Mind the Gap! Geographic Transferability of Economic Evaluation in Health

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Abstract

Transferring cost-effectiveness information from one domain to another offers the potential to invest analytical resources more efficiently. However, it is difficult for decision-makers to know when they can rely on cost-effectiveness evidence produced for another context. This paper explores the transferability of economic evaluation results produced for one geographic area to another location of interest, and outlines an approach to identify factors to predict when this is appropriate.

Essentially, the problem of evidence transfer is one of *'analogical inference'*. We link this theoretical framework to the statistical concept of *'exchangeability'*, and specify a *'cross-classified multilevel model'* to integrate secondary cost-effectiveness data. This approach makes the exchangeability assumption explicit and facilitates the assessment of contextual effects on a country level; whilst enabling control for baseline characteristics within, and across, studies included in the dataset.

We illustrate our model with a secondary data integration exercise on the use of Statins in the primary and secondary prevention of cardiovascular disease (CVD). We abstracted 464 estimates of incremental net monetary benefit of Statins vs. *'doing nothing'* applicable to 16 geographic domains from 16 studies, together with covariates on the data, study and country level. Using this example, we assessed the potential of our approach compared to other regression techniques which do not acknowledge cross-classified structures in secondary data analysis. Further research is warranted to identify the *'appropriate set of covariates'* to include.

Keywords

Economic evaluation, transferability, exchangeability, multilevel modelling, covariate adjustment

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Background

Decision makers from an increasing number of countries require cost-effectiveness information to decide on the provision and reimbursement of new health technologies [1]. If a new health technology is to be launched in a specific target market, manufacturers therefore need to provide evidence of not just safety and clinical efficiency, but also cost-effectiveness in the context of a particular healthcare market. However, this absorbs analytical resources, which are scarce and expensive. If economic evaluation results could be transferred from one geographic domain to another, this would free HTA analysts to study other important questions [2]. Therefore, it would be helpful to '*provide evidence for decision makers to establish the relevance or to adjust the results of a specific study to their location of interest*' [3].

However, a key barrier to transferability of economic evaluation results is a lack of understanding on the causes of variability in measures of cost effectiveness. There is a plethora of literature discussing potential causes of variability [3-4], however many of the suggested variability factors are fuzzy, hard or impossible to measure, and dependent on the health technology under consideration. Little is known about the relative impact of such variability factors on measures of cost-effectiveness. Sculpher et al. (2004) highlight that '*research is required to identify (higher level) covariates which are empirically useful [...] in terms of explaining differences in efficiency between locations and useful for policy-making purposes'* [3]. This opinion is being shared with Drummond et al. (2009) [1].

To fill this gap, we aim to develop and test a technique for the integration of secondary cost-effectiveness data elicited from existing economic evaluation studies and applicable to different geographic domains. This will allow us to assess the impact of variability factors within and between economic evaluation studies and, ultimately, between geographic domains. We develop a '*cross-classified multilevel model*' for secondary data integration, and apply this to an illustrative set of secondary cost-effectiveness data on the use of Statins within the primary and secondary prevention of cardiovascular disease (CVD).

Multilevel modelling is not new to Health Economics [1, 3, 5-6] and there are several applications of multilevel models, mainly, but not exclusively, within the arena of multinational trial-based economic evaluations [7-22]. Within this body of literature, a strict two-level hierarchical data structure is commonly assumed, with individual patient data clustered in centres or countries [9-13, 15-17, 21-22]. These studies use incremental net monetary benefit (INMB) as a response variable in a univariate framework [7-11, 14-15, 18-21], or incremental costs and incremental effects simultaneously in a bivariate multilevel model [12-13, 16-17, 22].

Our contribution is adapted from research on school performance [23], and is new within the field of health economic evaluation. We analyse cost-effectiveness estimates which are clustered within studies (each study may yield more than one estimate from subgroup or sensitivity analyses) and within countries. Furthermore, we allow for cross-classification between studies and countries, as some studies provide estimates for more than one country. The need for such a method of secondary data integration has been highlighted by Sculpher et al (2004) [3].

Theory

As with any representation of the real world, a health economic evaluation, whether trial-based or model-based, is only useful to *'the degree to which it captures the reality as observed within the original setting'*.[24] Therefore, establishing the relevance of economic evaluation results to any setting - including the one for which it was originally designed for - is a process within which we need to test whether the characteristics of that setting are appropriately reflected in the evaluation. We thus need to establish a correspondence between characteristics of the economic evaluation and the characteristics of the setting of interest. This is an argument by analogy [25]. Analogical reasoning involves a mapping of attributes between a base domain, about which more is apparently known, and a, less studied, target domain [26-28]. Then, the additional information about the base domain is hypothesised to hold in the target by virtue of the correspondences of those attributes, which determine the information of interest [25, 27, 29]. Hence, through the mapping of attributes we explicitly model our *a priori* belief that domains are similar in aspects which determine the information to be transferred. To estimate the attributes of interest for this mapping we need to know a) what causes variability in cost-effectiveness data and b) how to quantify the relative impact of such factors on measures of cost-effectiveness. There are numerous publications speculating about possible variability factors [3-4], but little is known about the quantitative impact of such factors. This requires an analysis of cost-effectiveness studies across geographic domains. However, variability factors do not only impact between geographic domains– there is also variation between studies within domains. When focussing on the *'higher level variability*', it is hence imperative to control for any variability introduced on lower levels.

In conclusion, we need a statistical approach which explicitly and simultaneously models and tests the *a priori* belief of similarity between a) cost-effectiveness studies, and b) geographic domains. To identify such a quantitative technique, we need to define more precisely what we mean by an *'a priori belief of similarity'*. This definition is provided by the statistical concept of *'exchangeability'*.

