

HANDLING MISSING DATA IN WITHIN-TRIAL COST-EFFECTIVENESS ANALYSIS: A REVIEW WITH FUTURE RECOMMENDATIONS

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Introduction

Missing data are common in CEAs, especially within a RCT framework, in both effect and cost variables. According to recent reviews (Noble et al., 2012; Diaz-Ordaz et al., 2014), the standard approach is to work only with the observed cases (CCA) but this may cause problems. Examples are loss in efficiency, possible biases in the parameter estimates and possible misleading conclusions of CEA.

Objectives

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

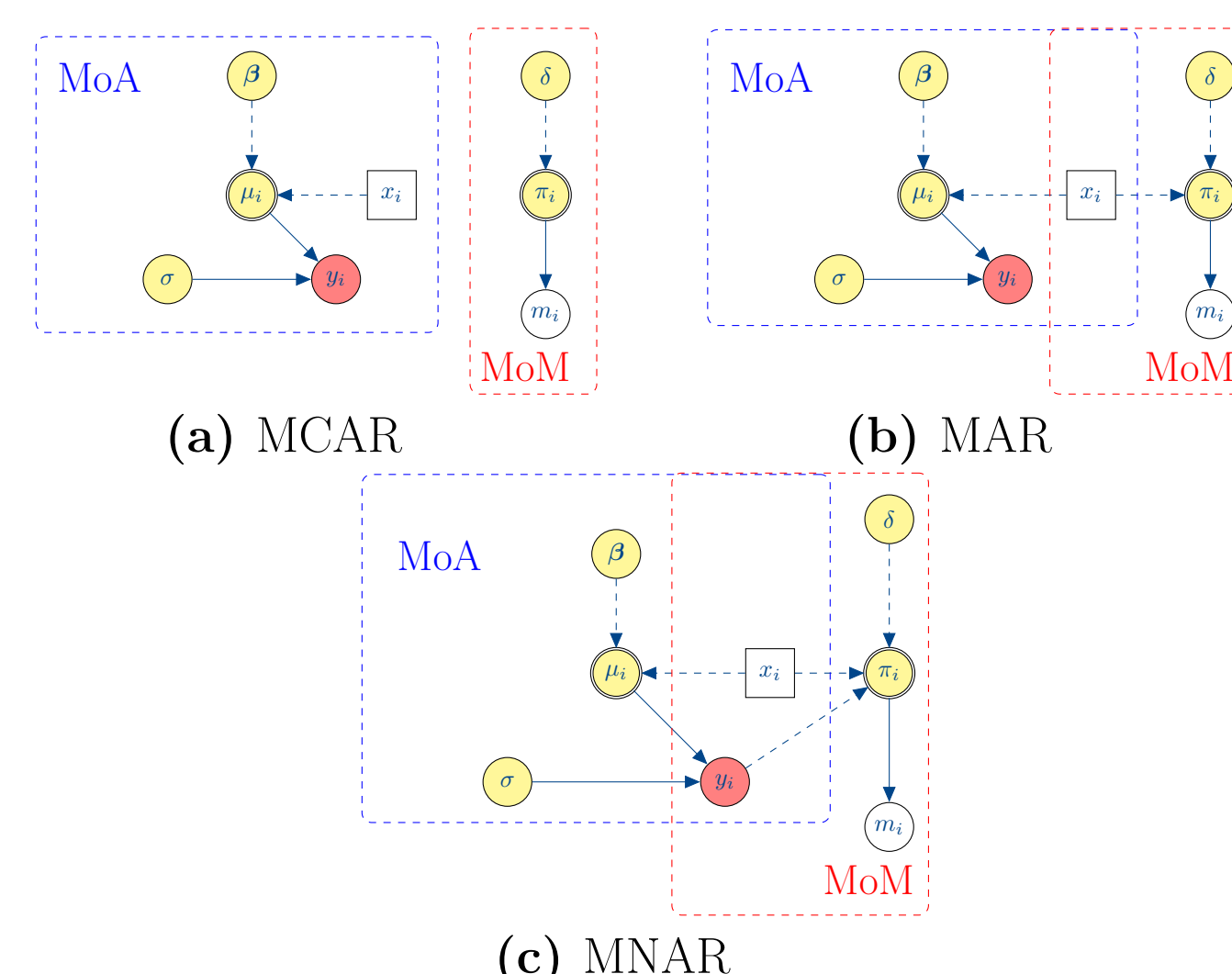
Missing Data Mechanisms

To conduct inferences with partially observed variables we rely on the joint consideration of two modules. The analysis model (MoA), representing the data generating process, and the missingness model (MoM), describing the missing data mechanism. Rubin (Rubin, 1987) identifies three types of MoM according to the way the missingness probability is generated.

Missing Completely At Random (MCAR). Fully observed cases can be thought as a representative sample of the full data sample

Missing At Random (MAR). Partially observed cases are systematically different from fully observed cases with the difference being captured by x_i

Missing Not At Random (MNAR). Partially observed cases are systematically different from fully observed cases even after taking into account the effect of x_i



Missing Data Methods

