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A multivariate discrete failure time model for the analysis of infant motor development

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Abstract

We develop a multivariate discrete failure time model for the analysis of infant motor development. We use the model to jointly evaluate the time (in months) to achievement of three well-established motor milestones: sitting up, crawling, and walking. The model includes a subject-specific latent factor that reflects underlying heterogeneity in the population and accounts for within-subject dependence across the milestones. The factor loadings and covariate effects are allowed to vary flexibly across milestones, and the milestones are permitted to have unique at-risk intervals corresponding to different developmental windows. We adopt a Bayesian inferential approach and develop a convenient data-augmented Gibbs sampler for posterior computation. We conduct simulation studies to illustrate key features of the model and use the model to analyze data from the Nurture study, a birth cohort examining infant health and development during the first year of life.

Keywords

discrete failure time model; grouped survival data; healthy eating index; latent factor model; maternal diet; motor milestones

1 | INTRODUCTION

Infant gross motor development is an important predictor of long-term health. Earlier achievement of gross motor milestones, such as sitting up, crawling, and walking, is associated with improved language abilities, cognitive function, and educational attainment later in childhood and into adulthood.^{1–3} Earlier motor milestone achievement may also help prevent later obesity.⁴ Conversely, delayed motor milestone achievement has been associated with increased sedentary time and lower levels of physical activity in later childhood⁵ and even psychiatric disorders such as schizophrenia in adulthood.⁶ Thus, it is of clinical and

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public health importance to identify determinants of delayed motor achievement that are suitable targets for intervention.

Motor development is influenced by both biological and behavioral factors. Predictors of motor milestone achievement include infant birth weight and gestational age,¹ breastfeeding,¹ and gestational diabetes.⁷ Previous studies have also assessed nutrient intake during pregnancy and motor development.^{8,9} However, these studies have focused on specific components of maternal diet (eg, fish intake) rather than diet quality as a whole. To our knowledge, no prior studies have examined overall diet quality in pregnancy and offspring motor development, even though there is strong evidence that maternal diet is an important predictor of fetal development,¹⁰ which may, in turn, affect motor milestone achievement.

There are, however, a number of statistical challenges associated with the analysis of infant motor development. First, clinical researchers commonly treat time to milestone achievement as a continuous random variable and base their analyses on accelerated failure time models with underlying Weibull or log-logistic distributions.^{11,12} However, milestones are typically recorded up to the nearest month during infancy. Because the data are grouped into discrete time intervals, it is often preferable to analyze the data using a discrete or “grouped” time-to-event model that can accommodate the excessive number of ties that ensue^{13–15} (see the work of Hedeker et al¹⁴ for further discussion). Second, the milestones can have unique durations corresponding to different biologically plausible developmental windows. For example, according to the World Health Organization (WHO),¹⁶ over 99% of infants sit up between 3 and 10 months of age, crawl between 5 and 14 months, and walk between 8 and 18 months (a small percentage of infants advance directly to walking without crawling). The probability of achieving milestones outside of these windows is effectively zero. Thus, a suitable model for motor development should permit unique discrete “at-risk” intervals for each milestone. Third, covariates are likely to impact milestones differently. For example, healthy maternal diet and breastfeeding may be associated with earlier walking and crawling, but later sitting up. Hence, an appropriate model should have the flexibility to accommodate milestone-specific, time-varying, and time-invariant covariates and covariate effects. Finally, previous studies on infant motor development have modeled milestones independently,^{11,12} even though they are likely to be highly correlated.¹⁷ For example, infants who crawl early may tend to walk early as well. Therefore, a statistical analysis of developmental milestones should account for this within-subject association. This can be accomplished, for instance, by including a subject-specific frailty term that induces within-subject dependence and accounts for infants’ propensities to achieve milestones at different rates.

To address this last challenge, several authors have proposed random effect models for correlated sequential, discrete, and grouped survival data. Tutz¹⁸ developed a sequential Rasch model for item-response analysis. Ten Have and Uttal¹³ proposed a multivariate continuation ratio model with subject-specific random effects. Ten Have¹⁹ developed a similar model for ordinal discrete survival data with ordered survival and failure states. More recently, Hedeker et al¹⁴ introduced a multilevel discrete failure time (DFT) model for grouped survival data with a random intercept to account for clustering.

We build on this work to develop a flexible DFT model for the analysis of infant motor development. Our model has several appealing features. First, we permit milestone-specific covariate effects, thus allowing variables such as birth weight and breastfeeding to impact milestones in unique ways. Next, we introduce a subject-specific frailty term that is also allowed to have differential effects on each milestone. In this sense, our model can be viewed as a latent factor model with milestone-specific factor loadings. Third, our model can easily accommodate time-dependent covariates and covariate effects, relaxing proportionality assumptions commonly made in time-to-event analyses. Finally, the model can be conveniently fit in either a frequentist or Bayesian inferential framework, the latter using a computationally tractable data-augmentation algorithm. We conduct simulation studies to examine the performance of the model and apply it to data from the Nurture study, a birth cohort examining infant health and development in the first year of life.

2 | THE NURTURE STUDY

The Nurture study is a birth cohort of predominately black women and their infants residing in the southeastern United States conducted between 2013 and 2016.²⁰ The aim of the study was to identify factors related to feeding, physical activity and motor development, sleep, and stress that contribute to excessive weight gain in infancy. Women enrolled during pregnancy and provided additional informed consent for their infants to participate in the study shortly after birth. The Institutional Review Board of Duke University Medical Center approved this study and its protocol.

The study followed mothers and infants for 12 months after birth to collect data on maternal feeding practices, such as breastfeeding; infant weight, physical activity, and gross motor development; infant sleep behavior; and indicators of infant stress. Information on infant motor milestone achievement was collected monthly, either by automated interactive voice response telephone interviews or by home visits. Each month, mothers reported whether their infants achieved each of three gross motor milestones: sitting up without assistance, crawling using all four limbs and walking without assistance. We derived developmentally appropriate intervals for achievement of motor milestones using the WHO windows for motor milestone achievement: 3 to 10 months for sitting up, 5 to 14 months for crawling, and 8 to 18 months for walking. These developmental windows are consistent with our previous study examining achievement of gross motor milestones and later adiposity.⁴

The goal of our analysis was to examine associations between maternal diet quality during pregnancy and subsequent motor development. To assess maternal diet quality in pregnancy, mothers completed the Block Food Frequency Questionnaire (FFQ)²¹ between 20 and 36 weeks' gestation. We scored responses to the FFQ using the Alternate Healthy Eating Index²² modified for pregnancy (AHEI-P).²³ The AHEI-P quantifies diet quality based on the consumption of both nutrients (eg, calcium) and individual foods (eg, vegetables). The original AHEI-P did not include a category for nuts/soy/beans because these were not previously recommended for pregnant mothers. However, because current recommendations no longer include these restrictions, we incorporated the nuts/soy/beans category into our assessment per the original AHEI. Per protocol, we assigned a score of 0 to 10 points for each AHEI-P category based on recommended intake levels. After including the nuts/soy/

beans category, the AHEI-P scores ranged from 0 to 100, with higher scores indicating better diet quality.

