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Pairwise Fitting of Piecewise Mixed Models for the Joint Modeling of Multivariate Longitudinal outcomes, in a Randomised Crossover Trial

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Abstract

Many statistical models have been proposed in the literature for the analysis of longitudinal data. One may propose to model two or more correlated longitudinal processes simultaneously, with a goal of understanding their association over time. Joint modeling is then required to carefully study the association structure among the outcomes as well as drawing joint inferences about the different outcomes. In this study, we sought to model the associations among six nutrition outcomes while circumventing the computational challenge posed by their clustered and high dimensional nature. We analyzed data from a 2×2 randomized crossover trial conducted in Kenya, to compare the effect of high-dose and low-dose iodine in household salt on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in women of reproductive age and their household matching pair of school aged children. Two additional outcomes, namely urinary iodine concentration (UIC) in women and children were measured repeatedly to monitor the amount of iodine excreted through urine. We

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extended the model proposed by Mwangi et al. (2021) allowing flexible piecewise joint models for six outcomes to depend on separate random effects, which are themselves correlated. This entailed fitting 15 bivariate general linear mixed models and deriving inference for the joint model using pseudo-likelihood theory. We analyzed the outcomes separately and jointly using piecewise linear mixed effects (PLME) model and further validated the results using current state-of-the-art Jones & Kenward (2014) methodology (JKME model) used for analyzing randomized crossover trials. The results indicate that high-dose iodine in salt significantly reduced blood pressure compared to low-dose iodine in salt. Estimates for the random effects and residual error components showed that SBP and DBP had strong positive correlation, with effect of the random slope indicating that significantly related outcomes are strongly associated in their evolution. There was a moderately strong inverse relationship between evolutions of UIC and blood pressure both in women and children. These findings confirmed the original hypothesis that high-dose iodine salt has significant lowering effect on blood pressure. We further sought to evaluate the performance of our proposed PLME model against the widely used JKME model, within the multivariate joint modeling framework through a simulation study mimicking a 2×2 crossover design. From our findings, the multivariate joint PLME model performed exeptionally well both in estimation of random effects matrix (G) and hessian matrix (H), allowing satifactory model convergence during estimation. It allowed a more complex fit to the data with both random intercepts and slopes effects compared to the multivariate joint JKME model that allowed for random intercepts only. When a hierarchical view-point is adopted, in the sense that outcomes are specified conditionally upon random effects, the variance-covariance matrix of the random effects must be positive-definite (Oliveira et al., 2017). In some cases, additional random effects could explain much variability in the data, thus improving precision in estimation of the estimands (effect size) parameters. The key highlight in this evaluation shows that multivariate joint JKME model is a powerful tool especially while fitting mixed models with random intercepts only, in crossover design settings. Addition of random slopes may lead to model compexities in some cases, resulting in unsatifactory model convergence during estimation. To circumvent convergence pitfalls, extention of JKME model to PLME model allows a more flexible fit to the data (generated from crossover design settings), especially in the multivariate joint modeling framework.

Keywords:longitudinal, repeated measures, crossover design, piecewise model

1 Introduction

Many statistical models have been proposed in the literature for the analysis of longitudinal data. One may propose to model two or more correlated longitudinal processes simultaneously, with a goal of understanding their association over time. For example, in many AIDS studies both viral load and CD4 are measured repeatedly over time which are known to be correlated. Joint mod-

eling is required and gives more efficient inference than separate analyses when we are interested in the association structure among the outcomes or when we are interested in drawing joint inferences about the different outcomes (Molenberghs & Verbeke, 2005; Fitzmaurice et al., 2008; Tsiatis & Davidian, 2004). There is no simple methodology that accommodates all facets of repeated measures experiments and surveys. In some cases, repeated measurements may be recorded at equally spaced times, while others at irregularly spaced times. Some subjects may experience drop outs as the experiment progresses, which may be random, or may be caused by the treatment the subject is receiving. In some experiments, the repeated measures factor can be randomized, while in others, the repeated measures factor is time or space and cannot be randomized. In addition, the outcome variable or variables may be continuous, discrete, or a combination of the two, leading to different possibilities for drawing inference from the experiment or survey. Methodologies have been developed for continuous, Gaussian data, as well as for non-Gaussian settings, such as binary, count, and ordinal data. Overviews can be found in Verbeke & Molenberghs (2009) for the Gaussian case and in Molenberghs & Verbeke (2005) for the non-Gaussian setting

A number of longitudinal cohort studies on hypertension have been conducted (Fan et al., 2018; Dregan et al., 2016 and Wang et al., 2006). The objective was to monitor the trend in blood pressure (BP) measurements over time. BP is a measure of the force that the circulating blood exerts on the walls of the main arteries. It is described by two measured quantities considered important biomarkers of hypertension, namely, systolic blood pressure (SBP) and diastolic blood pressure (DBP). The pressure wave transmitted along the arteries with each heartbeat is easily felt as the pulse. Systolic pressure is created by the heart contracting and the diastolic pressure is measured as the heart fills (Lawes et al., 2004). BP serves as a biomarker for the disease hypertension (TD et al., 2009). Hypertension or High blood pressure (HBP) has been identified as the leading global risk for mortality worldwide, and is ranked third as a cause of disability-adjusted life-years (Hendriks et al., 2012) and responsible for 13% of deaths globally (WHO, 2009). Hypertension affects approximately 20% of adults worldwide and is a major, but modifiable, contributory factor to cardiovascular disease such as coronary heart disease and stroke (Parker & Glasziou, 2009). It is a chronic disease known to be a risk factor for the development of a number of disease processes. Its progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature, and other organs and lead to premature morbidity and death if not treated properly (Giles et al., 2005). Preventive interventions have been proposed to mitigate on the risk of developing cardiovascular diseases. One such initiative is the hypertension follow up study described in the next section, where two primary outcomes i.e. SBP and DBP, were measured repeatedly for each mother-child pair at every household and the focus was to investigate changes in the two outcomes over time as well as to detect the role of two dosages of iodine treatment associated with a more rapid progression. One

secondary outcome namely urinary iodine concentration (UIC) was measured repeatedly to monitor the amount of iodine excreted through urine. In addition to accounting for between and within-subject variations, a flexible joint mixed modeling approach is implemented to account for the possible correlation in the six (three mother-child paired) outcomes for valid inferences.

In statistical literature, a number of approaches to joint modeling of multiple outcomes, where some or all of the outcomes are ascertained longitudinally, have been proposed, such as multivariate marginal models (Molenberghs & Verbeke, 2005), conditional models (Cox & Wermuth, 1992), shared parameter model (Tsiatis & Davidian, 2004), and joint random effects model (Verbeke & Molenberghs, 2009). In this article, we use the joint random-effects model that allows more fexible correlation patterns (Fieuws & Verbeke, 2004; Chakraborty et al., 2003; Molenberghs & Verbeke, 2005; Fitzmaurice et al., 2008) in order to simultaneously model maternal-child paired SBP, DBP and UIC processes. We extend the model proposed by Mwangi et al. (2021) allowing a flexible piecewise models for the six outcomes to depend on separate random effects, which are themselves correlated. We implemented a piecewise randomly correlated joint model of multivariate longitudinal outcomes within the context of a randomized crossover trial. To validate our findings, we compared our model results to the current widely used state-of-the-art Jones & Kenward (2014) model for analyzing randomized crossover trials. We futher conduct a simulation study comparing performance of our proposed piecewise linear mixed-effects (PLME) model to the Jones & Kenwards mixed-effects (JKME) model. The remainder of the article is organized as follows: Section 2 describes the motivating case study, Section 3 gives an overview of methods applied, Section 4 presents the analysis results, and finally Section 5 offers concluding remarks.

2 Motivating Case Study

A 2-arm, double blind, randomized 6 weeks cross-over trial to compare the effect of high-dose (84mg/kg) and low-dose (50mg/kg) iodine in household salt, on systolic and diastolic blood pressure in women of reproductive age (15 to 49 years) and their household matching pair of school aged children (8 to 12 years), was conducted in Kenya between 22-Oct-2013 and 29-Nov-2013, with a first paper already published by Bukania et al. (2015). The aim of the study was to investigate the role of iodine intake in modulating blood pressure. The two iodine dosages (high and low) were extreme ranges within the Kenyan mandatory salt iodization level (50-84mg/kg), (Kenji et al., 2003). A total of 174 mother-child pair randomized into two independent treatment sequences were followed for six weeks, constituting two treatment periods of three weeks each with no washout between each treatment period. The absence of a washout period, contrary to standard cross-over design studies, was informed by ethical issues. It was considered unethical denying participants iodized household salts because of potential health risks associated with non-consumption of io-

dine fortified salt (Hetzel, 2004; Jooste et al., 2001). In the first sequence, 85 participants received high-dose iodine salt during the first period and later swapped to low-dose iodine salt during the second period. In the second sequence, 89 participants received low-dose iodine salt during the first period and later swapped to high-dose iodine salt during the second period. Treatment 1, denoted as Tr_1, represents high-dose iodine salt and Treatment 2, denoted as Tr_0, represents low-dose iodine salt. Each participant was expected to use the assigned treatment every day. Table 1 summarizes the sample design.

Table 1: Cross-over design

		Period	
Sequence	Subjects	1	2
1	n = 85	Tr_1	Tr_0
2	n = 89	Tr_0	Tr_1

Two primary outcome measurements (SBP and DBP) and one secondary outcome (UIC) were measured repeatedly over the duration of study. To determine the duration effect, the outcomes for each individual were measured at seven equally spaced time-points; baseline (week 0), week 1, and then through to week 6. The expected total number of measurements for each outcome across the seven time-points was 1218. However, due to drop-out and failure to attend some scheduled appointments, there were varying number of missing values in the dataset. Among women, 90 matched measurements for SBP and DBP were missing with 111 for UIC, whereas for children, 100 matched measurements for SBP and DBP were missing with 122 for UIC. Appendix 1 presents the list of variables under consideration.

3 Joint Modeling: Random-Effects Approach

3.1 *Univariate Mixed Models*

Longitudinal data are (often non-uniformly) ordered in time, and missing data are very common. Furthermore, serial measurements of one subject are potentially correlated, and the between-subject variance is not constant over time due to possibly diverging trajectories (Bernal-Rusiel et al., 2013). The linear mixed-effects model (LMM) is a flexible model to handle such data. (Laird & Ware, 1982)

Let y_{ij} denote the j^{th} measurement, $j = 1, 2, \ldots, n_i$; available for the i^{th} individual, $i = 1, 2, \ldots, N$. The algebraic notation of the LMM can be expressed in vector form as:

$$Y_i = X_i\beta + Z_i b_i + \epsilon_i, \tag{1}$$

where Y_i is an $n_i \times 1$ dimensional vector of observed outcomes $(y_{i1}, y_{i2}, \ldots, y_{in_i})$. X_i is a $n_i \times p$ matrix of known covariates associated with a p-dimensional vector β of unknown fixed-effects parameters. Z_i is a $n_i \times q$ matrix of known covariates, $b_i \sim N(0, G)$ is the q-dimensional vector of unknown random-effects parameters, $\epsilon_i \sim N(0, R_i)$ is the vector of unknown residual error components. R_i is an $n_i \times n_i$ covariance matrix that depends on i only through its dimension n_i. (In case of conditional independence, we have $R_i = \sigma^2 I_{n_i}$). See Bernal-Rusiel et al. (2013), Verbeke & Molenberghs (2000, 2009) for the real-life application of the LME model. Restricted maximum likelihood (ReML) is used to estimate all parameters in the marginal model. Computational details are found in Lindstrom & Bates (1988), Laird & Ware (1982) and Molenberghs & Verbeke (2005). Details on hypothesis testing can be found in Bernal-Rusiel et al. (2013).

