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Mixed Effects Logistic Regression Models for Longitudinal Ordinal Functional Response Data with Multiple-Cause Drop-Out from the Longitudinal Study of Aging

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SUMMARY. In the context of analyzing ordinal functional limitation responses from the Longitudinal Study of Aging, we investigate the association between current functional limitation and previous year's limitation and its modification by physical activity and multiple causes of drop-out. We accommodate the longitudinal nature of the multiple causes of informative drop-out (death and unknown loss-to-follow-up) with a mixed effects logistic model. Under the proposed model with a random intercept and slope, the ordinal functional outcome and multiple discrete time survival profiles share a common random effect structure. This shared parameter selection model assumes that the multiple causes of drop-out are conditionally independent of the functional limitation outcome given the underlying random effect representing an individual's trajectory of general health status across time. Although it is not possible to fully assess the adequacy of this assumption, we assess the robustness of the approach by varying the assumptions underlying the proposed model, such as the random effects distribution and the drop-out component. It appears that between-subject differences in initial functional limitation are strongly associated with future functional limitation and that this association is stronger for those who do not have physical activity regardless of the random effects and informative drop-out specifications. In contrast, the association between current functional limitation and previous trajectory of functional status within an individual is weaker and more sensitive to changes in the random effects and drop-out assumptions.

KEY WORDS: Approximate conditional; Normal random effects; Shared parameter.

1. Introduction

Longitudinal studies of aging typically focus on the relationships between current and previous outcomes of health, such as functional limitation. A key issue that has not been thoroughly addressed in these investigations is accommodating multiple causes of drop-out, such as unknown loss-to-follow-up, institutionalization, and death. Assuming that drop-out is unrelated to outcome may not be feasible here given that institutionalization and death may be due to health factors underlying longitudinal health outcomes, such as functional limitation. We attempt to account for multiple causes of informative drop-out with an extension of the mixed effects logistic model for longitudinal ordinal data arising from the Longitudinal Study on Aging (LSOA).

The LSOA is a multistage probability sample of elderly adults based on the Supplement on Aging (SOA) to the 1984 National Health Interview Survey (NHIS). The multiple stages of sampling consisted of primary sampling units (PSUs), segments, households, and subjects with repeated measures. Having been sampled with unequal probabilities of selection in 1984, 5151 SOA participants aged 70 and older were targeted for follow-up through reinterviews in 1986, 1988, and 1990. Of these 5151 subjects, 2167 had missing data due to incomplete data collection during a particular visit during the study period. The reasons for incomplete data collection on these 2167 subjects were most likely due to logistical constraints and interviewer–study subject issues unrelated to functional limitation. Data from the remaining 2984 participants were analyzed for this paper. Among these subjects, those who missed an entire interim visit were designated as having dropped out at that visit. Hence, the drop-out components of our model accounted for any informed missing interim visits, although we did not include any subsequent follow-up visits for these individuals. Finally, we exclude 18 subjects who were institutionalized, as they could not provide sufficient information for estimation of the drop-out component characterizing their drop-out process.

In all of our analyses presented in this paper, we accommodate only one level of clustering (multiple time points per subject), as the degree of correlation due to higher levels of cluster factors (e.g., PSU) is negligible (Miller et al., unpublished manuscript). Because of the unequal probabilities of

selection, one may consider weighted analyses using weights equal to probabilities of selection at the subject level. However, we present only an unweighted analysis since the resulting inference did not differ from inference based on a weighted analysis.

The data analyzed at each of these interviews consisted of (1) death status; (2) physical functional limitation, i.e., an ordinal variable indicating the number of current physical functional limitations (none, 1–3, 4–5); (3) an analogous ordinal variable counting the number of functional limitations in the previous year; (4) sex; (5) age in 1986 and change in age since 1986; (6) physical activity, i.e., indicator of whether the individual reported in 1984 walking 1 mile or more at least 1 day per week; and (7) interaction between physical activity and physical functional limitation. The question of interest in this analysis pertains to the association between current and previous years' levels of functional limitation and its interaction with physical activity, controlling for certain covariates and different sources of informative drop-out. Our focus in this paper is on the impact of adjusting for different sources of drop-out on inference.

We propose a mixed effects logistic model for longitudinal ordinal response data with a certain type of informative drop-out. Diggle and Kenward (1994) used the term informative drop-out to denote drop-out processes that depend on unobserved outcomes. Such a missing data process is nonignorable (i.e., needs to be explicitly adjusted for) according to the criteria defined by Rubin (1976) because likelihood inference that ignores the drop-out process is biased.

