ-5D-3L utilities after hip replacement.

```
init <- c(0, 0, 0, 0, 0, 0, 0.7283)
lo <- c(-Inf, -Inf, -3, -Inf, -Inf, -3, -Inf)
hi <- c(Inf, Inf, Inf, Inf, Inf, Inf, Inf)

fit1_ustr <- aldvmm::aldvmm(eq5d ~ hr | 1,
  data = df,
  psi = c(0.883, -0.594),
  ncmp = 2,
  init.est = init,
  init.lo = lo,
  init.hi = hi)

summary(fit1_ustr)
```

Table 5: Regression results of model1 with the "L-BFGS-B" method, parameter constraints and user-defined starting values

		Estimate	Std. Err.	z	P> z	[95% Conf. Interval]
E[y X, c]						
Comp1	(Intercept)	-0.092	0.009	-10.805	0.000	-0.109 -0.075
	hr	0.232	0.002	101.849	0.000	0.228 0.237
	lnsigma	-1.641	0.009	-183.981	0.000	-1.658 -1.623
Comp2	(Intercept)	0.393	NaN	NaN	NaN	NaN NaN
	hr	2.525	7.479	0.338	0.736	-12.135 17.184
	lnsigma	-0.765	NaN	NaN	NaN	NaN NaN
P[c X]						
Comp1	(Intercept)	6.852	0.539	12.717	0.000	5.796 7.908
N = 10549 ll = -627.78 AIC = 1269.55 BIC = 1320.40						

5.1.4 Single-component model

As the solution of the “hjn” algorithm included a component with very low probability, we also estimate a single-component model.

```
fit <- aldvmm::aldvmm(eq5d ~ hr,
  data = df,
  psi = c(0.883, -0.594),
  ncmp = 1,
  init.method = "zero",
  optim.method = "nlminb")
```

```
summary(fit)
```

The coefficients of the single-component model are relatively similar to the parameters in the second component of model 1 from the “hjn” algorithm (table 6). The Akaike information criterion amounts to 1’275.61 which is larger than the values of the “nlminb” (-1’398.65) and “hjn” (-66’100.87) solutions of the two-component model and thus suggests worse fit of the single-component model.²

Table 6: Regression results of model1 with 1 component, zero starting values in "nlminb" algorithm

		Estimate	Std. Err.	z	P> z	[95% Conf. Interval]	
E[y X, c]							
Comp1	(Intercept)	-0.089	0.009	-10.410	0.000	-0.105 -0.072	
	hr	0.232	0.002	101.468	0.000	0.227 0.236	
	lnsigma	-1.636	0.009	-184.242	0.000	-1.654 -1.619	
N = 10549		ll = -634.81	AIC = 1275.61	BIC = 1297.40			

5.2 Model 2

As an alternative specification, we explore model 2 with a coefficient of the Oxford Hip score in the multinomial logit model of component membership. For this fit, we use the method “nlminb” with estimates from Hernández Alava and Wailoo (2015) as starting values.

```
init <- c(-.40293118, .30502755, .22614716, .14801581, -.70755741, 0,  
         -1.2632051, -2.4541401)
```

```
fit2 <- aldvmm::aldvmm(eq5d ~ hr | hr,  
                      data = df,  
                      psi = c(0.883, -0.594),  
                      ncmp = 2,  
                      init.est = init,  
                      optim.method = "nlminb")
```

```
summary(fit2)
```

The Akaike information criterion of model 2 fitted using the “nlminb” method amounts to -1’862.44 which is smaller than the Akaike information criterion of model 1 (-1’398.65) with the same method. The smaller Akaike information criterion suggests that the increase in the log-likelihood after inclusion of a coefficient of the Oxford Hip Score on the probability of component membership is sufficiently large to justify the extra parameter.³

5.3 Comparison to STATA[®] results

To validate the R implementation of adjusted limited dependent variable mixture models, we estimate the four models presented in Hernández Alava and Wailoo (2015) as reference cases in R and STATA[®].⁴

1. Model 1 with default options
2. Model 1 with parameter constraints
3. Model 1 with initial values from constant-only model
4. Model 2 with user-defined initial values

²In the aldvmm() output, smaller values of the Akaike information criterion indicate better goodness of fit.