3.1.1 Modeling Crossover Data

This article considers the simplest design of crossover studies, with a two-sequence and two-period design for comparing two treatments (or 2×2). In crossover clinical trials with one active (A) and one placebo/standard (B) treatment, participants are randomly assigned to a sequence of AB or BA (Grizzle 1965). That is, all participants are supposed to take one treatment during the first period and the other treatment during the second period in a random order. Let S_i denote a randomization assignment sequence indicator for the i^{th} participant ($i = 1, 2, \ldots, N$), with $S_i = 0$ denoting sequence AB and $S_i = 1$ denoting sequence BA. Furthermore, let $T_{ij} = 0$ if the i^{th} participant is assigned to treatment A at time t_j ($j = 1, 2, \ldots, n_i$), and $T_{ij} = 1$ if assigned to treatment B. $P_j = 0$ for all measurements during the first period and $P_j = 1$ during the second period. y_{ij} is the outcome variable for the i^{th} participant assigned to treatment T_{ij}, during period P_j at time t_j.

Next, we implement the Jones & Kenward mixed model and piecewise linear mixed model in the identification and estimation of parameters under the following Soltanian & Faghihzadeh (2012) assumptions:
(I) Random assignment: Pre-treatment variables including potential outcome and baseline variables are independent of randomization.
(II) Absence of carryover effects.
(III) Fixed compliance: A subject would have the same compliance behaviour across the two periods in each sequence.
(IV) Fixed treatment effect: Each treatment has a fixed effect across the two periods, that is, there is no interaction between treatment and period.

Assumptions I, II and III, applies to both models. Assumption IV applies to the Jones & Kenward mixed model, but can be relaxed for the piecewise linear mixed model.

3.1.2 Jones and Kenward Mixed Effects Model

The Jones & Kenward mixed effects (JKME) model is an extention to Grizzle (1965) with inclusion of two interaction terms. The algebraic notation for the JKME model is given by:

$$Y_{ij} = \beta_0 + \beta_1 t_j + \beta_2 P_j + \beta_3 P_j t_j + \beta_4 T_{ij} + \beta_5 T_{ij} t_j + b_{i0} + b_{i1} t_j + \epsilon_{ij}, \quad (2)$$

Here, b_{i0} is the random intercept and b_{i1} is the random slope (averaged over first and second period) for the i^{th} participant, ϵ_{ij} is the random error in the measurement for the i^{th} participant assigned to treatment T_{ij}, during period P_j, at time t_j. The assumptions for the random elements are:

$$\begin{bmatrix} b_{i0} \\ b_{i1} \end{bmatrix} \sim MVN \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_0^2 & \sigma_0\sigma_1 \\ \sigma_0\sigma_1 & \sigma_1^2 \end{bmatrix} \right), \quad (3)$$

and $\epsilon_{ij} \sim N(0, \sigma^2)$. The components in $[b_{i0}, b_{i1}]'$ and ϵ_{ij} are independent. The vector $[\beta_0, \beta_1, .., \beta_p]'$ of fixed effects describes the average evolution of the outcome variable, and the vector $[b_{i0}, b_{i1}]'$ of random effects describes how the profile of the i^{th} participant deviates from the average evolution.

3.1.3 Piecewise Linear Mixed Effects Model

The piecewise linear mixed effects (PLME) model has an extended parametrization beyond the Jones & Kenward model. The fact that the model does not assume fixed treatment effect across periods makes it flexible in modeling nonlinear trends (in different periodic phases), without putting contraints on the curve evolution. The algebraic notation for the PLME model is given by:

$$\begin{aligned} Y_{ij} = {} & \beta_0 + \beta_1 t_j + \beta_2 P_j + \beta_3 P_j t_j + \beta_4 T_{ij} + \beta_5 T_{ij} t_j + \beta_6 P_j T_{ij} + \beta_7 P_j T_{ij} t_j \\ & + b_{i0} + b_{i1} t_j (1 - P_j) + b_{i2} t_j P_j + \epsilon_{ij}, \end{aligned} \quad (4)$$

b_{i0} is the random intercept for the i^{th} participant, b_{i1} is the random prechange slope for the i^{th} participant during the first period (P_j=0), b_{i2} is the random postchange slope for the i^{th} participant during the second period (P_j=1), ϵ_{ij} is the random error in the measurement for the i^{th} participant assigned to treatment T_{ij}, during period P_j, at time t_j. Note that the fixed intercepts and slopes are period specific, but for the random effects only the slopes are period-specific. The assumptions for the random elements are:

$$\begin{bmatrix} b_{i0} \\ b_{i1} \\ b_{i2} \end{bmatrix} \sim MVN \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_0^2 & \sigma_0\sigma_1 & \sigma_0\sigma_2 \\ \sigma_0\sigma_1 & \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_0\sigma_2 & \sigma_1\sigma_2 & \sigma_2^2 \end{bmatrix} \right), \quad (5)$$

and $\epsilon_{ij} \sim N(0, \sigma^2)$. The components in $[b_{i0}, b_{i1}, b_{i2}]'$ and ϵ_{ij} are independent.

We further examine the time, treatment and period effects on the mean outcome profile for model (4). At t_j=t_4 it can be shown that β_2=-$t_4\beta_3$ and

β_6=-$t_4\beta_7$. For implementation of a two piecewise linear spline model, the linear mean profile plot was fitted over time t_j with a knot at time t_4, where the curve was expected to change, hence a time spline t_j^* for all t_j>t_4 was created:

$$t_j^* = \begin{cases} 0, & \text{if } t_j \leq t_4. \\ t_j \text{ - } t_4, & \text{if } t_j > t_4. \end{cases} \tag{6}$$

Using two time variables, t_j and t_j^*, two separate lines were fitted before and after t_4.

3.2 *Joint Mixed Model*

In a multivariate context, more than one outcome variable is observed at each occasion. Hence, we measure a vector of outcomes, W_i, at each occasion and thus we can use equation (1), where:

$$\begin{aligned} b_i &\sim MVN(0, G) \\ \epsilon_i &= [\epsilon_{i1}, \ldots, \epsilon_{in_i}]^T \sim MVN(0, R_i) \\ Cov(b_i, \epsilon_i) &= 0 \end{aligned}$$

Here the assumption of conditional independence does not hold because, given b_i, the observations measured at the same occasion on the same individual might be correlated. As a result,

$$R_i = I_{ni} \otimes \Sigma_{m \times m} \tag{7}$$

where $\Sigma_{m \times m}$ is the variance covariance matrix of the m outcome variables conditional on b_i. The joint model assumes a mixed model for each outcome, and these univariate models are combined through specification of a joint multivariate distribution for all random effects.

Consider the problem in its simplest form when we have only two continous outcomes W_1 and W_2 measured over time for a number of subjects. Each of the variables is described using the linear mixed effects model:

$$W_{1i}(t) = \mu_{1i}(t) + b_{01i} + b_{11i}(t) + \epsilon_{1i}(t) \tag{8}$$

$$W_{2i}(t) = \mu_{2i}(t) + b_{02i} + b_{12i}(t) + \epsilon_{2i}(t) \tag{9}$$

where $\mu_{1i}(t)$ and $\mu_{2i}(t)$ refer to the average evolutions, b_{01i} and b_{02i} represent subject-specific random intercepts, $b_{11i}(t)$ and $b_{12i}(t)$ are random slopes that describe how the subject specific profiles deviate from the average evolution for the two outcomes, $\epsilon_{1i}(t)$ and $\epsilon_{2i}(t)$ are residual error terms. Both outcome trajectories are tied together through a joint distribution for the random effects, as:

$$\begin{bmatrix} b_{01i} \\ b_{11i} \\ b_{02i} \\ b_{12i} \end{bmatrix} \sim MVN(0, G) \tag{10}$$

where the variance-covariance matrix for the random effects, G, has the following structure:

$$\begin{bmatrix} \sigma^2_{01i} & \sigma_{01i}\sigma_{11i} & \sigma_{01i}\sigma_{02i} & \sigma_{01i}\sigma_{12i} \\ \sigma_{11i}\sigma_{01i} & \sigma^2_{11i} & \sigma_{11i}\sigma_{02i} & \sigma_{11i}\sigma_{12i} \\ \sigma_{02i}\sigma_{01i} & \sigma_{02i}\sigma_{11i} & \sigma^2_{02i} & \sigma_{02i}\sigma_{12i} \\ \sigma_{12i}\sigma_{01i} & \sigma_{12i}\sigma_{11i} & \sigma_{12i}\sigma_{02i} & \sigma^2_{12i} \end{bmatrix} \tag{11}$$

The error components for each outcome, which are independent of the random effects, can be taken to be uncorrelated ($\sigma_{12} = 0$) and not associated with the random effects, such that the error components are defined as,

$$\begin{bmatrix} \epsilon_{1i} \\ \epsilon_{2i} \end{bmatrix} \sim MVN(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma^2_1 & \sigma_{12} \\ \sigma_{12} & \sigma^2_2 \end{bmatrix}) \tag{12}$$

Assuming $\sigma_{12} = 0$ implies that, conditional on the random effects, both outcome trajectories are independent. In which case the identity matrix with size n_i is used for the covariance matrix. The assumption of conditional independence could alternatively be relaxed and the random errors could be taken to be dependent by allowing for a nonzero covariance between the error components $\sigma_{12} \neq 0$.

Association of the evolution (AE) of W_1 and W_2 is typically derived from the covariance matrix of the random effects, given by:

$$AE = \frac{\text{Cov}(b_{11}, b_{12})}{\sqrt{\text{Var}(b_{11})}\sqrt{\text{Var}(b_{12})}} = \frac{\sigma_{b_{11}b_{12}}}{\sqrt{\sigma_{b_{11}}}\sqrt{\sigma_{b_{12}}}} \tag{13}$$

It summarizes how the slope of W_1 (denoted as b_{11}) is associated with the slope of W_2 (denoted as b_{12}).

Evolution of the Association (EA): The joint model also shows how the association between the outcomes evolves over time. The marginal correlation given random effects (conditional correlation) between W_1 and W_2 at time t is given as:

$$EA = \frac{\text{Cov}(W_1(t), W_2(t))}{\sqrt{\text{Var}(W_1(t))}\sqrt{\text{Var}(W_2(t))}} =$$

$$\frac{\sigma_{b_{01}b_{02}} + t\sigma_{b_{01}b_{12}} + t\sigma_{b_{02}b_{11}} + t^2\sigma_{b_{11}b_{12}} + \sigma_{12}}{\sqrt{\sigma^2_{b_{01}} + 2t\sigma_{b_{01}b_{11}} + t^2\sigma^2_{b_{11}} + \sigma^2_1}\sqrt{\sigma^2_{b_{02}} + 2t\sigma_{b_{02}b_{12}} + t^2\sigma^2_{b12} + \sigma^2_2}} \tag{14}$$

It summarizes how the association between W_1 and W_2 evolves over time (Gao et al. (2017)).

The smaller the measurement errors of both outcomes, the closer the marginal correlation at $t = 0$ approximates the correlation between the random intercepts. Moreover, when t increases the marginal correlation converges to the correlation between the random slopes. It is important to note that the covariance parameters of the random effects (together with the variances of the error components) determine the shape of the marginal correlation function.

The joint model assumes a mixed model for each outcome, and these univariate models are combined through specification of a joint multivariate distribution for all random effects. Obviously, the joint model can be considered as a new mixed model of the form (1), but with a random-effects vector b_i of a higher dimension. As the number of outcome variables (or the dimension of multivariate outcomes) increases, the number of covariance parameter increases exponentially and the problem of estimation of covariance parameters becomes more and more difficult.