The concept of exchangeability goes back to Bruno de Finetti and has been extensively discussed in Bernardo and Smith (1994) [30]. It means, in our context, that the joint probability distribution of the output parameters for each cost-effectiveness study is the same for all studies [30-31]. Likewise, without having any additional information on each geographic setting, we would not have any expectation of more, or less, favourable estimates of cost-effectiveness [1]. Hence, we assume that each set of cost-effectiveness measures available represents a *'random sample'* of some (hypothetical) population of measures of cost-effectiveness for that technology. This is the standard assumption for random-effects meta-analysis [32, 33]. Spiegelhalter et al (2004) state that '*if a prior assumption of exchangeability is considered reasonable, a Bayesian approach to multiplicity is thus to integrate all the units into a single model, in which it is assumed that study parameters are drawn from some common prior distribution whose parameters are unknown: this is known as a hierarchical or multilevel model'* [32]. This class of models is referred to as *'multilevel',* as allowing study and country parameters to vary randomly enables us to fit models for these parameters *'above'* the model for the actual cost-effectiveness data [34]. Hence, the overall model structure can follow the way the data is *'clustered'* within studies and geographic domains. This, as it turns

out, is a key challenge when fitting models of this class to existing cost-effectiveness data from different geographic domains, as we cannot establish a strict hierarchical structure between the study and the country levels. As a solution to this problem, we propose fitting a '*cross-classified'* model for secondary data integration (this is discussed in the Methods section below).

Within this multilevel framework, we can model exchangeability whilst also controlling for variability factors working between studies and between geographic domains, by allowing for covariate adjustment through the assumption of conditional independence [35, 16, 1]. This should enable us to integrate cost-effectiveness data, and to quantify the impact of variability factors on data, study, and country level. If we are successful in this endeavour, we could then extrapolate from existing data to domains for which cost-effectiveness information is currently missing. This can be achieved within the proposed framework and in accord with the principles of analogical reasoning if and only if *'the analyst has identified the appropriate set of covariates for the exchangeability assumption to hold; and that the characteristics of the country of interest are represented appropriately by countries in the dataset'* [1]. In this way, as Gelman (2004) points out, '*exchangeable models become almost universally applicable, because any information to distinguish different units should be encoded.'* [35, cited from 16]

In the next section we show how the proposed framework translates into a cross-classified multilevel model suitable for the integration of existing cost-effectiveness data from different geographic domains, and how this, in turn, will enable us to quantify the relative impact of variability factors working on data, study, and country level on measures of cost effectiveness. Then, within the second part of this paper, we demonstrate our model within a pilot study analysing published cost-effectiveness data on the use of Statins in the primary and secondary prevention of CVD. Building up from a single level regression framework, we introduce the relevant features of our model - step by step - and show how this changes the value and significance levels of covariates, and, of course, the overall fit of the model. Within the discussion section we highlight the main advantages and disadvantages of our approach, as well as further areas of research.

Methods

Consider a single level ordinary least squares (OLS) regression model of the form:

$$y_i \sim N(XB, \Omega) \quad (1)$$

$$y_i = \beta_0 + \beta_1 x_{1i} + e_i \quad \text{with}$$

$$e_i \sim N(0, \sigma^2)$$

The y_i are observations of cost effectiveness elicited from the literature (i=1, 2,…, N), expressed as incremental net monetary benefits (INMB). INMB statistics have advantages in interpretation and superior statistical properties to the more widely used Incremental Cost Effectiveness Ratio (ICER) statistic for

regression modelling [36-40]. The model includes some vector of explanatory variables x_{1i}, intercept β_0 and vector of slope coefficients β_1. The error term e_i is assumed to be normally distributed with zero mean, common variance σ^2, and it is assumed that errors are mutually independent [41]; though we know that the latter assumption cannot hold because of our data being clustered within studies and geographic domains [e.g. 42-44]. Rather than assuming that study parameters are exchangeable, this model implies *'identical'* parameters if INMBs from all studies and countries are pooled, or *'independent'* parameters if we apply model 1 to each data cluster separately [32]. Also, there is no distinction as to whether explanatory variables refer to the data, study, or country level, hence spuriously inflating the amount of information supplied by higher level covariates [9].

To allow study-level parameters to vary randomly, we can posit a model for such parameters *'above'* the model for the INMB data [34]. To derive this model, we introduce a second error term u_j which encapsulates the random variation between the overall mean INMB and the individual means of the studies included in the dataset. The new subscript 'j' denotes the higher level unit (studies), so that y_{ij} stands for the ith INMB estimate in the jth study.

$$y_i \sim N(XB, \Omega) \quad (2)$$

$$y_{ij} = \beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2j} + u_j + e_{ij} \text{ with}$$

$$u_j \sim N(0, \sigma_u^2)$$

$$e_{ij} \sim N(0, \sigma_e^2)$$

The same model can be used to allow country-level parameters to vary randomly, with index j now reflecting the country rather than the study, though this would ignore that data is also clustered in studies. To make this more clear, equation (2) reflects a two-level structure which can be used to model a strict hierarchy of INMB estimates clustered either within studies, or within countries. However, the analyst has to choose between one of these two alternative hierarchies, meaning that the actual data structure of INMB estimates clustered within studies and countries simultaneously is not captured.

