Executive Summary

1. Backgrounds and Objectives

A systematic review is a research method which summarizes the results of all relevant studies through systematic and scientific processes in order to answer a specific research question. For this reason, a systematic review is one of the most frequently used methods in assessing the effectiveness and safety of interventions as a part of Health Technology Assessment [HTA]. However, systematic reviews are subjected to reporting bias because the methods are fundamentally based on the studies which are already existed. Among various kinds of reporting bias, publication bias leads to overestimation of effect size in systematic reviews with meta-analyses, which could affect the credibility of study results. Therefore, it is important to investigate and adjust publication bias when meta-analyses are conducted in systematic reviews.

The purposes of this study are followed:

- A. Introducing various methods of detecting small study effect & publication bias, and methods of adjusting publication bias through reviewing major text books and updated relevant studies
- B. Investigating the current status of meta-analysis studies exploring small study effect & publication bias from major journals
- C. Exploring small study effect & publication bias to compare the results reported by authors and the adjusted results by the current study and to investigate how the effect estimates in meta-analyses could change between the results

2. Methods

1) Methodology

In order to review methods of exploring small study effect & publication bias and of adjusting publication bias, major text books, updated relevant studies, and additional relevant studies from their bibliographies were selected by themes. The selected books and studies were thoroughly reviewed and organized into a) the method using graphs, b) statistical models, c) sensitivity analyses through seminar sessions.

2) Current status

The Journal of American Medical Association [JAMA], The Lancet, British Medical Journal [BMJ], The New England Journal of Medicine [NEJM] were selected as major journals to be inspected of the current status of exploring publication bias. Among systematic reviews with meta-analyses published in these journals in 2001-2010, those which had meta-analyses of primary outcomes including ten or more randomized controlled trials were selected as adequate to exploring and adjusting publication bias. The studies were selected following predetermined inclusion/exclusion criteria.

As for the selected systematic reviews, following information was extracted: general information (i.e. author, year), whether the presence of small study effect & publication bias was explored, the terms indication small study effect & publication bias, and the methods used for exploring small study effect & publication bias.

The selection of studies and extracting data were conducted by four paired investigators exclusively. Discrepancy were resolved by consensus.

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3) Adjusting publication bias

The studies selected for exploration of current status were screened whether they had study level data of meta-analyses. Ones without study level data were excluded because exploring and adjusting publication bias required them. The remains were organized by the unit of meta-analysis, and the meta-analyses of continuos data without significant between study heterogeneity were regarded optimal to explore and adjust publication bias, and therefore selected.

On the purpose of comparing the results of exploration and adjustment with those reported by authors, following information was extracted: general information (i.e. author, year), whether small study effect & publication bias were explored by authors, the methods author used, the result and conclusion on the possibility of publication bias, effect estimation, confidence interval of effect estimation. In addition, study level effect estimation and standard error of effect estimation were extracted to be used in investigation and adjusting publication bias.

Contour-enhanced funnel plot, Egger's test, Begg's test were applied to explore small study effect & publication bias, and for the adjustment, Egger's variance regression model was adopted. The observation was focused on whether the effect estimation chanced after adjustment, the direction it changed (i.e. whether the effectiveness of intervention increased or decreased), the effect of the change of the study conclusion.

3. Results

1) Methodology

(1) Investigation of small study effect & publication bias

For the methods using graphs, there were funnel plots to visually

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inspect the relation between the precision of included studies and their size of effects, and contour-enhanced funnel plots which provided additional information on the statistical significancy of included studies.

Begg's test and Egger's tests were frequently used as statistical models to explore small study effect & publication bias. Begg's test was a non-parameter method to test rank correlation between effect estimation and variance. Egger's test, a kind of meta-regression analysis, tested the linear relation between effect estimation and standard error. Other models were proposed at Harbord 2006, Peters 2006, and Rücker 2008.

