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Methodological overview: Meta-analyses of adverse effects data from case-control studies as compared to other observational studies

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Background: A diverse range of study designs are used in the evaluation of adverse effects in systematic reviews, including case-control studies. However, case-control studies have potential biases that may lead to divergent findings compared to studies that use other methods. The extent of any discrepancy or heterogeneity between the pooled risk estimates from case-control studies and other types of observational study designs is a key concern for systematic reviewers.

Objective: To ascertain whether the risk estimates from meta-analyses of case-control studies differ from those of other observational study designs.

Methods: Searches were carried out in 10 databases in addition to reference checking, contacting experts, and handsearching key journals and conference proceedings. Studies were included where a pooled relative measure of an adverse effect (odds ratio or risk ratio) from case-control studies could be directly compared with the pooled estimate for the same adverse effect arising from other types of observational studies. The potential discrepancy between the pooled odds ratios (OR) from meta-analyses of different study designs was checked by (i) quantitatively and graphically comparing the ratio of the pooled odds ratios from each study design, and (ii) comparing the separate point estimates and overlap in confidence intervals.

In order to quantitatively describe the extent of discrepancy between study designs, the ratio of odds ratios (ROR) was calculated by taking the pooled OR for the adverse outcome from one study design divided by the pooled OR for the adverse outcome from another study design.

Results: Eighty-two meta-analyses were included. Pooled estimates of harm from the different study designs had 95% confidence intervals that overlapped in 78/82 instances (95%). Of the 23 cases of discrepant findings with statistically significant harm identified in meta-analysis of one type of study design, but not with the other study design, 16 (70%) stemmed from elevated pooled estimates from case-control studies.

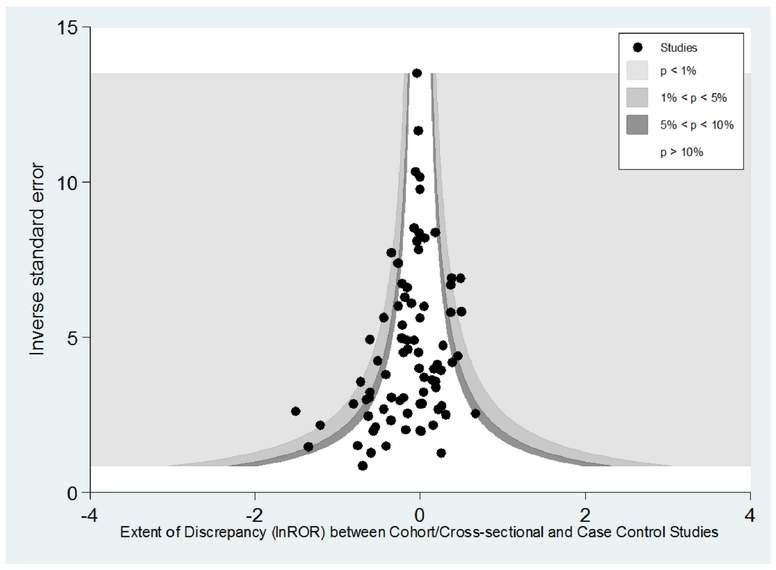

Figure 1: Funnel plot of distribution of RORs from meta-analyses of cohort/cross-sectional studies compared to case-control studies

There was associated evidence of funnel plot asymmetry consistent with higher risk estimates from case-control studies (Figure 1).

On average, cohort or cross-sectional studies yielded pooled odds ratios 0.94 (95% CI 0.88-1.00) times lower than that from case-control studies (Figure 2). Although the differences between study designs did not reach the conventional threshold of statistical significance, the low to moderate heterogeneity seen overall is an indicator that there may be a consistent pattern of variation between study designs.

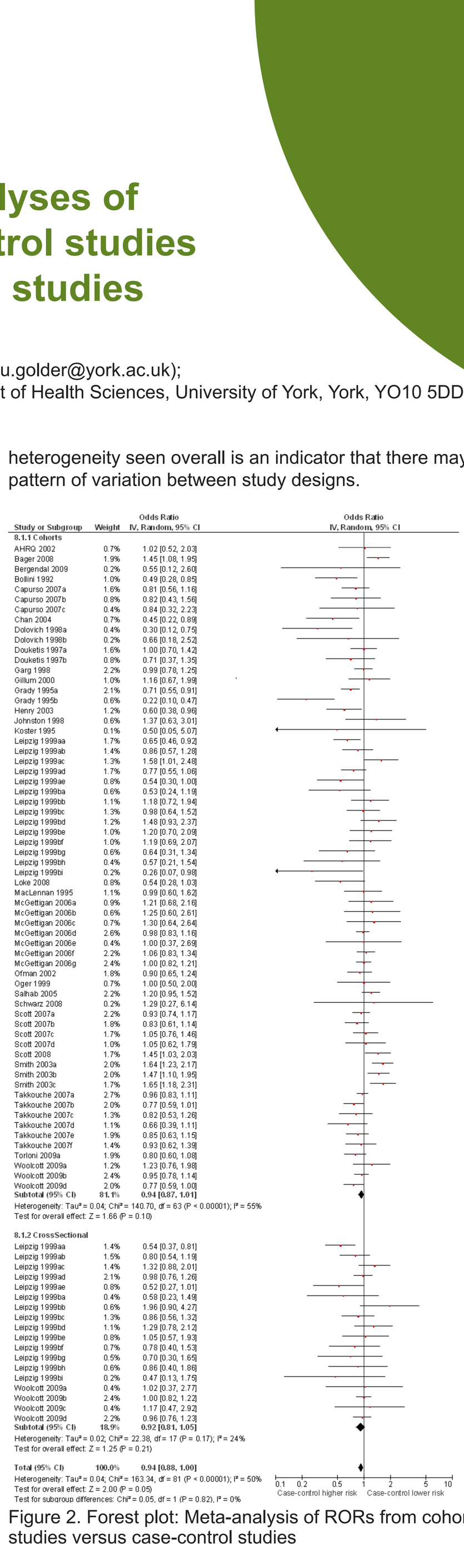

Figure 2. Forest plot: Meta-analysis of RORs from cohort/ cross-sectional studies versus case-control studies

Conclusions: Empirical evidence from this overview indicates that meta-analyses of case-control studies tend to give slightly higher estimates of harm as compared to meta-analyses of other observational studies.

An explanation for the tendency for slightly higher estimates of harm from case-control studies is difficult to ascertain. However it is impossible to rule out potential confounding from differences in drug dose, duration and populations when comparing study designs.

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