In equation (2), β_0 is the intercept for y_{ij} (across all higher level units) and u_j is the difference between a study's (or country's) intercept and β_0, whilst e_{ij} is the difference between the y_{ij} for the ith measurement and the group mean of that study (or country) [45]. Furthermore, this model has two vectors of explanatory variables referring to each level of the data hierarchy. The total variance is the sum of the variances of u_j and e_{ij}, which allows calculation of the proportion of the total variance attributable to differences between higher level units, which is referred to as the *'variance partition coefficient'* ($vpc = \sigma_u^2/(\sigma_u^2 + \sigma_e^2)$) [45]. Finally, as the exchangeability assumption compromises between assuming either identical or independent parameters, *'shrinkage estimates'* ($S = \hat{\sigma}_u^2/(\hat{\sigma}_u^2 + \left(\frac{\hat{\sigma}_e^2}{n_j}\right)$) are used to pull study (or country) parameters towards the overall mean depending on variability and sample sizes within each data cluster [e.g. 45-47]. The idea is that the higher the variance within each data cluster, or the lower the sample size within that cluster, the more strength is *'borrowed'* from other clusters; and the stronger is the effect of

shrinkage towards the overall mean INMB [e.g. 11, 42-47]. We could easily elaborate this model by allowing not just intercepts, but also slopes to vary randomly across studies, or introducing cross-level interaction terms, etc [45, 47]. However, a crucial disadvantage remains, that the analyst has to choose between modelling INMB estimates clustered in either studies or countries.

Figure 1a

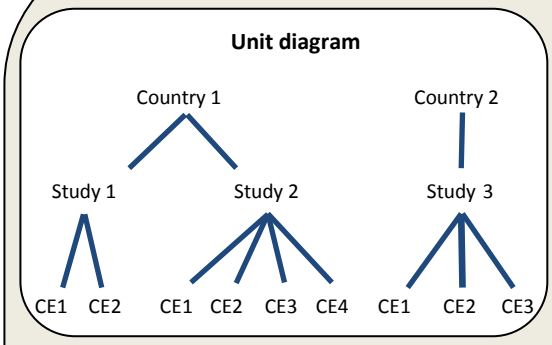


Figure 1a: Unit and classification diagrams of a three level hierarchical structure with cost-effectiveness estimates being nested in economic evaluation studies and studies being nested in geographic domains

Figure 1b

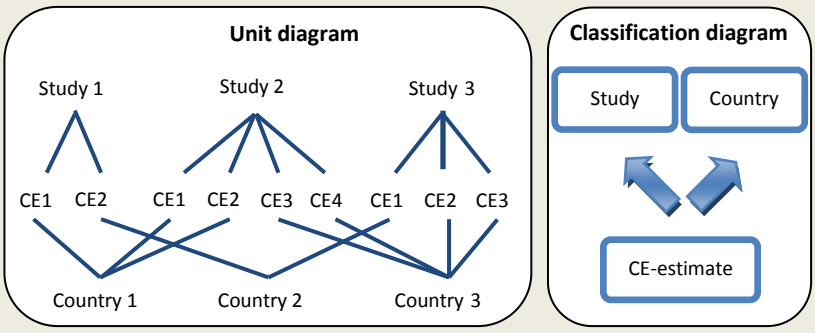


Figure 1b: Unit and classification diagrams of a cross-classified dataset with cost-effectiveness estimates classified in different studies and countries.

To solve this issue, one could fit a third level, assuming a strict hierarchy of INMB values clustered in studies, and studies clustered in countries as illustrated in Figure 1a. We would simply add another error term v_{0k} for the geographic location, with locations receiving the subscript 'k'. However, this does not reflect our data structure, as economic evaluations conducted alongside multinational RCT often report results for each participating jurisdiction, and modelling studies sometimes make estimates for more than one country. As a result, cost-effectiveness estimates are nested within studies, and they are also nested within geographic domains. But studies are not nested within geographic domains and vice versa. Rather, studies and countries are *'cross-classified' (see* figure 1b). The question is now how to model cross-classified data. As mentioned above, we introduce a third error term for the countries represented in the data, and countries receive the subscript 'k'. But to clarify that studies and countries are cross-classified on the same level of the data-hierarchy, we denote the error terms with u_k for country and u_j for study, and we use parenthesis to group together the subscripts 'j' and 'k' [23, 45].

$$y_i \sim N(XB, \Omega) \tag{3}$$

$$y_{i(jk)} = \beta_0 + \beta_1 x_{1i(jk)} + \beta_2 x_{2j} + \beta_3 x_{3k} + u_{0k} + u_{0j} + e_{0i(jk)} \quad \text{with}$$

$$u_{0k} \sim N(0, \sigma^2_{u0k})$$

$$u_{0j} \sim N(0, \sigma^2_{u0j})$$

$$e_{0i(jk)} \sim N(0, \sigma^2_{e0})$$

Explanatory variables may be introduced for each classification in the model to assess country-level covariates whilst controlling for differences within and between studies. Note, however, that within the cross-classified model, the estimation procedure is more complicated. Strictly hierarchical data structures have *'block-diagonal'* covariance matrices, hence simplifying estimation procedures [45]. However, the

cross-classified model requires a non-block diagonal covariance structure [23, 45]. We implement this model in MLwiN software, using Iterative Generalised Least Squares (IGLS) estimation by creating a third level on top of the study-level with one unit that spans the entire dataset [23, 45, 47]. We then create a dummy variable for each geographic location with random coefficients at level three and a separate variance for each country, and the variances constrained to be equal [23, 45]. Hence, we estimate one variance component for the countries, and by creating a separate level for countries we ensure that the covariance between studies and countries is zero [47]. Although technically this model uses three data-levels, we refer to it as a two level cross-classified model [45, 47]. Again, we could elaborate this model through fitting random slopes, or including cross-level interaction terms etc, although data and storage requirements increase drastically when implementing such features within the cross-classified framework [45, 47]

An illustrative example

In this section we apply the models introduced above to a set of secondary cost-effectiveness data. We chose the example of Statins for the primary and secondary prevention of CVD as this is an extensively studied area, with many cost-effectiveness studies across many countries, hence allowing for random parameters on study and country level.

