HHS Public Access

Author manuscript

Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Arthritis Care Res (Hoboken). 2020 May ; 72(5): 615–621. doi:10.1002/acr.23881.

An Application of Traditional and Emerging Methods for the Joint Analysis of Repeated Measurements with Time-to-Event Outcomes in Rheumatology

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Abstract

Objective: The goal of this paper is to describe approaches for the joint analysis of repeatedly measured data with time-to-event endpoints, first separately and then in the framework of a single comprehensive model, emphasizing the efficiency of the latter approach. Data from the Johnston County Osteoarthritis Project (JoCo OA) will be used as an example to investigate the relationship between the change in repeatedly measured body mass index (BMI) and the time-to-event endpoint of incident worsening of radiographic knee OA that was defined as an increased Kellgren-Lawrence (K-L) grade in at least one knee over time.

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Conflict of interest: There were no financial support or other benefits from commercial sources for the work reported in the manuscript, or any other financial interests of any of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

Methods: First, we provide an overview of the methods for analyzing repeated measurements and time-to-event endpoints separately. Then, we describe traditional (Cox proportional hazards model, CoxPH) and emerging (joint model, JM) approaches allowing combined analysis of repeated measures with a time-to-event endpoint in the framework of a single statistical model. Finally, we apply the models to JoCo OA data, and interpret and compare the results from the different approaches.

Results: Applications of JM (but not CoxPH) showed that the risk of worsening radiographic OA is higher when BMI is higher or increasing, thus illustrating the advantages of JM for analyzing such dynamic measures in a longitudinal study.

Conclusion: Joint models are preferable for simultaneous analyses of repeated measurement and time-to-event outcomes, particularly in a chronic disease context, where dependency between the time-to-event endpoint and the longitudinal trajectory of repeated measurements is inherent.

Keywords

repeated measurements; longitudinal data; time-to-event; joint models

Introduction

Longitudinal studies in which data are collected on participants over years or even decades have become increasingly popular in many epidemiological fields. Such studies enable the analysis of individual-level changes, represented by repeatedly measured variables, and relate the changing patterns to the development of conditions or diseases causing disability and death. Despite the advantages of having multiple time points, there are several challenges associated with longitudinal data analysis, including non-ignorable missing data and sparse examination times (1–4).

In addition, to monitor risk factors and health outcomes, these studies collect repeated measurements that can encompass different types of variables. Two of these, longitudinally measured variables (e.g., biomarkers, patient-reported outcome measures) and the time to occurrence of an event (e.g., joint replacement, death), are very common in epidemiological studies. These two types of data are often analyzed separately, without considering that longitudinal and survival processes are related (5). However, in a chronic disease context, dependency between time-to-event outcomes and longitudinal trajectories is inherent. The essential characteristic of such chronic conditions is that the course of disease is different from one person to another and can change over time for the same person. The repeatedly measured variables can help in understanding the nature of disease progression and provide better estimation of the risk for the event of interest (e.g., death, development or progression of disease, or hospital discharge after surgery).

Investigation of such longitudinal relationships between repeatedly measured variables and the event of interest can provide clinically relevant information about the likely course of disease in a given person. For example, to optimize treatment strategies in early rheumatoid arthritis (RA), it is important to understand the relationship between disease activity over time, represented by longitudinal DAS-28 measurements, and time to subsequent

radiographic joint damage. To evaluate the impact of the longitudinal response trajectory on the time-to-event outcome of interest *over time*, the data should be analyzed jointly (6). This is because neither the changes in evolution of longitudinal response (e.g., DAS-28) nor the risk for event (e.g., radiographic progression of RA) are observable *continuously* over time, only *intermittently* during clinic visits. Such analyses require statistical methodology that can relate these unobservable values both to each other and to observable data. However, epidemiological analyses for various chronic diseases, including rheumatic and musculoskeletal disease (RMDs), which might benefit from jointly using these data, often do not utilize this approach. This didactic paper on the use of joint models in rheumatology is therefore designed to provide an example of this methodology in a field where these models are not yet commonly used, despite their appropriateness.

