

GEE for longitudinal ordinal data: Comparing R-geepack, R-multgee, R-repolr, SAS-GENMOD, SPSS-GENLIN

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Corresponding Author: Ms. Nazanin Noorae, MSc

Corresponding Author's Institution: University Medical Center Groningen

First Author: Nazanin Noorae, MSc

Order of Authors: Nazanin Noorae, MSc; Geert Molenberghs, Ph.D.; Edwin R van den Heuvel, Ph.D.

Dear Prof. Kontoghiorghes,

First of all, we would like to thank you, the associate editor, and the reviewers for taking their time and providing us with very useful comments. We believe that this has improved our manuscript substantially.

Hereby, we submit the revised version of our manuscript entitled: GEE for longitudinal ordinal data: Comparing R-geepack, R-multgee, R-repolr, SAS-GENMOD, SPSS-GENLIN.

We addressed all the questions and comments raised by Associated Editor and the reviewers. In agreement with the Associate Editor and the reviewer's advice, we updated all the analyses with the last version of each software package. We also included a newly developed package in R into our comparison. In regard with this improvement, the title of the manuscript has been modified. The manuscript has been prepared according to the guideline of the "Computational Statistics and Data Analysis" journal and Ms. Elizabeth Groom, who is a native English speaker, reviewed our revised manuscript on English spelling & grammar, which improved our paper even further.

We really appreciate to have the opportunity to revise our manuscript for publication in Computational Statistics and Data Analysis and we hope that it is suitable for publication.

Yours sincerely,

Nazanin Noorae
PhD student in Medical Statistics
University Medical Center Groningen
The Netherlands

Response to reviewers' comments:

Associate Editor: The two reviewers appreciate the high quality of the paper. While one reviewer has only few further suggestions, the other reviewer recommends to include STATA for comparison. I also think that the paper would receive more attention with such a comparison. Also using the latest versions of the other software packages is a good recommendation.

Response:

- We greatly appreciate the positive feedback.
- When we started our comparison, we considered STATA as a possible package. However, we believed that STATA could not handle GEE for ordinal data and that is why STATA was not included. We do know that procedure xtgee STATA is very flexible to fit the marginal models using the GEE method to different types of data with a wide range of link functions, but GEE for ordinal/categorical variables has not been implemented in this command. To confirm this, we contacted the official technicians at STATA via e-mail on January 7, 2014 (please see the full correspondence at the end of this document). Dr Gustavo Sanchez replied: "We do not currently have an official command to fit population average repeated ordinal outcome models." He pointed us to alternative commands like "meologit", "meoprobit" and "gsem" for ordinal outcomes, but the first two commands fit a mixed-effects models and the latter command fits the generalized structural equation modeling via the maximum likelihood approach.
- To accommodate the comment of the second referee, we updated all the results with the latest versions of each software, i.e. R version 3.0.2, SAS version 9.4 and SPSS version 22.0.0. Additionally, we included multgee, which is a new package in R to perform GEE on ordinal outcomes, developed in: "Touloumis, A., Agresti, A. and Kateri, M. (2013). GEE for multinomial responses using a local odds ratios parameterization. Biometrics, 69, 633-640".

Reviewer #1:

The authors undertake a simulation study to explore the various properties of the algorithms implemented in R and SPSS to estimate model parameters for repeated ordinal score data using the method of Generalized Estimating Equations (GEE).

I found this to be a well written and well-structured manuscript that covered the most widely used methods for ordinal regression comprehensively. The results were clear, as were the recommendations. One minor comment is that equation (2), as I am sure the authors will recognise, is incorrectly stated; I think the second D_i should be replaced by V_i and the third D_i by Y_i .

I should declare that I am a co-author of one of the R packages reviewed in this manuscript. As such I have often been asked about the relative merits of available software for longitudinal ordinal data. The results described in this manuscript, do indeed concur with my experience of these packages and I think do reflect their relative merits and deficiencies. This is a topic of some wide interest and I would recommend this as acceptable for publication in CSDA.

Response to reviewer #1:

We are grateful for the thorough and positive review. We fully admit that there is a typo in equation (2) and apologize for this error. The equation is corrected in the revised version.

Reviewer #2:

This manuscript is interesting to read and is generally well-written. Following are my comments.

-Thank you very much for the positive feedback and valuable comments.

1. There is one glaring omission from the list of evaluated software packages. The authors really should include Stata in their evaluation. I know of individuals who use Stata to perform GEE for longitudinal data analysis, and it is not unusual to see questions regarding GEE appear on the Stata listserv. The appropriate procedure to run GEE in Stata is xtgee. This procedure should be able to fit the types of models that the authors describe - it contains several options for link functions, including the logit function, and correlation structures, including the independent, exchangeable, and unstructured matrices. I think that this will add a lot to the evaluation, and will certainly make the manuscript more complete. The authors may be able to obtain a complimentary review copy of Stata directly from Stata Corp. if they let the people at Stata know that the software is being evaluated for GEE capabilities and accuracy of GEE analyses.

Response to comment #1:

We fully agree with the reviewer that it is a, perhaps somewhat unfortunate, omission to exclude STATA. As we described our response to the Associate Editor, we wanted to include STATA from the outset, as we did know that procedure xtgee in STATA is very flexible to fit the marginal models using the GEE method to different types of data with a wide range of link functions, but unfortunately GEE for ordinal/categorical variables has not been implemented, neither in xtgee nor in any other command. We had some emails correspondence with the technical support of STATA (please see the end of this document) and Dr Gustavo Sanchez replied: "We do not currently have an official command to fit population average repeated ordinal outcome models." He pointed us toward alternative commands like "meologit", "meoprobit" and "gsem" for ordinal outcomes, but the first two commands fit a mixed-effects models and the latter command fits the generalized structural equation modeling via maximum likelihood approach.

2. The authors should consider citing the following published papers and text, and include brief mention of them in the background section, as they are follow-ups to some of the papers and texts that the authors already cite. However, if the authors don't believe that these will be helpful for the background section, then they do not need to cite them.

Hardin, J.W., Hilbe, J.M., 2012. Generalized estimating equations. 2nd edition. Chapman and Hall/CRC Press.

Oster, R.A., Hilbe, J.M., 2008. An examination of statistical software packages for parametric and nonparametric data analyses using exact methods. The American Statistician 62 (1), 74-84.

Oster, R.A., Hilbe, J.M., 2008. Rejoinder to "An Examination of Statistical Software Packages for Parametric and Nonparametric Data Analyses Using Exact Methods". The American Statistician 62 (2), 173-176.

Response to comment #2:

Thank you for pointing out these references. We included the first two references before the last paragraph in the Background section. Because the last article is a rejoinder and it does not address GEE, we decided not to include it.

3. The authors mention the versions of the software that they are evaluating in the "conclusions and recommendations" section. However, these versions should be mentioned in the "introduction" section. All software packages that the authors are evaluating should be mentioned in the abstract.

Response to comment #3:

The version of all software packages are mentioned in both abstract and introduction.

4. Related to comment #3, the authors should revise and update their results by using version 22 of SPSS, which is the most recent version. They used version 20 for their evaluation. They should also revise and update their results by using version 3.0.2 of R, which is the most recent version. They used version 2.15.3 for their evaluation. The authors are already using the current version of SAS (version 9.4 was just released but is not yet in widespread use). Related to comment #1, the version of Stata that the authors should use is version 13, which is the most recent version. Proceeding in this manner will ensure that the manuscript is up-to-date.

Response to comment #4:

All the results are updated with the last versions of software. We analyzed all the simulated data with R 3.0.2, SAS 9.4, and SPSS 22.0.0. All the presented results in the current revision are based on these versions.

In the R version 3.0.2 we realized a new developed package which is capable to perform GEE for ordinal outcomes based on the method described in “Touloumis, A., Agresti, A. and Kateri, M. (2013). GEE for multinomial responses using a local odds ratios parameterization. *Biometrics*, 69, 633-640”. In the revised version, we included this package in our comparisons as well.

As mentioned earlier, STATA 13 is not capable to perform GEE for ordinal/categorical outcomes (please see the response to the comment 1).

5. The results section would be a little more interesting if the authors would report more of their results for n=300 subjects. Is it possible to add one or two tables containing these results? The authors make mention of some of these results in the text, but it would be nice to see them displayed in the manuscript.

Response to comment #5:

We have now included Tables 7 and 12 which are fully devoted to parameter estimations and coverage probabilities for the analysis of the data with 300 subjects.

Email correspondence with technical specialist of STATA

Response from: Stata Technical Support [<mailto:tech-support@stata.com>]

Dear Edwin,

Thank you for your interest in adding Stata to your paper.

We do not currently have an official command to fit population average repeated ordinal outcome models. `-meologit-` and `-meoprobit-` are our current official alternatives for longitudinal data ordinal outcome models. I would suggest that you have a look at the manual entries for those two estimation commands:

<http://www.stata.com/manuals13/memeologit.pdf>
<http://www.stata.com/manuals13/memeoprobit.pdf>

And the corresponding postestimation commands:

<http://www.stata.com/manuals13/memeologitpostestimation.pdf>
<http://www.stata.com/manuals13/memeoprobitpostestimation.pdf>

There is also a more general command `-gsem-` that includes the two models above, as well as a large set of generalized structural equation models.

The manual entry below shows the different family and link options for `-gsem-`:

<http://www.stata.com/manuals13/semgsemfamily-and-linkoptions.pdf>

I hope this helps.