We are currently systematically reviewing this body of literature, so our illustrative example uses a limited dataset; with data collected from studies previously identified by Franco et al. (2005) (details about search strategy, study selection process, etc. can be obtained from this source) [48]. We included only studies comparing Statins with '*do nothing'*. Although some studies estimate QALYs, most do not, so for this exercise we used life years saved (LYS) as the measure of effect. We also excluded studies not reporting incremental costs and incremental effects separately, as INMB could not be calculated for these studies.

From the remaining 16 papers, INMB estimates were collected for the base case, as well as for subgroup analysis, and sensitivity analyses exploring variation by: efficacy of intervention, baseline risk, annual drug costs of Statin therapy, duration of Statin therapy in years, costs of CHD related events, and discount rates for costs and effects. This resulted in a total of 464 data points, clustered in 16 studies, and applicable to 16 geographic domains. Local currencies were transferred to Pounds Sterling using Purchasing Power Parities (PPP) and updated to 2009 using country specific GDP deflators [49-50] For countries which adopted the Euro, historic currencies were first converted to Euros using irrevocable Euro conversion rates as adopted by the Council of the European Union on January 1, 1999. [51]. For this study we assumed a cost-effectiveness threshold level (λ) of £30,000 per LYS. This does not equate to £30,000 per QALY gained, as most additional years of life will be lived in less than perfect health states.

The set of potential explanatory variables in our analysis is drawn from a long list of variability factors suggested by previous authors [3-4]. Though we will focus our future efforts on finding the *'most appropriate set of covariates'*, this illustrative example is based on a much reduced dataset, with only a

few variables which we found to be significant when fitting the models illustrated above. Table 1 provides some details on the studies included in the dataset. Further information on the studies included is obtainable from Franco (2005) [48].

Table 1 Study characteristics and descriptive statistics

Study	Nj*	K**	Study type+	Prevention category++	Age range	Mean TCL mmol/L	Mean Δ Costs 2009 GBP	Mean Δ Effects LYS	Mean INMB (λ= £30.000) 2009 GBP
Ashraf, 1996 [52]	9	1	2	2	60	6.000	1228.13	0.157	3471.87
Caro, 1997 [53]	1	1	1	1	45-64	7.008	2758.28	0.098	181.72
Grover, 1999 [54]	48	1	2	2	40-70	6.500	16387.34	2.169	48668.91
Grover, 2000 [55]	52	1	2	both	40-70	6.512	25873.50	1.73	26020.73
Hamilton, 1995 [56]	20	1	2	1	30-70	7.220	19734.27	0.97	9395.73
Johannesson,1997 [57]	39	1	2	2	35-70	6.750	1120.40	0.22	5433.45
Muls, 1998 [58]	15	1	2	2	60	6.000	1885.21	0.16	2814.79
Perreault, 1998 [59]	36	1	2	1	44-57	8.137	18697.70	0.64	452.30
Pharoa, 1996 [60]	46	1	2	both	45-64	7.100	5452.21	0.09	-2670.51
Szucs, 1998 [61]	42	1	2	2	45-65	5.405	3574.57	0.29	5041.28
Szucs, 2000 [62]	8	1	2	2	45-65	5.616	3588.42	0.41	8561.58
Van Hout, 2001 [63]	5	1	2	both	25-75	?	11524.18	0.93	16435.82
Jonsson, 1996 [64]	18	10	1	2	35-70	6.740	1790.59	0.24	5409.41
Jonsson, 1999 [65]	109	11	1	2	35-70	6.741	1341.59	0.30	7723.08
Ganz, 2000 [66]	12	1	2	2	75-84	?	3856.49	0.26	3793.51
Martens, 1994 [67]	4	1	2	1	45	5.560	7222.56	0.19	-1485.06
Sum:	**464**	**16**		**Mean:**	**57.06**	**6.664**	**8677.79**	**0.677**	**11632.04**

* Number of INMB estimates clustered within a study

** Number of countries included in that study

\+ 1 = Primary modelling (directly based on observations from trial data) / 2 = Secondary modelling (studies based on any form of decision analytic model (DAM))

++ 1 = primary prevention / 2 = secondary prevention

See also Franco et al (2005) for additional information on study characteristics [48]

Most studies included in the dataset were based on some sort of decision analytic modelling, although three [53, 64-65] were directly based on clinical trial data. Studies included populations without any known history of CVD (primary prevention), those with at least one prior event of CVD (secondary prevention), or both. Subgroup analysis was usually performed with respect to age, gender, and pre-treatment cholesterol level. As can be seen in Table 1, when assuming a threshold value (λ) of £30,000, mean INMBs within each study range from £-2,670 [60] to over £48,660 [54], with an overall mean INMB of £11,632 across all studies included in the dataset.

Table 2 provides some characteristics and summary statistics of the countries included. As INMB measurements within one country may stem from several studies with differential timing, values elicited on GDP per capita, healthcare spending as percentage of GDP and life expectancy at birth are presented as mean values across the years for which INMB measures were reported. Again, there is a considerable spread in mean INMB's across countries, ranging from £-552 (UK) to £24,296 (Canada), assuming λ= £30,000. Looking at the third column in both tables, we can see that most studies (14 out of 16) report data applicable to one geographic domain only. However, two studies [64-65] report data which applies to several geographic domains, resulting in studies and countries being cross-classified.