3.3 Pairwise Fitting Approach

To circumvent the computational complexity of high dimensional joint random effects models, the dimensionality of the problem needs to be reduced. One possible strategy might be fitting first all pairwise bivariate models separately, instead of maximizing the likelihood of the full joint multivariate model. Assuming the full joint model is correct, all possible pairwise models are correct (Fieuws & Verbeke, 2006; Fieuws et al., 2007).

For the m number of outcomes that need to be modelled jointly, the pairwise-fitting approach starts from fitting all $m(m-1)/2$ bivariate models, that is, all joint models for all possible pairs.

$$(W_1, W_2), (W_1, W_3), \ldots, (W_1, W_m), (W_2, W_3), \ldots, (W_2, W_m), \ldots, (W_{m-1}, W_m)$$

This approach is equivalent to maximizing a pseudo-likelihood function of the following form:

$$pl(\Theta) = l(W_1, W_2|\Theta_{1,2})l(W_1, W_3|\Theta_{1,3}) \ldots l(W_{m-1}, W_m|\Theta_{m-1,m}) = \prod_{r=1}^{m-1} \prod_{s=r+1}^{m} l(W_r, W_s|\Theta_{r,s}) \tag{15}$$

The pseudo-log likelihood can be written as:

$$pll(\Theta) = \sum_{r=1}^{m-1} \sum_{s=r+1}^{m} ll(W_r, W_s|\Theta_{r,s}) \tag{16}$$

where $l(W_r, W_s|\Theta_{r,s})$, $ll(W_r, W_s|\Theta_{r,s})$ and $\Theta_{r,s}$ represent likelihood, log likelihood and the vector of all parameters in the bivariate joint mixed model corresponding to the r^{th} and s^{th} outcome variable, respectively.

Assume we have P possible pairs from m outcome variables, where $P = m(m-1)/2$. $pll(\Theta)$ can be written as follows:

$$pll(\Theta) = \sum_{p=1}^{P} ll(W_p|\Theta_p) \tag{17}$$

where, W_p contains all the observations in the p^{th} pair. Similarly, Θ_p contains all the parameters of the p^{th} pair.

Let, Θ^* be the vector containing all parameters (fixed effect parameters as well as covariance parameters) of the full multivariate joint mixed model and Θ be the stacked vector combining all pair-specific parameter vectors $\Theta_p (p = 1, \ldots, P)$. Also, assume that $\hat{\Theta}_p$ is the maximizer of $l(W_p|\Theta_p)$. Then $\hat{\Theta}$, the stacked vector combining all $\hat{\Theta}_p$, would maximize the $pll(\Theta)$.

Asymptotic normality of the pseudo-likelihood estimator in the single parameter case and in the vector-valued parameter case is discussed in B. C. Arnold & Strauss (1991) and in Geys et al. (1999), respectively. The asymptotic multivariate normal distribution for $\hat{\Theta}$ is given by

$$\sqrt{N}(\hat{\Theta} - \Theta) \sim MVN(0, J^{-1}KJ^{-1}) \tag{18}$$

where J is a block-diagonal matrix with diagonal blocks J_{pp}, and where K is a symmetric matrix containing blocks K_{pq} (Fieuws & Verbeke, 2006) , given by:

$$J = \begin{bmatrix} J_{11} & \ldots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \ldots & J_{pp} \end{bmatrix} \quad \text{and} \quad K = \begin{bmatrix} K_{11} & \ldots & K_{1q} \\ \vdots & \ddots & \vdots \\ K_{p1} & \ldots & K_{pq} \end{bmatrix},$$

,

$$J_{pp} = -1\frac{1}{N}\sum_{i=1}^{N} E\left(\frac{\partial^2 ll_i(W_p|\Theta_p)}{\partial\Theta_p \partial\Theta_p^T}\right) \quad \text{and} \quad K_{pq} = -1\frac{1}{N}\sum_{i=1}^{N} E\left(\frac{\partial ll_i(W_p|\Theta_p)}{\partial\Theta_p}\frac{\partial ll_i(W_q|\Theta_q)}{\partial\Theta_q^T}\right),$$

$p, q = 1, \ldots, P$.

Let $\hat{V}_{i,p} = Z_{i,p}\hat{G}_p Z_{i,p}^T + \hat{R}_{i,p}$ and $\hat{Q}_{i,p} = \hat{V}_{i,p}^{-1}$. Then J_{pp} and K_{pq} are estimated as follows:

$$\hat{J}_{pp} = \frac{1}{N}\sum_{i=1}^{N} X_{i,p}^T \hat{Q}_{i,p} X_{i,p} \quad \text{and} \quad \hat{K}_{pq} = \frac{1}{N}\sum_{i=1}^{N} X_{i,p}^T \hat{Q}_{i,p}\epsilon_{i,p}(X_{i,q}^T \hat{Q}_{i,q}\epsilon_{i,q})^T \tag{19}$$

where $X_{i,p}$, $Z_{i,p}$ and $\epsilon_{i,p}$ are contributions from the i^{th} subject in X_p (design matrix pertaining to fixed effects), Z_p (design matrix pertaining to random effects) and ϵ_p (residual error vector) respectively. Rewritting

$$\hat{H}_p = \sum_{i=1}^{N} X_{i,p}^T \hat{Q}_{i,p} X_{i,p} \quad \text{and} \quad \hat{G}_p = [X_{1,p}^T \hat{Q}_{1,p} \epsilon_{1,p} \quad \dots \quad X_{N,p}^T \hat{Q}_{N,p} \epsilon_{N,p}] \tag{20}$$

and assuming

$$\hat{H} = \begin{bmatrix} \hat{H}_1 & \dots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \dots & \hat{H}_p \end{bmatrix} \quad \text{and} \quad \hat{G} = \begin{bmatrix} \hat{G}_1 \\ \vdots \\ \hat{G}_p \end{bmatrix}$$

then

$$\hat{J} = \frac{1}{N}\hat{H} \quad \text{and} \quad \hat{K} = \frac{1}{N}\hat{G}\hat{G}^T$$

It is important to note that the parameter vectors Θ^* and Θ are not identical. Some parameters in Θ^* will have a single counterpart in Θ, for example, the covariance between random effects from two different outcomes. Other elements in Θ^* will have a multiple counterpart in Θ, for example, the covariance between random effects from the same outcome. In later case, a single estimate is obtained by averaging all corresponding ML estimates in $\hat{\Theta}$. This is obtained by $\hat{\Theta^*} = A\hat{\Theta}$ with $\hat{\Theta^*}$ following a multivariate normal distribution with mean Θ^* and covariance matrix $A\sum(\hat{\Theta})A'$. A is a matrix containing the appropriate coefficients to calculate the averages and $\sum(\hat{\Theta})$ equals the covariance matrix for $\hat{\Theta}$ obtained by expression (18).

4 Results

4.1 *Summary statistics*

Analysis tables and figures presented in this section contain variables with acronyms defined in Apendix 1. In the actual dataset of the cross-over trial, a relatively small proportion of missing data was observed across time points (see Table 2 and Figure 1). Overall, missing data ranged from 7.4% in SBP_{WRA} and DBP_{WRA} to 10.0% in UIC_{SAC}. SBP_{WRA} was missing if-and-only-if DBP_{WRA} was missing. A similar pattern was observed for SBP_{SAC} and DBP_{SAC}. The heatmap shows a pattern of missing at random (MAR). No missing data was observed in the four baseline covariates.

Results from the analysis of baseline covariates and outcome measurements are presented in Tables 3 and 4. Aligned with expected results, mean values for BMI_{WRA}, Age_{WRA}, BAZ_{SAC}, Age_{SAC} and for the six baseline outcome measurements were statistically comparable between the two treatment sequences. Noticeably, repeatedly measured UIC values were scaled different compared to SBP and DBP both in women and children. To harmonize the scale for all outcome measurements, we rescaled UIC using the square root function resulting in square root urinary iodine concentration (sqrtUIC). In general, the mean value of all outcomes reduced across time points relative to baseline. All outcome measurements taken at week 0 (baseline value) were included in the outcome vector. Modeling of the six outcomes repeatedly measured at seven timepoints commenced with exploratory data analysis presented in the next subsection.

Table 2: Missing data pattern

Group	BMI_{WRA}	Age_{WRA}	BAZ_{SAC}	Age_{SAC}	SBP_{WRA}	DBP_{WRA}	UIC_{WRA}	SBP_{SAC}	DBP_{SAC}	UIC_{SAC}	Freq	Percent
1	X	X	X	X	X	X	X	X	X	X	997	81.86
2	X	X	X	X	X	X	X	X	X	.	38	3.12
3	X	X	X	X	X	X	X	.	X	X	1	0.08
4	X	X	X	X	X	X	X	.	.	X	20	1.64
5	X	X	X	X	X	X	X	.	.	.	33	2.71
6	X	X	X	X	X	X	.	X	X	X	30	2.46
7	X	X	X	X	X	X	.	X	X	.	5	0.41
8	X	X	X	X	X	X	.	.	.	X	1	0.08
9	X	X	X	X	X	X	.	.	.	.	3	0.25
10	X	X	X	X	.	.	X	X	X	X	14	1.15
11	X	X	X	X	.	.	X	X	X	.	1	0.08
12	X	X	X	X	.	.	X	.	.	X	2	0.16
13	X	X	X	X	.	.	X	.	.	.	1	0.08
14	X	X	X	X	.	.	.	X	X	X	30	2.46
15	X	X	X	X	.	.	.	X	X	.	2	0.16
16	X	X	X	X	.	.	.	.	.	X	1	0.08
17	X	X	X	X	.	.	.	.	.	.	39	3.20
Number missing	0	0	0	0	90	90	111	101	100	122		
% missing	0.0%	0.0%	0.0%	0.0%	7.4%	7.4%	9.1%	8.3%	8.2%	10.0%		

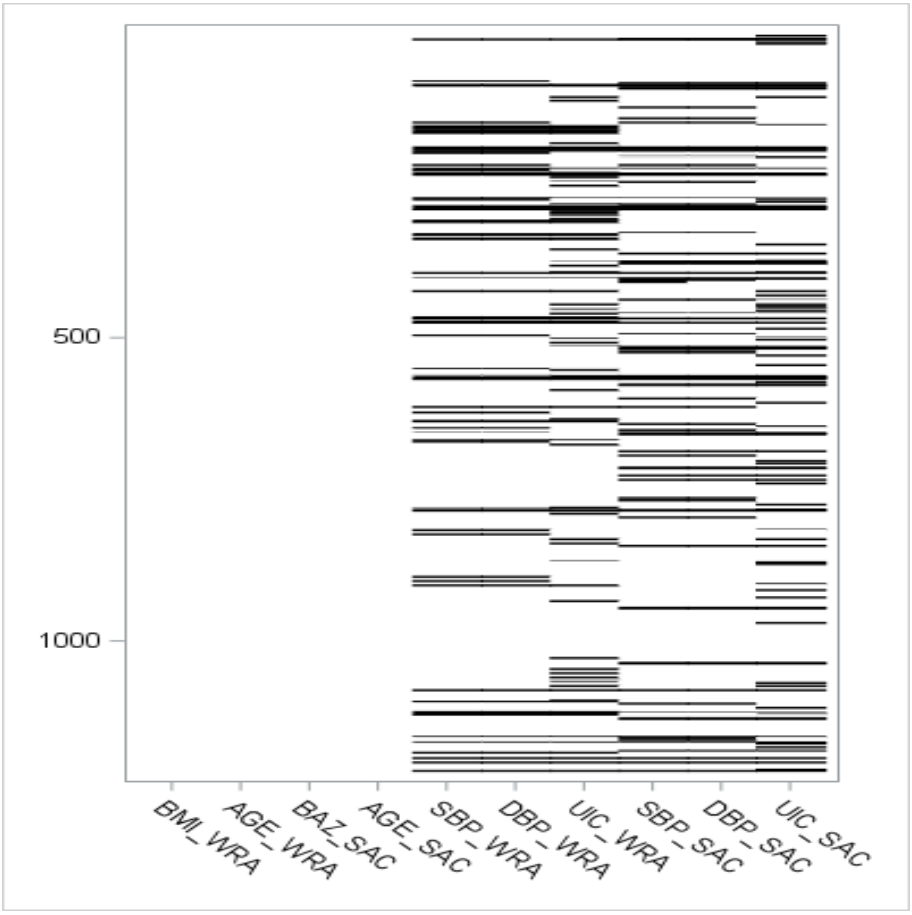

Figure 1: A heatmap showing missing data pattern

4.2 *Exploratory Data Analysis*

Individual profiles presented in Apendix 2 show evidence of random intercept in all outcomes. Generally, those starting at relatively high values remained high, while those starting at relatively low values remained low (between-subject variability). There was considerable within-subject variability indicated by irregular fluctuation up-down at different gradients, depicting evidence of random slopes. Individuals evolution showed tendency to moderate decrease in all outcomes. Figure 2 presents a box-and-whisker plot showing overall trend in the outcomes.

