Bayesian methods for addressing missing data in health economic evaluation

Andrea Gabrio

(Thanks to Gianluca Baio and Alexina J. Mason)

http://www.ucl.ac.uk/statistics/research/statistics-health-economics/

ucakgab@ucl.ac.uk

DEPARTMENT OF STATISTICAL SCIENCE
UNIVERSITY COLLEGE LONDON

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Health Economic Evaluation

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Statistical model $\longrightarrow$ Economic model

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$$\text{EIB} = k\text{E}[\Delta_e] - \text{E}[\Delta_c]$$
$$\text{CEAC} = \Pr(k\Delta_e - \Delta_c > 0)$$

Statistical model → **Economic model** → **Decision analysis**

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- Summarises the economic model by computing suitable measures of "cost-effectiveness"
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Uncertainty analysis

- Assesses the impact of uncertainty (eg in parameters or model structure) on the economic results
- Mandatory in many jurisdictions (including NICE)
- Fundamentally Bayesian

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- The available data usually look something like this:

		Demographics			HRQL data				Resource use data			
ID	**Trt**	Sex	Age	...	u_0	u_1	...	u_J	c_0	c_1	...	c_J
1	1	M	23	...	0.32	0.66	...	0.44	103	241	...	80
2	1	M	21	...	0.12	0.16	...	0.38	1 204	1 808	...	877
3	2	F	19	...	0.49	0.55	...	0.88	16	12	...	22
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and the **typical** analysis is based on the following steps:

1. Compute individual QALYs and total costs as

$$e_i = \sum_{j=1}^{J} (u_{ij} + u_{ij-1}) \frac{\delta_j}{2} \quad \text{and} \quad c_i = \sum_{j=0}^{J} c_{ij}, \qquad \left[\text{with: } \delta_j = \frac{\text{Time}_j - \text{Time}_{j-1}}{\text{Unit of time}}\right]$$

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2. (Often implicitly) assume normality and linearity and model **independently** individual QALYs and total costs by controlling for baseline values

$$\begin{aligned} e_i &= \alpha_{e0} + \alpha_{e1} u_{0i} + \alpha_{e2}\text{Trt}_i + \varepsilon_{ei}\,[+\ldots], \qquad &\varepsilon_{ei} \sim \text{Normal}(0, \sigma_e) \\ c_i &= \alpha_{c0} + \alpha_{c1} c_{0i} + \alpha_{c2}\text{Trt}_i + \varepsilon_{ci}\,[+\ldots], \qquad &\varepsilon_{ci} \sim \text{Normal}(0, \sigma_c) \end{aligned}$$

What's wrong with this?

- Potential correlation between costs & clinical benefits
    - Strong positive correlation — effective treatments are innovative and are associated with higher unit costs
    - Negative correlation — more effective treatments may reduce total care pathway costs e.g. by reducing hospitalisations, side effects, etc.

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  - Costs usually skewed and benefits may be bounded in $[0;1]$
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- ... and of course **Partially Observed** data
  - Can have item and/or unit non-response
  - Missingness may occur in either or both benefits/costs
  - Focus in decision-making — not inference!

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    - Missing Completely At Random (MCAR)
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- Well-defined statistical model for the complete data, and explicit assumptions about the missing value mechanism —"principled" approach to missingness

Missing Data Mechanism: MCAR

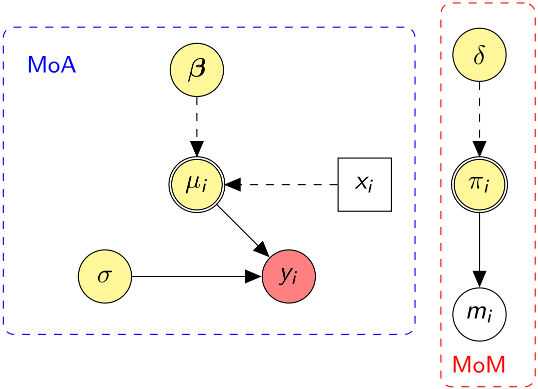
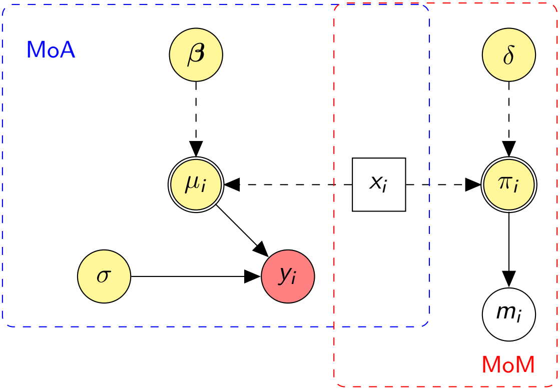


