Supplementary Material to 'Power and Sample Size Calculations for Longitudinal Studies Estimating a Main Effect of a Time-Varying Exposure' by X. Basagaña, X. Liao and D. Spiegelman

Web Appendix A Intraclass correlation

Web Appendix A.1 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.6, 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 A.2 Upper bound for ρ_e

For binary variables, we have the constraint $\mathbb{E}\left[E_j E_{j'}\right] \leqslant \min\left(p_{ej}, p_{ej'}\right) \;\; \forall j, j'$. In Web Appendix C.6 we derived the equality

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

from where it can be deduced that

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

Then, it is easily shown that

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

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,

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

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

[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 $\mathbb{E}\left(\mathbf{Y}_i\right) = a_i\mathbf{1} + \mathbf{X}_i\beta$, where $\mathbf{1}$ is a vector of ones, $\mathbf{X}_i$ a matrix of covariates and β a vector of regression parameters. Assuming normality of $\mathbf{Y}_i$ and $Var\left(\mathbf{Y}_i\right) = \mathbf{\Sigma}_i$, the probability density function has the expression

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

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

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

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 $\mathbf{1}'\mathbf{\Sigma}_i^{-1}a_i\mathbf{1} + \mathbf{1}'\mathbf{\Sigma}_i^{-1}\mathbf{X}_i\beta$ 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

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

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

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

Using property B.3.5 of [2], page 536,

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

we can write then the conditional likelihood as

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

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

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

The maximum likelihood estimator of β is

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

and

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

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, $\hat{\beta}$ and $Var\left(\hat{\beta}\right)$ 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 C Derivation of formulas for σ_1^2

Web Appendix C.1 Model (2.2)

The $[g, h]$ term of the matrix $\mathbb{E}_X\left[\mathbf{X}'_i\boldsymbol{\Sigma}^{-1}\mathbf{X}_i\right]$ can be written as $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(\psi^{jj'}\mathbb{E}\left[x_{ijg}x_{ij'h}\right]\right)$, where x_{ijg} is the value of the gth covariate for subject i at time j. Model (2.2) contains only two covariates, a column of ones and the column of exposures. The [1,1] component of $\mathbb{E}_X\left[\mathbf{X}'_i\boldsymbol{\Sigma}^{-1}\mathbf{X}_i\right]$ is $\sum_{j=0}^{r}\sum_{j'=0}^{r}\psi^{jj'}$, the [2,1] and [1,2] components are $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}p_{ej}\right)$ and the [2,2] component is $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)$. Then, the [2,2] component of the inverse is

$$\boldsymbol{\Sigma}_{\mathrm{B}}\left[2,2\right]=\sigma_1^2=\frac{\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\right)}{\left(\sum_{j=0}^{r}\sum_{j'=0}^{r}v^{jj'}\right)\left(\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)\right)-\left(\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}p_{ej}\right)\right)^2}.$$

Web Appendix C.2 Model (2.3)

Based on Web Appendix B, $\boldsymbol{\Sigma}_{\mathrm{B}}=\left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$. In model (2.2), $\mathbf{X}_i$ contains a column of ones and the column of exposures at the previous time point. Since $\boldsymbol{\Delta}\mathbf{1}=\mathbf{0}$,

$$\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]=\begin{pmatrix}0 & 0\\ 0 & \sum_{j=0}^{r}\sum_{j'=0}^{r}\left(m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)\end{pmatrix}$$

and the [2,2] component of the $\left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$ is

$$\sigma_1^2=\left(\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)\right)^{-1}.$$

Web Appendix C.3 Model (2.4)

Model (2.4) contains a column of ones, the column of exposures and the column of times, and the $[g,h]$ term of the matrix $\mathbb{E}_X\left[\mathbf{X}'_i\boldsymbol{\Sigma}^{-1}\mathbf{X}_i\right]$ can be written as $\sum_{j=0}^{r}\sum_{j'=0}^{r}\left(v^{jj'}\mathbb{E}\left[x_{ijg}x_{ij'h}\right]\right)$. The [1,1], [1,2] , [2,1] and [2,2] components were derived in Web Appendix C.1. The [3,1] and [1,3] components are

