Analyzing Incomplete Longitudinal Clinical Trial Data

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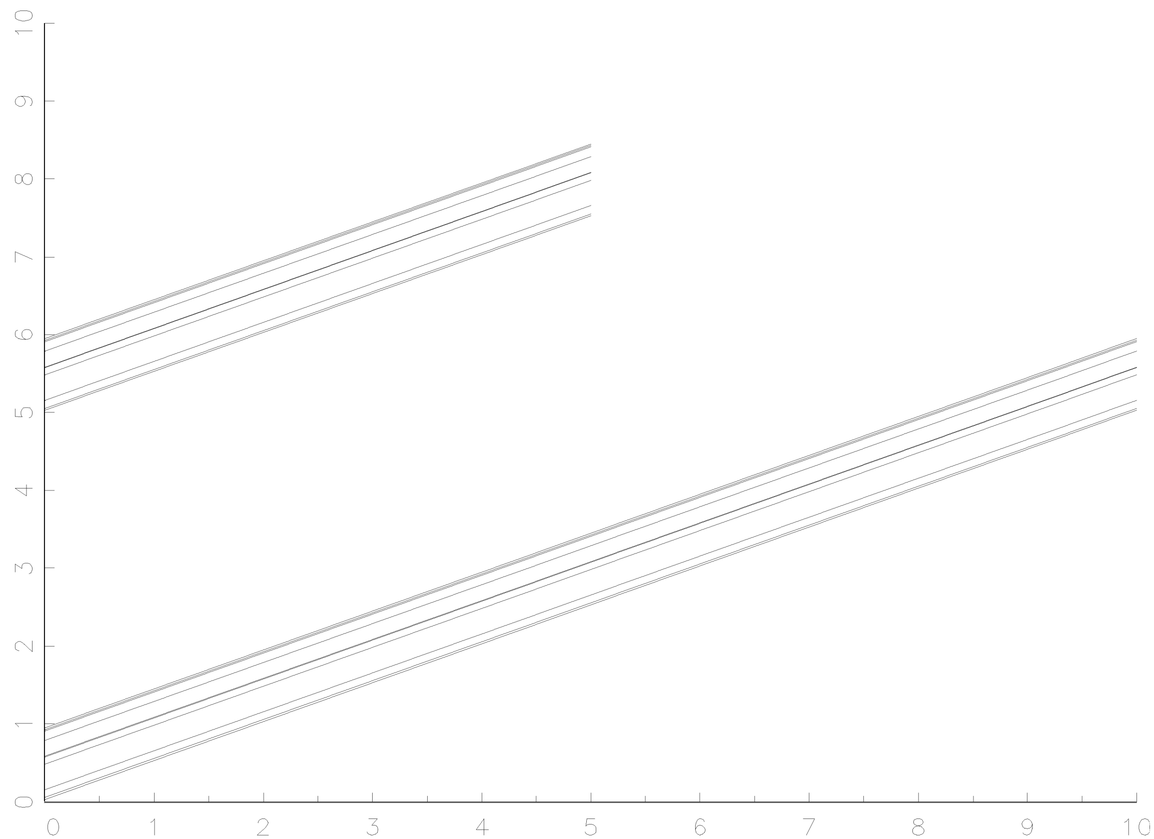
Incomplete Longitudinal Data



Scientific Question

- In terms of **entire longitudinal profile**
- In terms of **last planned measurement**
- In terms of **last observed measurement**