Table 2: Country characteristics and descriptive statistics

Country	Nk*	J**	GDP***+ per capita	Health care spending***+ % of GDP	Life exp. at birth***+ years	Mean Δ Costs 2009 GBP	Mean Δ Effects LYS	Mean INMB (λ=30.000) 2009 GBP
Australia	1	1	21541	8.0	77.83	1967.03	0.240	5232.97
Belgium	23	3	22556	7.8	76.84	1854.91	0.201	4180.31
Canada	160	5	22696	9.5	78.05	20179.42	1.483	24296.52
Denmark	11	1	25259	8.0	75.95	854.34	0.305	8290.21
Finland	11	1	20968	7.4	76.88	1686.71	0.305	7457.84
France	8	2	21556	9.6	78.28	1101.43	0.285	7437.32
Germany	62	4	23289	10.8	76.84	3137.12	0.305	6005.72
Italy	12	2	22460	7.6	78.58	1091.84	0.299	7890.66
Netherlands	5	1	26933	8.2	77.83	11524.18	0.932	16435.82
New Zealand	1	1	17143	7.3	76.73	3011.64	0.240	4188.36
Norway	8	2	27416	7.6	78.09	1370.57	0.285	7168.18
Portugal	12	2	14324	7.9	75.39	2012.84	0.299	6969.66
Spain	12	2	17554	7.4	78.55	1541.54	0.299	7440.96
Sweden	58	3	22161	8.5	78.83	1127.30	0.238	6007.01
UK	59	4	20241	6.9	76.91	4607.27	0.135	-561.71
USA	21	2	29919	14.0	76.17	2730.05	0.213	3655.66
Sum / mean	**464**	**16**	**22473**	**9.05**	**77.58**	**8677.79**	**0.677**	**11632.04**

* Number of INMB estimates clustered within a country
** Number of studies providing INMB estimates for that country
**** As INMB measurements within one country may stem from several studies with differential timing, the values in these columns represent means across the years for which INMB values are reported
\+ Source: OECD Health Data, 1999 [68]

We applied models 1 to 3 illustrated in the Methods section to the above data to illustrate the features introduced with each model.

Results

Table 3 shows the results for models 1 to 3 without explanatory variables. Model 1 represents an empty OLS regression model, were the intercept is simply the pooled mean INMB across all studies and countries. Models 2a, 2b and 3 are variance components models, which take into account hierarchical data structures. We can see that in model 2a, 7.3% of the total variation is attributable to differences between countries. Comparing models 1 and 2a through calculating the log-likelihood statistic with 1 degree of freedom (as we estimated one additional parameter in model two) [43], we can see that model 2a is a better fit. However, moving on to model 2b, which also assumes a two level hierarchy, but with INMB values clustered in studies rather than countries, we can see that there is much stronger variation between studies than between countries (31.1% as opposed to 7.3%), and that this model fits the data better than model 2a. Moving on to model 3, were INMB values are clustered in both studies and countries, we see that the variation attributable to the country level almost disappears. Again, the difference in -2log likelihood values indicates that model 3 fits the data better than any of the previous models.

Table 3: Variance components models for secondary cost-effectiveness data

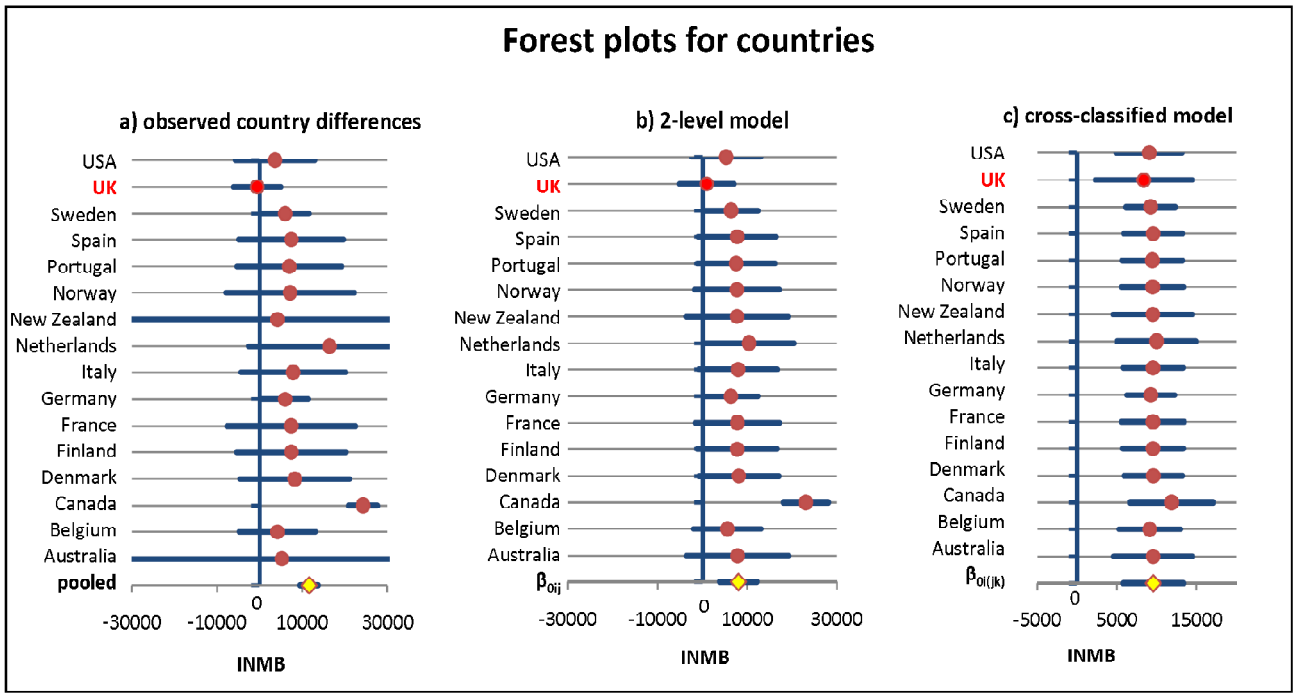
	Model 1 (single level OLS)	Model 2.a (2-level model with data clustered in countries only)	Model 2.b (2-level model with data clustered in studies only)	Model 3 (Cross-classified model with data clustered in studies and countries)
Fixed part:				
Intercept (λ=£30.000)	£11632	£8002	£9367	£9581
Random part:				
σ^2_{u0j} (Study)	--	--	154350192	193738848
σ^2_{u0k} (Country)	--	36518980	--	341225
σ^2_{e0} (Data)	546704192	465314432	342254272	343655648
VPC - study	--	--	31.08%	36.03%
VPC - country	--	7.3%	--	0.06%
-2 Log likelihood	10652.185	10591.907	10471.097	10436.151

