Ecole Nationale de la Statistique et de l'Administration Economique

Handling of missing data in clinical trials

Power calculations for delta-adjusted pattern-mixture models under Not Missing At Random (MNAR) assumption

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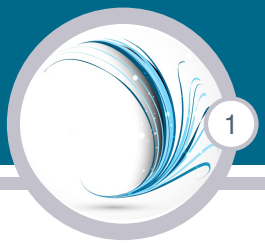
November 25, 2015

Content



- *Primary analysis*: study of the principal target outcome according to the ITT(Intend-To-Treat) concept.
- *Sensitivity analysis*: study of the impact the outcome of a variable from the primary analysis has if it was different from what it is assumed to be.

Origin of missing data

- Huge quantities of data collected $\Rightarrow$ **missing data** $\Rightarrow$ biased results
- Not related to the study:
  - human error in recording data
  - a patient moves to another city or country
- Related to the study:
  - a patient feels pain
  - he considers the treatment to be inefficient

- **MCAR** *missing completely at random*: missingness is completely independent of both observed and unobserved data.
  - a subject dropouts because he moves to another city or country.
- **MAR** *missing at random*: missingness is considered independent of unobserved data, given observed data.
  - a subject drops out from the study because he considers, from previous visits, that the treatment is not efficient.
- **MNAR** *missing not at random*: missingness is related to unobserved data.
  - a subject decides to drop out because of sudden unobserved side-effects from a drug or because of sudden unrecorded drop in efficacy.

Characteristics

- Specification of mixed linear models: time is a classification variable.
- Longitudinal data: measurements are collected for different patients at different time points.
- Correlation between repeated visits.
- Variance-covariance used to estimate the outcome at each visit.

The model

- Mixed model: $\boldsymbol{Y} = \boldsymbol{X}\beta + \boldsymbol{Z}\gamma + \boldsymbol{e}$.
- No random effects: $\boldsymbol{Z} = 0$.
- MMRM: $Cov[\boldsymbol{Y}] = Cov[\boldsymbol{e}] = \boldsymbol{M}$ where $\boldsymbol{M}$ is a diagonal block matrix.

Different covariance structures are in backup slide.

- R: apparent time of dropout of a subject.
- θ: set of model parameters.
- $\mathbf{Y}$: $\mathbf{Y}_{obs}$ and $\mathbf{Y}_{mis}$.

Marginal distribution:

$$f(\boldsymbol{Y}_{obs}, R) = \int f(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis}, R)\, \mathrm{d}\boldsymbol{Y}_{mis}$$

$$= \int \underbrace{f(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis}; \boldsymbol{\theta})}_{\textbf{outcome data model}} \underbrace{P(R|\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis}; \gamma)}_{\textbf{missing data model}}\, \mathrm{d}\boldsymbol{Y}_{mis}$$

Factorization of the joint likelihood:

$$f(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis}, R) = f(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis}|R)P(R)$$

$\Rightarrow$ **One model for each pattern of missingness.**

Application to missing data
Notations

Notations used in the following presentation:

- n subjects
- J+1 treatment groups
- T postbaseline measurements of the outcome variable
- $A_i = 0$ for placebo and $A_i = j$ for active treatment group j where j = 1,...,J
- $(y_{i,0}, y_{i,1},...,y_{i,T})$ full response vector for subject i
- L_i data pattern corresponding to the last postbaseline time point with observed data for subject i
- $\mathbf{y}_{i,s} = (y_{i,0}, y_{i,1},...,y_{i,s})$ partial vector of the full response
- $\phi_j = Pr(A_i=j)$

Application to missing data
Notations

- $\pi_i^{(t)}$ = Pr(L_i=t | A_i=j) where j = 1,...,J and t=1,...,T
- $\sigma_{j,s}$ treatment effect for active treatment j at postbaseline time point s
- α_s intercept
- β_s=($\beta_{s,0}$,...,$\beta_{s,s-1}$) regression coefficients
- σ_s^2 residual variance
- θ set of model parameters

Application to missing data
Model definition and Delta-method

- Conditional distribution of an observed postbaseline measurement given the measurement history within each observed data pattern and treatment group:
  for 1 $\leq$ s $\leq$ t $\leq$ T and j=0,...,J

$$y_{i,s}|\boldsymbol{y}_{i,s-1}, L_i = t, A_i = j, \theta \sim N(\alpha_s + \beta_s'\boldsymbol{y}_{i,s-1} + \gamma_{j,s} I(j > 0), \sigma_s^2)$$

- Missing data distribution is the following:
  for 1 $\leq$ t $\leq$ s $\leq$ T and j=0,...,J

$$y_{i,s}|\boldsymbol{y}_{i,s-1}, L_i = t, A_i = j, \theta \sim N(\alpha_s+\beta_s'\boldsymbol{y}_{i,s-1}+(\gamma_{j,s}+\Delta_{j,s})I(j > 0), \sigma_s^2)$$

$\Delta_{j,s}$: **delta-adjustment for treatment j at time point s**.

Different possibilities

- $\Delta_{j,s} = -\Phi\gamma_{j,s}$
- $\Delta_{j,s} = 0.5\Phi\sigma_s$
- $\Delta_{j,s} = \Phi$C, where C is a fixed threshold

Power calculation
Introduction

- **Power**: probability of the trial to put into relief a difference between a placebo and a treatment, or between treatments, that does exist.

Regression parameters estimates
Covariance matrix of parameters estimates
Partial derivatives of treatment effects estimates
$\Downarrow$
Treatment effects
Associated covariance matrix
$\Downarrow$
Power

MMRM with PROC MIXED $\Rightarrow$

- $\delta^{\star}_{j,s}$ expected treatment differences under MAR at postbaseline time points
- $\omega_{u,v}$ conditional variances and covariances of postbaseline measurements given the baseline measurements

$$\Rightarrow \begin{cases} \beta_s & \text{regression parameters} \\ \gamma_s & \text{treatment effects for active groups at time point s} \\ \sigma^2_s & \text{residual variance} \end{cases}$$

The details of formulas and demonstration are in backup slides.

Power calculation
Treatment effects

- Transformed coefficients: $\xi_{s,t} = \sum_{l=t}^{s-1} \beta_{s,l}\xi_{l,t}$, for 1 $\leq$ t $\leq$ s-1.
- Overall mean at each time point within each treatment group: $\mu_{j,s} = E(y_{is}|A_i = j) = \sum_{t=1}^{T} \pi_j^{(t)} \mu_{j,s}^{(t)}$.
- Total probability of patterns with missing data at time point l in treatment group j: $\pi_j^{(<l)} = \sum_{t=1}^{l-1} \pi_j^{(t)}$.

