Systematic review and Meta-analysis

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Narrative reviews, Systematic reviews, Meta-analyses

NARRATIVE REVIEWS tend to be:

- mainly descriptive
- do not involve a systematic search of the literature
- often focus on a subset of studies in an area chosen based on availability or author selection.

PROBLEMS: Thus narrative reviews while informative, can often include an element of selection bias.
They can also be confusing at times, particularly if similar studies have diverging results and conclusions.

Narrative reviews, Systematic reviews, Meta-analyses

SYSTEMATIC REVIEWS, as the name implies, typically involve a detailed and comprehensive plan and search strategy derived a priori, with the goal of reducing bias by identifying, appraising, and synthesizing all relevant studies on a particular topic. Often, systematic reviews include a meta-analysis component.

META-ANALYSES involve using statistical techniques to synthesize the data from several studies into a single quantitative estimate or summary effect size.

Uman SU. Systematic Reviews and Meta-Analyses. J Can Acad Child Adoesc Psychiatry 2011; 20(1):57-59

Meta-analysis

- Meta-analysis is a kind of observational/ecological study, where single studies are statistical units.
- It is a two-step process. In the first step, an appropriate effect measure is computed for each study. In the second step, the above-mentioned statistics are combined to compute a pooled estimate.

NB: an ECOLOGICAL STUDY investigates the time and/or spatial relation between outcome and exposure at population level (e.g. town, region, country), rather than at individual level.

Literature search strategy

The literature search was conducted independently by three investigators by searching the electronic databases MEDLINE, the Cochrane Library, Embase and PubMed, along with the Google and Google Scholar websites. Bibliographies of articles retrieved were searched manually. The 'related articles' function in PubMed was also used. These databases were analysed from the date of the earliest report of CP in 1988[4] to December 2010.

The following keywords were used in all searches: 'central pancreatectomy', 'middle pancreatectomy', 'Dagradi–Serio–Iacono operation', 'Dagradi–Serio–Iacono procedure', 'intermediate pancreatectomy', 'median pancreatectomy', 'medial pancreatectomy', 'segmental resection of pancreas', 'limited conservative pancreatectomy', 'central *versus* distal pancreatectomy', 'low grade malignant pancreatic tumors' and 'benign pancreatic tumor'. The searches were performed without restriction with regard to the number of patients reported, type of publication or assessment of methods and outcomes.

Study selection was performed as indicated in *Fig. 2*. Data were extracted from each included study by four investigators independently, using prespecified selection criteria. Any disagreements were resolved by discussion and re-evaluation with the main investigator.

The data items extracted were: authors, country, journal, study design (retrospective *versus* prospective, matched or unmatched), study period, number of patients, sex, age, type of disease, size of tumour, type of pancreatic resection, type of treatment of distal and proximal stumps, perioperative data (duration of operation, estimated blood loss, blood transfusion, local and systemic complications, reoperation rate, mortality rate and hospital stay) and postoperative data (endocrine pancreatic insufficiency, exocrine insufficiency, survival, disease-free survival and recurrence rate).

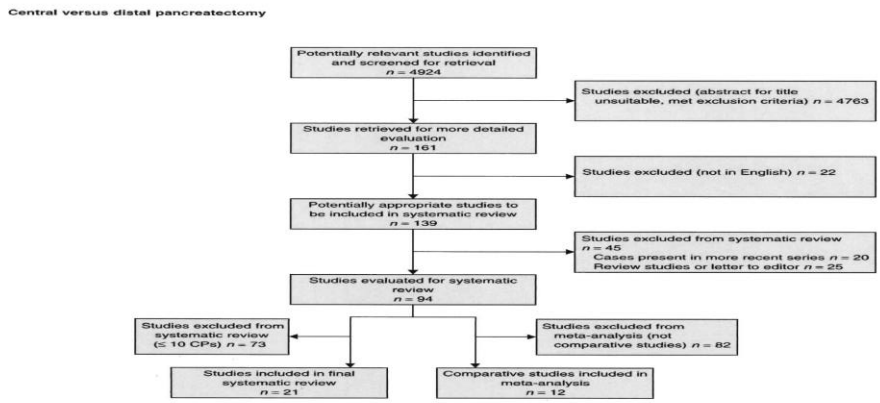


Fig. 2 Articles identified and evaluated during the review process. CP, central pancreatectomy

