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

$$\mathbb{E}[E_j E_{j'}] = \rho_x \sqrt{p_{ej}(1 - p_{ej})} \sqrt{p_{ej'}(1 - p_{ej'})} + p_{ej} p_{ej'}$$

where $\rho_x$ is the common correlation between exposures at different time points. From Web Appendix C.6, we have

$$\mathbb{E}[E_j E_{j'}] = \bar{p}_e r \ (r + 1) \ [\bar{p}_e (1 - \rho_e) + \rho_e].$$

Therefore, we have that

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

Solving for $\rho_x$, we have

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

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 \( \rho_e \)

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

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

from where it can be deduced that

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

Then, it is easily shown that

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

Now,

\[
\sum_{j=0}^{r} \sum_{j' \neq j} \min(p_{ej}, p_{ej'}) = 2 \left( \sum_{j=0}^{r-1} (r-j)p_e(j) \right),
\]

where \( p_e(j) \) is the \( j \)th order statistic. Then,

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

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

\(^1\) proved this equivalence for the mixed effects model, where \( \Sigma_i = Z_i D Z_i' + \sigma^2_w I \).

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, $\Sigma_i$, and thus extends their results. Suppose that we have subject-specific intercepts $a_i$, which can be fixed or random, and assume that $E(Y_i) = a_i 1 + X_i \beta$, where $1$ is a vector of ones, $X_i$ a matrix of covariates and $\beta$ a vector of regression parameters. Assuming normality of $Y_i$ and $Var(Y_i) = \Sigma_i$, the probability density function has the expression

$$f(Y_i|a_i, X_i) = \frac{1}{(2\pi)^{r/2} |\Sigma_i|^{1/2}} \exp \left( -\frac{1}{2} (Y_i - a_i 1 - X_i \beta)' \Sigma_i^{-1} (Y_i - a_i 1 - X_i \beta) \right) \left/ \frac{1}{(2\pi)^{r/2} |\Sigma_i|^{1/2}} \exp \left( -\frac{1}{2} \left[ (Y_i - X_i \beta)' \Sigma_i^{-1} (Y_i - X_i \beta) - 2 (Y_i - X_i \beta)' \Sigma_i^{-1} a_i + a_i^2 1' \Sigma_i^{-1} 1 \right] \right) \right.$$

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

$$f(Y_i|s_i, X_i) = \frac{f(Y_i|a_i, X_i)}{f(s_i|a_i, X_i)} = \frac{1}{(2\pi)^{r/2} |\Sigma_i|^{1/2}} \frac{\exp \left( -\frac{1}{2} \left[ (Y_i - X_i \beta)' \Sigma_i^{-1} (Y_i - X_i \beta) - 2 (Y_i - X_i \beta)' \Sigma_i^{-1} a_i + a_i^2 1' \Sigma_i^{-1} 1 \right] \right)}{\exp \left( -\frac{1}{2} \left( Y' \Sigma_i^{-1} Y_i - 1' \Sigma_i^{-1} a_i 1 - 1' \Sigma_i^{-1} X_i \beta \right)^2 \right)} \left/ \frac{1}{(2\pi)^{r/2} |\Sigma_i|^{1/2}} \exp \left( -\frac{1}{2} Y' \Sigma_i^{-1} 1 \left( 1' \Sigma_i^{-1} 1 \right)^{-1} 1' \Sigma_i^{-1} \right) (Y_i - X_i \beta) \right. \right.$$

Using property B.3.5 of $^2$, page 536,

$$\Sigma_i^{-1} - \Sigma_i^{-1} 1 \left( 1' \Sigma_i^{-1} 1 \right)^{-1} 1' \Sigma_i^{-1} = \Delta' (\Delta \Sigma_i \Delta')^{-1} \Delta,$$
we can write then the conditional likelihood as

\[
L(\beta|s_1, \ldots, s_N, X) = \prod_{i=1}^{N} \left| \frac{1^t \Sigma_i^{-1} | 1}{(2\pi)^{1/2}} \right| \exp \left( \frac{1}{2} (Y_i - X_i \beta)' (\Delta \Sigma_i \Delta')^{-1} \Delta (Y_i - X_i \beta) \right)
\]

and the log-likelihood \( \log L(\beta|s_1, \ldots, s_N, X) \) will then be proportional to

\[
\frac{N}{2} \log |Y \Sigma_i^{-1} Y| - \frac{1}{2} \sum_{i=1}^{N} \left( (Y_i - X_i \beta)' (\Delta \Sigma_i \Delta')^{-1} \Delta (Y_i - X_i \beta) \right).
\]