The performance of each method depends on the plausibility of the missing data assumptions they rely on. Some of the most popular are:

Complete Case Analysis. Partially observed cases are simply deleted. Efficiency loss and possible bias.

Single Imputation. Imputation with a single value (mean, median, etc.). Very restrictive assumptions and uncertainty not considered.

Multiple Imputation. Imputation of missing data given observed data, repeated K times to account for uncertainty. Estimates combined via Rubin's rules (Rubin, 1987). Correct imputation model is essential.

Sensitivity Analysis. Exploration of plausible departures from base-case missingness assumption to account for more uncertainty in assessing the robustness of the results. Typically requires explicit modelling of the missing data mechanism.

The original review focused only on missing costs in 88 within-trial CEAs between 2003-2009 (Noble et al., 2012). We include missing effects and update the analysis from 2009 to 2015 (81 articles). Articles taken from three online full-text journal repositories: *Science-Direct*, *BMJ* and *DARE-NHS EED*.

Review: Base-case Method Analysis

- Period 2003-2009 (Fig. a and b)
 - CCA is the most popular method in both cost and effect measures
 - Other methods much less used
 - Many studies have non-clearly defined methods
- Period 2009-2015 (Fig. c and d)
 - MI use overcomes CCA in both measures
 - CCA is still significantly used
 - Decrease in the number of not clearly defined methods for the effects

