Web-based Supplementary Materials for 'Power and Sample Size Calculations for Longitudinal Studies Comparing Rates of Change with a Time-Varying Exposure' by X. Basagaña and D. Spiegelman

Web Appendix A Equivalence of conditional likelihood and a model on differences

Verbeke et al.[1] proved this equivalence for the mixed effects model, where $\mathbf{\Sigma}_i = \mathbf{Z}_i\mathbf{D}\mathbf{Z}'_i + \sigma^2_w\mathbf{I}$. This model has the special feature that conditional on the random effects, the observations are independent. The DEX model does not follow this structure. The proof given here is for a general response covariance matrix, $\mathbf{\Sigma}_i$, and thus extends their results. Suppose that we have subject-specific intercepts a_i, which can be fixed or random, and assume that $\mathbb{E}(\mathbf{Y}_i) = a_i\mathbf{1} + \mathbf{X}_i\gamma$, where $\mathbf{1}$ is a vector of ones, $\mathbf{X}_i$ a matrix of covariates and γ a vector of regression parameters. Assuming normality of $\mathbf{Y}_i$ and $Var(\mathbf{Y}_i) = \mathbf{\Sigma}_i$, the probability density function has the expression

$$f\left(\mathbf{Y}_i|a_i,\mathbf{X}_i\right)=\frac{1}{\left(2\pi\right)^{\frac{r+1}{2}}\left|\mathbf{\Sigma}_i\right|^{1/2}}\exp\left(-\frac{1}{2}\left(\mathbf{Y}_i-a_i\mathbf{1}-\mathbf{X}_i\gamma\right)'\mathbf{\Sigma}_i^{-1}\left(\mathbf{Y}_i-a_i\mathbf{1}-\mathbf{X}_i\gamma\right)\right)=$$

$$\frac{1}{\left(2\pi\right)^{\frac{r+1}{2}}\left|\mathbf{\Sigma}_i\right|^{1/2}}$$

$$\exp\left(-\frac{1}{2}\left[\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Sigma}_i^{-1}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)-2\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Sigma}_i^{-1}a_i\mathbf{1}+a_i^2\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right]\right).$$

By the factorization theorem, a sufficient statistic for a_i is $s_i=\mathbf{Y}_i'\mathbf{\Sigma}_i^{-1}\mathbf{1}=\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{Y}_i$. The sufficient statistic s_i is distributed as a univariate normal with expected value $\mathbf{1}'\mathbf{\Sigma}_i^{-1}a_i\mathbf{1}+\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{X}_i\gamma$ and variance $\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}$. Then, the density of $\mathbf{Y}_i$ conditioning on the sufficient statistic s_i is

$$f\left(\mathbf{Y}_i|s_i,\mathbf{X}_i\right)=\frac{f\left(\mathbf{Y}_i|a_i,\mathbf{X}_i\right)}{f\left(s_i|a_i,\mathbf{X}_i\right)}=\frac{\frac{1}{\left(2\pi\right)^{\frac{r+1}{2}}\left|\mathbf{\Sigma}_i\right|^{1/2}}}{\frac{1}{\left(2\pi\right)^{\frac{1}{2}}\left|\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right|^{1/2}}}$$

$$\frac{\exp\left(-\frac{1}{2}\left[\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Sigma}_i^{-1}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)-2\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Sigma}_i^{-1}a_i\mathbf{1}+a_i^2\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right]\right)}{\exp\left(-\frac{1}{2\left(\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right)}\left(\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{Y}_i-\mathbf{1}'\mathbf{\Sigma}_i^{-1}a_i\mathbf{1}-\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{X}_i\gamma\right)^2\right)}=$$

$$\frac{\left|\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right|^{1/2}}{\left(2\pi\right)^{\frac{r}{2}}\left|\mathbf{\Sigma}_i\right|^{1/2}}\exp\left(-\frac{1}{2}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\left[\mathbf{\Sigma}_i^{-1}-\mathbf{\Sigma}_i^{-1}\mathbf{1}\left(\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right)^{-1}\mathbf{1}'\mathbf{\Sigma}_i^{-1}\right]\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)\right).$$

Using property B.3.5 of Seber[2],

$$\mathbf{\Sigma}_i^{-1}-\mathbf{\Sigma}_i^{-1}\mathbf{1}\left(\mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{1}\right)^{-1}\mathbf{1}'\mathbf{\Sigma}_i^{-1}=\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta},$$

we can write then the conditional likelihood as

$$L(\gamma|s_1,\ldots,s_N,\mathbf{X}) = \prod_{i=1}^{N} \frac{\left|\mathbf{1}'\mathbf{\Sigma}_i{}^{-1}\mathbf{1}\right|^{1/2}}{(2\pi)^{\frac{r}{2}}\left|\mathbf{\Sigma}_i\right|^{1/2}} \exp\left(-\frac{1}{2}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)\right)$$

and the log-likelihood $\log L(\gamma|s_1,\ldots,s_N,\mathbf{X})$ will then be proportional to

$$\frac{N}{2}\log\left|\mathbf{1}'\mathbf{\Sigma}_i{}^{-1}\mathbf{1}\right| - \frac{N}{2}\log\left|\mathbf{\Sigma}_i\right| - \frac{1}{2}\sum_{i=1}^{N}\left(\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)'\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}\left(\mathbf{Y}_i-\mathbf{X}_i\gamma\right)\right).$$

The maximum likelihood estimator of γ is

$$\hat{\gamma} = \left(\sum_{i=1}^{N}\left(\mathbf{X}_i'\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}\mathbf{X}_i\right)\right)^{-}\left(\sum_{i=1}^{N}\left(\mathbf{X}_i'\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}\mathbf{Y}_i\right)\right)$$

and

$$Var(\hat{\gamma}) = \left(\sum_{i=1}^{N}\left(\mathbf{X}_i'\mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}\mathbf{X}_i\right)\right)^{-} = \left(\sum_{i=1}^{N}\left(\mathbf{X}_i'\mathbf{M}_i\mathbf{X}_i\right)\right)^{-},$$

where the notation $\mathbf{A}^{-}$ indicates the generalized inverse of $\mathbf{A}$. Note that $\mathbf{\Delta}\mathbf{X}_i$ will contain columns of zeros for those variables that are time-invariant, and first order differences for the time-varying variables. It is readily seen that, when $\mathbf{\Sigma}_i$ is known, $\hat{\gamma}$ and $Var(\hat{\gamma})$ from the conditional approach are equivalent to the solution to the regression of $\mathbf{\Delta}\mathbf{Y}_i$ on $\mathbf{\Delta}\mathbf{X}_i$ by GLS using the covariance matrix $\mathbf{\Delta}\mathbf{\Sigma}_i\mathbf{\Delta}'$.