Framework

$$f(\boldsymbol{Y}_i, D_i | \boldsymbol{\theta}, \boldsymbol{\psi})$$

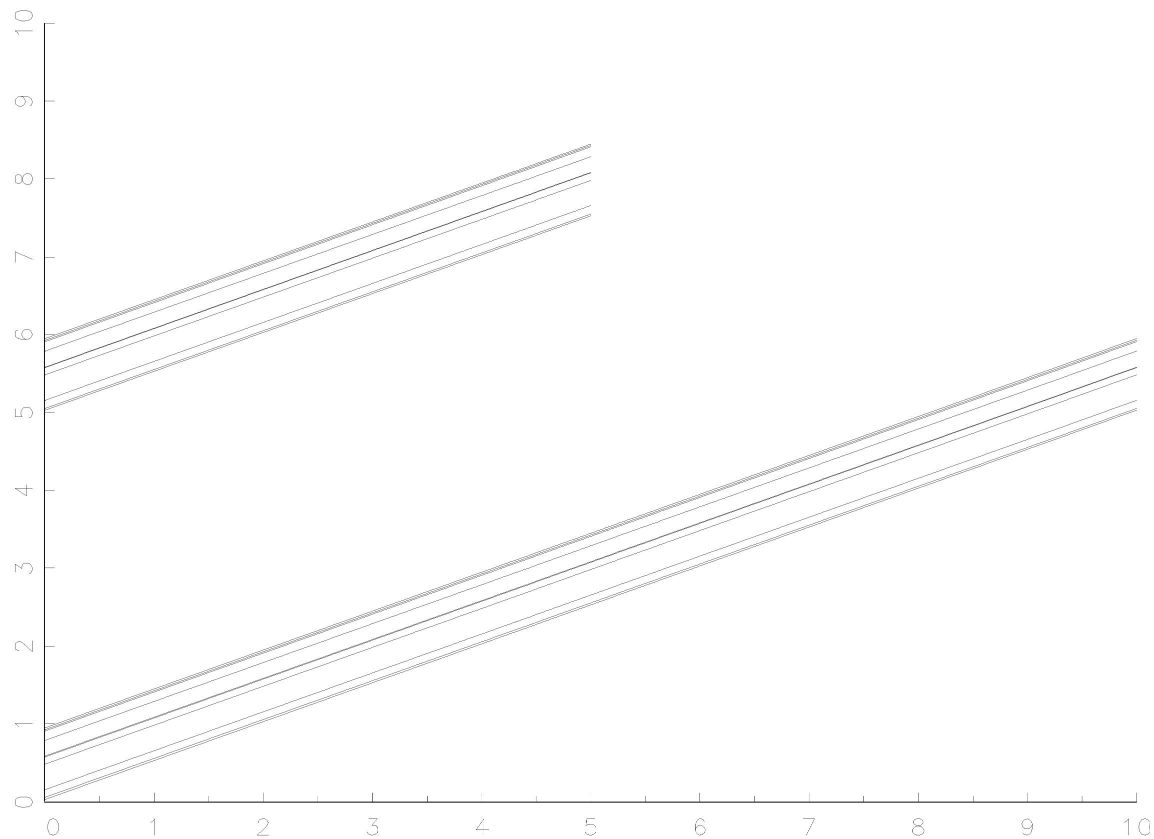
Selection Models: $f(\boldsymbol{Y}_i|\boldsymbol{\theta})\, f(D_i|\boldsymbol{Y}_i^o, \boldsymbol{Y}_i^m, \boldsymbol{\psi})$

MCAR	$\longrightarrow$	MAR	$\longrightarrow$	MNAR
CC ?		**direct likelihood !**		joint model !?
LOCF ?		expectation-maximization (EM).		sensitivity analysis ?!
imputation ?		multiple imputation (MI).		
$\vdots$		**(weighted) GEE !**		