* significant at the 10%-level
** significant at the 5%-level
*** significant at the 1%-level

Figure 2 shows the impact of shrinkage estimation within the multilevel framework. The three forest plots provide mean INMB values (assuming λ=£30.000) and their respective 95% confidence intervals. Figure 2a shows '*naive'* mean estimates for the countries included [10], as these are based on simply splitting the data by country, hence assuming independent parameters. The pooled estimate presented at the bottom of figure 2a is the result obtained from the empty OLS-regression model in Table 1. Figure 2b shows country-specific INMB estimates as obtained from model 2a, were INMB values are clustered in countries only, whilst figure 2c provides country specific estimates obtained from the cross-classified model. It can be seen that the confidence intervals of the naive estimates are always larger than the shrunken estimates. This is expectable as countries with only a few INMB-estimates available, or those with large variation, are heavily shrunken towards the overall mean value.

Finally, we tested a set of explanatory variables in each model (Table 4). All continuous variables were centred around their means, which has the advantage that the intercept is easier to interpret as it represents the predicted INMB for average values for each explanatory variable [43]. All models include three variables on the data-level (mean pre-treatment total cholesterol level (TCL), age and percentage of females in the sample), and two variables on the country-level (GDP per capita and total life expectancy at birth). Although we tested a range of study level variables (e.g. general study design, timing, time horizon, or whether sensitivity analysis was reported), we have not yet found a set of covariates which captures the extent of variation across the studies included in the dataset.

Figure 2: Effect of shrinkage on country estimates



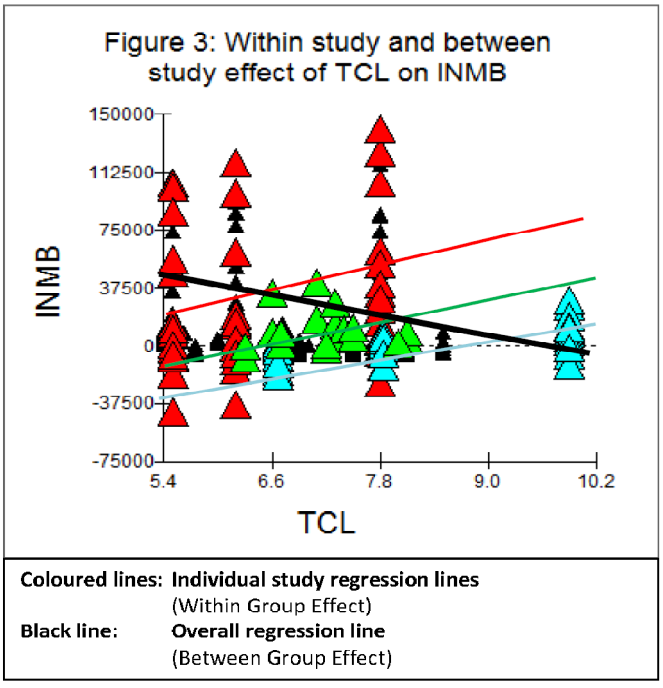
Given that TCL is a risk factor for CVD, and that Statins reduce TCL, we would obviously expect a positive relationship between TCL and INMB. For age, prediction is less straightforward. In general, we may expect a positive relationship between age and INMB as older people have a higher risk of a CVD event. However, this relationship may also be negative, especially beyond a certain age, as older patients may have less to gain from cholesterol reduction [69]. The effect of gender is clearer, as men are generally at higher risk and benefit more from Statin therapy, especially in primary prevention [69]. As for the country level variables, we hypothesise a positive relationship between INMB for Statins and GDP per capita, as a higher level of economic attainment may be associated with higher healthcare costs potentially being avoided through Statin therapy. Likewise, we expect a positive relationship between INMB and life expectancy at birth, as avoiding a CVD event in societies with a higher life expectancy obviously leads to more life years saved.

We can see from table 4 that our prediction for age and gender has been confirmed by each model in the dataset. However, Models 1 and 2a show a (non significant) negative relationship between the INMB for Statins and TCL. The reason may be that, within our data, TCL has both an effect within, as well as between studies. Specifically, whilst the relationship between INMB and TCL may be positive within each study, it may turn out to be negative between studies. This could be the case, for example, as studies which focus on high risk groups only report generally lower INMB-values; although, within that study, the anticipated positive relationship between TCL and INMB still applies. We illustrate what happens within and between studies in Figure 3, which shows INMB against TCL across all studies, highlighting some of the studies in the dataset. In conclusion, using a model which does not acknowledge that data is clustered in studies (models 1 and 2a) may simply lead to wrong inferences

Table 4: Random intercepts models for secondary cost-effectiveness data (2009-GBP)

	Model 1 (single level OLS)	Model 2.a (2-level model with data clustered in countries only)	Model 2.b (2-level model with data clustered in studies only)	Model 3 (Cross-classified model with data clustered in studies and countries)
Fixed part:				
Intercept	12107	£9762	£8396	£8066
TCL (SE)	-1145 (1139)	-1675* (1137)	4013*** (1119)	4031*** (1114)
Age (SE)	-1045*** (138)	-807*** (138)	-974*** (116)	-976*** (118)
% women (SE)	-11159*** (2587)	-13346*** (2509)	-13876*** (2112)	-13904*** (2106)
GDP (SE)	1.48*** (0.46)	1.63*** (0.66)	0.12 (0.45)	0.13 (0.46)
Life expectancy at birth (SE)	5358*** (1155)	648 (2034)	364 (1278)	356 (1285)
Random part:				
σ^2_{u0j} (Study) σ^2_{u0k} (Country) σ^2_{e0} (Data)	-- -- 449880704	 55614192 400137568	210684928 269516096	279913696 413570 273600160
VPC - study VPC - country	-- --	-- 12.2%	43.87% --	50.05% 0.07%
-2 Log likelihood	10174.78	10141.04	9985.68	9951.93