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

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

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

Without loss of generality, the time variable can be centered at the mean initial time so that $\mathbb{E}\left[t_0\right] = 0$ and $\mathbb{E}\left[t_0^2\right] = V\left(t_0\right)$. Defining ρ_{e_j,t_0} as the correlation between initial time (or age at entry) and exposure at the jth time, then the [3,2] and [2,3] components are

$$\sqrt{V(t_0)}\sum_{j=0}^{r}\sum_{j'=0}^{r} \rho_{e_j,t_0}\sqrt{p_{ej}(1-p_{ej})}v^{jj'} + s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' v^{jj'}.$$

The [3,3] component is

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

Let $a = \sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}$, $b = \sum_{j=0}^{r}\sum_{j'=0}^{r} j v^{jj'}$, $c = \sum_{j=0}^{r}\sum_{j'=0}^{r} j j' v^{jj'}$, $d = \sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} p_{ej}$, $e = \sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$, $f = \sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' v^{jj'}$ and $g = \sum_{j=0}^{r}\sum_{j'=0}^{r} \rho_{e_j,t_0}\sqrt{p_{ej}(1-p_{ej})}v^{jj'}$. Then,

$$\mathbf{\Sigma}_{\mathrm{B}}\left[2,2\right] = \sigma_1^2 = \frac{b^2 s^2 - a\left(cs^2 + aV(t_0)\right)}{\left(b^2 e + c\left(d^2 - ae\right) - 2bdf + af^2\right)s^2 - 2\left(bd - af\right)gs\sqrt{V(t_0)} + a\left(d^2 - ae + g^2\right)V(t_0)}.$$

If the prevalence of exposure is constant over time, then $d = p_e a$ and $f = p_e b$. Therefore,

$$\sigma_1^2 = \frac{b^2 s^2 - a\left(cs^2 + aV(t_0)\right)}{\left(b^2 e + c\left(p_e^2 a^2 - ae\right) - p_e^2 ab^2\right)s^2 + a\left(p_e^2 a^2 - ae + g^2\right)V(t_0)}.$$

If, in addition to the prevalence of exposure being constant over time, $V(t_0) = 0$ or $\rho_{e_j,t_0} = 0\ \forall j$, then $\sigma_1^2 = \frac{1}{e - p_e^2 a}$, which equals the variance for model (2.2).

Web Appendix C.4 Model (2.5)

Based on Web Appendix C.1, $\boldsymbol{\Sigma}_{\mathrm{B}} = \left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$. In model (2.4), $\mathbf{X}_i$ contains a column of ones, the column of exposures and the column of times. Since $\boldsymbol{\Delta}\mathbf{1} = \mathbf{0}$, we have $\mathbf{1}'\mathrm{M} = \mathbf{0}$, i.e. the sum of each column of $\mathbf{M}$ is zero. This implies that the [1,1], [1,2], [1,3], [2,1] and [3,1] components of $\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]$ are zero. The [2,2] component is $\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$, as derived in Web Appendix C.2. Without loss of generality, the time variable can be centered at the mean initial time so that $\mathbb{E}\left[t_0\right] = 0$ and $\mathbb{E}\left[t_0^2\right] = V\left(t_0\right)$. Then, the [2,3] and [3,2] components are

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

The first term of the last expression is equal to $\sum_{j=0}^{r}\mathbb{E}\left[E_j t_0\right]\sum_{j'=0}^{r} m^{jj'} = 0$. The [3,3] term is

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

and since the two first elements of this expression are zero, the [3,3] term is $s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} j j' m^{jj'}$. Then,

$$
\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right] = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right] & s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'} \\ 0 & s\sum_{j=0}^{r}\sum_{j'=0}^{r} p_{ej} j' m^{jj'} & s^2\sum_{j=0}^{r}\sum_{j'=0}^{r} j j' m^{jj'} \end{pmatrix}
$$

and the [2,2] component of the $\left(\mathbb{E}\left[\mathbf{X}_i'\mathbf{M}\mathbf{X}_i\right]\right)^{-}$ is

$$\boldsymbol{\Sigma}_{\mathrm{B}}\left[2,2\right] = \sigma_1^2 = \frac{\sum_{j=0}^{r}\sum_{j'=0}^{r} jj'm^{jj'}}{\left(\sum_{j=0}^{r}\sum_{j'=0}^{r} jj'm^{jj'}\right)\left(\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right) - \left(\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}j'p_{ej}\right)^2}.$$