The maximum likelihood estimator of \( \beta \) is

\[
\hat{\beta} = \sum_{i=1}^{N} \left( X_i' \Delta' (\Delta \Sigma_i \Delta')^{-1} \Delta X_i \right)^{-1} \sum_{i=1}^{N} \left( X_i' \Delta' (\Delta \Sigma_i \Delta')^{-1} \Delta Y_i \right)
\]

and

\[
Var(\hat{\beta}) = \sum_{i=1}^{N} \left( X_i' \Delta' (\Delta \Sigma_i \Delta')^{-1} \Delta X_i \right)^{-1} = \sum_{i=1}^{N} \left( X_i' M_i X_i \right)^{-1},
\]

where the notation \( A^- \) indicates the generalized inverse of \( A \). Note that \( \Delta X_i \) 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 \( \Sigma_i \) is known, \( \hat{\beta} \) and \( Var(\hat{\beta}) \) from the conditional approach are equivalent to the solution to the regression of \( \Delta Y_i \) on \( \Delta X_i \) by GLS using the covariance matrix \( \Delta \Sigma_i \Delta' \).

**Web Appendix C  Derivation of formulas for \( \sigma^2_1 \)**

**Web Appendix C.1  Model (2.2)**

The \([g, h]\) term of the matrix \( E_X [X'_i \Sigma^{-1} X_i] \) can be written as

\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} \left( \delta' \mathbb{E}[x_{ijg} x_{ij'h}] \right),
\]

where \( x_{ijg} \) is the value of the \( g \)th 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 \( E_X [X'_i \Sigma^{-1} X_i] \) is

\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} \delta_{jj'},
\]
the \([2,1]\) and \([1,2]\) components are \(\sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'} p_{ej})\) and the \([2,2]\) component is \(\sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_j E_{j'})\). Then, the \([2,2]\) component of the inverse is

\[
\Sigma_B[2,2] = \sigma_1^2 = \frac{\sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'})}{\sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'} E_j E_{j'}) - \sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'} p_{ej})}.
\]

**Web Appendix C.2  Model (2.3)**

Based on Web Appendix B, \(\Sigma_B = (E[X_i'MX_i])^{-1}\). In model (2.2), \(X_i\) contains a column of ones and the column of exposures at the previous time point. Since \(\Delta 1 = 0\),

\[
E[X_i'MX_i] = \begin{pmatrix} 0 & 0 \\ 0 & \sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_j E_{j'}) \end{pmatrix},
\]

and the \([2,2]\) component of the \((E[X_i'MX_i])^{-1}\) is

\[
\sigma_1^2 = \sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_j E_{j'})^{-1}.
\]

**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 \(E_X [X_i' \Sigma^{-1} X_i]\) can be written as \(\sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_{x_{ijg}x_{ij'h}})\). 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

\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_{t_j}) = \sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta^{jj'} E_{t_0 + sj}) = E[t_0] \sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'}) + s \sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'}).\]
The [3,2] and [2,3] component are
\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} \left( v^{jj'} \mathbb{E}[E_j t_{j'}] \right) = \sum_{j=0}^{r} \sum_{j'=0}^{r} \left( v^{jj'} \mathbb{E}[E_j (t_0 + sj')] \right) = \\
\sum_{j=0}^{r} \sum_{j'=0}^{r} \left( v^{jj'} \mathbb{E}[E_j t_0] \right) + s \sum_{j=0}^{r} \sum_{j'=0}^{r} \rho_{ej,t_0} v^{jj'}.
\]

Without loss of generality, the time variable can be centered at the mean initial time so that \( \mathbb{E}[t_0] = 0 \) and \( \mathbb{E}[t_0^2] = V(t_0) \). Defining \( \rho_{ej,t_0} \) as the correlation between initial time (or age at entry) and exposure at the \( j \)th time, then the [3,2] and [2,3] components are
\[
\sqrt{V(t_0)} \sum_{j=0}^{r} \sum_{j'=0}^{r} \left( \rho_{ej,t_0} \mathbb{E}[p_{ej} (1 - p_{ej}) v^{jj'}] \right) + s \sum_{j=0}^{r} \sum_{j'=0}^{r} \rho_{ej,t_0} v^{jj'}.
\]

The [3,3] component is
\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} \left( v^{jj'} \mathbb{E}[E_j t_{j'}] \right) = \mathbb{E}[t_0^2] \sum_{j=0}^{r} \sum_{j'=0}^{r} \left( v^{jj'} + 2s \mathbb{E}[t_0] \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} + s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} \rho_{ej,t_0} v^{jj'} \right).
\]

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

Then,
\[
\Sigma_B[2,2] = \sigma_1^2 = \frac{b^2s^2 - a(cs^2 + aV(t_0))}{(b^2e + c(d^2 - ae) - 2bdf + af^2)s^2 - 2(bd - af)gs\sqrt{V(t_0)} + a(d^2 - ae + g^2)V(t_0)}.
\]

If the prevalence of exposure is constant over time, then \( d = p_e a \) and \( f = p_e b \).