Figure: MoA=Model of Analysis, MoM=Model of Missingness

Missing Data Mechanism: MAR



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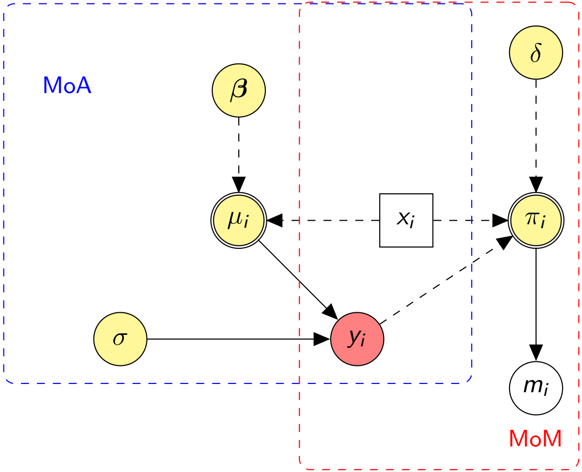

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Missing Data Methods

- **Complete Case Analysis**
  - Elimination of partially observed cases
  - Simple but reduce efficiency and possibly bias parameter estimates
- **Single Imputation**
  - Imputation of missing data with a single value (mean, median, LVCF)
  - Does not account for the uncertainty in the imputation process
- **Multiple Imputation** (Rubin, 1987)
  - Missing data imputed H times to obtain H different imputed datasets
  - Each dataset is analysed and H sets of estimates are derived
  - Parameter estimates are combined into a single quantity
  - The uncertainty due to imputation is incorporated but the validity relies on the correct specification of the imputation model

Bayesian Modelling

- Parameters are given probability distributions that describe the uncertainty before (**prior**) and after (**posterior**) observing the data

$$p(\boldsymbol{\theta} \mid y) \propto p(y \mid \boldsymbol{\theta}) p(\boldsymbol{\theta})$$

- Incorporate both individual and parameter (missing data) uncertainty
- Naturally encode alternative missingness assumptions through the priors and assess the robustness of the results — **Sensitivity Analysis**
- Often not analytically tractable and iterative approximation methods, e.g. MCMC (Brooks et al., 2011), are required

A simple example

- For simplicity assume a Bivariate Normal for $\mathbf{MoA}(\boldsymbol{e}, \boldsymbol{c})$
- Can represent a joint distribution as a **conditional regression**

$$p(e, c) = p(e)p(c \mid e) = p(c)p(e \mid c)$$

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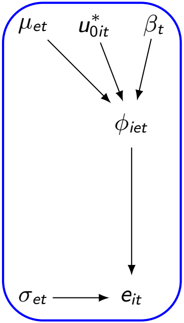
Marginal model for e



$$e_{it} \sim N(\phi_{iet}, \sigma_{et})$$

$$\phi_{iet} = \mu_{et} + \beta_t u^*_{0it}$$

$$\phi_{iet} = \text{marginal mean}$$
$$\sigma_{et} = \text{marginal sd}$$

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$$c_{it} \mid e_{it} \sim N(\phi_{ict}, \psi_{ict})$$

$$\phi_{ict} = \mu_{ct} + \rho(e_{it} - \mu_{et})$$

$$\psi_{ict} = \sqrt{\sigma^2_{ct} - \sigma^2_{et}\rho^2}$$

ϕ_{ict} = conditional mean
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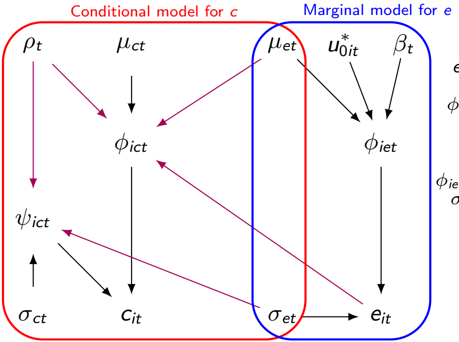

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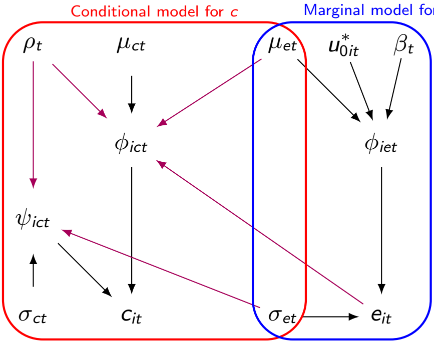

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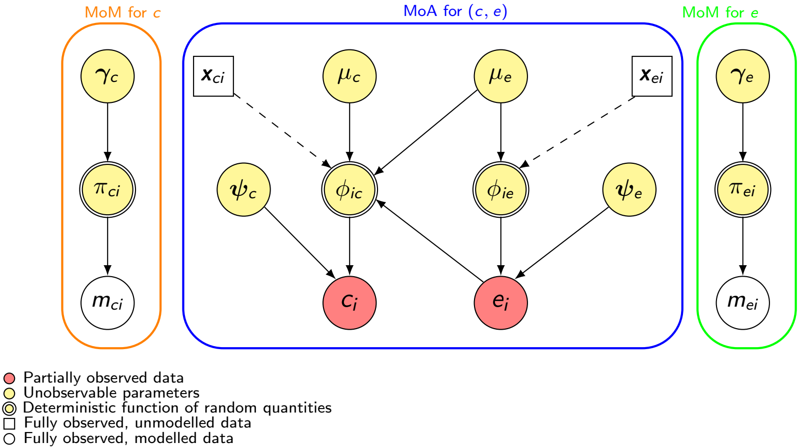
- Under MAR, no need to explicitly model the **MoM**