- Treatment differences in overall means: $\delta_{j,s} = \mu_{j,s} - \mu_{0,s}$.

Under MNAR: $\delta_{j,s} = \sum_{l=1}^{s} \xi_{s,l}(\gamma_{j,l} + \Delta_{j,l}\pi_j^{(<l)})$

Under MAR: $\delta^{\star}_{j,s} = \sum_{l=1}^{s} \xi_{s,l}\gamma_{j,l}$

Power calculation
Treatment effects

Estimates:

- Regression parameters: $(\hat{\alpha}_s, \hat{\beta}_s, \hat{\gamma}_s, \hat{\sigma}_s^2)$ for s=1,...,T.
- Treatment-specific pattern probabilities: $\hat{\pi}_j^{(t)} = n_j^{(t)}/n_j$.
- First method: $\hat{\Delta}_{j,s} = -\Phi\hat{\gamma}_{j,s}$.
- Second method: $\hat{\Delta}_{j,s} = 0.5\Phi\hat{\sigma}_s$.
- Third method: $\hat{\Delta}_{j,s} = \Phi C$.

Under MNAR: $\hat{\delta}_{j,s} = \sum_{l=1}^{s} \hat{\xi}_{s,l}(\hat{\gamma}_{j,l} + \hat{\Delta}_{j,l}\hat{\pi}_j^{(<l)})$

Under MAR: $\hat{\delta}^{\star}_{j,s} = \sum_{l=1}^{s} \hat{\xi}_{s,l}\hat{\gamma}_{j,l}$

Power calculation
Covariance matrix

Block matrices of covariances and partial derivatives:

$$V = \left(\begin{array}{c|c|c} Cov(\hat{\pi}_j) & 0 & 0 \\ \hline 0 & Cov\_reg & 0 \\ \hline 0 & 0 & Var(\hat{\sigma}_s^2) \end{array}\right)$$

$$P = \left(\begin{array}{c|c|c|c} 0 & \frac{\partial \delta^\star}{\partial \beta} & \frac{\partial \delta^\star}{\partial \gamma} & 0 \\ \hline \frac{\partial \delta}{\partial \pi} & \frac{\partial \delta}{\partial \beta} & \frac{\partial \delta}{\partial \gamma} & 0 \end{array}\right)$$

$$\textbf{Covariance of treatment effects} = PVP' \qquad (1)$$

Details of covariances and derivatives in backup slides.

Power associated to the design of a new trial:

$$H_0: \delta_j \leq 0 \text{ against } H_1: \delta_j > 0$$

Power $\Longleftrightarrow$ probability to detect a significant treatment effect

$$\begin{aligned} Power(j) &= P(z_j \geq q_{1-\alpha/2} | H_1 : \delta_j = \delta_{j,T}) \\ &= P\left(\frac{\hat{\delta}_j - \delta_{j,T}}{\sqrt{Var(\hat{\delta}_j)}} \geq q_{1-\alpha/2} - \frac{\delta_{j,T}}{\sqrt{Var(\hat{\delta}_j)}}\right) \\ &= 1 - \Phi\left(q_{1-\alpha/2} - \frac{\delta_{j,T}}{\sqrt{Var(\hat{\delta}_j)}}\right) \end{aligned}$$

- z-statistic: $z_j = \frac{\hat{\delta}_j}{\sqrt{Var(\hat{\delta}_j)}}$.
- α: Type I error.

Longitudinal data

- LDL cholesterol measurements in mmol/L
- 284 subjects with day 1 visit and at least one postbaseline measurement
- 5 postbaseline measurements (Weeks 4, 8, 12, 16, 24)
- Variable of interest: difference from baseline in %
- Treatment hyper efficient: diff_pct_chg = diff_pct + 40 for treated

	difference week	Base	varcat	armcat	visitcat	diff_pct
1	-1.6058	2.2274	1	SAR236553/REGN727	40	-72.09302326
2	-1.3209	2.2274	1	SAR236553/REGN727	80	-59.30232558
3	-0.9583	2.2274	1	SAR236553/REGN727	120	-43.02325581
4	0.2849	2.2274	1	SAR236553/REGN727	160	12.790697674
5	0.0518	2.2274	1	SAR236553/REGN727	240	2.3255813953
6	-0.1036	2.9526	2	Placebo	40	-3.50877193
7	-0.1554	2.9526	2	Placebo	80	-5.263157895
8	0.3626	2.9526	2	Placebo	120	12.280701754
9	0.4403	2.9526	2	Placebo	160	14.912280702
10	2.2533	2.9526	2	Placebo	240	76.315789474

Figure: Used Dataset Extract

MMRM with PROC MIXED $\Rightarrow \delta^{\star}_{j,s}$ and $\omega_{u,v}$

Unstructured case:

Diagonal coefficients increase globally

$\Downarrow$

Variances tend to increase as visits are farther apart

Estimated R Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	524.91	304.72	368.16	280.72	214.06
2	304.72	534.27	345.39	248.37	217.84
3	368.16	345.39	655.20	404.57	345.40
4	280.72	248.37	404.57	648.18	412.60
5	214.06	217.84	345.40	412.60	703.93

Figure: Estimated covariance matrix

LDL Cholesterol Study

MMRM Results

Estimated R Correlation Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.5754	0.6278	0.4813	0.3522
2	0.5754	1.0000	0.5838	0.4221	0.3552
3	0.6278	0.5838	1.0000	0.6208	0.5086
4	0.4813	0.4221	0.6208	1.0000	0.6108
5	0.3522	0.3552	0.5086	0.6108	1.0000

Figure: Estimated correlation matrix

Estimates					
Label	Estimate	Standard Error	DF	t Value	Pr > |t|
treatment effect at week 4	8.6754	2.9036	274	2.99	0.0031
treatment effect at week 8	13.3691	2.9565	272	4.52	<.0001
treatment effect at week 12	9.8187	3.2548	273	3.02	0.0028
treatment effect at week 16	12.2618	3.2984	262	3.72	0.0002
treatment effect at week 24	5.6467	3.4270	271	1.65	0.1006

Figure: Estimates

Results for heterogeneous and autoregressive (1) structures are in backup slides.

Function *powerpara* inputs

- α: level of significance.
- C: threshold in the expression of Δ for the third delta-method.
- n: number of subjects.
- Ω: covariance matrix of postbaseline measurements given the baseline measurement.
- T: number of postbaseline time points
- J_a: number of active treatments.
- $\delta^\star$: expected treatment differences under MAR at postbaseline time points.
- Pp: treatment-specific pattern probabilities. (Example)
- ϕ: randomization probabilities.
- PhiM: Φ, fraction used in the delta-method.
- Dmethod: delta-method used, this value can be 1, 2 or 3.