The main goals of this paper are to (1) describe mainstream statistical approaches for the analysis of such data, (2) convince the reader of the advantages of joint analysis of longitudinal measures with time-to-event outcomes, and (3) demonstrate how to apply these methods in a real and relevant dataset, using data from the Johnston County Osteoarthritis Project (JoCo OA). First, we review the methods for analyzing time-to-event and repeated measurements outcomes separately. Then we describe traditional (the Cox proportional hazards model) and emerging (joint model) approaches allowing combined analysis of repeated measures with time-to-event outcomes in the framework of a single, comprehensive statistical model. Finally, we apply the models to the JoCo OA data, and then interpret and compare the results from the different approaches.

Overview of statistical models

Repeated Measurements and Linear Mixed Effects Model

The linear mixed effects model, or LMM, is a commonly used approach for analysis of repeated measurements (7). The term “mixed” refers to the fact that both fixed and random effects are included in the same model, where fixed effects relate to the mean cohort trajectory, and random effects are individual-specific characteristics that take into account the variability in individual trajectories within a cohort. LMM is valid under the assumption that the data are missing at random (8), which means that missing data can depend on some baseline characteristics and non-missing observations of the outcome at previous visits. Since this might be assumed in many situations where missingness is not associated with the outcome of interest, the use of LMM is justified in such applications. However, when attrition (for example, due to death, worsening of symptoms, or ineligibility of the participant) depends on missing data, e.g., is “informative”, the data are called “missing not at random.” In this situation, as the data collection is discontinued for such a person, leading to informative missingness, modeling the evolution of the longitudinal response using LMM may produce biased estimates (2, 3, 9).

Analysis of time-to-event data

When the main outcome under assessment is the length of the interval from the time origin until the occurrence of the event of interest (e.g., survival time until death), an appropriate methodology is required, as these data have unique properties that cannot be addressed with

standard statistical procedures. First, methods based on the normal distribution are not applicable for the analysis of survival times because they tend to be positively skewed, leading to violation of the normality assumption. Second and even more important, it is common that at the end of a study the actual survival times will often be censored, i.e., they are not observed for all individuals. The most common type of censoring, and the focus in this paper, is “right censoring” that occurs when a participant does not experience the event of interest by the end of his/her study follow-up.

The Cox proportional hazards model (CoxPH) (10) is one of the most commonly used approaches for analysis of time-to-event outcomes. In this model, the measure of interest is a ‘hazard’, which is the instantaneous risk of the event given that a person has not experienced this event up to a specific time. CoxPH allows the analysis of the effect of one or more explanatory variables that may impact the hazard. Predictors that do not change over time are called time-independent variables and are among the most commonly analyzed in CoxPH. These predictors often include baseline measurements (e.g., exposure variables, risk factors, covariates, and/or confounders) or variables that do not change over time (e.g., sex, race, or a birth cohort).

The CoxPH model can also be extended to incorporate important explanatory variables that do change over the follow-up time period (11, 12). This extension, CoxPH with time varying covariates (TVCs), offers the opportunity to analyze data collected at different follow-up times for the same individual. In this model, a TVC is assumed to remain constant between two observations. Therefore, this model is appropriate for variables that either change in a known way (e.g., age, the dose of an administered drug,) or exist independently of individuals (e.g., air pollution levels) (13). These covariates can be associated with the risk for the event, but are independent of an individual’s time-to-event outcome.

However, the CoxPH with TVCs has limited ability to handle explanatory variables with fluctuation and measurement errors (14). As an illustration, consider how longitudinal measurements of BMI are handled in the CoxPH with TVCs. To obtain the value of BMI, both weight and height need to be measured. Although height is largely stable in the adult population, weight is subject to daily, weekly and seasonal variability due to fluid balance, food consumption and other factors such as physical exertion and external temperature (15, 16). Measurement errors due to clothing and the calibration of the scale can lead to additional small fluctuations in weight and height. The intervals between visits might be intermittent, spanning a few weeks up to several years. In the CoxPH with TVCs, a value of BMI, observed and recorded only at a specific time, is assumed to remain constant between two visits and may be associated with the risk of the event at future time points until the next visit, as shown graphically in Figure 1. The blue dashed line in the bottom panel corresponds to the approximation of BMI trajectory in the Cox model, which is not a realistic description of the BMI evolution. Application of the CoxPH model to “internal” TVCs that can be collected only when the individual is available (such as variables measured with errors and not fully observed) can lead to biased results and incorrect inference (14, 17). Two approaches, developed in parallel in different scientific areas and for different purposes, can capture the biological fluctuations and heterogeneity in longitudinal trajectories: stochastic process models (18–20) and joint models (21). In the next sections, we focus on the latter

approach, which is more mainstream in biostatistics and thus may be easier to use for those familiar with LMM and CoxPH. Review and discussion of stochastic process models can be found elsewhere (19).

