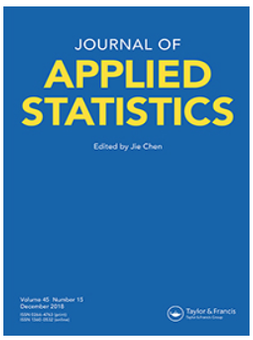

Journal of Applied Statistics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/cjas20

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To cite this article: Shengxiao Vincent Feng, Willem van den Boom, Maria De Iorio, Gladi J. Thng, Jerry K. Y. Chan, Helen Y. Chen, Kok Hian Tan & Michelle Z. L. Kee (2023): Joint modelling of mental health markers through pregnancy: a Bayesian semi-parametric approach, Journal of Applied Statistics, DOI: 10.1080/02664763.2022.2154329

To link to this article: https://doi.org/10.1080/02664763.2022.2154329

JOURNAL OF APPLIED STATISTICS
https://doi.org/10.1080/02664763.2022.2154329

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APPLICATION NOTE

Joint modelling of mental health markers through pregnancy: a Bayesian semi-parametric approach

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ABSTRACT

Maternal depression and anxiety through pregnancy have lasting societal impacts. It is thus crucial to understand the trajectories of its progression from preconception to postnatal period, and the risk factors associated with it. Within the Bayesian framework, we propose to jointly model seven outcomes, of which two are physiological and five non-physiological indicators of maternal depression and anxiety over time. We model the former two by a Gaussian process and the latter by an autoregressive model, while imposing a multi-dimensional Dirichlet process prior on the subject-specific random effects to account for subject heterogeneity and induce clustering. The model allows for the inclusion of covariates through a regression term. Our findings reveal four distinct clusters of trajectories of the seven health outcomes, characterising women's mental health progression from before to after pregnancy. Importantly, our results caution against the loose use of hair corticosteroids as a biomarker, or even a causal factor, for pregnancy mental health progression. Additionally, the regression analysis reveals a range of preconception determinants and risk factors for depressive and anxiety symptoms during pregnancy.

ARTICLE HISTORY
Received 11 April 2021
Accepted 23 September 2022

KEYWORDS
Bayesian non-parametrics; Dirichlet process; Gaussian process; mental health; pregnancy; trajectory clustering

1. Introduction

Depression and anxiety disorders are prevalent across society but affect more women than men, especially during their childbearing years (38). Women affected by these mental health disorders may fail to provide appropriate quality of care and attention to their young children (18), resulting in serious implications to the offspring's developmental

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Supplemental data for this article can be accessed here. https://doi.org/10.1080/02664763.2022.2154329

and psychological outcomes. Children of mothers with anxiety and depression are also at elevated risks of developing psychiatric problems by 18 years of age (34), leading to a vicious cycle of significant health and economic burden worldwide (39). The significant downstream impact of maternal mental health on child's developmental health underscores the importance of understanding, firstly, the trajectories of maternal depressive and anxiety symptoms, as well as, secondly, their potential risk factors from preconception in order to provide a timely and effective interventional program to society. We propose a model towards this goal that not only holistically captures indicators of mental health over time, but is also able to accommodate patients' heterogeneity and clustering of the subjects according to their mental health profile over time.

A wide variety of risk factors, including prior history of mental illness, childhood maltreatment, poor parental care, high control, poor social or partner support, personality traits, can all affect development of antenatal depression and anxiety. We are interested in providing more insights on these risk factors. On the other hand, we are keen to explore the relationship and association between commonly used physiological markers and peripartum maternal mental health. Based on existing literature, physiological markers such as cortisol and cortisone have been examined in relation to peripartum maternal mental health as a function of hypothalamic–pituitary–adrenal (HPA) axis regulation. However, the relationship between the corticosteroids and maternal mental health is inconsistent, with reports revealing significant and no associations. Thus, results on hair corticosteroids and maternal mental health still remain divided and inconclusive. Section S1 of the Supplemental Material contains a more detailed introduction to the medical problem.

To our knowledge, no study thus far has concurrently and jointly investigated the trajectories of both women's non-physiological mental health markers and their corticosteroids levels from preconception to post-partum. Hence, we sought to address this gap and identify determinants of women's mental well-being at specific time points from preconception to the post-partum period. Our approach is to jointly model seven interdependent indicators of depression and anxiety, while allowing for and finding clusters among the time trajectories of these outcomes, and concurrently regressing on a wide range of covariates within a Bayesian inference framework.

We hypothesise that (1) women's symptoms of anxiety and depression remain largely stable across preconception to the post-partum period, and (2) hair cortisol and cortisone measures are not associated with anxiety and depression symptoms over the same period. We test these hypotheses using a preconception cohort study in which women were recruited prior to conception and examined for anxiety and depression symptoms as well as hair cortisol and cortisone levels from preconception to the postnatal period. The women's psychosocial factors such as childhood adversities faced and social support were also collected across the same period to be used as covariates.

The non-physiological outcomes exhibit a substantially different temporal dependence and evolution than the corticosteroids levels. This heterogeneity poses a challenge to data analysis and the use of existing methods. To our knowledge, no trajectory clustering methods that explicitly and effectively account for such heterogeneity exist. We therefore propose a model with two substantially distinct temporal processes for both trajectory types, namely an autoregressive and a Gaussian process. It must be noted that the two modelling strategies allow for different levels of flexibility. As discussed more in detail later, we link the different processes in an interpretable and probabilistically sound way through the

specification of an appropriate random effects distribution. This also has the advantage to lead to data-driven clustering based on the combined information from all the temporal trajectories.

Previously, similar population-based prospective cohort studies (4; 19) make use of various modelling techniques, such as latent class analyses and semi-parametric group-based modelling strategies. Evidence from these analyses shows that most mothers commonly fall into three levels of depression symptoms across time – low, moderate and high (4; 19). This motivates Bayesian non-parametric clustering of the trajectories. Specifically, we use a Dirichlet process (DP) prior (8) to flexibly model subject-specific random effects in mental health trajectories through pregnancy, to better model the heterogeneity in the outcome measures. This has many advantages: mainly (1) it enables the automatic, data-driven determination of the number of clusters from the data themselves, (2) it adds considerable flexibility to the model (24; 23) since the DP does not make stringent assumptions on the distribution of the trajectory over time as compared to its parametric counterparts and (3) it allows for straightforward inclusion of time-varying and time-homogeneous covariates.