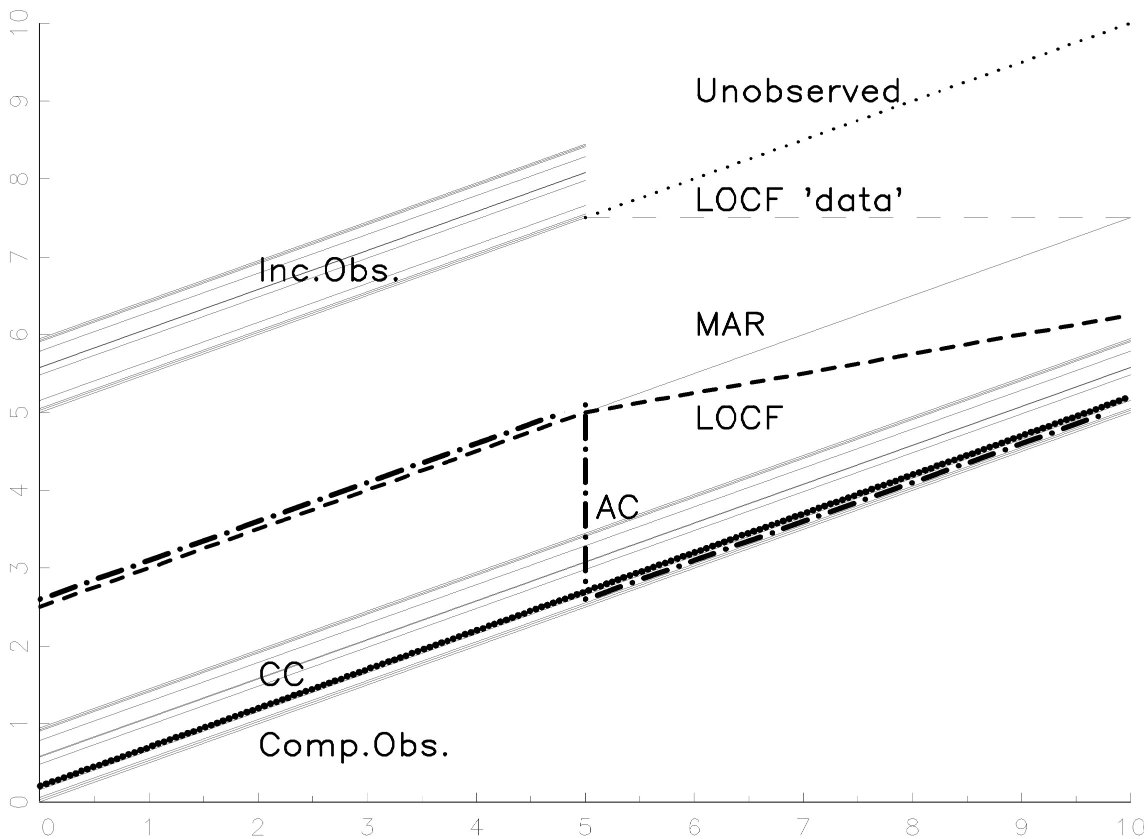
Pattern-Mixture Models: $f(\boldsymbol{Y}_i|D_i, \boldsymbol{\theta})f(D_i|\boldsymbol{\psi})$

Shared-Parameter Models: $f(\boldsymbol{Y}_i|\boldsymbol{b}_i, \boldsymbol{\theta})f(D_i|\boldsymbol{b}_i, \boldsymbol{\psi})$