Therefore,
\[
\sigma_1^2 = \frac{b^2s^2 - a(cs^2 + aV(t_0))}{(b^2e + c(p_e^2a^2 - ae) - p_e^2ab^2)s^2 + a(p_e^2a^2 - ae + g^2)V(t_0)}.
\]

If, in addition to the prevalence of exposure being constant over time, \( V(t_0) = 0 \) or \( \rho_{ej,t_0} = 0 \) \( \forall j \), then \( \sigma_1^2 = \frac{1}{e - p_e^2a} \), which equals the variance for model (2.2).
Web Appendix C.4  Model (2.5)

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

$$\sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[E_jt_{j'}]) = \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[E_j(t_0 + s_{j'})])$$

$$= \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[E_jt_0]) + s \sum_{j=0}^{r} \sum_{j'=0}^{r} (p_{ej} j'm_{jj'}).$$

The first term of the last expression is equal to $\sum_{j=0}^{r} \mathbb{E}[E_jt_0] \sum_{j'=0}^{r} (m_{jj'}) = 0$. The [3,3] term is

$$\sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[t_{j'}t_{j'}])$$

$$= \mathbb{E}[t_0^2] \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'}) + 2s \mathbb{E}[t_0] \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'}) + s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} j'm_{jj'}$$

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

$$\mathbb{E}[X_i'MX_i] = \begin{pmatrix}
0 & 0 & 0 \\
0 & \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[E_jE_{j'}]) & s \sum_{j=0}^{r} \sum_{j'=0}^{r} p_{ej} j'm_{jj'} \\
0 & s \sum_{j=0}^{r} \sum_{j'=0}^{r} (p_{ej} j'm_{jj'}) & s^2 \sum_{j=0}^{r} \sum_{j'=0}^{r} j'm_{jj'}
\end{pmatrix}.$$
and the $[2,2]$ component of the $(\mathbb{E}[X_i'MX_i])^{-1}$ is

$$\Sigma_B[2,2] = \sigma^2_1 = \frac{\sum_{j=0}^{r} \sum_{j'=0}^{r} ij'm_{jj'}}{\sum_{j=0}^{r} \sum_{j'=0}^{r} m_{jj'}\mathbb{E}[E_j E_{j'}]} - \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} j'p_{ej})^2.$$ 

If the prevalence of exposure is constant over time, then

$$\rho_e \sum_{j=0}^{r} \sum_{j'=0}^{r} m_{jj'} = p_e \sum_{j=0}^{r} \sum_{j'=0}^{r} j'p_{ej} = p_e 1'Mt,$$

and since $1'M = 0$, the second term in the denominator vanishes. Therefore,

$$\sigma^2_1 = \sum_{j=0}^{r} \sum_{j'=0}^{r} (m_{jj'} \mathbb{E}[E_j E_{j'}])^{-1},$$

as for model (2.3).

**Web Appendix C.5** Proof that, under CS response, $\rho_{ej,ej'} \forall j, j'$ do not need to be provided for models (2.2)-(2.5), but only $\rho_e$. 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 $\Sigma^{-1}$ and $M$ under CS. If $\Sigma$ has CS structure, then $\Sigma^{-1}$ has diagonal elements equal to

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

and off-diagonal elements equal to

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

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

$$\sum_{j=0}^{r} u_{jj'} = \sum_{j'=0}^{r} (jj') = \frac{1}{\sigma^2 (1 + r\rho)}.$$
and the sum of all elements of the inverse matrix is
\[
\sum_{j=0}^{r} \sum_{j' = 0}^{r} \nu^{jj'} = \frac{r + 1}{\sigma^2 (1 + r \rho)}.
\]