If the prevalence of exposure is constant over time, then $\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}j'p_{ej} = p_e\sum_{j=0}^{r}\sum_{j'=0}^{r} j'm^{jj'} = p_e\mathbf{1}'\mathrm{M}\mathbf{t}$, and since $\mathbf{1}'\mathrm{M} = 0$, the second term in the denominator vanishes. Therefore,

$$\sigma_1^2 = \left(\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)^{-1},$$

as for model (2.3).

Web Appendix C.5 Proof that, under CS response, $\rho_{e_j,e_{j'}}\ \forall j,j'$ do not need to be provided for models (2.2)-(2.5), but only ρ_e. Proof that, under CS response, $p_{ej}\ \forall j$ do not need to be provided for models (2.2)-(2.3) but only $\bar{p}_e$

First, we derive the form of the matrices $\boldsymbol{\Sigma}^{-1}$ and M under CS. If $\boldsymbol{\Sigma}$ has CS structure, then $\boldsymbol{\Sigma}^{-1}$ has diagonal elements equal to

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

and off-diagonal elements equal to

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

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

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

and the sum of all elements of the inverse matrix is

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

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 $\left(\mathbf{\Delta\Sigma\Delta}'\right)^{-1}$ 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 $j, j' = 1, \ldots, r^3$, which can be rewritten as

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

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

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

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

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

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 $\mathbf{M} = \mathbf{\Delta}'\left(\mathbf{\Delta\Sigma\Delta}'\right)^{-1}\mathbf{\Delta}$ 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 $\mathbf{M}$ is zero.

Based on Web Appendix C.1-Web Appendix C.4, the only components that depend on $\rho_{e_j,e_{j'}}\ \forall j, j'$ for models (2.2)-(2.5) are $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$ and $\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$. From the form of $\mathbf{\Sigma}^{-1}$ we have that

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

Since the exposure is binary, then $\mathbb{E}\left(E_j^2\right) = \mathbb{E}\left(E_j\right) = p_{ej}$, and $\sum_{j=0}^{r}\mathbb{E}\left(E_j^2\right) = \sum_{j=0}^{r} p_{ej} = (r+1)\,\bar{p}_e$. Now, we define $E_{i\cdot} = \sum_{j=0}^{r} E_{ij}$ as the total number of exposed periods for subject i . Then, by the properties of the expectation we have

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

and $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_j E_{j'}\right] = \mathbb{E}\left(E_{i\cdot}^2\right) - \mathbb{E}\left(E_{i\cdot}\right)$. Since $\mathbb{E}\left(E_{i\cdot}\right) = (r+1)\,\bar{p}_e$, the only additional unknown for the [2,2] component is $\mathbb{E}\left(E_{i\cdot}^2\right)$. Instead of providing $\mathbb{E}\left(E_{i\cdot}^2\right)$, we can base the formulas on the intraclass correlation of exposure, which has the expression

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

4. Then, $\mathbb{E}\left(E_{i\cdot}^2\right) = \bar{p}_e\left(r+1\right)\left(1+\bar{p}_e r(1-\rho_e)+\rho_e r\right)$, $\sum_{j=0}^{r}\sum_{j'\neq j}\mathbb{E}\left[E_j E_{j'}\right] = \bar{p}_e r\left(r+1\right)\left[\bar{p}_e(1-\rho_e)+\rho_e\right]$ and we have that

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

which only depends on $\bar{p}_e$ and ρ_e.

From the form of M under CS, we have

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

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

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

which only depend $\bar{p}_e$ and ρ_e. Thus, $\rho_{e_j,e_{j'}}\,\forall j,j'$ do not need to be provided for models (2.2)-(2.5), but only ρ_e.