Joint Model

A joint model (JM) consists of two sub-models representing the dynamics of (a) the longitudinal sub-model and (b) the time-to-event sub-model, as reviewed elsewhere (6, 21–24). The fundamental difference between the JM and the CoxPH with TVCs is that, unlike CoxPH, the JM combines the time-to-event model with an appropriate model for the repeated measurements of TVCs to *simultaneously* make inference on time-to-event and longitudinal processes. The JM technique is more appropriate than CoxPH with TVCs if there is interest in the effect of a TVC measured with error on the survival process. This is because the CoxPH with TVCs can severely underestimate the association between longitudinal and time-to-event data (17). In a standard specification of JM, at each time point the risk of event is associated with an unobserved value of the longitudinal outcome at the same time (Figure 1, red solid line). These are usually called the “true” values, as opposed to the “observed” longitudinal data (collected intermittently and potentially with errors), which are represented in the longitudinal sub-model as a sum of such unobserved “true” values and errors (usually modeled using LMM). The flexibility in parameterization of JM (e.g., through various extensions available in the R package JM(25)) allows incorporating not only the current value, but also dynamic characteristics of the longitudinal response in the model, e.g., the rate of change, cumulative history, or deviations from population trajectories (5). The survival process can depend on the current slope of the longitudinal trajectory (Figure 1, red arrows) to capture the situation where two individuals have comparable levels of a biomarker, but the rate of change is different and affects the risk of an event. We use the term “current” for both slope and value, meaning that the risk for an event at a particular time depends on the concurrent unobserved value of longitudinal outcome as well as the concurrent value of the slope of the true longitudinal trajectory. Alternatively, cumulative effects parameterization allows the entire history of a longitudinal response to be associated with the hazard of event.

Although JMs are becoming increasingly popular in different epidemiologic fields such as oncology (26, 27), cardiovascular diseases(28), nephrology(29), and endocrinology(30), these models are still not widely applied in rheumatology. Recently, JM was applied to a sample of seropositive arthralgia patients to investigate whether a change in individual levels of antibodies to citrullinated proteins/peptides (ACPAs) over time improves the prediction of future RA (31). Higher time-dependent ACPA levels were found to be significantly associated with the development of arthritis, but no difference over baseline measurements of ACPA levels was shown in predictive models.

In our working example, we use repeatedly measured BMI, which is a useful indicator of obesity, to investigate the effect of the longitudinal trajectory of BMI on the time-to-event outcome of worsening K-L grade in the knee. We chose this relationship given that 1) obesity is one of the most important knee OA risk factors (32); 2) BMI is a good example of a biomarker potentially measured with error; 3) BMI is a potentially modifiable risk factor;

4) the rate and direction of change in BMI may be as important as the value itself. Various parameterizations of JM can address known and previously discussed challenges in studying change in BMI and its effect on OA outcomes(33). We emphasize that most (if not all) of the challenges in dealing with repeatedly measured BMI and its change can be applied to other relevant variables in studying their impact on OA and other RMDs.

Working example

Data and measurements

The data used in this paper were collected from non-Hispanic African American and Caucasian men and women enrolled in the JoCo OA which is an ongoing, longitudinal population-based prospective study with clearly defined and repeatedly measured radiographic OA, comorbidities, various biomarkers, socio-demographic and physiological variables (34). JoCo OA was designed to determine risk factors associated with the occurrence and progression of osteoarthritis (OA). Our final sample comprised 2,286 participants with 5,325 longitudinal measurements of BMI collected at four time-points: baseline and three follow-up visits (see Supplementary materials for the details on the selection procedure and for the baseline characteristics of this cohort). The time-to-event outcome, worsening radiographic OA (rOA) of the knee, was defined as an increase of one K-L grade or more from any baseline K-L score in at least one knee between two consecutive or intermittent visits. It is important to note that we include here a working example with a simplified analysis for brevity. In practice, other relevant covariates might be included in the analysis as appropriate.