Iacono C, Verlato G, Ruzzenente A, Campagnaro T, Bacchelli C, Valdegamberi A, Bortolasi L, Guglielmi A (2013) Systematic review of central pancreatectomy and meta-analysis of central *versus* distal pancreatectomy *Brit J Surg*, 100:873-885

Search strategy and study selection

The systematic review and meta-analysis were conducted according to the PRISMA guidelines [6]. A comprehensive electronic search was separately performed by V.M., A.V. and E.Z., using PubMed, PMC and Cochrane Library for English language articles and China National Knowledge Infrastructure and Wangfang Data search engine for Chinese language articles. Research included publications from January 1990 to February 2019 and combined the following Medical Subject Headings (MeSH) terms: "gastric cancer", and "gastrectomy" or "surgery", and "drain" or "abdominal drainage". A further search on the reference lists of all relevant articles was also undertaken to identify any additional study considering the role of prophylactic abdominal drain after gastrectomy. After assessment of all full text articles, RCTs or cohort studies comparing post-operative outcomes of patients with or without prophylactic abdominal drain after gastrectomy for gastric cancer were included in the analysis. The exclusion criteria for the meta-analysis were reviews, case reports or other meta-analyses and studies considering cohort of patients who had undergone surgery for benign disease as obesity.

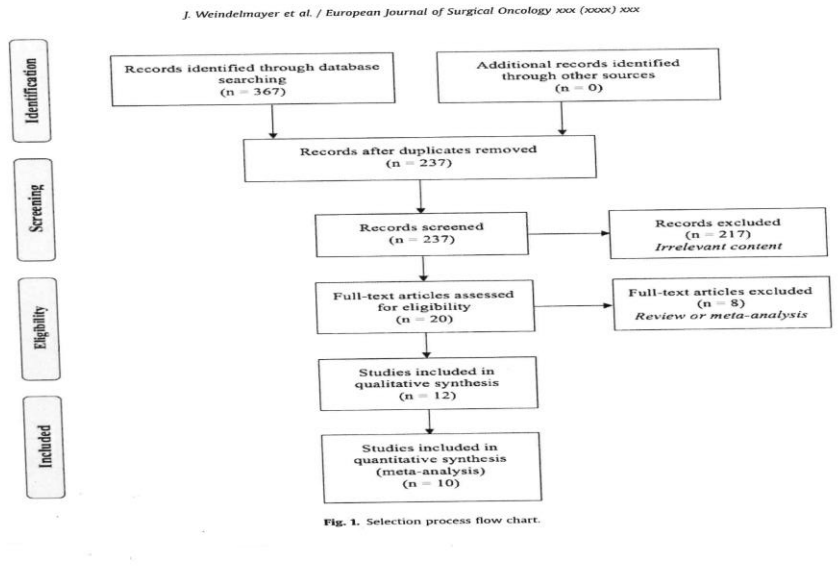


Fig. 1. Selection process flow chart.

