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INVITED REVIEW

Biostatistics of generalized estimating equations in developmental medicine and child neurology

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Abstract

This review provides clinicians and researchers in developmental medicine and paediatric neurology with a guide to using generalized estimating equations (GEEs) for longitudinal paediatric data. We present a concise primer on core GEE concepts for non-statistical audiences, emphasizing paediatric applications. Using a randomized trial of oestrogen versus placebo for postnatal depression, we provide a reproducible workflow (in R code) for continuous and binary outcomes. We compare exchangeable and autoregressive (first-order autoregressive model) working correlations and discuss implications for efficiency and interpretation. Because the data set is maternal and contains no child outcomes, we treat it as a perinatal case study relevant to child development and use it to illustrate marginal (population-averaged) inference in longitudinal clinical data. GEEs yielded stable marginal estimates across correlation structures when the mean model was correctly specified. Oestrogen was associated with significantly lower odds of postnatal depression than placebo, with negligible differences in model fit (correlation information criterion). Statistical choices mainly affected efficiency and standard errors rather than effect sizes. GEEs provide a robust, interpretable framework for analysing correlated outcomes in paediatric research. Paired with a reproducible example, this helps clinicians and researchers select appropriate models, report working correlations transparently, and interpret marginal effects in practice.

In many areas of developmental medicine and child neurology, researchers work with correlated data, that is, observations that are not statistically independent. In statistics, data are considered independent when the value of one observation does not provide any information about another. Related data, also called correlated or dependent data, occur when observations are connected, such as repeated measurements from the same patient over time or individuals grouped within schools, clinics, or families.

This type of data is common in longitudinal studies, where the same child is followed over time, and in clustered designs, where participants are grouped within defined units. Traditional statistical methods, such as generalized linear models (GLMs), assume independence between observations; applying them to correlated data can lead to misleading results, primarily because of underestimated standard errors (SEs), which increase the risk of type I errors (false positives), but also, in some cases, to inflated SEs, which may reduce statistical power and increase the risk of type II errors (false negatives). This misspecification can also produce biased confidence intervals (CIs) and potentially distort effect estimates.

Generalized estimating equations (GEEs) are a statistical method designed for analysing correlated data and were introduced by Liang and Zeger[1] to address this issue by extending the GLM framework to explicitly model correlations within participants or clusters. They are particularly useful in repeated measures of clinical outcomes, such as motor function in children with cerebral palsy or emotional well-being in adolescents with chronic illness, and are widely applied in longitudinal clinical studies and multi-site trials.

GEEs broaden the scope of GLMs, which relate a dependent variable to predictors using a link function and a specified error distribution, by incorporating correlation structures while remaining robust to certain model assumptions.[1] In statistics, an estimator is considered robust when

Abbreviations: AR(1), first-order autoregressive model; GEE, generalized estimating equation; GLM, generalized linear model; QIC, quasi-likelihood information criterion.

its essential properties, most notably consistency and asymptotic normality, remain valid even when some model assumptions are violated.[2,3] In the context of GEEs, robustness refers to the ability to provide consistent regression parameter estimates and valid SEs even if the working correlation matrix, that is, the assumed structure describing how observations within a cluster are correlated, is misspecified.

GEEs are semiparametric models because they combine parametric and non-parametric components. A parametric model assumes that the data follow a specific distribution described by a fixed number of parameters, such as the mean and standard deviation in a normal distribution.[4,5] A non-parametric model makes fewer assumptions about the shape of the data, does not predefine the number of parameters, and adapts its complexity to the data, offering greater flexibility but usually requiring larger sample sizes.[6,7] In GEEs, the mean model, the part of the model that specifies the relationship between the mean of the response variable and the explanatory variables and linking predictors to outcomes, is parametric, while the working correlation structure is specified non-parametrically, that is, it does not require full knowledge of the data's joint probability distribution. GEEs rely only on the first two moments of the outcome distribution (mean and variance) to produce estimates, which contributes to their robustness: even if the correlation structure is wrong, estimates remain consistent as long as the mean model is correct.