Web Appendix B Relationship between correlation coefficient and intraclass correlation when the exposure prevalence is not constant over time

If the prevalence of exposure is not constant over time but the exposure process follows CS, we have $\mathbb{E}\left[E_j E_{j'}\right] = \left(\rho_x \sqrt{p_{ej}(1-p_{ej})}\sqrt{p_{ej'}(1-p_{ej'})} + p_{ej}p_{ej'}\right)$, where ρ_x is the common correlation between exposures at different time points. From Web Appendix C, we have $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_j E_{j'}\right] = \bar{p}_e r\,(r+1)\left[\bar{p}_e(1-\rho_e)+\rho_e\right]$. Therefore, we have that

$$\rho_x \sum_{j=0}^{r}\sum_{j'\neq j}\sqrt{p_{ej}(1-p_{ej})}\sqrt{p_{ej'}(1-p_{ej'})} + \sum_{j=0}^{r}\sum_{j'\neq j} p_{ej}p_{ej'} = \bar{p}_e r\,(r+1)\left[\bar{p}_e(1-\rho_e)+\rho_e\right].$$

Solving for ρ_x, we have

$$\rho_x = \frac{\bar{p}_e r\,(r+1)\left[\bar{p}_e(1-\rho_e)+\rho_e\right] - \sum_{j=0}^{r}\sum_{j'\neq j} p_{ej}p_{ej'}}{\sum_{j=0}^{r}\sum_{j'\neq j}\sqrt{p_{ej}(1-p_{ej})}\sqrt{p_{ej'}(1-p_{ej'})}}.$$

Note that if $p_{ej} = p_e\,\forall j$ then $\rho_x = \rho_e$. Equivalently one can deduce

$$\rho_e = \frac{\rho_x \sum_{j=0}^{r}\sum_{j'\neq j}\sqrt{p_{ej}(1-p_{ej})}\sqrt{p_{ej'}(1-p_{ej'})} + \sum_{j=0}^{r}\sum_{j'\neq j} p_{ej}p_{ej'} - \bar{p}_e^2 r\,(r+1)}{\bar{p}_e r\,(r+1)\,(1-\bar{p}_e)}.$$

Web Appendix C Upper bound for ρ_e

Let $E_{i\cdot} = \sum_{j=0}^{r} E_{ij}$ be the total number of exposed periods for subject i. Then, the intraclass correlation of exposure can be written as

$$\rho_e = \frac{\mathbb{E}\left(E_{i\cdot}^2\right) - (r+1)\,\bar{p}_e\left(1+\bar{p}_e r\right)}{r\,(r+1)\bar{p}_e\left(1-\bar{p}_e\right)}$$

[3]. By the properties of the expectation we have

$$\begin{aligned}\mathbb{E}\left[E_j E_{j'}\right] &= \mathbb{E}\left(\mathbb{E}\left[E_{ij}E_{ij'} \middle| E_{i\cdot}\right]\right) = \mathbb{E}\left(P\left(E_{ij}=1 \cap E_{ij'}=1 \middle| E_{i\cdot}\right)\right) \\ &= \mathbb{E}\left(\frac{E_{i\cdot}\left(E_{i\cdot}-1\right)}{(r+1)r}\right) = \frac{1}{r(r+1)}\left[\mathbb{E}\left(E_{i\cdot}^2\right) - \mathbb{E}\left(E_{i\cdot}\right)\right],\end{aligned}$$

and $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_jE_{j'}\right] = \mathbb{E}\left(E_{i\cdot}^2\right) - \mathbb{E}\left(E_{i\cdot}\right) = \mathbb{E}\left(E_{i\cdot}^2\right) - (r+1)\,\bar{p}_e$. Therefore, the intraclass correlation of exposure can be rewritten as

$$\rho_e = \frac{1}{1-\bar{p}_e}\left[\frac{\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_jE_{j'}\right]}{\bar{p}_e r\,(r+1)} - \bar{p}_e\right].$$

For binary variables, we have the constraint $\mathbb{E}\left[E_jE_{j'}\right] \leqslant \min\left(p_{ej}, p_{ej'}\right)\ \forall j, j'$. Then, it is easily shown that

$$\rho_e \leqslant \frac{1}{1-\bar{p}_e}\left[\frac{\sum_{j=0}^{r}\sum_{j'\neq j}\min\left(p_{ej}, p_{ej'}\right)}{\bar{p}_e r\,(r+1)} - \bar{p}_e\right].$$

Now,

$$\sum_{j=0}^{r}\sum_{j'\neq j}\min\left(p_{ej}, p_{ej'}\right) = 2\left(rp_{e(0)} + (r-1)p_{e(1)} + \cdots + p_{e(r-1)}\right) = 2\sum_{j=0}^{r-1}(r-j)p_{e(j)},$$

where $p_{e(j)}$ is the jth order statistic. Then,

$$\rho_e \leqslant \frac{1}{1-\bar{p}_e}\left[\frac{2\sum_{j=0}^{r-1}(r-j)p_{e(j)}}{\bar{p}_e r\,(r+1)} - \bar{p}_e\right].$$

Web Appendix D Derivation of $\tilde{\sigma}^2$

The derivations in Web Appendix D are valid only when $\Sigma_i = \Sigma$, and therefore they are not valid if the covariance of the response is RS and $V(t_0) > 0$, in which case a distribution for the time variable would need to be assumed. When the covariance is RS and $V(t_0) = 0$ the derivations in this appendix apply.

Web Appendix D.1 Derivation of $\tilde{\sigma}^2$ for model (3)

Model $\mathbb{E}\left(Y_{i,j+1}|\mathbf{X}_i\right) = \gamma_0 + \gamma_t t_{ij} + \gamma_{e*}E^*_{ij}$ includes three covariates. As defined in the paper, $E^*_{i,-1}$ is the cumultive exposure before entering the study for subject i, so that the cumulative exposure at time j is $E^*_{ij} = E^*_{i,-1} + \sum_{k=0}^{j} E_{ik}$.

The $[g,h]$ term of the matrix $\mathbb{E}\left[\mathbf{X}'_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ can be written as

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\mathbb{E}\left[x_{ijg}x_{ij'h}\right]\right).$$

Then, the [1,1] component of $\mathbb{E}\left[\mathbf{X}'_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ is $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}$. The [2,1] and [1,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_j\right]v^{jj'}\right) = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_0+sj\right]v^{jj'}\right) = \mathbb{E}\left(t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'} + s\sum_{j=0}^{r}\sum_{j'=0}^{r}jv^{jj'}.$$

The [3,1] and [1,3] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j^*\right]v^{jj'}\right)=\mathbb{E}\left[E_{-1}^*\right]\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\right)+\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\sum_{k=0}^{j}p_{ek}\right).$$

The [2,2] component is

$$\mathbb{E}\left(t_0^2\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}+2s\mathbb{E}\left(t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}jv^{jj'}+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}jj'v^{jj'}.$$

The [2,3] and [3,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j^*t_{j'}\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[\left(E_{-1}^*+\sum_{k=0}^{j}E_k\right)(t_0+sj')\right]v^{jj'}\right)=$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[\left(E_{-1}^*+\sum_{k=0}^{j}E_k\right)(t_0+sj')\right]v^{jj'}\right)=\mathbb{E}\left(E_{-1}^*t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}+$$
$$s\mathbb{E}\left(E_{-1}^*\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}j'v^{jj'}+\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j}\mathbb{E}\left(E_kt_0\right)v^{jj'}+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j}p_{ek}j'v^{jj'}.$$

The [3,3] component is

$$\mathbb{E}\left[E_{-1}^{*^2}\right]\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\right)+\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k'=0}^{j'}\mathbb{E}\left(E_{-1}^*E_{k'}\right)v^{jj'}+$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j}\mathbb{E}\left(E_{-1}^*E_k\right)v^{jj'}+\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j}\sum_{k'=0}^{j'}\mathbb{E}\left(E_kE_{k'}\right)v^{jj'}.$$

Then, $\mathbb{E}\left[\mathbf{X'}_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ needs to be inverted, and the [3,3] component of the inverse is $\tilde{\sigma}^2$.