³In the aldvmm() output, smaller values of the Akaike information criterion indicate better goodness of fit.

⁴The STATA[®] and R code for model estimation is included in the appendix.

Table 7: Regression results of model 2 with user-defined starting values in the "nlminb" algorithm

		Estimate	Std. Err.	z	P> z	[95% Conf.	Interval]
E[y X, c]							
Comp1	(Intercept)	-0.119	0.015	-7.932	0.000	-0.149	-0.090
	hr	0.080	0.006	13.665	0.000	0.069	0.092
	lnsigma	-1.872	0.035	-53.692	0.000	-1.940	-1.804
Comp2	(Intercept)	0.201	0.006	31.772	0.000	0.189	0.213
	hr	0.156	0.002	94.616	0.000	0.153	0.159
	lnsigma	-2.213	0.011	-202.408	0.000	-2.235	-2.192
P[c X]							
Comp1	(Intercept)	1.774	0.131	13.534	0.000	1.517	2.031
	hr	-1.353	0.044	-30.574	0.000	-1.439	-1.266

N = 10549 ll = 939.22 AIC = -1862.44 BIC = -1804.33

The parameter estimates and standard errors obtained in R are very similar to the results from STATA[®] (table 8 and table 9). R did not obtain any standard errors in reference model 2 while STATA[®] returned standard errors for the first component and the probability of belonging to component 1. Although reference models 1 and 3 yield different parameter estimates, they converged at the same log-likelihood which further supports the hypothesis of multiple local optima of the likelihood. The log-likelihood is consistently smaller in R than in STATA[®], but the relative ordering of models is consistent across platforms.

Table 8: Comparison of point estimates to the results of the STATA package

		(1)		(2)		(3)		(4)	
		R	STATA	R	STATA	R	STATA	R	STATA
E[y X, c]									
Comp1	(Intercept)	-0.431	-0.427	-0.092	-0.092	0.236	0.236	0.003	0.006
	hr	0.313	0.312	0.232	0.232	0.146	0.146	0.097	0.095
	lnsigma	-1.248	-1.251	-1.641	-1.641	-2.462	-2.463	-1.268	-1.274
Comp2	(Intercept)	0.236	0.236	100.000	100.000	-0.431	-0.427	0.182	0.182
	hr	0.146	0.146	0.000	0.000	0.313	0.312	0.161	0.161
	lnsigma	-2.462	-2.463	0.000	0.000	-1.248	-1.251	-2.281	-2.280
P[c X]									
Comp1	(Intercept)	-0.728	-0.725	6.856	6.855	0.728	0.725	2.445	2.448
	hr							-1.390	-1.393
N = 10549	ll	706.32	715.84	-627.78	-613.7	706.32	715.84	941.36	953.2

Table 9: Comparison of standard errors to the results of the STATA package.

		(1)		(2)		(3)		(4)	
		R	STATA	R	STATA	R	STATA	R	STATA
E[y X, c]									
Comp1	(Intercept)	0.022	0.022	NA	0.009	0.007	0.007	0.028	0.028
	hr	0.007	0.006	NA	0.002	0.002	0.002	0.012	0.012
	lnsigma	0.022	0.021	NA	0.009	0.018	-0.018	0.031	0.032
Comp2	(Intercept)	0.007	0.007	NA		0.022	0.022	0.007	0.007
	hr	0.002	0.002	NA		0.007	0.006	0.002	0.002
	lnsigma	0.018	0.018	NA		0.022	0.021	0.013	0.013
P[c X]									
Comp1	(Intercept)	0.061	0.061	NA	0.540	0.061	0.061	0.172	0.172
	hr							0.057	0.056
N = 10549	ll	706.32	715.84	-627.78	-613.7	706.32	715.84	941.36	953.2

Fitted values show very similar marginal distributions on both platforms (figure 7). R does not return fitted values in reference case 2. The summary statistics of differences in fitted values between R and STATA[®] suggest that individual predictions are quite similar across platforms as well (table 10).

Standard errors of fitted values differ visibly between platforms (figure 8 and table 11). The difference is particularly pronounced in reference case 1, but the standard errors from STATA[®] seem quite extreme compared to all other reference cases. R does not return standard errors of fitted values in reference case 2.