Of the 666 infants enrolled in the study, 20% had no milestone or diet data and were excluded from the analysis. We excluded an additional eight records with milestones that fell clearly outside the WHO windows (eg, walking in month 1 or 2), resulting in a final sample of 526 infants. Table 1 presents summary statistics for maternal and infant characteristics included in our analysis. Infants were predominately black, and just over half were male. The sample median birth weight z-score was slightly below the median for the WHO population. The median ages for sitting up, crawling, and walking were 6, 8, and 12 months, respectively. AHEI-P scores in the sample ranged from 19 to 97 with a mean of 69 and a median of 70, which are slightly higher than those reported in prior studies.²³ Only 46% of the mothers breastfed, and this percentage waned over the course of the study as mothers began to introduce solid foods.

Figure 1 presents discrete-time Kaplan-Meier plots for the three milestones for two groups formed by a median split of the AHEI-P maternal diet quality scores (low diet quality = below median; high diet quality = above median). The y -axis denotes the probability of *not* achieving the milestone at each month, which is the survival function in this context. Infants in the low diet quality group tended to sit up earlier than those in the high diet quality group, as indicated by the lower survival function for the low-quality group (dashed line) compared to the high-quality group (dotted line). For example, the probability of sitting up in month 3—the onset of the milestone window—was 0.08 for the low-quality group compared to 0.06 for the high-quality group. By the end of month 6, the probability of sitting up was 0.78 for the low-quality group and 0.71 in the high-quality group. As expected, all infants had probability 1 of sitting up by month 10, as this represents the upper limit of the milestone window. By contrast, there was little difference in the timing of crawling for the two groups. Finally, infants in the high-quality group tended to walk somewhat earlier than those in the low-quality group, particularly at the end of the study. For example, by the end of 12 months, the probability of walking was 0.68 for infants in the high-quality group and 0.57 for the low-quality group.

3 | MULTIVARIATE DISCRETE FAILURE TIME MODEL

For $i = 1, \dots, n$ and $j = 1, \dots, J$, let $T_{ij} = k$ if infant i achieves milestone j (or is censored) at month k since the start of the WHO milestone window. Here, k ranges from 1 to $K_j = u_j - l_j + 1$, where l_j is the lower bound of the j th milestone window and $u_j = \min(\text{upper bound of milestone window } j, 13)$. The value $u_j = 13$ implies that the milestone exceeds the 12-month study period. For example, according to WHO guidelines, sitting up without assistance occurs during months 3 to 10 inclusive. Thus, $K_1 = 10 - 3 + 1 = 8$ so that k ranges from 1 to 8 for sitting up. Likewise, crawling occurs during months 5 to 14 (inclusive), implying that $u_2 = 13$ and $K_2 = 13 - 5 + 1 = 9$. Finally, because walking occurs between months 8 and 18, $u_3 = 13$ and hence $K_3 = 13 - 8 + 1 = 6$.

The discrete-time hazard, $\pi_{ijk} = \Pr(T_{ij} = k | T_{ij} \geq k)$, is the conditional probability of achieving milestone j in month k given no prior achievement. To accommodate time-varying

covariates and covariate effects (thus relaxing proportional hazard assumptions), it is common to expand the data into “person-time” format in which each row represents an at-risk time interval and the corresponding outcome is a dichotomous variable indicating whether or not the milestone was achieved in that interval.¹⁵ Specifically, let Y_{ijk} be a binary indicator taking the value 1 if the i th infant achieves milestone j in month k since the start of the milestone window. Expressed in terms of Y_{ijk} , the discrete hazard is given by

$$\pi_{ij1} = \Pr(Y_{ij1} = 1) \quad (1)$$

$$\pi_{ijk} = \Pr(Y_{ijk} = 1 \mid Y_{ij1} = \dots = Y_{ij(k-1)} = 0), \quad k = 2, \dots, K_j - 1$$

$$\pi_{ijK_j} = \prod_{k=1}^{K_j-1} (1 - \pi_{ijk}),$$

where the final category K_j is achieved only if $Y_{ijk} = 0$ for all $k < K_j$; that is, the milestone is not achieved prior to interval K_j .

We model π_{ijk} as

$$g(\pi_{ijk}) = \eta_{ijk} = \mathbf{x}_{ijk}^T \boldsymbol{\beta}_j + \lambda_j b_i, \quad i = 1, \dots, n; \quad j = 1, \dots, J; \quad k = 1, \dots, K_j - 1, \quad (2)$$

where $g(\cdot)$ is a binary link function; $\mathbf{x}_{ijk}$ is a $p_j \times 1$ vector of milestone-specific covariates, some of which may be time varying; $\boldsymbol{\beta}_j$ is the corresponding $p_j \times 1$ vector of milestone-specific (and potentially time-varying) regression parameters; b_i is a normally distributed subject-specific latent factor or “frailty” term; and λ_j is the corresponding milestone-specific factor loading quantifying the effect of the frailty on the j th milestone. One can view b_i as representing unobserved subject-level factors that impact the milestones differentially through the factor loadings λ_j . Note that model (2) reduces to a conventional random intercept model when $\lambda_j = 1$ for all j . Common choices for $g(\cdot)$ include the probit and logit link functions, both of which lead to straightforward Bayesian inference via data augmentation.^{15,24} A complementary log-log link yields the discrete-time analog to the Cox model. Hedeker et al¹⁴ note that the three link functions tend to yield similar results in practice.

Suppose infant i achieves milestone j in month k ($k = 1, \dots, K_j - 1$) of the milestone window or, alternatively, is censored at month k . We define $\mathbf{Y}_{ij} = (0, \dots, 0, \delta_{ij})^T$ to be a $k \times 1$ response vector for milestone j , where δ_{ij} is a milestone-specific achievement indicator taking the value 1 if infant i achieves milestone j during the study and 0 if censoring occurs. Note that $\delta_{ij} = Y_{ijk}$ if k is the final month of observation. Censoring can arise due to dropout during the study or study completion if $u_j = 13$. Throughout, we assume that the censoring mechanism is noninformative, as we have no a priori reason to believe that late milestone

achievers drop out more frequently than early achievers. In Section 6, we discuss extensions to allow for informative censoring.

