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A SHORT NOTE ON DETECTION OF AND ADJUSTING FOR PUBLICATION BIAS IN META-ANALYSIS

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Funnel plots (i.e. plots of effect size estimates against sample size) can be useful to detect publication bias (Light and Pillemer, 1984; Egger, Smith, Schneider and Minder, 1997). Publication bias may seriously affect results of meta-analyses (eg. Begg and Berlin 1988). As precision of effect estimates is a function of sample size there is larger variation in studies with small sample sizes (Light and Pillemer 1984). Assuming that small sample size studies are as likely to produce small effect estimates and large effect estimates, a plot of estimates against sample size should be symmetrical and funnel shaped (Light and Pillemer 1984). A non-symmetrical plot may indicate a lack of studies with small effect estimates. The shape of the plot may be affected by several factors, such as the choice of the metric, the coding of the outcome or the choice of the weight on the vertical axis (inverse variance, inverse standard error, sample size etc.; Lau, Ioannidis, Terrin, Schmid and Olkin, 2006, Sterne and Egger 2001, Tang and Liu 2000). Asymmetry can be evaluated via visual inspection (Egger et al., 1997) but this might be misleading (Tang and Liu 2000) and detection of publication bias using funnel plots was found to have accuracy only near change (Lau et al. 2006). To counteract problems of subjective interpretation, formal tests of funnel plot asymmetry can be used. Commonly used tests are rank correlation test (Begg and Mazumdar 1994) and tests based on regression (e.g. Egger et al., 1997; Macaskill, Walter and Irwig, 2001). Regression methods perform somewhat better than the rank correlation method (Sterne, Gavaghan and Egger, 2000; Macaskill et al. 2001). Concordance between the different methods showed to be modest (Ioannidis and Trikalinos, 2007). In regression methods high type I error rates may be problematic (Macaskill et al. 2001; Peters, Sutton, Jones, Abrams and Rushton, 2006). The major concern about tests of asymmetry is, that high false-positive rates in the precence of heterogeneity of treatment effects (and thus effect estimates) across studies may arise (Sterne et al., 2000; Terrin, Schmid, Lau and Olkin, 2003). The *Cochrane Handbook for Systematic Reviews of Interventions* takes up a critical stance to the use of these tests (Higgins and Green, 2006). Strictly speaking, asymmetry of funnel plots shows whether small studies with little precision yield different results from larger studies with higher precision. Asymmetry may result from true bias (publication bias, retrieval bias, etc.) but may also reflect true differences between smaller and larger studies that arise from true inherent between-study heterogeneity. In case of heterogeneity (that is, when studies estimate different effects), the funnel plot itself is judged to be inappropriate (Terrin et al., 2003). To adjust meta-analysis estimates of effects, the trim and fill method can be used. This approach provides different estimators and methods (eg. Egger et al., 1997; Duval and Tweedie, 2000a, 2000b). When publication bias is present, the trim and fill method can give less biased estimates of true effects (Peters et al., 2006). However, when there is no publication bias and the between-study heterogeneity is large, this method can underestimate the true effect (Peters et al., 2007) and inappropriately adjust for publication bias where none exists (Terrin et al., 2003). In various meta-analysis scenarios Peters et al. (2006) found great variability in the performance of

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different trim and fill estimators and methods and recommend the use of the trim and fill method as a form of sensitivity analysis.

Altogether, asymmetrical funnel plot may reflect publication bias but also true heterogeneity. The trim and fill method is useful to give adjusted effect estimates within sensitivity analysis. An interpretation of asymmetrical funnel plots as clear evidence for publication bias as well as the interpretation of trim and fill estimates as unbiased estimates of true effects (i.e. unbiased by publication bias) should be given with some caution.

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