Sincerely,

Gustavo

Gustavo Sanchez, Ph.D.
Senior Statistician
tech-support@stata.com
StataCorp LP

Our request from STATA Technical Service:

Dear Specialist,

We are currently working on a paper that compares GEE for repeated ordinal outcomes from different software packages (R, SPSS, SAS). We would like to include STATA as well in this comparison. From searching the internet we have the impression that the procedure `xtgee` supports GEE for repeated binary data, but it does not support GEE for repeated ordinal data. Could you tell us if this is correct? If so (i.e. `xtgee` is not capable of performing GEE for repeated ordinal data), is there another procedure that does support this type of analysis?

Thank you very much for your support,

Best regards,

Edwin

Prof. dr. E.R. van den Heuvel
Medical Statistics
Department of Epidemiology
University Medical Center Groningen
The Netherlands

GEE for longitudinal ordinal data: Comparing R-geepack, R-multgee, R-repolr, SAS-GENMOD, SPSS-GENLIN

Nazanin Noorae^{a,*}, Geert Molenberghs^{b,c}, Edwin R van den Heuvel^a

^aUniversity of Groningen, University Medical Center Groningen, Groningen, The Netherlands

^bI-BioStat, Katholieke Universiteit Leuven, Leuven, Belgium

^cI-BioStat, Universiteit Hasselt, Diepenbeek, Belgium

Abstract

Studies in epidemiology and social sciences are often longitudinal and outcome measures are frequently obtained by questionnaires in ordinal scales. To understand the relationship between explanatory variables and outcome measures, generalized estimating equations can be applied to provide a population-averaged interpretation and address the correlation between outcome measures. It can be performed by different software packages, but a motivating example showed differences in the output. This paper investigated the performance of GEE in R (version 3.0.2), SAS (version 9.4), and SPSS (version 22.0.0) using simulated data under default settings. Multivariate logistic distributions were used in the simulation to generate correlated ordinal data. The simulation study demonstrated substantial bias in the parameter estimates and numerical issues for data sets with relative small number of subjects. The unstructured working association matrix requires larger numbers of subjects than the independence and exchangeable working association matrices to reduce the bias and diminish numerical issues. The coverage probabilities of the confidence intervals for fixed parameters were satisfactory for the independence and exchangeable working association matrix, but they were frequently liberal for the unstructured option. Based on the performance and the available options, SPSS and multgee, and repolr in R all perform quite well for relatively large sample sizes (e.g. 300 subjects), but multgee seems to do a little better than SPSS and repolr in most settings.

Keywords: Correlated ordinal data, generalized estimating equations, copula, multivariate

*Corresponding author. Address: University of Groningen, University Medical Center Groningen, Department of Epidemiology, Hanzeplein 1, 9700 RB, Groningen, The Netherlands. Tel: +31 503612273

Email addresses: n.noorae01@umcg.nl (Nazanin Noorae), geert.molenberghs@uhasselt.be (Geert Molenberghs), e.r.van.den.Heuvel@umcg.nl (Edwin R van den Heuvel)

1. Introduction

1.1. Motivating example

Change in Quality of Life was investigated in a study of women who underwent a laparoscopic hysterectomy (surgery). In total, 72 patients were measured using the Short Form-36 Health Survey questionnaire before surgery (baseline), and six weeks after surgery, and then six months after surgery. One specific domain is the emotional role (ER). It was scored with just one item having four possible outcome levels, coded $\{1, 2, 3, 4\}$. Higher scores indicate a higher quality of life. The goal was to investigate whether ER was affected by surgery and to determine the role of some explanatory variables, such as age (a), comorbidity (cm), blood loss (bl) and complications (c) during surgery, and duration (d) of surgery. We decided to implement the following model

$$\text{logit}[P(O_{ij} \leq c)] = \beta_{0c} + \beta_1 a_i + \beta_2 cm_i + \beta_3 t_{ij} + \delta_{t_{ij}} (\alpha_1 bl_i + \alpha_2 c_i + \alpha_3 d_i),$$

with O_{ij} the j^{th} ordinal response for subject i , t_{ij} the j^{th} time moment for subject i ($t_{i1} = 0$, $t_{i2} = 6$, and $t_{i3} = 26$ weeks), and with δ_x an indicator variable equal to one when $x > 0$ and zero otherwise. The indicator δ_x is needed because the covariates bl , d , c can only affect ER after surgery. The parameter β_3 would indicate the effect of surgery over time when corrected for other variables.

We decided to estimate the parameters with generalized estimating equations (GEE) to obtain a population-averaged interpretation and to address the correlation between subject outcomes. We applied the `geepack` (`ordgee` function), `repolr` (`repolr` function) and `multgee` (`ordLORgee` function) packages in R under default settings and selected the most complex working association structure available in each package: unstructured working association in `geepack` and `multgee`, and exchangeable working correlation in `repolr`. `Geepack` and `multgee` provided surprisingly different results (Table 1), while `repolr` produced no parameter estimates due to the estimation of cell probabilities equal to one. The highest score of 4 was indeed frequently observed: almost 90 percent after six months of surgery. Not yet completely satisfied with the results, we decided to analyse this data also with SAS (`GENMOD` procedure) and SPSS (`GENLIN` command) to verify the parameter estimates of `multgee` and `geepack`. We chose unstructured working correlation matrix in SPSS and

independence structure in SAS, based on the options available. Similar to `repolr`, SPSS did not converge, but SPSS was able to produced results with the exchangeable correlation structure. The results are listed again in Table 1. Comparing the results demonstrates several differences. First,

Table 1: The parameter estimates (robust/empirical standard error) under an independent working correlation matrix.

Parameters	geepack	multgee	SPSS	SAS	multgee
	Unstructured	Unstructured	Exchangeable	Independent	Exchangeable
Threshold 1	0.702(1.040)	0.533(0.947)	0.846(0.932)	0.289(1.063)	0.647(0.995)
Threshold 2	1.139(1.020)	1.007(0.907)	1.306(0.902)	0.739(1.009)	1.090(0.918)
Threshold 3	1.464(1.019)	1.368(0.925)	1.657(0.916)	1.077(1.023)	1.438(0.934)
Age	-0.035(0.019)	-0.033(0.017)	0.039(0.017)	-0.026(0.019)	-0.034(0.017)
Comorbidity	-0.910(0.551)	-0.506(0.411)	0.508(0.414)	-0.631(0.439)	-0.556(0.421)
Time	-0.025(0.020)	-0.025(0.017)	0.025(0.018)	-0.022(0.018)	-0.023(0.017)
Blood loss	-0.002(0.001)	-0.002(0.001)	0.003(0.001)	-0.002(0.001)	-0.003(0.001)
Complication	0.592(1.001)	1.832(0.677)	-1.725(0.626)	1.812(0.800)	1.700(0.654)
Duration	0.000(0.000)	0.000(0.000)	0.000(0.000)	0.000(0.000)	0.000(0.000)

not all packages seem to converge, but secondly, there exist differences in the parameter estimates between the packages (Table 1). This could be due to the different choices in correlation structure, but differences remain even when the same class of structure is chosen. Indeed, as we already mentioned, `geepack` and `multgee` provided different results for the unstructured association, but also SPSS and `multgee` produce different results under the exchangeable structure (Table 1). Not only did the estimates differ in this case, they are also opposite in sign. When each package is run with the independence structure, all packages are identical (to the results of SAS in Table 1), except for `geepack`, which leads to completely different results, and for SPSS, which gives opposite signs, but the same absolute numbers.

These different results in performance and in estimates encouraged us to investigate the similarities and discrepancy between the GEE methods in R (version 3.0.2), SAS (version 9.4), and SPSS (version 22.0.0) for longitudinal ordinal data using simulation studies. In these studies we would know what mean models the software should estimate. Note that they all estimate the same mean model, and that they treat the associations as nuisance parameters, although they may have

implemented different association structures (even in the same class).

45 *1.2. Background*

Generalized estimating equations (GEE) were introduced by Liang and Zeger (1986) and Zeger and Liang (1986) as general approach for handling correlated discrete and continuous outcome variables. It only requires specification of the first moments, the second moments, and correlation among the outcome variables. The goal of this procedure is to estimate fixed parameters without specifying the joint distribution. Prentice (1988) extended the GEE approach by improving
50 the estimation of the correlation parameters using a second set of equations based on Pearson's residuals, see also Lipsitz and Fitzmaurice (1996). Others modeled the association parameter as an odds ratio (Lipsitz et al., 1991; Liang et al., 1992; Carey et al., 1993). An alternative approach considered latent variables with a bivariate normal distribution underneath the correlated binary
55 variables (see Qu et al., 1992).

Extending GEE to ordinal data is not immediately obvious because the first and second moments are not defined for ordinal observations. It requires the introduction of a vector of binary variables that relates one-to-one to the ordinal variables (Clayton, 1992). With this set of binary variables the original GEE method (Liang and Zeger, 1986; Zeger and Liang, 1986) as well as the
60 method for estimation of the association parameters can be extended to ordinal data (Lipsitz et al., 1994; Heagerty and Zeger, 1996; Parsons et al., 2006; Touloumis et al., 2013). Different approaches have been used to estimate the association parameters in GEE. Lipsitz et al. (1994) used Pearson's residual, while Parsons et al. (2006) minimized the logarithm of the determinant of the covariance matrix of the fixed parameters, i.e. minimized the standard errors of the parameter estimates.