Web Appendix D.1.1 Derivation of $\tilde{\sigma}^2$ for model (3) when $E_{i,-1}^*=0\ \forall i$ and $V(t_0)=0$

If $E_{i,-1}^*=0\ \forall i$ then $\mathbb{E}\left[E_{-1}^*\right]=0$, $\mathbb{E}\left[E_{-1}^{*^2}\right]=0$, $\mathbb{E}\left(E_{-1}^*E_{k'}\right)=0$, $\mathbb{E}\left(E_{-1}^*E_k\right)=0$ and $\mathbb{E}\left(E_{-1}^*t_0\right)=0$. If, in addition, $t_{i0}=0\ \forall i$, then $\mathbb{E}\left(t_0\right)=0$, $\mathbb{E}\left(t_0^2\right)=0$

and $\mathbb{E}(E_k t_0) = 0$. Using this and the results in Web Appendix D.1, we obtain the following symmetric matrix,

$$\mathbb{E}\left[\mathbf{X'}_i \boldsymbol{\Sigma}^{-1} \mathbf{X}_i\right] = \begin{pmatrix} \sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} & & \\ s\sum_{j=0}^{r}\sum_{j'=0}^{r} j v^{jj'} & s^2 \sum_{j=0}^{r}\sum_{j'=0}^{r} j j' v^{jj'} & \\ \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\sum_{k=0}^{j} p_{ek}\right) & s\sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j} p_{ek} j' v^{jj'} & \sum_{j=0}^{r}\sum_{j'=0}^{r}\sum_{k=0}^{j}\sum_{k'=0}^{j'} \mathbb{E}(E_k E_{k'}) v^{jj'} \end{pmatrix},$$

and all its elements are determined by just knowing $v^{jj'}$, $p_{ej'}$ and $\mathbb{E}[E_j E_{j'}]$ for all j, j'. Then, to derive $\tilde{\sigma}^2$ one needs to invert this matrix and take the [3,3] component.

Web Appendix D.2 Derivation of $\tilde{\sigma}^2$ for model (4)

Model $\mathbb{E}(Y_{i,j+1} - Y_{i,j} | \mathbf{X}_i) = \gamma_t^W + \gamma_{e*}^W E_{ij}$ includes two covariates. The vector of differences $Y_{i,j+1} - Y_{i,j}$, $\boldsymbol{\Delta}\mathbf{Y}_i$, has covariance matrix $\boldsymbol{\Delta\Sigma\Delta}'$. Let $w_{jj'}$ be $[j, j']$ element of $(\boldsymbol{\Delta\Sigma\Delta}')^{-1}$, $j = 1, \ldots, r$; $j' = 1, \ldots, r$. Then,

$$\boldsymbol{\Sigma}_\Gamma = \left(\mathbb{E}\left[\mathbf{X'}_i \left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1} \mathbf{X}_i\right]\right)^{-1}.$$

The [1,1] component of the matrix $\mathbb{E}\left[\mathbf{X'}_i \left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1} \mathbf{X}_i\right]$ is $\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'}$; The [2,1] and [1,2] components are $\sum_{j=1}^{r}\sum_{j'=1}^{r} p_{ej} w^{jj'}$; and the [2,2] component is $\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}[E_j E_{j'}] w^{jj'}\right)$. All the elements of $\mathbb{E}\left[\mathbf{X'}_i \left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1} \mathbf{X}_i\right]$ are determined by just knowing $w^{jj'}$, $p_{ej'}$ and $\mathbb{E}[E_j E_{j'}]$ for all j, j'. The [2,2] component of the inverse of $\mathbb{E}\left[\mathbf{X'}_i \left(\mathbf{\Delta\Sigma\Delta'}\right)^{-1}\mathbf{X}_i\right]$ is

$$\tilde{\sigma}^2 = \frac{\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'}}{\left(\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'}\right)\left(\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)\right) - \left(\sum_{j=1}^{r}\sum_{j'=1}^{r} p_{ej} w^{jj'}\right)^2}.$$

Web Appendix D.2.1 Proof that $\tilde{\sigma}^2$ is minimized at the upper bound of ρ_e if $w^{jj'} \geqslant 0 \; \forall j \neq j'$ for model (4). Proof that this condition hold for CS and DEX but not for RS

For model (4) we have from Web Appendix D.2 that

$$\tilde{\sigma}^2 = \frac{\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'}}{\left(\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'}\right)\left(\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)\right) - \left(\sum_{j=1}^{r}\sum_{j'=1}^{r} p_{ej} w^{jj'}\right)^2},$$

where $w^{jj'}$ is the $[j, j']$ element of $\left(\mathbf{\Delta\Sigma\Delta'}\right)^{-1}$. When $p_{ej} \; \forall j$ are fixed, only $\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)$ is affected by changes in the exposure distribution, so $\tilde{\sigma}^2$ will be affected by changes on ρ_e only through $\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)$. Since $\left(\mathbf{\Delta\Sigma\Delta'}\right)^{-1}$ is positive definite then $\sum_{j=1}^{r}\sum_{j'=1}^{r} w^{jj'} > 0$ and an increase in $\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)$ decreases $\tilde{\sigma}^2$, so in order to minimize $\tilde{\sigma}^2$ we need to maximize $\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}\right)$. In addition, since $\mathbb{E}\left[E_j E_j\right] = p_{ej}$ and $p_{ej} \; \forall j$ are fixed, only $\sum_{j=1}^{r}\sum_{j' \neq j}\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}$ need to be maximized. If $w^{jj'} \geqslant 0 \; \forall j \neq j'$, then $\sum_{j=1}^{r}\sum_{j' \neq j}\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}$ will be maximized when all terms $\mathbb{E}\left[E_j E_{j'}\right] \; \forall j \neq j'$ take their upper bound, $\min\left(p_{ej}, p_{ej'}\right)$. It can be derived that

$$\rho_e = \frac{1}{(1-\bar{p}_e)}\left[\frac{\sum\limits_{j=1}^{r}\sum\limits_{j'\neq j}\mathbb{E}\left(E_j E_{j'}\right)}{\bar{p}_e r\left(r-1\right)} - \bar{p}_e\right]$$

(Web Appendix C). Therefore, when all terms $\mathbb{E}\left[E_j E_{j'}\right]\ \forall j \neq j'$ are equal to their upper bound, so does ρ_e. So, $\tilde{\sigma}^2$ will be minimum when ρ_e takes its maximum (i.e. $\rho_e = 1$, the time-invariant exposure case, if the prevalence is constant over time), and equivalently, it can be derived that $\tilde{\sigma}^2$ takes its maximum when ρ_e takes its minimum.