LDL Cholesterol Study
Different delta-adjusted methods

First method: $\Delta_{j,s} = -\Phi\gamma_{j,s}$

gamma				
-8.6754	-8.332869	-0.663919	-5.295076	3.0294168

Figure: Gamma

- $\gamma_{j,s} < 0$ for s=1,..,4
- $\gamma_{j,5} > 0 \rightarrow$ high influence on results
- Difference between placebo and treatment: $\delta_{j,s} = \sum_{l=1}^{s} \xi_{s,l}(\gamma_{j,l} + \Delta_{j,l}\pi_j^{(<l)})$

$\gamma_{j,s} > 0 \Rightarrow$ negative penalties $\Rightarrow$ lower $\delta_{j,s}$

$\Rightarrow$ advantage to the treatment and **higher power**

LDL Cholesterol Study

Different delta-adjusted methods

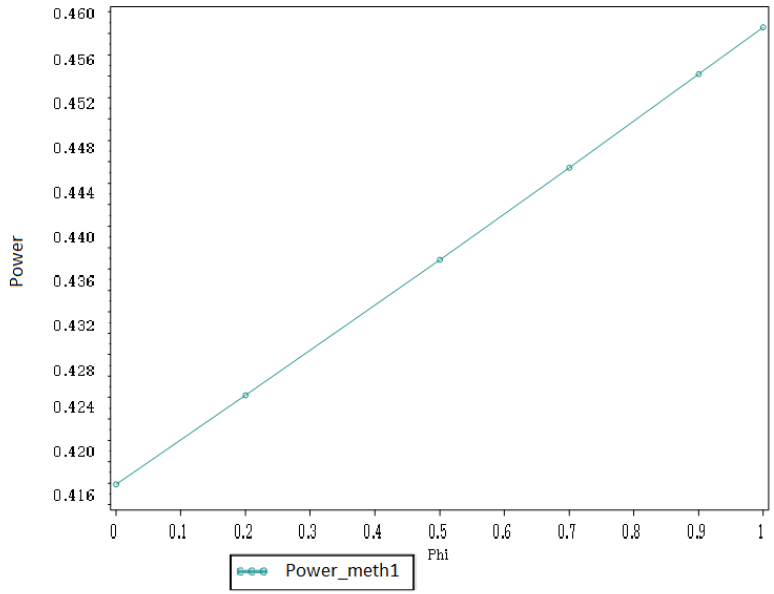


Figure: Power with respect to Φ for method 1, unstructured covariance

Φ increases $\Rightarrow$ negative $\Delta_{j,s}$ decreases $\Rightarrow$ **power increases**

LDL Cholesterol Study
Different delta-adjusted methods

2^{nd} and 3^{rd} methods: $\Delta_{j,s} = 0.5\Phi\sigma_s$ and $\Delta_{j,s} = \Phi C$

Φ increases $\Rightarrow$ positive $\Delta_{j,s}$ increases $\Rightarrow$ higher $\delta_{j,s}$

$\Rightarrow$ advantage to the placebo and **lower power**

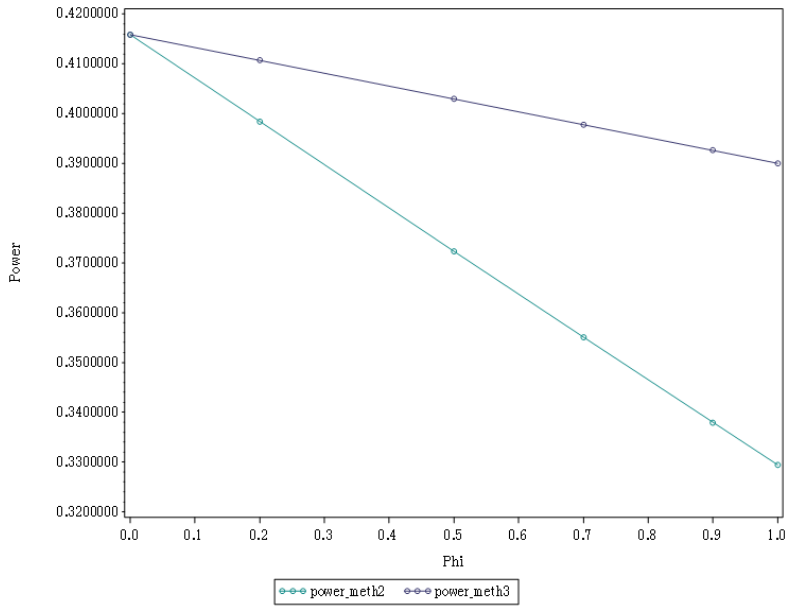


Figure: Power with respect to Φ for method 2 and 3 (C=3), unstructured covariance

LDL Cholesterol Study

Impact of the missing data pattern probabilities

Power evolutions with different repartitions of dropouts:

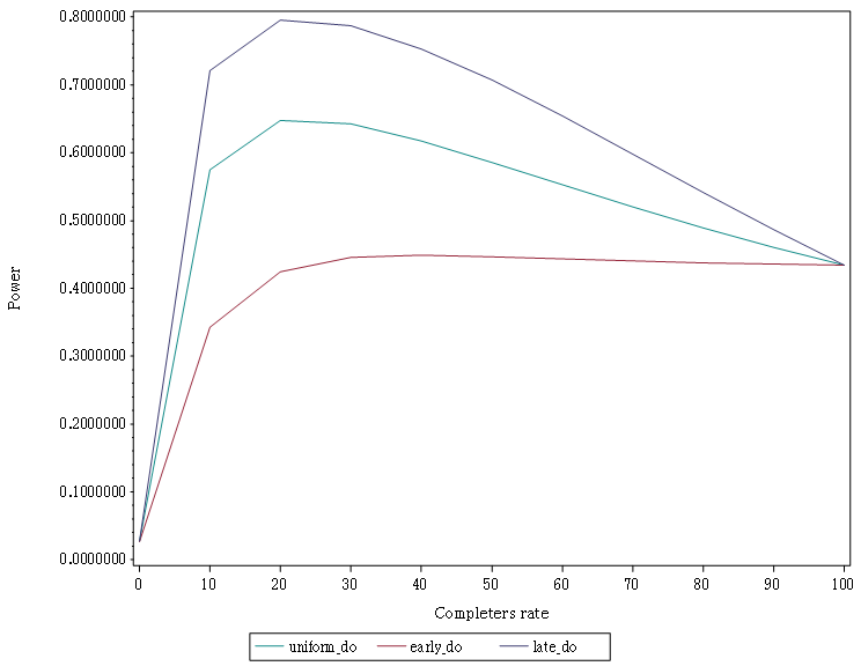


Figure: Power with respect to completers rate with method 1 and unstructured covariance