What this paper adds

- Generalized estimating equation (GEEs) yielded stable marginal estimate across correlation structures when the mean model was correctly specified.
- Oestrogen was associated with significantly lower odds of postnatal depression than placebo.
- GEEs provide a robust, interpretable framework for analysing correlated outcomes in paediatric research.

THE USE OF GENERALIZED ESTIMATING EQUATIONS IN DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY

In clinical research, robustness is essential. Real-world paediatric and neurological data sets are rarely perfectly balanced or normally distributed: follow-up intervals may vary, participants may drop out, and measurement tools may perform differently across ages. GEEs handle such imperfections better than many fully parametric models, while still producing valid population-level conclusions.

In developmental medicine and child neurology, repeated measurements are common, for example, tracking a child's motor development over multiple visits or monitoring symptom progression at several follow-up points. In these situations, the correlation between measurements from the same individual or cluster is inevitable. GEEs explicitly account for this correlation, ensuring that statistical inferences remain valid despite irregular follow-up schedules, missing data patterns, or heterogeneous measurement conditions. This makes GEEs particularly useful when the research question focuses on the overall treatment effects or trends at the population level, rather than predicting individual trajectories. By accommodating complex, imperfectly balanced data structures, they offer a practical and reliable approach for analysing clinical data sets in these fields. GEEs produce marginal or population-averaged estimates rather than individual-specific predictions. This is a key distinction from mixed-effects models, which answer the question 'How does the relationship vary for each individual patient?', making them ideal for modelling variability in disease progression or treatment response. GEEs, on the other hand, answer the question 'On average, how does the predictor affect the outcome across the entire population?', making them particularly relevant for public health, large-scale interventions, and policymaking. This focus makes GEEs suitable for longitudinal studies with repeated measures (e.g. monitoring changes in motor function over several therapy sessions), clustered designs (e.g. multicentre trials, school-based interventions), and epidemiological surveillance focusing on overall trends rather than individual trajectories. However, GEEs are not the best choice when the goal is individual-level prediction. In those cases, mixed-effects models are preferable. Moreover, GEEs estimate population-averaged rather than individual-specific effects; therefore, they cannot model random effects as in generalized linear mixed models.[1,8] Although coefficient estimates remain consistent even when the working correlation is misspecified, efficiency is reduced, leading to inflated SEs and more conservative p-values. SEs can be biased in small numbers of clusters, but small-sample corrections are available.[9]

STATISTICAL NOTIONS FOR GENERALIZED ESTIMATING EQUATIONS

GEEs extend the GLM framework to analyse correlated data, such as repeated measurements from the same individual or clustered observations. Rather than fully specifying the joint distribution, GEEs separate two components: the mean model and the working correlation structure. The mean model describes how the average outcome is related to the predictors of interest, while the working correlation structure specifies how measurements in the same cluster are related to one another. This separation allows population-averaged inference while accommodating intracluster dependence. Estimation relies on the first two moments (mean

and variance), which improves robustness when ideal distributional assumptions do not hold.

Mean model

The mean model is defined by a link function that relates the expected outcome to a linear predictor:

$$g\left(\mu_{ij}\right) = \mathbf{X}_{\mathrm{ij}}{}^{T}\,\boldsymbol{\beta}$$

where $\mathbf{X}_{\mathbf{ij}}$ is the covariate vector and $\boldsymbol{\beta}$ is the vector of the regression coefficients. Link choices typically include logit for binary outcomes, log for counts, and identity for continuous outcomes.

The variance is expressed as a function of the mean with a dispersion parameter:

$$Var\left(Y_{ij}\right) = \varphi\, V\left(\mu_{ij}\right)$$

For example, in a study of postpartum depression, it defines how the average probability of depression changes according to time, treatment group, or other variables, without modelling the exact trajectory of each individual participant.