As derived in Web Appendix D.2.2, the off-diagonal elements of $\left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1}$ when $\boldsymbol{\Sigma}$ has a CS structure are equal to

$$w^{jj'} = \frac{1}{\sigma^2(1-\rho)(r+1)}\left[j(r+1-j')\right]$$

for $j < j'$, and therefore they are all positive. For DEX, we performed a grid search for values of $r \leqslant 50$ and ρ and θ in [0,1] and found that the off-diagonal elements of $\left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1}$ where always greater or equal than zero. For RS, examples can be found where some off-diagonal elements of $\left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1}$ are negative. For example, for $r = 3$, $\sigma_w^2 = 0.1$, $\sigma_{b_0}^2 = 0.12$, $\sigma_{b_1}^2 = 0.15$, $\rho_{b_0 b_1} = -0.52$,

$$\left(\boldsymbol{\Delta\Sigma\Delta}'\right)^{-1} = \begin{pmatrix} 3.52 & -0.29 & -1.47 \\ -0.29 & 2.94 & -0.29 \\ -1.47 & -0.29 & 3.52 \end{pmatrix}.$$

Web Appendix D.2.2 Derivation of $\tilde{\sigma}^2$ for model (4) when both the response and the exposure follow CS and $p_{ej} = p_e \, \forall j$

If $p_{ej} = p_e \, \forall j$ then the expression for $\tilde{\sigma}^2$ reduces to

$$\frac{1}{\left(\sum_{j=1}^{r} \sum_{j'=1}^{r} \left(\mathbb{E}\left[E_j E_{j'} \right] w^{jj'} \right) \right) - p_e^2 \sum_{j=1}^{r} \sum_{j'=1}^{r} w^{jj'}}.$$

Under CS, the matrix $\mathbf{\Delta \Sigma \Delta'}$ is a $r \times r$ tridiagonal matrix of the form

$$\sigma^2(1-\rho) \begin{pmatrix} 2 & -1 & 0 & \cdots & 0 \\ -1 & 2 & -1 & \ddots & \vdots \\ 0 & -1 & 2 & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & -1 \\ 0 & \cdots & 0 & -1 & 2 \end{pmatrix}.$$

The $[j, j']$ element of $(\mathbf{\Delta \Sigma \Delta'})^{-1}$, i.e. $w^{jj'}$, is of the form

$$\frac{1}{4\sigma^2(1-\rho)(r+1)} \left[(j + j' - |j' - j|) \, (2r + 2 - |j' - j| - j - j') \right]$$

for $j, j' = 1, \ldots, r$ [4], which can be rewritten as

$$\frac{1}{2\sigma^2(1-\rho)(r+1)} \left[(r+1)j + (r+1)j' - 2jj' - (r+1) \, |j' - j| \right].$$

From this formula, we have that, if $j = j'$ then

$$w^{jj} = \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j(r+1-j) \right];$$

if $j < j'$ then

$$w^{jj'} = \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j(r+1-j') \right];$$

and if $j > j'$ then

$$w^{jj'} = \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j'(r+1-j) \right].$$

Then we can derive

$$\sum_{j=1}^{r} \sum_{j'=1}^{r} w^{jj'} =$$

$$\sum_{j=1}^{r} \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j(r+1-j) \right] + 2 \sum_{j=1}^{r-1} \sum_{j'=j+1}^{r} \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j(r+1-j') \right]$$

$$= \frac{1}{\sigma^2(1-\rho)(r+1)} \left[(r+1) \sum_{j=1}^{r} j - \sum_{j=1}^{r} j^2 + 2(r+1) \sum_{j=1}^{r-1} \sum_{j'=j+1}^{r} j - 2 \sum_{j=1}^{r-1} \sum_{j'=j+1}^{r} jj' \right].$$

Since

$$\sum_{j=1}^{r} j = \frac{r(r+1)}{2} \qquad \sum_{j=1}^{r} j^2 = \frac{r(r+1)(2r+1)}{6}$$

$$\sum_{j=1}^{r-1} \sum_{j'=j+1}^{r} j = \frac{r(r-1)(r+1)}{6} \qquad \sum_{j=1}^{r-1} \sum_{j'=j+1}^{r} jj' = \frac{r(r+1)(r-1)(2+3r)}{24},$$

we can deduce that

$$\sum_{j=1}^{r} \sum_{j'=1}^{r} w^{jj'} = \frac{r(r+1)(r+2)}{12(1-\rho)\sigma^2}.$$

Also, if we assume that the exposure process follows CS, the matrix $\mathbb{E}\left[E_j E_{j'}\right]$ has diagonal elements p_e and off-diagonal elements $\rho_e p_e(1-p_e) + p_e^2$. Therefore, the matrix with elements $\mathbb{E}\left[E_j E_{j'}\right] w^{jj'}$ has diagonal elements equal to

$$p_e \frac{1}{\sigma^2(1-\rho)(r+1)} \left[j(r+1-j) \right]$$

and off-diagonal elements equal to

$$\left(\rho_e p_e(1-p_e)+p_e^2\right)\frac{1}{\sigma^2(1-\rho)(r+1)}\left[j(r+1-j')\right]$$

if $j < j'$ and

$$\left(\rho_e p_e(1-p_e)+p_e^2\right)\frac{1}{\sigma^2(1-\rho)(r+1)}\left[j'(r+1-j)\right]$$

if $j > j'$. Then,

$$\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_jE_{j'}\right]w^{jj'}\right)=$$

$$\sum_{j=1}^{r}p_e\frac{1}{\sigma^2(1-\rho)(r+1)}\left[j(r+1-j)\right]+2\sum_{j=1}^{r-1}\sum_{j'=j+1}^{r}\frac{(\rho_e p_e(1-p_e)+p_e^2)}{\sigma^2(1-\rho)(r+1)}\left[j(r+1-j')\right].$$

Using the previous results we derived in this section, we can derive

$$\sum_{j=1}^{r}\sum_{j'=1}^{r}\left(\mathbb{E}\left[E_jE_{j'}\right]w^{jj'}\right)=\frac{p_e r(r+2)\left(2+p_e(r-1)(1-\rho_e)-\rho_e+r\rho_e\right)}{12(1-\rho)\sigma^2}.$$

Then,

$$\tilde{\sigma}^2=\frac{1}{\left(\sum\limits_{j=1}^{r}\sum\limits_{j'=1}^{r}\left(\mathbb{E}\left[E_jE_{j'}\right]w^{jj'}\right)\right)-p_e^2\sum\limits_{j=1}^{r}\sum\limits_{j'=1}^{r}w^{jj'}}=\frac{12(1-\rho)\sigma^2}{p_e(1-p_e)r(r+2)\left(2+(r-1)\rho_e\right)}.$$

Web Appendix D.3 Derivation of $\tilde{\sigma}^2$ for model (5)