65 Instead of using correlations, Lumley (1996) applied common odds ratios for the association of multivariate ordinal variables to reduce the number of association parameters. Williamson et al. (1995) suggested a GEE method for bivariate ordinal responses with the global odds ratio as measure of dependency. In this context, two sets of equations were used: one for the fixed parameters and one for the association parameters. To make the approach available to others,
70 Williamson et al. (1999) developed two SAS macros but they were not officially incorporated in SAS. Yu and Yuan (2004) developed one macro that extended these two macros to unbalanced data and it is only available upon request from the authors. The approach with two sets of equations was further extended to multivariate ordinal outcomes using global odds ratios as measure of

dependency, while the two sets of equations can be integrated into one set of equations for the
75 fixed and association parameters simultaneously (see Heagerty and Zeger, 1996). Nores and del
Pilar Díaz (2008) investigated the efficiency and convergence of this approach via simulation.
They applied function `ordgee` of R. Recently, Touloumis et al. (2013) extended the GEE method
for ordinal outcomes by considering local odds ratios as the measure of association.

Several overviews of GEE have been provided. Ziegler et al. (1998) developed a bibliography
80 of GEE, and Zorn (2001) indicated the use of GEE in Political science. To recent books of Ziegler
(2011); Hardin and Hilbe (2012) were fully dedicated to GEE, while Agresti and Natarajan (2001);
Liu and Agresti (2005); Agresti (2010) discussed comprehensive reviews of more general models
and methods for (correlated) categorical data. Two particular overviews focused on the models
and tests that were programmed in the software packages LogXact 4.1, SAS 8.2, Stata 7, StatXact
85 5, and Testimate 6 for (correlated) categorical outcomes, including GEE (Oster, 2002, 2003). Oster
and Hilbe (2008) also presented a general overview of software packages on exact methods, but
they did not investigate the performance of these packages. Ziegler and Groping (1998); Horton
and Lipsitz (1999) did compare software packages for the analysis of correlated data via GEE, but
they focused on binary outcomes only. A comprehensive comparison of frequently used software
90 packages for correlated ordinal data using GEE has not yet been conducted.

We applied a simulation study to compare the functions `ordgee` in `geepack`, `ordLORgee` in
`multgee` and `repolr` in package `repolr` in R 3.0.2, the procedure `GENMOD` in SAS 9.4, and finally
the procedure `GENLIN` in SPSS 22.0.0. We took the perspective of a general user with limited
knowledge of the mathematical and numerical details of GEE. This means that we mainly used
95 default settings in the simulation study. We simulated moderately to highly correlated multivariate
logistic distributed latent variables using copula functions to obtain correlated ordinal data. This
choice implies the logit models for the marginal distributions, but the correlation between the
binary variables coding the ordinal outcomes is different from choices implemented in the software.
We investigated the frequency of simulation runs with numerical convergence issues, and the bias
100 in parameter estimates. We reported the coverage probabilities of the confidence intervals on these
parameters using the Wald statistic. Finally we provided rejection rates of the proportionality test
(if available).

2. Generalized estimating equations

Generalized estimating equations for ordinal outcomes require several aspects. The first aspect
 105 is to choose a model for the covariates and a non-linear link function to connect the model to the
 cumulative probabilities. Then the second aspect is to create a set of binary variables describing
 all possible outcomes for the ordinal observations (Clayton, 1992). The third aspect is to choose a
 working correlation matrix or working association structure to describe the possible association be-
 tween all binary variables. The fourth and final aspect is the estimation method for the association
 110 parameters involved in the association structure.

To illustrate these aspects in more detail, consider a random sample of observations from n
 subjects. Let $O_i = (O_{i1}, O_{i2}, \dots, O_{in_i})$ be the ordinal responses of subject i and O_{it} takes values
 in $\{1, 2, \dots, C\}$ and let $X_i^\top = (X_{i1}^\top, X_{i2}^\top, \dots, X_{in_i}^\top)$ be a $p \times n_i$ dimensional matrix of time varying
 and/or time stationary covariates for subject i . Then the connection between the covariates and
 115 the conditional probabilities of each ordinal outcome is described by

$$h[P(O_{it} \leq c | X_{it} = x_{it})] = \beta_{0c} + x_{it}^\top \beta_1, \quad (1)$$

for $c = 1, 2, \dots, C-1$, β_{0c} the threshold parameter for level c , β_1 the vector of regression coefficients
 corresponding to the covariates and with h a known link function. Any monotone increasing func-
 tion h which would transfer the interval $(0, 1)$ to $(-\infty, \infty)$ could be applied as the link function
 (McCullacgh, 1980), e.g. logit, probit and complementary log-log. The cumulative logits model is
 120 very popular for clustered ordinal outcomes due to its simple and comprehensive interpretation,
 the same as in logistic regression. This model is often referred to as the proportional odds model
 (Agresti, 2010). The cumulative probabilities with probit link function is more popular in econo-
 metrics, but then the model should no longer be interpreted as an odds ratio. The formulation in
 (1) is ascending in terms of level of ordinal outcomes but the model can be changed to descending
 125 in which $O_{it} \leq c$ is replaced by $O_{it} > c$.

There are three options for choosing the binary variables $Y_{it}^\top = (Y_{it1}, Y_{it2}, \dots, Y_{itC-1})$, with
 dimension $C - 1$. The first option selects $Y_{itc} = I(O_{it} = c)$ (see Lipsitz et al., 1994; Touloumis
 et al., 2013) the second option selects $Y_{itc} = I(O_{it} > c)$ (see Heagerty and Zeger, 1996), and
 finally the third option selects $Y_{itc} = I(O_{it} \leq c)$ (see Parsons et al., 2006). Note that for
 130 all options $c = 1, 2, \dots, C - 1$ and $I(\cdot)$ is the indicator function equal to one when the argu-
 ment is true and zero otherwise. Consequently, the mean vector $\mu_i = E(Y_i | X_i = x_i)$ is the

mean of all binary variables $Y_i^\top = (Y_{i1}^\top, \dots, Y_{in_i}^\top)$. Now the vector of regression parameter $\beta = (\beta_{01}, \beta_{02}, \dots, \beta_{0C-1}, \beta_{11}, \beta_{12}, \dots, \beta_{1p})^\top$ can be estimated using the GEE method by solving

$$u(\beta) = \sum_{i=1}^N D_i^\top V_i^{-1} [Y_i - \mu_i] = 0, \quad (2)$$

where $D_i = \partial \mu_i / \partial \beta$ and V_i is the so-called weight matrix or working covariance matrix of \mathbf{Y}_i . This matrix may depend on the vector of parameters β and the vector of association parameters α for the binary variables.

Liang and Zeger (1986); Lipsitz et al. (1994) showed that given any parameterisations of the matrix V_i and assuming that the marginal model (1) is correctly specified, the solution $\hat{\beta}$ for (2) is a consistent estimator of β and $\sqrt{n}(\hat{\beta} - \beta)$ has an asymptotic multivariate normal distribution with mean vector $\mathbf{0}$ and covariance matrix $V_\beta = \lim_{n \rightarrow \infty} nV_\beta(n)$, with $V_\beta(n)$ defined by

$$V_\beta(n) = \left(\sum_{i=1}^n D_i^\top V_i^{-1} D_i \right)^{-1} \left[\sum_{i=1}^n D_i^\top V_i^{-1} COV(Y_i) V_i^{-1} D_i \right] \left(\sum_{i=1}^n D_i^\top V_i^{-1} D_i \right)^{-1}. \quad (3)$$

This form of variance is referred to as the empirical or robust variance estimator since it provides a consistent estimator regardless of the (mis)specification of V_i (Lipsitz et al., 1994). A model-based standard error would be obtained when $COV(Y_i)$ in (3) is replaced by matrix V_i and then the covariance matrix in (3) would reduce to the last term in (3), which means that $V_\beta^{-1}(n) = \sum_{i=1}^n D_i^\top V_i^{-1} D_i$. It should be noted however, that the choice for a model-based estimator does not imply that the working covariance matrix V_i for the binary vector Y_i is a true covariance matrix. Issues related to covariance matrices for multivariate binary outcome variables were discussed by Chaganty and Joe (2004, 2006). Fortunately, these issues do not cause difficulties in applying GEE, since the multivariate distribution can always partially be described by semi-parametric models (see Molenberghs and Kenward, 2010).

To be able to determine GEE estimates, the vector of association parameters α should be estimated. Commonly, the matrix V_i is re-parameterized by

$$V_i = A_i^{\frac{1}{2}} R_i(\alpha) A_i^{\frac{1}{2}}, \quad (4)$$

with A_i a $n_i(C-1) \times n_i(C-1)$ diagonal matrix with elements given by the variance of the binary variable Y_{itc} , and the matrix $R_i(\alpha)$ consists of the associations between the binary variables. The R_i matrix contains three parts of associations. The first part is the association between the binary

variables at one time point. The second one is the association of the same coded binary variables across time, and the third and final part is the association of two differently coded binary variables across time. Thus the “variance” of each ordinal outcome and the association between any pair of ordinal outcomes are represented by matrices rather than scalars.