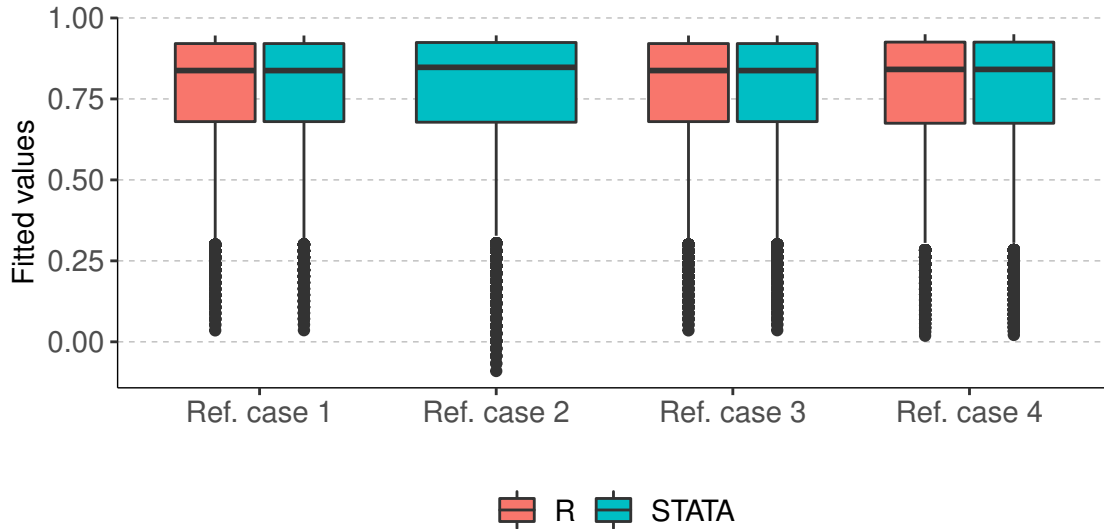


Figure 7: Fitted values in R and STATA

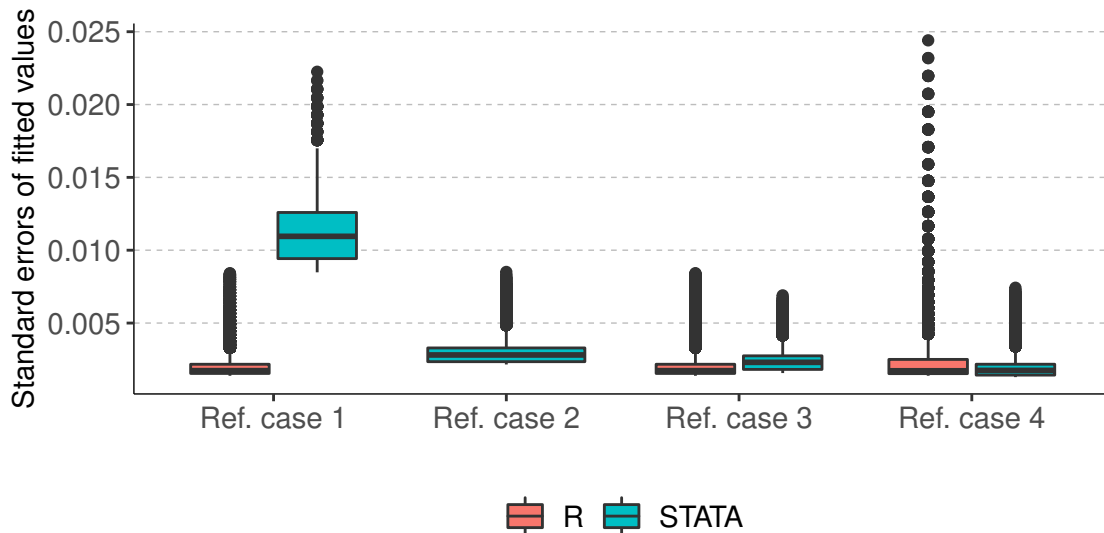


Figure 8: Standard errors of fitted values in R and STATA

The comparison of the R and STATA[®] packages showed that the R implementation sometimes behaves differently than the STATA[®] package, but the results are not indicative of technical errors in the R implementation.

