Journal of Clinical Epidemiology 79 (2016) 41–45

Journal of Clinical Epidemiology

Evidence of nicotine replacement's effectiveness dissolves when meta-regression accommodates multiple sources of bias

T.D. Stanley[a,b,*], Shelby Massey[c]

[a]Department of Economics, Hendrix College, 1600 Washington, Conway, AR 72032, USA
[b]Faculty of Arts and Education, Deakin University, 221 Burwood HWY, Burwood, Victoria 3125, Australia
[c]Oklahoma State University, College of Osteopathic Medicine, 1111 W. 17th St, Tulsa, OK 74107, USA

Accepted 9 March 2016; Published online 11 April 2016

Abstract

Objectives: To accommodate and correct identifiable bias and risks of bias among clinical trials of nicotine replacement therapy (NRT).

Study Design and Setting: Meta-regression analysis of a published Cochrane Collaboration systematic review of 122 placebo-controlled clinical trials.

Results: Both identified risks of bias and potential publication (or reporting or small sample) bias are associated with an increase in the reported effectiveness of NRT. Whenever multiple sources of biases are accommodated by meta-regression, no evidence of a practically notable or statistically significant overall increased rate of smoking cessation remains. Our findings are in stark contrast with the 50% to 70% increase in smoking cessation reported by the Cochrane Collaboration systematic review.

Conclusion: After more than 100 randomized clinical trials have been conducted, the overall effectiveness of NRT is in doubt. Simple, well-established meta-regression methods can test, accommodate, and correct multiple sources biases, often mentioned but dismissed by conventional systematic reviews.

Keywords: Meta-regression; Risks of bias; Publication bias; Nicotine replacement therapy; Egger regression; Precision-effect test

1. Introduction

Smoking tobacco is the leading cause of preventable death in the United States [1]. Yet, quitting smoking is difficult for those addicted to nicotine. A number of nicotine replacement therapies (NRTs) are available to help smokers quit, which the World Health Organization regards as essential medicine [2]. In general, NRTs are considered effective. The most recent and authoritative systematic review concludes that NRT increases "the rate of long-term quitting by approximately 50% to 70% regardless of setting" ([3], p. 23, Authors' Conclusions). Nonetheless, when meta-regression is used on all the NRT vs. placebo comparisons from this same Cochrane review, little evidence remains that NRT increases smoking cessation. Meta-regression analysis (MRA) can go beyond state-of-the-art systematic reviews by simultaneously accommodating both risks of bias and small sample, reporting, or publication bias.

Risks of bias refer to the routine assessment of potential limitations or weaknesses in how clinical trials are conducted [4]. Cochrane Collaboration systematic reviews are expected to code for these potential threats to the validity of randomized clinical trials (RCTs). Publication bias concerns the selective reporting of statistically significant findings [5–10]. It represents a different source of potential bias in RCTs, one, that is, expected to operate in a "positive" direction. Cochrane Collaboration systematic reviewers are also asked to assess the threat of publication bias.

Is NRT better than a placebo? Are there differences among the types of NRT? Are clinical trials selectively reported or published to show that NRT has statistically positive effects on smoking cessation? We find that when potential biases from multiple sources are simultaneously accounted for, statistical traces of NRTs effectiveness dissolve.

This study statistically analyzes 122 NRT trial results published in a Cochrane review ([3], Figure 2, p. 14). One hundred twenty of these findings come from NRT vs. placebo comparisons. The remaining two compare a combination of NRT to no NRT, "which did not affect the overall estimate" ([3], Figure 2, p. 13). We use all

* Corresponding author. Tel.: 501-450-1276; fax: 501-450-1400.
E-mail address: Stanley@hendrix.edu (T.D. Stanley).

http://dx.doi.org/10.1016/j.jclinepi.2016.03.024
0895-4356/

What is new?

Key finding

- When a multiple meta-regression of over 100 clinical trials of nicotine replacement therapy (NRT) allows for multiple sources of bias or risks of bias, no evidence of the effectiveness of NRT remains. This result is quite different from the 50–70% increase in quitting reported by the 2012 Cochrane Collaboration systematic review.