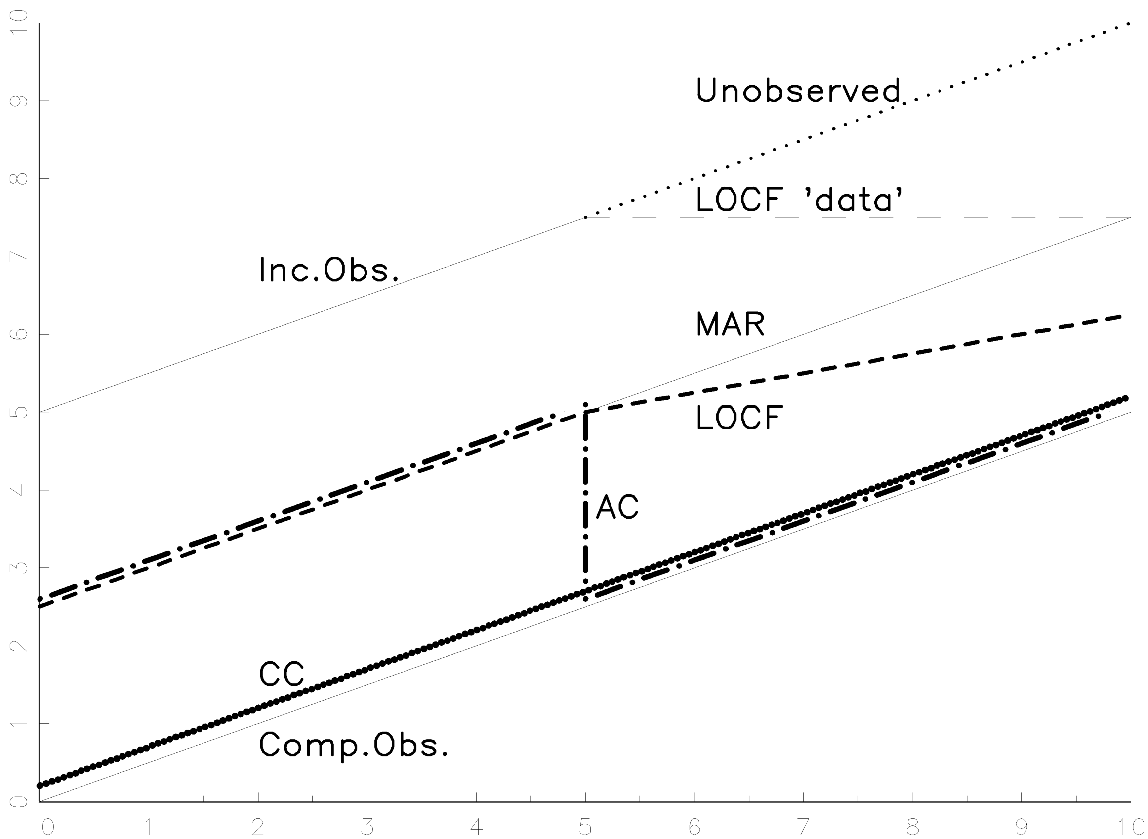
Incomplete Longitudinal Data



Data and Modeling Strategies



Modeling Strategies



Quantifying the Bias

Dropouts $t_{ij} = 0$	**Completers** $t_{ij} = 0, 1$
Probability p_0	Probability p_1
$E(Y_{ij}) = \beta_0 + \beta_1 T_i + \beta_2 t_{ij} + \beta_3 T_i t_{ij}$	$E(Y_{ij}) = \gamma_0 + \gamma_1 T_i + \gamma_2 t_{ij} + \gamma_3 T_i t_{ij}$

$$\Downarrow$$

	CC	**LOCF**
MCAR	0	$(p_1 - p_0)\beta_2 - (1 - p_1)\beta_3$
MAR	$-\sigma[(1-p_1)(\beta_0 + \beta_1 - \gamma_0 - \gamma_1)$ $-(1-p_0)(\beta_0 - \gamma_0)]$	$p_1(\gamma_0 + \gamma_1 + \gamma_2 + \gamma_3) + (1 - p_1)(\beta_0 + \beta_1)$ $-p_0(\gamma_0 + \gamma_2) - (1 - p_0)\beta_0 - \gamma_1 - \gamma_3$ $-\sigma[(1-p_1)(\beta_0 + \beta_1 - \gamma_0 - \gamma_1) - (1-p_0)(\beta_0 - \gamma_0)]$

$T_i = 0, 1$: treatment assignment

$\sigma \propto$ covariance between both measurements

Direct Likelihood Maximization

$$\text{MAR} : f(\boldsymbol{Y}_i^o|\boldsymbol{\theta})\, f(D_i|\boldsymbol{Y}_i^o, \boldsymbol{\psi})$$

$$\left.\begin{array}{r} \text{Mechanism is MAR} \\ \boldsymbol{\theta} \text{ and } \boldsymbol{\psi} \text{ distinct} \\ \text{Interest in } \boldsymbol{\theta} \\ \text{Use observed information matrix} \end{array}\right\} \Longrightarrow \quad \text{Likelihood inference is valid}$$

Outcome type	Modeling strategy	Software
Gaussian	Linear mixed model	SAS procedure MIXED
Non-Gaussian	Generalized linear mixed model	SAS procedure NLMIXED

(Weighted) Generalized Estimating Equations

MAR and non-ignorable !