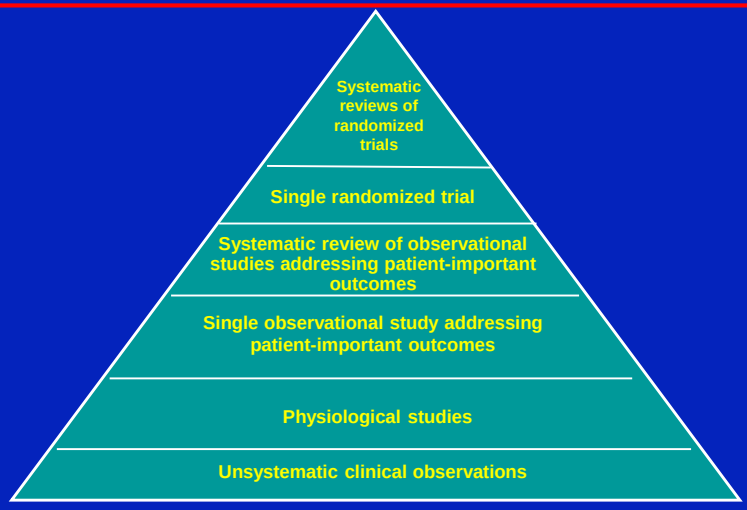
Weindelmayer J, Mengardo V, Veltri A, Torroni L, Zhao E, Verlato G, de Manzoni G. Should we still use prophylactic drain in gastrectomy for cancer? A systematic review and meta-analysis. EJSO- Eur J Surg Oncol 2020; 46(8):1396-1403

Outcomes of interest and quality assessment

Three authors extracted and checked the data independently. Any disagreement was resolved by a fourth reviewer. The following study characteristics were recorded for the review: country, study period, type of gastrectomy, type of lymphadenectomy, tumour stages included, resection margins, percentage of patients treated with neoadjuvant treatment, percentage of patients treated with minimally invasive surgery. The following variables were used for comparison between the two groups: anastomotic leak, reoperation rate, additional drain procedure, length of stay, postoperative morbidity (considering both 30 days and in hospital), postoperative mortality (considering both 30 days and in hospital), readmission rate and drain related complications.

To assess the risk-of-bias, randomized studies were evaluated by the Jadad score [7] while observational studies were evaluated by the Newcastle-Ottawa Scale (NOS) [8]. These tools are commonly used to assess the quality of medical research in randomized (Jadad score) or cohort/case control studies (NOS). The Jadad score consists of a three-point questionnaire and for each satisfied criteria the paper receives one or two point up to a maximum of 5. In our analysis we considered only two criteria: randomization and proportion of withdrawals/dropouts for a maximum of 3 points. The third component, blindness, was not deemed feasible for drainage placement. The Newcastle-Ottawa Scale (NOS) consist of an eight-point scale. NOS for cohort studies evaluates selection, comparability and outcome categories. One star for each satisfied item is assigned for the Selection and Outcome categories while a maximum of two stars can be assigned for Comparability. We included in the Meta-Analysis only studies with either good (Jadad 2; NOS: 7—8) or excellent score (Jadad 3; NOS: 9). A sensitivity analysis was performed by repeating the Meta-Analysis with all available studies.

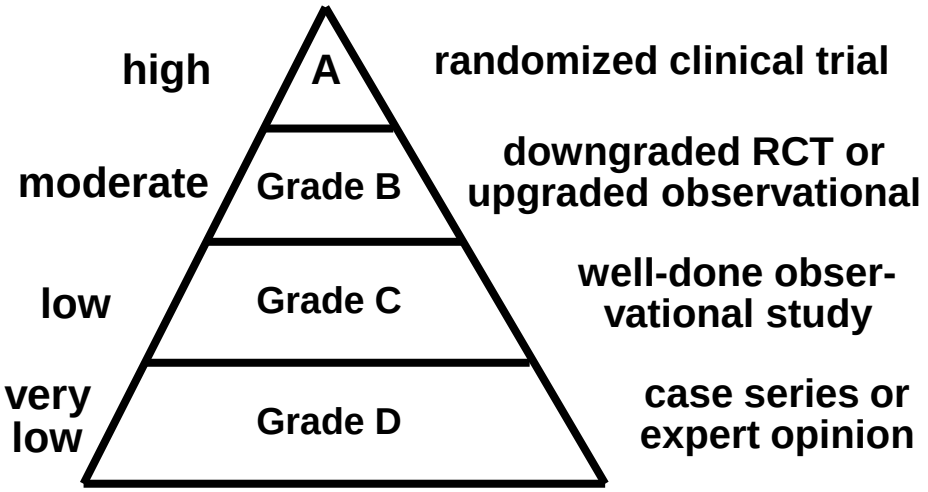
A Hierarchy of Strength of Evidence in Interventional Clinical Trials



Adapted from: Guyatt et al (2000) for the Evidence-Based Medicine Working Group. *JAMA* 284:1290-6

Also the quality of single studies should be assessed

Pyramid of evidence according to the GRADE system



The quality of observational studies is evaluated by the Newcastle-Ottawa Scale (NOS) score [Wells et al],

While the quality of experimental studies is assessed by the Jadad score [Jadad et al, 1996].

Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1–12

The Jadad score to evaluate clinical trials

It ranges between 0 (poor) and 5 (very good)

+1) *Was the study described as randomized?* **YES**

+1) *The method of randomisation was described in the paper, and that method was appropriate* (e.g. random numbers taken from tables or computer software)

-1) *The method of randomisation was described, but was inappropriate* (e.g. patients are alternatively allocated to either group according to increasing date of birth)

+1) *Was the study described as double blind?* **YES**

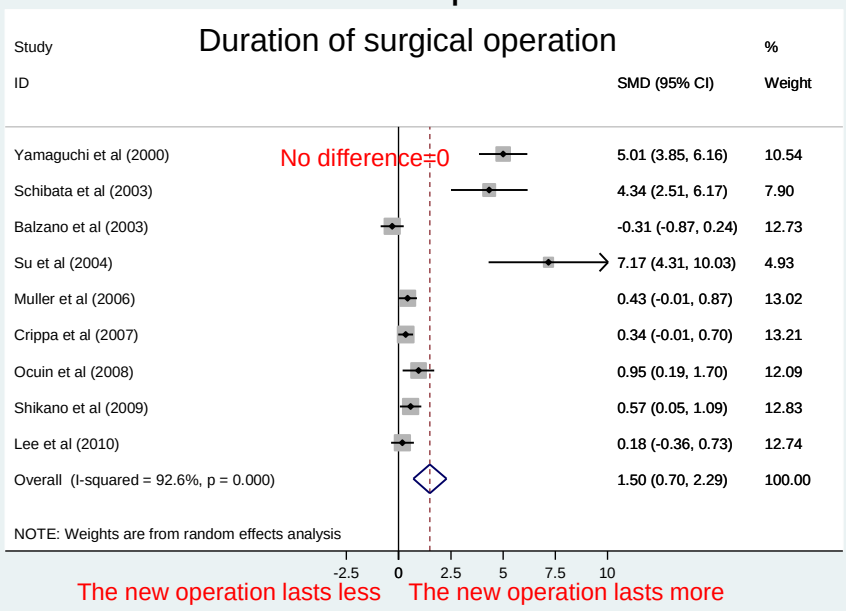
+1) *The method of blinding was described, and it was appropriate* (e.g. double dummy)

-1) *The method of blinding was described, but was inappropriate* (e.g. placebo per os while drug intravenously)

+1) *Was there a description of withdrawals and dropouts?* **YES**

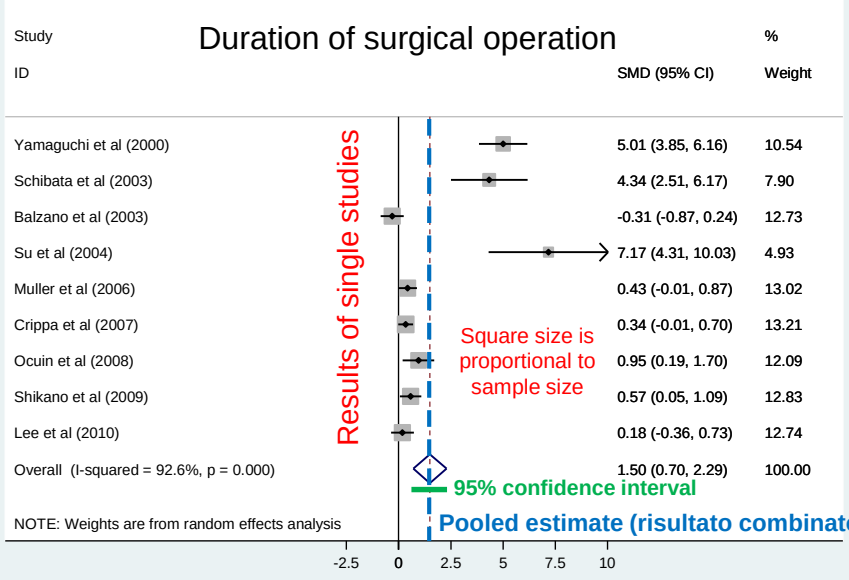
The results of a meta-analysis are synthetized through the Forest plot