Correlation structure

A defining feature of GEEs is the specification of a working correlation structure that models the association between repeated observations within a cluster, represented by a working correlation matrix. Common options include an independent structure, which assumes no within-individual correlation and is rarely realistic for longitudinal data; an exchangeable (compound symmetry) structure, which assigns the same correlation to all pairs of observations; a first-order autoregressive model (AR [1]) structure, in which correlation decays as the time gap increases; and an unstructured form, which estimates a separate correlation for each pair and is flexible but data-intensive:

$$Corr\left(Y_{it}, Y_{is}\right) = \rho^{|t-s|}$$

In GEEs, the choice of correlation structure influences the efficiency of the estimates (i.e. smaller SEs) but does not affect their consistency when the mean model is correctly specified. In paediatric and clinical research, exchangeable and AR(1) structures are most frequently used because they provide a good balance between realism and parsimony. If no temporal decay in correlations is expected, the exchangeable structure represents a parsimonious default. Model comparison can be further guided by quasi-likelihood information criteria (QICs).

$R(\alpha)$ encodes the within-cluster correlation among the components of Y_i. Specifying $R(\alpha)$ is needed to account for intracluster dependence and improve efficiency (model-based SEs); even if misspecified, the GEE estimator of the mean model coefficients, $\widehat{\beta}$ (i.e., the population-averaged regression effects) stays consistent with a correct mean model and robust SEs. The 'nature of the correlation' is $Corr(Y_{ij}, Y_{ik} / X)$ for two outcomes on the same individual at different occasions (e.g. AR [1]: $\rho^{|t_j - t_k|}$), not between predictors nor across individuals.

Parameter estimates are obtained by solving the following estimating equation:

$$\sum_{i=1}^{N} D_i{}^{T}\, V_i{}^{-1}\, \left(Y_i - \mu_i\right) = 0$$

with the working covariance written as:

$$V_i = A_i{}^{1/2}\, R(\alpha)\, A_i{}^{1/2}$$

where Y_i stacks the outcomes for child $_i$, μ_i their means, and $D_i = \alpha\mu_i / \alpha\,\beta^{T}$, $A_i = \mathrm{diag}[\phi \mathrm{V}(\mu_{ij})]$.

SEs are obtained via the robust ('sandwich') estimator, which remains valid under correlation misspecification provided that the mean model is correct. In studies with fewer clusters, small-sample corrections to the sandwich variance are recommended.

Summary

GEEs separate the mean model from the correlation structure and rely on the first two moments of the outcome. This yields robust, interpretable, population-level estimates across a wide range of correlated data settings.

A detailed presentation of the formal statistical formulation and the estimating equations used in the GEEs is provided in Appendix S1 for readers interested in the technical aspects.

SOFTWARE FOR GENERALIZED ESTIMATING EQUATIONS

R (R Foundation for Statistical Computing, Vienna, Austria) provides a robust environment for implementing GEEs through several dedicated packages. For instance, geepack[10] allows users to fit GEE models using the geeglm() function, which accommodates several working correlation structures (e.g. exchangeable, autoregressive, unstructured) and response distributions (e.g. Gaussian, binomial, Poisson).

The package also provides robust variance estimators to ensure valid SEs and *p*-values even when the working correlation structure is misspecified. In geeglm(), key arguments include id, which specifies the individual or cluster identifier (e.g. patient ID or classroom ID) and defines the grouping for correlated observations; family, which sets the outcome distribution, for example, Gaussian for continuous outcomes such as motor scores, or binomial for binary outcomes such as screening positive versus negative for anxiety; and corstr, which defines the working correlation structure

and encodes assumptions about within-cluster correlation patterns.

In clinical and developmental research, these parameters have direct interpretability. For example, in a paediatric asthma follow-up study with monthly symptom scores, using family = Gaussian and corstr = ar1 would reflect the expected temporal correlation. In a school-based screening for anxiety (positive/negative), family = binomial and corstr = exchangeable could be a parsimonious default.

Beyond model fitting, diagnostics and robustness checks are essential. While GEEs do not provide likelihood-based measures, such as the Akaike information criterion, model comparison can be done using quasi-likelihood under the independence model criterion (i.e. QIC).[11] Researchers are encouraged to inspect residual plots over time or across clusters, check influence diagnostics at the cluster level, and run sensitivity analyses by changing correlation structures (e.g. from exchangeable to ar1) and adding or removing potential confounders to assess the stability of results. Such steps help ensure that observed treatment effects, such as an odds reduction of depression under a new therapy, are not artefacts of model assumptions.