Table 10: Summary statistics of differences of fitted values in R and STATA (positive values suggest larger values in STATA)

	Ref. case 1	Ref. case 2	Ref. case 3	Ref. case 4
Min.	-0.000038		-0.000038	-0.000051
1st Qu.	-0.000036		-0.000036	-0.000044
Median	-0.000033		-0.000033	0.000008
Mean	0.000037		0.000037	0.000035
3rd Qu.	0.000047		0.000047	0.000070
Max.	0.000567		0.000567	0.002319

Table 11: Summary statistics of differences of standard errors of fitted values in R and STATA (positive values suggest larger values in STATA)

	Ref. case 1	Ref. case 2	Ref. case 3	Ref. case 4
Min.	0.005897		-0.002063	-0.016984
1st Qu.	0.006898		-0.000551	-0.000823
Median	0.008690		0.000189	-0.000364
Mean	0.008917		0.000171	-0.000515
3rd Qu.	0.011050		0.001054	0.000354
Max.	0.013830		0.001530	0.000792

6 Discussion

Adjusted limited dependent variable mixture models are powerful tools for regression analysis of health state utilities. Unlike standard regression models, adjusted limited dependent variable mixture models account for limits, gaps and multi-modal distributions.

The comparison of different optimization methods with EQ-5D-3L utility data from English patients after hip replacement in 2011 and 2012 (NHS Digital 2013) shows that the likelihood function can be challenging to maximize and can converge at extreme solutions. Parameter estimates vary considerably across optimization methods and even across methods with the same maximum log-likelihood. However, fitted values are very similar across the four reference cases which suggests that the model is more robust for the identification of incremental and average marginal effects than for parameter identification.

The ‘aldvmm’ package offers a variety of optimization algorithms and methods for generating initial values which is an important strength in such challenging situations. It is essential to assess different optimization algorithms and methods for initial values before interpreting the parameter estimates or predictions of adjusted limited dependent variable mixture models.

The analysis of the EQ-5D-3L utility data also suggests that simpler models with fewer components should be considered when multi-component models are difficult to fit. Even single-component adjusted limited dependent variable mixture models can improve fit compared to traditional regression techniques because they account for limits and gaps.

Although coefficients can be interpreted as marginal effects within each component, they cannot be interpreted in terms of overall expected values. Thus, average marginal effects and average treatment effects need to be calculated from predictions using the generic function `predict()`. Standard errors of marginal effects or average treatment effects can be calculated using the standard errors of fitted values for observed and counterfactual covariate values.

In situations with repeated utility measures, the ‘aldvmm’ package only allows fixed effects estimations with individual/group and time fixed effects which can be an important limitation in the analysis of clinical data. However, time fixed effects can be an appropriate modeling strategy in the presence of general time trends and dynamic selection in the population, e.g. because health state utilities decrease over time and treated individuals survive longer and thus are over-represented in later measurements. In light of the trade-off

between the efficiency of the random effects model and the causal interpretation of treatment effects in a fixed-effects model it is recommended to assess the uncorrelatedness of random effects with the treatment using the Hausman test in a generalized linear model.

Possible extensions of the ‘aldvmm’ package could include adjusted limited dependent variable beta mixture models (Gray and Hernández Alava 2018), a mixed model implementation for repeated measures and a method for the calculation of average marginal effects and their standard errors.