In Section 2, we describe the data and conduct a preliminary analysis. In Section 3, we introduce the semi-parametric Bayesian model for temporal trajectories, while in Section 4 posterior inference results are presented alongside model comparison and MCMC diagnostic results. Section 5 discusses the clinical implications of our analysis extensively. We conclude the paper in Section 6.

2. Data on mental health across pregnancy

2.1. Cohort description and data preprocessing

This study is based on a subset of participants from the Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) cohort (21). The women, recruited from Singapore's population, are between 18 and 45 years old, and were planning a pregnancy at the time of recruitment. Written informed consent was provided by participants. Ethical approval was obtained from the SingHealth Centralised Institutional Review Board (reference 2014/692/D). Exclusion criteria preclude recruitment of women who are diagnosed with type 1 or type 2 diabetes mellitus, have received assisted fertility treatment, have taken contraceptives in the month before recruitment, or have received systemic steroids, anticonvulsants, HIV or hepatitis B or C medications in the month before recruitment.

The raw data comprise measurements of 237 variables for 1039 subjects at 6 time points: preconception (denoted as t_0), every trimester (t_1, t_2, t_3), as well as three and six months post delivery (t_4, t_5). Some variables are not time-varying and measured only at t_0. Others vary over 3–6 time points. This work is based on initial data collection while S-PRESTO is still ongoing. As such, the data present high missingness. Of the 215 non-demographic variables, more than 201 have at least 10% missing data and 156 variables have more than 30% missing.

We handle missing values as follows. Firstly, subjects with more than 55% of all variables not missing are included in the study, leading to 237 subjects. We choose the number 55% as it provides a suitable balance between the number of subjects included into the study and the missingness of their variables after exclusion of subjects. We conduct a sensitivity analysis on this choice of a 55% threshold in Section S7 of the Supplemental Material

using two alternative thresholds, 35% and 75%. They yield highly similar results in terms of clustering and estimation of covariates effects, leaving the key conclusions of the analysis substantially unchanged.

Subsequently, covariates with a missing rate greater than 25% are excluded. The remaining missing values are imputed via multiple imputation by chained equations using the R package `mice` (36). That is, missing values are first imputed by the corresponding sample mean. Then, a separate imputation model is fit for each variable with missing data by regressing that variable onto the others. The latter imputation is repeated until convergence. Table S3 in the Supplemental Material summarises the demographics of the 237 selected subjects. Finally, continuous variables are log-transformed, to make them more normally distributed, and demeaned, to aid interpretation of the random effects as described in Section 3.1.

2.2. Outcome variables

A total of seven outcome variables are used in the analysis. Table 1 summarises them. Two outcomes are physiological markers while the other five are non-physiological. Jointly, they capture subjects' anxiety and depression progression through pregnancy. Section S2 of the Supplemental Material displays the outcomes.

Hair cortisol and cortisone measurements are the two physiological markers. They are obtained, analysed and measured from hair segments at the posterior vertex region of the head measuring at least three centimetres proximal to the scalp. Obvious outliers are removed from the analysis.

Anxiety and depression-related symptoms are recorded via questionnaires administered at six time points ($t_0 - t_5$), from preconception to six months after birth. These are the non-physiological indicators. The Edinburgh Postnatal Depressive Scale (EPDS) (5) and the

Table 1. Summary of available variables.

Outcome variables	**Over 6 time points ($t_0 - t_5$):** • BDI, EPDS, STAI-s, STAI-t, STAI-p **Over 5 time points ($t_0 - t_3, t_5$):** • Cortisol, Cortisone
Time-invariant covariates (measured at t_0)	**Continuous:** • PBI: paternal protection (patprot), paternal care (patcare), maternal protection (matprot), maternal care (matcare) • CTQ: sexual abuse (sexabu), physical negligence (phyneg), physical abuse (phyabu), emotional negligence (emoneg), emotional abuse (emoabu), minimization denial (minden) • BFI: openness (ope), neuroticism (neu), extraversion (ext), conscientiousness (con), agreeableness (agr) • Others: months of trying to conceive, years at job, age, geneal health questionaire (GHQ) **Categorical:** • Binary: working status (yes/no), weight lifting (yes/no) • Non-binary: household income (3 levels), general health (3 levels). Table S3 of Supplemental Material details these levels.
Time-varying covariates	**Over 3 time points ($t_1 - t_3$):** • PES: intensity ratio, frequency ratio • PAQ **Over 4 time points ($t_0 - t_3$):** • MSPSS: significant other, family, friends • PSS

Beck Depression Inventory-II (BDI) (1) assess depressive symptoms. These questionnaires are validated, self-report instruments of 10 and 21 items, respectively, and assess common depressive symptoms over the week before the questionnaire is administered. Both measures are sensitive and reliable in detecting both antenatal and postnatal depression in women.

The Spielberger State-Trait Anxiety Inventory (STAI) (33) assesses anxiety symptoms. The STAI consists of 40 items on a 4-point Likert scale which measure both transient ('state'; STAI-s) and stable ('trait'; STAI-t) characteristics of anxiety. Additionally, a 'positive' score (STAI-p) is calculated from STAI by summing the positive well-being related items such as calmness. It is important to note that the absence of elevated symptoms of depression or anxiety does not necessarily imply positive psychological well-being. Negative and positive mental well-being have shown distinct effects on pregnancy (14; 27). We therefore include STAI-p into the set of outcome variables.

2.3. Covariates

Table 1 also summarises the covariates used in the regression analysis. They cover five main domains: socio-economic variables, developmental history, personality, mental well-being and stress, and social support. For more detailed description and explanation of these covariates, refer to Section S4 of the Supplemental Material.

2.4. Exploratory analysis

The main goal of the analysis is to investigate the trajectories of both stress hormones cortisol and cortisone, and mental health processes BDI, EPDS, STAI-t, STAI-s and STAI-p over time, and to gain a better understanding of their interrelationship. As an initial exploratory analysis, structural equation modelling (SEM) is performed between each pair of outcome variables to explore the potential cause–effect relationship amongst the seven responses.