Nonignorable Missingness — Selection Models

MCAR (e, c)



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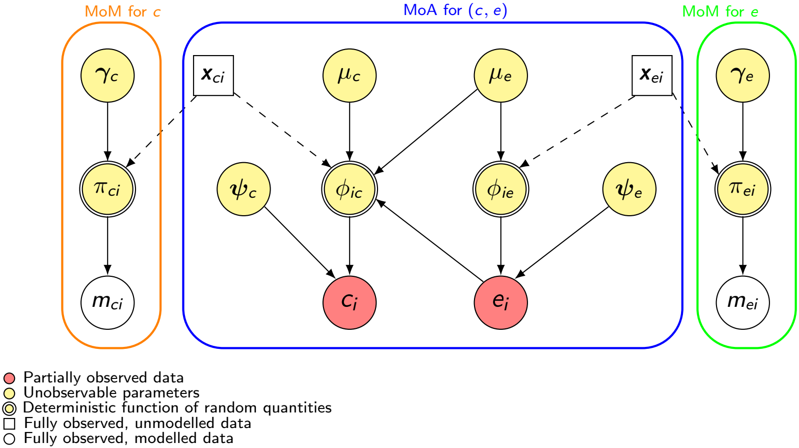

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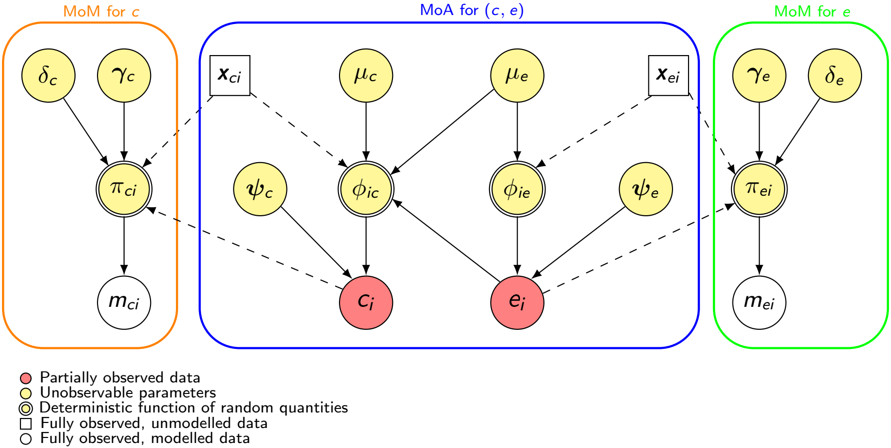

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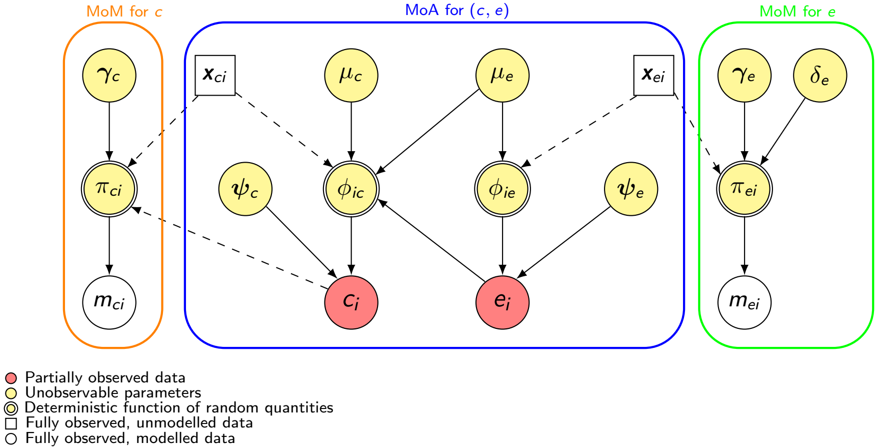

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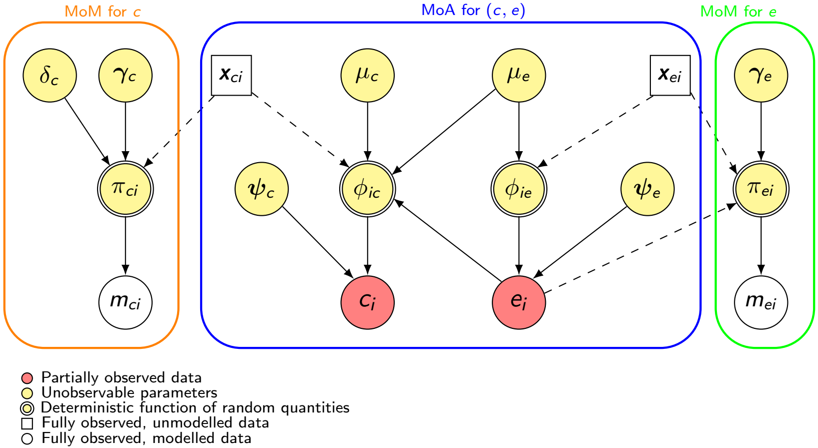