7 References

- Dixon, Pdraig, William Hollingworth, and John Sparrow. 2020. “Mapping to Quality of Life and Capability Measures in Cataract Surgery Patients: From Cat-Prom5 to EQ-5d-3l, EQ-5d-5l, and ICECAP-o Using Mixture Modelling.” *MDM Policy & Practice* 5 (1): 2381468320915447.
- Dolan, Paul. 1997. “Modeling Valuations for EuroQol Health States.” *Medical Care*, 1095–1108.
- Dowd, Bryan E, William H Greene, and Edward C Norton. 2014. “Computation of Standard Errors.” *Health Services Research* 49 (2): 731–50.
- Fuller, Gordon Ward, Monica Hernandez, David Pallot, Fiona Lecky, Mathew Stevenson, and Belinda Gabbe. 2017. “Health State Preference Weights for the Glasgow Outcome Scale Following Traumatic Brain Injury: A Systematic Review and Mapping Study.” *Value in Health* 20 (1): 141–51.
- Gray, Laura A, and Mónica Hernández Alava. 2018. “A Command for Fitting Mixture Regression Models for Bounded Dependent Variables Using the Beta Distribution.” *The Stata Journal* 18 (1): 51–75.
- Gray, Laura A, Mónica Hernández Alava, and Allan J Wailoo. 2018. “Development of Methods for the Mapping of Utilities Using Mixture Models: Mapping the AQLQ-s to the EQ-5d-5l and the Hui3 in Patients with Asthma.” *Value in Health* 21 (6): 748–57.
- Gray, Laura A, Allan J Wailoo, and Mónica Hernández Alava. 2018. “Mapping the FACT-b Instrument to EQ-5d-3l in Patients with Breast Cancer Using Adjusted Limited Dependent Variable Mixture Models Versus Response Mapping.” *Value in Health* 21 (12): 1399–1405.
- Hernández Alava, Mónica, and Allan Wailoo. 2015. “Fitting Adjusted Limited Dependent Variable Mixture Models to EQ-5d.” *The Stata Journal* 15 (3): 737–50.
- Hernández Alava, Mónica, Allan J Wailoo, and Roberta Ara. 2012. “Tails from the Peak District: Adjusted Limited Dependent Variable Mixture Models of EQ-5d Questionnaire Health State Utility Values.” *Value in Health* 15 (3): 550–61.
- Hernández Alava, Mónica, Allan Wailoo, Fred Wolfe, and Kaleb Michaud. 2013. “The Relationship Between EQ-5d, HAQ and Pain in Patients with Rheumatoid Arthritis.” *Rheumatology* 52 (5): 944–50.
- . 2014. “A Comparison of Direct and Indirect Methods for the Estimation of Health Utilities from Clinical Outcomes.” *Medical Decision Making* 34 (7): 919–30.
- Mukuria, Clara, Donna Rowen, Sue Harnan, Andrew Rawdin, Ruth Wong, Roberta Ara, and John Brazier. 2019. “An Updated Systematic Review of Studies Mapping (or Cross-Walking) Measures of Health-Related Quality of Life to Generic Preference-Based Measures to Generate Utility Values.” *Applied Health Economics and Health Policy*, 1–19.
- Mulhern, Brendan, Yan Feng, Koonal Shah, Mathieu F Janssen, Michael Herdman, Ben van Hout, and Nancy Devlin. 2018. “Comparing the UK EQ-5d-3l and English EQ-5d-5l Value Sets.” *Pharmacoeconomics* 36 (6): 699–713.
- NHS Digital. 2013. “Finalised Patient Reported Outcome Measures (PROMs) in England - April 2011 to March 2012. Patient Reported Outcome Measures (PROMs).” <https://Digital.nhs.uk/Data-and-Information/Publications/Statistical/Patient-Reported-Outcome-Measures-Proms/Finalised-Patient-Reported-Outcome-Measures-Proms-in-England-April-2011-to-March-2012> October 15, 2013.
- Pennington, Becky M, Mónica Hernández Alava, Philip Hykin, Sobha Sivaprasad, Laura Flight, Abualbisher Alshreef, and John Brazier. 2020. “Mapping from Visual Acuity to EQ-5d, EQ-5d with Vision Bolt-on, and VFQ-UI in Patients with Macular Edema in the LEAVO Trial.” *Value in Health* 23 (7): 928–35.
- Whitmore, GA. 1986. “Prediction Limits for a Univariate Normal Observation.” *The American Statistician* 40 (2): 141–43.

- Xu, Richard Huan, Eliza Lai Yi Wong, Jun Jin, Ying Dou, and Dong Dong. 2020. “Mapping of the EORTC QLQ-C30 to EQ-5d-5l Index in Patients with Lymphomas.” *The European Journal of Health Economics* 21 (9): 1363–73.
- Yang, Fan, Carlos KH Wong, Nan Luo, James Piercy, Rebecca Moon, and James Jackson. 2019. “Mapping the Kidney Disease Quality of Life 36-Item Short Form Survey (KDQOL-36) to the EQ-5d-3l and the EQ-5d-5l in Patients Undergoing Dialysis.” *The European Journal of Health Economics* 20 (8): 1195–1206.