* significant at the 10%-level
** significant at the 5%-level
*** significant at the 1%-level



Another interesting finding relates to the country level variables in our dataset. Using a single level OLS, we would infer that both GDP per capita and life expectancy at birth are positive and highly significant, which accords with our expectation. However, in model 2a life expectancy at birth is not significantly related to INMB, and in model 2b, neither GDP nor life expectancy at birth is significant. As mentioned before, treating country level variables as if they referred to the data level spuriously inflates the amount of information they provide, and hence, overestimates precision [9]. To obtain correct standard errors we need to take into account the structure of our data.

Finally, turning to model 3, we can see that, after covariate adjustment on data and country level, about 50% of the overall variation in the data refers to the study level, and country level variation is negligible. The log-likelihood ratio indicates a better fit of the model, although both covariates and standard errors are similar to those in model 2b.

Discussion

From the analysis within this pilot study we confirm three key points. First, that ignoring the clustering, which occurs naturally when integrating secondary cost effectiveness data, induces the risk of overestimated precision and, potentially, wrong inferences about factors causing variability in measures of cost-effectiveness. This can be seen by comparing the single level specification (model 1) with the more sophisticated multilevel models. Secondly, when our aim is to examine the exchangeability assumption between geographic locations in order to assess country level covariates through the assumption of conditional independence, we cannot simply ignore the clustering which occurs on study level. This is apparent from a comparison of models 2a and 2b. Finally, as there is no strict hierarchy between studies and countries, we need a cross-classified multilevel model, which then allows us to acknowledge that data is clustered in studies and countries simultaneously.

However, the results of the two-level hierarchical model with INMB's clustered in studies (model 2b) gives similar results to those of the cross-classified model 3. Does that mean that our cross-classified model is redundant and that we should simply use a two-level hierarchical model for the purposes of assessing factors causing variability in measures of cost-effectiveness? We suggest not. Whilst, within the boundaries of this pilot study, the simpler model may have been sufficient to approximate the results of the cross-classified model, we believe that this is related to the nature of our pilot study data than the potential benefits of the cross-classified framework. We have three major reasons to support this conclusion.

First, as shown in Table 1, 14 out of 16 studies included in our sample dataset were strictly clustered in geographic domains. Only two studies [64 and 65] introduced the problem of cross-classification between studies and countries. As these two studies provide 127 data points (27.4% of the whole dataset), this provides strong justification for not simply dropping these studies. It also means that, with this considerable number of INMB measurements clustered in two studies, their impact on study level is strong. However, on country level, these observations are being spread across 10 [64] and 11 [65] countries respectively, with most countries represented in one of the other studies too. As a result, for 14 studies the study level coincides with the country level, and for the two studies which introduce cross-classification, their impact on study level may be stronger than their effect on country parameters. Therefore, in this concrete example, a two level hierarchy of INMB's clustered in studies provides a close approximation to the results obtained by the cross-classified model. However, increasing the scale of our dataset might introduce more cross-classified studies, hence decreasing the share of studies where the study level and the country level coincide. An extreme example would be to use our model strictly for the

integration of individual patient data of different multinational trials only, which would increase the share of cross-classified data to 100%.

The second reason to defend our model lies in the two included cross-classified studies themselves; though it also discloses a problem which we need to address in future work. Having a closer look at these two studies [64-65], we learn that both originate from the same country (Canada), and that they use the same set of effectiveness and resource use data for all countries. Hence, adaptation of the cost-effectiveness results to each jurisdiction was achieved only through the use of country-specific unit cost estimates. It is not uncommon in economic evaluations, both trial based and model based, to apply data collected in one country to other locations of interest, without appropriately recognising or exploring issues of transferability [70]. We suggest that this may explain the lack of additional geographic variation found in the cross-classified model. One way to address this problem is through a categorical variable on study level capturing the likely degree of geographic variability, and we identified a potentially appropriate system to classify studies with respect to their degree of variability which has been previously developed by Barbieri et al. (2005) [71].

This leads to the third reason to defend our model, relating to the identification and use of appropriate covariates, especially on study level. Whilst this pilot aimed to test the feasibility and potential of our analytical framework, there is considerable work to be done to define this appropriate set of covariates to explain variability in measures of cost-effectiveness. This holds especially for study-level covariates, as our model clearly showed that this is the dominating source of variability in INMB-values, after adjusting for covariates on the data-level, but we have not yet found the '*right*' set of covariates to explain variation across studies. However, within a multilevel framework, controlling for variability on other levels is key to disclose the actual amount of variability between countries, and hence, making the right inferences regarding higher-level covariates. [45] Therefore, we are currently identifying a much larger set of potential covariates on all levels, drawn from a long list of variability factors published in the literature [3, 4]. However, operationalising these factors is not straightforward. There are challenges around defining, measuring and selecting covariates. One key problem is the need to combine different methodological elements of an economic study into some sort of '*methodological profile'*, which may then be translated into a single explanatory variable (or a small number thereof) suitable for multilevel modelling. We are therefore looking into the usage of '*multilevel factor analysis'* [44] to address this problem. Another problem relates to study quality, which may be a major cause for variability in cost effectiveness data. One way to incorporate this information in our analysis would be to apply an instrument which supplies us with a single score reflecting the study quality of economic evaluations, as for example the QHES instrument. [72]