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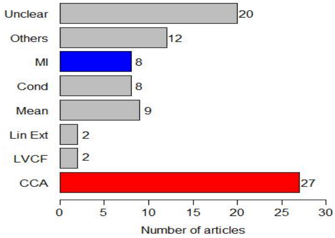
Systematic Literature Review

Two-fold purpose:

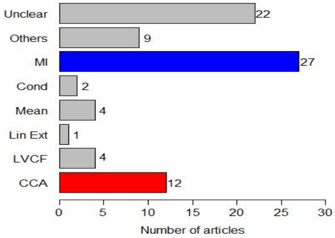
1. Provide some guidelines on the reporting and analysis of missingness
2. Review of the missing data methods in CEAs (2003-2015), updating the work of Noble et al. (2012)

- Original review focused only on missing costs in within-trial CEA studies
  - 88 articles between 2003-2009
- Include missing effects and update the review
  - 81 studies between 2009-2015

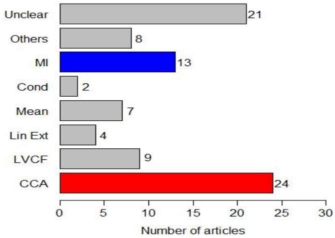
Current Methods



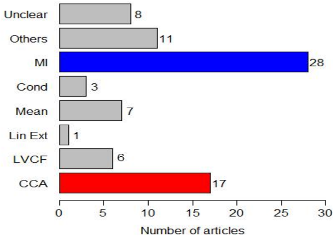
(a) Missing costs (2003-2009)



(b) Missing costs (2009-2015)



(c) Missing effects (2003-2009)



(d) Missing effects (2009-2015)

Conclusions

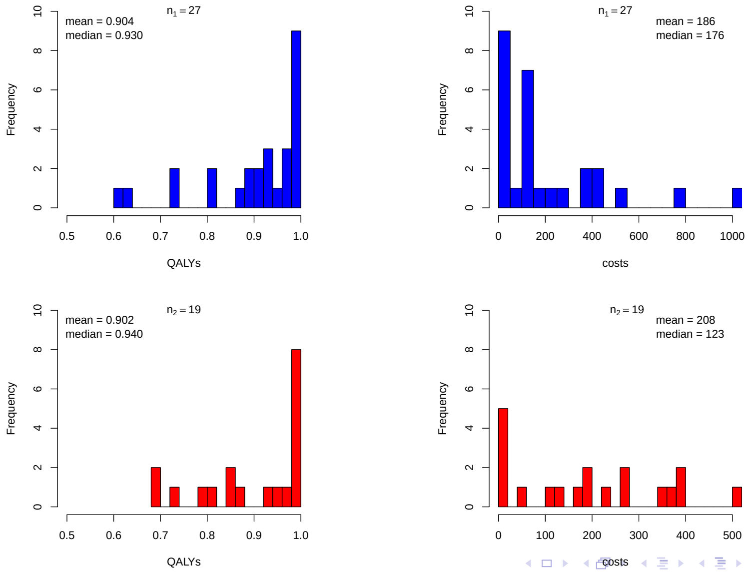
- High missing data proportions in within-trial CEAs may lead to imprecise economic evidences
- The review shows a movement towards more flexible methods in terms of missingness assumptions but:
  - Many studies do not provide transparent missing data information
  - Almost no study performs a sensitivity analysis
- Missing data handling can be improved by explicitly defining the assumptions and assess their impact on the conclusions.

The MenSS Trial

- The MenSS pilot RCT (Bailey et al., 2016) evaluates the cost-effectiveness of a new digital intervention to reduce the incidence of STI in young men with respect to the SOC
  - QALYs calculated from utilities (EQ-5D 3L)
  - Total costs calculated from different components (no baseline)

Time	**Type of outcome**	**observed (%)**	**observed (%)**
		Control (n_1=75)	Intervention (n_2=84)
Baseline	utilities	72 (96%)	72 (86%)
3 months	utilities and costs	34 (45%)	23 (27%)
6 months	utilities and costs	35 (47%)	23 (27%)
12 months	utilities and costs	43 (57%)	36 (43%)
Complete cases	utilities and costs	27 (44%)	19 (23%)

Complete Cases



Modelling strategy

model	**MoA (e, c)**	**MoM (e)**	**MoM (c)**
Base-Case	Independent Normal	MAR	MAR
MAR(e, c)	Joint Normal	MAR	MAR
MNAR(e)	Joint Normal	MNAR	MAR
MNAR(c)	Joint Normal	MAR	MNAR

- MNAR(e): $e^{mis} \approx (5 - 10\%)$ lower than $e^{obs} \rightarrow \delta_e \sim \text{N}(-2, 1)$
- MNAR(c): $c^{mis} \approx (60 - 70\%)$ higher than $c^{obs} \rightarrow \delta_c \sim \text{N}(0, 1)$

