Meta-analysis of economic evaluation studies: Data Harmonisation and Methodological issues

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Abstract:

Background: In the context of ever-growing health expenditure and limited resources, economic evaluations aid in making evidence-informed policy decisions. Cost utility analyses (CUA) are often used in this context, but limitations include pairwise contrasts, missing contrasts, and different sources or quality of data.

Results: Synthesis of CUA data from multiple studies is therefore desirable to assist policy makers, but there are many challenging methodological issues including: inconsistent reporting of results using different economic parameters, and multiple sources of heterogeneity including: setting, time horizon, perspective, modelling approaches and assumptions, currency, willingness to pay (WTP) threshold, level of country income, and input parameters. In this paper, we provide a step by step description of the methods for data harmonisation and synthesis of aggregated data from CUA studies, as well as a framework for handling heterogeneity; we demonstrate these methods using the example of agents for type 2 diabetes.

Conclusion: These meta-analytic methods for the synthesis of economic evidence synthesis should be useful for policy makers.

Background:

In the context of ever-growing health expenditure and limited resources, identifying healthcare services that yield the highest benefit at the lowest cost is a priority. Economic evaluation studies (EES) provide a framework to systematize both clinical and economic outcomes[1] Cost-utility analysis (CUA) is commonly applied to compare clinical and economic outcomes by estimating an incremental cost-effectiveness ratio (ICER). The costs are usually measured in a specific country currency, while the health benefit is usually measured as a quality adjusted life year (QALY), i.e., the product of years lived and health utility score ranging from 0 (death) to 1 (perfect health), or disability adjusted life years (DALY)[2, 3]. The ICER is calculated by $(Cost_{intervention} - Cost_{comparator})/(QALY_{intervention} - QALY_{comparator})$, if the ICER is under the willingness to pay (WTP) threshold (measured in monetary cost per QALY gained), the health intervention is considered to be cost-effective.

However, many methodological issues in the data synthesis of EESs are more challenging than clinical studies because there are many sources of heterogeneity including: study characteristics (e.g., setting, WTP, country, country income), methodology (time horizon, perspective, data source, model type, input parameters, and assumptions). This is perhaps why most previous systematic reviews of EESs have performed only descriptive analyses and reported only qualitative findings without applying a meta-analysis (MA) to estimate pooled effect measures. Although Crespo et al [4] have described a MA for pooling EES (known as the COMparative Efficiency Research, COMER), it has yet been widely adopted as such MA for clinical outcomes. This might be due to the fact either EESs are too heterogeneous to pool or they chose the lesser known parameter "incremental net benefit" (INB) as the effect measure rather than the more commonly used ICER. However, we believe the choice for pooling INB was justified due to the limitations of the ICER [5]. For instance, a negative ICER may indicate a lower cost compared with higher effectiveness or higher cost along with lower effectiveness of

interventions, thus introducing ambiguity in interpretation [4, 6]. In contrast, positive and negative INBs directly indicate cost-effectiveness and non-cost-effectiveness of interventions, respectively, which is the information required by policy makers [7, 8]. Furthermore, the COMER method mainly focused on the statistical methods for pooling, but did not suggest a step-by-step process for data harmonisation and processing to aid the synthesis of economic studies.

Hence, in this tutorial paper, we provide step by step of the methods for data harmonisation and synthesis of EESs. Data for cost-effectiveness of diabetic drug controls are used as a demonstration.

Methods

Methods are similar to other systematic reviews and MAs [9, 10], and should follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] guidelines. This methodological study was a part of previous MAs, in which some additional specific issues apply to EESs are as follows[12-15].

Step 1: Data extraction

All relevant data for comparative EESs (e.g., CUA) should be extracted as follows utilising the PICOS (Population Intervention Comparator Outcome and Study type) framework:

- General characteristics of EESs including study setting/country, study design (e.g., CUA with model-based, primary CUA alongside RCT/cohort), study perspective, time horizon, discount rate for cost and utility, type of EESs (e.g., CUA or cost-effectiveness analysis (CEA)), willingness to pay (WTP; country specific or gross domestic products (GDP)-base) or country-level cost-effectiveness threshold[16] where appropriate if WTP was not available, and type of economic models.
- Characteristics of patients (P) including indication for treatment, sample size, type of

patients (e.g., children/adult, general/specific disease, etc.), mean age, percent male/female, mean body mass index (BMI), etc.