(2) Adjustment of publication bias

Trill-and-fill and fail-safe N were available to adjust publication bias. They were under an assumption that the observed small study effect was caused soley by publication bias, and, as a kind of sensitivity analysis, provided the result when publication bias was not existing anymore. Trill-and fill eliminated small studies causing asymmetry on the funnel plot to observe changed effect estimation after elimination. Fail-safe N explored the number of further needed null studies in order to remove statistical significancy of effect estimation.

The models of small study effect were proposed to be used for adjusting publication bias. The model of Egger's test was adequate for continuos data, and for dichotomous data, any models of Harbord's test, Peters' test, Rücker's test were recommended. The adjustment was under the assumption of the effect without small study effect was true effect, and the effect was estimated by regression.

(3) Current status

A hundred and seventy two studies were identified for investigation current status of major journals exploring small study effect & publication bias. Among 170 studies, only 82 (48.2%) were exploring publication bias, indicating the publication bias were not being explored

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as mandatory. The terms of small study effect & publication bias were observed total 92 studies because 10 additional studies which did not explore publication bias but mentioned the term were available. Out of 93 studies, 82 (89.1%) studies used 'publication bias' alone as the most frequently used. There were only one study for 'small study effect' and two studies for both terms.

Among 82 studies which explored small study effect & publication bias, one was excluded for not reporting any method. Out of 81 of which methods to explore publication bias were observable, funnel plot alone were used in the most studies, 31 (38.3%), and the second most frequently used was the combination of funnel plot and Egger's test (10 studies, 12.3%). Nine (11.1%) studies reported the combination of funnel plot, Egger's test, and Begg's test, and another nine reported funnel plot plus others(e.g., trill and fill, fail-safe N).

Some studies only used statistical models: Egger's test alone in seven studies (8.6%), Egger's test plus Begg's test in six studies (7.4%), Begg's test alone in three studies (3.7%).

(4) Adjusting publication bias

Among the 170 studies selected for investigating current status, twenty six were excluded because study level data of meta-analyses were not available. The remaining 146 studies were found to include 345 meta-analyses, and among them meta-analyses with continous data without between study heterogeneity were select for exploring and adjusting publication bias, which left seventeen meta-analyses.

All authors of seventeen meta-analyses did not explore small study effect & publication bias or reported low possibility of them. However, the results of exploration showed nine out of seventeen presented possibility of small study effect. One of them were found not resulted from publication bias, however, in the other eight, it was possible the source of small study effect were publication bias.

All of eight meta-analyses were aim to examine the effectiveness of

interventions and the results showed significant effectiveness. However, in five of the eight, after adjusting publication bias, the confidence intervals of effect estimations were changed to include 0, therefore, the results became no longer significant. In other words, the studies which included those five meta-analyses came to be incapable of conclude the significant effectiveness of the interventions.

4. Discussion and conclusion

In this study, the methods for exploring and adjusting publication bias, which is one of the major issues in systematic review with meta-analyses, were reviewed with wide range. Futhermore, the current status of exploring publication bias were investigated in the publications of major journals for recent ten years, as well as the effect of publication on study results and conclusions by adjusting publication bias in meta-analyses.

Studies in which meta-analyses were performed for primary outcomes with ten or more randomized controlled trials were selected, but the result of investigating current status presents only about half of them conducted exploration. Moreover, funnel plot asymmetry have been found as the most frequently used to examine the possibility of publication bias, however, few of the studies have pay attention whether publication bias is really the source of asymmetry. Additionally, the sole use of funnel plots has been used more frequently than comprehensive investigation, while it is necessary to consider various methods of exploring publication bias and select the most proper ones in accordance with the context of meta-analyses to which methods are applied.

In sixteen of seventeen meta-analyses selected for exploring and adjusting publication bias, authors have reported no evidence of

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publication bias or have not explored it at all. However, the investigation of this study has found eight of seventeen analyses presented possibility of publication bias, and the study conclusions of five (29.4%) studies changed due to the probable publication bias.

The study findings suggest, it is useful to explore small study effect & publication bias when conducting systematic reviews with meta-analyses. Therefore, it is proposed to evaluate publication bias and adjust it using adequate methods in order to improve validity of study results.