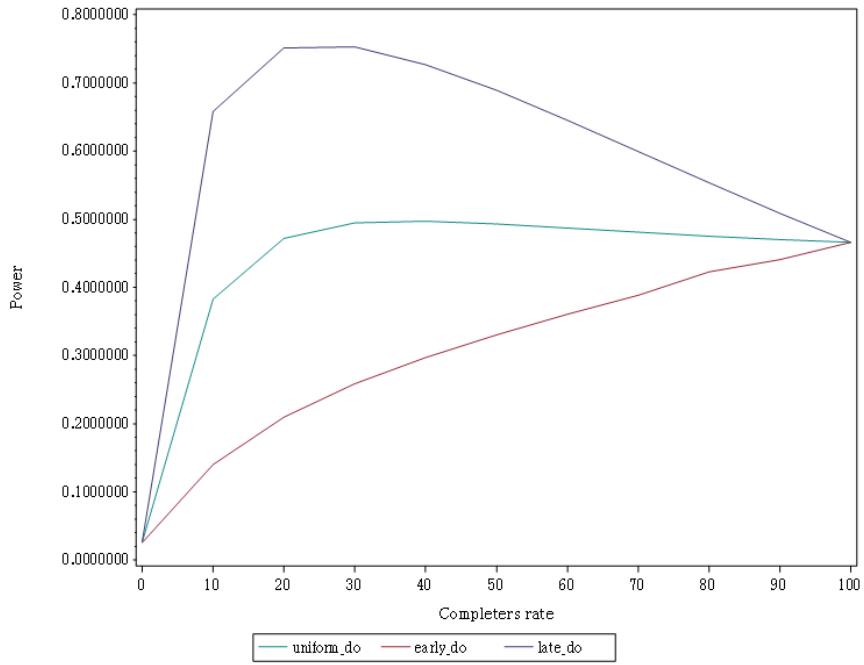


Figure: Power with respect to completers rate with method 1 and AR(1) covariance

LDL Cholesterol Study

Impact of the missing data pattern probabilities

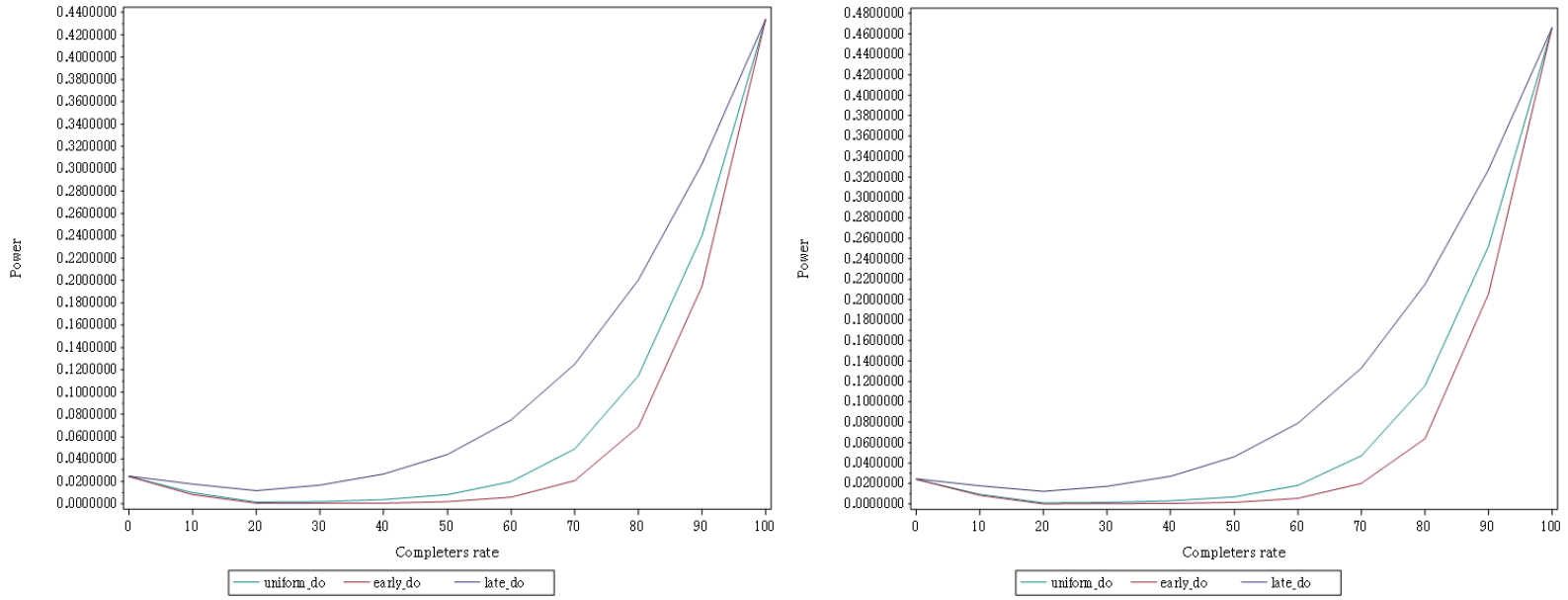


Figure: Power with respect to completers rate with method 2

More completers $\Rightarrow$ **higher power**

Same results with method 3.