In this initial analysis, only STAI-p is used out of all three STAI variables for simplicity. The results are not sensitive to this choice of the STAI variable. A total of 10 pairwise comparisons are made amongst the 5 variables cortisol, cortisone, BDI, EPDS and STAI-p employing the R package `lavaan` (30). For each pair, three possible cause–effect directions ($A \rightarrow B, B \rightarrow A, A \leftrightarrow B$) are assessed and compared using as model fit measures the Tucker–Lewis index (TLI), the comparative fit index (CFI), the root mean square error of approximation (RMSEA), the standardised root mean square residual (SRMR), the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). A good fit of the model is indicated by TLI and CFI close to one, RMSEA and SRMR close to zero, and AIC and BIC as low as possible when compared to alternative model choices. By comparing the fit measures, a best fit direction is chosen amongst the three possible directions between each pair. Here, we preclude the possibility of no or low causal effect. Figure 1 shows a path diagram constructed using `semPlot` (6) from all the pairwise SEM comparisons. Note that we use the model fit measures to decide on the best-fit direction between each pair of variables, and as such they are not displayed in the path diagram. The results highlight a potential dependence structure among the outcomes, which will be investigated in depth in what follows.

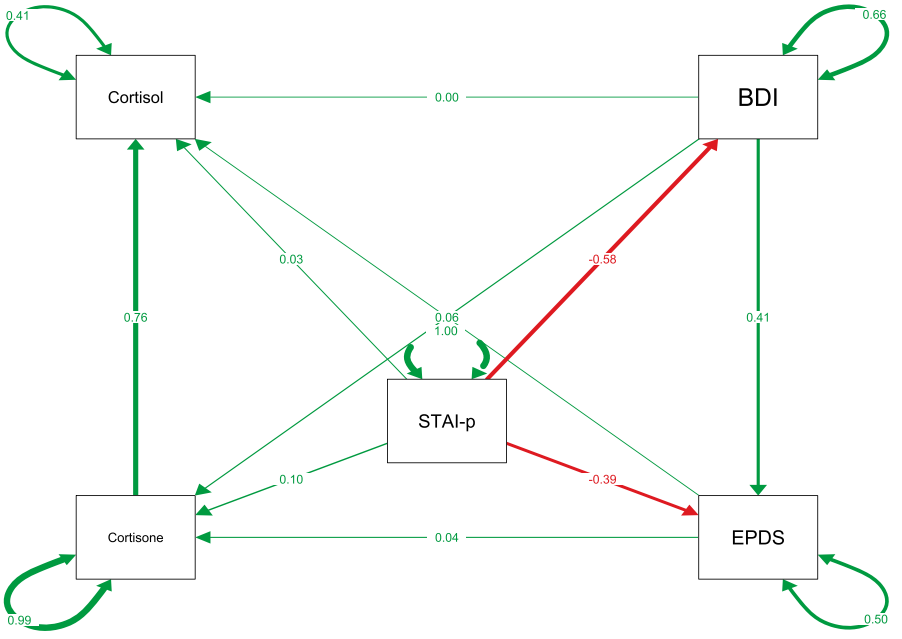

Figure 1. A path diagram amongst outcome variables based on pairwise SEM comparison. The numbers on single-headed directional arrows represent the unstandardised regression coefficients between the two variables in the direction indicated. The number on double-headed curved arrows denotes variance of said variable.

3. Bayesian joint model

3.1. Model specification

Response data are available on $N = 237$ subjects at the same number of visits. In contrast, some time-varying covariates are not available for each visit, resulting in 3–6 time points for each time-varying variable as detailed in Table 1.

Temporal patterns in the time series plots of the seven outcomes in Figures S3 and S4 of the Supplemental Material differ markedly between the non-physiological and physiological outcomes, with higher variance across time in the hormones than in the non-physiological outcomes. We thus use different modelling strategies for the temporal dependence with each set of outcomes.

For each subject i, time t_j and mental health outcome k, $y_{ij}^{(k)}$ denotes the measured value where $i = 1, 2, \ldots, N$, $j = 0, 1, \ldots, 5$, and $k \in \{\text{BDI, EPDS, STAI-s, STAI-t, STAI-p}\}$. The outcomes are log-transformed to make their empirical distribution resemble a Gaussian density. The model is specified as follows:

$$y_{ij}^{(k)} \mid \mu_{ij}^{(k)}, \tau^{(k)} \sim \mathcal{N}(\mu_{ij}^{(k)}, 1/\tau^{(k)}) \tag{1}$$

independently for $i = 1, 2, \ldots, N$, $j = 0, 1, \ldots, 5$ and all mental health outcomes k, where $\tau^{(k)}$ is the precision parameter for outcome k and the mean is defined

as

$$\mu_{ij}^{(k)} = \begin{cases} m_{1i}^{(k)} + X_{ij}^T \beta_j^{(k)} & \text{for } j = 0, \\ m_{1i}^{(k)} + m_{2i}^{(k)}(y_{i(j-1)}^{(k)} - m_{1i}^{(k)}) + X_{ij}^T \beta_j^{(k)} & \text{for } j = 1, \ldots, 5. \end{cases} \tag{2}$$

Here, $m_{1i}^{(k)}$ and $m_{2i}^{(k)}$ are subject-specific random effects that account for dependency between observations from the same subject across time, X_{ij} is the vector of covariates of subject i at time t_j, and $\beta_j^{(k)}$ is the vector of appropriate dimension of regression coefficients. Note that dimension of X_{ij} might vary with j.

We do not consider random slopes as it would lead to a less parsimonious model with a large number of random coefficients due to the numerous covariates included. Specifically, we have 326 covariates such that the dimensionality of the resulting random effects distribution would be unwieldy from both a computational and interpretation perspective. Nevertheless, we note that, in general, it is straightforward to include also the regression coefficients in the DP prior, leading to what it is generally known as a DP mixture of regressions. Note that the model for $\mu_{ij}^{(k)}$ includes an autoregressive term on the observation at the previous time point. If the q-th covariate is not recorded at time t_j, then we drop it from X_{ij}. Note that each time-varying covariate in X_{ij} has corresponding time-varying coefficients in $\beta_j^{(k)}$, allowing for time-varying covariate effects.