The type of informative drop-out that we consider here is dependent on an unobserved random effect underlying the observed and unobserved ordinal outcomes. Random effects models for analogous informative drop-out processes with continuous outcome data have been investigated by a number of researchers, some of whom term such models as shared parameter models because the outcome and drop-out processes share a random effects structure (Wu and Carroll, 1988; De Gruttola and Tu, 1994). Wu and Carroll (1988) presented a mixed effects linear model that shared a random effect structure with a discrete time survival model for the drop-out process. Schluchter (1992) and De Gruttola and Tu (1994) fitted similar mixed effects linear models with linear or log-linear continuous time survival models characterizing drop-out processes. Ten Have et al. (1998) presented analogous mixed effects models for longitudinal binary responses with informative drop-out. We propose an extension of their model to the ordinal functional status response in the LSOA data.

The concept of a random effect manifested as an ordinal response and impacting the different processes leading to drop-out applies well to these data. The process leading to deteriorating functional ability may also lead to unknown loss to follow-up and institutionalization. Viewing death this way, as a consequence of an underlying trajectory of functional ability, may be appropriate if death is the culmination of this deterioration process rather than a haphazard, unrelated event. Such missing data are nonignorable for analyses such as maximum likelihood estimation of mixed effects models that do not account for the informative drop-out mechanism.

A critical assumption of the shared parameter models is the conditional independence between the drop-out and longitudinal outcome processes given the random effects structure underlying both processes. Although complete verification of this assumption is not possible, Little (1995) recommended sensitivity analyses, which we perform in the context of the ordinal response model fitted to the LSOA data by varying the random effects and drop-out assumptions.

The proposed shared parameter model is addressed in Section 2 and the corresponding maximum likelihood estimation procedure is addressed in Section 3. Because of the problems with identifiability with informative drop-out models, we focus on sensitivity analyses in Section 4. The results from analyzing the LSOA data are presented in Section 5. Finally, extensions of the proposed methodology are addressed in Section 6.

2. Models

We present the shared parameter model for the general case of I persons, each of whom is followed for at most J discrete time points. In this discrete time framework, we assume that the baseline risk of drop-out is constant between the discrete time points. Such an assumption has been shown to work well for random effects models for correlated survival profiles (Andersen et al., 1997). Baker (1998) made a similar assumption for annual interval survival data.

For the longitudinal ordinal outcome with K (= 3 for the functional limitation data) levels, let R_{ij} be the ordinal response for the ith subject at the jth time point: $R_{ij} \in 1, 2, 3$ if subject i has no, 1–3, or > 3 functional limitations, respectively, at time j for all i and $j = 1, \ldots, J$. For purposes of presenting the likelihood, we define a $(K \times 1)$ multinomial vector, $\mathbf{Y}_{ij}^{\mathrm{T}} = (Y_{ij1} \cdots Y_{ijK})$, where $Y_{ijk} = 1$ if $R_{ij} = k$ and $Y_{ijk} = 0$ otherwise. Also define $\mathbf{x}_{ij}$ and $\mathbf{v}_{ij}$ to be the observed covariate vectors corresponding to the fixed and random effects, respectively, for the ith subject at time j. Subject-level (e.g., physical activity) and time-dependent (e.g., previous outcome and time) covariates may be included in $\mathbf{x}_{ij}$ and $\mathbf{v}_{ij}$.

In defining the variables for the drop-out process, we extend the drop-out components of previous shared parameter models (e.g., Wu and Carroll, 1988; Ten Have et al., 1998) to accommodate the multiple causes of drop-out. Let Z_i be the variable indicating the last time point before which the ith subject drops out and let D_i be the indicator variable of the reason the ith person dropped out. In our example, $D_i \in \{1, 2\}$, corresponding to unknown loss to follow-up and death, respectively. Because drop-out is defined not to occur after time J, Z_i takes on the integer values ranging 1–J, with $Z_i = J$ indicating that a subject did not drop out during the study period. For each cause of drop-out, we specify a separate discrete survival model, which we address in the next subsection. This approach to modeling multiple causes of drop-out is similar to that taken by Baker (1998) in modeling competing risks for discrete time data measured annually.

2.1 *Shared Parameter Model*

We specify ordinal response logistic and continuation ratio logit (CRL) models for the longitudinal functional limitation and each of the drop-out responses, respectively, such that the two sets of models share a common random effects vector for the ith subject, say $\boldsymbol{\tau}_i$. (We refer to the logistic model for functional limitation responses as the longitudinal component and the collection of CRL models for drop-outs as the drop-out component.) Let $\mathbf{y}_i^{\mathrm{T}} = (\mathbf{y}_{i1}^{\mathrm{T}} \cdots \mathbf{y}_{iZ_i}^{\mathrm{T}})$ denote the vector of observed longitudinal multinomial responses and let z_i and

d_i represent the observed responses for Z_i and D_i, respectively. The resulting marginal likelihood for the ith subject for both the longitudinal and drop-out components is then

$$f_{Y,Z}(\mathbf{y}_i, z_i, d_i) = \int f_Y(\mathbf{y}_i \mid \boldsymbol{\tau}) f_{D,Z}(d_i, z_i \mid \boldsymbol{\tau}) f_\tau(\boldsymbol{\tau})\, d\boldsymbol{\tau}, \tag{1}$$

where $f_Y(\cdot \mid \boldsymbol{\tau})$ and $f_{D,Z}(\cdot \mid \boldsymbol{\tau})$ are the conditional models given $\boldsymbol{\tau}$ for $\mathbf{Y}_i$ and the pair (D_i, Z_i), respectively, and $f_\tau(\cdot)$ is the random effects density. (Following convention, we drop the index i from τ_i when integrating with respect to it.)