Forest plot



Iacono C, Verlato G, et al. Systematic review of central pancreatectomy - The Dagradi-Serio-Iacono procedure - and meta-analysis versus distal pancreatectomy. Brit J Surg 2013; 100:873-885

Forest plot



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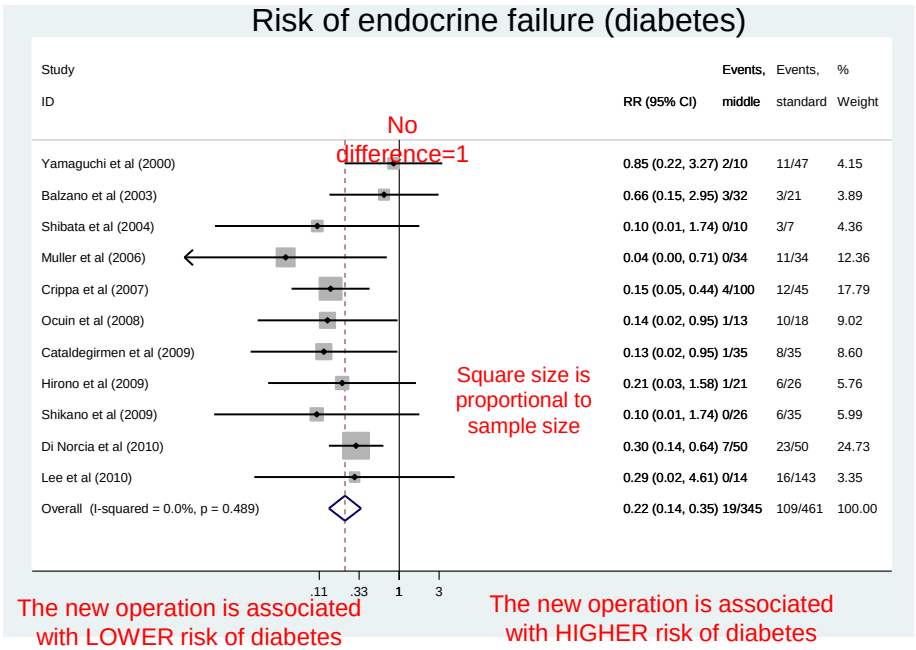


Effect measures in Meta-analysis

Hypothesis testing gives us information about statistical significance, i.e. whether the observed difference can be attributed to random variability or to real difference in the source populations.

Effect sizes measure the strength of the relationship between two variables, thereby providing information about the magnitude of the intervention effect (i.e., small, medium, or large).

The type of effect size calculated generally depends on the type of outcome and intervention being examined as well as the data available from the published trials; however, some common examples include odds ratios (OR), weighted/standardized mean differences (WMD, SMD), and relative risk or risk ratios (RR).