160 Although Pearson’s correlation has been applied to the association between binary variables within the same time point, different association measures have been applied to model the dependency between binary variables across time. Lipsitz et al. (1994) assumed Pearson’s correlation for all associations between binary variables and estimate the association parameters α with Pearson’s residuals. Restricting to the logit link function, Parsons et al. (2006) described the association
 165 between each pair of the binary variables over time as a product of a function of single parameter α and Pearson’s correlation of the same pair of binary variable within a time point, i.e. $g_{st}(\alpha) \exp(-|\beta_{0c} - \beta_{0k}|/2)$ (see Kenward et al., 1994). This scalar parameter is estimated by minimizing the logarithm of the determinant of the covariance matrix ($\log |\hat{V}_\beta(n)|$) of the parameter estimates in each step of the fitting algorithm for solving (2). As an alternative to Pearson’s
 170 correlation, one can use the odds ratio. Heagerty and Zeger (1996) applied global odds ratios for the association of repeated binary variables in the matrix V_i . They applied a second set of estimating equations of the form (2) to obtain these association parameters. This choice was first introduced for binary outcomes by Prentice (1988), and for ordinal outcomes by Miller et al. (1993). Touloumis et al. (2013) utilized local odds ratios to capture the association parameters
 175 in the V_i matrix. They used the Goodman’s row and column effects model (Goodman, 1985) to reparameterize the local odds, and then estimated the parameters using the iterative proportional fitting procedure (Deming and Stephan, 1940).

All papers use the same definition for an independence, exchangeable and unstructured association matrix, but this does not imply that they fit identical associations. Under the independence
 180 working assumption all off-diagonal blocks are constant and equal to zero. Exchangeability over time indicates that the association between the binary variables Y_{itc} and Y_{isk} , for time t and s , $t \neq s$, is independent of time, but it may depend on the levels c and k . Finally, for unstructured associations there are no restrictions implied.

2.1. Software packages

185 2.1.1. R

R software offers several options for fitting marginal ordinal models with GEE approach. In the current paper, we compare all three packages: `geepack`, `repolr` and `multgee`.

The function `ordgee` in `geepack` (Yan et al., 2012a) produces estimations according to the method of Heagerty and Zeger (1996) (Højsgaard et al., 2005). The function allows to choose logit, 190 probit, and complementary log-log link function as well as four association structures (independence, exchangeable, unstructured, and user-defined). Selection of initial values for the regression parameters and odds ratio parameters are possible. An option is also available to change the default setting from descending to ascending. This package offers the robust estimator for the covariance matrix of the fixed parameters and the Wald statistic for testing the statistical significance of each 195 coefficient in the model. The numerical procedure is the Fisher-scoring algorithm with the default number for the maximum number of iterations 25. The iteration procedure stops when the change in the parameter estimates is less than 0.0001.

Another function, `repolr`, is implemented in the `repolr` package (Parsons, 2012). `Gee` package needs to be uploaded in advance. The function `repolr` has implemented the GEE method of 200 Parsons et al. (2009) which exclusively supports the logit link function. An independence, uniform (exchangeable) and AR(1) working correlation structure can be selected. Under the uniform (exchangeable) assumption each element on the off-diagonal block of the matrix $R_i(\alpha)$ is defined with $\text{CORR}(Y_{itc}, Y_{isk}) = \alpha \exp(-|\beta_{0c} - \beta_{0k}|/2)$. Under AR(1) the correlation is $\text{CORR}(Y_{itc}, Y_{isk}) = \alpha^{|s-t|} \exp(-|\beta_{0c} - \beta_{0k}|/2)$. `Repolr` has an option to choose an initial value for the correlation parameter. It automatically provides standard errors of the parameter estimates based on both the 205 robust estimator and the model-based estimator. Furthermore, the function also has an option to test the proportionality assumption based on the score test (Stiger et al., 1999). The numerical procedure is the Newton-Raphson algorithm and the default setting for convergence of the numerical procedure is a relative change in parameters estimates less than 0.001 or a maximum number 210 of iterations equal to 10.

The final option to perform GEE for ordinal outcomes in R is to use the `ordLORgee` function which is implemented in the `multgee` package (Touloumis, 2013). This package requires the user to upload `gnm` and `VGAM` packages in advance. The `ordLORgee` function uses the method of

Touloumis et al. (2013). Beside the cumulative link functions logit, probit, cauchit, and cloglog, it
215 could also fit adjacent-category logit models. An independence, uniform, category exchangeable,
time exchangeable, unstructured, and a user-defined structure can be used. Under the uniform
structure, all local odds ratios are identical. Relaxing this structure a little bit leads to two types
of exchangeability assumptions. The category exchangeability structure assumes that local odds
ratios are the same within time pairs, but could still be different between time pairs. An alternative
220 is time exchangeability, which assumes that local odds ratios are independent of time, but could
change with ordinal levels. Finally, the unstructured association is indicated by RC in this package.
Robust and model-based variance estimators can be used. The numerical procedure for estimation
of the fixed effects uses the Fisher-scoring algorithm. It stops if the relative change in the parameter
estimates between two successive iterations is smaller than 0.001, or whenever it completes to 15
225 iterations.

2.1.2. SAS

PROC GENMOD in SAS software is a procedure to fit models for correlated binary and ordinal
data (see Stokes et al., 2000). The SAS system selects $Y_{itc} = I(O_{it} = c)$ as binary coding for the
ordinal outcome. It can also change from ascending to descending. The procedure supports logit,
230 probit, and complementary log-log link function, but is limited to the independence working corre-
lation matrix for ordinal data. It is possible to specify initial values for the regression parameters.
The quasi information criterion (QIC) (Pan, 2001), type I and type III testing using either the
Wald statistic or the generalized score statistic are available in this procedure.

Although the default setting in SAS is the use of the robust estimator, model based standard
235 errors can be obtained as well. The numerical procedure for solving (2) is Newton-Raphson (Jen-
nrich and Sampson, 1976), but another alternative is to use the Fisher scoring algorithm. For
parameter estimates with an absolute value larger than 0.08, the numerical iteration procedure
stops when the relative change in the regression parameter estimates is less than 0.0001 for two
successive iterations. For parameter estimates with an absolute value smaller or equal to 0.08,
240 convergence is based on absolute change. The default number of maximum iterations is 50.

2.1.3. SPSS

The GENLIN command in SPSS performs GEE. It can also be selected from the menu using Analyze / Generalized Linear Models / Generalized Estimating Equations. SPSS has implemented the binary coding $Y_{itc} = I(O_{it} = c)$. It also has the option to change the reference category from the highest level to the lowest. Moreover, it provides five options for the working correlation matrix: independent, exchangeable, AR(1), M-independent, and unstructured. SPSS uses Pearson's correlation as the association parameter and applies some functions of Pearson's residual, the so-called Pearson-like residuals, to estimate the association parameters. All of these options can be used with both logit and probit link function.

The robust estimator is the default setting, but a model-based estimator can also be selected. In addition, users are able to choose type I and type III tests using the Wald statistic (default) and the generalized score statistic.

One of the three numerical methods (Newton-Raphson, Fisher scoring and hybrid) for iteration can be chosen. The hybrid procedure is the default. The numerical procedure stops when the absolute change in parameter estimates is less than 0.000001. There is an option to choose for a relative change. The default value for the maximum number of iterations is set to 100, but this can be changed as well.

3. Simulation study

3.1. Simulation method: multivariate logistic distributions

In our simulation, we used multivariate logistic distributions to generate repeated continuous data first and then changed them to ordinal variables using suitable intervals. Both the k-dimensional logistic Gumbel distribution and a generalization of the k-dimensional Farlie-Gumbel-Morgenstern (FGM) distribution (Kotz et al., 2000) were applied. The standardized multivariate Gumbel distribution has only one parameter θ , and its joint distribution function is given by

$$F_G(y_1, \dots, y_k) = \exp \left[- \left\{ \sum_{i=1}^k (\log(1 + e^{-y_i}))^\theta \right\}^{\frac{1}{\theta}} \right], \quad (5)$$

where θ must satisfy: $\theta \geq 1$. This distribution specifies an exchangeable correlation structure among the continuous logistic distributed variables. This means that the correlation of any pair

of the k -dimensional vector (Y_1, \dots, Y_k) would be the same. Kendall's tau correlation coefficient is given by $\tau = (\theta - 1) / \theta$, but there is no closed form for Pearson's correlation coefficient. Pearson's correlation coefficient can be determined numerically for different values of θ , see Table 2.

Table 2: Pearson's correlation coefficient for Gumbel copula.

θ	2	3	4	5
ρ	0.7	0.85	0.91	0.95

270 The standardized (generalization of the) FGM distribution with $2^s - s - 1$ parameters is given by

$$F_{FGM}(y_1, \dots, y_k) = \left\{ \prod_{i=1}^k \frac{e^{y_i}}{1 + e^{y_i}} \right\} g(y_1, y_2, \dots, y_k), \quad (6)$$

with

$$g(y_1, y_2, \dots, y_k) = 1 + \sum_{j=2}^k \sum_{1 \leq r_1 < \dots < r_j \leq k} \lambda_{r_1 r_2 \dots r_j} \left(\frac{1}{1 + e^{y_{r_1}}} \right) \left(\frac{1}{1 + e^{y_{r_2}}} \right) \dots \left(\frac{1}{1 + e^{y_{r_j}}} \right),$$

and each parameter must at least satisfy $|\lambda_{r_1 r_2 \dots r_j}| \leq 1$. There are some other restrictions that require that the absolute value of sums of the parameters are also less than one (see Armstrong
275 and Galli, 2002). Choosing different values for elements of the λ 's would create an unstructured correlation matrix, i.e. each pairwise correlation of the k -dimensional vector (Y_1, \dots, Y_k) could be another value. For example, if the higher order parameters are taken equal to zero and only the bivariate parameters λ_{ij} are non-zero, the correlation of Y_i and Y_j is equal to $3\lambda_{ij}/\pi^2$ ($i \neq j$).