For the SBP and DBP data of women introduced in Section 2, Mwangi et al. (2021) proposed a piecewise linear mixed effects model to analyze the evolution of two blood pressure outcomes for women in univariate setting. In addition to

Table 3: Distribution of baseline covariates

		Total		Low-to-high iodine		High-to-low iodine
Variable	n	Mean(95% CI)	n	Mean(95% CI)	n	Mean(95% CI)
BMI_{WRA}	174	24.1(23.5-24.8)	89	24.6(23.7-25.5)	85	23.6(22.8-24.5)
Age_{WRA}	174	35.6(34.6-36.5)	89	35.6(34.5-36.8)	85	35.5(34.0-37.0)
BAZ_{SAC}	174	-0.89(-1.01 to -0.77)	89	-1.03(-1.19 to -0.86)	85	-0.74(-0.90 to -0.59)
Age_{SAC}	174	120.3(117.8-122.9)	89	118.1(114.6-121.6)	85	122.7(118.9-126.4)

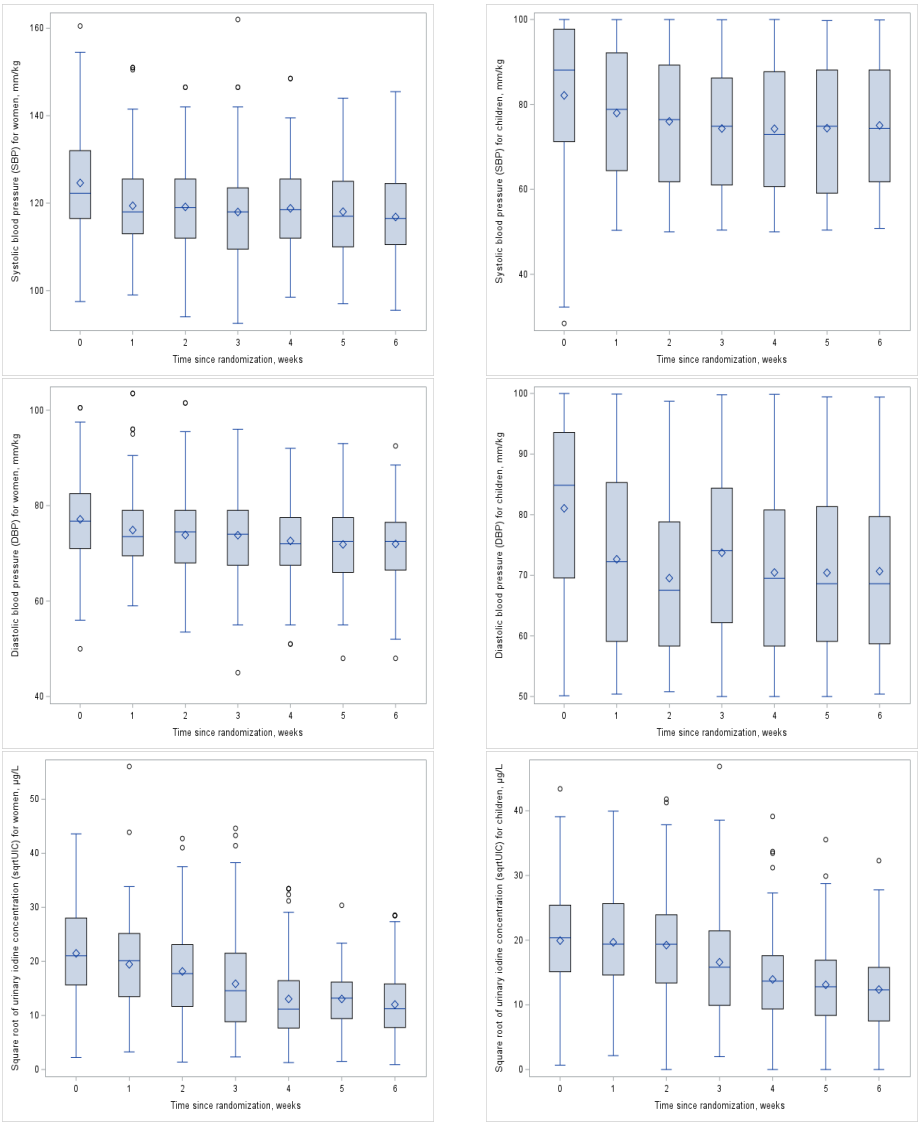

Figure 2: A box-and-whisker plot of outcomes

Table 4: Distribution of repeated outcome measurements

	Total		Low-to-high iodine		High-to-low iodine	
Variable	n	Mean(95% CI)	n	Mean(95% CI)	n	Mean(95% CI)
SBP_{WRA}						
Week 0	174	124.6(122.8-126.4)	89	124.8(122.2-127.4)	85	124.4(121.8-127.0)
Week 1	165	119.4(117.8-121.0)	84	118.5(116.2-120.7)	81	120.4(118.1-122.6)
Week 2	161	119.1(117.5-120.8)	87	119.5(117.4-121.6)	74	118.8(116.2-121.3)
Week 3	154	118.0(116.3-119.7)	78	118.9(116.6-121.3)	76	117.0(114.5-119.5)
Week 4	158	118.8(117.3-120.3)	87	118.7(116.6-120.8)	71	119.0(116.8-121.1)
Week 5	159	118.0(116.5-119.6)	85	117.5(115.3-119.6)	74	118.7(116.4-121.0)
Week 6	157	116.8(115.3-118.4)	84	116.6(114.6-118.6)	73	117.1(114.7-119.5)
DBP_{WRA}						
Week 0	174	77.1(75.8-78.4)	89	77.2(75.4-79.0)	85	77.0(75.2-78.9)
Week 1	165	74.9(73.6-76.1)	84	74.5(72.8-76.2)	81	75.3(73.5-77.0)
Week 2	161	73.9(72.6-75.1)	87	74.3(72.6-76.1)	74	73.3(71.5-75.1)
Week 3	154	73.8(72.4-75.2)	78	75.7(73.8-77.6)	76	71.8(69.8-73.9)
Week 4	158	72.6(71.3-73.9)	87	72.2(70.6-73.8)	71	73.1(70.9-75.3)
Week 5	159	71.9(70.6-73.1)	85	72.5(70.9-74.1)	74	71.2(69.2-73.2)
Week 6	157	72.0(70.8-73.1)	84	71.9(70.5-73.2)	73	72.1(70.2-74.1)
UIC_{WRA}						
Week 0	174	541.5(483.1-599.8)	89	607.2(527.7-686.7)	85	472.6(389.1-556.2)
Week 1	155	447.8(388.9-506.7)	77	388.0(336.4-439.5)	78	506.8(402.6-611.0)
Week 2	149	388.7(337.2-440.2)	85	422.7(357.5-487.8)	64	343.6(261.2-426.0)
Week 3	158	323.5(270.4-376.5)	84	234.2(194.7-273.8)	74	424.7(325.3-524.2)
Week 4	157	223.1(184.4-261.9)	83	183.9(141.0-226.8)	74	267.1(201.6-332.6)
Week 5	158	197.8(174.6-221.0)	86	231.1(195.8-266.4)	72	158.0(132.2-183.8)
Week 6	156	179.2(153.1-205.3)	83	208.4(169.0-247.8)	73	146.0(114.3-177.7)
SBP_{SAC}						
Week 0	173	82.1(79.3-84.9)	89	80.2(76.0-84.4)	84	84.1(80.4-87.8)
Week 1	161	78.0(75.6-80.3)	83	78.6(75.4-81.7)	78	77.4(73.8-80.9)
Week 2	158	76.0(73.7-78.3)	88	74.5(71.5-77.5)	70	77.9(74.3-81.5)
Week 3	152	74.3(72.0-76.7)	80	74.8(71.5-78.0)	72	73.8(70.5-77.2)
Week 4	161	74.3(71.9-76.6)	86	73.3(70.1-76.6)	75	75.3(71.9-78.8)
Week 5	158	74.4(72.0-76.8)	83	74.4(71.4-77.4)	75	74.4(70.6-78.2)
Week 6	154	75.1(72.7-77.4)	78	74.1(70.8-77.5)	76	76.0(72.7-79.4)
DBP_{SAC}						
Week 0	174	81.0(78.9-83.2)	89	81.2(78.3-84.1)	85	80.9(77.7-84.1)
Week 1	161	72.6(70.4-74.9)	83	73.1(70.0-76.2)	78	72.2(68.9-75.5)
Week 2	158	69.5(67.5-71.5)	88	67.2(64.8-69.6)	70	72.4(69.1-75.7)
Week 3	152	73.7(71.6-75.9)	80	74.0(70.9-77.1)	72	73.4(70.4-76.5)
Week 4	161	70.5(68.4-72.5)	86	69.2(66.4-72.0)	75	71.9(68.8-75.0)
Week 5	158	70.4(68.4-72.5)	83	69.0(66.2-71.9)	75	72.0(68.9-75.0)
Week 6	154	70.7(68.5-72.8)	78	70.5(67.4-73.6)	76	70.8(67.7-73.9)
UIC_{SAC}						
Week 0	167	460.7(411.6-509.8)	87	492.4(422.2-562.6)	80	426.1(358.1-494.2)
Week 1	153	441.1(392.8-489.5)	80	335.1(288.7-381.4)	73	557.4(477.5-637.2)
Week 2	154	432.8(381.4-484.3)	84	462.3(395.4-529.3)	70	397.4(318.0-476.9)
Week 3	158	336.1(286.6-385.7)	81	243.2(195.7-290.6)	77	433.9(350.4-517.4)
Week 4	151	240.7(204.0-277.4)	82	189.5(156.7-222.3)	69	301.6(233.7-369.4)
Week 5	154	216.6(184.5-248.8)	80	267.7(225.1-310.2)	74	161.5(115.8-207.2)
Week 6	154	196.5(166.9-226.0)	80	208.4(168.0-248.9)	74	183.6(140.3-226.9)

accounting for variability between and within treatment, three correlated random effects namely intercept, prechange slope in Period 1 and postchange slope in Period 2 were fitted. For this article, we adjusted the fixed effects part by adding four baseline covariates while maintaining the random structure. These was implemented for all six outcomes in univariate setting. To alleviates the problem of data missingness, REML estimation method was used hence missingness did not impact on estimation of parameters for both PLME and JKME models. REML estimation method is valid under missing at random (MAR).