For different time profiles:

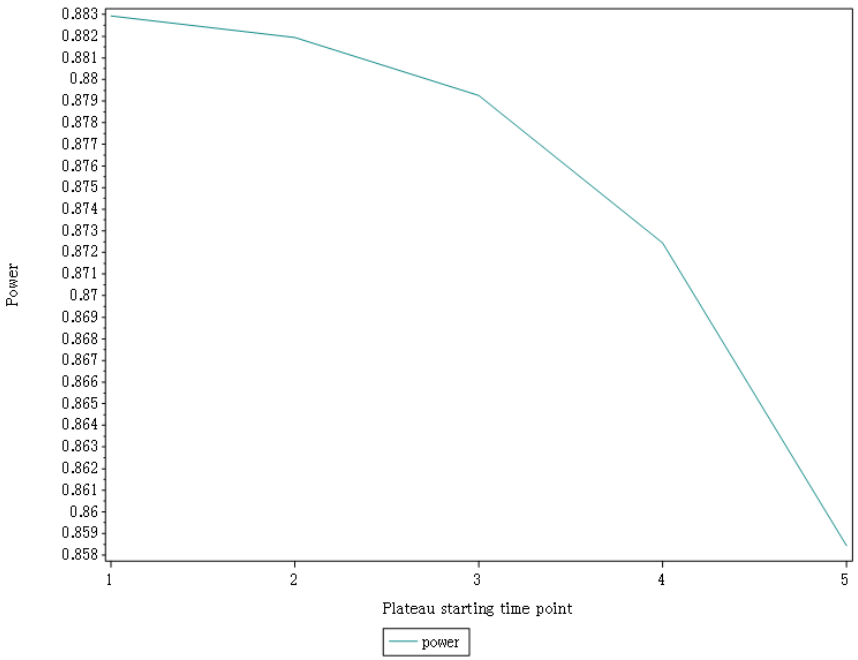


Figure: Power with respect to time profile with method 1 and unstructured covariance

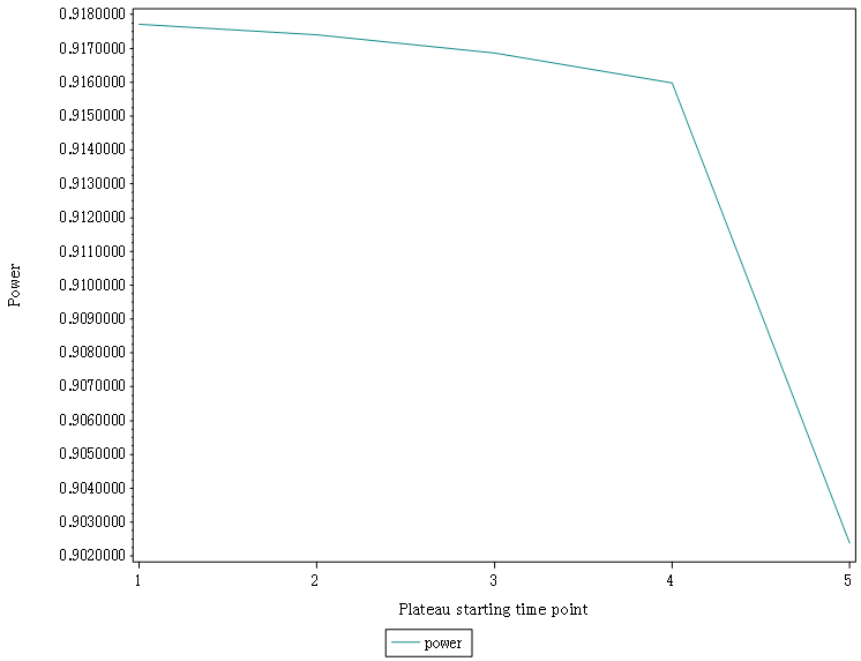


Figure: Power with respect to time profile with method 1 and AR(1) covariance

Conclusion

- MAR assumption: unverifiable from observed data, sometimes questionable
- Test its robustness: MNAR through sensitivity analyses
  - MMRM under MAR
  - Delta-adjustment

- Power calculation under MNAR
- Sample size estimation

Thank you for your attention !

The variance-covariance structure

Unstructured

- Heterogeneous variances
- Heterogeneous covariances
- J(J+1)/2 parameters

$$\begin{pmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 \end{pmatrix}$$

Toeplitz

- Homogeneous variances
- Covariances depend on lag
- J parameters

$$\begin{pmatrix} \sigma^2 & \sigma_1 & \sigma_2 \\ \sigma_1 & \sigma^2 & \sigma_1 \\ \sigma_2 & \sigma_1 & \sigma^2 \end{pmatrix}$$

The variance-covariance structure

Heterogeneous Toeplitz

- Heterogeneous variances
- Covariances depend on lag
- 2J-1 parameters

$$\begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2\rho_1 & \sigma_1\sigma_3\rho_2 \\ \sigma_1\sigma_2\rho_1 & \sigma_2^2 & \sigma_2\sigma_3\rho_1 \\ \sigma_2\sigma_3\rho_2 & \sigma_2\sigma_3\rho_1 & \sigma_3^2 \end{pmatrix}$$

Autoregressive AR(1)

- Homogeneous variances
- Covariances decrease as visits become farther apart
- 2 parameters

$$\begin{pmatrix} \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 \\ \sigma^2\rho & \sigma^2 & \sigma^2\rho \\ \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 \end{pmatrix}$$

Back

Power calculation
MMRM Application

For s = 2,...,T:

$$\begin{pmatrix} \beta_{s,1} \\ \vdots \\ \beta_{s,s-1} \end{pmatrix} = \begin{pmatrix} \omega_{1,1} & \cdots & \omega_{1,s-1} \\ \cdots & \cdots & \cdots \\ \omega_{s-1,1} & \cdots & \omega_{s-1,s-1} \end{pmatrix}^{-1} \begin{pmatrix} \omega_{s,1} \\ \vdots \\ \omega_{s,s-1} \end{pmatrix}$$

For j=1,...,J and s=1,...,T:

$$\gamma_{j,s} = \delta^{\star}_{j,s} - \sum_{l=1}^{s-1} \beta_{s,l} \delta^{\star}_{j,l}$$

For s=1,...,T:

$$\sigma^2_s = \omega_{s,s} - \sum_{l=1}^{s-1} \beta_{s,l} \omega_{s,l}$$

Normal Multivariate Distribution

$\mathbf{Y}$: $\mathbf{Y}_{obs}$ and $\mathbf{Y}_{mis}$

$$\boldsymbol{Y} \sim NMV(\mu, \Sigma)$$

$$\mu = \begin{pmatrix} \mu_{obs} \\ \mu_{mis} \end{pmatrix}$$

$$\Sigma = \begin{pmatrix} \Sigma_{obs,obs} & \Sigma_{obs,mis} \\ \Sigma_{mis,obs} & \Sigma_{mis,mis} \end{pmatrix}$$

Goal: find the distribution of $\mathbf{Y}_{mis} \mid \mathbf{Y}_{obs}$

$$f(\boldsymbol{Y}_{mis} | \boldsymbol{Y}_{obs}) = \frac{f(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{mis})}{f(\boldsymbol{Y}_{obs})}$$