8 Appendix

8.1 Example calculation of average treatment effects on the treated

```
# Create treatment indicator
#-----

df$treated <- as.numeric(df$SEX == "2")

# Fit model
#-----

formula <- eq5d ~ treated + hr | 1

fit <- aldvm(m(formula,
               data = df,
               psi = c(-0.594, 0.883))

# Predict treated
#-----

# Subsample of treated observations
tmpdf1 <- df[df$treated == 1, ]

# Design matrix for treated observations
X1 <- aldvm.mm(data = tmpdf1,
               formula = fit$formula,
               ncmp = fit$k,
               lcoef = fit$label$lcoef)

# Average expected outcome of treated observations
mean1 <- mean(predict(fit,
                     newdata = tmpdf1,
                     type = "fit",
                     se.fit = TRUE)[["yhat"]], na.rm = TRUE)

# Predict counterfactual
#-----

# Subsample of counterfactual observations
tmpdf0 <- tmpdf1
rm(tmpdf1)
tmpdf0$treated <- 0

# Design matrix for counterfactual observations
X0 <- aldvm.mm(data = tmpdf0,
               formula = fit$formula,
               ncmp = fit$k,
               lcoef = fit$label$lcoef)

# Average expected outcome of counterfactual observations
mean0 <- mean(predict(fit,
                     newdata = tmpdf0,
                     type = "fit",
```

```

se.fit = TRUE)["yhat"], na.rm = TRUE)

rm(tmpdf0)

# Standard error of ATET
#-----

atet.grad <- numDeriv::jacobian(func = function(z) {

  yhat1 <- aldvmm.pred(par = z,
                      X = X1,
                      y = rep(0, nrow(X1[[1]])),
                      psi = fit$psi,
                      ncmp = fit$k,
                      dist = fit$dist,
                      lcoef = fit$label$lcoef,
                      lcmp = fit$label$lcmp,
                      lcpair = fit$label$lcpair)["yhat"])

  yhat0 <- aldvmm.pred(par = z,
                      X = X0,
                      y = rep(0, nrow(X0[[1]])),
                      psi = fit$psi,
                      ncmp = fit$k,
                      dist = fit$dist,
                      lcoef = fit$label$lcoef,
                      lcmp = fit$label$lcmp,
                      lcpair = fit$label$lcpair)["yhat"])

  mean(yhat1 - yhat0, na.rm = TRUE)

},
x = fit$coef)

se.atet <- sqrt(atet.grad %*% fit$cov %*% t(atet.grad))

# Summarize
#-----

out <- data.frame(atet = mean1 - mean0,
                 se = se.atet,
                 z = (mean1 - mean0) / se.atet)
out$p <- 2*stats::pnorm(abs(out$z), lower.tail = FALSE)
out$ul <- out$atet + stats::qnorm((1 + 0.95)/2) * out$se
out$ll <- out$atet - stats::qnorm((1 + 0.95)/2) * out$se

print(out)

```

8.2 Covariance matrices across optimization methods

Covariance matrices were incomplete or missing entirely (FALSE) in multiple optimization approaches (table 12)

Table 12: Covariance matrix by optimization method

	Nelder-Mead	BFGS	CG	L-BFGS-B	nlminb	Rcgmin	Rvmmin	hjn
zero	FALSE	TRUE	TRUE	FALSE	TRUE	TRUE	TRUE	TRUE
random	FALSE	TRUE	FALSE	FALSE	TRUE	TRUE	FALSE	FALSE
constant	FALSE	TRUE	FALSE	FALSE	TRUE	TRUE	FALSE	TRUE
sann	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	TRUE

8.3 Modified Hosmer-Lemeshow test

```

# Number of percentiles
ngroup <- 10

# Extract expected values and residuals
yhat <- fit1_all[["zero"]][["Nelder-Mead"]][["pred"]][["yhat"]]
res <- fit1_all[["zero"]][["Nelder-Mead"]][["pred"]][["res"]]

# Make groups
group <- as.numeric(cut(yhat, breaks = ngroup), na.rm=TRUE)

# Auxiliary regression
aux <- stats::lm(res ~ factor(group))

# Data set of predictions from auxiliary regressions
newdf <- data.frame(group = unique(group)[order(unique(group))])
predict <- predict(aux,
                    newdata = newdf,
                    se.fit = TRUE,
                    interval = 'confidence',
                    level = 0.95)

plotdat <- as.data.frame(rbind(
  cbind(group = newdf$group,
        outcome = "mean",
        value = predict$fit[ , 'fit']),
  cbind(group = newdf$group,
        outcome = "ll",
        value = predict$fit[ , 'lwr']),
  cbind(group = newdf$group,
        outcome = "ul",
        value = predict$fit[ , 'upr'])
))

# Make plot
plot <- ggplot2::ggplot(plotdat, aes(x = factor(as.numeric(group)),
                                     y = as.numeric(value),
                                     group = factor(outcome))) +
  geom_line(aes(linetype = factor(outcome)))