What this adds to what was known?

- When statistical significance is used as a criterion for suppressing studies, selecting which outcomes to report or for choosing which statistical analyses to perform, systematic reviews are likely to exaggerate clinical effects. This problem can be further exacerbated when poorly designed studies are able to find large effects. Simple meta-regression models that allow for several types of bias, test genuine effects beyond publication bias, and adjust findings accordingly revise previous authoritative assessments of the clinical effectiveness of NRT.

What is the implication and what should change now?

- Systematic reviewers need to do more than mention potential risks of bias, including publication, selective reporting, and small-sample biases. They must also control for these multiple sources of bias, explicitly and simultaneously, using a meta-regression or similar analysis. The clinical use of NRT should be reconsidered and further evaluated.

122 NRT effect sizes because they form the basis of the conclusion by Stead et al. [3], and we wish to introduce no selective reporting bias. In addition to risk ratios and their confidence intervals, Stead et al. [3] classify the risk of bias for each clinical trial of NRT and report the type of NRT used: patch, gum, nasal spray, lozenge, oral spray, and inhaler. We re-evaluate this Cochrane review using a meta-regression model that is capable of simultaneously filtering out potential biases and risks of bias. When multiple vectors for bias are explicitly allowed, clear evidence of the overall effectiveness of NRT disappears.

2. Methods

2.1. Meta-regression

MRA is used to allow multiple dimensions of NRT research to be considered simultaneously. Meta-regression allows us to accommodate the effects of: publication bias, reporting bias, small-sample bias, identified risks of bias, and heterogeneity, simultaneously, on NRT effectiveness. We also corroborate our multiple meta-regression findings by investigating subsets of high-quality research.

The simple Egger meta-regression has often been used to detect publication (or small sample or reporting) bias and for the presence of an authentic effect beyond publication bias (e.g., [5–8,10,11]).

$$y_i = \beta_0 + \beta_1 s_i + \varepsilon_i \quad (1)$$

where y_i is a reported log risk ratio (log *RR*), and s_i is its standard error. The Egger test for publication bias is a conventional regression *t*-test of H_0: $\beta_1 = 0$ [6]. If reported results are selected to be significantly positive, studies with small log *RR*s, small samples, or large standard errors, s_i, are more likely be suppressed, due to statistical insignificance. When published, they are more likely to have discrepant reporting of outcomes [12]. Such selective reporting, should it exist, causes the reported outcome measure to be correlated with its standard error, and this can be captured by the β_1 s_i term in Equation (1) [6–8,10,12]. It is also possible that this β_1 s_i term reflects some type of small-sample bias, but for our purposes, this distinction is immaterial. Bias is bias. Our objective is not to label the source of bias, but rather to accommodate and thereby filter out any bias, regardless of its source. The "precision-effect test" examines whether there is a genuine overall effect beyond the reach of potential contamination from publication, reporting, or small-sample bias—H_0: $\beta_1 = 0$ in Equation (1) [8,10]. Simulations show that this precision-effect test has considerable statistical power to detect a genuine effect should one exists [8,13,14].

Because different trials use different sample sizes, there are considerable differences in how accurately each log *RR* is estimated. To accommodate this heteroscedasticity, meta-regression model (1), above, is routinely estimated using weighted least squares (WLSs), with $1/s_i^2$ as the weight. This unrestricted WLS meta-regression approach is somewhat different than either fixed- or random-effects meta-regression [15]. Stanley and Doucouliagos [16] show that this unrestricted WLS approach statistically dominates random-effects meta-analysis when there is publication bias and is as good as random-effects when there is no publication selection bias.

Meta-regression model (1) is easily expanded to allow for differential effects from other risks of bias (or study quality) and from different types of NRT [5,9,10].

$$y_i = \beta_0 + \beta_1 s_i + \sum \alpha_k Z_{ki} + \varepsilon_i \quad (2)$$

where the Z_{ki}s are indicators of risks of bias and binary (0/1) variables for different types of NRT. We also investigate subsets of trials with higher quality or lower risks of bias, separately.