- Type of interventions and comparators (I & C) (with duration of treatment/dosage/day, etc.)
- Data needed to estimate INB and its variance (O); this includes currency and year, source of cost data (actual data cost collected from patients, central hospital/country costs, etc.) type of cost (e.g., direct/non-direct medical cost, indirect medical cost), and effectiveness outcomes (e.g., life year, QALY, ICER, etc.).

Specific data required for pooling include costs or incremental cost (ΔC), and incremental effectiveness (ΔE) along with their standard deviation (SD), standard error (SE), or 95% confidence interval (CI). Some studies may report ICER along with one-way and/or probabilistic sensitivity analysis (PSA). To calculate the INB and its variance, mean and variance of the costs and effectiveness of interventions and comparators along with WTP thresholds are required. In the model-based CUA, studies usually report point estimates of deterministic and/or probabilistic costs and outcomes. We suggest using primarily the measures of central tendency and dispersion measures from PSA results for pooling, as it could be a better representative of real-life situation considering the distribution of all input variables, and conducting sensitivity analyses using point estimates from the deterministic analysis to see robustness of results. The WTP threshold was initiated by the Commission on Macroeconomics and Health in 2002 by the World Health Organization CHOosing Interventions that are Cost-Effective (WHO CHOICE). The WTP threshold in each country usually refers from the standard country guideline based on a fixed value or per capita GDP with returns on investments in health to define whether a health intervention would be (very) cost–effective. [17, 18]. We suggest using the same WTP threshold in monetary units used in the study with further adjustment as per currency conversions as mentioned below.

Step 2: Data harmonisation

Currency conversions

We need to standardize money units usually reported in different currencies (i.e., US $, €, £, ¥) and years by converting to purchasing power parity (PPP) adjusted to US$ for the latest year of analysis. For example, if a study reported cost, ICER, and thresholds in Euros for 2012 and we plan to pool for the current year (e.g., 2020), this currency is firstly converted to 2020 Euros using the historical consumer price index (CPI) of that country. Then, the Euro 2020 value is converted to PPP adjusted US$ rate using conversion rates from the International Monetary Fund [19]. In addition, GDP-based WTP threshold (K) values also need to be corrected for the current CPI 2020 year and PPP; however, standard/country specific or fixed WTP values only need PPP correction. The variance is calculated as follows:

$$Var_{PPP_{2020}} = Var_{Euros_{2012}} x \left(\frac{CPI_{Euros_{2020}}}{CPI_{Euros_{2012}}} x \frac{1}{PPP_{2020}} \right)^2 \text{-----(1)}$$

Estimation of INB and its variance

After currency conversions for cost and K, the INB can be further estimated as follows:

$$INB = Kx\Delta E - \Delta C \text{----------(2)} \quad \text{or}$$
$$INB = \Delta E(K - ICER) \text{----------(3)}$$

where K is the WTP, and ΔC and ΔE are incremental cost and incremental effectiveness respectively.

A positive INB favours treatment, i.e., intervention is cost-effective, whereas a negative INB favours the comparator, i.e., intervention is not cost-effective [4, 7, 8].

Variance of INB can be estimated as follows:

$$Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{\Delta C} - 2K\sigma_{\Delta E\Delta C} \text{ ------(4)} \quad \text{or}$$

$$Var(INB) = K^2\sigma^2_{\Delta E} + \sigma^2_{ICER} \text{ ----------(5)}$$

Where $\sigma^2_{\Delta C}, \sigma^2_{\Delta E}, \sigma_{\Delta E\Delta C}$ are variances of ΔC and ΔE and their covariance, and σ^2_{ICER} is variance of ICER. However, economic studies can report many different parameters; the 5 scenarios below show how to obtain INB and variance starting with different reported data [20].

