New numerical methods for calculating the effective sample size after population adjustment

Landan Zhang

Sylwia Bujkiewicz

Dan Jackson

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Introduction to Landan Zhang

About me

- BSc Mathematics with Statistics - University of Bristol
- MSc Financial Mathematics - King's College London
- PhD in Mathematics - King's College London
- 2021 to 2024 - AstraZeneca | Oncology | Statistical Innovation Reimbursement Evidence
  - Postdoc Fellow - Research in methods for population-adjusted indirect comparisons
- Since 2024 - Bayer | Medical Affairs
  - Senior Statistician
  - Lead Statistician

Content

Background

Background

- Population is an important concept in epidemiology and statistics, e.g. ‘P’ in PICO (population, intervention, comparison and outcome) statements.
- Often assume sample is representative of the population of interest (not always true).
- Population adjustment might be required.
  - Regression-based approaches.
  - **Weighting-based approaches.** (e.g. survey weighting, propensity score weighting, inverse probability weighting, inverse probability of censoring weighting…)
    - Loss of information.
- The effective sample size (ESS) has been proposed as a descriptive statistic, to accompany the weighted approaches. It is an indication of number of subjects contributing to the analysis after use weighting to perform population adjustment.
- The example in this talk based on the matching-adjusted indirect comparison (MAIC), but theory is applicable to any other weighting approaches for population adjustment .

Four approaches to calculate effective sample size

Existing approach: The conventional ESS formula (1)

- Effective sample size (ESS) is the sample size required in an unweighted sample that produces the same level of precision as the weighted sample.
- Assume independent and homoscedastic outcome data $var(y_i) = \sigma^2$ for i=1,…n.
  - Variance of an unweighted sample mean: $var(\overline{y_u}) = var\left(\frac{\sum y_i}{n}\right) = \frac{\sigma^2}{n}$ (1)
  - Variance of a weighted sample mean: $var(\overline{y_w}) = var(\frac{\sum w_i y_i}{\sum w_i}) = (\frac{1}{\sum w_i})^2 \sum w_i^2 \sigma^2 = \sigma^2 \frac{\sum w_i^2}{(\sum w_i)^2}$ (2)
- The standard ESS formula mentioned in NICE TECH DSU 18: By equating the variances of unweighted sample mean and weighted sample mean
  - $var(\overline{y_u}) = var(\overline{y_w})$
  - we solve required sample size n

$$n = ESS = \frac{(\sum w_i)^2}{\sum w_i^2}$$

Existing approach: The conventional ESS formula (2)

Why always lose information (precision) after weighting?

- Under the assumption of independent and homoscedastic outcome data $var(y_i) = \sigma^2$ for i=1,…n.
  - Variance of an unweighted sample mean: $var(\overline{y_u}) = var\left(\frac{\sum y_i}{n}\right) = \frac{\sigma^2}{n}$ (1)
  - Variance of a weighted sample mean: $var(\overline{y_w}) = var\left(\frac{\sum w_i y_i}{\sum w_i}\right) = \left(\frac{1}{\sum w_i}\right)^2 \sum w_i^2 \sigma^2 = \sigma^2 \frac{\sum w_i^2}{\left(\sum w_i\right)^2}$ (2)
- By Cauchy-Schwarz inequality for any $w_1, \dots, w_n$ and $b_1, \dots, b_n$

$$w_1 b_1 + \cdots + w_n b_n \le \sqrt{w_1^2 + \cdots + w_n^2}\,\sqrt{b_1^2 + \cdots + b_n^2}$$