We first present the longitudinal component of the shared parameter model. Let $\boldsymbol{\pi}_{ij} = (\pi_{ij1} \cdots \pi_{ijK})$, such that $\Sigma_{k=1}^{K} \pi_{ijk} = 1$, be the vector of multinomial probabilities for $\mathbf{Y}_{ij}$ given $\boldsymbol{\tau}_i$, i.e., the conditional distribution for Y_{ij} is multinomial($\boldsymbol{\pi}_{ij}$) so that $f_Y(\mathbf{y}_i \mid \boldsymbol{\tau})$ is a product of these conditional multinomial mass functions across time (denoted by the index j). We specify the ordinal logistic model for $\boldsymbol{\pi}_{ij}$ as

$$\log\left(\frac{\gamma_{ijk}}{1-\gamma_{ijk}}\right) = \boldsymbol{\tau}_i^{\mathrm{T}} \boldsymbol{\Sigma} \mathbf{v}_{ij} + \alpha_k + \boldsymbol{\beta}^{\mathrm{T}} \mathbf{x}_{ij}, \tag{2}$$

$k = 1, \ldots, K-1$, and where $\gamma_{ijk} = \Sigma_{k'=1}^{k} \pi_{ijk'}$ and α_k is the cutpoint for the kth cumulative probability, $\boldsymbol{\beta}$ is the vector of log odds ratios interpreted as differences in the covariate vector $\mathbf{x}_{ij}$ between observations within a subject, $\boldsymbol{\tau}_i$ has a multivariate normal distribution with mean $\mathbf{0}$ and variance–covariance equal to the appropriately dimensioned identity matrix, and $\boldsymbol{\Sigma}$ is a square matrix of appropriate dimensions such that $\boldsymbol{\Omega} = \boldsymbol{\Sigma}^{\mathrm{T}}\boldsymbol{\Sigma}$ is positive definite and the diagonal elements of $\boldsymbol{\Sigma}$ are positive for identifiability reasons. For the current paper, $\boldsymbol{\Sigma}$ is the Cholesky decomposition of $\boldsymbol{\Omega}$. As with the standard mixed effects logistic model, it is assumed that the elements of $\mathbf{Y}_i$, i.e., ordinal responses of a subject, are conditionally independent given $\boldsymbol{\tau}_i$. Hedeker and Gibbons (1994) specify a similar model for clustered ordinal response data.

We now consider the parameterization of the two drop-out components corresponding to the two different types of drop-out: unknown cause and death. For the dth type of drop-out, we define the following conditional probability: $\lambda_{dij} = \Pr(D_i = d, Z_i = j \mid Z_i > j-1;\ \boldsymbol{\tau}_i)$ for all i; $j = 1, \ldots, J-1$; $d = 1, 2$. The risk set for drop-out d in a particular time period consists of all subjects who have not dropped out for any reason prior to time j. The λ_{dij} parameters are interpreted as cause-specific, discrete time hazard rates (e.g., Baker, 1998), i.e., the conditional probability of dropping out for reason d. For example, $\lambda_{2ij} = \Pr(D_i = 2, Z_i = j \mid Z_i > j-1;\ \boldsymbol{\tau}_i)$ is interpreted as the conditional probability that subject i drops out due to death between times j and $j+1$, inclusive of time $j+1$, given the underlying random effect $\boldsymbol{\tau}_i$ and given that that subject has not dropped out due to any cause prior to time j. As discussed previously, we assume that the risk characterized by λ_{dij} does not change between times j and $j+1$, i.e., we assume a piecewise constant hazard.

Now consider the likelihood component for drop-out, which is constructed by specifying separate discrete time survival likelihood components for each drop-out. Within the likelihood in (1), the conditional log-likelihood for drop-out type $d_i = d$ after time $z_i = j$ until time $j+1$, given the unobserved random effects of the ith subject, is

$$\log\left[f_{D,Z}(d, j \mid \boldsymbol{\tau}_i)\right] = \log \psi_{dij} + \sum_{d'=1}^{2} \sum_{j'=1}^{j} \log(1 - \lambda_{d'ij'}) \tag{3}$$

for all d, i, and $j = 1, \ldots, J-1$ and $\psi_{dij} = \lambda_{dij}(1 - \lambda_{dij})^{-1}$. For those subjects who do not drop-out, the drop-out component of the log-likelihood analogous to (3) is $\Sigma_{d'=1}^{2} \Sigma_{j'=1}^{J-1} \log(1 - \lambda_{d'ij'})$.

