AN APPLICATION OF A BIVARIATE RANDOM EFFECTS META-ANALYSIS IN A COST-EFFECTIVENESS ANALYSIS OF TREATMENT FOR SLEEP APNOEA

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Introduction

Systematic reviews to identify the current evidence for health technologies often form the basis for an economic evaluation. Where multiple trials provide information on the same outcome measure a meta-analysis may be conducted to synthesise the available evidence. Often more than one clinical outcome will be of interest in determining overall health outcomes. Frequently multiple outcomes are synthesised individually in a series of univariate meta-analyses. This paper explores the use of multivariate meta-analysis in an evaluation of continuous positive airways pressure (CPAP) for the treatment of sleep apnoea.

Case study

Sleep apnoea describes a disorder where repeated collapse of the upper airway during sleep causes a reduction/obstruction of respiratory airflow. When accompanied by clinical symptoms such as excessive daytime sleepiness it is known as obstructive sleep apnoea-hypopnoea syndrome (OSAHS). The main treatment goal is to reduce daytime sleepiness. Treatments include the administration of CPAP during sleep, the use of dental devices to reposition the tongue or mandible and lifestyle modifications. The National Institute for Health and Clinical Excellence (NICE) in the UK requested an evaluation of CPAP in comparison to best supportive care, placebo and dental devices. This evaluation forms the basis for a comparison of alternative methods to synthesise the available data on clinical outcomes.

Systematic review

The primary outcome measures were subjective daytime sleepiness (Epworth Sleepiness Scale (ESS)) and objective sleepiness (e.g. Maintenance of Wakefulness Test (MWT)). The numerous secondary outcomes measures included blood pressure (BP), cardiovascular events (CVEs), road traffic (RTAs) and occupational accidents, quality of life. The review identified 38 RCTs comparing CPAP to placebo, of which 23 reported information on ESS, 5 on MWT, 10 on BP. The measures of daytime BP included those taken by ambulatory measurement (7 studies) and during office visits (3 studies). No RCTs reported information about CVEs, occupational accidents or RTAs.

Decision-analytic model

The primary outcome measure was the cost per quality-adjusted life-year (QALY) gained. A Markov model was developed which estimated QALYs as a function of survival, daytime sleepiness, CVEs and RTAs. A set of individual patient data were used to map ESS scores to utility values. The Framingham risk equations predicted risk of CVEs as a function of BP; the utility decrement for CVEs was obtained from published studies. Thus from the range of outcomes identified in the systematic review, mean difference in ESS score and mean difference in systolic BP at follow-up were selected for input into the decision-analytic model. Given uncertainty as to whether treatment effects based on ambulatory BP were comparable to those based on office measurements a scenario incorporating only ambulatory BP was included. This allows a comparison of the bivariate and univariate approaches when there are fewer data to inform the estimate of the between study correlation.

Figure 1. Model structure

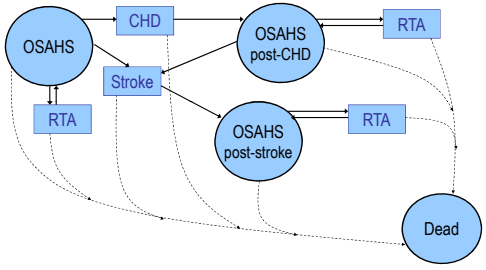
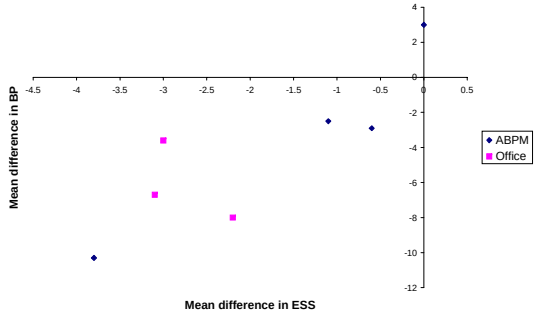


Table 1. Study characteristics and outcomes (CPAP vs placebo) for inclusion in meta-analysis