Under CS, the matrix \(\Delta \Sigma \Delta'\) is a \(r \times r\) tridiagonal matrix of the form
\[
\sigma^2 (1 - \rho) \begin{pmatrix}
2 & -1 & 0 & \cdots & 0 \\
-1 & 2 & -1 & \cdots & \vdots \\
0 & -1 & 2 & \cdots & 0 \\
\vdots & \ddots & \ddots & \ddots & -1 \\
0 & \cdots & 0 & -1 & 2
\end{pmatrix}.
\]

The \([j, j']\) element of \((\Delta \Sigma \Delta')^{-1}\) is of the form
\[
\frac{1}{4\sigma^2 (1 - \rho)(r + 1)} [(j + j' - |j' - j|) (2r + 2 - |j' - j| - j - j')]
\]
for \(j, j' = 1, \ldots, r^3\), which can be rewritten as
\[
\frac{1}{2\sigma^2 (1 - \rho)(r + 1)} [(r + 1)j + (r + 1)j' - 2jj' - (r + 1) |j' - j|].
\]

If we pre-multiply by \(\Delta'\), the \([j, j']\) element of \(\Delta' (\Delta \Sigma \Delta')^{-1}\) is
\[
\frac{1}{2\sigma^2 (1 - \rho)(r + 1)} \sum_{k=1}^{r} \left( I \{k = j\} - I \{k = j + 1\} \right) ((r + 1)k + (r + 1)j' - 2kj' - (r + 1) |j' - k|),
\]
where \(I \{k = j\}\) is an indicator function that is one if \(k = j\) and zero otherwise.

The last expression can be simplified to
\[
\frac{1}{2\sigma^2 (1 - \rho)(r + 1)} ((r + 1) |j' - j - 1| - |j' - j| - 1 + 2j'),
\]
for \(j = 0, \ldots, r; j' = 1, \ldots, r\). Now, post-multiplying the result by \(\Delta\) we can derive
the \([j, j']\) element of \(\Delta' (\Delta \Sigma \Delta')^{-1} \Delta\), which is
\[
\frac{1}{2\sigma^2 (1 - \rho)(r + 1)} \sum_{k=1}^{r} \left( (r + 1) |k - j - 1| - |k - j| - 1 + 2k) (I \{k = j'\} - I \{k = j' + 1\})
\]
for \( j = 0, \ldots, r; j' = 0, \ldots, r \). The last expression simplifies to

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

Note that this expression is \( \frac{r}{\sigma^2(1-\rho)(r+1)} \) for \( j' = j \) and \( \frac{\sigma^2-1}{\sigma^2(1-\rho)(r+1)} \) for \( j' \neq j \). Therefore, the matrix \( M = \Delta' (\Delta \Sigma \Delta')^{-1} \Delta \) has diagonal elements \( \frac{r}{\sigma^2(1-\rho)(r+1)} \) and off-diagonal elements \( \frac{\sigma^2-1}{\sigma^2(1-\rho)(r+1)} \). It is then easily proven that the sum of any row or column of \( M \) 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 \( \sum_{j=0}^{r} \sum_{j'=0}^{r} (\delta_{jj'} \mathbb{E} [E_j E_{j'}]) \) and \( \sum_{j=0}^{r} \sum_{j'=0}^{r} m_{jj'} \mathbb{E} [E_j E_{j'}] \).

From the form of \( \Sigma^{-1} \) we have that

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

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

\[
\mathbb{E} [E_j E_{j'}] = \mathbb{E} (\mathbb{E} [E_{ij} E_{ij'} | E_i]) = \mathbb{E} (P (E_{ij} = 1 \cap E_{ij'} = 1 | E_i))
\]

\[
= \mathbb{E} \left( \frac{E_{i} (E_{i} - 1)}{(r+1)r} \right) = \frac{1}{r(r+1)} \left[ \mathbb{E} (E_{i}^2) - \mathbb{E} (E_{i}) \right].
\]

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

\[
\rho_e = \frac{\mathbb{E} (E_i^2) - (r + 1) \bar{p}_e (1 + \bar{p}_e r)}{r(r+1)\bar{p}_e (1 - \bar{p}_e)}
\]
4. Then, \( \mathbb{E} \left( E_i^2 \right) = \bar{p}_e (r + 1) \left( 1 + \bar{p}_e r (1 - \rho_e) + \rho_e r \right) \), \( \sum_{j=0}^{r} \sum_{j' \neq j} \mathbb{E} [E_j E_{j'}] = \bar{p}_e r (r + 1) [\bar{p}_e (1 - \rho_e) + \rho_e] \) and we have that
\[
\sum_{j=0}^{r} \sum_{j' = 0}^{r} v^{jj'} \mathbb{E} [E_j E_{j'}] = \frac{\bar{p}_e (r + 1) [1 + \rho (r - 1 - \bar{p}_e r (1 - \rho_e) - \rho_e r)]}{(1 - \rho) \sigma^2 (1 + r \rho)},
\]
which only depends on \( \bar{p}_e \) and \( \rho_e \).