The parameter ψ_{dij} is a continuation ratio and can be interpreted as the conditional odds of subject i dropping out for reason d after time j until time $j+1$. We parameterize the logarithm of ψ_{dij} as a linear combination of parameters (i.e., CRL model),

$$\log \psi_{dij} = \boldsymbol{\tau}_i^{\mathrm{T}} \boldsymbol{\Sigma}_d^* \mathbf{v}_{dij} + \alpha_0 + \boldsymbol{\rho}_d^{\mathrm{T}} \mathbf{u}_{dij}, \tag{4}$$

where $\boldsymbol{\Sigma}_d^* = \boldsymbol{\Sigma} + \boldsymbol{\Delta}_d$ and $\boldsymbol{\rho}_d$ is a vector of log odds ratios corresponding to $\mathbf{u}_{dij}$, a vector of covariates specific to the drop-out process for subject i. We specify that $\boldsymbol{\Sigma}_d^*$ is the Cholesky decomposition of $\boldsymbol{\Sigma}_d^{*T}\boldsymbol{\Sigma}_d^*$, which implies that $\boldsymbol{\Delta}_d$ is an upper triangular matrix, as is $\boldsymbol{\Sigma}$. Note that $\boldsymbol{\Sigma}_d^*$ represents the factor loadings between the survival response and the underlying random effect, $\boldsymbol{\tau}_i$. Similarly, $\boldsymbol{\Sigma}$ corresponds to the factor loadings between the functional limitation outcomes and the same random effect, $\boldsymbol{\tau}_i$. Sammel, Ryan, and Legler (1997) apply a similar interpretation to variance component-related parameters for random effects.

The parameterization of $\boldsymbol{\Sigma}_d^*$ allows us to assess whether the random effects covariance structures of the longitudinal and drop-out components differ by evaluating the nonzero components of $\boldsymbol{\Delta}_d$; i.e., we can assess whether the impact of the underlying random effect structure differs between the longitudinal and drop-out components.

The fixed effects vectors in (2) and (4), $\mathbf{x}_{ij}$ and $\mathbf{u}_{dij}$, respectively, may or may not correspond to the same covariates. Under (4), an element of $\boldsymbol{\rho}_d$ is interpreted as the change in conditional odds of a subject dropping out at a particular time due to drop-out type d, corresponding to unit differences in covariates in $\mathbf{u}_{dij}$.

We compare the results of the cause-specific discrete time survival specification to a single discrete time survival model that does not distinguish between the types of drop-out (single drop-out model), i.e., $\lambda_{ij}^* = \Pr(Z_i = j \mid Z_i > j-1;\ \boldsymbol{\tau}_i) = \Pr(D_i = d, Z_i = j \mid Z_i > j-1;\ \boldsymbol{\tau}_i)$ for all d, i, and $j = 1, \ldots, J-1$. The λ_{ij}^* parameters are interpreted as discrete time hazard rates, i.e., the conditional probability of dropping out for any reason. The comparison of the results from the cause-specific and single drop-out specifications and the mixed effects analyses assuming the data missing at random (MAR) comprises the sensitivity analysis of the drop-out assumption. We refer to the MAR model as the naive model.

3. Estimation

Under the shared parameter model, the estimators of $\boldsymbol{\beta}$, $\boldsymbol{\rho}_d$, $\boldsymbol{\Sigma}$, and $\boldsymbol{\Delta}_d$ are obtained by maximizing the marginal likelihood derived from (1). We obtained this marginal likelihood by approximating the normal random effects distribution with a mixture of binomial distributions so that integration of the likelihood was achieved by summing with respect to the binomial distributions (Mauritsen, 1990; Ten Have et al., 1998). This approximation is also employed in the software package EGRET, which is limited to a random intercept model for binary responses, however.

Letting L (= 2 for the functional limitation data) be the dimension of $\boldsymbol{\tau}$, we approximated the following integral for cluster i:

$$\int f_Y(\mathbf{y}_i \mid \boldsymbol{\tau})\, f_{Z,D}(z_i, d_i \mid \boldsymbol{\tau})\,(2\pi)^{-L/2} \times \exp\left(\sum_{l=1}^{L} \tau_l^2/2\right) \mathrm{d}\,\tau_1 \cdots \mathrm{d}\,\tau_L \approx \sum_{\nu_1=0}^{V} \cdots \sum_{\nu_L=0}^{V} f_Y(\mathbf{y}_i \mid \boldsymbol{\tau}_i)\, f_{Z,D}(z_i\, d_i \mid \boldsymbol{\tau}) \times \prod_{l=1}^{L} \left[\binom{V}{\nu_l} q^{\nu_l}(1-q)^{V-\nu_l}\right], \quad (5)$$

