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 $\mathbf{\Sigma}_i = \mathbf{Z}_i\mathbf{D}\mathbf{Z'}_i + \sigma_w^2\mathbf{I}$. 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

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

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

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

The maximum likelihood estimator of γ is

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

and

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

where the notation $\mathbf{A}^{-}$ indicates the generalized inverse of $\mathbf{A}$. Note that $\boldsymbol{\Delta}\mathbf{X}_i$ 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 $\boldsymbol{\Sigma}_i$ is known, $\hat{\gamma}$ and $Var\left(\hat{\gamma}\right)$ from the conditional approach are equivalent to the solution to the regression of $\boldsymbol{\Delta}\mathbf{Y}_i$ on $\boldsymbol{\Delta}\mathbf{X}_i$ by GLS using the covariance matrix $\boldsymbol{\Delta}\boldsymbol{\Sigma}_i\boldsymbol{\Delta}'$.

Web Appendix B Relationship between correlation coefficient and intra-class 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 $\sum_{j=0}^{r}\sum_{j'\neq j}\left(\mathbb{E}\left[E_j E_{j'}\right]\right. = \left.\bar{p}_e r\left(r+1\right)\left[\bar{p}_e(1-\rho_e)+\rho_e\right]\right.$. Therefore, we have that

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

Solving for ρ_x, we have

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

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

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

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

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

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

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

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

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

For binary variables, we have the constraint $\mathbb{E}\left[E_j E_{j'}\right] \leqslant \min\left(p_{ej}, p_{ej'}\right)\ \forall j, j'$. 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,

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

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

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

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 $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\right.$. The [2,1] and [1,2] components are

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

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

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

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

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

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\mathbb{E}\left[\left(E_{-1}^*+\sum_{k=0}^{j}E_k\right)(t_0+sj')\right]v^{jj'}\Bigg)=\mathbb{E}\left(E_{-1}^*t_0\right)\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}+$$

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

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, $\mathbb{E}\left[\mathbf{X}'_i\boldsymbol{\Sigma}^{-1}\mathbf{X}_i\right]$ 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,

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

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 $\boldsymbol{\Delta}\boldsymbol{\Sigma}\boldsymbol{\Delta}'$. Let $w_{jj'}$ be $[j, j']$ element of $(\boldsymbol{\Delta}\boldsymbol{\Sigma}\boldsymbol{\Delta}')^{-1}$, $j = 1, \ldots, r$; $j' = 1, \ldots, r$. Then,

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

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

nent of the inverse of $\mathbb{E}\left[\mathbf{X'}_i \left(\mathbf{\Delta\Sigma\Delta'}\right)^{-1} \mathbf{X}_i\right]$ is

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

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

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

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

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

(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 $(\mathbf{\Delta\Sigma\Delta}')^{-1}$ when $\mathbf{\Sigma}$ 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 $(\mathbf{\Delta\Sigma\Delta}')^{-1}$ where always greater or equal than zero. For RS, examples can be found where some off-diagonal elements of $(\mathbf{\Delta\Sigma\Delta}')^{-1}$ are negative. For example, for $r = 3$, $\sigma^2_w = 0.1$, $\sigma^2_{b_0} = 0.12$, $\sigma^2_{b_1} = 0.15$, $\rho_{b_0 b_1} = -0.52$,

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

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

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

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 $\left(\mathbf{\Delta\Sigma\Delta}'\right)^{-1}$, i.e. $w^{jj'}$, is of the form

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

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

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

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

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

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

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

Since

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

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

we can deduce that

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

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

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

if $j<j'$ and

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

if $j>j'$. Then,

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

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

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,

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

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

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

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

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

Finally, the [4,4] component is

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

Now, let us call $a=\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}$, $b=\sum_{j=0}^{r}\sum_{j'=0}^{r}jv^{jj'}$, $c=\sum_{j=0}^{r}\sum_{j'=0}^{r}jj'v^{jj'}$, $d=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(p_{ej}v_{jj'}\right)$, $e=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jE_{j'}\right]v^{jj'}\right)$, $f=\sum_{j=0}^{r}\sum_{j'=0}^{r}j'p_{ej}v^{jj'}$, $g=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jt_0\right]v^{jj'}\right)$, $h=\sum_{j=0}^{r}\sum_{j'=0}^{r}jp_{ej}v^{jj'}$, $k=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(jj'p_{ej'}v^{jj'}\right)$, $l=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_{j'}t_0^2\right]v^{jj'}\right)$, $m=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)$, $n=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}\left[E_{j'}t_0\right]v^{jj'}\right)$, $o=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jE_{j'}t_0\right]v^{jj'}\right)$, $p=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j'\mathbb{E}\left[E_jE_{j'}\right]v^{jj'}\right)$, $q=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\mathbb{E}\left[E_jE_{j'}t_0^2\right]v^{jj'}\right)$, $u=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(jj'\mathbb{E}\left[E_jE_{j'}\right]v^{jj'}\right)$, $v=\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(j\mathbb{E}\left[E_jE_{j'}t_0\right]v^{jj'}\right)$. 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,