Scenario-1: The primary EES ideally reports the point estimates and variances for every parameter required for calculation of INB and its variance. The INB can be calculated accordingly to equations (2) to (5)

Scenario-2: The study reports the means and measures of dispersion (95% CIs) of incremental costs & outcomes, and ICER. The variance of the ICER can be calculated using the following formulas:

$$95\%CI \text{ of } \mu_{ICER} = \hat{\mu}_{ICER} \pm Z_{\alpha/2} xSE$$
$$UL_{ICER} = \hat{\mu}_{ICER} + Z_{\alpha/2} xSE$$
$$SE = \frac{UL_{ICER} - \hat{\mu}_{ICER}}{Z_{\alpha/2}} \text{ ----------(6)}$$
$$\hat{\sigma}^2_{ICER} = SE^2$$

UL_{ICER} = Upper limit of ICER

$Z_{\alpha/2}$ = Standardize normal =1.96

$\hat{\mu}_{ICER}$ = mean ICER

Once we know the variance of the ICER, the variance of the INB can be estimated using equation (5).

Scenario-3: The study reports means and 95% CI, SD/SE of costs/outcomes, or ΔC/ΔE, but does not provide the ICER or its variance. Data for ΔC and ΔE are then used to simulate ΔC and ΔE with 1000 replications using Monte Carlo methods with a gamma and normal distributions for ΔC and ΔE, respectively. The covariance ($\sigma_{\Delta E \Delta C}$) between ΔC and ΔE as well as $\hat{\sigma}^2_{\Delta C}$ & $\hat{\sigma}^2_{\Delta E}$ can be then estimated. If the 95% CI is provided, this is converted to SE using equation (6) above, and used to simulate data. The INB and its variance can be further calculated using equations (2) and (5).

Scenario-4: The study does not report any dispersion, but does provide the CE plane graphs, a scatter plot of ΔC on Y-axis and ΔE on X-axis, in which individual values of ΔC and ΔE data can be manually extracted from the CE plane using Web-Plot-Digitizer software [21]. Then, means of ΔC, ΔE, and their variances and co-variances can be estimated accordingly. Finally, the INB and its variance can be estimated using equations (2) and (5).

Scenario-5: The study reports neither any dispersion nor the CE-plane graph, but only provides the means (or point estimates) of costs, outcomes, and ICER. In such situations, the measures of dispersions can be borrowed from another similar study if they fulfil the following criteria:

- They are in the same stratum of country income,
- Their ICERs are not much different, e.g., ±50% to 75%
- They are similar in intervention, comparator, time period, country region
- Similar model type and inputs (i.e., discounting, time horizon).

If there is more than one study that meets the criteria, the average of the variances of those studies can be used.

Step 3: Pooling INB

When pooling INBs from many studies, we strongly recommend stratifying by level of country income, model type, time horizon, and perspective in order to reduce heterogeneity. The

country income should be classified as low (LIC), lower-middle (LMIC), upper-middle (UMIC) and high (HIC) as per the World Bank classification[8]. Economic models can include Markov, decision tree, discrete event simulation, or others. Study perspective should include societal, third-party payer, and patient perspectives. Time horizon should be lifetime and non-lifetime (e.g., 5-, 10-years, etc.).

The INB can be pooled across studies using a fixed-effect or a random-effect model depending on the degree of heterogeneity [4, 12, 13, 20].

A) Fixed-effects model

$$\mathrm{INB_p} = \frac{\sum_{i=1}^{S} w_i.\mathrm{INB_i}}{\sum_{i=1}^{S} w_i} \text{ ----------(7)}$$

$$w_i = \frac{1}{Var(INB_i)} \text{ ----------(8)}$$

B) Random-effects model

$$\mathrm{INB_p} = \frac{\sum_{i=1}^{S} w_i^*.\mathrm{INB_i}}{\sum_{i=1}^{S} w_i^*} \text{ ----------(9)}$$

$$w_i^* = \frac{1}{Var(INB_i)+\tau^2} \text{ ----------(10)}$$

$$\tau^2 = \frac{Q-(S-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \text{ ----------(11)}$$

Similar to MA in other areas, heterogeneity needs to be assessed before pooling INB. Heterogeneity can be visualized by inspection of the forest plot, and quantitated by using the Cochrane-Q test and the I^2 statistic [4, 12, 13, 20].

$$\mathrm{Q} = \sum_{i=1}^{S} w_i\left(\mathrm{INB_i} - \mathrm{INB}_p\right)^2 \text{ ----------(12)}$$

$$\mathrm{I^2} = 100\%\mathrm{x}\ \frac{\mathrm{Q}-(\mathrm{S}-1)}{\mathrm{Q}} \text{ ----------(13)}$$