Results

Parameter	Base-Case		MAR (e,c)			MNAR (e)			MNAR (c)		
	Mean	95% CI	Mean	95% CI		Mean	95% CI		Mean	95% CI	
Control $(t=1)$											
mean QALY (μ^e_1)	0.886		0.874	0.840	0.907	0.855	0.807	0.893	0.863	0.826	0.899
mean cost (μ^c_1)	214		207.770	115.363	302.901	207.912	113.226	301.081	290.324	126.971	452.932
sd QALY (σ^e_1)			0.081	0.061	0.110	0.081	0.064	0.103	0.081	0.064	0.103
sd cost (σ^c_1)			257.964	197.201	341.123	259.517	191.160	344.420	267.924	197.633	356.626
Intervention $(t=2)$											
mean QALY (μ^e_2)	0.918		0.913	0.868	0.956	0.847	0.715	0.929	0.912	0.860	0.967
mean cost (μ^c_2)	189		189.170	110.778	267.963	188.497	108.829	267.280	316.032	106.835	516.946
sd QALY (σ^e_2)			0.092	0.066	0.130	0.094	0.070	0.124	0.092	0.069	0.122
sd cost (σ^c_2)			174.082	124.350	252.623	176.378	121.666	249.735	190.872	128.897	275.189
Incremental											
mean QALY increment (Δ_e)	0.032	-0.02 0.08	0.039	-0.016	0.095	-0.008	-0.122	0.072	0.049	-0.011	0.114
mean cost increment (Δ_c)	-25	-145 97	-18.600	-141.081	102.463	-19.415	-140.283	104.196	25.708	-121.593	194.326

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mean QALY increment (Δ_e)	0.032	-0.02 0.08	0.039	-0.016	0.095	-0.008	-0.122	0.072	0.049	-0.011	0.114
mean cost increment (Δ_c)	-25	-145 97	-18.600	-141.081	102.463	-19.415	-140.283	104.196	25.708	-121.593	194.326

Results

	Base-Case			MAR (e, c)			MNAR (e)			MNAR (c)		
Parameter	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
Control $(t = 1)$												
mean QALY (μ_1^e)	0.886			0.874	0.840	0.907	0.855	0.807	0.893	0.863	0.826	0.899
mean cost (μ_1^c)	214			207.770	115.363	302.901	207.912	113.226	301.081	290.324	126.971	452.932
sd QALY (σ_1^e)				0.081	0.061	0.110	0.081	0.064	0.103	0.081	0.064	0.103
sd cost (σ_1^c)				257.964	197.201	341.123	259.517	191.160	344.420	267.924	197.633	356.626
Intervention $(t = 2)$												
mean QALY (μ_2^e)	0.918			0.913	0.868	0.956	0.847	0.715	0.929	0.912	0.860	0.967
mean cost (μ_2^c)	189			189.170	110.778	267.963	188.497	108.829	267.280	316.032	106.835	516.946
sd QALY (σ_2^e)				0.092	0.066	0.130	0.094	0.070	0.124	0.092	0.069	0.122
sd cost (σ_2^c)				174.082	124.350	252.623	176.378	121.666	249.735	190.872	128.897	275.189
Incremental												
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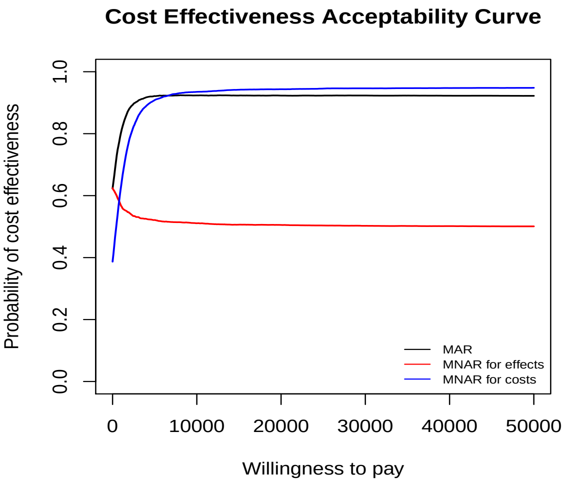
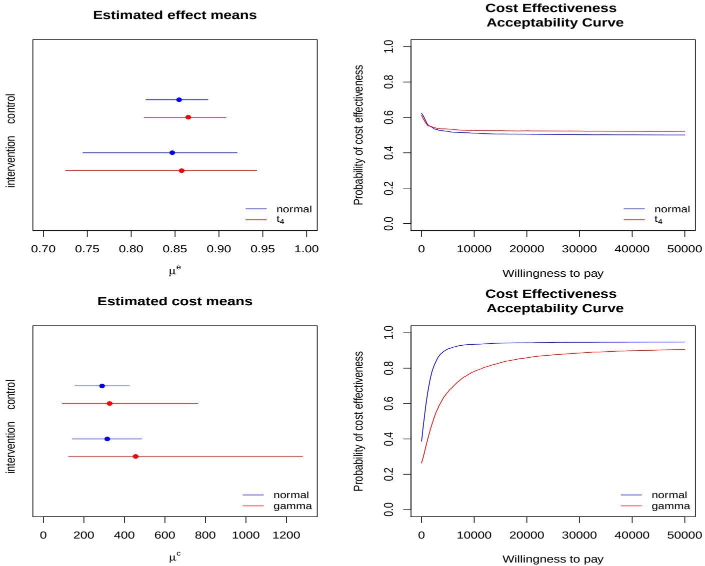
Economic Evaluation