While fitting sqrtUIC for women and DBP for children, introduction of postchange slope in Period 2 resulted in convergence problem. We further explored the convergence status of all 15 paired analysis (of the six outcomes) in baivariate setting. None of the children outcomes allowed a postchange slope in period 2. Table 5 summarizes information about the hessian matrix for each outcome; upon implementing the piecewise linear mixed effects (PLME) model and Jones & Kenward mixed effects (JKME) model. Allowing for models whose hessian matrix was positive definite, the findings reveal that each outcome had specific structure of the mixed model some with reduced dimensions of the shared random effects. The PLME model allowed a more complex fit to the data than JKME model thus able to explain much variability in the data. Next we describe the results obtained from the univariate and multivariate analysis of the data using PLME model and further validate our findings against the current widely used state of art JKME model (in the analysis of clinical trials).

Table 5: Information about estimated hessian matrix

Model	PLME						JKME			
Random effect	I		I+Ps		I+Ps+Qs		I		I+Ps	
Outcome	WRA	SAC	WRA	SAC	WRA	SAC	WRA	SAC	WRA	SAC
SBP	PD	PD	PD	PD	PD	NPD	PD	PD	PD	NPD
DBP	PD	PD	PD	PD	PD	NPD	PD	PD	PD	NPD
sqrtUIC	PD	PD	PD	PD	NPD	NPD	PD	PD	NPD	NPD

WRA - Women of reproductive age; SAC - School aged children;
I - Intercept; Ps - Prechange slope; Qs - Postchange slope; PD - Positive definite;
NPD - Not positive definite

4.3 *Univariate mixed models*

First we anlyzed the outcomes in univariate piecewise linear mixed effects model. Table 5 presents the estimated parameters for the fixed and random effects. Results for the baseline covariates show that BMI_{WRA} was positively correlated with SBP_{WRA}, DBP_{WRA} and $sqrtUIC_{WRA}$. Whereas Age_{WRA} was positively correlated with DBP_{WRA}, Age_{SAC} was negatively correlated with DBP_{SAC}. The two time variables (Time and Timespl1) appearing in Table 6 and any other subsequent presentation refers to t_j and t_j^* respectively (see explaination in section 3.1.3, equation 6).

Table 6: Estimates (standard error) for the fixed and random effects in univariate piecewise linear mixed models

Model	WRA			SAC		
Outcome	SBP	DBP	$sqrtUIC$	SBP	DBP	$sqrtUIC$
Fixed effects:						
Intercept	107.78(6.69)*	56.87(5.09)*	20.28(3.11)*	85.69(6.99)*	88.57(5.46)*	18.62(3)*
Time	-1.52(0.34)*	-0.63(0.26)$^\#$	-2.87(0.31)*	-1.97(0.65)*	-2.57(0.60)*	-1.86(0.31)*
Timespl1	1.53(0.58)*	-0.04(0.45)	1.25(0.51)	2.49(1.17)$^\#$	3.13(1.06)*	0.14(0.54)
Treatment	0.81(1.37)	1.33(0.99)	-4.65(1.22)	2.87(2.2)	0.60(1.98)	-1.72(1.15)
Time*Treatment	-0.57(0.50)	-1.1(0.37)*	1.75(0.46)	-1.03(0.94)	-0.04(0.87)	1.11(0.46)$^\#$
Timespl1*Treatment	0.53(0.83)	1.61(0.64)$^\#$	-1.15(0.75)	0.72(1.73)	-0.90(1.56)	-0.92(0.78)
BMI_{WRA}	0.34(0.15)$^\#$	0.36(0.12)*	0.15(0.07)$^\#$	0.18(0.16)	0.05(0.12)	-0.02(0.07)
Age_{WRA}	0.04(0.11)	0.23(0.08)*	-0.09(0.05)	-0.06(0.11)	-0.10(0.09)	0.01(0.05)
BAZ_{SAC}	-0.28(0.87)	0.20(0.66)	0.21(0.39)	0.80(0.92)	-1.15(0.71)	0.58(0.39)
Age_{SAC}	0.04(0.04)	0.02(0.03)	0.03(0.02)	-0.06(0.04)	-0.08(0.03)$^\#$	0.03(0.02)
Random effects:						
Intercept	97.68	47.26	44.56	75.71	52.51	29.24
Intercept∗`Time`	-8.36	-2.60	-7.29	-7.71	-7.63	-4.74
`Time`	3.56	1.82	1.34	2.43	1.89	0.95
Intercept∗`Timespl1`	3.41	0.34				
`Time`∗`Timespl1`	-3.87	-2.21				
`Timespl1`	6.16	3.71				
Residual	35.14	21.02	37.86	186.15	161.20	39.99

$^*p < 0.01, ^\# p < 0.05$

4.4 *Multivariate mixed model*

Likelihood estimation in multivariate mixed models have been discussed extensively in literature. With increased number of outcomes, coupled with a random-effects vector of a higher dimension, the number of likelihood data points increase exponentially. Likelihood estimation of a full multivariate mixed model encounters computational difficulty with standard software. Standard MLE or REML fails even for a single outcome with large sample size and increased number of random effects. A pairwise fitting approach (based on pseudo-likelihood

theory) proposed by Fieuws & Verbeke (2006), circumvents this computational challenge by fitting joint models to all pairs of outcomes separately, followed by summarizing the estimates over possible number of pairs. With increased number of random effects, our proposed method have a large number of parameters, even for a single outcome. We therefore proceeded to fitting our multivariate joint mixed-effects model using pairwise fitting approach.

We implemented a randomly correlated joint model of multivariate longitudinal outcomes maintaining the structure for the fixed and random effects as implemented in a univariate setting. We allowed flexible piecewise models for the six outcomes to depend on separate random effects, which are themselves correlated. Table 7 presents the results for the multivariate piecewise linear mixed effects model. Estimates for the parameters with respective standard errors (see Table 10) are relatively close to those generated in a univariate analysis as presented in Table 6.

Table 7: Estimates (standard error) for the fixed effects in multivariate piecewise linear mixed model

Model	WRA			SAC		
Outcome	SBP	DBP	$sqrtUIC$	SBP	DBP	$sqrtUIC$
Fixed effects:						
Intercept	107.67(6.06)*	56.64(4.67)*	20.15(2.77)*	85.91(6.43)*	88.63(4.99)*	18.91(2.63)*
Time	-1.49(0.37)*	-0.62(0.29)$^\#$	-2.88(0.32)*	-1.97(0.73)*	-2.57(0.54)*	-1.84(0.30)*
Timespl1	1.51(0.61)*	-0.04(0.49)	1.25(0.52)	2.50(1.21)$^\#$	3.16(0.97)*	0.10(0.53)
Treatment	0.94(1.30)	1.33(0.95)	-4.74(1.32)	2.85(2.34)	0.63(1.94)	-1.75(1.10)
Time*Treatment	-0.61(0.52)	-1.10(0.39)*	1.76(0.51)	-1.03(0.96)	-0.03(0.82)	1.07(0.45)$^\#$
Timespl1*Treatment	0.57(0.82)	1.62(0.64)$^\#$	-1.16(0.81)	0.73(1.65)	-0.98(1.41)	-0.86(0.74)
BMI_{WRA}	0.34(0.15)$^\#$	0.36(0.11)*	0.15(0.07)$^\#$	0.19(0.15)	0.05(0.12)	-0.02(0.07)
Age_{WRA}	0.04(0.09)	0.23(0.07)*	-0.09(0.05)	-0.05(0.11)	-0.10(0.07)	0.01(0.04)
BAZ_{SAC}	-0.25(0.86)	0.21(0.64)	0.22(0.35)	0.92(0.92)	-1.12(0.67)	0.59(0.34)
Age_{SAC}	0.04(0.03)	0.02(0.03)	0.03(0.02)	-0.07(0.04)	-0.08(0.03)$^\#$	0.03(0.02)

$^*p < 0.01, ^\# p < 0.05$

To explore results for the covariance parameters, Tables 8 and 9 show combined results of the 14 x 14 variance-covariance matrix of the random effects with corresponding matrix of correlation coefficients. The results of the correlation matrix for the 14 x 6 random prechange slopes and 14 x 2 random postchange slopes indicate that significantly related outcomes are more strongly associated in their evolutions than insignificantly related outcomes. Correlation of prechange slopes revealed that the evolution of systolic blood pressure for women (SBP_{WRA}) was strongly associated to the evolution of diastolic blood pressure for women (DBP_{WRA}); correlation coefficient = 0.664. Similarly, the evolution of systolic blood pressure for children (SBP_{SAC}) was strongly related to the evolution of diastolic blood pressure for children (DBP_{SAC}); correlation

coefficient = 0.764.

The evolution of square root of urinary iodine concentration for women ($sqrtUIC_{WRA}$) was negatively correlated with evolution of systolic blood pressure for women (SBP_{WRA}), correlation coefficient = -0.198; and evolution of diastolic blood pressure for women (SBP_{WRA}), correlation coefficient = -0.123. Similarly, the evolution of square root of urinary iodine concentration for children ($sqrtUIC_{SAC}$) was negatively correlated with evolution of systolic blood pressure for children (SBP_{SAC}), correlation coefficient = -0.189. However, it was not related with evolution of diastolic blood pressure for children (DBP_{SAC}); correlation coefficient = 0.031.

Correlation of postchange slopes revealed that the evolution of systolic blood pressure for women (SBP_{WRA}) was strongly associated to the evolution of diastolic blood pressure for women (DBP_{WRA}); correlation coefficient = 0.662. Tables 9 shows results of the variance-covariance estimates with correlation coefficient for the random error in the multivariate PLME model.

Table 8: Variance-covariance estimates with correlation coefficient for the random effects in the multivariate PLME model (a)