Based on Web Appendix C.1-Web Appendix C.2, the only other component, apart from the ones just derived, that may depend on $p_{ej}\,\forall j$ for models (2.2)-(2.3) is $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}p_{ej}$, and using the form of $\mathbf{\Sigma}^{-1}$ under CS we have

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}p_{ej} = \sum_{j=0}^{r} p_{ej}\sum_{j'=0}^{r} v^{jj'} = \frac{1}{\sigma^2\left(1+r\rho\right)}\sum_{j=0}^{r} p_{ej} = \frac{(r+1)\bar{p}_e}{\sigma^2\left(1+r\rho\right)},$$

which only depends on $\bar{p}_e$. Therefore, for models (2.2)-(2.3) under CS, $p_{ej}\,\forall j$ do not need to be provided, but only $\bar{p}_e$.

Web Appendix C.6 Expression for σ_1^2 for model (2.2) under CS covariance of the response

For model (2.2), $\mathbb{E}_X\left[\mathbf{X'}_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ is a $[2 \times 2]$ matrix. Using the results of Web Appendix C.5, the [1,1] component is $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} = \frac{r+1}{\sigma^2(1+r\rho)}$, the [1,2] and [2,1] component are

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} p_{ej} = \frac{(r+1)\bar{p}_e}{\sigma^2\left(1+r\rho\right)},$$

and the [2,2] component is

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

Then, the [2,2] component of the inverse of $\mathbb{E}_X\left[\mathbf{X'}_i\mathbf{\Sigma}^{-1}\mathbf{X}_i\right]$ is

$$\sigma_1^2 = \frac{\sigma^2(1-\rho)\left(1+r\rho\right)}{\bar{p}_e\left(1-\bar{p}_e\right)\left(r+1\right)\left(1-\rho\left(1-r+r\rho_e\right)\right)}.$$

Web Appendix C.7 Variance formula for model (2.3) under CS covariance of the response

Using the results of Web Appendix C.5, the formula for σ_1^2 for model (2.3) derived in Web Appendix C.2 reduces to

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

when CS of the response is assumed.

Web Appendix D 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 correlation 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 [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 E Proof that under AR(1) covariance of response and $V(t_0) = 0$, σ_1^2 for models (2.2) and (2.4) is exactly calculated by knowing p_{ej} $\forall j$ and ρ_{e_1}, regardless of the covariance of the exposure

If $\boldsymbol{\Sigma}$ is AR(1), then $\boldsymbol{\Sigma}^{-1}$ has the form

$$\boldsymbol{\Sigma}^{-1} = \frac{1}{(1-\rho^2)\,\sigma^2} \begin{pmatrix} 1 & -\rho & 0 & 0 & \cdots & 0 \\ -\rho & 1+\rho^2 & -\rho & 0 & & 0 \\ 0 & -\rho & 1+\rho^2 & \ddots & \ddots & \vdots \\ 0 & 0 & \ddots & \ddots & -\rho & 0 \\ \vdots & & \ddots & -\rho & 1+\rho^2 & -\rho \\ 0 & 0 & \cdots & 0 & -\rho & 1 \end{pmatrix}$$

[7] page 201. In models (2.2) and (2.4), once p_{ej} $\forall j$ is fixed and $V(t_0) = 0$ is assumed, only the term $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$ is not known in the formula for σ_1^2. Since under AR(1) $v^{jj'} = 0$ for $|j - j'| > 1$, and $v^{jj'} = \frac{-\rho}{(1-\rho^2)\sigma^2}$ for $|j - j'| = 1$,

$$\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right] = \frac{1}{\left(1-\rho^2\right)\sigma^2}\left(p_{e0} + p_{er} + (1+\rho^2)\sum_{j=1}^{r-1} p_{ej} - 2\rho\sum_{j=0}^{r-1}\mathbb{E}\left[E_j E_{j+1}\right]\right)$$

and only $\sum_{j=0}^{r-1}\mathbb{E}\left[E_j E_{j+1}\right]$ is unknown. The first order autocorrelation of exposure is

$$\rho_{e_1} = \frac{\mathbb{E}\left[\frac{1}{r}\sum_{j=0}^{r-1}\left(E_j - \mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'}\right)\right)\left(E_{j+1} - \mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'+1}\right)\right)\right]}{\left[\mathbb{E}\left(\frac{1}{r}\sum_{j=0}^{r-1}\left(E_j - \mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'}\right)\right)^2\right)\right]^{\frac{1}{2}}\left[\mathbb{E}\left(\frac{1}{r}\sum_{j=0}^{r-1}\left(E_{j+1} - \mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'+1}\right)\right)^2\right)\right]^{\frac{1}{2}}}$$