where τ_l is the lth element of $\boldsymbol{\tau}$ ($l = 1, 2$ indexing the random intercept and slope for the LSOA data) and is reparameterized as a standardized binomial random variable, $\tau_l = (\nu_l - Vq)/[Vq(1-q)]^{1/2}$, where $\nu_k \sim$ binomial(V, q). The specification of q governs the symmetry of the random effects distribution in the integral approximated by the weighted sum in (5). A normal random effects distribution is approximated with $q = 0.5$, whereas skewed distributions are approximated with alternate values of q. Varying q allows us to assess the sensitivity of the proposed approach to the random effects assumption. The integer V is specified in advance; increasing it improves the accuracy of the binomial approximation (Mauritsen, 1984). For the purposes of the analysis, $V = 5$. Because of the multiple sum in (5), this value led to results that did not differ considerably from results with higher values of V, which required much more time to generate. A similar approximation was employed for the marginal likelihood of the mixed effects logistic model that assumes MAR.

We maximize (5) with respect to the parameters in (2) and (4) using a quasi-Newton approach with first derivatives based on (5). Initial values for the fixed effects parameters may be obtained from logistic regression assuming independence. The estimates resulting from the quasi-Newton approach are, in general, robust with respect to the initial values for $\boldsymbol{\Sigma}$ and $\boldsymbol{\Delta}_d$ with the constraint that the initial diagonal elements of $\boldsymbol{\Sigma}$ are nonzero (Mauritsen, 1990). The inverse of the hessian of the final marginal likelihood yielded standard errors for the corresponding estimates of the fixed and random effects parameters. We implemented this estimation procedure in a FORTRAN program, which is available from the first author.

4. Assessment of Assumption Validity

In general, assessing the lack of fit of models in the context of informative drop-out is difficult because of the lack of identifiability, i.e., a number of models with different assumptions may provide similar fits to the observed data. With this caveat in mind, we attempt to assess the validity of the assumptions underlying the proposed model in a number of ways.

First, we assess the robustness of our results to different specifications of the random effects distribution by allowing $\boldsymbol{\Delta}_d$ to vary across $d = 1, 2$ and then be constant for all d, by specifying different values for q (0.3, 0.5, 0.7), and then by constraining to zero the variance component of the random slope. Second, we investigate the sensitivity of our results to the informative drop-out assumptions by specifying separate cause-specific hazard rates and alternatively a common hazard (single drop-out model) for the two types of drop-out and also by omitting the drop-out component, yielding the MAR naive random intercept and slope model.

5. Data Analysis Results

Section 5.1 presents a preliminary analysis entailing the initial proposed model. The results from this analysis lead to a decomposition of the first-order Markov effect of previous functional limitations on current limitation. Section 5.2 presents the resulting proposed model and sensitivity analyses assessing its stability in terms of the random effects and drop-out assumptions.

5.1 *Initial Model*

Table 1 presents for each of the 3 years cross-tabulations of current functional limitation, death, and unknown loss to follow-up with previous limitation level. These data appear to suggest that limitation in the previous year are associated with current limitation. Additional tables stratified by baseline physical activity (but not shown) indicate that this Markov association is especially strong for those who did not have defined physical activity. Other tables not shown here reveal evidence of weak second-order Markov associations between current and 2 years previous limitation that do not alter significantly the effects of the previous year's limitation status. Hence, we consider only first-order Markov associations in this analysis. Finally, Table 1 also reveals that drop-out, especially that due to death, is positively associated with previous limitation.

Preliminary analyses in addition to scientific input have yielded the following shared parameter model, which we refer to as the base model. In fitting this model, all factors, except for the age variables, were coded with zero–one dummy variables. The covariates in the functional limitation outcome component include limitation at the previous visit (none is the reference level), physical activity in 1984 (no is the reference level), the interaction between physical activity and functional limitation, sex (male is the reference level), age in 1986, and change in age since 1986 (time effect). The covariates in the unknown drop-out component consist of functional limitation at the previous visit, age in 1986, sex, poverty line index

Table 1

Raw frequencies and row percentages of functional limitation outcomes, institutionalization, death, and loss-to-follow-up by previous functional limitation and year