Measure		Variance-covariance estimate						Correlation coefficient					
Population		WRA			SAC			WRA			SAC		
	Outcome	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$
WRA	SBP_I	97.64	54.93	-13.05	21.06	1.57	0.68	1	***0.809***	***-0.198***	0.246	0.022	0.013
	DBP_I	54.93	47.17	-5.64	8.64	1.67	-2.21	0.809	1	***-0.123***	0.145	0.033	-0.059
	$sqrtUIC_I$	-13.05	-5.64	44.66	-1.25	2.71	29.73	-0.198	-0.123	1	-0.021	0.056	0.821
SAC	SBP_I	21.06	8.64	-1.25	75.22	48.19	-5.71	0.246	0.145	-0.021	1	***0.765***	***-0.122***
	DBP_I	1.57	1.67	2.71	48.19	52.81	-1.64	0.022	0.033	0.056	0.765	1	***-0.042***
	$sqrtUIC_I$	0.68	-2.21	29.73	-5.71	-1.64	29.36	0.013	-0.059	0.821	-0.122	-0.042	1
WRA	SBP_{Ps}	-8.40	-3.75	3.25	0.43	1.59	-0.18	-0.448	-0.288	0.257	0.026	0.116	-0.017
	DBP_{Ps}	-3.16	-2.59	0.92	-0.13	1.39	0.88	-0.237	-0.280	0.102	-0.011	0.142	0.120
	$sqrtUIC_{Ps}$	2.28	1.53	-7.31	1.09	-0.93	-5.36	0.199	0.192	-0.946	0.108	-0.111	-0.855
SAC	SBP_{Ps}	-2.62	-1.92	1.58	-7.62	-5.50	0.34	-0.170	-0.179	0.152	-0.563	-0.486	0.040
	DBP_{Ps}	2.06	0.99	-0.59	-8.37	-7.72	-0.34	0.151	0.105	-0.064	-0.698	-0.769	-0.045
	$sqrtUIC_{Ps}$	0.35	0.63	-4.55	1.42	-0.56	-4.77	0.036	0.094	-0.694	0.167	-0.079	-0.899
WRA	SBP_{Qs}	3.50	-0.90	-3.45	-3.85	-4.73	0.47	0.141	-0.052	-0.206	-0.177	-0.260	0.034
	DBP_{Qs}	0.47	0.35	-0.82	-1.67	-3.72	-0.66	0.025	0.027	-0.064	-0.100	-0.265	-0.063
	Outcome	SBP_{Ps}	DBP_{Ps}	$sqrtUIC_{Ps}$	SBP_{Ps}	DBP_{Ps}	$sqrtUIC_{Ps}$	SBP_{Ps}	DBP_{Ps}	$sqrtUIC_{Ps}$	SBP_{Ps}	DBP_{Ps}	$sqrtUIC_{Ps}$
WRA	SBP_I	-8.40	-3.16	2.28	-2.62	2.06	0.35	-0.448	-0.237	0.199	-0.170	0.151	0.036
	DBP_I	-3.75	-2.59	1.53	-1.92	0.99	0.63	-0.288	-0.280	0.192	-0.179	0.105	0.094
	$sqrtUIC_I$	3.25	0.92	-7.31	1.58	-0.59	-4.55	0.257	0.102	-0.946	0.152	-0.064	-0.694
SAC	SBP_I	0.43	-0.13	1.09	-7.62	-8.37	1.42	0.026	-0.011	0.108	-0.563	-0.698	0.167
	DBP_I	1.59	1.39	-0.93	-5.50	-7.72	-0.56	0.116	0.142	-0.111	-0.486	-0.769	-0.079
	$sqrtUIC_I$	-0.18	0.88	-5.36	0.34	-0.34	-4.77	-0.017	0.120	-0.855	0.040	-0.045	-0.899
WRA	SBP_{Ps}	3.60	1.70	-0.35	0.75	-0.08	0.35	1	***0.664***	***-0.158***	0.254	-0.029	0.189
	DBP_{Ps}	1.70	1.82	-0.22	0.27	-0.29	-0.01	0.664	1	***-0.143***	0.126	-0.155	-0.010
	$sqrtUIC_{Ps}$	-0.35	-0.22	1.34	-0.69	0.06	0.89	-0.158	-0.143	1	-0.382	0.039	0.787
SAC	SBP_{Ps}	0.75	0.27	-0.69	2.43	1.69	-0.29	0.254	0.126	-0.382	1	***0.784***	***-0.188***
	DBP_{Ps}	-0.08	-0.29	0.06	1.69	1.91	0.04	-0.029	-0.155	0.039	0.784	1	***0.031***
	$sqrtUIC_{Ps}$	0.35	-0.01	0.89	-0.29	0.04	0.96	0.189	-0.010	0.787	-0.188	0.031	1
WRA	SBP_{Qs}	-3.94	-1.49	0.30	-0.92	0.54	-0.60	-0.828	-0.440	0.102	-0.235	0.154	-0.244
	DBP_{Qs}	-2.16	-2.22	0.28	-0.44	0.80	-0.17	-0.592	-0.853	0.124	-0.146	0.300	-0.090

WRA - Women of reproductive age; SAC - School aged children; I - Intercept; Ps - Prechange slope; Qs - Postchange slope

Table 9: Variance-covariance estimates with correlation coefficient for the random effects in the multivariate PLME model (b)

Measure		Variance-covariance		Correlation coefficient	
Population		WRA		WRA	
	Outcome	SBP_{Qs}	DBP_{Qs}	SBP_{Qs}	DBP_{Qs}
WRA	SBP_I	3.50	0.47	0.141	0.025
	DBP_I	-0.90	0.35	-0.052	0.027
	$sqrtUIC_I$	-3.45	-0.82	-0.206	-0.064
SAC	SBP_I	-3.85	-1.67	-0.177	-0.100
	DBP_I	-4.73	-3.72	-0.260	-0.265
	$sqrtUIC_I$	0.47	-0.66	0.034	-0.063
WRA	SBP_{Ps}	-3.94	-2.16	-0.828	-0.592
	DBP_{Ps}	-1.49	-2.22	-0.440	-0.853
	$sqrtUIC_{Ps}$	0.30	0.28	0.102	0.124
SAC	SBP_{Ps}	-0.92	-0.44	-0.235	-0.146
	DBP_{Ps}	0.54	0.80	0.154	0.300
	$sqrtUIC_{Ps}$	-0.60	-0.17	-0.244	-0.090
WRA	SBP_{Qs}	6.30	3.20	1	***0.662***
	DBP_{Qs}	3.20	3.71	0.662	1

WRA - Women of reproductive age; SAC - School aged children; I - Intercept; Ps - Prechange slope; Qs - Postchange slope

4.5 *Validation of the PLME multivariate model Results*

To validate the PLME model results, we compared our findings with the current state-of-the-art Jones & Kenward (2014) methodology for analyzing randomized crossover trials. We maintained the same structure for the fixed effects but reduced the random structure to intercept only. Appendix 3 show the results of the variance-covariance estimates with corresponding correlation coefficients for the random effects and residual (error) component in the multivariate PLME and JKME models.

Implementation of the PLME model yielded similar results to the JKME model. For example, the magnitude of correlation between random intercepts for systolic blood pressure for women (SBP_{WRA}) and those of diastolic blood pressure for women (DBP_{WRA}) was the same for both models (PLME model = 0.798, JKME model = 0.798). Similarly, magnitude of correlation between random intercepts for systolic blood pressure for children (SBP_{SAC}) and those of diastolic blood pressure for children (DBP_{SAC}) was comparable between the two models (PLME model = 0.605, JKME model = 0.613). Correlation coefficients of the error components between systolic blood pressure for women (SBP_{WRA}) and diastolic blood pressure for women (DBP_{WRA}) was similar for both models (PLME model = 0.545, JKME model = 0.550). Similarly, magnitude of Correlation coefficients of the error components between systolic blood pressure for children (SBP_{SAC}) and diastolic blood pressure for children

Table 10: Variance-covariance estimates with correlation coefficient for the random error in the multivariate PLME model

Population		WRA			SAC		
	Outcome	SBP	DBP	$sqrtUIC$	SBP	DBP	$sqrtUIC$
Measure		Variance-covariance estimate					
WRA	SBP	35.10	13.61	1.52	0.23	3.01	-1.38
	DBP	13.61	21.03	0.62	3.46	4.15	-0.24
	$sqrtUIC$	1.52	0.62	37.84	-2.82	3.89	12.16
SAC	SBP	0.23	3.46	-2.82	186.14	44.99	3.44
	DBP	3.01	4.15	3.89	44.99	161.18	-1.22
	$sqrtUIC$	-1.38	-0.24	12.16	3.44	-1.22	40.00
Measure		Correlation coefficient					
WRA	SBP	1	***0.501***	0.042	0.003	0.040	-0.037
	DBP	0.501	1	0.022	0.055	0.071	-0.008
	$sqrtUIC$	0.042	0.022	1	-0.034	0.050	0.312
SAC	SBP	0.003	0.055	-0.034	1	***0.260***	0.040
	DBP	0.040	0.071	0.050	0.260	1	-0.015
	$sqrtUIC$	-0.037	-0.008	0.312	0.040	-0.015	1

WRA - Women of reproductive age; SAC - School aged children

(DBP_{SAC}) was the same for both models (PLME model = 0.288, JKME model = 0.288). A similar parttern is observed in all estimated parametes.

5 Simulation Study

Our simulation study tries to mirror real-life situation by deriving true underlying parameters from empirical data. We considered multiple continuous repeated measures evaluation setting. Assuming four outcomes repeatedly measured seven times for individual i,

$$W_{i1} = w_{i11}, w_{i12}, \ldots, w_{i17}$$

$$W_{i2} = w_{i21}, w_{i22}, \ldots, w_{i27}$$

$$W_{i3} = w_{i31}, w_{i32}, \ldots, w_{i37}$$

$$W_{i4} = w_{i41}, w_{i42}, \ldots, w_{i47}$$

follow a multivariate normal distribution within the general linear mixed effects framework. Simultaneous simulation of four repeatedly measured continuous blood pressure outcomes (SBP_{WRA}, DBP_{WRA}, SBP_{SAC} and DBP_{SAC}), for maternal-child pair, was implemented using the following set of ingredients: Let $X_i \in (0, 1)$ be an indicator denoting assignment to two treatment sequences with an equal allocation ratio, where assignment is generated using $X_i \sim \text{Bern}(0.5)$;

vector of parameters for the fixed effects

$$\beta = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{bmatrix}$$

where,

$$\beta_1 = \begin{bmatrix} 122.8000 & -1.5202 & 1.5155 & 0.7391 & -0.5579 & 0.5670 \end{bmatrix}^T,$$

$$\beta_2 = \begin{bmatrix} 75.9594 & -0.6328 & -0.0443 & 1.2296 & -1.0757 & 1.6276 \end{bmatrix}^T,$$

$$\beta_3 = \begin{bmatrix} 79.9301 & -1.9449 & 2.4154 & 2.8466 & -1.0683 & 0.8824 \end{bmatrix}^T,$$

$$\beta_4 = \begin{bmatrix} 78.2049 & -2.6441 & 3.0212 & -0.1231 & 0.1109 & -0.6555 \end{bmatrix}^T;$$

variance-covariance matrix of the random effects

$$G = \begin{bmatrix} G_1 & 0 & 0 & 0 \\ 0 & G_2 & 0 & 0 \\ 0 & 0 & G_3 & 0 \\ 0 & 0 & 0 & G_4 \end{bmatrix}$$

where,

$$G_1 = \begin{bmatrix} 97.9956 & -8.3895 & 3.7696 \\ -8.3895 & 3.5714 & -3.8839 \\ 3.7696 & -3.8839 & 6.1758 \end{bmatrix},$$

$$G_2 = \begin{bmatrix} 48.7846 & -2.1354 & 0.0418 \\ -2.1354 & 1.8259 & -2.2249 \\ 0.0418 & -2.2249 & 3.7287 \end{bmatrix},$$

$$G_3 = \begin{bmatrix} 122.8400 & -31.3064 & 36.2701 \\ -31.3064 & 13.6510 & -15.8098 \\ 36.2701 & -15.8098 & 19.2251 \end{bmatrix},$$

$$G_4 = \begin{bmatrix} 51.2783 & -6.1942 & -0.2157 \\ -6.1942 & 0.6549 & 1.2444 \\ -0.2157 & 1.2444 & 0.0000 \end{bmatrix};$$

and the residual error components

$$\Sigma = \begin{bmatrix} \sigma_1 & 0 & 0 & 0 \\ 0 & \sigma_2 & 0 & 0 \\ 0 & 0 & \sigma_3 & 0 \\ 0 & 0 & 0 & \sigma_4 \end{bmatrix}$$

where,

$$\sigma_1 = 35.1327, \sigma_2 = 21.0231, \sigma_3 = 178.6400, \sigma_4 = 160.9300.$$

Clinical trials with cross-over designs often have small samples sizes. With additional random effects, our proposed PLME method (see equation 4) has a large number of parameters compared to the widely used JKME method (see equation 2). Therefore, we sort to evaluate the stability (including convergence) of the estimation in small and medium sample sizes allowing for estimation of equal number of parameters. The data-generating mechanism adopted the following scenarios: small ($n = 10$) and medium ($n = 50$) sample sizes with unstructured covariance for the random effects. As previously reported by Burton et al. (2006), two common replicates used in simulation studies include; $c_{sim} = 500$ and $c_{sim} = 1000$. Owing to the large number of parameters for estimation both in PLME and JKME models, we opted for the former, mainly to keep computing time within a reasonable limit. Five hundred replicates were done under each sampling scenario. The fixed- and random-effects parameters used in the simulation process were estimated from the univariate PLME model applied to the real-life data introduced in Section 2 (R simulation code can be accessed upon request).