Statistical analysis

The counting process form of the CoxPH model (12, 13) was used to evaluate the association of two TVCs, BMI and its change, with worsening knee rOA, with adjustment for baseline age and sex. The change in BMI was defined as percent change in BMI relative to a participant's measurement at the previous visit. We used hazard ratios (HR) as measures of these associations, and 95% confidence intervals (CI) were used to express the variation around the HRs.

We fitted several JMs using the R package JM(25). A full mathematical description of the models, variables transformation and interpretation of coefficients are provided in the Supplementary material. In short, the first (basic) model (JM1) consists of the linear mixed-effects model for longitudinal BMI data with normally distributed errors and a survival sub-model that specifies the hazard of event as a function of the "true" longitudinal outcome (see definition in "Joint Model" section) with adjustment for gender and age at the baseline. In the second joint model (JM2), the risk depends on the slope of the "true" trajectory at that time. In the third model (JM3), we assumed that the risk depends on both the current "true" level *and* the slope of BMI at the same time. JM3 allows us to capture the situations where participants have similar levels of BMI but different rates of change, with this difference affecting the risk of an event. Longitudinal BMI values were logarithmically transformed to satisfy assumptions of normality. In this case, one unit increase of current level of TVC, which is *log (BMI)* now, corresponds to 2.7 *fold* (a mathematical constant, the base of the

natural logarithm) difference in BMI. Therefore, HR quantifies how many times higher the risk of event is for the same participant if his/her BMI *at the same time* would be 2.7 *times* higher. To convert it to more interpretable terms, we calculated the HR for a difference of 25% in BMI at the same time for the same participant as follows. As a 25% (e.g., 1.25 fold) difference in BMI level corresponds to log (1.25) = 0.22 in log (BMI), the *HR for BMI* (Table 2) was calculated relative to 0.22 units difference in the current level of log (BMI) by taking the exponent of the corresponding coefficient multiplied by 0.22. For the longitudinal change of the BMI, we calculated the *HR for BMI slope* (Table 2) that compares an increase of 10% over time to an increase of 5% following the procedure previously described (29). The three JMs were compared using Bayesian Information Criterion (BIC) (35) to select the model with the best fit.

Results

In the CoxPH model with TVCs, higher BMI was associated with higher risk of worsening knee rOA (HR per 5 kg/m^2, 1.49; 95% CI, 1.42–1.55). We also found, counter-intuitively, that increasing BMI over time was negatively associated with worsening rOA; specifically, the risk decreased by 8% for each 5% increase in BMI over time (HR per 5%, 0.92; 95% CI, 0.89–0.95).

The results for JM analysis are shown in Table 1 representing the coefficients from the survival sub-model.

As previously mentioned, the corresponding coefficients can be interpreted in terms of percentage change rather than absolute change (see Supplementary materials). As shown in Table 2, JM1 finds the association between the current level of BMI and the risk for increase of K-L grade such that if a participant had a 25% higher BMI at the same time, the K-L grade risk was 1.4 times as high (HR, 1.39; 95% CI, 1.31–1.48). In JM2, the slope of BMI trajectory was found to have an association with incident increase in the K-L grade: if BMI increased by 10% each year, the risk for increase of the K-L grade is 4.6 times as high as compared to a 5% increase (HR, 4.59; 95% CI, 2.14–9.86). In JM3, both the current level (HR, 1.37; 95% CI, 1.29–1.46) and the slope of BMI (HR, 2.29; 95% CI, 1.20–4.36) were associated with worsening rOA. According to the BIC (Table 2), JM3 provided the best fit to the data compared to JM1 and JM2, providing evidence that the risk for an increase of the K-L grade depends on both the level and the slope of BMI at the current time.