If heterogeneity is present, i.e., the $I^2 \geq 25\%$ or p-value of Q test is less than 0.1, the INBs can be pooled using a random-effects model, otherwise a fixed-effect model can be applied [4, 12, 13, 20]. Exploring source/s of heterogeneity is strongly recommended. This can be done using a meta-regression to fit each potential source (e.g., time horizon, percent discount rate, threshold values, source of effectiveness measure, etc.) one-by-one. If that potential factor explains some proportion of the heterogeneity, including it in the meta-regression model should reduce the I^2 accordingly. There are no established criteria how much I^2 should be decreased by to consider that factor as a significant source of heterogeneity. In our experience, if the I^2 is reduced by about 50% or more from the baseline model (i.e., the model without any factor), such factor/s may be source/s of heterogeneity. A post-hoc subgroup analysis by that factor should be performed accordingly. In addition, sensitivity analyses excluding a few studies with very different characteristics compared to the rest can be used to see if heterogeneity of INBs can be reduced.

Similar to general MA, publication bias should be assessed using a funnel plot and Egger's test. A funnel plot graphs INB estimates on the x-axis against their precision on y-axis. If all studies are estimating the same true INB, their INBs should be randomly scattered around the true value and form a funnel shape. Egger's test formally tests if the funnel is symmetrical; if this is significant, it usually indicates that there is heterogeneity or missing studies (publication bias) or both. A contour-enhanced funnel plot is further recommended [22]. This plot will contour area of the funnel into non-significant (P-value >0.05-<0.1) and significant areas (P-value <0.01 and < 0.05), which will help to differentiate the cause of the asymmetry. For instance, if missing studies fall into the non-significant area, asymmetry might be due to missing studies or publication bias. Conversely, if missing studies are in significant areas, heterogeneity is more likely to be the explanation.

Example: We used data from a MA of CUA of glucagon-like peptide 1 agonists (GLP1) for treatment of type 2 diabetic (T2D) patients who failed to achieve control with metformin monotherapy [12]. A total of 56 studies with 82 comparisons were eligible for pooling INBs. We included comparisons of GLP-1 and dipeptidyl peptidase-4 inhibitors (DPP4i) (N=10); study characteristics are described in Table 1. All studies were from HICs and used country specific WTP threshold; 9/10 studies used the third-party payer perspective, and 7/10 used a life time horizon.

---Table 1 here---

In terms of preparing the data for pooling, 7, 1, and 2 studies provided data matching scenarios 3, 4, and 5, respectively (Table 1). Data for mean cost, QALY, and their incremental values are described in Table 2. Costs and WTP thresholds from each study were converted to $US currency using PPP adjusted for the year 2019 using formula (1).

For the 7 studies matching scenario 3 (where mean C and E data along with SDs were reported), the Monte-Carlo method was used to simulate 1000 replicated-data based on gamma and normal distributions for cost and QALY data, respectively. Then, ΔC and ΔE along with variance and co-variance ($\sigma_{\Delta E \Delta C}$)were calculated. The INB and variance was then calculated following formulas (2) and (4).

The study matching scenario 4 provided CE-plane graphs. Data for ΔC and ΔE were directly extracted from the CE plane using Web-Plot-Digitizer [21]. Then, variance and covariance ($\sigma_{\Delta E \Delta C}$) were calculated leading to estimation of the INB and its variance using formulas (2) and (4).

For the 2 studies [23, 24] matching scenario 5, the INB variance was adopted from other studies following the steps outlined above. Of the 10 included studies, 2 other studies [25, 26] were also conducted in the USA. For the selection of variance values for the Guillermin et al study[24], the study period, time-horizon, study perspective, ICER values, drug comparison (Sitagliptin) were most similar to Lee et al [26] (Table 1 and Table 2) and hence the INB variance value of the latter was used to estimate the former. The values for Lee et al also matched the second study [23] most closely.

--- Table 2 here----

INB data along with variances are shown in Table 3. These were then pooled across studies using a fixed-effects (inverse variance) model yielding a pooled INB (95% CI) of US$ 4012.21 (-571.43, 8595.85) with I^2 of 0%, see Figure 1a. In the presence of heterogeneity, as indicated by $I^2 \geq 25\%$ or Cochrane-Q $p<0.1$, a random-effects model (DerSimonian and Laird model) could be used [27]. The pooled INB value is positive but its 95% CI covers 0, i.e., GLP1 agonists might be cost-effective as compared to DPP4 inhibitors but the results did not reach statistical significance.