In addition to the non-physiological variables, the physiological outcome variables $y_{ij}^{(h)}$ are also measured for each subject $i = 1, 2, \ldots, N$, time t_j ($j = 0, 1, 2, 3, 5$) and $h \in \{\text{Cortisol}, \text{Cortisone}\}$. The inspection of the longitudinal trajectories of these two hormones in Figure S4 of the Supplemental Material shows no evidence of an autoregressive structure. Thus, we assume a Gaussian process for both of them:

$$y_i^{(h)} \mid \mu_i^{(h)}, \Sigma^{(h)} \sim \mathcal{N}(\mu_i^{(h)}, \Sigma^{(h)} + \eta^{(h)} I_5), \tag{3}$$

independently for $i = 1, 2, \ldots, N$ and $h \in \{\text{Cortisol}, \text{Cortisone}\}$. Here, $y_i^{(h)}$ is a 5-dimensional vector denoting cortisol or cortisone measured at 5 time points $(t_0 - t_3, t_5)$, and $\mu_i^{(h)}$ is a 5-dimensional mean vector where its elements are defined by

$$\mu_{ij}^{(h)} = \gamma_i^{(h)} + X_{ij}^T \beta_j^{(h)}, \quad j = 0, 1, 2, 3, 5, \tag{4}$$

where $\gamma_i^{(h)}$ is a subject-specific random effect. The vectors $\beta_j^{(h)}$ and X_{ij} are defined similarly as for (2).

The 5×5 covariance matrix $\Sigma^{(h)}$ derives from an absolute exponential covariance function. Specifically, $\Sigma_{m,n}^{(h)} = (\sigma^{(h)})^2 \exp(-\rho^{(h)} |T_m - T_n|)$ such that the diagonal of $\Sigma^{(h)}$ equals $(\sigma^{(h)})^2$. Here, $T = (0, 3, 6, 9, 15)^T$ represents the time in months of the 5 time points $(t_0 - t_3, t_5)$. Finally, $\eta^{(h)}$ is the nugget parameter.

Finally, $\gamma_i^{(h)}$ is a subject-specific random effect and does not capture any temporal structure, differently from $m_{2i}^{(k)}$ in (2), while $\Sigma^{(h)}$ captures dependence between observations at different time points.

3.2. Prior specification

To perform joint clustering of the trajectories of all seven outcome variables, we specify a DP prior on the subject-specific mean coefficients $m_{1i}^{(k)}$ and $\gamma_i^{(h)}$. From here onward,

for simplicity of notation, we denote the vector of mean level coefficients $m_{1i}^{(k)}$ ($k \in \{\text{BDI, EPDS, STAI-s, STAI-t, STAI-p}\}$) and $\gamma_i^{(h)}$ ($h \in \{\text{Cortisol, Cortisone}\}$) as M_i, where each M_i is 7-dimensional. Then, $M_i \mid G \sim G$ independently for $i = 1, \ldots, N$ where $G \mid G_0, \alpha \sim \text{DP}(\alpha, G_0)$, G_0 is the base measure of the DP around which G is centred and α is the concentration parameter, representing the variability around the base measure G_0. G is almost surely discrete and admits the well-known 'stick-breaking' construction (31), by which the random measure G can be represented as an infinite mixture of point masses:

$$G(\cdot) = \sum_{k=1}^{\infty} p_k \delta_{\theta_k}(\cdot), \tag{5}$$

where δ_{θ_k} is a point mass at $\theta_k \overset{\text{iid}}{\sim} G_0$ and the weights p_k of each point mass are defined through the stick breaking construction:

$$p_k = \xi_k \prod_{j=1}^{k-1} (1 - \xi_j), \tag{6}$$

where $\xi_k \overset{\text{iid}}{\sim} \text{Beta}(1, \alpha)$. Note that θ_k and ξ_k ($k = 1, 2, \ldots$) are independent. The specification of a DP prior on M_i as random effects distribution not only guarantees flexibility, but also allows data-driven clustering of the subjects based on the combined information contained in the seven trajectories.

The prior on the concentration parameter α is a uniform distribution $\mathcal{U}(0.3, 5)$ as this prior choice leads to more stable computations. The lower bound is set at 0.3 to avoid any computational difficulties that might arise from small values for p_k (25). The upper bound of 5 is to avoid overclustering the noises in the trajectories. Furthermore, the prior on α induces a prior on the number of clusters K: the mean and variance of K conditional on α and the sample size N are (20; 16)

$$E(K \mid \alpha) = \sum_{i=1}^{N} \frac{\alpha}{\alpha + i - 1}, \tag{7}$$

$$\text{var}(K \mid \alpha) = \sum_{i=1}^{N} \frac{\alpha(i-1)}{(\alpha + i - 1)^2}. \tag{8}$$

Monte Carlo estimation provides that marginally $E(K) = 12$ and $\text{var}(K) = 9$ for $N = 237$ and our prior on α.

It is typical to assign a prior on α (22). Such a strategy provides greater flexibility compared to fixing α a priori. In the latter case, setting α to one allows for reasonable uncertainty on the number of clusters K (37). For comparison, we fit our model with $\alpha = 1$. The corresponding results in Section S8 of the Supplemental Material show comparable results with those presented here where $\alpha \sim \mathcal{U}(0.3, 5)$.

We assume the components of M_i a priori independent in the base measure and marginally having a Gaussian distribution: $G_0 = \prod_{j=1}^{7} \mathcal{N}(\mu_j^G, \tau^G)$ with $\mu_j^G \sim \mathcal{N}(0, 100)$ independently for $j = 1, \ldots, 7$ and $\tau^G \sim \text{Gamma}(5, 3)$. Note that such independence in

the base measure of the DP prior does not restrict the dependence structure of the posterior on the components of M_i. The mixture of point masses induced by the DP allows for complex dependency structures among the elements of M_i.