From the form of \( M \) under CS, we have
\[
\sum_{j=0}^{r} \sum_{j' = 0}^{r} m^{jj'} \mathbb{E} [E_j E_{j'}] = \frac{r (r + 1) \bar{p}_e}{\sigma^2 (1 - \rho) (r + 1)} - \frac{\bar{p}_e r (r + 1) [\bar{p}_e (1 - \rho_e) + \rho_e]}{\sigma^2 (1 - \rho) (r + 1)}
\]
\[
= \frac{\bar{p}_e (1 - \bar{p}_e) r (1 - \rho_e)}{\sigma^2 (1 - \rho)},
\]
which only depend \( \bar{p}_e \) and \( \rho_e \). Thus, \( \rho_{e_j, e_{j'}} \forall j, j' \) do not need to be provided for models (2.2)-(2.5), but only \( \rho_e \).

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 \( \Sigma^{-1} \) under CS we have
\[
\sum_{j=0}^{r} \sum_{j' = 0}^{r} v^{jj'} p_{ej} = \sum_{j=0}^{r} p_{ej} \sum_{j' = 0}^{r} v^{jj'} p_{ej} = \frac{1}{\sigma^2 (1 + r \rho)} \sum_{j=0}^{r} p_{ej} = \frac{(r + 1) \bar{p}_e}{\sigma^2 (1 + r \rho)},
\]
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 $\sigma^2_1$ for model (2.2) under CS covariance of the response

For model (2.2), $E_X[X_i'\Sigma^{-1}X_i]$ is a $[2 \times 2]$ matrix. Using the results of Web Appendix C.5, the [1,1] component is

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

the [1,2] and [2,1] component are

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

and the [2,2] component is

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

Then, the [2,2] component of the inverse of $E_X[X_i'\Sigma^{-1}X_i]$ is

$$\sigma^2_1 = \frac{\sigma^2 (1 - \rho) (1 + r \rho)}{\bar{p}_e (1 - \bar{p}_e) (r+1) (1 - \rho (1 - r + r \rho_e))}.$$

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 $\sigma^2_1$ for model (2.3) derived in Web Appendix C.2 reduces to

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

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. 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. The process of obtaining the prevalence vector and the covariance matrix of the dichotomized variables is described by. To ensure that the space of possible values of $(p_e, \rho_e)$ 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 $V(t_0) = 0$, $\sigma^2$ for models (2.2) and (2.4) is exactly calculated by knowing $p_{ej} \forall j$ and $\rho_{e1}$, regardless of the covariance of the exposure

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

$$
\Sigma^{-1} = \frac{1}{(1 - \rho^2) \sigma^2} \begin{pmatrix}
1 & -\rho & 0 & 0 & \cdots & 0 \\
-\rho & 1 + \rho^2 & -\rho & 0 & 0 \\
0 & -\rho & 1 + \rho^2 & \ddots & \ddots & \vdots \\
0 & 0 & \ddots & \ddots & -\rho & 0 \\
\vdots & \ddots & -\rho & 1 + \rho^2 & -\rho \\
0 & 0 & \cdots & 0 & -\rho & 1
\end{pmatrix}
$$
In models (2.2) and (2.4), once \( p_{ej} \forall j \) is fixed and \( V(t_0) = 0 \) is assumed, only the term \( \sum_{j=0}^{r} \sum_{j'=0}^{r} \rho^{jj'} \mathbb{E} [E_j E_{j'}] \) is not known in the formula for \( \sigma_1^2 \). Since under AR(1) \( v^{jj'} = 0 \) for \(|j - j'| > 1\), and \( v^{jj'} = \frac{-\rho}{(1-\rho^2)\sigma^2} \) for \(|j - j'| = 1\),

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

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

\[
\rho_{e1} = \frac{\mathbb{E} \left( \left( \sum_{j=0}^{r-1} \frac{1}{r} \sum_{j'=0}^{r-1} E_j \right) \right) \left( \sum_{j=0}^{r-1} \frac{1}{r} \sum_{j'=0}^{r-1} E_{j+1} \right) \right)^{\frac{1}{2}}}{\left( \mathbb{E} \left( \left( \sum_{j=0}^{r-1} \frac{1}{r} \sum_{j'=0}^{r-1} (E_j') \right) \right)^2 \right)^{\frac{1}{2}} \left( \mathbb{E} \left( \left( \sum_{j=0}^{r-1} \frac{1}{r} \sum_{j'=0}^{r-1} (E_{j+1}) \right) \right)^2 \right)^{\frac{1}{2}}}
\]