It can be shown that

$$\mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'}\right) = \left((r+1)\bar{p}_e - p_{er}\right)/r$$

and

$$\mathbb{E}\left(\frac{1}{r}\sum_{j'=0}^{r-1}E_{j'+1}\right) = \left((r+1)\bar{p}_e - p_{e0}\right)/r,$$

so that the numerator of ρ_{e_1} becomes

$$\frac{1}{r}\sum_{j=0}^{r-1}\mathbb{E}\left[E_j E_{j+1}\right] - \left(\frac{(r+1)\bar{p}_e - p_{er}}{r}\right)\left(\frac{(r+1)\bar{p}_e - p_{e0}}{r}\right).$$

With the results above and the fact that $\sum_{j=0}^{r-1} E_j^2 = \sum_{j=0}^{r-1} E_j$ we can simplify the numerator of ρ_{e_1} and obtain

$$\rho_{e_1} = \frac{\frac{1}{r}\sum_{j=0}^{r-1}\mathbb{E}\left[E_j E_{j+1}\right] - \left(\frac{(r+1)\bar{p}_e - p_{er}}{r}\right)\left(\frac{(r+1)\bar{p}_e - p_{e0}}{r}\right)}{\sqrt{\frac{(r+1)\bar{p}_e - p_{er}}{r}\left(1 - \frac{(r+1)\bar{p}_e - p_{er}}{r}\right)}\sqrt{\frac{(r+1)\bar{p}_e - p_{e0}}{r}\left(1 - \frac{(r+1)\bar{p}_e - p_{e0}}{r}\right)}}$$

and

$$\sum_{j=0}^{r-1} \mathbb{E}\left[E_j E_{j+1}\right] = \frac{\rho_{e_1}}{r} \sqrt{((r+1)\bar{p}_e - p_{er})\left(r - ((r+1)\bar{p}_e - p_{er})\right)}\sqrt{((r+1)\bar{p}_e - p_{e0})\left(r - ((r+1)\bar{p}_e - p_{e0})\right)} + \left(\frac{(r+1)\bar{p}_e - p_{er}}{r}\right)((r+1)\bar{p}_e - p_{e0}) .$$

Thus, with the additional parameter ρ_{e_1}, the only unknown part of σ_1^2, which was shown to be $\sum_{j=0}^{r-1} \mathbb{E}\left[E_j E_{j+1}\right]$, is exactly determined.

Web Appendix F Proof that σ_1^2 is maximized at the upper bound of ρ_e if $v^{jj'} \leqslant 0 \ \forall j \neq j'$ for models (2.2) and (2.4); or if $m^{jj'} \leqslant 0 \ \forall j \neq j'$ for models (2.3) and (2.5). These conditions hold for CS and appear to hold for DEX

For model (2.2) we have from equation (3.1) that

$$\sigma_1^2 = \frac{\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}}{\left(\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\right)\left(\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]\right) - \left(\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} p_{ej}\right)^2},$$

where $v^{jj'}$ are the elements of $\mathbf{\Sigma}^{-1}$. When p_{ej} $\forall j$ are fixed, σ_1^2 will be affected by changes in ρ_e only through $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$, since $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$ is the only component of σ_1^2 affected by changes in the exposure distribution. Since $\mathbf{\Sigma}^{-1}$ is positive definite, $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'} > 0$ and a decrease in $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$ increases σ_1^2, so in order to maximize σ_1^2 we need to minimize $\sum_{j=0}^{r}\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$. In addition, since $\mathbb{E}\left[E_j E_j\right] = p_{ej}$ and p_{ej} $\forall j$ are fixed, only $\sum_{j=0}^{r}\sum_{j' \neq j} v^{jj'}\mathbb{E}\left[E_j E_{j'}\right]$ needs to be minimized. If $v^{jj'} \leqslant 0 \ \forall j \neq j'$, then $\sum_{j=0}^{r} \sum_{j' \neq j} v^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ will be minimized when all terms $\mathbb{E}\left[E_j E_{j'}\right] \ \forall j \neq j'$ take their upper bound, $\min\left(p_{ej}, p_{ej'}\right)$. As derived in Web Appendix C.6,

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

so

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

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. The proof is the same for model (2.4) once we realize that the formula for σ_1^2 derived in Web Appendix C.3 only depends on ρ_e through the term $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ after $p_{ej} \ \forall j$ are fixed. This term is the same one we studied for model (2.2) and the same reasoning applies.