- Standard GEE inference correct only under MCAR

- Under MAR: *weighted* GEE

Robins, Rotnitzky & Zhao (JASA, 1995)

Fitzmaurice, Molenberghs & Lipsitz (JRSSB, 1995)

- Weigh a contribution by inverse dropout probability

- Adjust estimating equations

(Weighted) Generalized Estimating Equations

MAR and non-ignorable !

- Decompose dropout time $\qquad D_i = (R_{i1}, \ldots, R_{in}) = (1, \ldots, 1, 0, \ldots, 0)$

- Weigh a contribution by inverse dropout probability

$$\nu_{id_i} \equiv P[D_i = d_i] = \prod_{k=2}^{d_i-1} (1 - P[R_{ik} = 0 | R_{i2} = \ldots = R_{i,k-1} = 1]) \times$$
$$P[R_{id_i} = 0 | R_{i2} = \ldots = R_{i,d_i-1} = 1]^{I\{d_i \le T\}}$$

- Adjust estimating equations

$$\sum_{i=1}^{N} \frac{1}{\nu_{id}} \cdot \frac{\partial \boldsymbol{\mu_i}}{\partial \boldsymbol{\beta}'} V_i^{-1} (\boldsymbol{y_i} - \boldsymbol{\mu_i}) = \mathbf{0}$$

A Full Selection Model

MNAR : $\int f(\boldsymbol{Y}_i|\boldsymbol{\theta}) f(D_i|\boldsymbol{Y}_i, \boldsymbol{\psi}) d\boldsymbol{Y}_i^m$

Diggle and Kenward (JRSSC 1994)

$f(\boldsymbol{Y}_i|\boldsymbol{\theta})$

Linear mixed model

$$\boldsymbol{Y}_i = X_i\beta + Z_i\boldsymbol{b}_i + \boldsymbol{\varepsilon}_i$$

&

$f(D_i|\boldsymbol{Y}_i, \boldsymbol{\psi})$

Logistic regressions for dropout

$$\textbf{logit}\left[P(D_i = j \mid D_i \geq j, Y_{i,j-1}, Y_{ij})\right]$$

$$= \psi_0 \ + \ \psi_1 Y_{i,j-1} \ + \ \psi_2 Y_{ij}$$

Criticism $\longrightarrow$ Sensitivity Analysis

"…, estimating the 'unestimable' can be accomplished only by making modelling **assumptions**,…. The consequences of model **misspecification** will (…) be more severe in the non-random case." (Laird 1994)

$$\Downarrow$$

- **Several plausible models** or **ranges of inferences**
- **Change distributional assumptions** (Kenward 1998)
- **Local and global influence methods**
- **Semi-parametric framework** (Scharfstein *et al* 1999)
- **Pattern-mixture models**

Pattern-Mixture Models

Pattern 3

Pattern 2

Pattern 1

Connection SEM–PMM

Molenberghs, Michiels, Kenward, and Diggle (Stat Neerl 1998) Kenward, Molenberghs, and Thijs (Bka 2002)