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

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

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

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

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

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,

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

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

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

and

$$u = \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(jj'\mathbb{E}\left[E_jE_{j'}\right]v^{jj'}\right) =$$
$$\sum_{j'=0}^{r}\left\{j'^2\left(\frac{p_e}{\sigma^2}\frac{(r-1)\rho+1}{[1+\rho(r-1)-\rho^2 r]}+\frac{\rho\left(\rho_e p_e(1-p_e)+p_e^2\right)}{\sigma^2(1-\rho)\left(1+r\rho\right)}\right)+\right.$$
$$\left.j'\frac{-\rho r(r+1)\left(\rho_e p_e(1-p_e)+p_e^2\right)}{2\sigma^2(1-\rho)\left(1+r\rho\right)}\right\}\left(\frac{r(r+1)}{\sigma^2(1-\rho)\left(1+r\rho\right)}\right.$$
$$\left\{\frac{p_e\left(1+(p_e+r-1)\rho+(1-p_e)\rho\rho_e\right)(2r+1)}{6}-\frac{\rho r(r+1)\left(\rho_e p_e(1-p_e)+p_e^2\right)}{4}\right\}\cdot\left(\right.$$

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

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

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

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

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

The variance of the coefficients under model (6) can be obtained as $\boldsymbol{\Sigma}_{\mathrm{B}} = \left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$, where $\mathbf{M} = \boldsymbol{\Delta}'\left(\boldsymbol{\Delta}\boldsymbol{\Sigma}\boldsymbol{\Delta}'\right)^{-1}\boldsymbol{\Delta}$ (Web Appendix A). Since $\boldsymbol{\Delta}\mathbf{1} = \mathbf{0}$, 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 $\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]$. The [2,3] and [3,2] components are

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

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

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

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

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

The [3,4] component is

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[t_jE_{j'}t_{j'}\right]=\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[(t_0+sj)(t_0+sj')E_{j'}\right]$$
$$=\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[t_0^2E_{j'}\right]+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}j\mathbb{E}\left[t_0E_{j'}\right]+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[t_0E_{j'}\right]$$
$$+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}p_{ej'}=\sum_{j=0}^{r}\mathbb{E}\left[t_0^2E_j\right]\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}+s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}j\mathbb{E}\left[t_0E_{j'}\right]$$
$$+s\sum_{j=0}^{r}j\mathbb{E}\left[t_0E_j\right]\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}p_{ej'}$$
$$=s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[t_0E_{j'}\right]+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}p_{ej'}$$

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

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[E_jt_jE_{j'}t_{j'}\right]=\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[(t_0+sj)(t_0+sj')E_jE_{j'}\right]=$$
$$\sum_{j=0}^{r}\sum_{j'=0}^{r}m^{jj'}\mathbb{E}\left[E_jE_{j'}t_0^2\right]+2s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[t_0E_jE_{j'}\right]+s^2\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[E_jE_{j'}\right].$$

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 $s\sum_{j=0}^{r}\sum_{j'=0}^{r}\binom{j}{j'}m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]$,

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

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

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

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

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

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

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

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

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

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

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

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

and

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

The [3,4] component becomes

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

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

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

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

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

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

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

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
```

References

[1] Verbeke G, Spiessens B, Lesaffre E. Conditional linear mixed models. *The American Statistician* 2001; **55**(1):25–34.

[2] Seber GAF. *Multivariate observations*. Wiley: New York, 1984.

[3] Ridout MS, Demetrio CG, Firth D. Estimating intraclass correlation for binary data. *Biometrics* 1999; **55**(1):137–48.

[4] Hu GY, O'Connell RF. Analytical inversion of symmetric tridiagonal matrices. *Journal of Physics A: Mathematical and General* 1996; **29**:1511–3.

[5] Leisch F, Weingessel A, Hornik K. On the generation of correlated artificial binary data. *Working Paper Series, SFB "Adaptive Information Systems and Modelling in Economics and Management Science"* 1998; **13**.

[6] Higham NJ. Computing a nearest symmetric positive semidefinite matrix. *Linear Algebra and its Applications* 1988; **103**:103–18.

[7] Medina-Ramon M, Zock JP, Kogevinas M, Sunyer J, Basagana X, Schwartz J, Burge PS, Moore V, Anto JM. Short-term respiratory effects of cleaning exposures in female domestic cleaners. *European Respiratory Journal* 2006; **27**(6):1196–203.