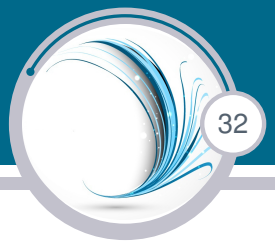
Linear combination of $\mathbf{Y}_{obs}$ and $\mathbf{Y}_{mis}$, independent of $\mathbf{Y}_{obs}$

$$\boldsymbol{Z} = \boldsymbol{Y}_{mis} - a\boldsymbol{Y}_{obs}$$

a such that $\mathbf{Z}$ and $\mathbf{Y}_{obs}$ are independent:

$$\begin{aligned} 0 &= Cov(\boldsymbol{Z}, \boldsymbol{Y}_{obs}) \\ &= Cov(\boldsymbol{Y}_{mis} - a\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{obs}) \\ &= Cov(\boldsymbol{Y}_{mis}, \boldsymbol{Y}_{obs}) - aCov(\boldsymbol{Y}_{obs}, \boldsymbol{Y}_{obs}) \\ &= \Sigma_{obs,mis} - a\Sigma_{obs,obs} \end{aligned}$$

$$\Rightarrow a = \Sigma_{obs,mis}\Sigma_{obs,obs}^{-1}$$



$$
\begin{aligned}
E(\boldsymbol{Z}) &= E(\boldsymbol{Y}_{mis}) - \Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}E(\boldsymbol{Y}_{obs}) \\
&= \mu_{mis} - \Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}\mu_{obs}
\end{aligned}
$$

$$
\begin{aligned}
Var(\boldsymbol{Z}) &= Var(\boldsymbol{Y}_{mis}) + Var(a\boldsymbol{Y}_{obs}) - 2Cov((\boldsymbol{Y}_{mis}, a\boldsymbol{Y}_{obs}) \\
&= \Sigma_{mis,mis} + a\Sigma_{obs,obs}a' - 2\Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}\Sigma_{mis,obs} \\
&= \Sigma_{mis,mis} + \Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}\Sigma_{obs,obs}\Sigma^{-1}_{obs,obs}\Sigma_{mis,obs} \\
&\qquad - 2\Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}\Sigma_{mis,obs} \\
&= \Sigma_{mis,mis} - \Sigma_{obs,mis}\Sigma^{-1}_{obs,obs}\Sigma_{mis,obs}
\end{aligned}
$$

$\boldsymbol{Y}_{mis} = \boldsymbol{Z} + a\boldsymbol{Y}_{obs}$:

$$
\begin{aligned}
E(\boldsymbol{Y}_{mis}|\boldsymbol{Y}_{obs} = y_{obs}) &= E(\boldsymbol{Z}) + ay_{obs} \\
&= \mu_{mis} + a(y_{obs} - \mu_{obs}) \\
Var(\boldsymbol{Y}_{mis}|\boldsymbol{Y}_{obs} = y_{obs}) &= Var(\boldsymbol{Z}) \\
&= \Sigma_{mis,mis} - \Sigma_{obs,mis}\Sigma_{obs,obs}^{-1}\Sigma_{mis,obs}
\end{aligned}
$$

Conidtional Distribution

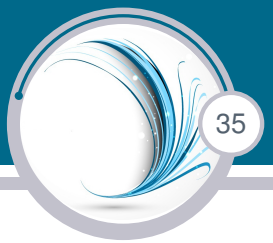
$$
\begin{aligned}
\boldsymbol{Y}_{mis}|\boldsymbol{Y}_{obs} &= y_{obs} \\
&\sim N(\mu_{mis} + a(y_{obs} - \mu_{obs}), \Sigma_{mis,mis} - \Sigma_{obs,mis}\Sigma_{obs,obs}^{-1}\Sigma_{mis,obs})
\end{aligned}
$$

Actual model:

$$\begin{pmatrix} y_{i,1} \\ \vdots \\ y_{i,s-1} \\ y_{i,s} \end{pmatrix} | y_{i,0}, A_i = j \sim \text{Normal Multivariate}(\Delta, \Omega)$$

$$\begin{pmatrix} y_{i,0} \\ \vdots \\ y_{i,s-1} \\ y_{i,s} \end{pmatrix} = \begin{pmatrix} \boldsymbol{y}_{i,s-1} \\ y_{i,s} \end{pmatrix} \qquad \Delta = \begin{pmatrix} \xi_1 + \delta^{\star}_{j,1} I(j > 0) + \theta_1 y_{i,0} \\ \vdots \\ \xi_s + \delta^{\star}_{j,s} I(j > 0) + \theta_s y_{i,0} \end{pmatrix}$$

$$\Omega = \left(\begin{array}{ccc|c} \omega_{1,1} & \dots & \omega_{1,s-1} & \omega_{1,s} \\ \dots & \dots & \dots & \dots \\ \omega_{s-1,1} & \dots & \omega_{s-1,s-1} & \omega s-1,s \\ \hline \omega_{s,1} & \dots & \omega_{s,s-1} & \omega_{s,s} \end{array}\right) = \left(\begin{array}{c|c} \Omega_{1,1} & \Omega_{1,2} \\ \hline \Omega_{2,1} & \Omega_{2,2} \end{array}\right)$$



From the article:

$$y_{i,s}|\boldsymbol{y}_{i,s-1}, L_i = t, A_i = j, \theta \sim N(\boldsymbol{\alpha}_s + \boldsymbol{\beta}'_s \boldsymbol{y}_{i,s-1} + \gamma_{j,s} I(j > 0), \sigma_s^2)$$

with the following equivalences:

$$\mu \sim \Delta$$
$$\Sigma \sim \Omega$$

For s=2: $\mu_{mis} + a(y_{obs} - \mu_{obs}) = \xi_2 + \delta^{\star}_{j,2} I(j > 0) + \theta_2 y_{i,0}$
$$+\omega_{1,2}\omega_{1,1}^{-1}(y_{i,1} - \xi_1 - \delta^{\star}_{j,1} I(j > 0) - \theta_1 y_{i,0})$$

By identification of terms in front of $I(j > 0)$, in front of y and variance:

$$\gamma_{j,2} = \delta^{\star}_{j,2} - \omega_{1,2}\omega_{1,1}^{-1}\delta^{\star}_{j,1}$$
$$\beta_{2,1} = \omega_{1,2}\omega_{1,1}^{-1}$$
$$\sigma_2^2 = \omega_{2,2} - \beta_{2,1}\omega_{2,1}$$

$$\Rightarrow \textbf{Iteration}$$

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Power calculation
Covariance matrix

Asymptotic covariance matrix of the estimated pattern probabilities in treatment j:

$$Cov(\hat{\pi}_j) = n^{-1}\phi_j^{-1}[diag(\pi_j) - \pi_j\pi_j']$$

Residual variance:

$$Var(\hat{\sigma}_s^2) = n^{-1}(\pi^{(\geq l)})^{-1}2\sigma_s^4$$

as $(\hat{\beta}_s^{\#}, \hat{\gamma}_s)$ are independent of the estimates of the residual variance.