```

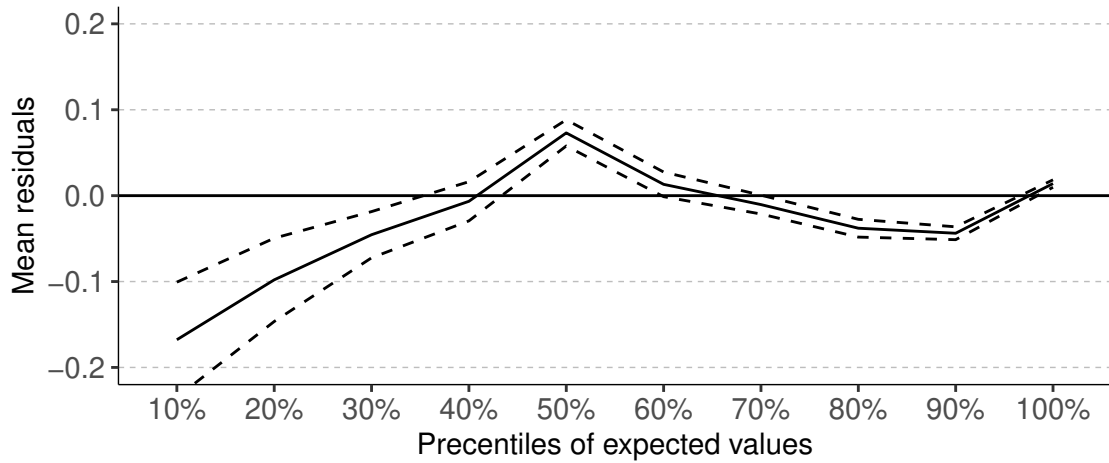


Figure 9: Mean residuals over deciles of expected values, “Nelder-Mead” with “zero” starting values

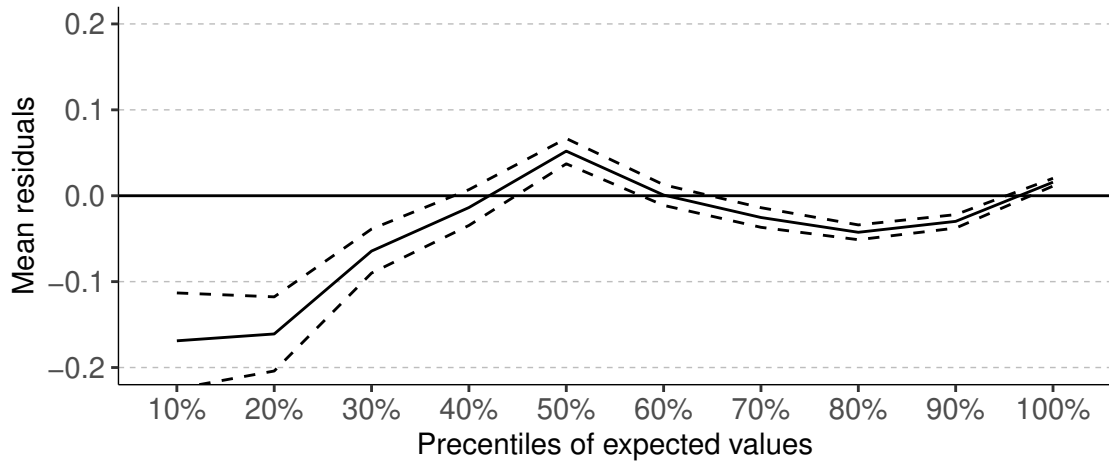


Figure 10: Mean residuals over deciles of expected values, “BFGS” with “zero” starting values