Model $\mathbb{E}\left(Y_{i,j+1}|\mathbf{X}_i\right)=\gamma_0+\gamma_t t_{ij}+\gamma_e E_{ij}+\gamma_{te}\left(E_{ij}\times t_{ij}\right)$ includes four covariates. The [1,1] component of $\mathbb{E}\left[\mathbf{X}'_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ is $\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}v^{jj'}$. The [2,1] and [1,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_j\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_0+sj\right]v^{jj'}\right)=\mathbb{E}\left(t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}+s\sum_{j=0}^{r}\sum_{j'=0}^{r}jv^{jj'}.$$

The [3,1] and [1,3] components are $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}p_{ej}v^{jj'}$. The [4,1] and [1,4] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jt_j\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j\left(t_0+sj\right)\right]v^{jj'}\right)=$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jt_0\right]v^{jj'}\right)+s\sum_{j=0}^{r}\sum_{j'=0}^{r}jp_{ej}v^{jj'}.$$

The [2,2] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_jt_{j'}\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[\left(t_0+sj\right)\left(t_0+sj'\right)\right]v^{jj'}\right)$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\left(\mathbb{E}\left(t_0^2\right)+s(j+j')\mathbb{E}\left(t_0\right)+s^2jj'\right)v^{jj'}\right)$$
$$=\mathbb{E}\left(t_0^2\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}+2s\mathbb{E}\left(t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}jv^{jj'}+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}jj'v^{jj'}.$$

The [2,3] and [3,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jt_{j'}\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j\left(t_0+sj'\right)\right]v^{jj'}\right)$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jt_0\right]v^{jj'}\right)+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'p_{ej}v^{jj'}\right).$$

The [2,4] and [4,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[t_jE_{j'}t_{j'}\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_{j'}\left(t_0^2+s\left(j+j'\right)t_0+s^2jj'\right)\right]v^{jj'}\right)$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_{j'}t_0^2\right]v^{jj'}\right)+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)+$$
$$s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(jj'p_{ej'}v^{jj'}\right).$$

The [3,3] component is $\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right)$. The [3,4] and [4,3] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'} t_{j'}\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}\left(t_0+sj'\right)\right]v^{jj'}\right)$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'} t_0\right]v^{jj'}\right)+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right).$$

Finally, the [4,4] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j t_j E_{j'} t_{j'}\right]v^{jj'}\right)=$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}\left(t_0^2+s\left(j+j'\right)t_0+s^2 jj'\right)\right]v^{jj'}\right)=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'} t_0^2\right]v^{jj'}\right)+$$
$$+2s\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}\left[E_j E_{j'} t_0\right]v^{jj'}\right)+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(jj'\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right).$$

Now, let us call $a=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}v^{jj'}$, $b=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}jv^{jj'}$, $c=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}jj'v^{jj'}$, $d=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(p_{ej}v_{jj'}\right)$, $e=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right)$, $f=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}j'p_{ej}v^{jj'}$, $g=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_j t_0\right]v^{jj'}\right)$, $h=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}j\,p_{ej}v^{jj'}$, $k=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(jj'p_{ej'}v^{jj'}\right)$, $l=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_{j'}t_0^2\right]v^{jj'}\right)$, $m=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(j\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)$, $n=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(j'\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)$, $o=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}t_0\right]v^{jj'}\right)$, $p=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(j'\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right)$, $q=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(\mathbb{E}\left[E_j E_{j'}t_0^2\right]v^{jj'}\right)$, $u=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(jj'\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right)$, $v=\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r}\left(j\mathbb{E}\left[E_j E_{j'}t_0\right]v^{jj'}\right)$. Without loss of generality, the time variable can be centered at the mean initial time so that $\mathbb{E}[t_0] = 0$ and $\mathbb{E}[t_0^2] = V(t_0)$. Then, we get the following symmetric matrix,

$$\mathbb{E}\left[\mathbf{X}'_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right] = \begin{pmatrix} a & & & \\ sb & V(t_0)a+s^2c & & \\ d & g+sf & e & \\ g+sh & l+sm+sn+s^2k & o+sp & q+2sv+s^2u \end{pmatrix},$$

and we are interested in the [4,4] component of its inverse, which has a very complicated expression.

Web Appendix D.3.1 Derivation of $\tilde{\sigma}^2$ for model (5) when $V(t_0) = 0$

If $V(t_0) = 0$ and we assume, without loss of generality, that $t_0 = 0$, we have that

$$g = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}[E_j t_0]\, v^{jj'}\right) = 0;\ l = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}[E_{j'} t_0^2]\, v^{jj'}\right) = 0;$$
$$m = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}[E_{j'} t_0]\, v^{jj'}\right) = 0\ ;\ n = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}[E_{j'} t_0]\, v^{jj'}\right) = 0;$$
$$o = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}[E_j E_{j'} t_0]\, v^{jj'}\right) = 0;\ q = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}[E_j E_{j'} t_0^2]\, v^{jj'}\right) = 0;$$

and $v = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}[E_j E_{j'} t_0]\, v^{jj'}\right) = 0$. Then, the matrix to invert has the form

$$\mathbb{E}\left[\mathbf{X}'_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right] = \begin{pmatrix} a & sb & d & sh \\ sb & s^2c & sf & s^2k \\ d & sf & e & sp \\ sh & s^2k & sp & s^2u \end{pmatrix},$$

and all its elements are determined by just knowing $v^{jj'}$, $p_{ej'}$ and $\mathbb{E}[E_j E_{j'}]$ for all j, j'. The form of the [4,4] component of the inverse is still quite complicated.

Web Appendix D.3.2 Derivation of $\tilde{\sigma}^2$ for model (5) when $V(t_0) = 0$, $p_{ej} = p_e \, \forall j$ and both the response and the exposure process follow CS

In addition to the reduction in terms derived in Web Appendix D.3.1 due to the fact that $V(t_0) = 0$, when $p_{ej} = p_e \, \forall j$ we have $d = \sum_{j=0}^{r} \sum_{j'=0}^{r} \left(p_{ej} v^{jj'} \right) = p_e \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} = p_e a$;

$f = \sum_{j=0}^{r} \sum_{j'=0}^{r} j' p_{ej} v^{jj'} = p_e \sum_{j=0}^{r} \sum_{j'=0}^{r} j' v^{jj'} = p_e b$;

$h = \sum_{j=0}^{r} \sum_{j'=0}^{r} j \, p_{e,j} v^{jj'} = p_e \sum_{j=0}^{r} \sum_{j'=0}^{r} j \, v^{jj'} = p_e b$;

and $k = \sum_{j=0}^{r} \sum_{j'=0}^{r} \left(j j' p_{ej'} v^{jj'} \right) = p_e \sum_{j=0}^{r} \sum_{j'=0}^{r} j j' v^{jj'} = p_e c$. Therefore,

$$\mathbb{E} \left[\mathbf{X}'_i \boldsymbol{\Sigma}^{-1} \mathbf{X}_i \right] = \begin{pmatrix} a & sb & p_e a & s p_e b \\ sb & s^2 c & s p_e b & s^2 p_e c \\ p_e a & s p_e b & e & sp \\ s p_e b & s^2 p_e c & sp & s^2 u \end{pmatrix},$$

and the [4,4] component of the inverse is

$$\frac{a p_e^2 - e}{s^2 \left(p^2 - 2 b p p_e^2 + \left(b^2 - ac \right) p_e^4 + e \left(c p_e^2 - u \right) + a p_e^2 u \right)}.$$