---Table 3 here---

The robustness of the pooled INB as well as heterogeneity can be assessed using various sensitivity and subgroup analyses. Sensitivity analyses omitting the study that used a societal perspective [28] and the study that did not use discounting [25] yielded a pooled INB of US$ 4,032.07 (US$−554.48, US$8,618.61) and US$4,068.19 (US$−650.66, US$8787.04), respectively.

The WTP threshold used for these comparisons ranged from US$ 29,382 to US$ 58,024 with a median of US $49,325. Subgroup analyses by median WTP threshold (< vs ≥ US $49,325), time horizon, and source of effectiveness measure were performed (see Table 4), indicating

GLP1s were not significantly cost-effective compared with DPP4i in any subgroup. In all these sensitivity and subgroup analyses, the results were similar to that of the overall pooled INB indicating that the results are robust.

--- Table 4 here---

As in general MA, publication bias was assessed using a funnel plot and Egger's test. There was no evidence of publication bias, seen either by asymmetry on the funnel plot (Figure 1b) or an Egger's test (coefficient=0.32, SE=0.73, p=0.672).

Discussion

We have developed MA methods for EESs focusing on data harmonisation; methodological issues include currency, time, discount, perspective, time horizon, and model used. INB and its variance are estimated based on 5 scenarios. MA is then applied to pool INBs across studies providing a summary estimated CE of treatment relative to control. This evidence should be useful for policy makers in making decisions regarding reimbursement of treatments to population in countries where resources are limited.

Despite the existence of several guidelines for reporting EESs, studies still vary in how they report the results. This data harmonisation process reported here under the 5 scenarios can help prepare data to calculate and pool INB values. The different monetary units and year can all be converted to a common standard currency.

We used INB instead of ICER as the economic effect measure because of limitations of the ICER in ambiguity of interpretation for negative ICER as mentioned above [4, 6]. On the other hand, positive INBs indicate cost-effectiveness, while negative INBs shows non-cost-effectiveness. This information will be required by policy makers [7, 8] in making decision from both resource-rich and resource-poor countries.

A few challenges should be highlighted when applying a MA in EESs. First, EEs are heterogeneous, which can be caused by model type, population, country income, GDP, perspective, time horizon, and discount rate. We applied the CPI and PPP to harmonise different economic backgrounds as well as the time-lag across the studies [29, 30]. However, it should be noted that using PPP may have some limitations as for the estimation method of price indices, which are calculated from individual prices of only selected commodities rather than all commodities in each country [31]. Considering not only country income, but also model type, time horizon, and perspective in stratified analyses may also reduce heterogeneity, if there are sufficient data for stratifying. Furthermore, sub-group and/or sensitivity analyses should be performed to identify specific types of studies/country income where treatments show cost-effectiveness. Economic factors should be considered for subgroups, including WTP, discount rate, type of EES (e.g., within-trial EES versus model-based EES), quality of EESs, type of health state, and percent herd immunity for vaccine, etc.). Different subgroups of these factors may result in different cost-effectiveness findings within HICs and UMICs.
Second, the health EESs are context specific, usually conducted in individual country settings. However, not all countries have EESs that fit their context because conducting well-designed EESs is very resource intensive and requires specialised expertise in economic evaluation. Therefore, there will be an even greater need for some systematic synthesis of evidence where resources are limited. Evidence from a MA will be useful if it is performed with a sensitivity to country contexts (e.g., country income, type of model, life-time, perspective, etc.).

In conclusion, we have demonstrated a tutorial of MA in EESs by applying the general methods of MA, additional with specific issues for EESs. The step-by-step approach of data harmonization is demonstrated for facilitating the process of MA. Although, evidence of CE is context specific for each country, conducting such specific individual study is challenging as

similar to CE studies due to various practical limitations (e.g., trained man-power, time, resources, etc.). Thus, the MA of EESs should be encouraged, evidence synthesis would be of immense values for policy decision making process as well as aid in comparability of such evidences across countries with similar contexts.