The integration of R's visualization tools, such as ggplot2,[12] further enhances the analysis by enabling intuitive graphical exploration of model results. Additionally, other packages like gee[13] and multgee[14] extend the GEEs framework to handle multinomial or ordinal outcomes, offering additional flexibility for complex data structures common in developmental medicine and child neurology.

POSTNATAL DEPRESSION TRIAL USING GENERALIZED ESTIMATING EQUATIONS

We illustrate GEEs with the depression data set from the R package glmtoolbox (v0.1.12),[15] based on a clinical trial comparing oestrogen to placebo for postnatal depression.[16] The data set contains longitudinal, correlated data, that is, 427 observations from 61 females assessed at baseline (visit −1) and six follow-ups (visits 1–6). Variables include participant ID, treatment group (placebo, oestrogen), visit number, continuous depression score (dep), and binary depression status (depressd).

To demonstrate the flexibility of GEEs, two models were fitted: a Gaussian GEE (identity link) for continuous depression scores and a logistic GEE (logit link) for binary depression status.

We selected the working correlation structure primarily using the correlation information criterion as implemented in the glmtoolbox package (v0.1.12),[15] which has been proposed as a robust alternative to QIC when comparing correlation structures in GEE. For transparency, we also report QIC and QICu using standard implementations. QIC assesses model fit based on the estimated working correlation, whereas QICu uses the independence model to compute a more stable penalty for model complexity; both are commonly used to guide the choice of correlation structure. In our data, correlation information criterion and QIC favoured the same (or closely similar) structure, and effect estimates were materially unchanged; therefore, we prioritized the parsimonious option for reporting.

Analyses were conducted in R using the following core commands (see Appendix S2 for the complete R code to reproduce all analyses, tables, and figures):

```
library(glmtoolbox)
data("depression", package = "glmtoolbox")

Gaussian GEE
gee_gauss<-glmgee(dep~group*visit,
id = subj,
 data = depression, family = Gaussian,
 corstr = "exchangeable")

Logistic GEE
gee_logit<-glmgee(depressd~group+visit,
id = subj,
 data = depression, family = binomi-
al("logit"),
 corstr = "exchangeable")
```

Results

In Table 1, the Gaussian GEE model with an exchangeable correlation structure showed a clear main effect of time, with depression scores decreasing significantly across visits (β = −0.45, 95% CI = −0.60 to −0.30, $p < 0.001$). The main effect of treatment group was not statistically significant (β = −0.52, 95% CI = −1.40 to 0.36, p = 0.249). However, the significant group × time interaction (β = −0.20, 95% CI = −0.35 to −0.05, p = 0.010) indicated that symptom reduction over time was greater in the oestrogen group than in the placebo group.

In Table 2, the estimated odds ratio (OR) for the treatment effect was highly consistent across structures (OR ≈ 0.16), indicating that oestrogen treatment was associated with a substantially lower odds of postnatal depression compared with placebo. The correlation information criterion index slightly

TABLE 1 GEE Gaussian model for depression score over time, with treatment group and time interaction.

Variable	Estimate	95% CI (lower)	95% CI (upper)	p
Intercept	18.21	17.50	18.92	< 0.001
Group (oestrogen)	−0.52[a]	−1.40	0.36	0.249
Visit	−0.45	−0.60	−0.30	< 0.001
Group × visit	−0.20	−0.35	−0.05	0.010

Abbreviations: CI, confidence interval; GEE, generalized estimating equation.
[a]Oestrogen was associated with significantly lower odds of postnatal depression than placebo.

TABLE 2 GEE logistic regression estimates for postpartum depression according to treatment group, comparing the exchangeable and AR(1) correlation structures.

Structure	Treatment OR[a] (oestrogen vs placebo) (95% CI)	*z*-score	*p*	CIC
Exchangeable	0.161 (0.053–0.494)	−3.198	0.001	8.048
AR(1)	0.169 (0.058–0.493)	−3.256	0.001	6.970

Abbreviations: AR(1), first-order autoregressive model; CI, confidence interval; CIC, correlation information criterion; GEE, generalized estimating equation; OR, odds ratio.