- Let $b_i = 1$ for all b and plug into Cauchy-Schwarz inequality

$$w_1 + \cdots + w_n \le \sqrt{w_1^2 + \cdots + w_n^2}\,\sqrt{n}$$

$$(w_1 + \cdots + w_n)^2 \le (w_1^2 + \cdots + w_n^2)n$$

$$\frac{1}{n} \le \frac{(w_1^2 + \cdots + w_n^2)}{(w_1 + \cdots + w_n)^2}$$

$$\frac{\sigma^2}{n} \le \sigma^2 \frac{\sum w_i^2}{\left(\sum w_i\right)^2} \quad \Rightarrow \quad var(\overline{y_u}) \le var(\overline{y_w}) \text{ and ESS} \le n$$

First new method: comparing the variances of adjusted and unadjusted estimates (1)

- Express variance of weighted sample mean $var(\overline{y_w})$ in terms of ESS
- Comparing the variances of weighted sample and unweighted sample

$$var(\overline{y_w}) = var(\frac{\sum w_i \, y_i}{\sum w_i}) = (\frac{1}{\sum w_i})^2 \sum w_i^2 \sigma^2 = \frac{\sigma^2}{ESS}$$

$$\frac{var(\overline{y_u})}{var(\overline{y_w})} = \frac{\frac{\sigma^2}{n}}{\frac{\sigma^2}{ESS}} = \frac{ESS}{n}$$

- An equivalent definition of the conventional ESS formula

$$ESS = \frac{n \times var(\overline{y_u})}{var(\overline{y_w})}$$

First new method: comparing the variances of adjusted and unadjusted estimates (2)

- We propose generalising equation by replacing
  - $\overline{y_u}$ with $\hat{\theta}_u$: the unweighted (i.e. the unadjusted) estimate of the estimand of interest;
  - $\overline{y_w}$ with $\hat{\theta}_w$: the weighted (i.e. the population adjusted) estimate of the estimand of interest,
- More generally, the ESS formula becomes

$$ESS = \frac{n \times var(\hat{\theta}_u)}{var(\hat{\theta}_w)} \quad (3)$$

- Suitable for any type of outcome data, estimand, and statistical model.

Second new method: re-sampling with reduced sample size

- Calculate the variance of estimate of the **weighted** sample $var(\hat{\theta}_w)$ (assume greater than $var(\hat{\theta}_u)$).
- Use bootstrapping (resampling) to calculate the variance of **unweighted** sample with reduced observations.
  - Step 1. Resample the dataset for multiple times (e.g. 500)
  - Step 2. We reduce 5k (for k=1) observations from each arm of each resampled dataset. Perform population adjustment and calculate the estimate.
  - Step 3. Calculate the variance of estimate in reduced sample by taking the variance of the estimates from all resampled datasets.
  - Step 4. Repeat step 1 to 3 for (k=2,3,…) until we get a variance $var_{k=m}(\hat{\theta}_u)$ greater than $var(\hat{\theta}_w)$ the variance of estimate of the weighted sample.
- $var_{k=m-1}(\hat{\theta}_u) \leq var(\hat{\theta}_w) \leq var_{k=m}(\hat{\theta}_u)$; $5(m-1) \leq ESS \leq 5m$
- Use linear interpolation to calculate the exact sample size which produce the variance of weighted sample.
- In the (unlikely) event that variance of unweighted sample greater than variance of weighted sample: use similar approach but sequentially **increase** the size of the unweighted resampled datasets in the re-sampling procedure.

Third new method: Scaling the unweighted variance formula with reduced sample size

- For outcomes with a closed form of variance that depends upon sample counts or rates.
- Calculate the variance of weighted sample.
- Use formula and ratio *p* (percentage of remaining observations) to calculate the variance of unweighted sample with reduced observations.
  - E.g. for binary outcomes, the variance of log OR:

$$var[\log(OR)] = \frac{1}{\sum y_A} + \frac{1}{n_A - \sum y_A} + \frac{1}{\sum y_B} + \frac{1}{n_B - \sum y_B}$$

  - Applying the ratio *p* to the counts:

$$var[\log(OR)] = \frac{1}{p(\sum y_A)} + \frac{1}{p(n_A - \sum y_A)} + \frac{1}{p(\sum y_B)} + \frac{1}{p(n_B - \sum y_B)}$$

- Use 'uniroot' in R to search value of p which we have $var[\log(OR)] = var(\hat{\theta}_w)$
- Calculate the corresponding sample size by $ESS = np$
- Another example: variance of the estimated log hazard ratio from a Cox proportional hazards model can be approximated by 4 / Total number of events.