To illustrate the response vector coding, suppose infant i achieves milestone j in month $k = 3$ of the milestone window. In this case, $\delta_{ij} = 1$ and the corresponding response vector is given by $\mathbf{Y}_{ij} = (0, 0, 1)^T$. Conversely, for an infant who is censored at month 3, $\delta_{ij} = 0$ and the corresponding response is $\mathbf{Y}_{ij} = (0, 0, 0)^T$. Likewise, an infant who achieves milestone j at interval K_j , ie, at the upper end of the milestone window, has $(K_j - 1) \times 1$ response vector $\mathbf{Y}_{ij} = (0, \dots, 0)^T$, which is tantamount to censoring at month $K_j - 1$. The corresponding $k \times 1$ linear predictor for milestone (i, j) is given by

$$\eta_{ij} = \mathbf{X}_{ij} \boldsymbol{\beta}_j + \lambda_j b_i \mathbf{1}_k, \quad (3)$$

$k \times 1 \quad k \times p_j \quad p_j \times 1$

where $\mathbf{1}_k$ denotes a $k \times 1$ vector of 1's. The column dimension of $\mathbf{X}_{ij}$ and the length of $\boldsymbol{\beta}_j$, denoted p_j , will depend on the number of months in the milestone window (ie, K_j), as well as the number of time-varying and time-invariant covariates. For example, suppose that milestone j occurs during a 5-month window from months 2 to 6 (inclusive) following birth, and suppose that infant i achieves the milestone in the third month of the window. Here, $K_j = 6 - 2 + 1 = 5$ and $k = 3$. Further, let X_1 denote a time-varying covariate and let X_2 denote a time-invariant covariate. Assuming time-varying intercepts but time-invariant covariate effects (ie, regression coefficients) for X_1 and X_2 , $\mathbf{X}_{ij}$ has dimension 3×6 with elements

$$\mathbf{X}_{ij} = \begin{pmatrix} \overbrace{\text{Intercepts}}^{\text{Month 1 Month 2 Month 3 Month 4}} & X_1 & X_2 \\ 1 & 0 & 0 & 0 & x_{1ij1} & x_{2ij} \\ 0 & 1 & 0 & 0 & x_{1ij2} & x_{2ij} \\ 0 & 0 & 1 & 0 & x_{1ij3} & x_{2ij} \end{pmatrix}, \quad (4)$$

where Month 1 to Month 4 correspond to the first 4 months of the milestone window. If we further allow time-varying coefficient effects for X_1 (in addition to time-varying covariate values), $\mathbf{X}_{ij}$ expands to dimension 3×9 with elements

$$X_{ij} =$$

$$\begin{pmatrix} \text{Intercepts} & \text{Month 1} & \text{Month 2} & \text{Month 3} & \text{Month 4} & \text{Month 1} & \text{Month 2} & \text{Month 3} & \text{Month 4} & \text{Time Invariant} \\ \text{Month 1} & 1 & 0 & 0 & 0 & x_{1ij1} & 0 & 0 & 0 & x_{2ij} \\ \text{Month 2} & 0 & 1 & 0 & 0 & 0 & x_{1ij2} & 0 & 0 & x_{2ij} \\ \text{Month 3} & 0 & 0 & 1 & 0 & 0 & 0 & x_{1ij3} & 0 & x_{2ij} \\ \text{Month 4} & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & x_{2ij} \end{pmatrix}.$$

(5)

The corresponding regression vector, $\beta_j = (\beta_{0j1}, \beta_{0j2}, \beta_{0j3}, \beta_{0j4}, \beta_{1j1}, \beta_{1j2}, \beta_{1j3}, \beta_{1j4}, \beta_{2j})^T$, includes four intercepts representing the baseline hazards for each month, four parameters for the time-varying effect of X_1 , and a parameter representing the time-invariant effect of X_2 .

Similarly, an infant i who achieves milestone j in month $K_j = 5$ (the upper bound of the milestone window) will have response vector $Y_{i1} = (0, 0, 0, 0)^T$, indicating that the infant did not achieve the milestone in the previous 4 months of the window. Again assuming time-varying regression effects for X_1 , the corresponding 4×9 linear predictor is

$$X_{ij} = \begin{pmatrix} 1 & 0 & 0 & 0 & x_{1ij1} & 0 & 0 & 0 & x_{2ij} \\ 0 & 1 & 0 & 0 & 0 & x_{1ij2} & 0 & 0 & x_{2ij} \\ 0 & 0 & 1 & 0 & 0 & 0 & x_{1ij3} & 0 & x_{2ij} \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & x_{1ij4} & x_{2ij} \end{pmatrix}. \quad (6)$$

Note that the time varying parameters $\beta_{0j} = (\beta_{0j1}, \beta_{0j2}, \beta_{0j3}, \beta_{0j4})^T$ and $\beta_{1j} = (\beta_{1j1}, \beta_{1j2}, \beta_{1j3}, \beta_{1j4})^T$ have length $K_j - 1 = 4$, since milestone j occurs with probability 1 in time interval K_j if it is not achieved in the prior $K_j - 1$ intervals. As a result, there are only $K_j - 1$ identifiable parameters for covariates with time-varying effects. The model can easily be extended to accommodate parametric functions of time (eg, linear or polynomial trends) rather than discrete period indicators as in Equations (5) and (6). To ensure an identifiable model, we impose standard constraints for latent factor models,²⁵ namely, we assume a standard normal $N(0, 1)$ distribution for b_i and restrict the first factor loading, λ_1 , to be positive. Finally, the J milestones are assumed to be conditionally independent given b_i .

3.1 | Inference

Statistical inference can be handled conveniently using either maximum likelihood or Bayesian methods. Maximum likelihood estimation (MLE) can be implemented using standard software such as the SAS[®] procedure NLMIXED (SAS Institute, Cary, North Carolina), which combines adaptive Gauss-Hermite quadrature for numerical integration with quasi-Newton-Raphson routines for maximization. By default, the number of quadrature points is selected adaptively, but the resulting value is often insufficient to ensure convergence for the correlated DFT model. We therefore recommend increasing the number of quadrature points using the `qpoints` option in NLMIXED. For the analyses below, we specified 50 quadrature points. Convergence can also be improved by adding a ridging term to the Newton-Raphson optimization routine; this can be implemented in NLMIXED by specifying `tech=nr ridge` in the MODEL statement. Finally, the BOUNDS statement is used to impose the identifiability constraint $\lambda_1 > 0$.

As evidenced from the simulation studies below, maximum likelihood can yield unstable estimates for small sample sizes. As an alternative, one can adopt a Bayesian approach with slightly informative priors on the factor loadings to stabilize the parameter estimates. As a default, we assign conditionally conjugate $N(0, 100)$ priors to the regression coefficients. For the first factor loading, λ_1 , we assign an $N(0, 0.10)$ prior truncated below by zero to ensure identifiability; we assign unconstrained $N(0, 0.10)$ priors to the remaining factor loadings. Based on extensive simulations, we have found that more diffuse priors for the factor loadings can lead to poor Markov chain Monte Carlo (MCMC) convergence when the sample sizes are low. This may be due to the fact that the factor loadings scale unobserved random effects rather than fixed covariates as in the case of regression coefficients. More generally, the prior variance for λ_j should be chosen to stabilize the factor loading estimates when sample sizes are small. In our experience, a variance of 0.10 leads to reasonable results for relatively small sample sizes (eg, $n = 500$), with little impact for larger samples. In practice, however, we recommend sensitivity analyses to examine how different choices of prior variance impact results.