Abbreviations used in the manuscript

- **ΔC** – incremental cost
- **ΔE** – incremental effectiveness
- **BMI** - body mass index
- **CE-** cost effectiveness
- **CE-plane** – cost effectiveness plane
- **CI** – confidence interval
- **CPI** – consumer price index
- **CEA** - cost effectiveness analysis
- **COMER** - COMparative Efficiency Research
- **CUA** – cost utility study
- **DALY** – disability adjusted life year
- **DPP4i -** dipeptidyl peptidase 4 inhibitors
- **EES-** economic evaluation studies
- **GDP** – gross domestic product
- **GLP1i** - glucagon-like peptide-1
- **HIC -** high income countries
- **ICER** – incremental cost effectiveness ratio
- **INB** – incremental net benefit
- **LIC -** low income countries
- **MA-** meta analysis
- **PPP**- purchasing power parity
- **PRISMA-P** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol
- **PSA** – probabilistic sensitivity analysis
- **SD** - standard deviation
- **SE** – standard error
- **QALY** – quality adjusted life years
- **UMIC -** upper middle-income countries
- **US** – united states
- **WHO** – world health organisation
- **WTP –** willingness to pay

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- **Authors' contributions**:

  1) Conceived and designed the experiments: BSB, AT
  2) Performed the experiments: BSB, AT
  3) Analyzed and interpreted the data: BSB, UC, AT
  4) Contributed reagents, materials, analysis tools or data: BSB, UC, NC, JA, AT
  5) Wrote the paper: BSB, UC, NC, JA, AT

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Figure legends

Figure 1: a) Forrest plot of pooling INBs of GLP1 vs DPP4i; b) Funnel plot of pooling INB of GLP1 vs DPP4i.

Figures

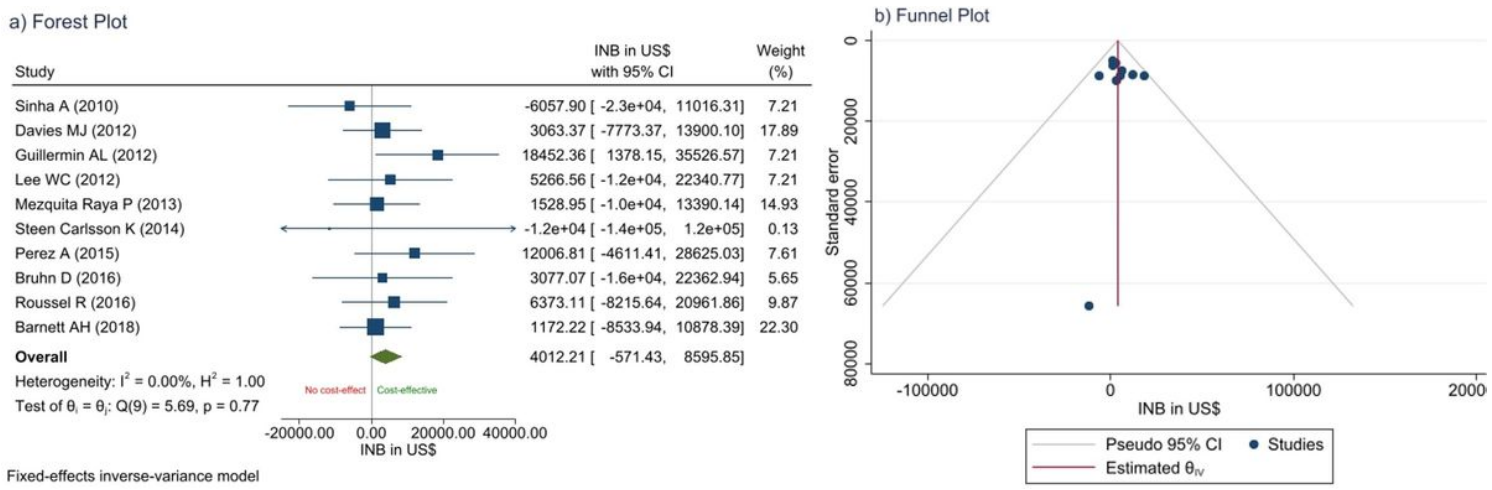

Figure 1

a) Forrest plot of pooling INBs of GLP1 vs DPP4i; b) Funnel plot of pooling INB of GLP1 vs DPP4i.