A numerical example

A numerical example

- Example from NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE (Phillippo et al. 2016).
- Binary outcome is simulated using the model
  - $\text{logit}(p_{it}) = 0.85 + 0.12 male_{it} + 0.05(age_{it} - 40) + (\beta_t - 0.08(age_{it} - 40))I(t \neq A)$
  - where $\beta_B = -2.1, \beta_C = -2.5$.
- Treating the outcome as an adverse event.

Variable	Variable type	Company's trial N=500 Independent patient data	Competitor trial N=300 Summary level data
Age	Effect modifier	Range: (45-75), Mean: 60, sd:9.0	Range: (45-55), Mean: 50; sd: 3.2
Sex	Prognostic variable	64% Female	80% Female
Treatment	Covariate	B vs A	C vs A

A numerical example

(1) Application of the existing approach

- Computed the 500 MAIC weights w_i for each patient in the company's trial
- Calculate the ESS use the formula: $\mathbf{ESS} = \frac{(\sum \boldsymbol{w_i})^2}{\sum \boldsymbol{w_i^2}}$ **= 185.6451**

(2) Application of approach 2: comparing the variances of estimates

- After preforming the MAIC, we can calculate the adjusted estimated log odds ratio $\hat{\theta}_w$=-3.2151 by using a weighted logistic regression of binary outcome data on treatment group with IPD from company's trial. Also calculate the sandwich standard error and its variance $var(\hat{\theta}_w) = 0.1628$
- The unadjusted estimated log odds ratio $\hat{\theta}_u$=-3.5717 and its variance $var(\hat{\theta}_u)$= 0.0653 is similarly obtained using an unweighted logistic regression.
- Having computed $var(\hat{\theta}_u)$ and $var(\hat{\theta}_w)$, and n=500 for company's trial, calculate the ESS by comparing the variances: $\mathbf{ESS} = \frac{\mathbf{n \times var}(\overline{y_u})}{\mathbf{var}(\overline{y_w})}$ **= 200.5176**

A numerical example

(3) Application of approach 3: resampling with reduced sample size

- Unadjusted analysis gave $var(\hat{\theta}_u)$= 0.0653
- In adjusted analysis, the robust standard error resulted $var(\hat{\theta}_w) = 0.1628$ loss of precision!
- Sequentially reduce the sample size until an unweighted analysis result in less precision (larger variance) than the weighted analysis
  - There are 500 patients in company's trial with 1:1 randomisation
  - Create multiple resamples of company's IPD, for each resampled dataset, remove the first five observations from both treatment groups and calculate the estimate. The variance is obtained by taking the variance of estimates from all resampled datasets with reduced sample size.
  - Repeat last step with more observations being removed until we obtained a variance larger than the variance of estimates in the weighted sample.

A numerical example

- Tabulate the variances:

Sample size Variance	500 0.0769	490 0.0709	480 0.0812	470 0.0828	460 0.0842	450 0.0850	440 0.0864	430 0.0897	420 0.0910	410 0.0899
Sample size Variance	400 0.0916	390 0.0950	380 0.0982	370 0.1010	360 0.1021	350 0.1010	340 0.1031	330 0.1065	320 0.1078	310 0.1115
Sample size Variance	300 0.1188	290 0.1230	280 0.1259	270 0.1311	260 0.1410	250 0.1476	240 0.1572	230 0.1652 (> 0.1628)		

- $var(\hat{\theta}_w) = 0.1628$ which is between 0.1572 (with sample size 240) and 0.1652 (with sample size 230).
- Linear interpolation is used to calculate the required sample size of the unweighted sample, which produces a variance of $var(\hat{\theta}_w) = 0.1628$ as $\boldsymbol{ESS} = \mathbf{233.005}$.
- If re-estimate the variance of weighted sample using bootstrapping $var(\hat{\theta}_w) = 0.1819$, then this produces the $\boldsymbol{ESS} = \mathbf{202.489}$.