For probit and logit link functions, efficient data-augmented Gibbs samplers are available for posterior computation.^{15,24} Suppose, for example, infant i achieves milestone j (or is censored) at month k ($k = 1, \dots, K_j - 1$). Under the probit link, we introduce k independent random variables $Z_{ij1}, \dots, Z_{ijk}$ such that $Y_{ijk} = \mathbb{1}(Z_{ijk} > 0)$ and $Z_{ijh} \sim N(\eta_{ijh}, 1)$ for $h = 1, \dots, k$, where $\mathbb{1}(\cdot)$ denotes the indicator function and $\eta_{ijh} = \mathbf{x}_{ijh}^T \boldsymbol{\beta}_j + \lambda_j b_i$. The latent variable Z_{ijh} ($h = 1, \dots, k$) represents the underlying propensity for infant i to achieve milestone j in month h . Conditional on b_i , Z_{ijh} and $Z_{ij'h}$ for milestones j and j' follow independent normal distributions with unit variance. Marginally, the variance of Z_{ijh} is given by

$$\begin{aligned} \text{Var}(Z_{ijh}) &= E[\text{Var}(Z_{ijh} | b_i)] + \text{Var}[E(Z_{ijh} | b_i)] \\ &= 1 + \lambda_j^2 \text{Var}(b_i) \\ &= 1 + \lambda_j^2. \end{aligned}$$

Similarly, the marginal covariance between Z_{ijh} and $Z_{ij'h}$, ie, between the latent propensity to achieve milestones j and j' in month h , is given by

$$\begin{aligned}\text{Cov}(Z_{ijh}, Z_{ij'h}) &= \text{Cov}[E(Z_{ijh}|b_i), E(Z_{ij'h}|b_i)] + E[\text{Cov}(Z_{ijh}, Z_{ij'h}|b_i)] \\ &= \text{Cov}(\lambda_j b_i, \lambda_{j'} b_i) + E(0) \\ &= \lambda_j \lambda_{j'} \text{Var}(b_i) \\ &= \lambda_j \lambda_{j'}.\end{aligned}$$

Thus, while the milestones are conditionally independent given the latent frailty b_i , they are marginally correlated, with the direction of the association determined by the signs of the factor loadings λ_j and $\lambda_{j'}$.

Gibbs sampling proceeds by selecting initial values for β_j , λ_j , and b_i from Equation (3) and then iterating through the following steps:

1. For milestones $j = 1, \dots, J$, cycle through the following updates:
 - a. For $i = 1, \dots, n$ and $h = 1, \dots, k_{ij}$, where k_{ij} denotes the month of milestone achievement or censoring for infant i and milestone j , update Z_{ijh} from its full conditional normal distribution truncated below (above) by zero for $Y_{ijh} = 1$ ($Y_{ijh} = 0$);
 - b. Update β_j from its multivariate normal full conditional;
 - c. Update λ_j from its normal full conditional (or truncated normal for λ_1);
2. For $i = 1, \dots, n$, update b_i from its normal full conditional.

A related data augmentation scheme exists for a logit link; see the work of Polson et al²⁴ for details. The Appendix provides the full conditionals for implementing the Gibbs sampler under both a probit and logit link. R²⁶ code for fitting the proposed Gibbs sampler is available at the first author's website (<http://people.musc.edu/~brn200/>), along with Proc NLMIXED code for MLE. Convergence is monitored using standard MCMC diagnostics such as trace plots. Because the Gibbs sampler relies entirely on closed-form, conditionally conjugate updates, we typically observe rapid convergence after only a few hundred iterations of the Gibbs sampler.

4 | SIMULATION STUDIES

We conducted two simulation studies to assess the properties of the model and to compare the maximum likelihood and Bayesian inferential approaches. For the first study, we generated datasets of size $n = 500$ and $n = 5000$ infants from the following trivariate DFT model:

$$\Phi^{-1}(\pi_{ijk}) = \mathbf{x}_{ijk}^T \beta_j + \lambda_j b_i, \quad i = 1, \dots, n; \quad j = 1, \dots, J; \quad k = 1, \dots, K_j - 1, \quad (7)$$

where $\Phi^{-1}(\cdot)$ denotes the inverse standard normal CDF and $J = 3$ corresponding to 3 milestones for each infant. We assumed a total study period of 6 months. The window for milestone 1 ranged from 1 to 5 months inclusive, so that $K_1 = 5 - 1 + 1 = 5$. Milestone 1 might correspond to a milestone such as sitting up that occurs during the first part of the study. The linear predictor for milestone 1 included time-varying intercepts for months 1 to 4, a time-invariant dichotomous covariate common to all milestones and time points (X_1), and a time-varying continuous covariate common to all milestones (X_2). The covariate effects for X_1 and X_2 were held constant over time. Thus, for an infant who achieved milestone 1 in month 3, the response vector was simulated as $\mathbf{Y}_{i1} = (0, 0, 1)^T$ and the linear predictor was generated as

$$\begin{aligned} \eta_{i1} &= \mathbf{X}_{i1} \boldsymbol{\beta}_1 + \lambda_1 b_i \mathbf{1}_3 \quad (8) \\ \mathbf{X}_{i1} &= \begin{pmatrix} 1 & 0 & 0 & 0 & x_{1i} & x_{2i1} \\ 0 & 1 & 0 & 0 & x_{1i} & x_{2i2} \\ 0 & 0 & 1 & 0 & x_{1i} & x_{2i3} \end{pmatrix} \end{aligned}$$

where $\boldsymbol{\beta}_1 = (\beta_{011}, \beta_{012}, \beta_{013}, \beta_{014}, \beta_{11}, \beta_{21})^T$. The first 4 elements of $\boldsymbol{\beta}_1$ correspond the intercepts for months 1 to 4, β_{11} denotes the time-invariant effect of X_1 on milestone 1, and β_{21} denotes the time-invariant effect of x_{2i} . Similarly, we assumed that milestone 2 occurred between months 1 to 6, so that $K_2 = 6 - 1 + 1 = 6$. Milestone 2 might represent a milestone that occurs strictly during the study period and not beyond. Lastly, we assumed that milestone 3 ranged from month 3 to month “7,” where month 7 denotes that the upper bound for milestone 3 exceeded the 6-month study period. This might represent a milestone such as walking that occurs during the latter part of the study and extends past the study period. Thus, for milestone 3, $u_3 = 7$ and $K_3 = 7 - 3 + 1 = 5$. The subject-level binary covariate x_{1i} was generated from a Bernoulli (0.50) distribution; the subject-level time-varying covariate x_{2ik} was simulated from an $N(0, 1)$ distribution for the first 3 months of the study, and from an $N(0.50, 1)$ distribution for months 4 to 6, indicating an increase in the mean of x_{2ik} at the midpoint of the study. The subject-specific frailties, b_i , were generated from a standard normal distribution.