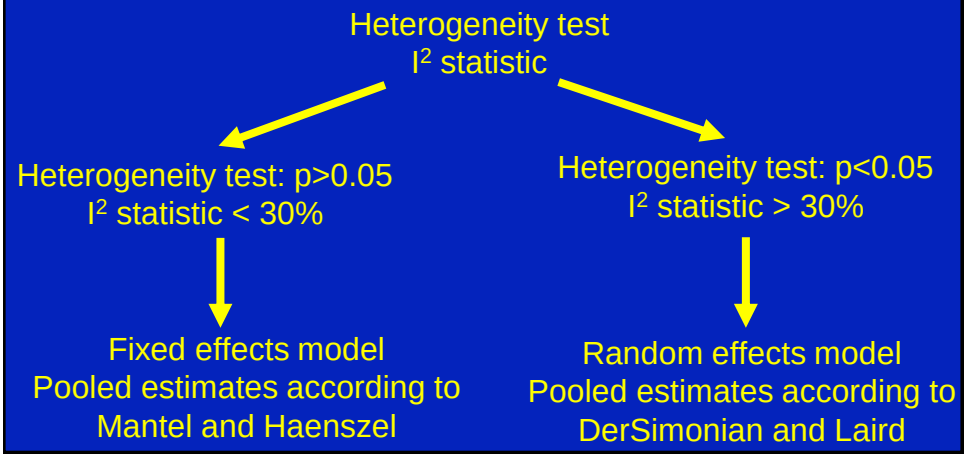
Standardized Mean Difference (SMD) was computed for quantitative variables (operation time, blood loss, length of hospital stay)

Relative risk (RR) was computed for qualitative variables (overall morbidity, exocrine failure, endocrine failure, pancreatic fistula, re-operation).

Choice of the statistical model in Meta-analysis

Fixed effects model = single studies can be considered as samples drawn from the same population.

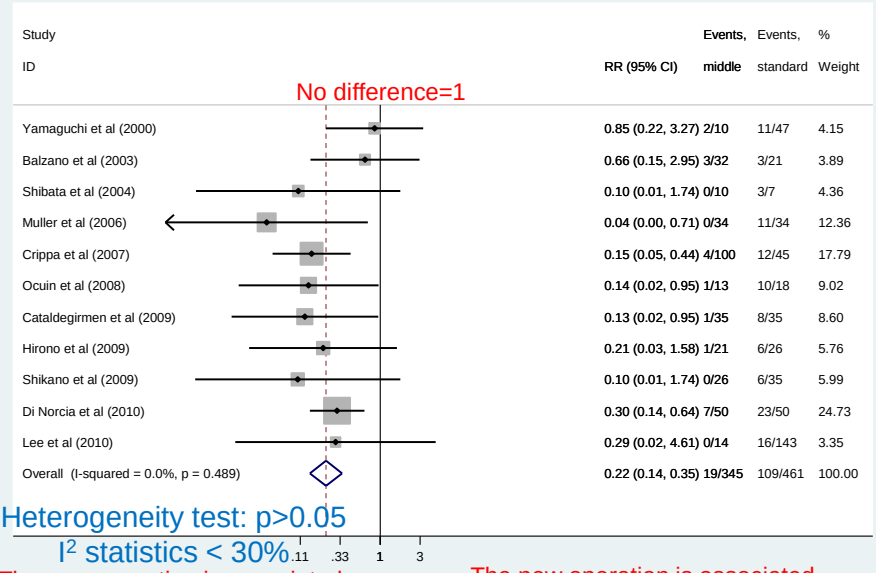
Random effects model = single studies should be viewed as samples drawn from different populations.



ENGLISH: The I-squared statistic indicates the proportion of total variation among the effect estimates attributed to heterogeneity rather than sampling error.

ITALIAN: La statistica I-quadrato indica la proporzione di variabilità tra le stime dei singoli studi che va attribuita all'eterogeneità anziché alla variabilità campionaria.

All studies found a lower risk of diabetes with the new procedure, which spares the pancreas tail, rich in islets producing insulin