[a]ORs for treatment effect under different correlation structures.

TABLE 3 Predicted probabilities according to visit, treatment, and correlation structure.

Visit	pred_ar1 – oestrogen	pred_ar1 – placebo	pred_exch – oestrogen	pred_exch – placebo
−1	0.889	0.979	0.853	0.973
1	0.697	0.931	0.653	0.921
2	0.551	0.879	0.517	0.869
3	0.396	0.795	0.379	0.791
4	0.260	0.675	0.258	0.683
5	0.158	0.526	0.165	0.551
6	0.091	0.372	0.101	0.411

favoured the AR(1) structure, but the difference from the exchangeable model was negligible.

Predicted probabilities from the logistic models are summarized in Table 3. Across all visits and under both correlation structures, the oestrogen group consistently displayed a lower predicted probability of postnatal depression compared with the placebo group. Differences between the correlation structures were minimal. The R code used to compute these predicted probabilities is provided in Appendix S3.

Figures 1 and 2 illustrate the predicted values from the Gaussian and logistic GEE models respectively. In Figure 1, using a Gaussian distribution with an identity link, predicted depression scores decreased almost linearly over time in both groups, with a steeper decline for the oestrogen group. In Figure 2, using a binomial distribution with a logit link, the predicted probabilities of depression also declined over time, again showing a greater and consistent reduction for the oestrogen group. In both figures, shaded areas represent 95% confidence intervals.

Interpretation

This example of a postnatal depression trial using GEEs illustrates how GEEs can accommodate within-individual

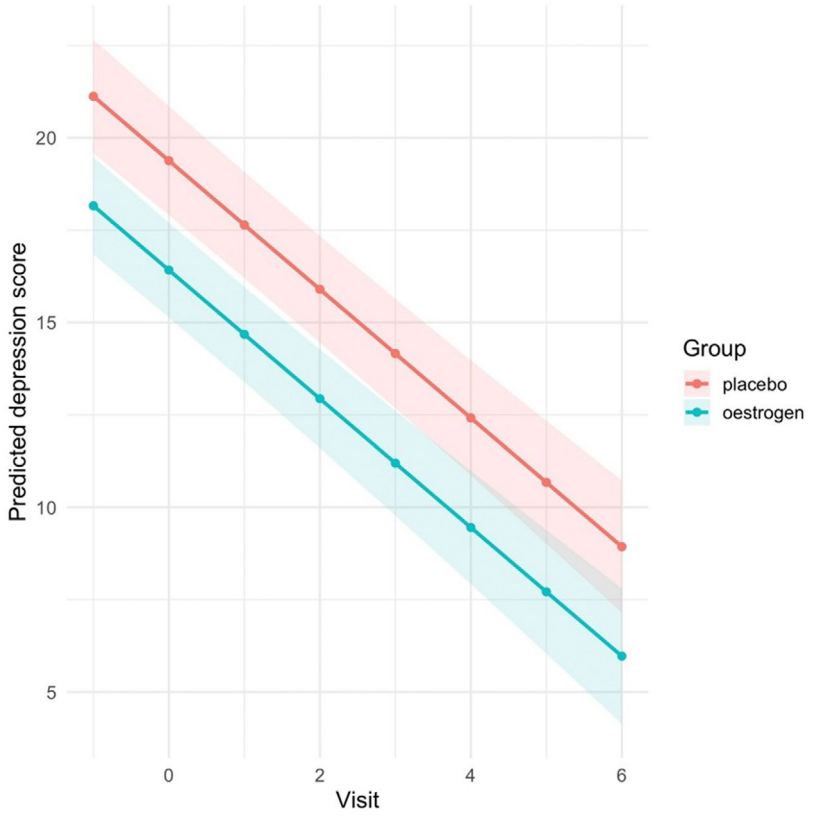

FIGURE 1 Continuous outcome. Predicted postnatal depression score over visits according to treatment group from generalized estimating equation models with exchangeable working correlation; shaded areas indicate the 95% confidence intervals.