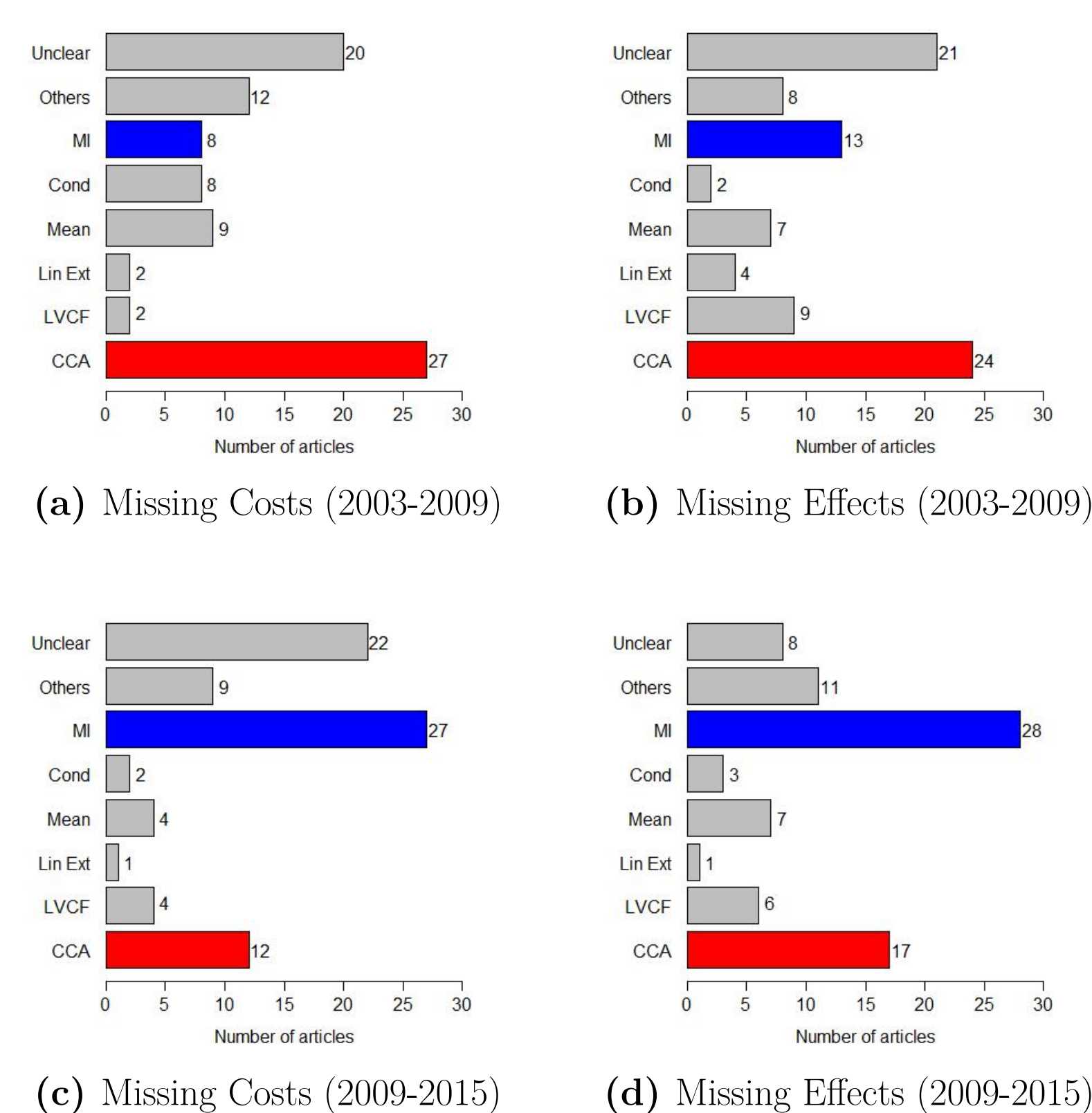


Fig. 2: Base-case Analysis

Review: Robustness Method Analysis

In both periods robustness analyses are rarely performed for both measures (25%).

- Period 2003-2009 (Fig. a and b)
 - Most of the articles do not use any robustness method
 - Very few cases of multiple robustness alternatives
- Period 2009-2015 (Fig. c and d)
 - Strong concentration around joint adoption of MI and CCA
 - Very few cases for all other methods

