Full Bayesian Models to Handle Missing Data in Health Economic Evaluations

A thesis submitted in partial fulfillment of the requirement for the Degree of M. Phil in Statistics

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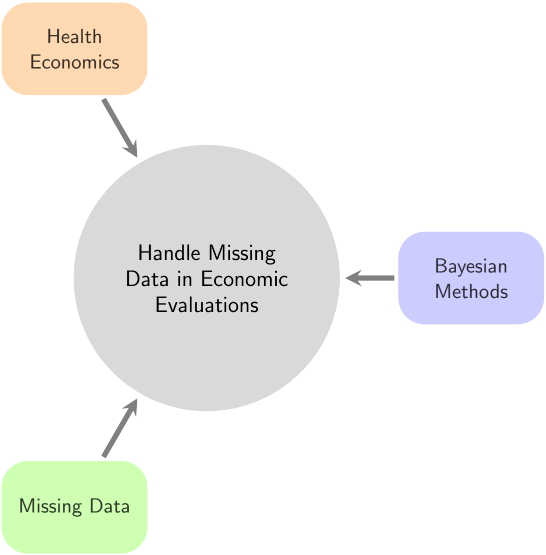
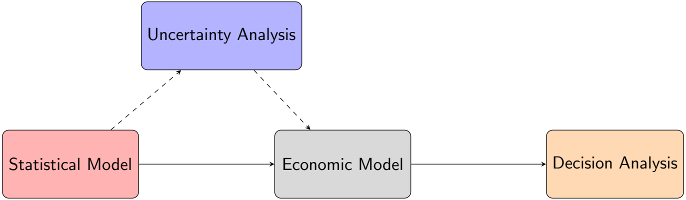
Research Question



Health Economics

- Health Economic Evaluation involves the application of economic theory to *health* and *health care*
- The main objective is the comparison of alternative options in terms of their *costs* and *benefits* (e.g. QALYs)
- Provides decision-makers with information that can help resource allocation decisions



Missing Data

- In CEAs missing data handling is particularly challenging:
  - Missingness may occur in both benefits/costs
  - Quantify impact of uncertainty on the output of the decision process
- Assumptions cannot be tested from the data but need to be formulated based on the available state of knowledge
- This formally translates into an assumed *missing data mechanism* (Rubin, 1987) that is linked to the data generating process
  - Missing Completely At Random (MCAR)
  - Missing At Random (MAR)
  - Missing Not At Random (MNAR)

Missing Data Mechanism: MCAR

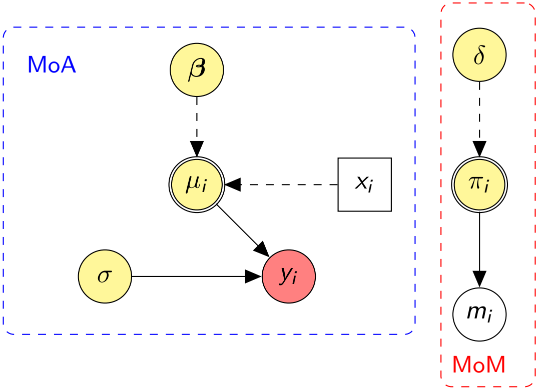


Figure: MoA=Model of Analysis, MoM=Model of Missingness

Missing Data Mechanism: MAR

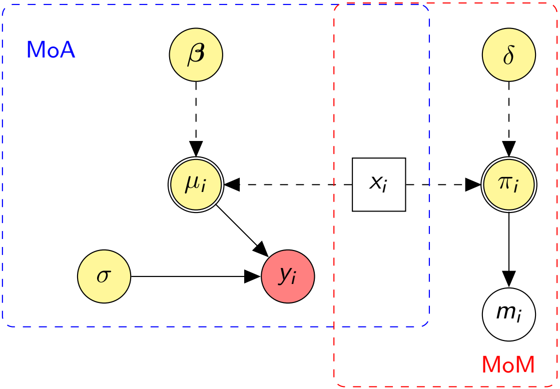


Figure: MoA=Model of Analysis, MoM=Model of Missingness

Missing Data Mechanism: MNAR

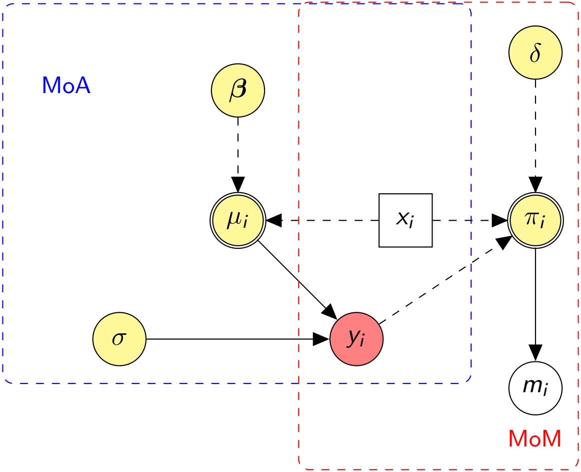


Figure: MoA=Model of Analysis, MoM=Model of Missingness

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

Full Bayesian Models

- 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

Nonignorable Missingness: Selection Models

- *Selection Models* factor the joint distribution (y, m) as:

$$p(y, m \mid x, \boldsymbol{\theta}^{MoA}, \boldsymbol{\theta}^{MoM}) = p(y \mid x, \boldsymbol{\theta}^{MoA})p(m \mid y, x, \boldsymbol{\theta}^{MoM})$$