To be able to simulate from these joint distributions, we applied copula functions. A copula
280 function C links the univariate marginal distributions to their full multivariate distribution (Nelson, 2006), i.e.

$$C[F_1(y_1), F_2(y_2), \dots, F_k(y_k)] = F(y_1, y_2, \dots, y_k).$$

If F_L is the standardized univariate logistic distribution, i.e. $F_L(y) = (1 + \exp(-y))^{-1}$, then Gumbel copula $C_G(u_1, \dots, u_k)$ is obtained by substituting $F_L^{-1}(u_i)$ for y_i in (5). The FGM copula $C_{FGM}(u_1, \dots, u_k)$ is obtained similarly, by substituting $F_L^{-1}(u_i)$ for y_i in (6). These copulas are
285 programmed in package copula of R and they can be used to simulate multivariate data (see Yan, 2007; Yan et al., 2012b).

For the standardized k-dimensional Gumbel logistic distribution, we need to use function archmCopula first and then apply the standard univariate logistic distribution as the marginal distributions for each variable in the function mvdc. The function rMvdc would then generate
290 k-dimensional random variables. For generating a set of k-dimensional variables from the Farlie-Gumbel-Morgenstern distribution, we need to use function fgmCopula first and again apply the standardized univariate logistic distributions as marginal distributions. Generating random variables with function rMvdc for the FGM copula returns a warning which means that the random generation needs to be properly tested. We investigated the generated data and they had the
295 appropriate means and covariances.

For the Gumbel distribution it is easy to generate highly correlated data, since this is determined by the parameter θ directly, see Table 2. For the FGM, the restrictions on the parameters imply that the correlations are low. To be able to increase the correlations we added a random intercept variable using the so-called bridge distribution function (Wang and Louis, 2003). The density of
300 this one-parameter distribution function is given by

$$f_b(x) = \frac{1}{2\pi} \frac{\sin(\phi\pi)}{\cosh(\phi x) + \cos(\phi\pi)}, \quad (7)$$

with $0 < \phi < 1$ and $-\infty < x < \infty$ and its distribution function is given by

$$F_b(x) = \frac{1}{\phi\pi \sin(\phi\pi)} \left\{ \arctan \left[\frac{1 - \cos(\phi\pi)}{\sin(\phi\pi)} \right] - \arctan \left[\frac{\cos(\phi\pi) - 1}{\sin(\phi\pi)} \tanh \left(\frac{\phi x}{2} \right) \right] \right\}. \quad (8)$$

The mean of the bridge distribution is zero and the variance is $\pi^2(\phi^{-2} - 1)/3$. The marginal distribution of the Y 's remain of the logistic form in (1) and therefore the regression parameters still have an odds ratio interpretation. The bridge distribution was developed for this purpose
305 (Wang and Louis, 2003).

The standardized latent variables generated with the multivariate logistic distributions are not yet related to any covariates. We have selected two explanatory variables time (x_1) and group (x_2) to shift the mean value of the latent variable Y_{it} from zero to η_{it} . We have chosen for η_{it} the following

$$\eta_{it} = -[\beta_T x_{1it} + \beta_G x_{2i} + \beta_{TG} x_{1it} x_{2i}], \quad (9)$$

310 with $\beta_T = 0.5$, $\beta_G = -0.5$, and $\beta_{TG} = -0.5$, with x_{1it} representing time points at which subject i has been observed and with $x_{2i} \in \{0, 1\}$ a group variable. The group variable may represent for

instance treatment or gender. Then the shifted latent variable is $Z_{it} = \eta_{it} + Y_{it}$ and the ordinal outcome $O_{it} \in \{1, 2, 3, 4\}$ is created by the cutpoints $\beta_{01} = -1$, $\beta_{02} = 0$, and $\beta_{03} = 1$ to indicate in which of the four intervals $(-\infty, -1]$; $(-1, 0]$; $(0, 1]$; and $(1, \infty)$ the variable Z_{it} is contained.

315 *3.2. Simulation method: working correlation matrices*

Now consider the binary variable $Y_{itc} = I(O_{it} \leq c) = I(Z_{it} \leq \beta_{0c})$ to transform an ordinal variable to a set of binary variables using the coding of Parsons et al. (2006). Using logit link function, Pearson's correlation coefficient between any pair of binary variables Y_{itc} and Y_{itk} within one time point t is given by $\exp(-|\beta_{0c} - \beta_{0k}|/2)$ and does not depend on time nor on any other
 320 covariate (see Kenward et al., 1994). This would also be true for the coding $Y_{itc} = I(O_{it} > c)$ but this is not the case for the coding $Y_{itc} = I(O_{it} = c)$.

Indeed, the correlation coefficient between $I(O_{it} = c)$ and $I(O_{it} = k)$ is determined by the multinomial distribution function and it is of the form $-\mu_{itc}\mu_{itk}/(1 - \mu_{itc})(1 - \mu_{itk})^{1/2}$, with μ_{itc} , in terms of the general model (1), given by

$$\mu_{itc} = \frac{\exp[\beta_{0c} + x_{it}^T \beta]}{1 + \exp[\beta_{0c} + x_{it}^T \beta]} - \frac{\exp[\beta_{0c-1} + x_{it}^T \beta]}{1 + \exp[\beta_{0c-1} + x_{it}^T \beta]}.$$

325 Hence the correlation between the coded binary variables $I(O_{it} = c)$ and $I(O_{it} = k)$ do depend on time t and on subject specific values of the covariates for subject i . Thus as soon as the simulated variables were affected by covariates, the Pearson correlation between the coded binary variables $Y_{itc} = I(O_{it} = c)$ would depend on the covariate time t and subject specific variables. Despite the difference in correlation coefficients between these choices of coding, sofar it all fits nicely with the
 330 theory and the software packages we are studying. The software packages have implemented these exact same correlations.

If we now investigate the correlation of the binary variables (Y_{itc}, Y_{isk}) from different time points t and s , with $t \neq s$, Pearson's correlation coefficient is given by

$$\text{CORR}(Y_{itc}, Y_{isk}) = \frac{F_{ts}(\beta_{0c}, \beta_{0k}) - F_t(\beta_{0c})F_s(\beta_{0k})}{\{F_t(\beta_{0c})[1 - F_t(\beta_{0c})]F_s(\beta_{0k})[1 - F_s(\beta_{0k})]\}^{\frac{1}{2}}}, \quad (10)$$

with $F_{ts}(\beta_{0c}, \beta_{0k})$ the bivariate distribution of the latent variables Z_{it} and Z_{is} evaluated in
 335 (β_{0c}, β_{0k}) . Note that the correlation in (10) holds when $c = k$ and $c \neq k$. This correlation coefficient will depend on the time points t and s through the means η_{it} and η_{is} of Z_{it} and Z_{is}

in (9) and through the correlation of the latent variables Z_{it} and Z_{is} . Thus for the Gumbel distribution, the correlations of the latent variables Z_{it} and Z_{is} are exchangeable but the correlation between the binary variables Y_{itc} and Y_{isk} are not exchangeable due to the time dependent mean in (9). Furthermore, the correlation in (10) does also depend on the subject specific variables of the covariates used in (9). This means that the correlation of the binary variables Y_{itc} and Y_{isk} would still depend on the subjects whenever the mean (9) would include covariates even if all subjects would have been observed at the exact same time points. This implies that the Gumbel and the FGM distribution using the mean in (9) would never impose the correct weight matrix or working correlation matrix for multgee, geepack, repolr, SAS and SPSS, due to the use of covariates in the latent variables. Note that this would remain true when we would use $I(O_{it} = c)$ or $I(O_{it} > c)$ for binary variables. Therefore the correlation between binary variables can be quite different from the correlation between the latent variables (Molenberghs and Verbeke, 2005).

Only in case the mean in (9) would be independent of the covariates and time, i.e. $\eta_{it} = \eta$ is constant, then the Gumbel distribution would provide the exact exchangeable working correlation used in SPSS. Indeed, the correlation coefficient in (10) for $I(O_{it} = c)$ is only a function of the cutpoints β_{0c} and β_{0k} , say ρ_{ck} , and independent of time. However, the correlation coefficient in (10) for the Gumbel distribution would not generate the uniform working correlation matrix of repolr, since they have implemented the form $\rho_{ck} = \alpha \exp(-|\beta_{0c} - \beta_{0k}|/2)$ which is unequal to (10). When the mean would be constant, any exchangeable multivariate latent variable would lead to the exchangeable working correlation matrix used in SPSS, but only a specific subset of this class of multivariate distributions would generate the uniform working correlation matrix of repolr. The mis-specification of the correlation matrices when (9) is used should not be an issue though, since GEE should still lead to the correct estimates of the parameters β when the mean in (1) is correctly specified (Molenberghs and Kenward, 2010).