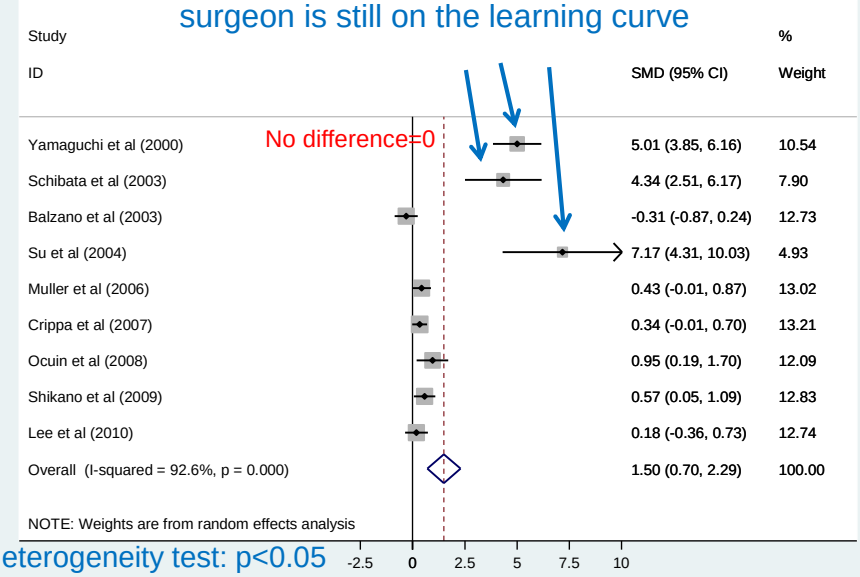
Heterogeneity test: p>0.05

I^2 statistics < 30%

The new operation is associated with LOWER risk of diabetes

The new operation is associated with HIGHER risk of diabetes

The new operation lasts longer in small series, where the surgeon is still on the learning curve

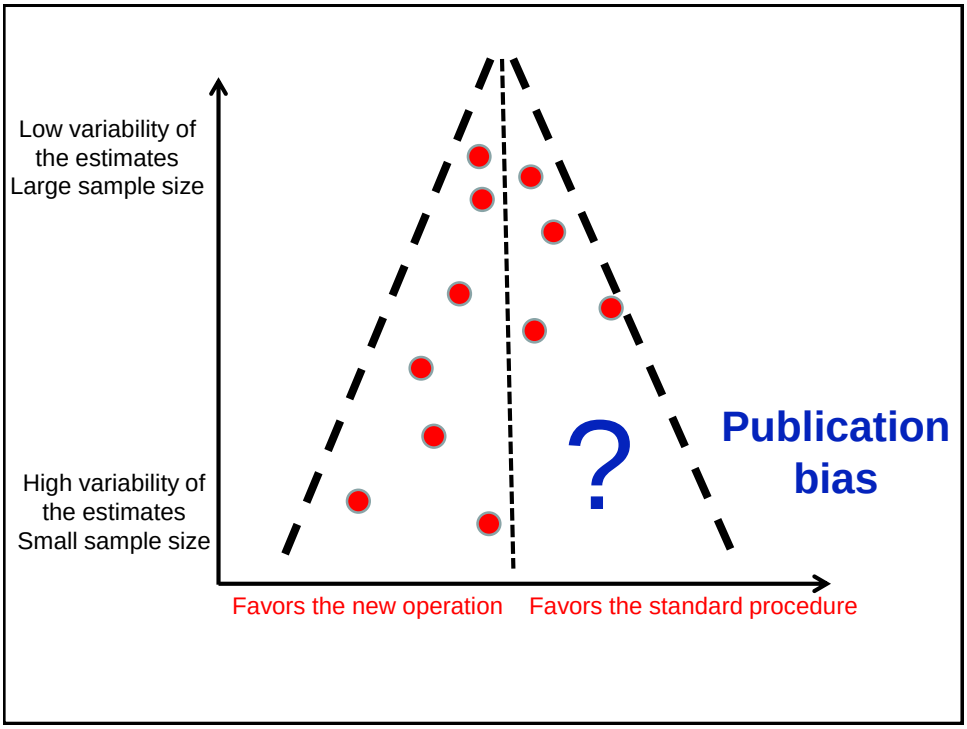


Heterogeneity test: p<0.05

I^2 statistics > 30%

The new operation lasts less

The new operation lasts more



Funnel plot (diagramma a imbuto)

It also allows to highlight small series bias (distorsione da studi di bassa numerosità)