For the regression coefficients, $\beta^{(k)}$ and $\beta^{(h)}$, we use a double exponential prior, Laplace$(0, \lambda)$, and place a Gamma$(2, 2)$ on the global hyper-parameter λ to induce variable selection on all covariates. We compare this choice of Laplace prior against the uninformative Gaussian prior $\mathcal{N}(0, 1000)$ on the regression coefficients. The main results of our analysis are the same for both prior choices (results not shown). With regard to model fit, the Laplace prior yields a log pseudo-marginal likelihood (LPML) of 233.24 and deviance information criterion (DIC) of 12,719.98, while the model with a flat Gaussian prior has an LPML of 152.85 and DIC of 13,930.89. Both metrics indicate that the Laplace prior results in overall better model fit.

We place flat conjugate priors on $m_{2i}^{(k)}$ and $\tau^{(k)}$ for efficient computations. We specify independent $\mathcal{N}(0, 100)$ priors for $m_{2i}^{(k)}$, and independent Gamma$(0.01, 0.01)$ for the precision parameters $\tau^{(k)}$. As for the parameters in the Gaussian processes, we assume $\sigma^{(h)} \sim U(0, 10)$, $\sqrt{\eta^{(h)}} \sim U(0, 10)$ and $\rho^{(h)} \sim U(0.1, 5)$ independently for $h \in \{\text{Cortisol}, \text{Cortisone}\}$. We present a sensitivity analysis to prior specification in Section S6 of the Supplemental Material, which yields similar results in terms of clustering and estimation of covariates effects, leaving the key conclusions of the analysis substantially unchanged.

4. Posterior inference

Posterior inference using Markov chain Monte Carlo (MCMC) is performed in JAGS (28) through R (29) using the interface package `R2jags` (35). To fit a DP process in JAGS, we truncate the infinite mixture to 20 components (15) which together with the prior choice for α implies an approximation error due to truncation of less than 10^{-3} (see (25)). Section S9 of the Supplemental Material contains the JAGS model code. The MCMC algorithm is run for 22,000 iterations with a burn-in of 2000 iterations and thinning every 10 iteration. The computation run-time is 6.1 hours. MCMC diagnostics in Section S3 of the Supplemental Material suggest good mixing and satisfactory convergence.

4.1. Goodness of fit

The goodness of fit of the model is assessed by visually inspecting 12 randomly selected subjects for all of the seven outcome variables that we jointly model. Figure 2 shows the model fit for hair cortisol measures only. It demonstrates a good fit of the model to the data. In particular, the model is able to recover the temporal pattern in the response. Plots for the other six outcome variables show similar good coverage, with almost no observed values outside the 95% credible interval (results not shown). Section S5 of the Supplemental Material contains posterior predictive checks which suggest satisfactory fit for all the outcome variables across time. Section S10 of the Supplemental Material contains a simulation study that highlights the accuracy and robustness of the model.

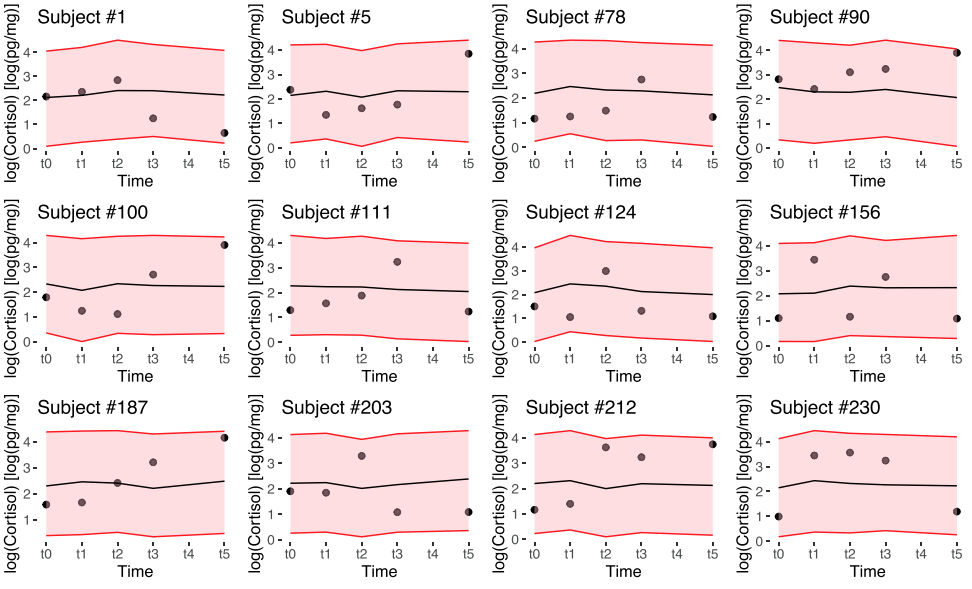

Figure 2. Model fit assessment for cortisol. The dots are the observed values. The lines are the fitted trajectories. The shaded regions define the 95% credible intervals.

4.2. Clustering

The 95% credible interval for the DP concentration parameter α is (0.33, 1.74) with a posterior mean of 0.82. Figure 3 shows the posterior marginal density of the parameters $m_1^{(k)}$ and $\gamma^{(h)}$. From the plots, it can be seen that the five mental health processes contribute to the final clustering results more so than cortisol or cortisone measurements as their densities are clearly multi-modal. This is further confirmed by the contour plots of the bivariate joint posterior densities for each pair of random effects parameters (see Figure S33 in Supplemental Material).

The DP priors on the subject-specific parameters $m_1^{(k)}$ and $\gamma^{(h)}$ induce clustering of the 237 subjects based on the seven response trajectories. The posterior coclustering probabilities are visualised by Figure S32 in the Supplemental Material. A posterior point estimate of the clustering allocation is obtained by minimising the posterior expectation of Binder's loss function (3) as implemented in the R package `mcclust` (9). This leads to a posterior estimate characterised by six clusters of fairly even size for the first four clusters (see Table 2). Since the first four clusters cover 98% of all subjects, and the remaining two contain very few subjects, we show the clustering results only for these four clusters.