It can be shown that

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

and

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

so that the numerator of \( \rho_{e1} \) becomes

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

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 \( \rho_{e1} \) and obtain

\[
\rho_{e1} = \frac{\frac{1}{r} \sum_{j=0}^{r-1} \mathbb{E} [E_j E_{j+1}] - \left( \frac{(r+1)\bar{p}_e - p_{er}}{r} \right) \left( \frac{(r+1)\bar{p}_e - p_{e0}}{r} \right)}{\sqrt{\left( \frac{(r+1)\bar{p}_e - p_{er}}{r} \right) \left( \frac{(r+1)\bar{p}_e - p_{e0}}{r} \right) \left( \frac{(r+1)\bar{p}_e - p_{e0}}{r} \right) \left( 1 - \frac{(r+1)\bar{p}_e - p_{e0}}{r} \right)}}
\]

14
and
\[
\sum_{j=0}^{r-1} \mathbb{E}[E_j E_{j+1}] = \frac{\rho_{e_1}}{r} \sqrt{((r+1)p_e - p_{e_1}) (r - ((r+1)p_e - p_{e_1}))} \sqrt{((r+1)p_e - p_{e_0}) (r - ((r+1)p_e - p_{e_0}))} + \frac{(r+1)p_e - p_{e_1}}{r} (r+1)p_e - p_{e_0}.
\]

Thus, with the additional parameter \( \rho_{e_1} \), the only unknown part of \( \sigma_1^2 \), which was shown to be \( \sum_{j=0}^{r-1} \mathbb{E}[E_j E_{j+1}] \), is exactly determined.

**Web Appendix F**  Proof that \( \sigma_1^2 \) is maximized at the upper bound of \( \rho_e \) if \( v^{jj'} \leq 0 \ \forall j \neq j' \) for models (2.2) and (2.4); or if \( m^{jj'} \leq 0 \ \forall j \neq j' \) 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
\[
\sigma_1^2 = \frac{\sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \left( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}[E_j E_{j'}] \right) - \sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'} p_{ej})}{\sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'}}^2,
\]
where \( v^{jj'} \) are the elements of \( \Sigma^{-1} \). When \( p_{ej} \ \forall j \) are fixed, \( \sigma_1^2 \) will be affected by changes in \( \rho_e \) only through \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}[E_j E_{j'}] \), since \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}[E_j E_{j'}] \) is the only component of \( \sigma_1^2 \) affected by changes in the exposure distribution. Since \( \Sigma^{-1} \) is positive definite, \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} > 0 \) and a decrease in \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}[E_j E_{j'}] \) increases \( \sigma_1^2 \), so in order to maximize \( \sigma_1^2 \) we need to minimize \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v^{jj'} \mathbb{E}[E_j E_{j'}] \). In addition, since \( \mathbb{E}[E_j E_j] = p_{ej} \) and \( p_{ej} \ \forall j \) are fixed, only \( \sum_{j=0}^{r} \sum_{j' \neq j} v^{jj'} \mathbb{E}[E_j E_{j'}] \) needs to be min-
imized. If \( v^{jj'} \leq 0 \ \forall j \neq j' \), then \( \sum_{j=0}^{r} \sum_{j' \neq j} v^{jj'} \mathbb{E}[E_j E_{j'}] \) will be minimized when all terms \( \mathbb{E}[E_j E_{j'}] \ \forall j \neq j' \) take their upper bound, \( \min(p_{ej}, p_{ej'}) \). As derived in Web Appendix C.6,

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

so

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

Therefore, when all terms \( \mathbb{E}[E_j E_{j'}] \ \forall j \neq j' \) are equal to their upper bound, so does \( \rho_e \). The proof is the same for model (2.4) once we realize that the formula for \( \sigma_1^2 \) derived in Web Appendix C.3 only depends on \( \rho_e \) through the term \( e = \sum_{j=0}^{r} \sum_{j' = 0}^{r} (m^{jj'} \mathbb{E}[E_j E_{j'}] \sigma_{1}^{2}) \) 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 \( \frac{1}{\sigma_1^2} \frac{-\rho}{(1-\rho)(1+r\rho)} \) and therefore are all negative. For DEX, we performed a grid search for values of \( r \leq 50 \) and \( \rho \) and \( \theta \) 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