3.3. Simulation method: parameter settings

We simulated three dimensional logistic distributed variables (three time points) using parameters $\theta \in \{2, 3, 4, 5\}$ for the Gumbel distribution (G_θ) and parameters $\lambda_{12} = 0.3$, $\lambda_{13} = -0.3$, $\lambda_{23} = 0.3$, and $\lambda_{123} = 0$ for the FGM distribution in combination with a bridge distribution having parameter $\phi = \sqrt{0.5}$. Pearson's correlation coefficients of the three-dimensional latent variable will be in the interval (0.45, 0.55) for this selected FGM distribution with bridge distribution. We

used the same number of subjects for both levels of the group variable x_2 . Furthermore, we used constant time points for all subjects, $x_{1i1} = 0$, $x_{1i2} = 1$, and $x_{1i3} = 2$ and time varying time points $x_{1i1} = 0$, $x_{1i2} = 1 + u_{i2}$, and $x_{1i3} = 2 + u_{i3}$, with u_{i2} and u_{i3} independently generated using the uniform distribution on $(-0.25, 0.25)$. The time varying time points were included to simulate data that is not perfectly balanced for the time and group variable. For binary data it has been demonstrated that the independent working correlation matrix is as efficient as the exchangeable working correlation matrix in such balanced settings (see Mancl and Leroux, 1996).

We also investigated the effect of some variance heterogeneity in the latent variable. The heterogeneity is determined by multiplying the latent variable, before shifting it with mean (9), at each time point with $\exp\{-0.1x_{2i}\}$. This means that the group of subjects with $x_{2i} = 1$ has a decreased variance of approximately 20% at each time point compared to the subjects with $x_{2i} = 0$. This variance heterogeneity does not affect the mean in (9) for the shifted latent variable Z_{it} , since only the variance of the latent variable has changed, but it does effect the linear relationship in (1) for the ordinal outcome variable.

The relationship becomes of the following form $\text{logit}[P(O_{it} \leq c)] = \beta_{0c} + \beta_T x_{1it} + \beta_{2c} x_{2it} + \beta_{12} x_{1it} x_{2it}$, with $\beta_{2c} = (\exp\{0.1\} - 1)\beta_{0c} + \beta_G \exp\{0.1\}$ and $\beta_{12} = (\exp\{0.1\} - 1)\beta_T + \beta_{TG} \exp\{0.1\}$, and β_T , β_G , and β_{TG} defined in (9). It destroys the assumption of proportionality for the main effect of the variable x_{2i} . Thus in this setting the linear relationship in (1) is incorrectly specified, although we have correctly selected the right variables and the linear relationship in (9) is still true for the latent variables. Thus both the mean in the logit scale and the working association matrix would be incorrectly specified when this variance heterogeneity is present in the latent variable. We evaluated how well the proportionality test, which is available in `repolr` only, would pick up this small violation compared to the other models for which proportionality would be true.

An overview of the parameter settings we used to simulate data are provided in the Table 3. The Gumbel distribution with $\theta = 3$ includes the heterogeneity in variance for the group variable. For each parameter setting, 1000 simulated data sets were determined. Each data set was analysed with R, SAS, and SPSS. On each data set, we applied “independence”, “exchangeable”, and “unstructured” association structures with each package (if available).

Table 3: Overview of settings for the simulations study.

Number of subjects	Time points are the same	Time points vary with individuals
15 subjects per groups	$G_2; FGM$	-
50 subjects per groups	$G_5; FGM$	$G_2; G_3; G_4; G_5; FGM$
150 subjects per groups	G_4	-

395 4. Results

4.1. Theoretical considerations

As mentioned in Section 2.1, SAS and SPSS work with the same set of coded binary variables that is also chosen in the approach of Lipsitz et al. (1994). They also used Pearson’s correlation coefficients to estimate of the working correlation. The difference in signs in the parameters estimates, shown in the example, is due to SPSS, which uses $\beta_{0c} - x_{it}^\top \beta_1$ in (1) rather than $\beta_{0c} + x_{it}^\top \beta_1$,
 400 which is used by other packages.

Recall that there were three ways of coding the ordinal outcomes into binary variables (Lipsitz et al., 1994; Touloumis et al., 2013; Heagerty and Zeger, 1996; Parsons et al., 2006) and that there were different estimation approaches for the association parameters. The difference in coding
 405 should, in principle, not lead to different estimates of the fixed parameters β , since there a linear transformation exists between the binary variables. If Y_{it}^L is a vector of binary variables with $Y_{itc}^L = I(O_{it} = c)$ and Y_{it}^P is a vector with $Y_{itc}^P = I(O_{it} \leq c)$, then $Y_{it}^L = GY_{it}^P$, with G a $(C - 1) \times (C - 1)$ lower triangular matrix. The matrix G is invertible since all the elements on the
 410 main diagonal are equal to one. This unique relationship between the binary variables connects the means and covariances between the two sets of binary variables: i.e. $\mu_i^L = G\mu_i^P$ and $V_i^L = GV_i^P G^\top$. Hence, under these two sets of coding the GEE equations solve the same set of parameters β . This would hold true with any two pair-wise comparisons of the three different theories. However, different parameterisations of the association parameters and different methods for estimation of these parameters could still lead to different estimation of α , and thus of β .

415 The parameter estimates generated by R-geepack in our case study compared to the estimates of the other packages (under independence) is awkward considering the linear transformation in binary variables. We could not identify what causes the difference, but we did observe an inconsistency with Pearson’s correlation coefficient for the association of binary variables within one time point.

The correlation coefficient between any pair $Y_{itc} = I(O_{it} > c)$ and $Y_{itk} = I(O_{it} > k)$ with the choice
 420 of the logit link function, results into $\exp(-|\beta_{0c} - \beta_{0k}|/2)$. For a small and simple data set, where
 the ordinal outcome has only three levels and two time points and were generated independently,
 we substituted the parameter estimates of `ordgee` in the GEE's. We used the incorrect value
 $\exp(|\beta_{0c} - \beta_{0k}|/2)$ for the correlation coefficient of Y_{itc} and Y_{itk} with the independence association
 structure and we obtained a set of equations that is almost equal to zero. This did not occur when
 425 we used the correct estimated correlation coefficients.

4.2. Simulation results

Due to the unexpected results of function `ordgee` in the `geepack` and the above explanation,
 we decided to exclude this package from our simulation study. The results of SAS were also
 excluded since it has only one option for the working correlation matrix. Furthermore, the SAS
 430 and SPSS results are the same with this choice of working correlation matrix (except of course for
 the difference in regression parameter signs). Hence, this simulation study provides the results of
 SPSS, `repolr` and `multgee` using the logit link function under independence, time exchangeability
 and unstructured association structures.

4.2.1. Simulation results: numerical convergence

435 Convergence problems were observed with SPSS, `repolr`, and `multgee`. Tables 4 and 5 present
 an overview of the percentages of simulation runs with numerical issues for each of the simulation
 studies.

Table 4: Percentages of convergence issues for simulated data sets with constant time points for individuals.

Analysis approach		G_2	G_3	G_4	G_5	FGM	FGM
		n = 30	n = 100	n = 300	n = 100	n = 30	n = 100
Exchangeable	SPSS	3.4%	0.01%	0	0.01%	1.5%	0
	<code>repolr</code>	14.1%	6.6%	0	4.3%	1.9%	0
	<code>multgee</code>	0.4%	0	0	0	0	0
Unstructured	SPSS	26.7%	3.7%	0.01	11.2%	17.8%	0
	<code>multgee</code>	32.2%	1.6%	0	16.2%	10.2%	0

For constant time points, `repolr` has more numerical issues than `multgee` and SPSS when the

exchangeable working association matrix is selected. It seems that the numerical issues for replor
 440 are related to the number of subjects. For the choice of coded binary variables used in replor, the
 correlation coefficient across time gets closer to the exchangeable structure and is more alike for
 each subject as the parameter θ of the Gumbel distribution decreases. This means that we expect
 fewer numerical issues at $\theta = 2$ than at $\theta = 5$. The relatively high percentage of 14.1% at $\theta = 2$
 compared to the percentage 4.3% at $\theta = 5$, suggests that the difference in sample size may play
 445 a role in the convergence. For the coding of binary variables used in SPSS all selected Gumbel
 distributions will yield working correlation matrices for the association over time that are quite
 different from exchangeability and are not alike for subjects from the different groups. Numerical
 issues with SPSS are limited to the choice of unstructured working correlation matrix. When
 the total number subjects is relatively small, substantial numbers of data sets will demonstrate
 450 numerical issues. Note that the unstructured working correlation matrix in SPSS requires 27
 correlation coefficients alone to describe all of the association parameters across time, which is
 substantial for this relative small set of subjects. Multgee shows the lowest numbers of non-
 convergence with respect to replor and SPSS for exchangeability, but it performs worse than SPSS
 for G_2 and G_5 when the unstructured association is applied. Similar to SPSS, sample size appears
 455 to affect the convergence for an unstructured association. This may be caused by estimated local
 odds ratios close to the boundary values (Touloumis et al., 2013).

Table 5: Percentages of convergence issues for simulated data sets with time varying time points for individuals.