Time period	Previous functional outcome	Drop-out		Disability outcomes		
		Unknown	Death	Severe	Moderate	None
1986	None	NA	NA	583	138	24
		NA	NA	(78.3)	(18.5)	(3.2)
1986	Moderate	NA	NA	289	528	188
		NA	NA	(28.8)	(52.5)	(18.7)
1986	Severe	NA	NA	97	403	719
		NA	NA	(8.0)	(33.1)	(59.0)
1988	None	118	182	457	115	8
		(13.4)	(20.7)	(51.9)	(13.1)	(0.9)
1988	Moderate	186	100	193	443	144
		(17.5)	(9.4)	(18.1)	(41.6)	(13.5)
1988	Severe	101	60	41	177	551
		(10.9)	(6.5)	(4.4)	(19.0)	(59.3)
1990	None	93	151	305	59	8
		(15.1)	(24.5)	(49.5)	(9.6)	(1.3)
1990	Moderate	126	62	144	311	86
		(17.3)	(8.5)	(19.8)	(42.7)	(11.8)
1990	Severe	77	45	41	172	367
		(11.0)	(6.4)	(5.8)	(24.5)	(52.3)

in 1986 (above the threshold is the reference level), house ownership in 1986 (no is the reference level), supply phone number in 1986 (no is the reference level), race (white is the reference level), and physical activity in 1984 (no is the reference level). Finally, the death component has the same covariates as the functional limitation outcome component except for the interaction between previous limitation and physical activity.

We fitted the above model with random effects for the intercept and slope involving change in age since 1986. In addition, we specified separate $\mathbf{\Delta}_d$ parameters for each drop-out type: death and unknown drop-out. Note that, because change in age (time effect) was not significant as a fixed effect in the unknown drop-out component, we are assuming the random slope effect for change in age has mean zero for this component.

We also decomposed the effect of previous limitation into between- and within-subject effects. These are sometimes called cross-sectional (or cohort) and longitudinal effects, respectively (Diggle, Liang, and Zeger, 1994). In the LSOA study, the between-cluster variation is represented by variation in the baseline (1984) limitation dummy variables, and the within-cluster variation is the change or trajectory of previous limitation levels from baseline limitation. Formally, this distinction between the two types of variation in the previous limitation covariates corresponds to the following decomposition for the previous moderate versus no-limitation dummy variable: $b_{1i} = x_{i11}$ and $c_{1i} = x_{i1j} - b_{1i}$ for $j = 1, \ldots, z_i$, where x_{i1j} is the moderate versus no-previous-limitation dummy variable at time j. The decomposition for the previous severe versus no-limitation dummy variable is performed similarly: $b_{2i} = x_{i21}$ and $c_{2i} = x_{i2j} - b_{2i}$, where x_{i2j} is the severe versus no-limitation dummy variable at time j. The resulting estimates for the base model outcome component are presented in the first column of estimates in Table 2.

5.2 *Sensitivity Analysis*

Table 2 displays the results for different shared parameter models distinguished by different random effects distributions described in Section 4. A noticeable difference among these models exists for the within-subject main effects of previous functional limitation (Severe—W and Moderate—W) between the shared parameter model excluding the random slope (random intercept model) and the other models in Table 2. Ignoring the temporal relationship between outcome and drop-out through the underlying random slope, which may represent the change in health of the individual, impacted the within-subject fixed effect of previous limitation, i.e., the trajectory of previous limitation. A substantial difference in the within-subject physical activity (Phys Act) × Moderate—W interaction also exists between the shared parameter model with the same random effects distribution for both drop-out causes (i.e., $\mathbf{\Delta}_d = \mathbf{\Delta}$) and the remaining models in Table 2. Again, changing the random effects assumption impacted within-subject estimates. Changing the symmetry of the random effects distribution by altering q from 0.5 to 0.7 (Asymm RE distr column in Table 2) did not alter parameter estimates of the base model substantially. Similarly, estimates did not change much when q was set to 0.3 (results not shown). Note that, among the shared parameter models with random slope presented in Table 2, there is, in general, less variability with respect to analogous standard error estimates and log-likelihoods, the log-likelihood of the $\mathbf{\Delta}_d = \mathbf{\Delta}$ model notwithstanding.

Table 2
Sensitivity analysis of base outcome model: random effects assumption. Parameter estimates are provided with standard errors in parentheses.

	Base model	Drop-out $\Delta_d = \Delta$	Asymm RE distr	Random intercept
Sex	0.75	0.76	0.74	0.60
	(0.14)	(0.13)	(0.14)	(0.11)
Base age	0.13	0.14	0.13	0.11
	(0.01)	(0.01)	(0.01)	(0.01)
Phys Act	−0.90	−0.92	−0.91	−0.69
	(0.20)	(0.19)	(0.19)	(0.16)
Time	0.17	0.29	0.15	0.18
	(0.03)	(0.04)	(0.03)	(0.02)
Moderate—B	2.95	2.82	2.77	2.51
	(0.20)	(0.20)	(0.19)	(0.16)
Severe—B	6.25	6.40	6.27	5.38
	(0.26)	(0.30)	(0.28)	(0.19)
Moderate—W	0.21	0.10	0.18	0.59
	(0.17)	(0.19)	(0.17)	(0.14)
Severe—W	0.36	0.29	0.45	1.15
	(0.28)	(0.31)	(0.26)	(0.21)
Phys Act × Moderate—B	−0.40	−0.44	−0.47	−0.28
	(0.30)	(0.30)	(0.30)	(0.24)
Phys Act × Severe—B	−1.78	−1.85	−1.79	−1.66
	(0.67)	(0.71)	(0.67)	(0.53)
Phys Act × Moderate—W	−0.31	−0.21	−0.32	−0.29
	(0.23)	(0.24)	(0.23)	(0.20)
Phys Act × Severe—W	0.27	0.74	0.36	0.33
	(0.38)	(0.40)	(0.36)	(0.33)
Random int var	6.70	7.45	6.94	3.65
Random slope var	0.25	0.34	0.29	NA
Log-likelihood	−10,105.62	−10,413.73	−10,122.67	−11,575.47