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

Proceeding as for model (2.2), \( \sigma_1^2 \) will be maximized when \( \sum_{j=0}^{r} \sum_{j' \neq j} (m^{jj'} \mathbb{E}[E_j E_{j'}]) \) is minimized. If \( m^{jj'} \leq 0 \ \forall j \neq j' \), then \( \sum_{j=0}^{r} \sum_{j' \neq j} (m^{jj'} \mathbb{E}[E_j E_{j'}]) \) will be minimized when all terms \( \mathbb{E}[E_j E_{j'}] \ \forall j \neq j' \) are equal to their upper bound, in which case \( \rho_e \) will
also take its upper bound. For model (2.5), we have from formula (3.3) that

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

and this formula only depends on \( \rho_e \) through \( \sum_{j=0}^{r} \sum_{j' \neq j} m_{jj'} \mathbb{E}[E_j E_{j'}] \) in the same way as model (2.3) did, so the same reasoning applies.

The off-diagonal elements of the inverse of the matrix \( \mathbf{M} \) 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 \( r \leq 50 \) and \( \rho \) and \( \theta \) in [0,1] and found that the off-diagonal elements of \( \mathbf{M} \) were always smaller than or equal to zero.

**Web Appendix G  Upper bounds for \( \sigma_1^2 \)**

**Web Appendix G.1 Optimization problem to solve to find the upper bound for \( \sigma_1^2 \) for known \( \rho_e \) and \( p_{ej} \ \forall j \) for model (2.2)**

We want to find an upper bound for \( \sigma_1^2 \) when \( \rho_e \) and \( p_{ej} \ \forall j \) are known. The only part of \( \sigma_1^2 \) in (3.1) that is not fixed is \( \sum_{j=0}^{r} \sum_{j'=0}^{r} v_{jj'} \mathbb{E}[E_j E_{j'}] \), and since \( \mathbb{E}[E_j^2] = p_{ej} \), the only non-fixed part is \( 2 \sum_{j=0}^{r-1} \sum_{j'=j+1}^{r} (v_{jj'} \mathbb{E}[E_j E_{j'}]) \). The unknowns in this problem are the \( r(r+1)/2 \) subdiagonal elements of the symmetric matrix \( \mathbf{E} \),

\[
\mathbf{E} = \begin{pmatrix}
  p_{e0} & \mathbb{E}[E_0 E_1] & p_{e1} & \cdots & \cdots & \mathbb{E}[E_0 E_r] \\
  \mathbb{E}[E_0 E_1] & p_{e1} & \mathbb{E}[E_1 E_2] & \cdots & \cdots & \mathbb{E}[E_1 E_{r-1}] \\
  \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\
  \mathbb{E}[E_0 E_r] & \cdots & \mathbb{E}[E_r E_{r-1}] & p_{er}
\end{pmatrix}, \quad (G.1)
\]
There are some constraints in this matrix. Fixing \( \rho_e \) and \( p_{ej} \) \( \forall j \) fixes \( \sum_{j=0}^{r} \sum_{j'=0}^{r} \mathbb{E}[E_j E_{j'}] \) (Web Appendix C.6), giving the equality constraint
\[
\sum_{j=0}^{r} \sum_{j'=0}^{r} \mathbb{E}[E_j E_{j'}] = \bar{p}_e (r+1) \left[ 1 + \bar{p}_e r (1-\rho_e) + \rho_e r^2 \right]. \tag{G.2}
\]

There exist upper and lower bounds for the correlations of binary variables, which are
\[
\max \left( -\sqrt{\frac{p_{ej} p_{ej'}}{1-p_{ej} (1-p_{ej'})}}, -\sqrt{\frac{(1-p_{ej}) (1-p_{ej'})}{p_{ej} p_{ej'}}} \right) \leq \rho_{ej,ej'} \leq \min \left( \sqrt{\frac{p_{ej} (1-p_{ej'})}{1-p_{ej} p_{ej'}}, \frac{(1-p_{ej}) p_{ej'}}{p_{ej} (1-p_{ej'})}} \right). \tag{G.3}
\]