Discussion

JM of longitudinal and time-to-event data continues as an emerging area of statistical research. In this paper, we demonstrated the usefulness and interpretability of the JM approach in rheumatology using OA, which is the most common form of arthritis and a leading cause of disability among adults in the USA(36, 37) and worldwide, as an exemplar. The association of body mass change over time in relation to OA is especially important as obesity is increasing in prevalence worldwide (38–41). While many studies have provided strong evidence that lowering body mass can reduce risk of OA development and progression (42–44), some have failed to demonstrate this effect potentially due to methodological difficulties in statistical analyses (33, 45). Our results using JM, but not

CoxPH, show that the risk of increasing K-L grade (i.e., worsening radiographic OA) is higher when BMI is increasing, illustrating the advantages of JM for such dynamic measures in a longitudinal study. We chose OA as an example to emphasize the importance of detailed modeling of longitudinal trajectories of patients outcomes, in particular in relation to development of an RMD that is strongly associated with older age (46) and frequently is slowly progressive. One can envision such individual trajectories as personal histories of change that led one individual to developing OA and allowed another one to avoid this health problem. Taking advantage of longitudinal design together with this methodology can improve our understanding of the mechanisms of development and progression of such conditions, which in turn can optimize diseases prevention and management strategies.

The JM approach can be applied to a very broad family of RMDs that affect people at almost any age. Application of JM to clinical questions in rheumatology may clarify why the course and the severity of symptoms of RMDs vary from patient to patient, and from time to time. In addition, these models provide a natural structure for dynamic individual predictions of longitudinal and time-to-event outcomes (47), which is important both from patient and health provider perspectives. In recent papers (48, 49) JMs were used as a tool for optimizing medical screening strategies, in particular the frequency of the screening procedures for people with different stages of disease, which may allow providers to choose the optimal screening schedule for individuals based on their longitudinal history. This approach could maximize benefits and minimize medical costs by avoiding unnecessary screenings and interventions.

Importantly, JMs are also being increasingly used in clinical trials that are crucial to advancements in new drug therapies. In this setting, dropout is a common problem and raises concerns of non-ignorable missing data, in particular if a participant leaves the study due to an adverse reaction or a lack of effectiveness of the treatment. As mentioned above, ignoring the mechanism of missingness can cause bias in estimates in LMM. Perhaps most notably, in the JM framework, dropout time can be considered as a survival outcome, while a longitudinal sub-model can be used to obtain valid inferences with the correction for non-ignorable dropout. Several papers have suggested that JM of longitudinal data and time to dropout not only provide unbiased estimates (6, 26), but also may require smaller sample sizes to achieve comparable power (50), both critical in driving the field forward to improve knowledge and health.

JMs also have some important limitations. First, JMs are computationally intensive and time consuming which might pose logistical challenges for researchers working with large data sets. Second, as with any statistical modeling, LMM and CoxPH (the two sub-models of JM) are based on specific assumptions, which should be properly tested. This prerequisite step becomes more critical when these models are being used jointly and should not be ignored. Our aim in this manuscript is to provide an introduction to the JM approach that is accessible for a clinical audience not necessarily familiar with advanced topics in mixed effects modelling and time-to-event analysis; we emphasize that collaboration with statistical experts in these methods is important in applying JMs in practice.

In summary, the potential applications of JM in RMDs is underappreciated, though these methods provide clear advantages over traditional approaches (while incorporating strengths from these methods). Software is readily available to facilitate applications of JM to address relevant research and clinical questions in a statistically rigorous and coherent fashion. We hope to stimulate interest in these models among RMD researchers, with increased benefits to society through its use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was funded in part by: CDC/SPH S043, S1734, S3486; NIAMS P60AR30701, P60AR049465, and P60 AR064166; CDC U01 DP003206 and U01 DP006266