- Typically, $m \sim \text{Bern}(\pi)$ with: $\text{logit}(\pi) = \gamma_0 + \gamma_1 x + \delta y$
  - δ represents the impact on π of the missing values (MNAR parameter)
- Possible SAs (Mason et al., 2012) are:
  - **Assumption Sensitivity**: Vary MoA and/or MoM form
  - **Parameter Sensitivity**: Vary MoM assumptions (priors)
- If results are not robust, more information may need to be gathered

Summary

- Missing data can bias inferences and mislead the decision output
- Most of the methods limit their validity to MAR, which may not hold and, more importantly, can never be verified from the data
- Full Bayesian models handle missingness by assessing and quantifying different types of uncertainty
- Selection Models are a possible choice to handle nonignorable missingness but SA is necessary to assess the robustness of the results to alternative assumptions

Literature Review

Two-fold purpose:

1. Provide some guidelines on the reporting and analysis of missingness (Quality Evaluation Scheme)
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

Literature Review: Quality Evaluation Scheme

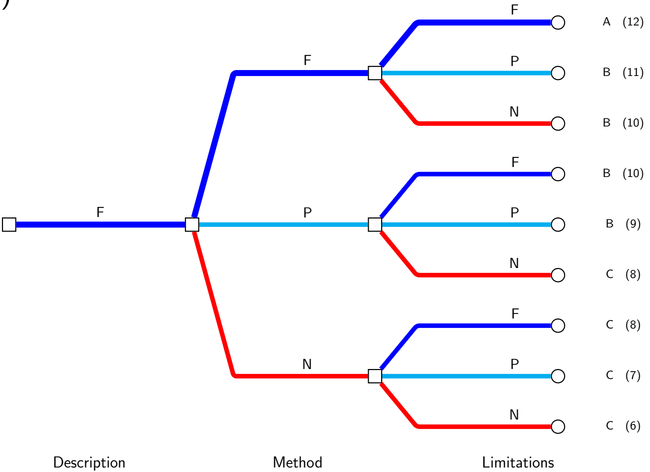
- Provide guidelines on how to report information on missingness:
    - **Description**: Missingness pattern and assumption
    - **Method**: Choose base-case and alternative methods
    - **Limitations**: Possible issues in assumptions

- Assign a grade to the articles based on the information in each component
- Match the articles to a score (0-12) based on the overall information provided, weighted by each component

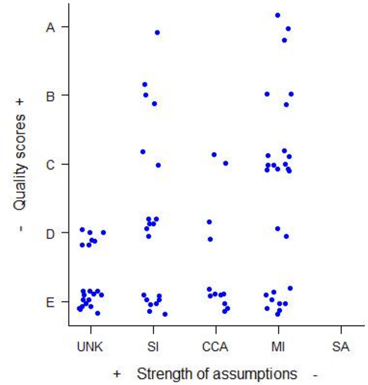
Content \ Score	**Description**	**Method**	**Limitations**
Full (F)	6	4	2
Partial (P)	3	2	1
Null (N)	0	0	0

Literature Review: Quality Evaluation Scheme

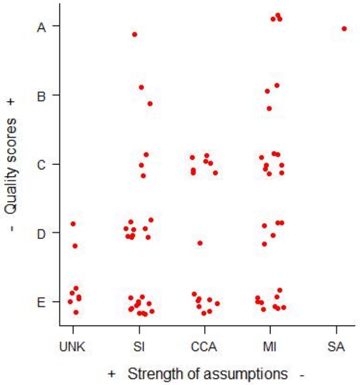
- Based on the grading, we group the articles into ordered categories (E-A)



Literature Review: Quality Evaluation Review



(a) Missing Cost Analyses (2009-2015)



(b) Missing Effect Analyses (2009-2015)

Literature Review: 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
- QES could represent a valuable tool to improve missing data handling
  - Explicitly define assumptions and assess their impact on the conclusions.