An numerical example

(4) Application of approach 4: Scaling method with reduced sample size.

- A closed formula for the variance of estimated log OR exists for the binary outcomes in this numerical example
  - the variance of log OR:

$$var[\log(OR)] = \frac{1}{\sum y_A} + \frac{1}{n_A - \sum y_A} + \frac{1}{\sum y_B} + \frac{1}{n_B - \sum y_B}$$

  - Applying the ratio *p:*

$$var[\log(OR)] = \frac{1}{p(\sum y_A)} + \frac{1}{p(n_A - \sum y_A)} + \frac{1}{p(\sum y_B)} + \frac{1}{p(n_B - \sum y_B)}$$

- Use the 'uniroot' function in R, to solve for the value of p that results in a variance of $var[\log(OR)] = var(\hat{\theta}_w) = 0.1628$
- This process provides $p = 0.401$, which is the proportion of observations remaining in a hypothetical unweighted sample that produces the same variance as a weighted analysis.
- Finally, the ESS is calculated as $\boldsymbol{ESS = np = 200.5178}$

A numerical example

Compare the results

Approach	Approach 1 Conventional ESS formula	Approach 2 Comparing the variance	Approach 3 Re-sampling	Approach 4 Scaling
ESS	185.6451	200.5176	202.4886	200.5178

Summary

Summary

- // It is challenging to evaluate the accuracy of each method because they do not estimate a population parameter.
- // In the numerical example, all methods produced similar ESS values, which suggests that all methods are feasible.
- // The conventional ESS formula may produce misleading results when the homoscedastic assumption on the outcome is violated.
- // The ‘comparing the variances of estimates’ may produce different values of ESS for the same dataset, because different models and outcomes will provide different values of variances. Same set of weights may have dissimilar consequences for estimation precision in different statistical analyses of the same data.
- // The ‘re-sampling method’ may be sensitive to the random seed used. The number of observations being removed at each step is arbitrary, which introduces further sensitivity to choices made by the analyst.
- // The ‘scaling method’ can only be used when a closed formula of variance exists.
- // The three new methods can be generalized to regression-based population-adjustment methods because the methods do not dependent on weights.

Publication

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RESEARCH **Open Access**

Three new methodologies for calculating the effective sample size when performing population adjustment

Landan Zhang[1], Sylwia Bujkiewicz[2] and Dan Jackson[3*]

Abstract

Background The concept of the population is of fundamental importance in epidemiology and statistics. In some instances, it is not possible to sample directly from the population of interest. Weighting is an established statistical approach for making inferences when the sample is not representative of this population.

Methods The effective sample size (ESS) is a descriptive statistic that can be used to accompany this type of weighted statistical analysis. The ESS is an estimate of the sample size required by an unweighted sample that achieves the same level of precision as the weighted sample. The ESS therefore reflects the amount of information retained after weighting the data and is an intuitively appealing quantity to interpret, for example by those with little or no statistical training.

Results The conventional formula for calculating ESS is derived under strong assumptions, for example that outcome data are homoscedastic. This is not always true in practice, for example for survival data. We propose three new approaches to compute the ESS, that are valid for any type of data and weighted statistical analysis, and so can be applied more generally.

Conclusion We illustrate all methods using an example and conclude that our proposals should accompany, and potentially replace, the existing approach for computing the ESS.

Keywords Weighted statistical analysis, Propensity score, Inverse probability weighting, Survey weights, Indirect treatment comparisons

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Any questions?

Backup slide

Variance of estimate