Study type	n	MD ESS	Var(MD ESS)	BP measure	MD BP	Var(MD BP)
Parallel	54	0	1.37	ABPM	3	13.01
Crossover	35	-1.2	0.17	-	NA	NA
Parallel	105	-5	1.25	-	NA	NA
Crossover	18	0.1	1.40	-	NA	NA
Crossover	23	-6	2.34	-	NA	NA
Parallel	111	-1.09	0.52	-	NA	NA
Crossover	37	-3	1.14	-	NA	NA
Crossover	71	-2.4	0.50	-	NA	NA
Parallel	142	-2.2	0.92	Office	-8	11.69
Crossover	42	-0.6	1.77	ABPM	-2.9	29.16
Parallel	60	-3.8	2.47	ABPM	-10.3	27.88
Crossover	114	-1	0.32	-	NA	NA
Crossover	31	-2.4	0.84	-	NA	NA
Parallel	72	-1	0.56	-	NA	NA
Parallel	56	-1.1	2.00	ABPM	-2.5	8.47
Parallel	101	-3	2.00	Office	-3.6	46.69
Crossover	35	-3.1	0.50	Office	-6.7	3.01
Parallel	42	-4	2.19	-	NA	NA
Parallel	107	-4.8	0.81	-	NA	NA
Parallel	45	-4	4.38	-	NA	NA
Parallel	48	-7.94	1.63	-	NA	NA
Parallel	71	-3	2.47	-	NA	NA
Parallel	118	-4.5	1.03	-	NA	NA
Crossover	13	NA	NA	ABPM	-1	5.62
Crossover	25	NA	NA	ABPM	0	4.45
Parallel	21	NA	NA	ABPM	-1	15.47

MD=Mean difference; ESS=Epworth Sleepiness Scale; BP=blood pressure; Var() = Variance; n = number of trial participants; ABPM = ambulatory blood pressure measurement

Figure 2. Treatment effect pairs from studies reporting both ESS and BP



Bivariate random effects meta-analysis

We first set out the framework for a bivariate random effects meta-analysis, which has been reported in Riley et al.(Riley et al. 2007a), among others. We then compare the results of bivariate approach to separate univariate analyses, and test the sensitivity of the model to alternative values for the within- and between-study correlation in treatment effects. A random effects analysis was performed where it was assumed that each study's summary statistics for mean difference in ESS (ess_i) and mean difference in BP (bp_i) represented an estimate of different underlying true values ($essMu_i$, $bpMu_i$), and these underlying true values were assumed to be drawn from a distribution with particular mean (essReMu, bpReMu) and variance ($essReSD^2$, $bpReSD^2$).

$$\begin{pmatrix} ess_i \\ bp_i \end{pmatrix} \sim N\left(\begin{pmatrix} essMu_i \\ bpMu_i \end{pmatrix}, \delta_i \right), \quad \delta_i = \begin{pmatrix} essSD_i^2 & \rho W_i.essSD_i.bpSD_i \\ \rho W_i.essSD_i.bpSD_i & bpSD_i^2 \end{pmatrix}$$

$$\begin{pmatrix} essMu_i \\ bpMu_i \end{pmatrix} \sim N\left(\begin{pmatrix} essReMu \\ bpReMu \end{pmatrix}, \Omega_i \right), \quad \Omega_i = \begin{pmatrix} essReSD^2 & \rho B.essReSD.bpReSD \\ \rho B.essReSD.bpReSD & bpReSD^2 \end{pmatrix}$$

Where $\rho W_i.essSD_i.bpSD_i$ is the within-study covariance and $\rho B.essReSD.bpReSD$ is the between-study covariance. None of the trials reported within-study covariance between mean difference in ESS and mean difference in BP, and so a set of patient-level data from a crossover trial was obtained from which an informative prior could be specified.

Results

Figure 3. Comparison of the results of the bivariate random effects meta-analysis to separate univariate analysis for ESS and BP

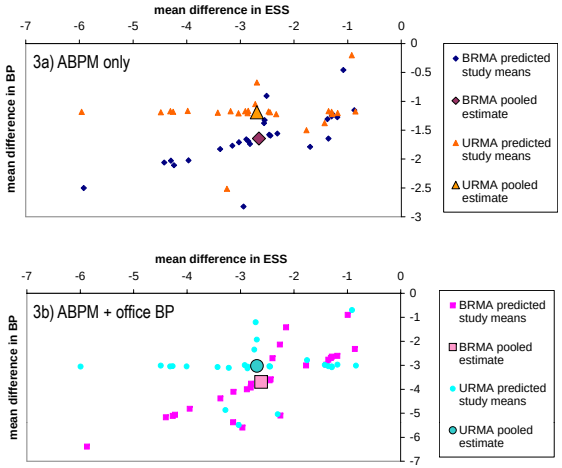


Table 2. Pooled estimates of treatment effect on ESS and BP, CPAP vs placebo

	Mean difference in ESS mean (SD)	Mean difference in BP mean (SD)
Ambulatory BP only		
URMA	-2.69 (0.44)	-1.19 (1.57)
BRMA	-2.65 (0.43)	-1.64 (1.72)
Ambulatory + office BP		
URMA	-2.69 (0.43)	-3.03 (1.54)
BRMA	-2.61 (0.43)	-3.70 (1.55)

SD = standard deviation; ; ESS = Epworth Sleepiness Scale; BP = blood pressure; URMA = univariate random effects meta-analysis; BRMA = bivariate random effects meta-analysis

The estimated between-study correlation (ρB) in treatment effects was 0.13 (SD=0.55) for ambulatory BP, and 0.36 (SD=0.50) when ambulatory and office measurements were combined.