Figure 4 shows the empirical average of the trajectories within each of the first four identified clusters for all seven outcomes variables. The results are interesting in two ways. Firstly, the temporal trajectories of the five mental health processes (BDI, EPDS, STAI-s, STAI-t and STAI-p) show a consistent pattern across the four clusters, e.g. the cluster-specific trajectories do not cross for each mean outcome. Moreover, Cluster 1 shows consistently the highest values for BDI, EPDS, STAI-s and STAI-t but the lowest for STAI-p, while Cluster 4 shows the opposite. This is clinically sound as lower STAI-p values correspond to worse mental health while the opposite is true for the other four outcomes. Similar

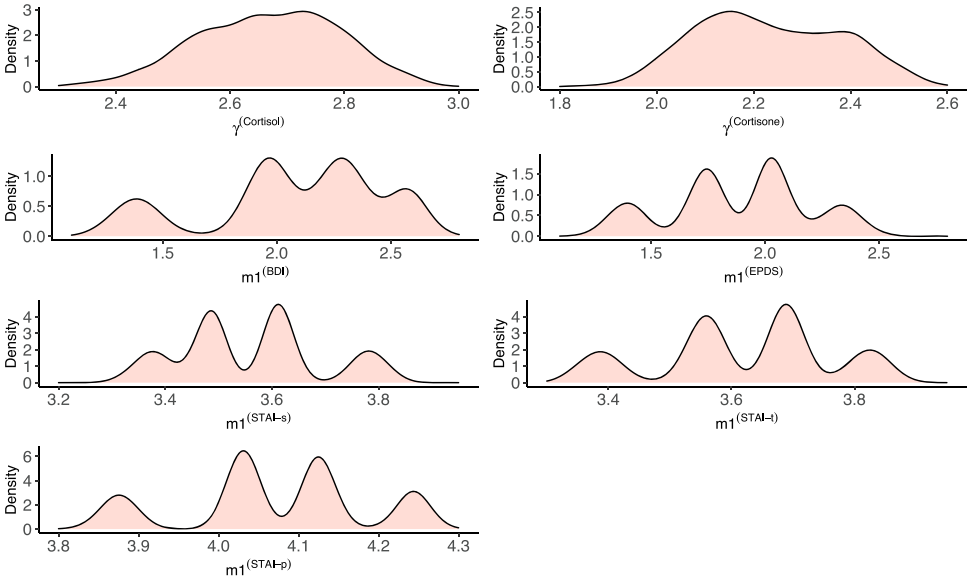

Figure 3. Posterior distribution of the $m_1^{(k)}$ and $\gamma^{(h)}$ random effects parameters.

Table 2. No. of subjects in each cluster.

Cluster	1	2	3	4	5	6
No. of subjects	36	82	70	45	3	1

conclusions can be drawn for the other clusters. On the other hand, cortisol and cortisone measurements show less distinguishable and separable trajectories among clusters. Although the clusters have rather different trajectories for their mental health outcomes, they share very similar time patterns when it comes to cortisol and cortisone. Their trajectories for the two hormones are more similar than their trajectories for the mental health outcomes.

To better characterise the clusters, we inspect the empirical distribution of the covariates within each cluster to detect potential differences. To this end, we conduct an analysis of variance (ANOVA). Of the 44 continuous covariates, 29 lead to a p-value below 0.05. Figure 5 contains the corresponding violin plots. This exploratory analysis supports the hypothesis that covariates measured both during preconception and during pregnancy affect mental health progression. In particular, covariates such as one's personality, childhood trauma and parental bonding seem to differentiate the clusters. This warrants further investigation as to the roles that those early-life events and traits play in determining a woman's mental health progression through pregnancy. Moreover, covariates such as perception of stress, pregnancy-related anxiety and social support are also deemed as relevant.

4.3. Regression

In Table 3, we report, for each outcome, covariates whose 95% credible intervals do not include zero, and the sign of these regression coefficients. Section 12 of the Supplemental

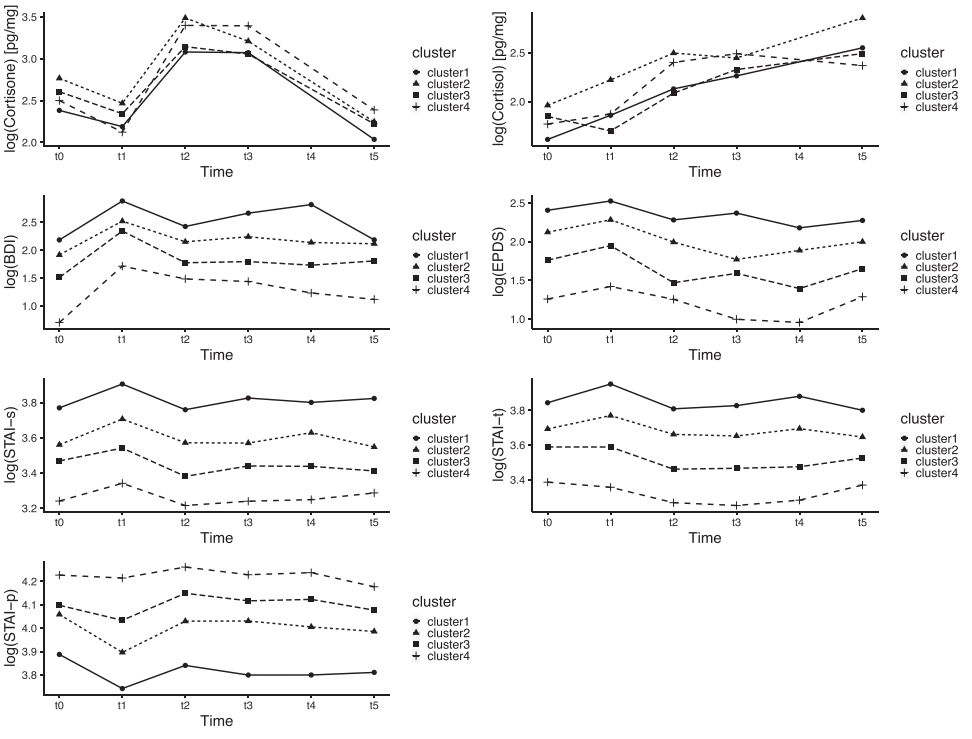

Figure 4. Average of the time trajectories in each of the four clusters for all seven outcome variables.