A comparison of the log discrete time hazard rate estimates for the death component in Table 3 indicates slight differences among the different random effects assumptions. The only noticeable difference corresponds to the time or change in age effect, which in this case corresponds to temporal changes in the baseline discrete time hazards rate. A similar comparison of the estimates for the unknown drop-out component (results not shown here) suggest that the estimates under the base model are larger than the estimates under the constant Δ_d assumption and the random intercept-only assumption.

The weak variance component estimates for the random effects displayed in Table 3 suggest that the death drop-out process does not relate very strongly to the underlying random effect and therefore, indirectly, to the functional limitation outcome process. Nonetheless, Table 4 shows that varying the drop-out process (e.g., going from the full drop-out specification under the baseline model to the naive model without any drop-out specification) does impact significantly the within-subject estimates. More specifically, omitting the drop-out component (naive model) similarly inflated the within-subject previous limitation estimates, as did omitting the random slope from both the outcome and drop-out components (intercept model) displayed in Table 2.

5.3 *Inference for Outcome Component*

We base inference for the outcome component on the estimates under the base model, which are displayed in the first column of estimates in Table 2. (Dropping the nonsignificant within-subject limitation main and interaction effects did not noticeably change estimates.) Among the no-functional-limitation and no-physical-activity covariate effects (i.e., sex, base age, and time), which are all very significantly positive, the sex log odds ratio is the largest in magnitude. Among all of the effects, the main effects for baseline limitation (both moderate and severe) are clearly the largest among all estimates, followed by the interaction between severe baseline limitation and physical activity. For those who did not participate in defined physical activity, baseline severe and moderate limitation are highly associated with current limitation. While such associations are also observed for the physical activity group,

Table 3
Sensitivity analysis of death drop-out model: random effects-out assumption. Parameter estimates are provided with standard errors in parentheses.

	Base model	$\boldsymbol{\Delta}_d = \boldsymbol{\Delta}$	Random intercept
Sex	−0.87	−0.81	−0.82
	(0.08)	(0.07)	(0.7)
Base age	0.06	0.06	0.05
	(0.01)	(0.01)	0.01
Phys Act	−0.46	−0.33	−0.32
	(0.11)	(0.09)	(0.09)
Time	0.20	0.02	0.01
	(0.04)	(0.02)	(0.02)
Moderate—B	0.32	0.30	0.27
	(0.11)	(0.10)	(0.11)
Severe—B	1.06	1.08	1.11
	(0.13)	(0.11)	(0.13)
Random int var	0.05	0.00	0.00
Random slope var	0.21	0.00	NA

Table 4
Sensitivity analysis of base outcome model: drop-out assumption. Parameter estimates are provided with standard errors in parentheses.

	Base model	Single drop-out	Naive model
Sex	0.75	0.83	0.56
	(0.14)	(0.14)	(0.09)
Base age	0.13	0.14	0.10
	(0.01)	(0.01)	(0.01)
Phys Act	−0.90	−0.93	−0.65
	(0.20)	(0.21)	(0.14)
Time	0.17	0.27	0.15
	(0.03)	(0.04)	(0.02)
Moderate—B	2.95	3.09	2.35
	(0.20)	(0.23)	(0.14)
Severe—B	6.25	6.60	5.06
	(0.26)	(0.32)	(0.18)
Moderate—W	0.21	0.09	0.63
	(0.17)	(0.20)	(0.14)
Severe—W	0.36	0.05	1.31
	(0.28)	(0.33)	(0.22)
Phys Act × Moderate—B	−0.40	−0.45	−0.22
	(0.30)	(0.32)	(0.22)
Phys Act × Severe—B	−1.78	−2.02	−1.30
	(0.67)	(0.72)	(0.48)
Phys Act × Moderate—W	−0.31	−0.34	−0.13
	(0.23)	(0.25)	(0.19)
Phys Act × Severe—W	0.27	0.35	0.35
	(0.38)	(0.41)	(0.32)
Random int var	6.70	8.08	2.71
Random slope var	0.25	0.38	0.00
Log-likelihood	−10,105.62	−9147.99	−51,754.44

the magnitude of these associations is less for at least those with severe baseline limitation. Whereas only between-subject information contributes to the estimation of the baseline limitation effect, this effect is interpreted as a within-subject effect under the model with random intercept and slope for subject (Zeger, Liang, and Albert, 1988). Accordingly, the interpretation of the baseline limitation effect (e.g., Moderate—B) is the change in log cumulative odds of the current limitation response for a subject associated with a cross-sectional change in baseline limitation for that particular subject. Contrast this interpretation with that of the true within-subject effect on the analogous log cumulative odds associated with the subject's temporal trajectory in limitation status from baseline (e.g., Moderate—W). These within-subject changes from baseline limitation do not associate with current limitation at least under the base model. However, models that ignore the informative nature of the drop-outs indicate that within-subject trajectories from baseline do associate with current limitation.