Table 3. Sensitivity of BRMA to extreme values for within and between-study correlation

	Mean difference in ESS mean (SD)	Mean difference in BP mean (SD)
Ambulatory BP only		
Full model	*-2.65 (0.43)*	*-1.64 (1.72)*
Between study correlation = 0	-2.68 (0.44)	-1.39 (1.57)
Within study correlation = 0	-2.69 (0.45)	-1.36 (1.75)
Between & within study correlation = 0	-2.69 (0.44)	-1.23 (1.65)
Between study correlation = 1	-2.61 (0.43)	-2.24 (1.96)
Within study correlation = 1	-2.55 (0.42)	-2.55 (1.74)
Between & within study correlation = 1	-2.43 (0.42)	-3.89 (1.91)
Ambulatory + office BP		
Full model	*-2.61 (0.43)*	*-3.70 (1.55)*
Between study correlation = 0	-2.65 (0.43)	-3.20 (1.45)
Within study correlation = 0	-2.65 (0.44)	-3.44 (1.54)
Between & within study correlation = 0	-2.67 (0.44)	-3.11 (1.50)
Between study correlation = 1	-2.53 (0.41)	-4.45 (1.42)
Within study correlation = 1	-2.48 (0.42)	-4.48 (1.43)
Between & within study correlation = 1	-2.40 (0.44)	-5.11 (1.08)

SD = standard deviation; ESS = Epworth Sleepiness Scale; BP = blood pressure; URMA = univariate random effects meta-analysis; BRMA = bivariate random effects meta-analysis

Discussion

In URMA missing endpoints are assumed missing completely at random (MCAR). Data may be considered MCAR if the mechanism for missingness:
i) is completely random;
ii) does not depend on the missing values themselves;
iii) does not depend on other variables in the dataset.

In BRMA missing endpoints are assumed to be missing at random (MAR)
Data may be considered MAR if the mechanism for missingness:
i) does not depend on the missing values themselves;
ii) but can be explained by other variables in the dataset.

If treatment effects on multiple outcomes are thought to be correlated missing data will be MAR; the MCAR assumption is violated and applying a univariate approach can result in biased pooled estimates. In CPAP missing outcomes may be explained by the observed between-study correlation in treatment effects as well as the individual pooled estimates.

Meta-analysis may be considered to be observational as they synthesise data from those RCTs that are published. This issue of publication bias, where positive or statistically significant results may be more likely to be published may have a corollary in that only those secondary outcomes on which the treatment effect is positive or statistically significant may get reported. If this is the case then the MAR assumption could be violated, as the missing data could depend on the missing value itself. However in the case of CPAP statistical significance does not seem to be important in reporting treatment effects on BP.

Often the number of studies available to inform the between-study correlation may be small. In this case study the 95% credible interval was wide with seven studies reporting both outcomes (-0.78 to 0.98). In many cases, no information may be available on the within-study correlation but even then it is still possible to employ a multivariate approach (Riley et al. 2007b).

The bivariate model described in this paper could be extended to incorporate more than two outcomes. A benefit of the approach is that the same set of studies is used to inform the pooled estimates for all of the outcomes. Also any correlation between parameters can be incorporated in subsequent analyses. By using the 10,000 iterations from which the pooled estimates are derived (i.e. the WinBUGS output) directly in the probabilistic decision-analytic model correlation between treatment effects was maintained. This in turn can affect the estimates of decision uncertainty and value of information analysis.

Conclusions

In general systematic reviews may focus on more than one outcome of interest. The model described here is generalisable to any number of outcome measures.

Advantages of multivariate meta-analysis:

1) Accounts for correlation when estimating mean effects if there is missing data;

2) Allows correlation in population parameter estimates to be incorporates in decision-analytic models;

3) Potentially allows for correlation between variables to be accounted for.

The difference between the URMA and BRMA may have important consequences when the results are used to inform a cost-effectiveness analysis, particularly in terms of characterising uncertainty and estimating the value of further research.

References

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