In addition if $\boldsymbol{\Sigma}$ has CS structure, then $\boldsymbol{\Sigma}^{-1}$ has diagonal elements equal to

$$\frac{1}{\sigma^2} \frac{1 + \rho(r-2) - \rho^2 (r-1)}{(1-\rho)^2 \, (1 + r\rho)}$$

and off-diagonal elements equal to

$$\frac{1}{\sigma^2} \frac{-\rho}{(1-\rho) \, (1 + r\rho)}.$$

Importantly, the sum of every row or column is the same and equal to

$$\sum_{j=0}^{r} v^{jj'} = \sum_{j'=0}^{r} v^{jj'} = \frac{1}{\sigma^2 \, (1 + r\rho)},$$

and the sum of all elements of the inverse matrix is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} = \frac{r+1}{\sigma^2\left(1+r\rho\right)}.$$

Then, it can be deduced that

$$a = \sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} = \frac{r+1}{\sigma^2\left(1+r\rho\right)}, \quad b = \sum_{j=0}^{r}\sum_{j'=0}^{r} j v^{jj'} = \frac{r(r+1)}{2\sigma^2\left(1+r\rho\right)}$$

$$c = \sum_{j=0}^{r}\sum_{j'=0}^{r} jj' v^{jj'} = \frac{r(r+1)\left(2+r(4+(r-1)\rho)\right)}{12\sigma^2(1-\rho)\left(1+r\rho\right)}.$$

Also,

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]\right) =$$
$$\frac{(r-1)\rho+1}{\sigma^2\left[1+\rho(r-1)-\rho^2 r\right]}\sum_{j=0}^{r}\mathbb{E}\left(E_j^2\right) - \frac{\rho}{\sigma^2\left(1+\rho(r-1)-\rho^2 r\right)}\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left(E_j E_{j'}\right)$$

and since $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left(E_j E_{j'}\right) = p_e r\left(r+1\right)\left[p_e(1-\rho_e)+\rho_e\right]$ (Web Appendix C) we have

$$e = \frac{p_e(r+1)\left[1+\rho\left(r-1-p_e r(1-\rho_e)-\rho_e r\right)\right]}{(1-\rho)\sigma^2\left(1+r\rho\right)}.$$

If, in addition, we assume that the exposure process also follows CS, then

$$p = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}\left[E_j E_{j'}\right]v^{jj'}\right) =$$
$$\sum_{j'=0}^{r}\Bigg\{ j'\left(\frac{p_e}{\sigma^2}\frac{(r-1)\rho+1}{\left[1+\rho(r-1)-\rho^2 r\right]} + \frac{\rho\left(\rho_e p_e(1-p_e)+p_e^2\right)}{\sigma^2(1-\rho)\left(1+r\rho\right)}\right) +$$
$$\frac{-\rho r(r+1)\left(\rho_e p_e(1-p_e)+p_e^2\right)}{2\sigma^2(1-\rho)\left(1+r\rho\right)}\Bigg\} = \frac{r(r+1)p_e}{2\sigma^2(1-\rho)\left(1+r\rho\right)}\left[1-\rho\left(1-(1-p_e)r(1-\rho_e)\right)\right];$$

and

$$u = \sum_{j=0}^{r} \sum_{j'=0}^{r} \left(jj' \mathbb{E}\left[E_j E_{j'}\right] v^{jj'} \right) =$$

$$\sum_{j'=0}^{r} \left\{ j'^2 \left(\frac{p_e}{\sigma^2} \frac{(r-1)\rho + 1}{\left[1 + \rho(r-1) - \rho^2 r\right]} + \frac{\rho \left(\rho_e p_e (1-p_e) + p_e^2\right)}{\sigma^2 (1-\rho)\left(1 + r\rho\right)} \right) + \right.$$

$$\left. j' \frac{-\rho r(r+1)\left(\rho_e p_e (1-p_e) + p_e^2\right)}{2\sigma^2(1-\rho)\left(1+r\rho\right)} \right\} = \frac{r(r+1)}{\sigma^2(1-\rho)\left(1+r\rho\right)}$$

$$\left\{ \frac{p_e \left(1 + (p_e + r - 1)\rho + (1-p_e)\rho\rho_e\right)(2r+1)}{6} - \frac{\rho r(r+1)\left(\rho_e p_e (1-p_e) + p_e^2\right)}{4} \right\}.$$

As derived above, the [4,4] component of the inverse of $\mathbb{E}\left[\mathbf{X'}_i \mathbf{\Sigma}^{-1} \mathbf{X}_i\right]$ is

$$\frac{a p_e^2 - e}{s^2 \left(p^2 - 2bpp_e^2 + (b^2 - ac)\, p_e^4 + e\left(cp_e^2 - u\right) + ap_e^2 u\right)},$$

which, using the simplifications derived in this section, reduces to

$$\frac{12\sigma^2(1-\rho)(1+r\rho)}{p_e(1-p_e)s^2 r(r+1)(r+2)\left[1 + r\rho - \rho(1-\rho_e)\right]}.$$

Web Appendix D.4 Derivation of $\tilde{\sigma}^2$ for model (6)

The variance of the coefficients under model (6) can be obtained as $\mathbf{\Sigma}_{\mathrm{B}} = \left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$, where $\mathbf{M} = \mathbf{\Delta}'\left(\mathbf{\Delta}\mathbf{\Sigma}\mathbf{\Delta}'\right)^{-1}\mathbf{\Delta}$ (Web Appendix A). Since $\mathbf{\Delta 1} = \mathbf{0}$, the sum of a column or a row of $\mathbf{M}$ is zero, and the first row and column of $\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]$ will be zero. The [2,2] component of $\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]$

is $\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$. The [2,3] and [3,2] components are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j t_{j'}\right] = \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j (t_0 + sj')\right]$$
$$= \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j t_0\right] + s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'}$$
$$= \sum_{j=0}^{r}\mathbb{E}\left[E_j t_0\right]\sum_{j'=0}^{r} m^{jj'} + s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'} = s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'}$$

since $\sum\limits_{j'=0}^{r} m^{jj'} = 0$. The [3,3] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[t_j t_{j'}\right] = \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[(t_0 + sj)(t_0 + sj')\right] = \mathbb{E}\left[t_0^2\right]\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'} +$$
$$2s\mathbb{E}\left[t_0\right]\sum_{j=0}^{r}\sum_{j'=0}^{r} j m^{jj'} + s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} = s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'},$$

since $\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r} m^{jj'} = 0$ and $\sum\limits_{j=0}^{r}\sum\limits_{j'=0}^{r} j m^{jj'} = 0$. The [2,4] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'} t_{j'}\right] = \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}(t_0 + sj')\right] =$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'} t_0\right] + s\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right].$$