- Total probability of patterns with observed data at time point s pooled across treatment groups: $\pi^{(\geq l)} = \sum_{j=0}^{J} \phi_j \sum_{t=s}^{T} \pi_j^{(t)}$
- $\beta_s^{\#}$ = ($\beta_{s,1}$,...,$\beta_{s,s-1}$) for s=2,...,T.

Power calculation
Covariance matrix

- $\overline{\mu}_{s;0} = \sum_{j=0}^{J} \phi_j (\sum_{t=s}^{T} \pi_j^{(t)} \mu_{j,0}^{(t)}) / \sum_{j=0}^{J} \pi_j^{(\geq s)}$: the weighted average of pattern-specific baseline means among all patterns with observed data at time point s.

- $\overline{\delta^{\star}}_{s;u}$: the weighted average of treatment effects under MAR at postbaseline time point u with weights proportional to the probability of observing y_{is} for u=1,...,s-1.

Asymptotic covariance matrix of the regression parameters $(\hat{\beta}_s^{\#}, \hat{\gamma}_s)$:

$$\text{Cov\_reg} = n^{-1}\sigma_s^2(\boldsymbol{I}_s^{\#})^{-1}$$

Power calculation
Covariance matrix

Asymptotic covariance matrix of the regression parameters $(\hat{\beta}_s^{\#}, \hat{\gamma}_s)$:

$$\text{Cov\_reg} = n^{-1}\sigma_s^2(\boldsymbol{I}_s^{\#})^{-1}$$

For s=1,...,T, u,v=1,...,s-1 and k, k'=1,...,J:

$$\boldsymbol{I}_{s;u,v}^{\#} = \sum_{j=0}^{J} \phi_j \pi_j^{(\geq s)} [(\delta_{j,u}^{\star} - \overline{\delta^{\star}}_{s;u})(\delta_{j,v}^{\star} - \overline{\delta^{\star}}_{s;v}) + \omega_{u,v}]$$

$$\boldsymbol{I}_{s;s-1+k,v}^{\#} = \phi_k \pi_k^{(\geq s)} (\delta_{k,v}^{\star} - \overline{\delta^{\star}}_{s;v})$$

$$\boldsymbol{I}_{s;s-1+k,s-1+k'}^{\#} = \phi_k \pi_k^{(\geq s)} I(k = k') - \phi_k \pi_k^{(\geq s)} \phi_{k'} \pi_{k'}^{(\geq s)} / \sum_{j=0}^{J} \phi_j \pi_j^{(\geq s)}$$

These equations are valid if $\overline{\mu}_{s;0} = \sum_{t=s}^{T} \pi_j^{(t)} \mu_{j,0}^{(t)} / \pi_j^{(\geq s)}$.

Power calculation
Covariance matrix

- Partial derivatives of the efficacy estimands with respect to the regression parameters:

$$\frac{\partial \delta^{\star}_{j,T}}{\partial \beta_{s,t}} = \sum_{l=1}^{T} \left(\frac{\partial \xi_{T,l}}{\partial \beta_{s,t}}\right) \gamma_{j,l} \text{ and } \frac{\partial \delta^{\star}_{j,T}}{\partial \gamma_{j,s}} = \xi_{T,s}.$$

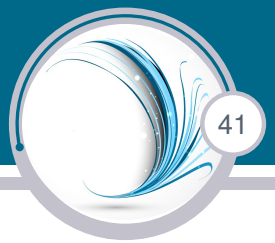
- Partial derivatives of the effectiveness estimands with respect to the pattern probabilities:

$$\frac{\partial \delta_{j,T}}{\partial \pi_j^{(s)}} = -\sum_{l=1}^{s} \xi_{T,l} \Delta_{j,l}.$$

- Partial derivatives of the effectiveness estimands with respect to the regression parameters:
for j=1,...,J and $1 \leq t < s \leq T$

$$\frac{\partial \delta_{j,T}}{\partial \beta_{s,t}} = \sum_{l=1}^{T} \left(\frac{\partial \xi_{T,l}}{\partial \beta_{s,t}}\right) \left(\gamma_{j,l} + \Delta_{j,l} \pi_j^{(<l)}\right)$$

$$\frac{\partial \delta_{j,T}}{\partial \gamma_{j,s}} = \begin{cases} \xi_{T,s}\left(1 - \Phi \pi_j^{(<s)}\right) & \text{if } \Delta_{j,s} = -\Phi \gamma_s, \\ \xi_{T,s} & \text{otherwise} \end{cases}$$



- Partial derivatives of the effectiveness estimands with respect to the residual variance:

$$\frac{\partial \delta_{j,T}}{\partial \sigma_s^2} = \begin{cases} 0.25 \xi_{T,s} \Phi \sigma_s^{-1} \pi_j^{(<s)} & \text{if } \Delta_{j,s} = 0.5 \Phi \sigma_s, \\ 0 & \text{otherwise} \end{cases}$$

And, for $1 \leq v \leq u \leq T$, $1 \leq t \leq s \leq T$:

$$\frac{\partial \xi_{u,v}}{\partial \beta_{s,t}} = \begin{cases} \xi_{t,v} & \text{if } u = s > t \geq v, \\ \sum_{j=\max(s,v+1)}^{u-1} \beta_{u,j} \frac{\partial \xi_{j,v}}{\partial \beta_{t,s}} & \text{if } u > \max(s,v), \\ 0 & \text{otherwise} \end{cases}$$

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LDL Cholesterol Study

MMRM Results

Estimated R Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	515.70	320.07	302.24	253.64	203.11
2	320.07	557.75	356.61	315.18	277.22
3	302.24	356.61	640.17	383.10	354.87
4	253.64	315.18	383.10	643.67	403.72
5	203.11	277.22	354.87	403.72	710.95

Figure: Estimated covariance matrix for **heterogeneous structure**

Estimated R Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	611.33	365.80	218.88	130.97	78.3687
2	365.80	611.33	365.80	218.88	130.97
3	218.88	365.80	611.33	365.80	218.88
4	130.97	218.88	365.80	611.33	365.80
5	78.3687	130.97	218.88	365.80	611.33