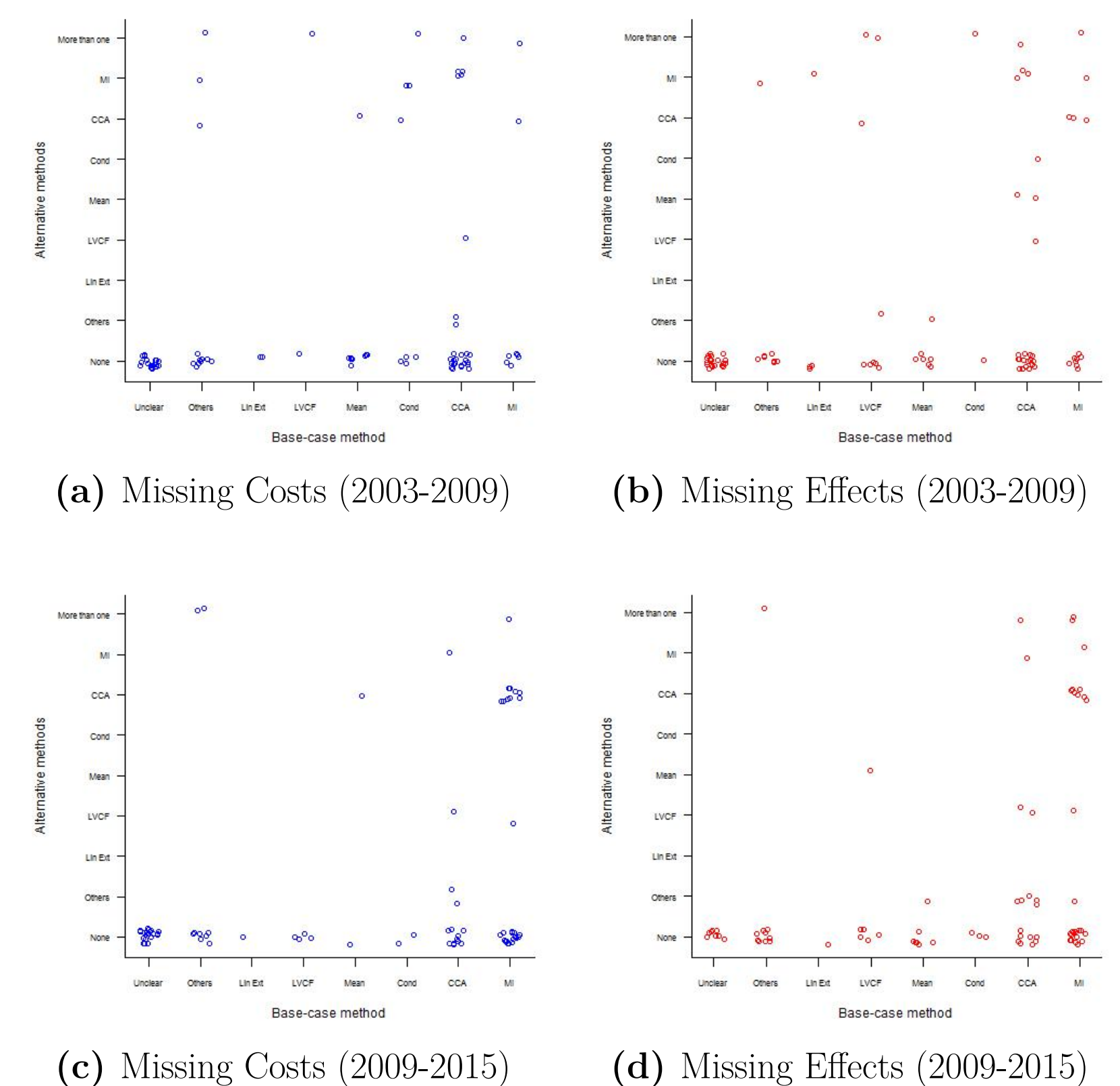


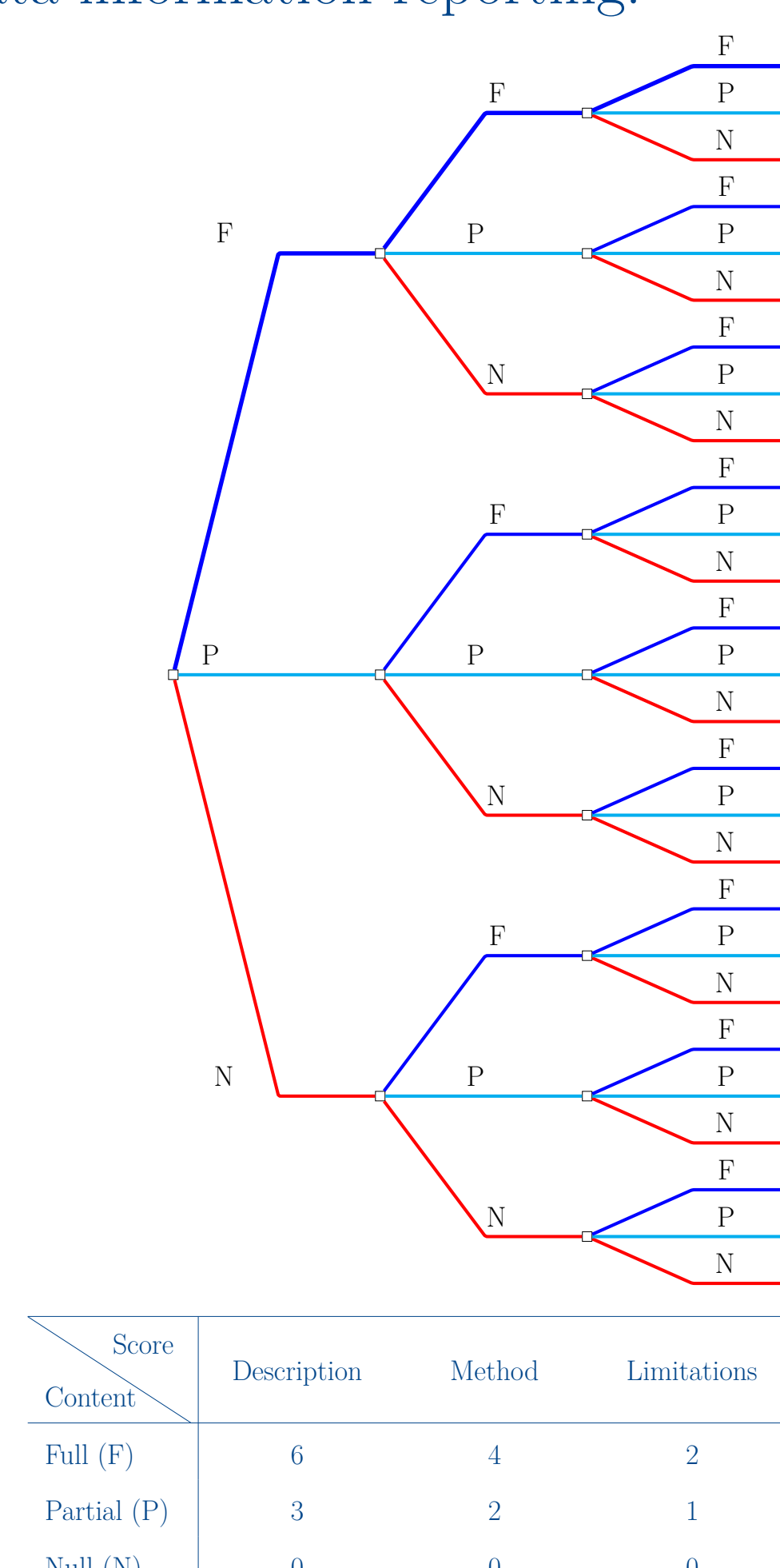
Fig. 3: Robustness Method Analysis

Quality Evaluation Scheme

We provide guidelines on missing data information reporting.

- Three ordered components: Description, Method and Limitations
- Grades assigned to articles based on the information provided on each component: Null, Partial, Full
- Articles matched to scores (0-12) and grouped into classes (E-A) based on grades

Description	Method	Limitations
Key considerations		
Missing data by treatment group	Missing data assumptions	Quantify impact of missingness on results
Missing data patterns for all variables	Primary method	Possible issues with method or assumptions
Reasons for missingness	Robustness analysis	
Optimal considerations		
Preliminary analysis details	Implementation details	



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

Quality Evaluation Review

We assess articles between 2009-2015 on both assumptions (methods) and justification (scores)

- Upward movement is always an improvement with top-right corner being the target: high score (A) and very flexible assumptions (SA)
- Most studies belong to the bottom part of the graphs
 - Lack of assumptions justification, especially for less flexible methods
 - Sensitivity Analysis (SA) is almost never used