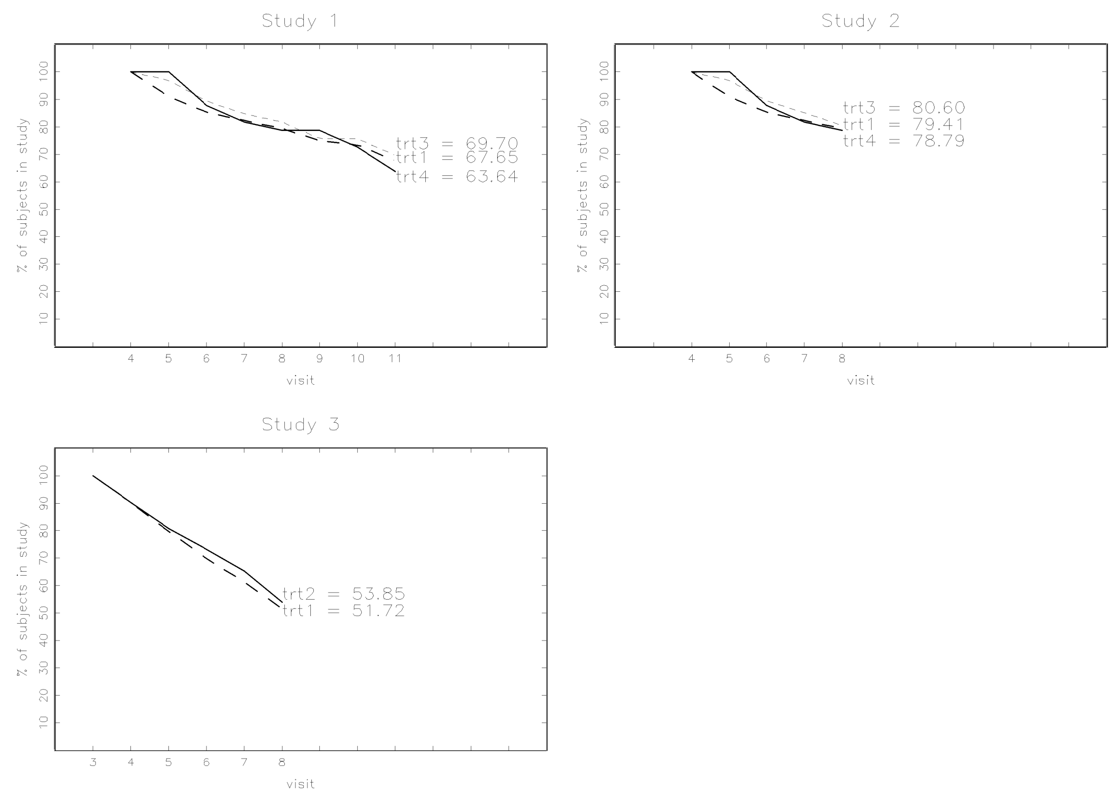
Selection Models: $f(D_i|\boldsymbol{Y}_i, \boldsymbol{\psi})$ $\longleftrightarrow$ $f(\boldsymbol{Y}_i|D_i, \boldsymbol{\theta})$: Pattern-Mixture Models

$$\begin{array}{lcccccccc}
 & & f(D_i) & & f(D_i|Y_{i1},\ldots,Y_{i,j-1}) & & f(D_i|Y_{i1},\ldots,Y_{i,j-1},Y_{ij}) & & f(D_i|Y_{i1},\ldots,Y_{i,j-1},Y_{ij},\ldots,Y_{in}) \\
\text{SeM} & : & \text{MCAR} & \subset & \text{MAR} & \subset & \neg\ \text{future} & \subset & \text{MNAR} \\
 & & \updownarrow & & \updownarrow & & \updownarrow & & \updownarrow \\
\text{PMM} & : & \text{MCAR} & \subset & \text{ACMV} & \subset & \neg\ \text{future} & \subset & \text{general}
\end{array}$$

Case Studies

Hamilton Depression Rating Scale (HAMD)