\(^8\) Expressed in terms of \( \mathbb{E}[E_j E_{j'}] \), the condition is equivalent to
\[
\max (-p_{ej} p_{ej'}, -(1-p_{ej})(1-p_{ej'})) + p_{ej} p_{ej'} \leq \mathbb{E}[E_j E_{j'}] \leq \min (p_{ej}(1-p_{ej'}), (1-p_{ej}) p_{ej'}) + p_{ej} p_{ej'}
\]
which is equivalent to \( \max (0, -(1-p_{ej} - p_{ej'})) \leq \mathbb{E}[E_j E_{j'}] \leq \min (p_{ej}, p_{ej'}) \). The constraints can be incorporated as
\[
\mathbb{E}[E_j E_{j'}] \geq 0 \ \forall j, j'; \tag{G.3}
\]
\[
p_{ej} + p_{ej'} - 1 \leq \mathbb{E}[E_j E_{j'}] \ \forall j, j'; \tag{G.4}
\]
\[
\mathbb{E}[E_j E_{j'}] \leq p_{ej} \ \forall j, j'; \tag{G.5}
\]
\[
\mathbb{E}[E_j E_{j'}] \leq p_{ej'} \ \forall j, j'. \tag{G.6}
\]
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 \( (0, 1, \ldots, r) \),
\[
\sum_{j=1}^{m} p_{l_e l_j} - 1 \leq \sum_{j=1}^{m-1} \sum_{j'=j+1}^{m} \mathbb{E}[E_{l_j} E_{l_{j'}}] \text{ for } 3 \leq m \leq r \tag{G.7}
\]
5. This implies

\[
\left( \frac{r+1}{3} \right) + \cdots + \left( \frac{r+1}{r} \right) = 2^{r+1} - \frac{(r+1)(r+2)}{2} - 2
\]

linear constraints. We define \( b \) as the vector of unknowns, \( b^t = (\mathbb{E}[E_0E_1], \mathbb{E}[E_0E_2], \ldots, \mathbb{E}[E_0E_r], \mathbb{E}[E_1E_2], \ldots, \mathbb{E}[E_1E_r], \ldots, \mathbb{E}[E_{r-1}E_r]) \). Then the optimization problem is \( \min_b \sum_{j=0}^{r-1} \sum_{j'=j+1}^r (v^{jj'} \mathbb{E}[E_jE_{j'}]) \) 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 \( \sigma^2_1 \) for known \( p_{ej} \ \forall j \) and \( \rho_e \) for model (2.3)

The formula for \( \sigma^2_1 \) is \( \sigma^2_1 = \sum_{j=0}^{r} \sum_{j'=0}^{r} (m^{jj'} \mathbb{E}[E_jE_{j'}])^{-1} \). To maximize \( \sigma^2_1 \), 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 \( \sigma^2_1 \) for known \( p_{ej} \ \forall j \) and \( \rho_e \) for model (2.4) with \( V(t_0) = 0 \)

From Web Appendix C.3,

\[
\sigma^2_1 = \frac{b^2 s^2 - a (cs^2 + aV(t_0))}{(b^2e + c(d^2 - ae) - 2bdf + af^2)s^2 - 2(bd - af)gs\sqrt{V(t_0)} + a(d^2 - ae + g^2)V(t_0)}.
\]
When $V(t_0) = 0$, this reduces to

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

where $a = \sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'}$, $b = \sum_{j=0}^{r} \sum_{j'=0}^{r} j_j v^{jj'}$, $c = \sum_{j=0}^{r} \sum_{j'=0}^{r} j'_j v^{jj'}$, $d = \sum_{j=0}^{r} \sum_{j'=0}^{r} (v^{jj'}p_{ej})$, $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'} \mathbb{E}[E_j E_{j'}]$, $f = \sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'} \mathbb{E}[E_j E_{j'}]$. If the prevalence at each time point is known, only $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'} \mathbb{E}[E_j E_{j'}]$ is not completely specified. In order to find an upper bound to $\sigma_1^2$, $e = \sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'} \mathbb{E}[E_j E_{j'}]$ needs to be minimized for a known value $\rho_e$. This problem reduces to the same problem solved in Web Appendix G.2.

**Web Appendix G.4 Upper bound for $\sigma_1^2$ for known $p_{ej}$ \forall j and $\rho_e$ for model (2.5)**

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

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

If the prevalence at each time point is known, only $\frac{\sum_{j=0}^{r} \sum_{j'=0}^{r} \xi_{jj'} \mathbb{E}[E_j E_{j'}]}{\sum_{j=0}^{r} \sum_{j'=0}^{r} j_j' m^{jj'}}$ is not fully specified. The problem of finding an upper bound for a given value of $\rho_e$ 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](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 vacuuming. 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

References


9 R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2006.