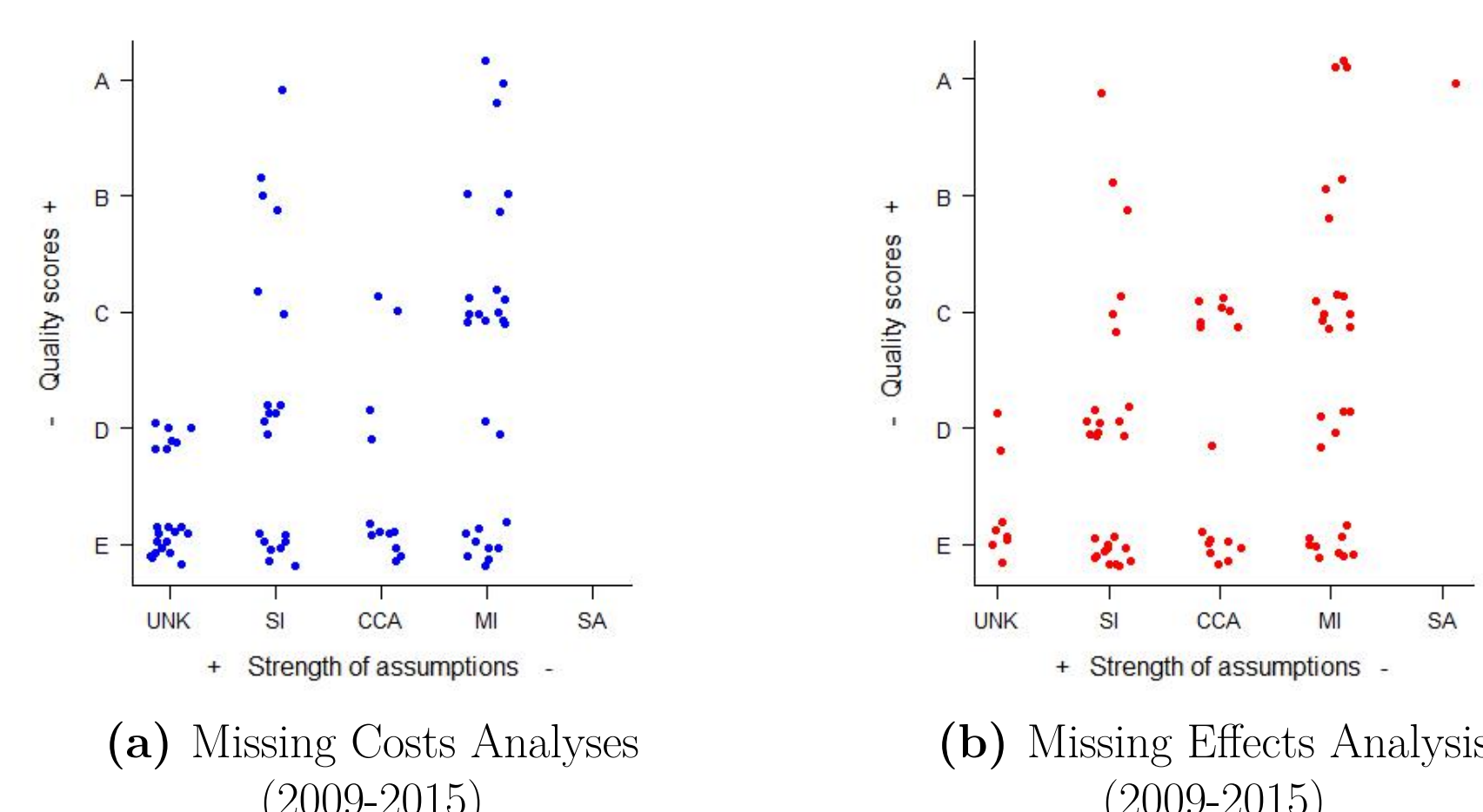


Fig. 4: Quality Evaluation Review

Conclusions

High missing data proportions in within-trial CEAs may lead to imprecise economic evidences. This is an issue for bodies who use these evaluations to inform policies on the cost-effectiveness of new treatments (NICE).

- Our review shows a shift towards more flexible missingness methods, but improvements are still needed, especially due to the small number of robustness analyses
- Our guidelines could represent a valuable tool to improve missing data handling. By explicitly stating all assumptions and assessing their impact on the conclusions we can better formalise and compare uncertainty

Discussion

- Between the two periods there is a shift in the most popular method from CCA to MI
 - MI may provide a more flexible handling of missingness (if correctly specified)
 - Increasing number of MI software packages available
- Reduction in the number of unclear effect methods compared to costs
 - Clinical outcomes are the main RCTs objective
 - Cost analyses less frequently used
- Only few studies implement a robustness analysis
 - Under-implementation of SA
 - Possible misleading CEA conclusions about the cost-effectiveness of new treatments

References

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