Analysis approach		G_2	G_3	G_4	G_5	FGM
		n = 100	n = 100	n = 100	n = 100	n = 100
	SPSS	28.2%	5.6%	2.5%	0.8%	0
Exchangeable	repolr	0.8%	3.6%	9.0%	5.4%	0
	multgee	0	0	0.01%	0.2%	0
Unstructured	SPSS	22.8%	9.24%	10.7%	14.2%	0.9%
	multgee	0	1.2%	8.2 %	20.9%	0

For varying time points we do see that the numerical issues of replor and multgee increase with
 the parameter θ of the Gumbel distribution. Note that the number of subjects is constant at 100.
 This is probably explained by the fact that the working association diverges from exchangeability

460 when θ increases. Comparing Gumbel distribution G_5 from Table 5 with the same distribution in
 Table 4, suggests that the varying time points for subjects enhance the numerical issues for repolr
 and multgee, because the working association matrix is now different for each subject due to the
 subject specific time points. For varying time points SPSS has substantial numerical issues when
 the unstructured working correlation matrix is selected, but also with the exchangeable working
 465 correlation matrix for Gumbel G_2 . We suspect that the true correlation matrix for the ordinal
 outcomes, that is induced by the latent variables strongly, mismatch with the choice of working
 correlation matrix that is estimated. This may indicate that the estimated working correlation
 matrix is not a genuine correlation matrix, which may imply that the estimated correlation matrix
 is not invertible (see Chaganty and Joe, 2004, 2006). This applies to for both SPSS and repolr,
 470 because they both reported a problem with the covariance matrix V_i for most of their numeri-
 cal issues (repolr: “grad2 < 0 minimum for alpha not achieved”; SPSS: “the Hessian matrix is
 singular”). Unfortunately, multgee does not provide any clear information useful to diagnose the
 non-convergence issue. Changing some of the default settings, such as relaxing the criteria of the
 convergence of the parameter estimates or the maximum number of iterations, solved only a few
 475 of the numerical issues.

4.3. Simulation results: parameter estimates

When the working association matrix is selected as independence or exchangeable and the
 number of subjects is moderate to large (say 100 subjects or more), most of the simulation cases
 provided a bias in the parameter estimates up to a few percent (0 – 4%). This is illustrated
 480 for the Gumbel distribution with $\theta = 5$ for 100 subjects and $\theta = 4$ with 300 subjects given in
 Tables 6 and 7, respectively. Furthermore, recall that the true parameters for G_5 are equal to
 $\beta_{01} = -1$, $\beta_{02} = 0$, $\beta_{03} = 1$, $\beta_T = 0.5$, and $\beta_G = \beta_{TG} = -0.5$. Significant bias is obtained for
 the simulations with only 30 subjects using independence or exchangeability. The bias increases to
 approximately 10% for the Gumbel distribution with $\theta = 2$ (Table 8) and to 17.2% for the *FGM*
 485 with constant time points across individuals (Table 9). Note that the true parameter values for
 the *FGM* distribution, combined with the bridge distribution, are equal to $\beta_{01} = -0.71$, $\beta_{02} = 0$,
 $\beta_{03} = 0.71$, $\beta_T = 0.35$, and $\beta_G = \beta_{TG} = -0.35$. This change in true value compared to the Gumbel
 distribution is caused by the additional variation of the random intercept value that follows the
 bridge distribution. When the unstructured working association is used, even higher biases are

Table 6: The mean parameter estimates (standard error) of 1000 simulated data sets, from the Gumbel distribution with $\theta = 5$, 100 subjects, and constant time points.

	Independence		Exchangeable		Unstructured	
	All*	SPSS	repolr	multgee	SPSS	multgee
β_{01}	-1.04(0.28)	-1.04(0.32)	-1.04(0.28)	-1.03(0.28)	-0.97(0.30)	-1.04(0.28)
β_{02}	-0.01(0.26)	0.00(0.32)	-0.01(0.26)	0.00(0.26)	0.04(0.29)	-0.01(0.26)
β_{03}	1.01(0.28)	1.02(0.34)	1.01(0.28)	1.02(0.28)	1.06(0.32)	1.01(0.28)
β_T	0.51(0.08)	-0.50(0.10)	0.51(0.08)	0.51(0.08)	-0.49(0.09)	0.50(0.08)
β_G	-0.50(0.36)	0.51(0.41)	-0.49(0.36)	-0.51(0.36)	0.59(0.40)	-0.52(0.36)
β_{TG}	-0.51(0.10)	0.51(0.12)	-0.51(0.10)	-0.50(0.10)	0.48(0.13)	-0.48(0.10)

* SPSS gives the same values but with opposite signs on β_T , β_G , and β_{TG} .

490 obtained. The bias with multgee can be as high as 20% for the FGM distribution combined with the bridge distribution (Table 9) while SPSS yields biases of 40% for both G_2 distribution (Table 8) and FGM distribution (Table 9). When the number of subjects increases to 100, the biases with multgee and SPSS under the unstructured association reduce to values as high as 4% and 18%, respectively (Table 6). When the number of subjects increases further to 300, the biases with
495 multgee and SPSS almost vanish (Table 7).

The bias results presented here were obtained from using simulations with constant time points across subjects. With varying time points, the bias was similar to the results for constant time points, except for SPSS, which gave biases as high as 16% for the parameter estimate of the group variable with the exchangeable working correlation matrix. For unstructured association
500 this increased to 26%. These inflation in biases were not seen with repolr and multgee.

Bias could possibly affect the coverage probability of the Wald confidence interval on the parameter. Absence of bias however, does not guarantee a nominal level of coverage, since the standard error of the parameter estimate would also affect the coverage probability. Tables 10 and 11 provide coverage probabilities for two simulation settings.

505 Overall, the coverage probabilities were relatively close to the nominal value of 95% when either the independence or exchangeable working association matrix was used. The coverage probabilities for the independence working association matrix ranged from 93.0% to 96.5%, and

Table 7: The mean parameter estimates (standard error) of 1000 simulated data sets, from the Gumbel distribution with $\theta = 4$, 300 subjects, and constant time points.

	Independence	Exchangeable			Unstructured	
	All*	SPSS	repolr	multgee	SPSS	multgee
β_{01}	-1.01(0.15)	-1.01(0.18)	-1.01(0.16)	-1.01(0.16)	-1.00(0.17)	-1.01(0.16)
β_{02}	-0.01(0.15)	0.00(0.19)	-0.01(0.15)	-0.01(0.15)	0.01(0.17)	0.00(0.15)
β_{03}	1.00(0.16)	1.01(0.19)	1.00(0.16)	1.00(0.16)	1.01(0.18)	1.00(0.16)
β_T	0.50(0.05)	-0.50(0.06)	0.50(0.05)	0.50(0.05)	-0.50(0.06)	0.50(0.05)
β_G	-0.49(0.21)	0.50(0.23)	-0.49(0.21)	-0.50(0.21)	0.52(0.22)	-0.50(0.21)
β_{TG}	-0.51(0.06)	0.50(0.07)	-0.51(0.06)	-0.50(0.06)	0.50(0.07)	-0.49(0.06)

* SPSS gives the same values but with opposite signs on β_T , β_G , and β_{TG} .

for exchangeability it ranged from 92.0% to 96.4%. The coverage probability has a tendency to be somewhat more liberal than being conservative for smaller sample sizes. In general however, the standard errors seem to be estimated at the correct level, despite the difference between the selected working association matrices and the true correlation matrix induced by the latent variable models, and the coverage probabilities are reasonably close to the nominal value.

For the unstructured association matrix we obtained in some cases poor coverage probabilities (see Tables 10 and 11). The observed range of coverage probabilities for the unstructured working association matrix was equal to 89.7% to 95.8% for all our simulation settings, which demonstrates liberal coverage probabilities. It should be noted that the bias for the parameter β_T in Table 10 was only 2.8% for multgee, but the coverage probability was still only 90.4%. This may indicate an underestimated standard error for this parameter when the unstructured association matrix is used. This issue has been reported before by Li and Schafer (2008), who indicated that these issues may be related to small sample sizes. On the other hand, this setting also demonstrated substantial numbers of simulated data sets with non-convergence, which could also be an explanation of the poor coverage.

4.4. Simulation results: test for proportionality

Only R-repolr has a test for the assumption of proportionality and we investigated the test in our simulation. The proportionality assumption was guaranteed for all our latent variable models,

Table 8: The mean parameter estimates (standard error) of 1000 simulated data sets, for the Gumbel distribution with $\theta = 2$, 30 subjects and constant time point.

	Independence	Exchangeable			Unstructured	
	All*	SPSS	repolr	multgee	SPSS	multgee
β_{01}	-1.05(0.48)	-1.05(0.55)	-1.06(0.48)	-1.04(0.47)	-0.91(0.52)	-1.03(0.47)
β_{02}	0.00(0.46)	0.01(0.55)	-0.01(0.47)	0.00(0.46)	0.12(0.52)	0.00(0.45)
β_{03}	1.04(0.49)	1.07(0.58)	1.04(0.49)	1.05(0.49)	1.20(0.60)	1.05(0.49)
β_T	0.53(0.22)	-0.51(0.26)	0.51(0.22)	0.51(0.21)	-0.45(0.28)	0.48(0.21)
β_G	-0.52(0.65)	0.55(0.71)	-0.51(0.65)	-0.53(0.64)	0.70(0.76)	-0.55(0.63)
β_{TG}	-0.54(0.30)	0.53(0.34)	-0.53(0.31)	-0.51(0.29)	0.43(0.42)	-0.47(0.29)

* SPSS gives the same values but with opposite signs on β_T , β_G , and β_{TG} .

except for the Gumbel distribution with $\theta = 3$, when we used constant time points for the 100 subjects. To violate the proportionality assumption, we introduced variance heterogeneity for the group variable. The rejection rates are presented in Table 13.