5.1 Modeling Simulation Data

Analysis of the simulated data was adjusted accordingly to address two commonly encountered modeling challenges, namely, (1) problem of the data and/or (2) complexity in model specification. We fitted a mixed-effects model with unstructured covariance of the random effects, across the two candidate models (PLME and JKME), for which estimates were computed. For a start, the fixed effects part of the model included time, treatment and period with interaction terms, while the random effects part included random intercept and slope. Convergence was satisfied for both models in real-life data settings. The same model structure was fitted to the simulated datasets where convergence problems and other warnings were checked (SAS analysis codes and simulated datasets can be accessed upon request).

5.2 Estimands

Differences in predicted means for each simulated outcome between high-dose (H) and low-dose (L) Iodized household salt for mothers and children were considered as estimands (θ), representing treatment effect in a randomised cross-over trial. The parameters were based on effect size, defined by differences in SBP_{WRA}, DBP_{WRA}, SBP_{SAC} and DBP_{SAC} for participants consuming low-dose ($T_{ij} = 0$) and high-dose ($T_{ij} = 1$) Iodized salt, during first and second periods in a randomised sequence. Table 11 shows values for the two candidate models, estimated from real-life data.

5.3 Performance Measures

The term "performance measure" describes a numerical quantity used to assess the performance of a method. The performance measures required in a simula-

Table 11: Parameter estimates for difference in means of each outcome

		PLME model				JKME model			
		95% CI				95% CI			
Random effect	Outcome	Δ_{H-L}(SE)	LCL	UCL	p value	Δ_{H-L}(SE)	LCL	UCL	p value
Intercept	SBP_{WRA}	-0.557(0.518)	-1.572	0.458	>0.05	-0.366(0.411)	-1.172	0.440	>0.05
	DBP_{WRA}	-1.095(0.382)	-1.844	-0.346	≤0.05	-0.738(0.315)	-1.356	-0.120	≤0.05
	SBP_{SAC}	-0.982(0.957)	-2.858	0.894	>0.05	-0.438(0.891)	-2.184	1.308	>0.05
	DBP_{SAC}	0.025(0.817)	-1.577	1.627	>0.05	0.928(0.720)	-0.484	2.340	>0.05
Intercept and slope	SBP_{WRA}	-0.569(0.594)	-1.734	0.596	>0.05	-0.365(0.398)	-1.146	0.416	>0.05
	DBP_{WRA}	-1.103(0.446)	-1.978	-0.228	≤0.05	-0.680(0.312)	-1.291	-0.069	≤0.05
	SBP_{SAC}	-0.973(0.942)	-2.818	0.872	>0.05	-0.432(0.886)	-2.169	1.305	>0.05
	DBP_{SAC}	0.079(0.820)	-1.528	1.686	>0.05	0.909(0.760)	-0.580	2.398	>0.05

PLME - Piecewise linear mixed effects; JKME - Jones & Kenwards mixed effects;
Δ_{H-L} - Estimand
95% CI - 95% confidence interval; LCL - Lower confidence limit; UCL - Upper confidence limit

tion study depend on the aims and targets for the study. When the target is an estimand, the most obvious performance measure to consider is bias. Precision and coverage of confidence intervals will also be of interest. A simulation study targeting an estimand may of course also assess power and type I error (Morris et al., 2019).

Our study focusses on seven measures to evaluate performance of the proposed PLME model against JKME model. These include; proportion of samples meeting convergence criteria, proportion of samples with random effects matrix G turning positive definite, proportion of samples with Hessian matrix H turning positive definite, bias of the estimator, mean standard error of the estimator, coverage probability (Cp) and empirical power (Ep).

Cp is the proportion of samples drawn from a sampling distribution for which the (known) population parameter is contained in the specified confidence interval (CI). The CI often has the form $\xi \pm \tau(\alpha, n)$, where ξ is an unbiased estimate of the parameter and $\tau(\alpha, n)$ is a width that depends on the significance level α, the sample size n, and the standard error of the estimate. The degree of certainty pre-specified by the analyst, referred to as the confidence level or confidence coefficient of the constructed interval, is effectively the nominal coverage probability of the procedure for constructing confidence intervals. The nominal coverage probability is often set at 0.95. A CP estimate closer to the nominal coverage probability is desired for a given estimator model. If all assumptions used to derive the confidence interval are met, nominal coverage equals CP. If any of the assumptions are not met, the CP may be smaller or larger than the nominal probability of application. When the CP is greater than the nominal coverage probability, the interval is called a conservative (confidence) interval;

when it is less than the nominal coverage probability, the interval is called a "non-conservative" or "acceptable" interval.

Ep of the design is the fraction of datasets with p-values smaller than or equal to 0.05 across the simulation runs (B. F. Arnold et al., 2011). This measure is key when the simulation study targets hypothesis testing. The higher the fraction the better for a given design. From the analysis of empirical (real-life) data, the direction of p-value corresponding to specific estimand (effect size) are shown in Table 11. This direction forms the basis of EP calculation in our study.

5.4 Simulation Results

The analysis was commenced by fitting models (2) and (4); for JKME and PLME models respectively, with random intercept and slope. Even though convergence criteria were met in all 500 simulated datasets across all sampling scenarios, the specified structure was complex to fit, in relatively high proportion of simulated datasets. While estimating variance-covariance matrix (G) and Hessian matrix (H) for this datasets, some variance components turned negative hence were forced to zero.

The concept of negative variance components in linear mixed-effects models has received considerable attention in the literature (Chernoff, 1954; Nelder, 1954). Broadly, negative variance components in linear mixed models are allowable if inferences are restricted to the implied marginal model (Verbeke & Molenberghs 2000). Hierarchical models arise where outcomes are modeled conditional upon covariates and random effects (Diggle et al. 2002, Molenberghs & Verbeke 2005). When a hierarchical view-point is adopted, in the sense that outcomes are specified conditionally upon random effects, the variance-covariance matrix of the random effects must be positive-definite (positive-semi-definite is also possible, but raises issues of degenerate distributions). Molenberghs & Verbeke (2011) further reviewed negative variance components in linear mixed models. Oliveira et al. (2017) highlights that whenever inference for variance components is required, one has to choose between a hierarchical and a marginal view. Under a marginal interpretation, the variance component can be negative as long as the resulting marginal variance-covariance matrix of the observations is positive definite. On the other hand, when a hierarchical view is adopted, random effects retain their interpretation and, hence, their variances must be non-negative.

The performance measures seen in our review are summarised in Table 12. Notably, analysis of all simulated datasets met convergence criteria, with H matrix turning positive-definite for both PLME and JKME models. Upon fitting a complex model with random intercept and slope, a high proportion of samples with estimated G matrix turning non-positive definite was reported. The JKME model had a problem fitting 98.8% of the small sample datasets compared to

32.2% for the PLME model. Similarly, the JKME model had a problem fitting 99.8% of the medium sample datasets, compared to none for the PLME model. To overcome the problem associated with estimated G matrix, we resolved the model complexity by specifying one random effect (intercept only). Both PLME and JKME models performed better with a less complicated model. Nonetheless, a finite proportion of sampled datasets (1.2%) turned non-positive definite in both models.

Assessment of bias revealed that PLME model yielded relatevely low estimates compared to JKME model across all four outcomes, consistent across two sampling scenarios. However, the converse was true with respect to mean square error (MSE). JKME model yielded low MSE estimates compared to PLME model across all outcomes, consistent in both sampling scenarios.

CP estimates across all the candidate models were $> 70\%$, ranging from 72.4% to 95.8%. Compared to the nominal coverage probability of 95%, the actual coverage probability both in PLME and JKME models was relatively low in three parameters (SBP_{WRA}, DBP_{WRA} and SBP_{SAC}), implying that the confidence interval was "non-conservative" or "acceptable". This could be due to low standard errors and/or reduced number of repetitions. In small sample scenario with random intercept only, the JKME model performed better than PLME model by approximately 3.5%, in SBP_{WRA}, DBP_{WRA} and SBP_{SAC} outcomes, but same performance in DBP_{SAC} outcome. Similarly, in small sample scenario with random intercept and slope, the JKME model performed better than PLME model by approximately 2.7%, in SBP_{WRA}, DBP_{WRA} and SBP_{SAC} outcomes. Nonetheless, in DBP_{SAC} outcome, the PLME model performed better than JKME model by 5.4%. In medium sample scenario with random intercept and slope, the JKME model performed comparable to PLME model, with marginal increase by approximately 1.3%, in SBP_{WRA}, DBP_{WRA} and SBP_{SAC} outcomes. However, in DBP_{SAC} outcome the PLME model performed significantly high than JKME model by 45.8%.

Results from the analysis of Ep revealed inconsistent inference across different outcomes and scenarios. In small sample scenario with random intercept only, the JKME model performed better than PLME model, with an increase by 2.8% in SBP_{WRA} and by approximately 7.0% in SBP_{SAC} and DBP_{SAC} outcomes. However, in DBP_{WRA} outcome the PLME model performed higher than JKME model by 11.6%. In small sample scenario with random intercept and slope, the JKME model performed better than PLME model by approximately 2.7%, in SBP_{WRA} and DBP_{SAC} outcomes and by 7.4% in SBP_{SAC}. However, the PLME model performed higher than JKME model by 8.2% in DBP_{WRA}. Similarly, in medium sample scenario with random intercept and slope, the JKME model performed better than PLME model by approximately 5.8%, in SBP_{WRA}, SBP_{SAC} and DBP_{SAC} outcomes. However, the PLME model performed significantly higher than JKME model by 30.4% in DBP_{WRA}.

Table 12: Performance measures for the PLME and JKME models

Performance measures	Outcome	N=10, Random I		N=10, Random I and S		N=50, Random I and S	
		PLME	JKME	PLME	JKME	PLME	JKME
Median computation time, in minutes (Minumum-Maximum)		18(15-62)	17(15-69)	22(16-63)	26(16-63)	56(53-194)	112(54-196)
% of datasets meeting convergence criteria		100	100	100	100	100	100
% of datasets with G matrix turning positive-definite		98.8	99.2	67.8	1.2	100	0.2
% of datasets with H matrix turning positive-definite		100	100	100	100	100	100
Bias	SBP_{WRA}	0.004	0.008	0.012	0.025	0.033	-0.011
	DBP_{WRA}	-0.009	0.115	0.006	0.097	0.058	0.117
	SBP_{SAC}	-0.258	-0.465	-0.259	-0.424	-0.077	-0.302
	DBP_{SAC}	0.147	-0.945	0.074	-0.914	0.006	-0.968
MSE	SBP_{WRA}	2.178	1.384	2.573	1.540	0.388	0.222
	DBP_{WRA}	1.191	0.839	1.344	1.122	0.230	0.166
	SBP_{SAC}	6.665	4.651	7.326	4.351	1.388	0.880
	DBP_{SAC}	1.803	1.599	1.836	0.938	0.281	1.060
Coverage probability (%)	SBP_{WRA}	82.0	86.0	79.0	81.0	87.6	90.2
	DBP_{WRA}	85.8	88.0	82.8	85.6	85.4	85.6
	SBP_{SAC}	73.6	77.6	72.4	75.6	76.4	77.4
	DBP_{SAC}	92.4	92.4	94.0	88.6	95.8	50.0
Emperical power (%)	SBP_{WRA}	81.2	84.0	77.6	80.8	73.6	79.6
	DBP_{WRA}	32.4	20.8	33.4	25.2	77.0	46.6
	SBP_{SAC}	69.0	76.2	66.6	74.0	59.2	66.6
	DBP_{SAC}	92.4	99.2	93.8	96.0	95.6	99.6

6 Concluding remarks

We sought to extend the proposed model by Mwangi et al. (2021) allowing flexible piecewise models for six outcomes to depend on separate random effects, which are themselves correlated. We formulated a piecewise linear mixed effects (PLME) model and the Jones & Kenward mixed effects (JKME) model within univariate settings, with further extentions to the joint modeling framework, using pairwise fitting approach (Fieuws & Verbeke, 2006; Fieuws et al., 2007). We estimated the separate and joint effects of covariates on six outcomes from an empirical real-life data set collected during a double blind randomized crossover trial conducted in Kenya, to compare the effect of high-dose and low-dose Iodized household salt on systolic and diastolic blood pressure in women of reproductive age and their household matching pair of school aged children. We examined the association between blood pressure and urinary Iodine concentration by estimating the strength of association among the outcomes using a correlated random effects joint model. We implemented the PLME model in univariate and multivariate settings, allowing all possible random effects with satisfactory model convergence. To validated the results from the multivariate joint PLME model, we compared our findings with those obtained from the current state-of-the-art Jones & Kenward (2014) methodology for analyzing randomized crossover trials. Upon fitting the main fixed effects, with random intercepts only, the multivariate joint PLME model yielded similar results to the multivariate joint JKME model.