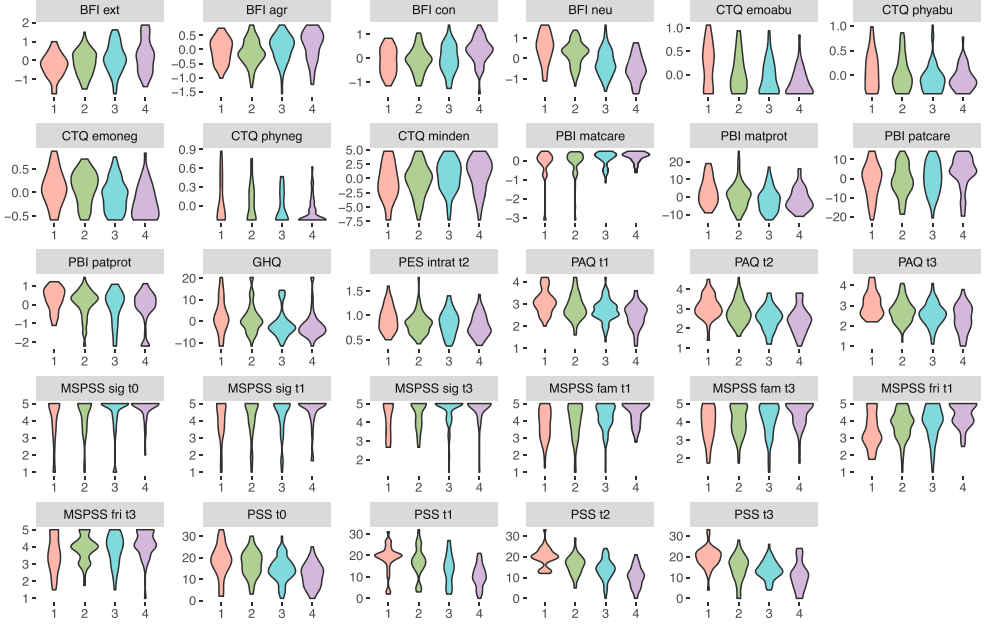

Figure 5. Comparative violin plots of continuous variables that differentiate the six clusters. The *x*-axis reports the cluster number.

Table 3. Summary of regression covariates that have an effect on outcomes. The plus and minus signs indicate positive and negative effects on the corresponding outcome variable, respectively.

Cortisol	**Time-invariant continuous (ti-con):** Nil **Time-invariant categorical (ti-cat):** Nil **Time-varying (tv):** PSS t_1 (+)
Cortisone	**ti-con:** Nil **ti-cat:** Nil **tv:** Nil
BDI	**ti-con:** Nil **ti-cat:** Nil **tv:**PSS t_0 (+)
EPDS	**ti-con:** Nil **ti-cat:** Nil **tv:** PES intrat t_1 (+), PSS t_0, t_2, t_3 (+)
STAI-s	**ti-con:** Nil **ti-cat:** Nil **tv:** PAQ t_1 (+), PSS t_0, t_2, t_3 (+), MSPSS sig t_0 (−)
STAI-t	**ti-con:** Nil **ti-cat:** Nil **tv:** PSS $t_0 - t_3$ (+), MSPSS sig t_1 (−)
STAI-p	**ti-con:** Nil **ti-cat:** Nil **tv:** PSS $t_1 - t_3$ (−), MSPSS fri t_0 (+)

Material shows the credible intervals for all regression coefficients. Section 5.2 discusses covariate effects more in details.

4.4. Model comparison

We compare our proposed model against several other competing models typically used in analysing longitudinal data sets. We first consider the finite mixture counterpart of our proposal, fixing the number of components at three, four and five, respectively, and placing a Dirichlet distribution as prior on the mixture weights. See, for example, (10). We then also consider the parametric version of our model which is equivalent to fixing the number of components equal to one. Lastly, a standard Bayesian mixed effects model with random intercept and random slope on time, detailed in Section S11 of the Supplemental Material, is also implemented for comparison.

We compare the six different models using as model selection criteria DIC as well as LPML. A better model fit leads to lower DIC and higher LPML. The comparison among the six models is shown in Table 4. The proposed model yields the best model fit based on both DIC and LPML as compared to the parametric and the mixed effects model. The model

Table 4. Model comparison.

Model	DIC	LPML
Main: DP mixture model	13945.14	144.38
Finite mixture model with three components	13842.58	144.24
Finite mixture model with four components	13857.72	145.51
Finite mixture model with five components	14320.46	145.40
Parametric version of the main model	14401.72	128.48
Mixed effects model	76231.16	127.51

fit is comparable to the models with fixed number of components, which do not learn the number of components from the data. This is not surprising as with the DP mixture model we obtain that 98% of the subjects fall into four clusters and we are fitting finite mixtures with three, four and five components. These comparisons support the use of the proposed model in our analysis.

5. Findings

5.1. Trajectories of women's mental health

We use a preconception cohort to investigate the trajectories of women's mental health and the determinants of depression and anxiety symptoms from preconception to six months post-partum. Our findings reveal that women's mental health, which includes symptoms of positive mood, depression and anxiety, are grouped into four distinct and stable trajectory profiles. In brief, women who show consistently high, moderately high, moderate, and low levels of anxiety or depressive symptoms display the corresponding inverse levels of positive mood from preconception to the postnatal period.

From a statistical point of view, the DP prior is able to deal with the heterogeneity present in our dataset well, and gives us separate and interpretable clusters that are consistent across both the time points and the multiple outcomes. The number of clusters four is consistent with the analysis of pregnant women's mental health by Lim *et al.* (19). A main advantage of our modelling approach is that the outcomes, which capture different but complementary aspects of the underlying mental health status, are modelled jointly, allowing for a combination of information from different sources.

Our findings are consistent with previous epidemiological studies, showing that most women diagnosed with depression or anxiety during pregnancy have had a prior history of mental health problems during preconception (32). A previous study of the same preconception cohort also highlights the stability of maternal depressive and anxiety symptoms from preconception into pregnancy with no distinct changes in the symptom profiles for both depression and anxiety from preconception into the second trimester of pregnancy (17). Whilst previous studies show stability of positive mental health over time, our analysis suggests that this stability in women precedes conception.