The off-diagonal elements of the inverse of CS matrix are all equal to $\frac{1}{\sigma^2} \frac{-\rho}{(1-\rho)(1+r\rho)}$ and therefore are all negative. 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 the inverse were always smaller than or equal to zero.

For model (2.3), we have from equation (3.2) that

$$\sigma_1^2 = \left(\sum_{j=0}^{r} \sum_{j'=0}^{r} m^{jj'} \mathbb{E}\left[E_j E_{j'}\right] \right)^{-1}.$$

Proceeding as for model (2.2), σ_1^2 will be maximized when $\sum_{j=0}^{r} \sum_{j' \neq j} m^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ is minimized. If $m^{jj'} \leqslant 0 \ \forall j \neq j'$, then $\sum_{j=0}^{r} \sum_{j' \neq j} m^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ will be minimized when all terms $\mathbb{E}\left[E_j E_{j'}\right] \ \forall j \neq j'$ are equal to their upper bound, in which case ρ_e will also take its upper bound. For model (2.5), we have from formula (3.3) that

$$\sigma_1^2 = \frac{\sum_{j=0}^{r}\left(\sum_{j'=0}^{r} jj'm^{jj'}\right)}{\sum_{j=0}^{r}\left(\sum_{j'=0}^{r} jj'm^{jj'}\right)\left(\sum_{j=0}^{r}\sum_{j'=0}^{r} m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right) - \left(\sum_{j=0}^{r}\left(\sum_{j'=0}^{r}\left(m^{jj'}j'p_{ej}\right)\right)\right)^2},$$

and this formula only depends on ρ_e through $\sum_{j=0}^{r}\sum_{j'\neq j} m^{jj'}\mathbb{E}\left[E_jE_{j'}\right]$ in the same way as model (2.3) did, so the same reasoning applies.

The off-diagonal elements of the inverse of the matrix M under CS are $\frac{-1}{\sigma^2(1-\rho)(r+1)}$, as derived in Web Appendix C.7, so they are all negative. 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 M were always smaller than or equal to zero.

Web Appendix G Upper bounds for σ_1^2

Web Appendix G.1 Optimization problem to solve to find the upper bound for σ_1^2 for known ρ_e and p_{ej} $\forall j$ for model (2.2)

We want to find an upper bound for σ_1^2 when ρ_e and p_{ej} $\forall j$ are known. The only part of σ_1^2 in (3.1) that is not fixed is $\sum_{j=0}^{r}\left(\sum_{j'=0}^{r} v^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)$, and since $\mathbb{E}\left[E_j^2\right] = p_{ej}$, the only non-fixed part is $2\sum_{j=0}^{r-1}\left(\sum_{j'=j+1}^{r}\left(v^{jj'}\mathbb{E}\left[E_jE_{j'}\right]\right)\right)$. The unknowns in this problem are the $r(r+1)/2$ subdiagonal elements of the symmetric matrix **E**,

$$\mathbf{E} = \begin{pmatrix} p_{e0} & & & \\ \mathbb{E}\left[E_0E_1\right] & p_{e1} & & \\ \vdots & & \ddots & \\ \mathbb{E}\left[E_0E_r\right] & \cdots & \mathbb{E}\left[E_rE_{r-1}\right] & p_{er} \end{pmatrix}. \tag{G.1}$$

There are some constraints in this matrix. Fixing ρ_e and p_{ej} $\forall j$ fixes $\sum_{j=0}^{r}\sum_{j'=0}^{r}\mathbb{E}\left[E_jE_{j'}\right]$ (Web Appendix C.6), giving the equality constraint

$$\sum_{j=0}^{r}\sum_{j'=0}^{r}\mathbb{E}\left[E_jE_{j'}\right]=\bar{p}_e\left(r+1\right)\left[1+\bar{p}_e r(1-\rho_e)+\rho_e r\right]. \tag{G.2}$$