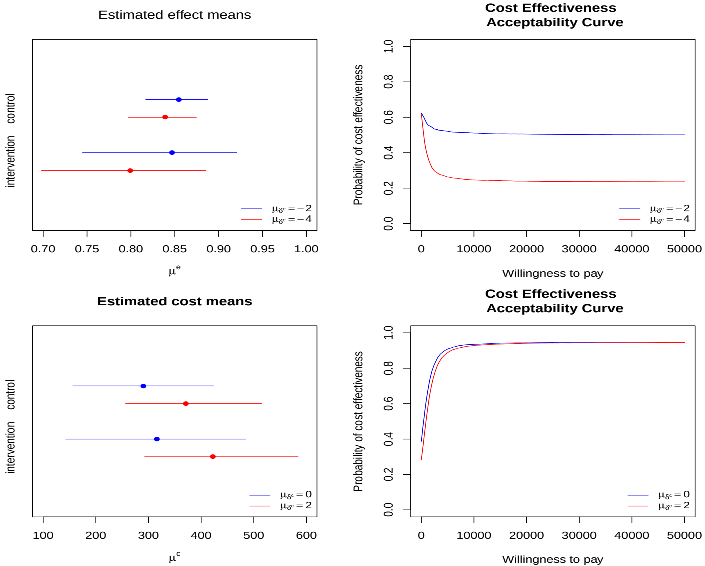


- Under $MNAR(e)$ the assessment radically changes, with the new interventions being not cost-effective compared with the control

Sensitivity Analysis (1)



Sensitivity Analysis (2)



Conclusions

- MAR is not likely to hold and the original study conclusions may overestimate the cost-effectiveness of the reference intervention
- The MNAR departures explored show how a relatively small variation in MoM(e) may substantially alter the decision output
- Lack of information about missingness may severely impair the analysis and force unrealistic assumptions
- Selection Models are a possible choice to handle nonignorable missingness but SA is necessary to assess the robustness of the results to alternative assumptions

Model Extension

- The models assume a Bivariate Normal for (e, c)
  - Simpler and closer to "standard" frequentist model
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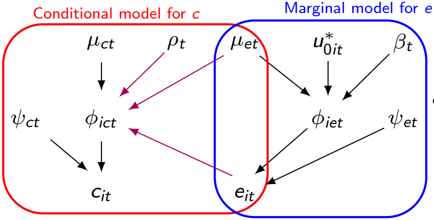
  - Model the relevant ranges: QALYs $\in (0, 1)$ and costs $\in (0, \infty)$
  - **But**: needs to rescale observed data to avoid 1 and 0 values
- Capture spike at 1 for QALYs with a Hurdle Model
  - Model e as a *mixture* of two components: $e^{<1}$ and e^{1}
  - e^{1} are considered as *structural values* (identically one)
  - May be extended to partially observed u_0

Beta-Gamma model

Conditional model for $c \mid e$

$$c_{it} \mid e_{it} \sim \text{Gamma}(\psi_{ct}\phi_{ict}, \psi_{ct})$$
$$\phi_{ict} = \mu_{ct} + \rho_t(e_{it} - \mu_{et})$$

$$\psi_{ct}\phi_{ict} = \text{shape}$$
$$\psi_{ct} = \text{rate}$$



Marginal model for e

$$e_{it} \sim \text{Beta}\left(\phi_{iet}\psi_{et}, (1-\phi_{iet})\psi_{et}\right)$$
$$\text{logit}(\phi_{iet}) = \mu_{et} + \beta_t u^*_{0it}$$

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Hurdle model for QALYs

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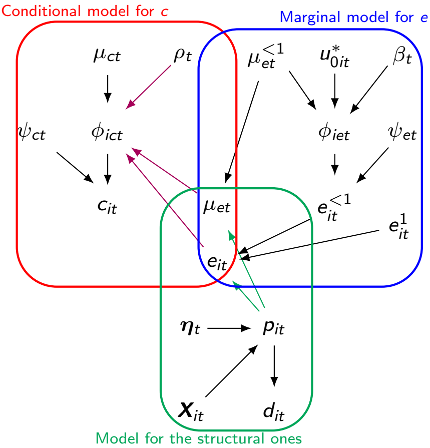


Marginal model for e

$$e_{it}^{1} : 1$$
$$e_{it}^{<1} \sim \text{Beta}\left(\phi_{iet}\psi_{et}, (1-\phi_{iet})\psi_{et}\right)$$
$$\text{logit}(\phi_{iet}) = \mu_{et} + \beta_t u_{0it}^{*}$$

$$e_{it} = p_{it}e_{it}^{1} + (1-p_{it})e_{it}^{<1}$$
$$\mu_{et} = p_t + (1-p_t)\mu_{et}^{<1}$$