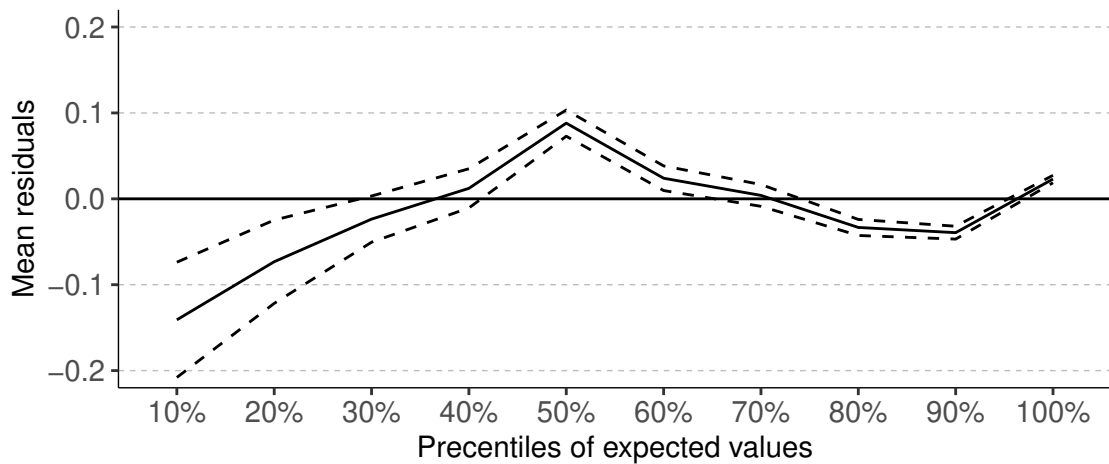


Figure 11: Mean residuals over deciles of expected values, “hjn” with “zero” starting values

8.4 R code for the estimation of reference cases

```
# (1) Reference case 1 with default optimization settings
fit1_default <- aldvmm::aldvmm(eq5d ~ hr | 1,
                             data = df,
                             psi = c(0.883, -0.594),
                             ncmp = 2,
                             init.method = "zero",
                             optim.method = "nlminb")

# (2) Reference case 1 with user-defined initial values and constraints on parameters
init <- c(0, 0, 0, 0, 0, 0, 0.7283)
lo <- c(-Inf, -Inf, -3, -Inf, -Inf, -3, -Inf)
hi <- c(Inf, Inf, Inf, Inf, Inf, Inf, Inf)

fit1_cstr <- aldvmm::aldvmm(eq5d ~ hr | 1,
                           data = df,
                           psi = c(0.883, -0.594),
                           ncmp = 2,
                           init.est = init,
                           init.lo = lo,
                           init.hi = hi)

# (3) Reference case 1 with initial values from constant-only model
fit1_const <- aldvmm::aldvmm(eq5d ~ hr | 1,
                             data = df,
                             psi = c(0.883, -0.594),
                             ncmp = 2,
                             init.method = "constant",
                             optim.method = "nlminb")

# (4) Reference case 2 with user-defined initial values.
init <- c(-.40293118, .30502755, .22614716, .14801581, -.70755741, 0,
          -1.2632051, -2.4541401)

fit2 <- aldvmm::aldvmm(eq5d ~ hr | hr,
                      data = df,
                      psi = c(0.883, -0.594),
                      ncmp = 2,
                      init.est = init,
                      optim.method = "nlminb")
```

8.5 STATA® code for the estimation of reference cases

```
* (1) Reference case 1
alvmm eq5d hr, ncomponents(2)

* (2) Reference case 1 with constraints
matrix input a = (0, 0, 0, 0, 0, 0, 0.7283)
constraint 1 [Comp_2]:hr10 = 0
constraint 2 [Comp_2]:_cons = 100
constraint 3 [lns_2]:_cons = 1e-30
alvmm eq5d hr, ncomp(2) from(a) c(1 2 3)

* (3) Reference case 1 initial values from constant-only model
alvmm eq5d hr, ncomp(2) inim(cons)

* (4) Reference case 2 user-defined initial values
matrix input start = (.14801581, .22614716, .30502755, -.40293118, 0,
                    -.70755741, -2.4541401, -1.2632051)
alvmm eq5d hr, ncomp(2) prob(hr) from(start)
```