For the analysis, we fit model (7) with a probit link. For maximum likelihood inference, we used SAS Proc NLMIXED with 50 quadrature points for numerical integration. We applied Newton-Raphson with ridging to maximize the integrated likelihood. For Bayesian inference, we implemented the data-augmented Gibbs sampler outlined in the previous section. We assigned independent $N(0, 100)$ priors to the regression coefficients, a zero-truncated $N(0, 0.10)$ prior for λ_1 , and unconstrained $N(0, 0.10)$ priors for λ_2 and λ_3 . We ran the Gibbs sampler for 6000 iterations, discarding the first 1000 as burn-in. MCMC diagnostics, including trace plots, indicated rapid convergence and excellent posterior mixing.

Figure 2 presents the unadjusted Kaplan-Meier plots for the dataset with sample size $n = 500$. Approximately 73% of infants achieved milestone 1 in the first month. Among those

remaining, the probability of achieving milestone 1 remained relatively constant at 0.23 until month 5, the upper end of the milestone window. About 29% of infants achieved milestone 2 in month 1, with small decreases in the survival function between months 3 and 5. About 30% of the infants achieved milestone 3 in month 3, the onset of the milestone window; 36% were censored at the end of the 6-month simulation study.

Table 2 presents the parameter estimates and 95% intervals under Bayesian and MLE. For $n = 500$, the Bayesian estimates were close to the true value, with posterior credible intervals (CrIs) that generally overlapped the simulated values. The maximum likelihood estimates (MLEs), on the other hand, were less accurate, especially for milestone 1. This may be due to the fact that over 70% of the infants achieved the milestone in month 1, leaving relatively low samples for estimating remaining intercept parameters. Even with an increase to 100 quadrature points, the MLEs were imprecise, suggesting that maximum likelihood may not be the best choice for small samples. For $n = 5000$, the Bayesian and maximum likelihood estimates coincided, although the Bayesian CrIs were generally narrower than the corresponding frequentist confidence intervals. In terms of computation, there was a distinct advantage for the Bayesian approach. For $n = 500$, the Gibbs sampler took 47 seconds to run 6000 iterations on a Dell® Precision T3610 workstation. In contrast, SAS Proc NLMIXED with 50 quadrature points took approximately 9 minutes to complete. For $n = 5000$, the discrepancy in run times was even more stark: Gibbs sampling required approximately 6 minutes, whereas NLMIXED took over an hour. Thus, from a purely computational standpoint, the Bayesian approach is preferable to MLE. As a sensitivity analysis, we increased the prior variance for the factor loadings from 0.10 to 1 and obtained posterior estimates similar to the MLEs, particularly for $n = 5000$, indicating little sensitivity to prior specification for moderate to large samples.

For the second simulation study, we extended model (7) to include two additional covariates, X_3 and X_4 , with time-varying coefficient effects, where X_3 was generated as a time-invariant binary covariate and X_4 was simulated as a 3-category, time-varying ordinal covariate. The resulting model contained 48 parameters. To test the model's robustness to misspecification, we simulated the frailty terms, b_i , from a t_8 distribution, which has heavier tails than the normal density and closely approximates a scaled logistic distribution.²⁷ Prior specification was similar to that for simulation study 1, but we assumed a more diffuse $N(0, 100)$ prior for the factor loadings to assess the impact of a less informative prior on the posterior estimates. We generated 5000 observations from this expanded model and used both Bayesian and MLE for inference. For Bayesian inference, we ran the Gibbs sampler for 6000 iterations, discarding the first 1000 as burn-in. For maximum likelihood, we fit the model that is Proc NLMIXED as before.

The results are presented in Table S1 of the Online Supplement. In general, the estimates and intervals were close to the simulated values for both Bayesian and MLE, suggesting that both approaches work well even under this more challenging scenario with additional parameters and a misspecified random effect distribution. Of note, however, the Gibbs sampler took approximately 6 minutes to run, whereas NLMIXED took 1.25 hours, indicating a practical advantage for the Bayesian approach.

5 | ANALYSIS OF THE NURTURE DATA

Next, we fit the proposed multivariate DFT model to the Nurture data. The dataset comprised 526 infants and a total of 5725 person-month observations. The model specification was similar to Equation (7). The model included the covariates presented in Table 1, with monthly breastfeeding status incorporated as a time-varying covariate (1 = breastfeeding during the month, 0 = not breastfeeding). Continuous predictors were standardized about their means. Prior specification was identical to that in Section 4. We ran the Gibbs sampler conservatively for 10 000 iterations after a burn-in of 1000. The sampler took approximately 4.5 minutes to run.

For model comparison, we fit a random intercept model in which λ_j was set to 1 for all j , the random effect variance, σ_b^2 , was left unspecified and assigned a conjugate inverse-gamma(0.01, 0.01) prior. We additionally fit a fixed effects model that excluded the subject-specific frailty term altogether. For each model, we computed the Watanabe Information Criterion (WAIC), a Bayesian model comparison measure,²⁸ with lower values indicating better model fit. The WAIC value for the proposed multivariate DFT model was 4476; the WAIC values for the random intercept and fixed effects models were 4553 and 4758, respectively, indicating superior fit for the proposed model. Lastly, we fit model (7) with a logit rather than probit link and obtained a WAIC value of 4520, suggesting better fit for the probit version of the model.

Figure 3 shows the estimated baseline hazards (intercepts) on the probit scale for the 3 milestones: sitting up, crawling, and walking. Each milestone has $K_j - 1$ intercepts, where $K_j = 8$ for sitting up, 9 for crawling, and 6 for walking. The horizontal dashed line represents the point at which the reference covariate group exceeds 0.50 probability of achieving the milestone, conditional on no prior achievement. Overall, we observe increasing trends in the baseline hazards for the 3 milestones, reflecting our intuition that the conditional probability of achieving a milestone should generally increase over time until the final month of the milestone window, at which point the conditional probability is 1, as infants must achieve milestone j at interval K_j if not before. However, it is possible to observe local decreases or flat regions corresponding to intervals of relatively constant hazard on the probit scale, particularly during months of peak milestone achievement. For sitting up, the baseline hazard increased steadily from month 3 (the start of the milestone window) through month 6 before leveling off during months 7 and 8, the period during which most infants sit up. Similarly, the baseline hazard for crawling increased steadily from months 5 to 9, followed by an interval of relatively constant hazard between months 10 and 11. The large intercept for crawling at month 12 indicates that few infants in the reference group crawled beyond month 12. Finally, the baseline hazard of walking increased from months 8–12, reflecting the fact that infants tend to walk around their first birthday.

Table 3 presents the posterior means and 95% CrIs for the infant and maternal covariates included in the model. AHEI-P diet score was negatively associated with sitting up, but positively associated with both crawling and, in particular, walking (posterior mean = 0.09; 95% CrI = [0.00, 0.19]). Moreover, infants born to older mothers showed delayed sitting up. Lastly, black race was associated with earlier motor development for all 3 milestones.