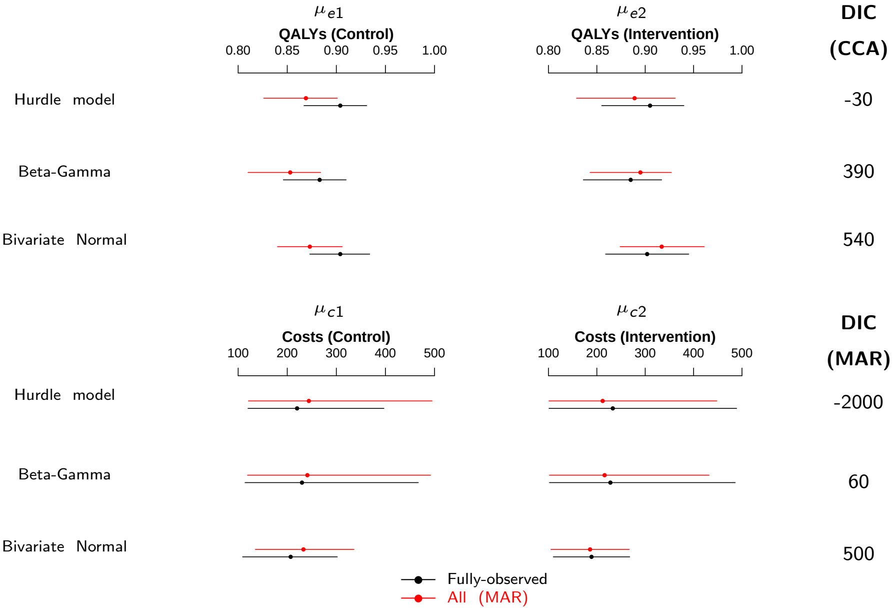
$$\phi_{iet}\psi_{et} = \text{shape}$$
$$(1-\phi_{iet})\psi_{et} = \text{shape}$$

Model for the structural ones

$$d_{it} : \mathbb{I}(e_{it}) = 1 \sim \text{Bernoulli}(p_{it})$$
$$\text{logit}(p_{it}) = \boldsymbol{X}_{it}\boldsymbol{\eta}_t$$

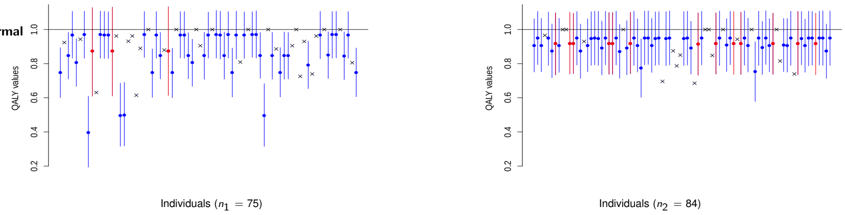
$$p_{it} = \text{probability of } e_{it}^{1}$$

Mean estimates (CCA + MAR)



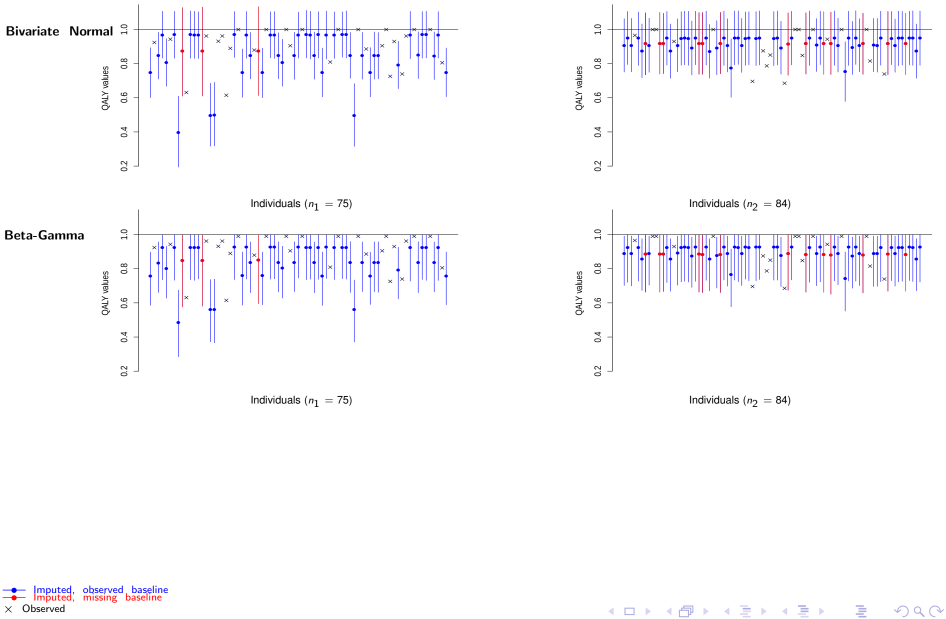
Imputations (under MAR)