Figure: Estimated covariance matrix for **autoregressive (1) structure**

LDL Cholesterol Study

MMRM Results

Estimated R Correlation Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.5968	0.5260	0.4402	0.3354
2	0.5968	1.0000	0.5968	0.5260	0.4402
3	0.5260	0.5968	1.0000	0.5968	0.5260
4	0.4402	0.5260	0.5968	1.0000	0.5968
5	0.3354	0.4402	0.5260	0.5968	1.0000

Figure: Estimated correlation matrix for **heterogeneous structure**

Estimated R Correlation Matrix for varcat 1					
Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.5984	0.3580	0.2142	0.1282
2	0.5984	1.0000	0.5984	0.3580	0.2142
3	0.3580	0.5984	1.0000	0.5984	0.3580
4	0.2142	0.3580	0.5984	1.0000	0.5984
5	0.1282	0.2142	0.3580	0.5984	1.0000

Figure: Estimated correlation matrix for **autoregressive (1) structure**

LDL Cholesterol Study

MMRM Results

Estimates					
Label	Estimate	Standard Error	DF	t Value	Pr > |t|
treatment effect at week 4	8.7473	2.8816	292	3.04	0.0026
treatment effect at week 8	13.2307	3.0146	277	4.39	<.0001
treatment effect at week 12	9.8185	3.2243	286	3.05	0.0025
treatment effect at week 16	12.2936	3.2879	277	3.74	0.0002
treatment effect at week 24	5.6961	3.4418	284	1.65	0.0990

Figure: Estimates for **heterogeneous structure**

Estimates					
Label	Estimate	Standard Error	DF	t Value	Pr > |t|
treatment effect at week 4	8.8267	3.1408	795	2.81	0.0051
treatment effect at week 8	13.2034	3.1544	811	4.19	<.0001
treatment effect at week 12	9.8501	3.1561	802	3.12	0.0019
treatment effect at week 16	12.2679	3.2093	828	3.82	0.0001
treatment effect at week 24	5.4997	3.2027	802	1.72	0.0863

Figure: Estimates for **autoregressive (1) structure**

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LDL Cholesterol Study
Power Function

Pptest				
0.02	0.02	0.02	0.02	0.92
0.005	0.005	0.005	0.043	0.942

Figure: Pattern probabilities of the dataset

- 92% of subjects in the placebo group completed the study
- 94.2% of subjects in the treatment group completed the study

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LDL Cholesterol Study

Impact of the missing data pattern probabilities

- Different completers rate
- Different repartition of dropouts for the rest of the subjects: early dropouts, uniform dropouts and late dropouts.

For example with 40% of completers rate:

Pptest40_unif				
0.15	0.15	0.15	0.15	0.4
0.15	0.15	0.15	0.15	0.4

Figure: Uniform dropouts

Pptest40_begin				
0.6	0	0	0	0.4
0.6	0	0	0	0.4

Figure: Early dropouts

Pptest40_end				
0	0	0	0.6	0.4
0	0	0	0.6	0.4

Figure: Late dropouts

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LDL Cholesterol Study

Impact of the missing data pattern probabilities

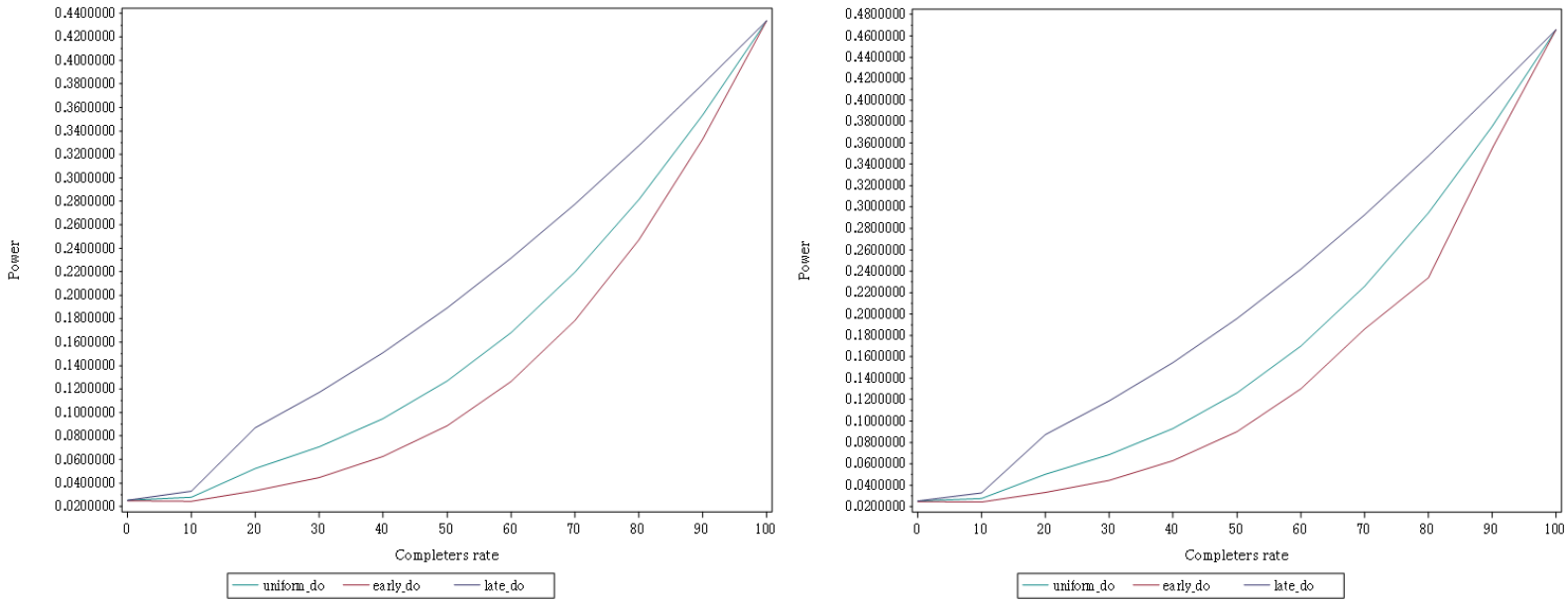

Figure: Power with respect to completers rate with method 3 and C=3

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- Different time profiles of MAR treatment effects

deltastartest_UN_1				
-10	-10	-10	-10	-10

Figure: Treatment effect from the beginning

deltastartest_UN_2				
0	-10	-10	-10	-10

Figure: Treatment effect starting later

deltastartest_UN_3				
0	0	-10	-10	-10

Figure: Treatment effect starting later

deltastartest_UN_4				
0	0	0	-10	-10

Figure: Treatment effect starting later

deltastartest_UN_5				
0	0	0	0	-10

Figure: Treatment effect at the end

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