Next to addressing the issues mentioned above, we see scope to further develop our framework. First, we propose a bivariate extension of our model, to recognise correlation between the two stochastic components of the INMB statistic, namely incremental costs and incremental effects. Doing so requires introduction of two response indicators 'r_d', which are dummies coded '1' for each observation on the response variable, and '0' otherwise [44-45]. This enables fitting of a different intercept for incremental costs and incremental effects, while interactions between explanatory variables and the response

indicators 'r_d' allow the effect of the explanatory variables to differ between incremental costs and incremental effects [44]. The response variable specific residuals are fitted by permitting the intercept of the response indicator to vary randomly across the measurements of incremental net monetary benefit

$$\begin{bmatrix} Y_{1,i(jk)} \\ Y_{2,i(jk)} \end{bmatrix} \sim BVN(XB, \Omega) \qquad (4)$$

$$y_{d,i(jk)} = (\beta_{0d} + \beta_{1d}x_{i(jk)} + \beta_{2d}x_j + \beta_{3d}x_k + u_{0dk} + u_{0dj} + e_{0di(jk)}) * r_{d,i(jk)}$$

$$r_{1,i(jk)} = \begin{Bmatrix} 1 \; if \; \Delta C \\ 0 \; if \; \Delta E \end{Bmatrix} \qquad r_{2,i(jk)} = 1 - r_1$$

with:

$$\begin{bmatrix} u_{0,0,k} \\ u_{0,1,k} \end{bmatrix} \sim BVN\ (0, \Omega_u) \quad \text{where } \Omega_{uk} = \begin{bmatrix} \sigma^2_{u0,0k} & \\ \sigma_{u0,01k} & \sigma^2_{u0,1k} \end{bmatrix}$$

$$\begin{bmatrix} u_{0,0,j} \\ u_{0,1,j} \end{bmatrix} \sim BVN\ (0, \Omega_u) \quad \text{where } \Omega_{uj} = \begin{bmatrix} \sigma^2_{u0,0j} & \\ \sigma_{u0,01j} & \sigma^2_{u0,1j} \end{bmatrix}$$

$$\begin{bmatrix} e_{0,0,i(jk)} \\ e_{0,1,i(jk)} \end{bmatrix} \sim BVN\ (0, \Omega_u) \text{ where } \Omega_e = \begin{bmatrix} \sigma^2_{e0,0} & \\ \sigma_{e0,01} & \sigma^2_{e0,1} \end{bmatrix}$$

A comparable model has been previously used by Goldstein et al (1997) for school performance research [23]. They used a cross-classified bivariate model to assess the influence of secondary and junior schools on year sixteen examination performance. Also, a number of authors have used bivariate multilevel modelling in health economics, especially within the field of analysing individual patient data from multinational trials, [12-13, 16-17, 22]. However, a bivariate model which accommodates cross-classified data structures, as required for our application, is more complex to fit.

Figure 4

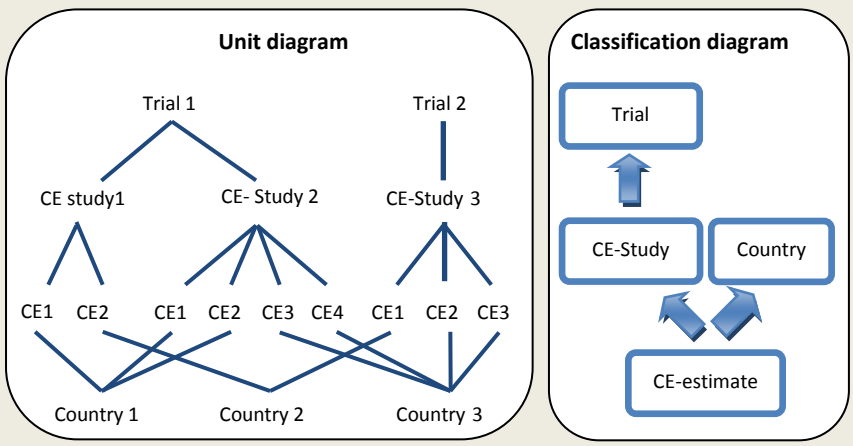


Figure 4: Unit and classification diagrams of a dataset within which:
a) measures of cost effectiveness are clustered in economic evaluations [CE-Study] and geographic locations [Country]
b) economic evaluations and countries are cross-classified and
c) economic evaluation studies are clustered in effectiveness trials [trial]

Finally, another potential extension of our approach relates to even more complex data structures. For example, when conducting our pilot study, we did not just find that cost-effectiveness data was clustered in studies and geographic locations, and that studies and countries were cross-classified; we also found that the effectiveness data underlying the INMB values in our dataset was elicited from one of 11 controlled trials conducted within the area of Statins in the primary and secondary prevention of CVD. As a result, we observed that there is not just cross-classification of economic evaluation studies and countries; there is also an issue of economic evaluation studies being clustered within the trials which served as the basis for cost-effectiveness estimates. We illustrate this data structure

in Figure 4. If the number of underlying effectiveness trials is low, then this issue could be tackled by adding a categorical variable on study level [45]. However, if there is a sufficient number of effectiveness trials present to permit random parameters, then one could try to reflect this data structure in an even more elaborate multilevel model.

Conclusion

This study illustrated the use of a cross-classified multilevel model for secondary data integration to make explicit the exchangeability assumption between economic evaluation studies and geographic domains. Within an illustrative example on the use of Statins in the primary and secondary prevention of CVD, we showed the potential of our approach compared to other regression techniques which do not acknowledge cross-classified structures in secondary data analysis. Further research is warranted to identify the *'appropriate set of covariates'* on each level of the data hierarchy, as this is the key premise for the transferability of economic evaluation results.

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