We further sought to evaluate the performance of our proposed PLME model against the widely used JKME model, within the multivariate joint modeling framework through a simulation study mimicking a 2×2 crossover design. From our findings, the multivariate joint PLME model performed exeptionally well both in estimation of random effects matrix (G) and hessian matrix (H), allowing satifactory model convergence during estimation. It allowed a more complex fit to the data with both random intercepts and slopes effects compared to the multivariate joint JKME model that allowed for random intercepts only. When a hierarchical view-point is adopted, in the sense that outcomes are specified conditionally upon random effects, the variance-covariance matrix of the random effects must be positive-definite (Oliveira et al., 2017). The multivariate joint PLME model is prefered especially in modeling increased number of random effects, compared to multivariate joint JKME model that works equally well with random intercepts only. In some cases, additional random effects could explain much variability in the data, thus improving precision in estimation of the estimands (effect size) parameters.

The key highlight demonstrated in this evaluation shows that multivariate joint JKME model is a powerful tool especially while fitting mixed models with random intercepts only. Addition of random slopes may lead to model compexities in some cases, resulting in unsatifactory model convergence during estimation. To circumvent convergence pitfalls, extention of JKME model to

PLME model allows a more flexible fit to the data (generated from crossover design settings), especially in the multivariate joint modeling framework.

The time variable t_j used in our analysis is of continuous type, in which case only monotonic increase (or decrease) over time was considered. In a simple linear mixed model, it is possible to include higher-order terms or time points as categorical variables. The assumption of a linear relationship is without loss of generality as one can easily extend the models with, e.g., polynomial terms or add dummy variables to allow for non-linear trends. However, with a complex model such as the PLME model, this may be difficult from the viewpoint of model stability. Hence the assumption of the model may be too strong where non-monotonic increase (or decrease) over time t_j is considered. This could be an interesting topic for further study.

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8 Conflict of Interest

The authors have declared no conflict of interest.

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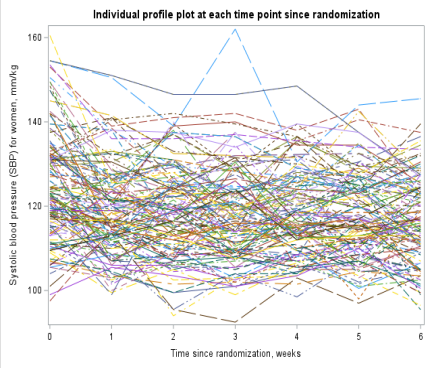
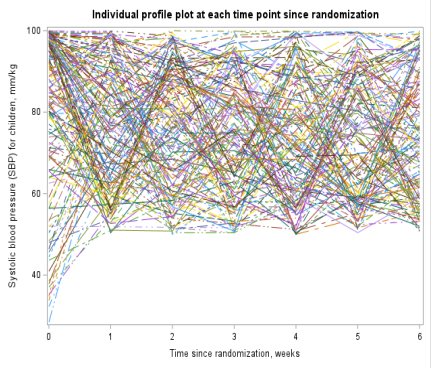
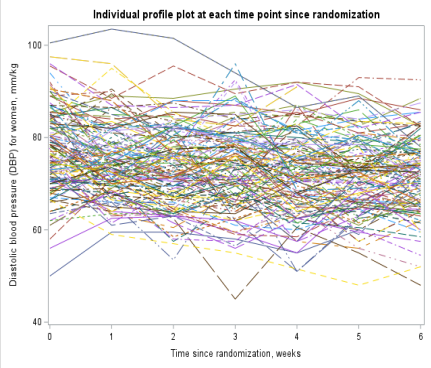
Appendix 1: Variables description

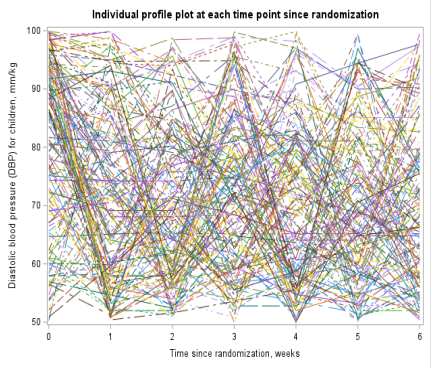
Variable	Description	Type	Value/Label/Range
Pno	Participant identification number	Discrete	1 - 174
Time	Time since randomization in weeks	Discrete	0 - 6
Sequence	Treatment sequence	Binary	0=High-to-Low dose, 1=Low-to-High dose
Treatment	Treatment arm	Binary	0=Low-dose Iodine, 1=High-dose Iodine
Period	Treatment period	Binary	0=Period 1, 1=Period 2
SBP_{WRA}	Systolic Blood Pressure for women of reproductive age in $mmHg$	Continuous	92.5 - 162.0
DBP_{WRA}	Diastolic Blood Pressure for women of reproductive age in $mmHg$	Continuous	45.0 - 103.5
UIC_{WRA}	Urinary iodine concentration for women of reproductive age in $\mu g/L$	Continuous	0.83 - 3142.58
SBP_{SAC}	Systolic Blood Pressure for school aged children in $mmHg$	Continuous	28.43 - 100.00
DBP_{SAC}	Diastolic Blood Pressure for school aged children in $mmHg$	Continuous	50.00 - 99.99
UIC_{SAC}	Urinary iodine concentration for school aged children in $\mu g/L$	Continuous	0.46 - 2195.76
BMI_{WRA}	Body mass index for women of reproductive age at baseline in Kg/M^2	Continuous	14.46 - 37.04
Age_{WRA}	Age for women of reproductive age at baseline in years	Discrete	15 - 49
BAZ_{SAC}	Body mass index for age z-score for school aged children at baseline	Continuous	-3.21 to 1.04
Age_{SAC}	Age for school aged children at baseline in months	Discrete	96 - 144

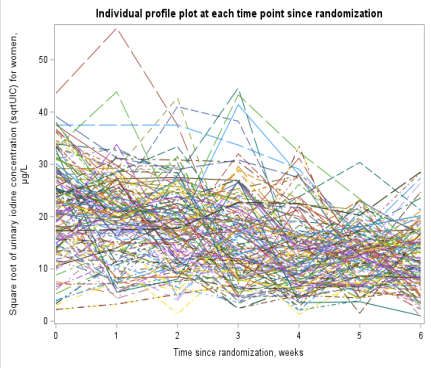
Appendix 2: Individual Profiles

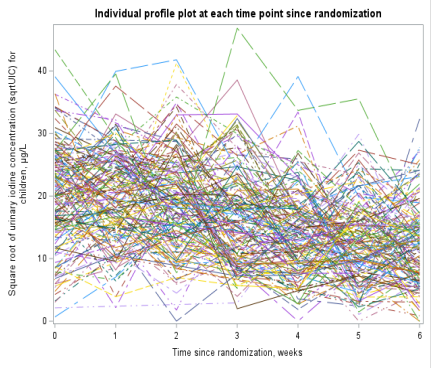












Appendix 3: Variance-covariance estimates with correlation coefficients for the random effects and residual (error) component in the multivariate model

Model		PLME model						JKME model					
Measure		Variance-covariance estimate for the random effects											
Population		WRA			SAC			WRA			SAC		
	Outcome	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$	SBP_I	DBP_I	$sqrtUIC_I$
WRA	SBP_I	70.06	42.15	-2.04	15.09	8.72	3.16	70.13	42.07	-2.26	15.24	9.00	2.94
	DBP_I	42.15	39.77	-0.26	2.39	4.77	1.33	42.07	39.66	-0.14	2.38	4.85	1.44
	$sqrtUIC_I$	-2.04	-0.26	12.00	0.83	-1.58	7.48	-2.26	-0.14	11.78	0.45	-2.27	7.20
SAC	SBP_I	15.09	2.39	0.83	49.17	19.95	-3.23	15.24	2.38	0.45	49.40	20.45	-3.38
	DBP_I	8.72	4.77	-1.58	19.95	22.10	-4.20	9.00	4.85	-2.27	20.45	22.55	-4.58
	$sqrtUIC_I$	3.16	1.33	7.48	-3.23	-4.20	8.81	2.94	1.44	7.20	-3.38	-4.58	8.55
Measure		Correlation coefficient for the random effects											
WRA	SBP_I	1	0.798	-0.070	0.257	0.222	0.127	1	0.798	-0.079	0.259	0.226	0.120
	DBP_I	0.798	1	-0.012	0.054	0.161	0.071	0.798	1	-0.007	0.054	0.162	0.078
	$sqrtUIC_I$	-0.070	-0.012	1	0.034	-0.097	0.728	-0.079	-0.007	1	0.019	-0.139	0.717
SAC	SBP_I	0.257	0.054	0.034	1	0.605	-0.155	0.259	0.054	0.019	1	0.613	-0.164
	DBP_I	0.222	0.161	-0.097	0.605	1	-0.301	0.226	0.162	-0.139	0.613	1	-0.330
	$sqrtUIC_I$	0.127	0.071	0.728	-0.155	-0.301	1	0.120	0.078	0.717	-0.164	-0.330	1
Measure		Variance-covariance estimate for the residual (error) component											
WRA	SBP_I	42.73	17.67	0.99	1.45	3.02	-0.78	42.34	17.80	1.35	1.53	3.04	-0.39
	DBP_I	17.67	24.64	0.06	3.88	4.63	-0.45	17.80	24.76	0.06	3.99	4.72	-0.53
	$sqrtUIC_I$	0.99	0.06	44.33	-6.07	4.30	16.25	1.35	0.06	43.82	-6.09	4.03	15.73
SAC	SBP_I	1.45	3.88	-6.07	197.83	52.80	2.17	1.53	3.99	-6.09	197.97	52.74	2.11
	DBP_I	3.02	4.63	4.30	52.80	169.94	-1.12	3.04	4.72	4.03	52.74	169.52	-1.45
	$sqrtUIC_I$	-0.78	-0.45	16.25	2.17	-1.12	44.43	-0.39	-0.53	15.73	2.11	-1.45	43.95
Measure		Correlation coefficient for the residual (error) component											
WRA	SBP_I	1	0.545	0.023	0.016	0.035	-0.018	1	0.550	0.031	0.017	0.036	-0.009
	DBP_I	0.545	1	0.002	0.056	0.072	-0.014	0.550	1	0.002	0.057	0.073	-0.016
	$sqrtUIC_I$	0.023	0.002	1	-0.065	0.049	0.366	0.031	0.002	1	-0.065	0.047	0.358
SAC	SBP_I	0.016	0.056	-0.065	1	0.288	0.023	0.017	0.057	-0.065	1	0.288	0.023
	DBP_I	0.035	0.072	0.049	0.288	1	-0.013	0.036	0.073	0.047	0.288	1	-0.017
	$sqrtUIC_I$	-0.018	-0.014	0.366	0.023	-0.013	1	-0.009	-0.016	0.358	0.023	-0.017	1

WRA - Women of reproductive age; SAC - School aged children