Next, we estimated survival functions for 2 maternal diet quality groups: the first with an AHEI-P score 1 standard deviation (SD) above the sample mean (high diet quality), and the second with an AHEI-P score 1 SD below the sample mean (low diet quality). To construct the estimates, we used the “standardization” method,²⁹ whereby we first assumed that each infant belonged to the high-quality group, obtained a predicted achievement probability at each time point, and then averaged the individual-level predictions to obtain average monthly achievement probabilities for the high-quality population. We repeated the process by next assuming each infant belonged to the low-quality group. The results are presented in Figure 4. As indicated by the lower survival function, higher diet quality was associated with later sitting up but earlier crawling and walking, confirming the results reported in Table 3. In particular, according to these estimates, an infant in the high-quality group (dotted line) has a 70% (95% CrI = [64, 76]) chance of walking in the first year of life, whereas an infant in the low-quality group (dashed line) has only a 62% (95% CrI = [56, 69]) chance, for a net difference of 8 percentage points (95% CrI = [0, 16]).

Table S1 and Figures S1-S3 in the Online Supplement provide additional comparisons between the proposed latent factor model with milestone-specific factor loadings and the random intercept model with $\lambda_j = 1$ for all j . The models differed modestly in terms of their fixed effect estimates and intervals (Table S2), particularly their estimates for race. They also differed noticeably in terms of their baseline hazard estimates (Figure S1), with the random intercept showing earlier sitting up but delayed crawling relative to the proposed model. There were slight differences in the population average Kaplan-Meier curves (Figure S2), but in general, the results were similar for the two models. However, there were noteworthy differences for specific individuals, suggesting different degrees of between-subject heterogeneity across the models. Figure S3 shows the difference in the Kaplan-Meier curves under the two models for a randomly selected infant (ID = 139). For this infant, the random intercept model showed earlier achievement of sitting up, but delayed crawling and (to a lesser extent) walking compared to the proposed latent factor model. These results suggest that the choice of model can have a clinically meaningful impact on results.

6 | DISCUSSION

We have proposed a multivariate DFT model for the analysis of correlated motor developmental milestones. The model accounts for within-subject association, while simultaneously allowing differential covariate effects across milestones. The model also accommodates different developmental windows for each milestone. We implemented both frequentist and Bayesian approaches for inference. For Bayesian inference, we developed a straightforward Gibbs sampler that relies entirely on closed-form full conditionals under either a probit or logit link. Our simulations suggest that the Bayesian approach provides accurate posterior estimates for a variety of sample sizes and may be preferable for studies with small samples. It is also superior to maximum likelihood in terms of computation time, as the latter typically requires a large number of quadrature points to ensure convergence.

To our knowledge, this is the first study to examine associations between overall maternal diet quality and motor milestone achievement in infants. Our analysis revealed that higher maternal diet quality was associated with earlier crawling and walking, but somewhat

delayed sitting up. These associations could be operating through a number of mechanisms. One previous study found a relationship between higher diet quality and reduced risk of small for gestational age infants,³⁰ a potential risk factor for delayed motor achievement. Better diet quality in pregnancy could also influence muscle development in utero and, in turn, impact motor development during the first year of life. These results also have important clinical implications for improving infant motor development. For example, pediatricians and other health professionals can monitor diet quality during pregnancy and make recommendations to promote earlier motor development. They might also assess the rate of gross motor achievement in infancy and use this information as a potential marker of developmental delays. Finally, understanding factors that influence motor achievement as a whole rather than each milestone individually could help clinicians design interventions to target the mechanisms underlying all milestones.

There are a number of areas for future work. For example, some infants may not manifest earlier milestones, such as crawling, but instead progress directly to the next developmental milestone. The proposed model could therefore be extended to allow for latent transition states. While our application limited milestone achievement to WHO-recommended developmental windows, in general, this is not necessary if no such restrictions apply. Unrestricted models would in fact be more straightforward to fit. The model could also be expanded to accommodate informative censoring by jointly modeling the dropout and discrete survival processes.³¹ Although we adopted a shared-parameter approach with a single random effect for all milestones, in longitudinal settings, one could incorporate milestone-specific random effects that are correlated across milestones through a multidimensional covariance matrix. Finally, the random effects could be modeled via skew-normal or skew- t distributions³² to accommodate potential departures from normality. More generally, the methods developed here could be applied to clinical settings where interest lies in jointly modeling correlated discrete or grouped time-to-event data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Here, we provide the full conditional updates for implementing the Gibbs sampler described in Section 3. We initialize the sampler by choosing values for β_j ($j = 1, \dots, J$), λ_j ($j = 1, \dots, J$), and b_i ($i = 1, \dots, n$). Under a probit link, we iterate through the following steps.

1. For milestones $j = 1, \dots, J$, cycle through the following updates.

- a. For $i = 1, \dots, n$ and $h = 1, \dots, k_{ij}$, where k_{ij} denotes the month of milestone achievement or censoring for infant i and milestone j , update Z_{ijh} from its $N(\eta_{ijh}, 1)$ full conditional truncated below (above) by zero for $Y_{ijh} = 1$ ($Y_{ijh} = 0$), where $\eta_{ijh} = \mathbf{x}_{ijh}^T \boldsymbol{\beta}_j + \lambda_j b_i$.
- b. Assuming an $N_{p_j}(\boldsymbol{\beta}_{0j}, \Sigma_{0j})$ prior for $\boldsymbol{\beta}_j$, update $\boldsymbol{\beta}_j$ from its $N_{p_j}(\boldsymbol{\mu}_j, \Sigma_j)$ full conditional, where

$$\Sigma_j = (\Sigma_{0j}^{-1} + \mathbf{X}_j^T \mathbf{X}_j)^{-1} \quad \text{and} \\ \boldsymbol{\mu}_j = \Sigma_j [\Sigma_{0j}^{-1} \boldsymbol{\beta}_{0j} + \mathbf{X}_j^T (\mathbf{Z}_j - \lambda_j \mathbf{B}_j)].$$

Here, $\mathbf{X}_j$ is an $N_j \times p_j$ design matrix for milestone j ,

$\mathbf{Z}_j = (Z_{1j1}, \dots, Z_{1jk_{1j}}, \dots, Z_{nj1}, \dots, Z_{njk_{nj}})^T$ is an $N_j \times 1$ vector of all latent normal variables for milestone j , $N_j = \sum_{i=1}^n k_{ij}$ is the total number of person-months in the sample for milestone j , and $\mathbf{B}_j$ is an $N_j \times 1$ concatenated vector of frailty terms, with b_i repeated k_{ij} times for $i = 1, \dots, n$. For the analyses presented in this paper, we chose $\boldsymbol{\beta}_{0j} = \mathbf{0}$ and $\Sigma_{0j} = 100\mathbf{I}_{p_j}$.