The [3,4] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[t_j E_{j'} t_{j'}\right] = \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[(t_0+sj)(t_0+sj')E_{j'}\right]$$
$$= \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[t_0^2 E_{j'}\right] + s\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'} j\mathbb{E}\left[t_0 E_{j'}\right] + s\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[t_0 E_{j'}\right]$$
$$+ s^2 \sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} p_{ej'} = \sum_{j=0}^{r}\mathbb{E}\left[t_0^2 E_j\right]\sum_{j'=0}^{r} m^{jj'} + s\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'} j\mathbb{E}\left[t_0 E_{j'}\right]$$
$$+ s\sum_{j=0}^{r} j\mathbb{E}\left[t_0 E_j\right]\sum_{j'=0}^{r} m^{jj'} + s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} p_{ej'}$$
$$= s\sum_{j=0}^{r}\sum_{j'=0}^{r} j m^{jj'}\mathbb{E}\left[t_0 E_{j'}\right] + s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} p_{ej'}$$

since $\sum_{j'=0}^{r} m^{jj'} = 0$. The [4,4] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j t_j E_{j'} t_{j'}\right] = \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[(t_0+sj)(t_0+sj')E_j E_{j'}\right] =$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'} t_0^2\right] + 2s\sum_{j=0}^{r}\sum_{j'=0}^{r} j m^{jj'}\mathbb{E}\left[t_0 E_j E_{j'}\right] + s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right].$$

Then, one needs to compute the generalized inverse of $\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]$, and the [4,4] component is $\tilde{\sigma}^2$.

Web Appendix D.4.1 Derivation of $\tilde{\sigma}^2$ for model (6) when $V(t_0)=0$

When $V(t_0) = 0$ and we assume, without loss of generality, that $t_0 = 0$, some of the terms derived in Web Appendix D.4.1 have a simpler expression. In particular, the [2,4] component reduces to $s\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$, the [3,4] component reduces to $s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} jj' m^{jj'} p_{ej'}$ and the [4,4] component reduces to $s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} jj' m^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$. Then, $\tilde{\sigma}^2$ only depend on the exposure through $p_{ej}\ \forall j$ and $\mathbb{E}\left[E_j E_{j'}\right]\ \forall j, j'$.

Web Appendix D.4.2 Derivation of $\tilde{\sigma}^2$ for model (6) when $V(t_0) = 0$, $p_{ej} = p_e \forall j$ and both the response and the exposure process follow CS

When the response covariance is CS, we derived in Web Appendix D.2.2 that the $[j, j']$ element of $(\mathbf{\Delta \Sigma \Delta}')^{-1}$, is

$$\frac{1}{2\sigma^2(1-\rho)(r+1)}\left[(r+1)j + (r+1)j' - 2jj' - (r+1)\left|j'-j\right|\right].$$

If we pre-multiply by $\mathbf{\Delta}'$, the $[j, j']$ element of $\mathbf{\Delta}'\left(\mathbf{\Delta \Sigma \Delta}'\right)^{-1}$ is

$$\frac{1}{2\sigma^2(1-\rho)(r+1)} \sum_{k=1}^{r} \left(I\left\{k=j\right\} - I\left\{k=j+1\right\}\right)\left((r+1)k + (r+1)j' - 2kj' - (r+1)\left|j'-k\right|\right),$$

where $I\left\{k=j\right\}$ is an indicator function that is one if $k=j$ and zero otherwise. The last expression can be simplified to

$$\frac{1}{2\sigma^2(1-\rho)(r+1)}\left((r+1)\left[\left|j'-j-1\right| - \left|j'-j\right| - 1\right] + 2j'\right),$$

for $j = 0, \ldots, r; j' = 1, \ldots, r$. Now, post-multiplying the result by $\mathbf{\Delta}$ we can derive the $[j, j']$ element of $\mathbf{\Delta}'\left(\mathbf{\Delta \Sigma \Delta}'\right)^{-1}\mathbf{\Delta}$, which is

$$\frac{1}{2\sigma^2(1-\rho)(r+1)} \sum_{k=1}^{r}\left((r+1)\left[\left|k-j-1\right| - \left|k-j\right| - 1\right] + 2k\right)\left(I\left\{k=j'\right\} - I\left\{k=j'+1\right\}\right)$$

for $j = 0, \ldots, r; j' = 0, \ldots, r$. The last expression simplifies to

$$\frac{1}{2\sigma^2(1-\rho)(r+1)} \left((r+1)\left[|j'-j-1| + |j'-j+1| - 2\,|j'-j|\right] - 2\right).$$

Note that this expression is $\frac{r}{\sigma^2(1-\rho)(r+1)}$ for $j' = j$ and $\frac{-1}{\sigma^2(1-\rho)(r+1)}$ for $j' \neq j$. Therefore, the matrix $\mathrm{M} = \boldsymbol{\Delta}' \left(\boldsymbol{\Delta}\boldsymbol{\Sigma}\boldsymbol{\Delta}'\right)^{-1} \boldsymbol{\Delta}$ has diagonal elements

$$\frac{r}{\sigma^2(1-\rho)(r+1)}$$

and off-diagonal elements

$$\frac{-1}{\sigma^2(1-\rho)(r+1)}.$$

It is then easily proven that the sum of any row or column of M is zero.

When both the response and the exposure have CS covariance, the components of $\boldsymbol{\Sigma}_{\mathrm{B}}$ derived in Web Appendix D.4 and Web Appendix D.4.1 simplify. The [2,2] component becomes

$$\begin{aligned}\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] &= \sum_{j=0}^{r} m^{jj} p_{ej} + \sum_{j=0}^{r}\sum_{j'\neq j} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] \\ &= \frac{r}{\sigma^2(1-\rho)(r+1)}\sum_{j=0}^{r} p_{ej} - \frac{1}{\sigma^2(1-\rho)(r+1)}\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_j E_{j'}\right].\end{aligned}$$

Now, $\sum_{j=0}^{r} p_{ej} = (r+1)\bar{p}_e$, $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_j E_{j'}\right] = \bar{p}_e r\,(r+1)\left[\bar{p}_e(1-\rho_e) + \rho_e\right]$ (Web Appendix C). Therefore,

$$\begin{aligned}\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] = \frac{r(r+1)\bar{p}_e}{\sigma^2(1-\rho)(r+1)} &- \frac{\bar{p}_e r\,(r+1)\left[\bar{p}_e(1-\rho_e) + \rho_e\right]}{\sigma^2(1-\rho)(r+1)} \\ &= \frac{\bar{p}_e(1-\bar{p}_e)r(1-\rho_e)}{\sigma^2(1-\rho)}.\end{aligned}$$