Bivariate Normal

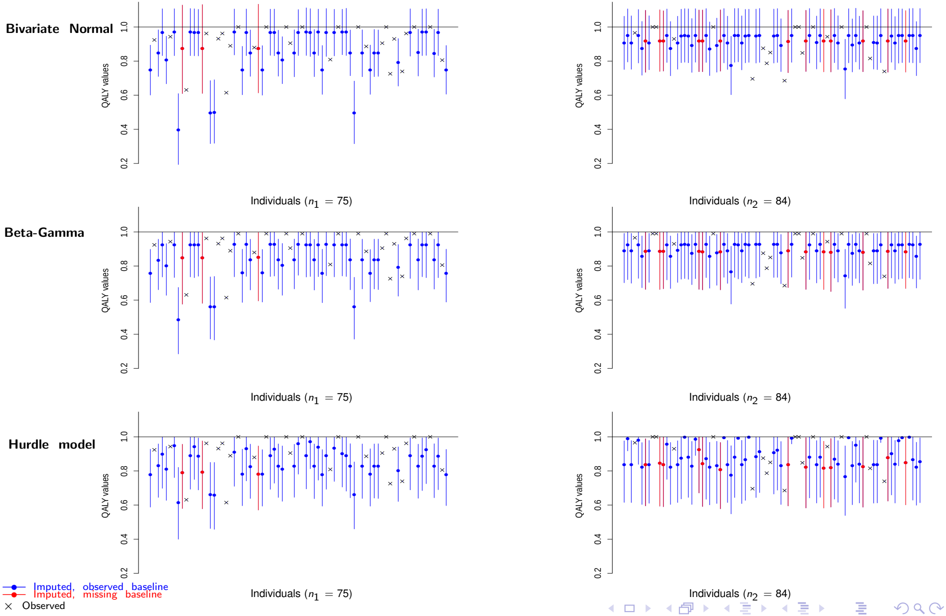


Imputed, observed baseline
Imputed, missing baseline
× Observed

Imputations (under MAR)



Imputations (under MAR)



MNAR

- We observe $n_{01} = 13$ and $n_{02} = 22$ individuals with $u_{0it} = 1$ and $u_{jit} = \texttt{NA}$, for $j = 1, 2, 3$
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MNAR1. Set $d_{it} = 1$ for all individuals with unit observed baseline utility

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MNAR3. Set $d_{it} = 1$ for the $n_{01} = 13$ individuals with $u_{0i1} = 1$ and $d_{it} = 0$ for the $n_{02} = 22$ individuals with $u_{0i2} = 1$

MNAR

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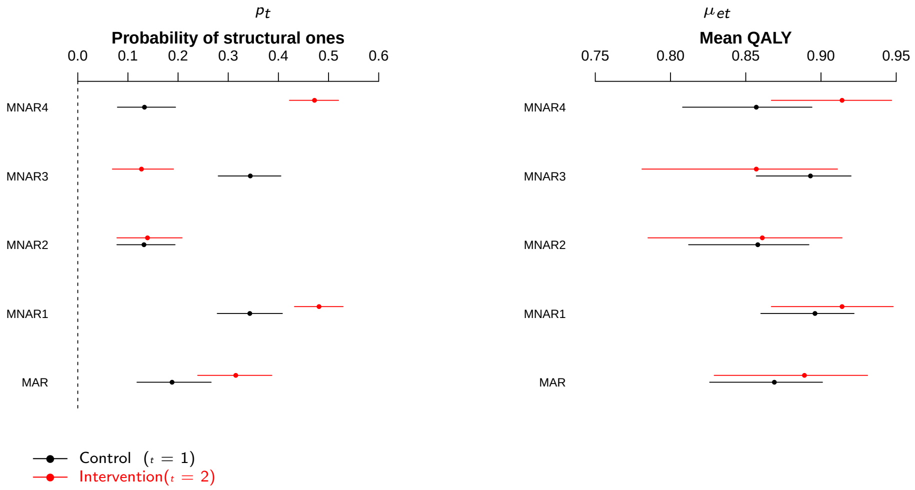
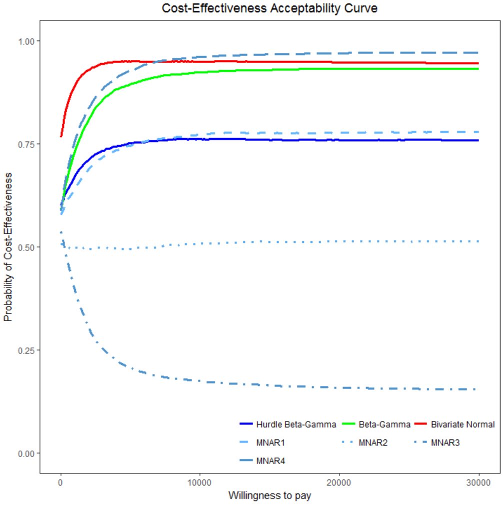
MNAR4. Set $d_{it} = 0$ for the $n_{01} = 13$ individuals with $u_{0i1} = 1$ and $d_{it} = 1$ for the $n_{02} = 22$ individuals with $u_{0i2} = 1$

Results — MNAR



Cost-effectiveness analysis



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- Particularly helpful in cost-effectiveness analysis, to account for
  - Asymmetrical distributions for the main outcomes
  - Correlation between costs & benefits
  - Structural values (eg spikes at 1 for utilities or spikes at 0 for costs)
- MNAR can never be ruled out
  - Necessary to explore plausible MNAR departures
  - Assess and quantify impact of uncertainty on inferences and (more importantly) on the decision process

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