- c. Assuming an $N(0, \tau_\lambda^{-1})$ prior, update λ_j from its $N(\mu_j, \sigma_j^2)$ full conditional (or truncated normal for λ_1), where

$$\sigma_j^2 = \left(\tau_\lambda + \sum_{i=1}^n k_{ij} b_i^2 \right)^{-1} \quad \text{and} \\ \mu_j = \sigma_j^2 (\mathbf{b}^T \mathbf{u}_j).$$

Here, $\mathbf{b} = (b_1, \dots, b_n)^T$ and

$\mathbf{u}_j = \left[\sum_{h=1}^{k_{1j}} (Z_{1jh} - \mathbf{x}_{1jh}^T \boldsymbol{\beta}_j), \dots, \sum_{h=1}^{k_{nj}} (Z_{njh} - \mathbf{x}_{njh}^T \boldsymbol{\beta}_j) \right]^T$ is a vector of length $n \times 1$.

2. Assuming an $N(0, 1)$ prior, update b_i ($i = 1, \dots, n$) from its $N(m_i, v_i)$ full conditional, where

$$v_i = \left(1 + \sum_{j=1}^J \lambda_j^2 k_{ij} \right)$$

$$m_i = v_i \left[\sum_{j=1}^J \lambda_j u_{ij} \right] \quad \text{and}$$

$$u_{ij} = \sum_{h=1}^{k_{ij}} (Z_{ijh} - \mathbf{x}_{ijh}^T \boldsymbol{\beta}_j).$$

For a logit link, we make the following minor modifications to the sampler.

1. For milestones $j = 1, \dots, J$, cycle through the following updates.
 - a. For $i = 1, \dots, n$ and $h = 1, \dots, k_{ij}$, draw latent weights w_{ijh} from a Pólya-Gamma $\text{PG}(1, \boldsymbol{\eta}_{ijh})$ distribution and set $Z_{ijh} = (Y_{ijh} - 1/2)w_{ijh}$. For details on the PG distribution, see the work of Polson et al.²⁴ Samples from the PG distribution can be generated efficiently using the `rpg` function from the R package `BayesLogit`.²⁴

- b. Update $\boldsymbol{\beta}_j$ from its $N_{p_j}(\boldsymbol{\mu}_j, \Sigma_j)$ full conditional, where

$$\Sigma_j = (\Sigma_{0j}^{-1} + \mathbf{X}_j^T \mathbf{W}_j \mathbf{X}_j)^{-1}$$

$$\boldsymbol{\mu}_j = \Sigma_j [\Sigma_{0j}^{-1} \boldsymbol{\beta}_{0j} + \mathbf{X}_j^T \mathbf{W}_j (\mathbf{Z}_j - \lambda_j \mathbf{B}_j)],$$

and $\mathbf{W}_j$ is an $N_j \times N_j$ diagonal matrix of weights w_{ijh} for milestone j .

- c. Update λ_j from its $N(\mu_j, \sigma_j^2)$ full conditional (or truncated normal for λ_1), where

$$\sigma_j^2 = \left(\tau_\lambda + \sum_{i=1}^n w_{ij} b_i^2 \right)^{-1} \quad \text{and}$$

$$\mu_j = \sigma_j^2 (\mathbf{b}^T \mathbf{u}_j).$$

Here, $w_{ij} = \sum_{h=1}^{k_{ij}} w_{ijh}$ and

$$\mathbf{u}_j = \left[\sum_{h=1}^{k_{1j}} w_{1jh} (Z_{1jh} - \mathbf{x}_{1jh}^T \boldsymbol{\beta}_j), \dots, \sum_{h=1}^{k_{nj}} w_{njh} (Z_{njh} - \mathbf{x}_{njh}^T \boldsymbol{\beta}_j) \right]^T.$$

2. Update b_i ($i = 1, \dots, n$) from its $N(m_i, v_i)$ full conditional, where

$$\begin{aligned}
 v_i &= \left(1 + \sum_{j=1}^J \lambda_j^2 w_{ij} \right) \\
 m_i &= v_i \left[\sum_{j=1}^J \lambda_j u_{ij} \right] \\
 w_{ij} &= \sum_{h=1}^{k_{ij}} w_{ijh} \quad \text{and} \\
 u_{ij} &= \sum_{h=1}^{k_{ij}} w_{ijh} (Z_{ijh} - \mathbf{x}_{ijh}^T \boldsymbol{\beta}_j).
 \end{aligned}$$

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FIGURE 1.

Kaplan-Meier plots for sitting up, crawling, and walking in the Nurture study for groups with low and high maternal diet quality. The groups were formed by a median split of the Alternate Healthy Eating Index-Pregnancy scores. Lower survival functions indicate earlier achievement [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 2. Unadjusted Kaplan-Meier plots of motor developmental milestones in simulation study 1 with $n = 500$ [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 3.

Estimated baseline hazards (intercepts) on probit scale for sitting up, crawling, and walking from the Nurture study. Dashed horizontal line denotes the point at which the baseline hazard probability exceeds 0.50. Each milestone has $K_j - 1$ intercepts, where $K_j = 8$ for sitting up, 9 for crawling, and 6 for walking [Colour figure can be viewed at wileyonlinelibrary.com]

FIGURE 4.

Estimated survival functions for two maternal diet quality groups: high quality = AHEI-P score 1 SD above the sample mean (dotted line); low quality = AHEI-P score 1 SD below sample mean (dashed line). Lower survival functions indicate earlier achievement. AHEI-P, Alternate Healthy Eating Index-Pregnancy; SD, standard deviation [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1Demographic characteristics of mothers and infants participating in the Nurture study ($n = 526$)

Characteristic	Median	IQR [†]
Infant birth weight for gestational age z-score	-0.40	(-0.97, 0.32)
Age of sitting up (months)	6	(5, 7)
Age of crawling (months)	8	(7, 9)
Age of walking (months)	12	(11, >12)
Maternal age (years)	27	(23, 32)
AHEI-P score [†]	70	(61, 79)
	<i>n</i>	%
Infant gender, male	265	50
Infant race, black	360	69
Maternal breastfeeding	242	46

[†]IQR: interquartile range. AHEI-P: Alternative Healthy Eating Index-Pregnancy.