There exist upper and lower bounds for the correlations of binary variables, which are

$$\begin{aligned}\max\left(-\sqrt{\frac{p_{ej}p_{ej'}}{(1-p_{ej})(1-p_{ej'})}},-\sqrt{\frac{(1-p_{ej})(1-p_{ej'})}{p_{ej}p_{ej'}}}\right)&\leqslant\rho_{e_j,e_{j'}}\\ &\leqslant\min\left(\sqrt{\frac{p_{ej}(1-p_{ej'})}{(1-p_{ej})p_{ej'}}},\sqrt{\frac{(1-p_{ej})p_{ej'}}{p_{ej}(1-p_{ej'})}}\right)\end{aligned}$$

[8]. Expressed in terms of $\mathbb{E}\left[E_jE_{j'}\right]$, the condition is equivalent to

$$\begin{aligned}\max\left(-p_{ej}p_{ej'},-(1-p_{ej})(1-p_{ej'})\right)+p_{ej}p_{ej'}&\leqslant\mathbb{E}\left[E_jE_{j'}\right]\\ &\leqslant\min\left(p_{ej}(1-p_{ej'}),(1-p_{ej})p_{ej'}\right)+p_{ej}p_{ej'}\end{aligned}$$

which is equivalent to $\max\left(0,-(1-p_{ej}-p_{ej'})\right)\leqslant\mathbb{E}\left[E_jE_{j'}\right]\leqslant\min\left(p_{ej},p_{ej'}\right)$. The constraints can be incorporated as

$$\mathbb{E}\left[E_jE_{j'}\right]\geqslant 0\ \forall j,j'; \tag{G.3}$$

$$p_{ej}+p_{ej'}-1\leqslant\mathbb{E}\left[E_jE_{j'}\right]\ \forall j,j'; \tag{G.4}$$

$$\mathbb{E}\left[E_jE_{j'}\right]\leqslant p_{ej}\ \forall j,j'; \tag{G.5}$$

$$\mathbb{E}\left[E_jE_{j'}\right]\leqslant p_{ej'}\ \forall j,j'. \tag{G.6}$$

The correlation matrix still needs another set of constraints so that the probability of at least m variables being one is not greater than one. This condition can be expressed as, for all possible choice of m indices $l_1,\ldots,l_m$ out of $(0,1,\ldots,r)$,

$$\sum_{j=1}^{m}p_{e,l_j}-1\leqslant\sum_{j=1}^{m-1}\sum_{j'=j+1}^{m}\mathbb{E}\left[E_{l_j}E_{l_{j'}}\right]\quad 3\leqslant m\leqslant r \tag{G.7}$$

[5]. This implies

$$\left(\begin{array}{c} r+1 \\ 3 \end{array}\right) + \cdots + \left(\begin{array}{c} r+1 \\ r \end{array}\right) = 2^{r+1} - \frac{(r+1)(r+2)}{2} - 2$$

linear constraints. We define $\mathbf{b}$ as the vector of unknowns, $\mathbf{b}' = (\mathbb{E}[E_0E_1], \mathbb{E}[E_0E_2], \ldots, \mathbb{E}[E_0E_r], \mathbb{E}[E_1E_2], \ldots, \mathbb{E}[E_1E_r], \ldots, \mathbb{E}[E_{r-1}E_r])$. Then the optimization problem is $\min_{\mathbf{b}} \sum_{j=0}^{r-1} \sum_{j'=j+1}^{r} \left(v^{jj'}\mathbb{E}[E_jE_{j'}]\right)$ subject to the constraints (G.2)-(G.7). The optimization function is a linear function of the unknowns, and the equality and inequality constraints are all linear. Our software solves this linear programming problem with the simplex algorithm using the "simplex" command of the "boot" library in R[9]. The constraints we included are necessary constraints for the covariance matrix of the exposure process to be positive definite, but they are not sufficient[8].