The proportionality test has an inflated type I rejection rate, since it frequently rejected the proportionality assumption more than 5%, which was the selected level of significance. The type I error rate was close to 5%, only for the FGM distribution combined with the bridge distribution using 100 subjects. Only 11.4% of the simulated data sets with a violated proportionality assumption was detected using heterogeneity setting. This is as large as the false rejection rates for situations where the proportionality is true. The difference in variance in the latent variable between the two groups of subjects ($x_2 = 0$ versus $x_2 = 1$) was only 20%. This could have been too small to be detected with the proportionality test, although a 20% change in variance could be clinically relevant.

5. Conclusions and recommendations

In this paper, we reviewed the GEE method for longitudinal ordinal data with five software packages: SAS 9.4 (GENMOD procedure), SPSS 22.0.0 (GENLIN command), repolr (function repolr), multgee (function ordLORgee), and geopack (function ordgee) in R 3.0.2. We saw that SPSS implements a minus sign for the regression parameters, implying a different interpretation

Table 9: The mean parameter estimates (standard error) of 1000 simulated data sets, for the FGM with the bridge distribution for 30 subjects and constant time point.

	Independence	Exchangeable			Unstructured	
	All*	SPSS	repolr	multgee	SPSS	multgee
β_{01}	-0.73(0.47)	-0.73(0.48)	-0.73(0.47)	-0.74(0.47)	-0.67(0.53)	-0.74(0.46)
β_{02}	0.01(0.46)	0.01(0.47)	0.01(0.46)	0.00(0.46)	0.08(0.52)	0.01(0.45)
β_{03}	0.76(0.47)	0.77(0.49)	0.77(0.47)	0.75(0.47)	0.86(0.59)	0.76(0.46)
β_T	0.36(0.27)	-0.36(0.28)	0.36(0.27)	0.36(0.26)	-0.32(0.32)	0.34(0.25)
β_G	-0.40(0.64)	0.41(0.65)	-0.41(0.64)	-0.40(0.64)	0.49(0.74)	-0.42(0.62)
β_{TG}	-0.35(0.38)	0.35(0.39)	-0.35(0.38)	-0.34(0.38)	0.29(0.47)	-0.30(0.36)

* SPSS gives the same values but with opposite signs on β_T , β_G , and β_{TG} .

of the coefficients. If an explanatory variable has a positive effect on the response, SPSS estimates a negative effect and vice versa. SAS provides only the independence working correlation matrix available, while SPSS is flexible in offering other types of working correlation matrices. Within
545 R, the geepack, multgee and repolr packages all use a different set of binary variables for coding ordinal data. SAS, SPSS, and multgee use the same coding. We demonstrated theoretically that this should not lead to different parameter estimates, since the coding of the ordinal outcome into binary variables are linearly related. The numerical procedures and the method of estimation of the
550 association parameters could lead to possible differences, however, particularly for the estimation of the standard errors. Ultimately, geepack provided results that differ significantly from the other packages. The parameter estimates may give rise to a correlation coefficient for the coded binary variables within a time point that is larger than one. The final comparison included SPSS, multgee, and repolr.

555 We applied copula functions for generating multivariate logistic distributed latent variables underneath the ordinal outcomes. This provided us with a completely specified multivariate distribution on which we could evaluate the performance of the software packages. The covariates in the mean of the latent variables induce a correlation matrix for the ordinal outcomes across time that does not seem to fit with the current choices of the software packages. The reason is that
560 the covariates change the associations across subjects for time dependent association, while SPSS,

Table 10: The percentage of coverage probability for the FGM distribution combined with bridge distribution with 30 subjects and constant time points.

	Independence			Exchangeable			Unstructured	
	SPSS	repolr	multgee	SPSS	repolr	multgee	SPSS	multgee
β_{01}	95.4	95.4	95.4	95.4	95.5	95.1	92.8	95.1
β_{02}	95.0	95.0	95.0	95.3	95.0	95.3	92.7	95.8
β_{03}	94.7	94.7	94.7	95.0	94.5	94.9	92.3	93.8
β_T	93.2	93.0	93.2	93.0	93.1	92.6	90.0	90.4
β_G	93.9	93.9	93.9	93.4	94.2	93.6	91.1	93.9
β_{TG}	95.1	95.1	95.1	95.5	95.0	94.9	90.4	93.4

Table 11: The percentage of coverage probability for the Gumbel distribution with $\theta = 5$ and 100 subject with time varying.

	Independence			Exchangeable			Unstructured	
	SPSS	repolr	multgee	SPSS	repolr	multgee	SPSS	multgee
β_{01}	95.1	94.7	95.1	94.8	94.8	94.2	91.0	93.8
β_{02}	94.8	94.3	94.8	93.4	95.0	94.2	92.2	94.1
β_{03}	94.3	93.9	94.3	95.0	94.4	93.9	93.1	93.5
β_T	94.1	93.5	94.1	92.5	93.7	92.7	89.9	92.2
β_G	95.6	95.6	95.6	95.9	95.6	95.1	94.1	94.8
β_{TG}	94.2	94.9	94.2	95.6	94.9	94.2	92.3	92.5

repolr, and multgee fit constant associations for subjects. Moreover, correlation of coded binary outcomes across time must satisfy a specific exponential form for repolr which is not required for multgee and SPSS when both packages use the exchangeable associations. Mis-specification of the working correlation should however not be any problem since GEE should still be able to estimate the mean parameters appropriately when the robust estimator is applied.

The sample size for subjects has a strong effect on the numerical process. SPSS, repolr, and multgee show non-convergence issues when we apply the non-independence association matrices. When we used time points that were exactly the same for each subject and the exchangeable working association matrix, SPSS appeared to have fewer numerical issues than repolr and multgee

Table 12: The percentage of coverage probability for the Gumbel distribution with $\theta = 4$ and 300 subject with time constant.

	Independence			Exchangeable			Unstructured	
	SPSS	repolr	multgee	SPSS	repolr	multgee	SPSS	multgee
β_{01}	94.3	94.3	94.3	94.3	94.2	94.7	93.8	94.5
β_{02}	94.1	94.0	94.0	94.7	94.1	94.1	94.3	94.1
β_{03}	94.3	94.3	94.3	94.1	94.2	93.6	93.9	93.7
β_T	93.6	93.6	93.6	94.9	93.8	93.9	94.3	94.3
β_G	95.2	95.2	95.2	95.1	95.2	95.2	95.2	95.4
β_{TG}	95.0	95.0	95.0	95.0	94.9	94.6	94.2	93.5

Table 13: Percentages of rejection the proportionality assumption in the simulated data sets.

	G_2	G_2	G_3	G_4	G_4	G_5	FGM	FGM
	n=30	n=100	n=100	n=100	n=300	n=100	n=30	n=100
Time points fixed	14.3%	NA	11.4%	NA	11.1%	16.1%	15.5%	5.2%
Time points varying	NA	8.5%	11.6%	14.3%	NA	13.7%	NA	5.9%

570 seems to have less numerical issues than SPSS. Multgee with exchangeable association is again the best for varying time points but no clear conclusion could be given between SPSS and repolr. For some settings repolr was (substantially) better, but in other settings SPSS seem to do better again. The unstructured association in SPSS and multgee, which is not offered by repolr, seem to cause the largest problems with numerical convergence. Multgee seems to do better than SPSS, although 575 multgee was worse than SPSS for settings with large correlations among the latent variables. Most numerical issues in SPSS were related to problems with non-invertible covariance matrices. It could almost never be resolved by changing the default settings. On the other hand, multgee did not provide clear information on the numerical issues at all.

580 For relative small numbers of subjects, say 30 subjects in total, we saw the largest bias in the parameter estimates. This bias declined to less than 4% when the number of subjects increased to more than 100 and the association matrix was equal to independence or exchangeable. The unstructured association matrix needed even more subjects ($N = 300$) to reduce the bias to acceptable levels on all parameters for both packages (although multgee had less bias than SPSS).

The coverage probabilities on the mean parameters were relatively close to the nominal value for
585 both the independence and exchangeable association matrices, although they would be more liberal than conservative. The coverage probabilities ranged from 93.0% to 96.5% and from 92.0% to 96.4%, respectively. The unstructured association matrix showed mostly liberal coverage probabilities, even for larger sample sizes and for settings without strong biases. The coverage probabilities ranged from 89.7% to 95.8%.

590 R-repolr, which can only fit the cumulative logistic link function, has an advantage over SPSS and multgee because it contains an option for testing the proportionality assumption. Unfortunately, the type I error rate of this test is highly inflated, which is consistent with results published on logistic regression (Agresti, 2010). When we introduced a simulation setting that has a violated proportionality assumption, by introducing variance heterogeneity in the latent variables across
595 subjects, the proportionality test did not find this violation frequently. This has to do with the size of the variance heterogeneity, which was in our setting at 20% difference, i.e. one group had a 20% lower variance than the other group systematically at across time points. We conclude that this test should be applied with care.

Overall, the GEE method performed quite well when there are more than 100 subjects and the
600 association structure is not too complex (no unstructured). GEE produced limited bias and the numerical procedures work appropriately. When sample size is small or proportionality is violated, the methods may result in biased estimates and more numerical issues. In all our simulated data sets the independence association structure with the robust estimator performed quite well and can be used at least as starting point for the analysis. Both SPSS and repolr are recommended but
605 in our simulation multgee outperformed SPSS and repolr in parameter estimation. Both SPSS and multgee provide more flexibility in their choice of association and allow different link functions, but repolr allows proportionality testing. Additional research on GEE is needed, in particular on addressing the subject-specific correlation of the ordinal outcomes across time, and for improving methods on detecting issues with the assumption of proportionality.

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