Case Study: 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)

	Control (n_1=75)		Intervention (n_2=84)	
Time	**observed**	**missing(%)**	**observed**	**missing(%)**
Baseline	72	4%	72	14%
3 months	34	55%	23	73%
6 months	35	53%	23	73%
12 months	43	43%	36	57%
complete cases	27	64%	19	77%

Case Study: 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-MoM: $\text{logit}(\pi) = \gamma_0 + \delta y$ (Selection Model for $y = e, c$)

- 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 $c^{obs} \rightarrow \delta^c \sim \text{N}(0, 1)$

Case Study: 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^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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Case Study: Results

Parameter	Base-Case Mean	Base-Case 95% CI		MAR (e,c) Mean	MAR (e,c) 95% CI		MNAR (e) Mean	MNAR (e) 95% CI		MNAR (c) Mean	MNAR (c) 95% CI	
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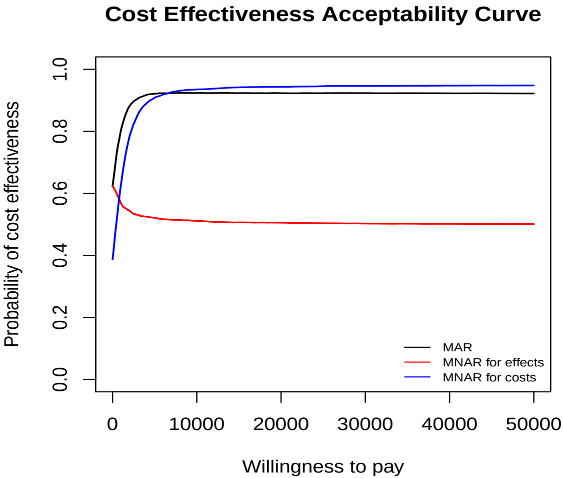
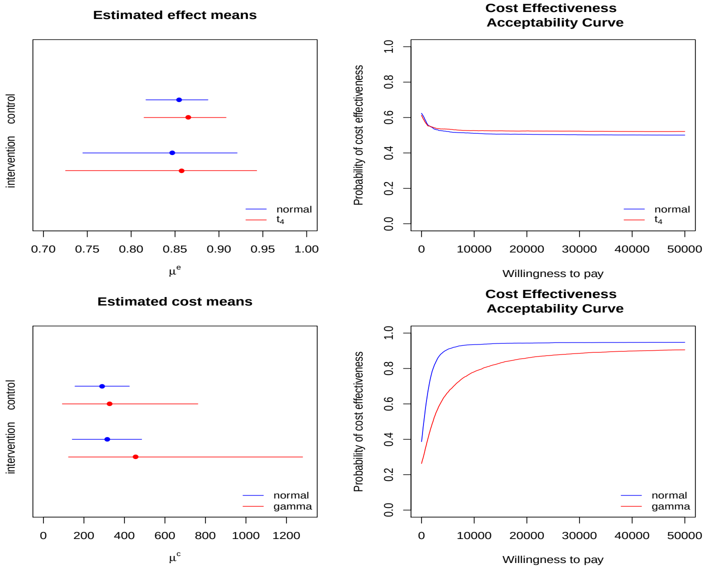
mean cost increment (Δ_c)	-25	-145	97	-18.600	-141.081	102.463	-19.415	-140.283	104.196	25.708	-121.593	194.326

Case Study: Economic Evaluation

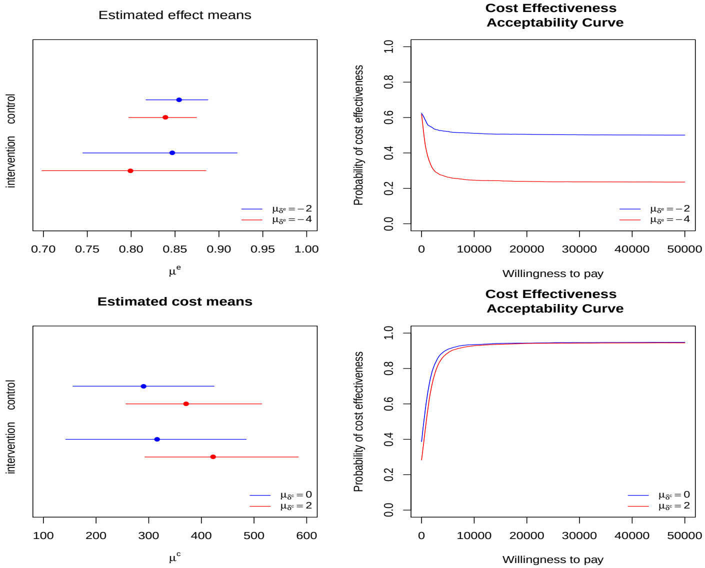


- Under $MNAR(e)$ the assessment radically changes, with the new interventions being not cost-effective compared with the control

Case Study: Sensitivity Analysis (AS)



Case Study: Sensitivity Analysis (PS)



Case Study: 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

Future Works

- Potential for Bayesian methods to handle nonignorable missingness in economic evaluations
- However, other extensions deserve further considerations
- Model Improvements
  - Explore other MoA distributions (e.g. truncated, skewed, mixture)
  - Consider alternative types of nonignorable models (e.g. PMM)
  - Model outcomes at disaggregated level (longitudinal models)
- Joint modelling of MNAR mechanisms
  - Explicitly include both MoMs and perform SA
  - Account for correlations between the two MoMs

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