TABLE 2

Parameter estimates and 95% intervals for multivariate discrete failure time model used in simulation study 1

<i>n</i>	Milestone	Parameter	Parameter Label	Simulated Value	Estimate (95% Interval)	
					Bayesian Inference [†]	MLE [‡]
500	1	β_{011}	Intercept 1 *	0.75	0.92(0.68, 1.20)	1.67(0.14, 3.20)
		β_{012}	Intercept 2	0.50	0.50(0.01, 1.06)	2.17(-0.79, 5.12)
		β_{013}	Intercept 3	0.25	0.09(-0.56, 0.76)	2.03(-1.33, 5.38)
		β_{014}	Intercept 4	-0.25	-0.67(-1.45, 0.12)	1.32(-2.13, 4.78)
		β_{11}	Effect of X_1 **	-0.25	-0.27(-0.55, -0.01)	-0.51(-1.21, 0.18)
		β_{21}	Effect of X_2 **	0.25	0.24(0.12, 0.38)	0.40(0.10, 0.80)
		λ_1	Factor loading	0.75	0.71(0.34, 1.12)	2.03(0.22, 4.28)
	2	β_{021}	Intercept 1	-0.50	-0.33(-0.47, -0.18)	-0.32(-0.46, -0.18)
		β_{022}	Intercept 2	-0.25	-0.07(-0.24, 0.09)	-0.07(-0.24, .09)
		β_{023}	Intercept 3	-0.75	-0.59(-0.80, -0.35)	-0.59(-0.81, -0.37)
		β_{024}	Intercept 4	-0.75	-0.64(-0.87, -0.39)	-0.65(-0.89, -0.41)
		β_{025}	Intercept 5	-0.25	-0.23(-0.49, 0.03)	-0.25(-0.50, 0.00)
		β_{12}	Effect of X_1	-0.50	-0.65(-0.81, -0.50)	-0.64(-0.80, -0.49)
		β_{22}	Effect of X_2	0.50	0.45(0.37, 0.54)	0.45(0.36, 0.53)
		λ_2	Factor Loading	-0.25	-0.19(-0.37, -0.04)	-0.16(-0.37, -0.05)
	3	β_{031}	Intercept 1	-0.50	-0.44(-0.60, -0.30)	-0.43(-0.57, -0.28)
		β_{032}	Intercept 2	-0.25	-0.21(-0.41, 0.01)	-0.25(-0.42, 0.07)
		β_{033}	Intercept 3	0.25	0.57(0.32, 0.97)	0.47(0.27, 0.68)
		β_{034}	Intercept 4	0.50	0.66(0.31, 1.26)	0.50(0.22, 0.77)
		β_{13}	Effect of X_1	-0.25	-0.36(-0.57, -0.19)	-0.33(-0.49, -0.17)
		β_{23}	Effect of X_2	-0.25	-0.28(-0.36, -0.19)	-0.27(-0.35, -0.18)
		λ_3	Factor loading	0.25	0.39(0.17, 0.80)	0.26(0.12, 0.40)
5000	1	β_{011}	Intercept 1	0.75	0.73(0.65, 0.83)	0.73(0.62, 0.85)
		β_{012}	Intercept 2	0.50	0.54(0.34, 0.81)	0.54(0.24, 0.86)
		β_{013}	Intercept 3	0.25	0.29(0.04, 0.66)	0.31(-0.10, 0.71)
		β_{014}	Intercept 4	-0.25	-0.14(-0.43, 0.27)	-0.13(-0.56, 0.32)
		β_{11}	Effect of X_1	-0.25	-0.34(-0.56, -0.25)	-0.34(-0.44, -0.25)
		β_{21}	Effect of X_2	0.25	0.24(0.20, 0.28)	0.24(0.20, 0.28)
		λ_1	Factor loading	0.75	0.77(0.60, 1.01)	0.78(0.51, 1.05)
	2	β_{021}	Intercept 1	-0.50	-0.54(-0.59, -0.49)	-0.54(-0.59, -0.49)
		β_{022}	Intercept 2	-0.25	-0.29(-0.35, -0.234)	-0.29(-0.35, -0.24)
		β_{023}	Intercept 3	-0.75	-0.76(-0.83, -0.69)	-0.75(-0.82, -0.68)
		β_{024}	Intercept 4	-0.75	-0.83(-0.91, -0.76)	-0.83(-0.91, -0.76)
		β_{025}	Intercept 5	-0.25	-0.27(-0.35, -0.19)	-0.27(-0.35, -0.19)
		β_{12}	Effect of X_1	-0.50	-0.47(-0.52, -0.42)	-0.47(-0.42, -0.41)

<i>n</i>	Milestone	Parameter	Parameter Label	Simulated Value	Estimate (95% Interval)	
					Bayesian Inference [†]	MLE [‡]
3		β_{22}	Effect of X_2	0.50	0.52(0.49, 0.55)	0.52(0.49, 0.54)
		λ_2	Factor Loading	-0.25	-0.25(-0.30, -0.20)	-0.25(-0.31, -0.19)
		β_{031}	Intercept 1	-0.50	-0.53(-0.58, -0.49)	-0.53(-0.58, -0.49)
		β_{032}	Intercept 2	-0.25	-0.25(-0.30, -0.20)	-0.25(-0.31, -0.20)
		β_{033}	Intercept 3	0.25	0.25(0.19, 0.31)	0.25(0.19, 0.31)
		β_{034}	Intercept 4	0.50	0.52(0.43, 0.61)	0.50(0.22, 0.77)
		β_{13}	Effect of X_1	-0.25	-0.22(-0.27, -0.17)	-0.22(-0.27, -0.17)
		β_{23}	Effect of X_2	-0.25	-0.26(-0.29, -0.23)	-0.26(-0.28, -0.23)
		λ_3	Factor loading	0.25	0.23(0.18, 0.29)	0.22(0.17, 0.28)

[†]Posterior means and 95% credible intervals obtained from Gibbs sampler described in Section 3.

[‡]Maximum likelihood estimates (MLEs) and 95% confidence intervals obtained using SAS Proc NLMIXED.

*Intercepts represent baseline hazards, on the probit scale, for the first $K_j - 1$ months of the milestone window, where $K_1 = 5$, $K_2 = 6$ and $K_3 = 5$.

** X_1 = Time-invariant binary covariate; X_2 = Time-varying continuous covariate.

TABLE 3

Posterior means and 95% credible intervals (CrIs) from the analysis of the Nurture data

Milestone	Variable	Posterior Mean	95% CrI
Sitting up	Gender, male	−0.05	(−0.21, 0.11)
	Race, black	0.22	(0.04, 0.40)
	Birthweight z-score	0.03	(−0.05, 0.11)
	Maternal age	−0.08	(−0.16, 0.00)
	Breastfeeding [†]	−0.02	(−0.19, 0.15)
	AHEI-P score	−0.03	(−0.11, 0.05)
	Factor loading	0.33	(0.23, 0.45)
Crawling	Gender, male	0.04	(−0.19, 0.27)
	Race, black	0.57	(0.28, 0.88)
	Birthweight z-score	−0.01	(−0.14, 0.11)
	Maternal age	0.00	(−0.12, 0.12)
	Breastfeeding	0.05	(−0.21, 0.30)
	AHEI-P score	0.06	(−0.06, 0.18)
	Factor loading	0.97	(0.66, 1.31)
Walking	Gender, male	0.03	(−0.17, 0.22)
	Race, black	0.34	(0.11, 0.56)
	Birthweight z-score	0.07	(−0.03, 0.18)
	Maternal age	−0.07	(−0.18, 0.03)
	Breastfeeding	0.13	(−0.11, 0.36)
	AHEI-P score	0.09	(0.00, 0.19)
	Factor loading	0.55	(0.40, 0.74)

[†] Monthly indicator of breastfeeding status (yes/no).

Abbreviation: AHEI-P, Alternate Healthy Eating Index-Pregnancy.