6. Discussion

We have presented an analysis of longitudinal ordinal functional limitation data with multiple types of drop-out, employing approaches that assume either ignorability or varying degrees of nonignorability of drop-outs. The results for within-subject previous limitation effects depend on the degree to which drop-outs are accounted for through the presence of the random slope linking outcomes and drop-out and the overall presence of the drop-out component. In contrast, estimation of between-subject baseline limitation effects appears more robust with respect to different random effects and drop-out assumptions. Again, this dependence of within-cluster effect estimates on the drop-out assumption has been observed by others for continuous and binary responses assuming a single cause of drop-out (e.g., Wu and Carroll, 1988; Wang-Clow et al., 1995; Ten Have et al., 1998).

Changing the random effect and drop-out assumptions represented a sensitivity analysis to assess the vulnerability of our models to lack of knowledge about the outcome–drop-out relationship. Extending Heckman's two-stage approach for incorporating the effects of selection bias, Copas and Li (1997) presented another approach to assessing the sensitivity of model estimation to different drop-out specifications. This approach, similar in spirit to our shared parameter model, entails specifying continuous outcome and drop-out models, which have correlated errors. The magnitude of this correlation between these outcome and drop-out errors reflects the strength of the nonignorable relationship, which is analogous to our random effects parameters $\boldsymbol{\Sigma}$ and $\boldsymbol{\Delta}_d$.

Several future research topics have been raised by the proposed methodology. First, it may be that the different types of drop-out are not all manifestations of a random effect also manifesting itself as a longitudinal outcome. For example, with sufficient data for institutionalization, it may be related directly to the potential functional limitation outcome that would have been observed had the subject not been institutionalized instead of being related to limitation through a random effect trajectory. Models with only direct relationships between outcome and drop-out have been proposed (e.g., Fitzmaurice, Laird, and Zahner, 1996;

Lesaffre, Molenberghs, and DeWulf, 1996; Sheiner, Beal, and Dunne, 1997). One may propose a hybrid model consisting of this direct relationship between institutionalization and the unobserved limitation outcome in addition to shared random effects for functional limitation, death, and unknown dropout. Second, the above Markov model needs to be extended to accommodate intermittent MAR missing data. Generally, this should not be a problem for the proposed methodology, although it does present difficulties for models with Markov effects. One possible solution entails using the EM algorithm with implicit estimation of the intermittent missing responses using sufficient statistics based on the observed data. Another approach would consist of empirical Bayes estimation under a Bayesian framework (Cole et al., 1995).

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Résumé

Dans le contexte de l'analyse de réponses ordinales de limitation fonctionnelle d'une étude longitudinale sur le vieillissement, nous étudions l'association entre la limitation fonctionnelle actuelle et la limitation de l'année précédente et sa modification par l'activité physique et les multiples causes de sortie d'étude. Nous prenons en compte la nature longitudinale des causes multiples de sortie informative (décès, perdus de vue) avec un modèle logistique à effets mixtes. Sous le modèle proposé avec une ordonnée à l'origine et une pente aléatoire, le critère fonctionnel ordinal et les profils multiples de survie à temps discrets partagent une structure commune pour l'effet aléatoire. Ce modèle partagé de sélection de paramètre fait l'hypothèse que les causes multiples de sortie sont conditionnellement indépendantes du critère de limitation fonctionnelle, étant donné l'effet aléatoire sous-jacent représentant une trajectoire individuelle du statut général de santé au cours du temps. Bien qu'il ne soit pas possible de tester complètement l'adéquation de cette hypothèse, nous testons la robustesse de cette approche en faisant varier les hypothèses sous-jacentes au modèle proposé telle que la distribution de l'effet aléatoire et la composante de sortie. Il apparaît que les différences entre sujets dans la limitation fonctionnelle initiale sont fortement associées avec une limitation fonctionnelle future, et que cette association est plus forte pour ceux qui n'ont pas d'activité physique quelque soit la spécification de l'effet aléatoire et des sorties informatives. Au contraire, l'association entre la limitation fonctionnelle actuelle et la trajectoire antérieure du statut fonctionnel chez un individu est plus faible et plus sensible aux changements dans les hypothèses sur les effets aléatoires et les sorties.

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