Study	N	**Weeks**
1	167	4-11
2	342	4-8
3	713	3-8



Results

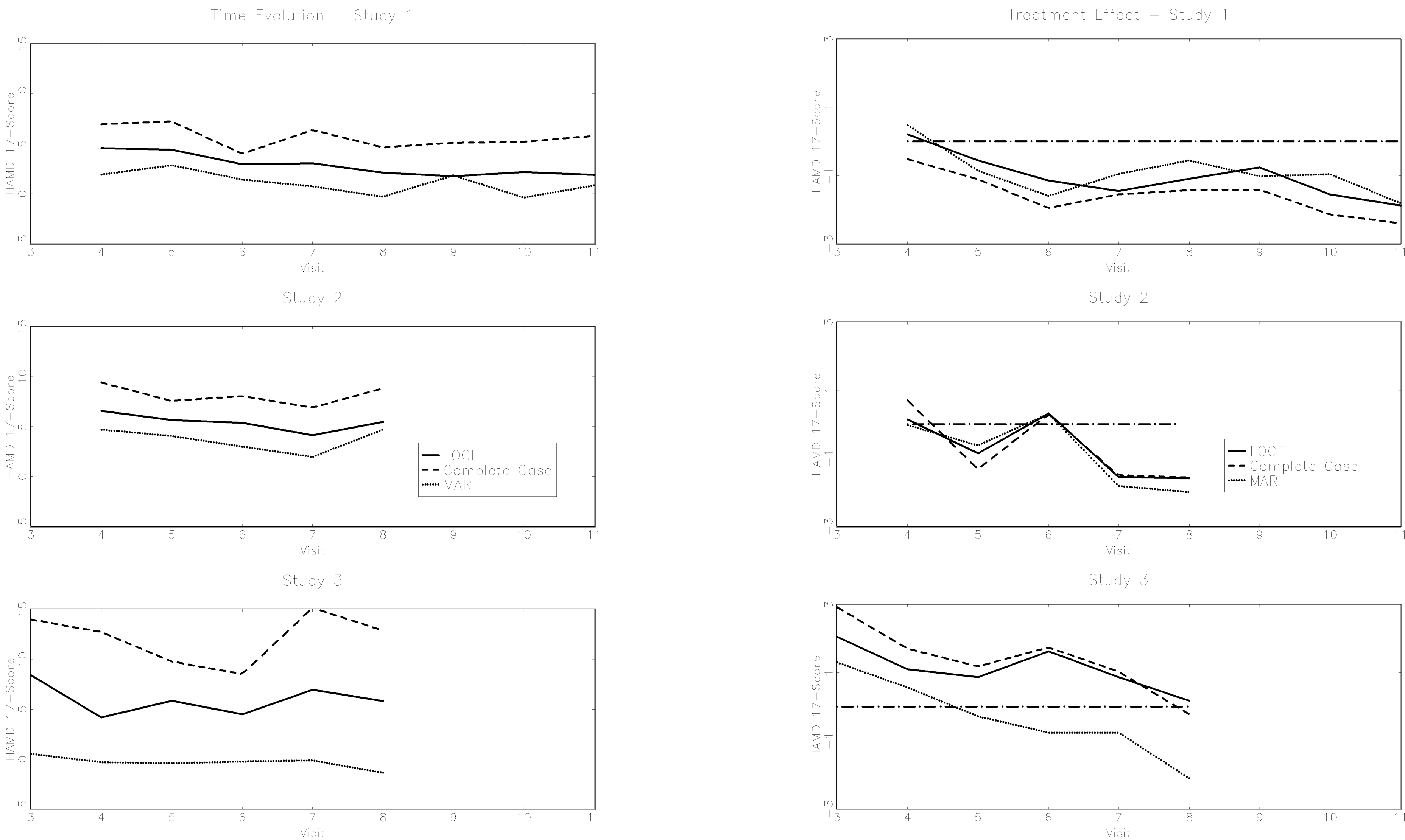
Treatment Effect at Last Visit (p values)

Method	Model	Study 1	Study 2	Study 3
CC	mixed	0.070	0.088	0.001
CC	t test	0.092	0.156	0.017
LOCF	mixed	0.056	0.082	0.001
LOCF	t test	0.246	0.172	0.120
MAR	mixed	0.047	0.077	0.001

Diggle and Kenward's Selection Model

	Treat. eff. (s.e.)			
	MAR	MNAR	χ^2	p value
1	-1.58(1.14)	-1.55(1.10)	0.90	0.32
2	-1.84(1.07)	-1.64(1.07)	9.65	0.0019
3	1.98(0.65)	2.04(0.64)	35.48	< 0.0001

Placebo Time Evolutions and Treatment Effects



Conclusions

MCAR/simple	CC	biased
	LOCF	inefficient
		not simpler than MAR methods
MAR	direct likelihood	easy to conduct
	weighted GEE	Gaussian & non-Gaussian
MNAR	variety of methods	strong, untestable assumptions
		most useful in sensitivity analysis