

Is nicotine replacement really ineffective? A reply to Stanley and Massey

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Drs Stanley and Massey ¹ used a series of meta-regression analyses of the Cochrane Library review of nicotine replacement therapy (NRT) for smoking cessation ², ³ to estimate what the effectiveness of NRT would be if there were no publication, reporting and small sample bias. They concluded NRT would not be effective. We believe this conclusion to be incorrect.

In their first analysis, the authors considered a subset of 46 studies at low risk of bias. Of these, 44 favored the intervention in that they report an estimated relative risk greater than 1. The authors used a meta-regression model assuming a linear relationship between the log-relative risk (log-RR) and its standard error (Figure, left panel), which they then extrapolated to the intercept, giving an estimated effect close to zero. This extrapolation yields an estimate not found in any of the individual studies.

We replicated their analyses and, as Stanley and Massey, and others have advocated ^{4, 5}, we did not assume a linear relationship and, in fact found a weighted quadratic relationship between log-RR and its standard error (Figure, right panel). This provides a better fit both visually and in the [Akaike Information Criterion](#) (23.7 vs 24.3). In this analysis, extrapolation to the intercept gives an estimated RR of 1.25 (95% confidence interval 1.19 to 1.32) which, though lower than the value of 1.6 given in the Cochrane Review ², is not trivial, considering the effects of smoking on health. For example, interventions that increase quit rates by even 5% have been shown to be more cost-effective than most health care interventions ⁶.

Stanley and Massey conclude that sufficiently powered studies with no methodological bias would find no effect of NRT, or that such studies have been done and they remain unpublished. Whilst not discounting the likely existence of some publication bias, we think it implausible that unpublished studies or substantial bias in those published could overturn the conclusion of efficacy derived from so many robust studies. For example, a recent very large study (NRT = 2022 and placebo = 2014 participants) replicated the efficacy of NRT in a real world setting ⁷. Also, NRT efficacy has been replicated more than all other treatments for addiction. For example, a prior review found that 102 of the 111 NRT RTCs (92%) in Cochrane found a higher rate of abstinence in the NRT condition ³.

In summary, we believe the results of Stanley and Massey may indicate that effect sizes in meta-analyses could be over-estimates but we do not believe their results are sufficient to abandon the confidence in the efficacy of NRT shown by previous meta-analyses ⁸ and adopted in multiple guidelines ⁹.

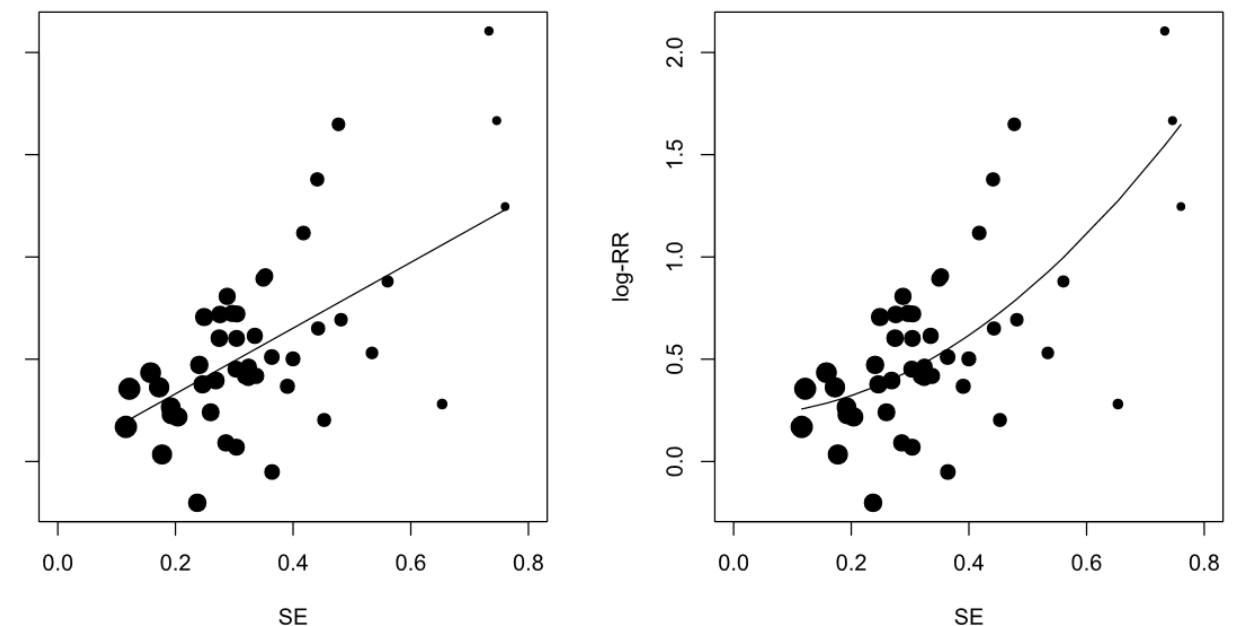


Figure: Funnel graph of NRT effect sizes among studies with low risk of bias assuming a linear pattern (left panel) vs allowing a quadratic pattern (right panel)

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