Since the prevalence is constant over time, the [2,3] component is

$$s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'} = sp_e \sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'} = 0,$$

because $\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'} = 0$. The [3,3] component becomes

$$\begin{aligned} s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} &= \frac{s^2}{\sigma^2(1-\rho)(r+1)}\sum_{j=0}^{r} j\left(rj - \left(\frac{r(r+1)}{2} - j\right)\right) \\ &= \frac{s^2}{\sigma^2(1-\rho)(r+1)}\left[(r+1)\sum_{j=0}^{r} j^2 - \frac{r(r+1)}{2}\sum_{j=0}^{r} j\right] \\ = \frac{s^2}{\sigma^2(1-\rho)(r+1)}&\left[\frac{r(r+1)^2(2r+1)}{6} - \frac{r^2(r+1)^2}{4}\right] = \frac{s^2 r(r+1)(r+2)}{12\sigma^2(1-\rho)}. \end{aligned}$$

The [2,4] component is $s\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$. Under CS of exposure, $\mathbb{E}\left[E_j E_{j'}\right]$ is p_e for $j = j'$ and $(\rho_e p_e(1-p_e) + p_e^2)$ for $j \neq j'$. So,

$$\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] = \frac{p_e}{\sigma^2(1-\rho)(r+1)}\left[-\left(\rho_e(1-p_e) + p_e\right)\left(\frac{r(r+1)}{2} - j\right) + rj\right]$$

and

$$\begin{aligned} &s\sum_{j=0}^{r}\sum_{j'=0}^{r} j' m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] = \\ &\frac{sp_e}{\sigma^2(1-\rho)(r+1)}\left[-\left(\rho_e(1-p_e) + p_e\right)\left[\frac{r(r+1)^2}{2} - \frac{r(r+1)}{2}\right] + \frac{r^2(r+1)}{2}\right] \\ &\qquad = \frac{sp_e r^2}{2\sigma^2(1-\rho)}\left(1 - \rho_e(1-p_e) - p_e\right). \end{aligned}$$

The [3,4] component becomes

$$s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'} p_{ej'} = s^2 p_e \sum_{j=0}^{r}\sum_{j'=0}^{r} jj' m^{jj'},$$

and using the results derived for the [3,3] component, it becomes

$$\frac{s^2 p_e r(r+1)(r+2)}{12\sigma^2(1-\rho)}.$$

For the [4,4] component, using some results derived for the [2,4] component, we can deduce

$$s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} j j' m^{jj'} \mathbb{E}\left[E_j E_{j'}\right] =$$

$$\frac{s^2 p_e}{\sigma^2(1-\rho)(r+1)} \sum_{j=1}^{r} j \left[-\left(\rho_e(1-p_e)+p_e\right)\left(\frac{r(r+1)}{2} - j\right) + rj \right] =$$

$$\frac{s^2 p_e}{\sigma^2(1-\rho)(r+1)}$$

$$\left[-\left(\rho_e(1-p_e)+p_e\right)\left(\frac{r^2(r+1)^2}{4} - \frac{r(r+1)(2r+1)}{6}\right) + \frac{r^2(r+1)(2r+1)}{6} \right]$$

$$= \frac{s^2 p_e r(r+1)}{12\sigma^2(1-\rho)(r+1)} \left[\left(p_e(r-1)(2+3r)(-1+\rho_e) + 2\rho_e + r\left(2 + r(4-3\rho_e) + \rho_e\right)\right] \right..$$

Then, the [4,4] component of the generalized inverse of $\mathbb{E}\left[\mathbf{X}_i' \mathbf{M} \mathbf{X}_i\right]$ is

$$\tilde{\sigma}^2 = \frac{12(1-\rho)\sigma^2}{p_e(1-p_e)s^2 r(r+2)(r+\rho_e)}.$$

Web Appendix E Generation of arbitrary prevalence vectors and correlation matrices

Arbitrary prevalence vectors can easily be generated by drawing numbers from a $Uniform[0,1]$. Arbitrary correlations matrices for binary data are more difficult to generate because they involve a lot of constraints [5]. Thus, we proceeded by first generating valid arbitrary covariance matrices for a multivariate normal distribution, and then deriving the covariance matrix that results from dichotomizing each of the normal variables so that a given prevalence at each time point is obtained. To generate arbitrary correlations matrices, random numbers were drawn from a $Uniform[-1, 1]$ for each pair of time points. If the resulting correlation matrix was not positive definite, it was transformed to the nearest positive definite one [6]. The process of obtaining the prevalence vector and the covariance matrix of the dichotomized variables is described by Leisch et al.[5]. To ensure that the space of possible values of $(\bar{p}_e, \rho_e)$ was evenly covered, prevalence vectors with a narrow range of prevalences and correlation matrices with positive and high correlations were given more weight.

Web Appendix F Demonstration of program use

More information can be found in a detailed user's manual at `http://www.hsph.harvard.edu/faculty/spiegelman/optitxs.html`. Here, we showed how to compute the required sample size for a study with 31 partiticipants and 14 post-baseline measures to detect a 5 L/min decrease in PEF associated with the use of air-freshener sprays with 90% power, assuming DEX covariance structure of the response. We assume the rates of change vary by exposure and a cumulative exposure effect, and we want to estimate the within-subject effect of exposure, so we assume the model $\mathbb{E}\left(Y_{ij} - Y_{i,j-1} | \mathbf{X}_i\right) = \gamma_t^W + \gamma_{e*}^W E_{ij}$. This example is based on a study on respiratory function and cleaning tasks/products [7].

```
> long.N()

* By just pressing <Enter> after each question, the default value,
  shown between square brackets, will be entered.

* Press <Esc> to quit

Enter the number of post-baseline measures (r) [1]: 14

Enter the desired power (0<Pi<1) [0.8]: .9

Enter the time between repeated measures (s) [1]: 1

Is the exposure time-invariant (1) or time-varying (2) [1]? 2

Do you assume that the exposure prevalence is constant over
 time (1), that it changes linearly with time (2), or you want
 to enter the prevalence at each time point(3) [1]? 2

Enter the exposure prevalence at time 0 (0<pe0<1) [0.5]: .35

Enter the exposure prevalence at time 14 (0<pe14<1) [0.5]: .45

Enter the intraclass correlation of exposure
 (-0.071<rho.e<0.808) [0.5]: .13

Constant mean difference (1) or Linearly divergent difference (2)
 [1]: 2

Which model are you basing your calculations on:
(1) Cumulative exposure effect model. No separation of between-
     and within-subject effects
(2) Cumulative exposure effect model. Within-subject contrast only
(3) Acute exposure effect model. No separation of between- and
     within-subject effects
(4) Acute exposure effect model. Within-subject contrast only
Model [1]: 2

Will you specify the alternative hypothesis on the absolute (beta
 coefficient) scale (1) or the relative (percent) scale (2) [1]? 1

Enter the interaction coefficient (gamma3) [0.1]: 5

Which covariance matrix are you assuming: compound symmetry (1),
```

```
 damped exponential (2) or random slopes (3) [1]? 2

Enter the residual variance of the response given the assumed
 model covariates (sigma2) [1]: 4570

Enter the correlation between two measures of the same subject
 separated by one time unit (0<rho<1) [0.8]: .88

Enter the damping coefficient (theta) [0.5]: .12

Sample size =  28

Do you want to continue using the program (y/n) [y]? n
```

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