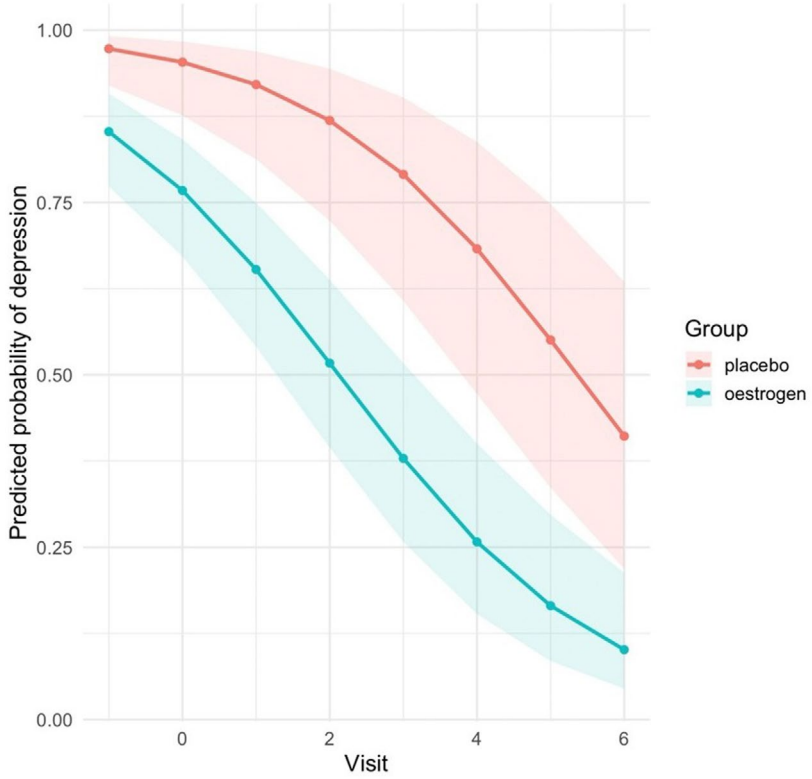

FIGURE 2 Binary outcome. Predicted probability of postnatal depression over visits according to treatment group from generalized estimating equation models with exchangeable working correlation; shaded areas indicate the 95% confidence intervals.

correlation in longitudinal analyses. Both the probability and mean level of postnatal depression declined over time, with greater reductions in the oestrogen group. Treatment effect estimates were highly consistent across plausible working correlation structures, with differences primarily in SEs rather than point estimates, as expected when the mean model is correctly specified. Oestrogen treatment was associated with approximately 84% lower odds of postpartum depression compared to placebo across the follow-up visits. Given the negligible correlation information criterion difference, the exchangeable structure offers a parsimonious and robust modelling choice in this context.

CONCLUSION

This review demonstrates how GEEs can be applied in developmental medicine and paediatric neurology research to address within-individual correlation in longitudinal data. By combining a clear theoretical overview with a fully reproducible real-world example, including annotated R code, tables, and visualizations, we illustrate how GEE models can yield robust, population-averaged estimates for both continuous and binary outcomes. The case study highlights that the choice of working correlation structure primarily affects estimation efficiency rather than the treatment effect itself, reinforcing the method's stability when the mean model is correctly specified. Beyond the specific data set, this step-by-step approach aims to equip researchers and clinicians with practical skills to implement GEEs in their own studies, ultimately improving statistical rigour and the interpretability of longitudinal analyses in paediatric populations.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that does not issue DOIs.The data that support the findings of this study are openly available in the Comprehensive R Archive Network (CRAN) within the R package "glmtoolbox" at https://CRAN.R-project.org/package=glmtoolbox, reference: dataset "depression" (postnatal depression), package version 0.1.12. Package DOI: 10.32614/CRAN.package.glmtoolbox.

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SUPPORTING INFORMATION

The following additional material may be found online:
Appendix S1. Statistical notions for GEEs
Appendix S2. Simple R code for the example
Appendix S3. Reproducible R code for the GEE analyses

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