Web Appendix G.2 Upper bound for σ_1^2 for known p_{ej} $\forall j$ and ρ_e for model (2.3)

The formula for σ_1^2 is $\sigma_1^2 = \left(\sum_{j=0}^{r} \sum_{j'=0}^{r} m^{jj'}\mathbb{E}[E_jE_{j'}]\right)^{-1}$. To maximize σ_1^2, we just need to minimize $\sum_{j=0}^{r} \sum_{j'=0}^{r} m^{jj'}\mathbb{E}[E_jE_{j'}]$. The procedure is equivalent to the one in Web Appendix G.1, we just need to substitute $v^{jj'}$ with $m^{jj'}$.

Web Appendix G.3 Upper bound for σ_1^2 for known p_{ej} $\forall j$ and ρ_e for model (2.4) with $V(t_0) = 0$

From Web Appendix C.3,

$$\sigma_1^2 = \frac{b^2s^2 - a\left(cs^2 + aV(t_0)\right)}{\left(b^2e + c\left(d^2 - ae\right) - 2bdf + af^2\right)s^2 - 2\left(bd - af\right)gs\sqrt{V(t_0)} + a\left(d^2 - ae + g^2\right)V(t_0)}.$$

When $V(t_0) = 0$, this reduces to

$$\sigma_1^2 = \frac{ac - b^2}{e\left(ac - b^2\right) - cd^2 + 2bdf - af^2},$$

where $a = \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'}$, $b = \sum_{j=0}^{r} \sum_{j'=0}^{r} j v^{jj'}$, $c = \sum_{j=0}^{r} \sum_{j'=0}^{r} j j' v^{jj'}$, $d = \sum_{j=0}^{r} \sum_{j'=0}^{r} \left(v^{jj'} p_{ej}\right)$, $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$, $f = \sum_{j=0}^{r} \sum_{j'=0}^{r} p_{ej} j' v^{jj'}$. If the prevalence at each time point is known, only $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ is not completely specified. In order to find an upper bound to σ_1^2, $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ needs to be minimized for a known value ρ_e. This problem reduces to the same problem solved in Web Appendix G.2.

Web Appendix G.4 Upper bound for σ_1^2 for known p_{ej} $\forall j$ and ρ_e for model (2.5)

For model (2.5) we have, according to equation (3.3) that

$$\sigma_1^2 = \frac{\sum_{j=0}^{r} \sum_{j'=0}^{r} j j' m^{jj'}}{\left(\sum_{j=0}^{r} \sum_{j'=0}^{r} j j' m^{jj'}\right) \left(\sum_{j=0}^{r} \sum_{j'=0}^{r} m^{jj'} \mathbb{E}\left[E_j E_{j'}\right]\right) - \left(\sum_{j=0}^{r} \sum_{j'=0}^{r} \left(m^{jj'} j' p_{ej}\right)\right)^2}.$$

If the prevalence at each time point is known, only $\sum_{j=0}^{r} \sum_{j'=0}^{r} m^{jj'} \mathbb{E}\left[E_j E_{j'}\right]$ is not fully specified. The problem of finding an upper bound for a given value of ρ_e reduces to the same problem solved in Web Appendix G.3.

Web Appendix H Demonstration of program use

More information can be found in the user's manual at `http://www.hsph.harvard.edu/faculty/spiegelman/optitxs.html`.

In this example, we compute the power of a study with 31 participants and 14 post-baseline measures, assuming CS covariance structure of the response, to detect a 10

L/min decrease in PEF associated with vaccuuming. We use model (2.3), assuming CMD, no effect of time and assume that interest is in the within-subject effect of exposure. This example is based on the dataset used in section 4.

```
> long.power()

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

* Press <Esc> to quit

Enter the total sample size (N) [100]: 31

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

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]? 1

Enter the mean exposure prevalence (0<pe<1) [0.5]: .37

Enter the intraclass correlation of exposure (-0.066<rho.e<1)
 [0.5]: .13

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

Which model are you basing your calculations on:
(1) Model without time. No separation of between- and within-
    subject effects
(2) Model without time. Within-subject contrast only
(3) Model with time. No separation of between- and within-subject
    effects
(4) Model with time. 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 value of the coefficient of interest in your model, i.e.
 the difference between exposed and unexposed periods (beta)
 [0.1]: 10

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

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

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
 (0<rho<1) [0.8]: .88

Power =  0.9796308

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

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