Additionally, we explore the association between hair corticosteroids and women's mental health using a cumulative measure of steroid exposure. Clusters of mental health trajectories did not match the patterns in the hair corticosteroids trajectories, as evident in Figure 4. We can see the clear separation of trajectories in the non-physiological indicators but not in the physiological corticosteroids trajectories. This lack of association between corticosteroid levels and mental health is consistent with previous mixed results (26). Hair corticosteroids were found to be weakly or not associated with maternal depression, anxiety or stress (11). Gerritsen *et al.* (12) observe that significantly higher levels of hair cortisol and corticosterone levels are found only in people with a co-morbid diagnosis of depression and anxiety disorders, but not in healthy people, or those diagnosed with either depression or anxiety disorders. Further research in larger samples or clinical populations is needed to identify suitable biomarkers relevant to the Asian population.

5.2. Determinants of women's mental health

Understanding the determinants of women's mental health could facilitate targeted, timely and effective intervention. While many studies examine covariates that explain peripartum maternal mental health, there remains a gap in understanding if these covariates also explain women's preconception mental health. Our findings reveal results for women prior to conception. Perceived stress and negative emotional valences about pregnancy and poor social support are known predictors of peripartum symptoms of depression and anxiety (2). The most notable difference between our findings and previous literature is the observation of risk factors for mental well-being at specific time points. Our analysis reveals that higher perceived stress associates with higher symptoms of depression or anxiety not only throughout pregnancy but particularly at preconception as well. This can be seen from the positive regression coefficients of PSS against BDI, EPDS, STAI-s and STAI-t at time t_0 in Table 3 and Figure S37 in the Supplemental Material. We also observe that lower perceived stress through all three trimesters is associated with higher positive mood in the same period. While Evans *et al.* (7) observe that only mothers with a comorbidity of depressive and anxiety disorders have significantly higher negative emotional valence towards pregnancy, our results reveal that this is time dependent and sensitive. In our study, mothers have more depressive or anxiety symptoms only at the first trimester of pregnancy (Table 3).

Interestingly, social support is a significant contributor only to anxiety and not to depressive symptoms. In particular, support from their spouse (specifically at preconception and during first trimester) protects women from experiencing anxiety. The support from friends also contributes to a higher positive mood in these women during preconception and the first trimester. In general, these findings suggest social support from spouse, family or friends may help to 'buffer' the negative effects experienced during day-to-day life, promoting better mental well-being (13). Socioeconomic covariates such has household income do not exhibit a statistically significant effect on mental health.

6. Conclusion

We jointly model temporal physiological and non-physiological mental health outcomes using Gaussian processes and autoregressive models. A DP prior on random effects detects distinct clusters among the mental health trajectories. Regression analysis with a range of predictors reveals patterns mostly in line with the existing clinical literature. Notably, hair corticosteroids measurements do not show a strong association with non-physiological measures for pregnancy mental health, crucially cautioning against its loose use as a biomarker. Additionally, the joint modelling, the clustering based on all the seven outcome trajectories and the long time span, from preconception to after delivery, allow for clinical insights that go beyond the existing literature as discussed in Section 5.

Acknowledgments

The data originate from the S-PRESTO study group which includes Airu Chia, Anna Magdalena Fogel, Anne Eng Neo Goh, Anne Hin Yee Chu, Anne Rifkin-Graboi, Anqi Qiu, Bee Wah Lee, Bernard Su Min Chern, Bobby Kyungbeom Cheon, Candida Vaz, Christiani Jeyakumar Henry, Ciaran Gerard Forde, Claudia Chi, Dawn Xin Ping Koh, Desiree Y. Phua, Doris Ngiuk Lan Loh, Elaine Phaik Ling Quah, Elizabeth Huiwen Tham, Evelyn Chung Ning Law, Evelyn Xiu Ling Loo, Fabian Kok Peng Yap, Faidon Magkos, Falk Müller-Riemenschneider, George Seow Heong Yeo, Hannah

Ee Juen Yong, Helen Yu Chen, Heng Hao Tan, Hong Pan, Hugo P S van Bever, Hui Min Tan, Ives Yubin Lim, Izzuddin Bin Mohd Aris, Jeannie Tay, Jerry Kok Yen Chan, Jia Xu, Joanne Su-Yin Yoong, Johan Gunnar Eriksson, Jonathan Tze Liang Choo, Jonathan Y. Bernard, Jonathan Yinhao Huang, Jun Shi Lai, Karen Mei Ling Tan, Keith M. Godfrey, Kenneth Yung Chiang Kwek, Keri McCrickerd, Kok Hian Tan, Kok Wee Chong, Kothandaraman Narasimhan, Kuan Jin Lee, Li Chen, Lieng Hsi Ling, Ling-Wei Chen, Lourdes Mary Daniel, Lynette Pei-Chi Shek, Marielle V. Fortier, Mary Foong-Fong Chong, Mei Chien Chua, Melvin Khee-Shing Leow, Michael J. Meaney, Michelle Zhi Ling Kee, Min Gong, Mya Thway Tint, Navin Michael, Neerja Karnani, Ngee Lek, Oon Hoe Teoh, Peter David Gluckman, Priti Mishra, Queenie Ling Jun Li, Sambasivam Sendhil Velan, See Ling Loy, Seng Bin Ang, Sharon Ng, Shiao-Yng Chan, Shirong Cai, Shu-E Soh, Si Hui Goh, Sok Bee Lim, Stella Tsotsi, Stephen Chin-Ying Hsu, Sue-Anne Ee Shiow Toh, Suresh Anand Sadananthan, Teng Hong Tan, Tong Wei Yew, Varsha Gupta, Victor Samuel Rajadurai, Wee Meng Han, Wei Wei Pang, Wen Lun Yuan, Yanan Zhu, Yap Seng Chong, Yin Bun Cheung, Yiong Huak Chan, Yung Seng Lee and Zai Ru Cheng.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Singapore Ministry of Education Academic Research Fund Tier 2 [MOE2019-T2-2-100], the Singapore Ministry of Health's National Medical Research Council under its Open Fund – Young Individual Research Grant [OFYIRG19nov-0010] and the Singapore National Research Foundation under its Translational and Clinical Research Flagship Programme and administered by the Singapore Ministry of Health's National Medical Research Council [NMRC/TCR/004-NUS/2008; NMRC/TCR/012-NUHS/2014]. Additional funding is provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research.

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