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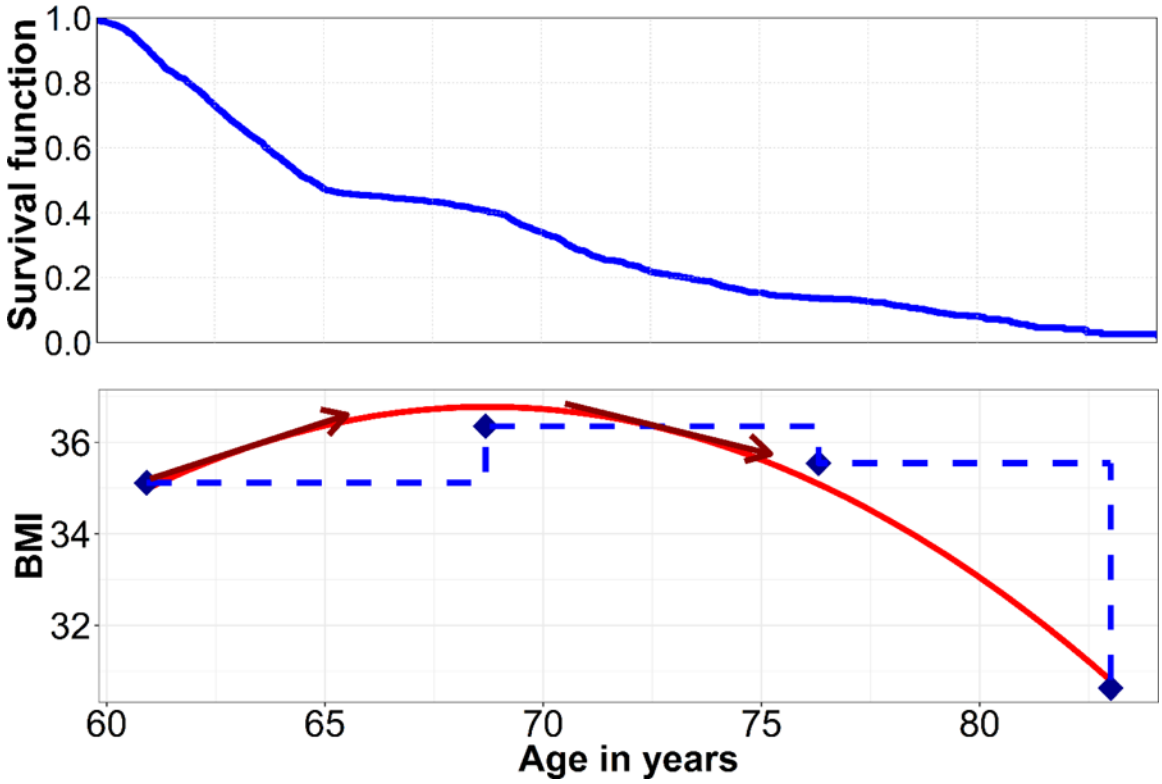

Figure1.
Graphical representation of features of the Joint Model

Table 1:

Three Joint Models for longitudinal BMI and/or longitudinal change in BMI with risk for incident worsening rOA of the knee fitted to JoCo OA data: Comparison under different parameterizations.

	JM1 (BIC = 2604.2)	**JM2 (BIC = 2688.7)**	**JM3 (BIC = 2602.8)**
Gender: male versus female	−0.08 (0.06)	−0.09 (0.06)	−0.09 (0.06)
Age at baseline[a] in years	**0.27 (0.03)**	**0.23 (0.03)**	**0.29 (0.03)**
Log (BMI)	**1.48 (0.14)**	*N/A*	**1.42 (0.14)**
slope of log (BMI)	*N/A*	**32.76 (8.38)**	**17.77 (7.09)**

The numbers in the table represent the coefficients with standard errors from the time-to-event sub-model.

rOA, radiographic OA

BMI, concurrent value of Body Mass Index

In JM1, the survival process depends on the level of BMI at the same time point (concurrent level).

In JM2, the survival process depends on the slope of BMI at the same time point (concurrent slope).

In JM3, the survival process depends on the level of BMI and slope of BMI at the same time point.

BIC, Bayesian Information Criterion

[a]Variable was standardized to have mean of 0 and standard deviation of 1

Table 2

Three Joint Models for longitudinal BMI and/or longitudinal change in BMI with risk for incident worsening rOA of the knee fitted to JoCo OA data: Examples of clinical interpretation

	HR for BMI*	HR for BMI slope**
JM1	1.39 [1.31; 1.48]	*N/A*
JM2	*N/A*	4.59 [2.14; 9.86]
JM3	1.37 [1.29; 1.46]	2.29 [1.20; 4.36]

BMI, concurrent value of Body Mass Index (logarithmically transformed)

In JM1, the survival process depends on the level of BMI at the same time point (concurrent level).

In JM2, the survival process depends on the slope of BMI at the same time point (concurrent slope).

In JM3, the survival process depends on the level of BMI and slope of BMI at the same time point.

HR, hazard ratio

*HR for a difference of 25% in BMI at the same time point for the same individual

**HR for increase of 10% versus increase of 5% at the same time point for the same individual