
# Reply to RB Yarandi



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## Effect of folate supplementation on insulin sensitivity and type 2 diabetes: a meta-analysis of randomized controlled trials

Dear Editor:

I read with great interest the recent article by Mads Vendelbo Lind et al. (1) published in the January 2019 issue of *The American Journal of Clinical Nutrition*, entitled "Effect of folate supplementation on insulin sensitivity and type 2 diabetes: a meta-analysis of randomized controlled trials". I would like to congratulate the authors for writing a high-quality scientific paper, as I assessed its methodological quality using a 16-item AMSTAR2 (2) appraisal tool. According to AMSTAR2, the study scored all 16 items and is classified as high quality.

Most review studies lose points from items related to risk of bias, heterogeneity, and publication bias assessment while these items were appropriately analyzed and considered in the paper. Still, there are some points that I would like to mention.

Publication bias was checked through Egger's regression and also the Funnel plot, whereas no remedy was considered in terms of significant results (e.g., fasting insulin), such as the trim-and-fill method of bias adjusting (3). In addition, to evaluate clinical significance, prediction interval (PI) was proposed in contrast to statistical significance presented as CI. I suggest that the authors calculate PI to evaluate clinical significance (4) especially when borderline significant CIs exist, such as the case of 'folate plus vitamin B12 with/without B6', for which the pooled effect size was estimated to be −0.18 (95% CI: −0.31, −0.04).

In conclusion, this systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

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## Reply to RB Yarandi

Dear Editor:

We thank Dr Yarandi for the interest in our recent publication (1) and the kind words regarding the quality of the study. As suggested, we performed a trim-and-fill analysis of the main results (2). This analysis showed no overall difference in the effect on fasting glucose, HOMA-IR and glycated hemoglobin (HbA1c), suggesting no small-study bias in these measures. However, for fasting insulin heterogeneity small-study effects were observed, and the trim-and-fill analysis attenuated the overall effect size considerably (**Table 1**). This confirms, as stated in the article, that the results should be interpreted with care. Additionally, we do not actually know how well filled studies approximate reality and estimates from this method should be interpreted with great caution (2,3). The results from the trim-and-fill analysis also further support the proposition in the article of the value of assessing glucose homeostasis and type 2 diabetes outcomes from previously conducted randomized controlled trials of folate supplementation. This could potentially overcome the uncertainty in the results reported in our analysis.

Dr Yarandi also recommended the use of prediction intervals. These have been reported in **Table 2**. The prediction interval helps in the clinical interpretation of the results when there is considerable heterogeneity/variability in the results of the original studies (4). However, in many of our analyses, such as for fasting glucose and HOMA-IR, little heterogeneity was found, and thus the prediction intervals resemble the confidence intervals. In line with our findings for the trim-and-fill analysis, the prediction intervals for fasting insulin show significant heterogeneity between studies, again highlighting the need to interpret these results with care.

In summary, the additional analyses underscore the original results as well as the need for careful interpretation of results when large

**TABLE 1** Trim-and-fill analysis of the main results

| | Effect size (95% CI) | Estimate of number of missing studies | $I^2$, % | *P* value |
|---|---|---|---|---|
| Fasting glucose | −0.03 (−0.10, 0.04) | 2 | 12 | 0.35 |
| Fasting insulin | −5.10 (−13.67, 3.46) | 5 | 69 | 0.24 |
| HOMA-IR | −0.57 (−0.76, −0.37) | 0 | 0 | <0.001 |
| HbA1c[1] | −0.02 (−0.24, 0.19) | 1 | 40 | 0.82 |

[1]HbA1c, glycated hemoglobin.

  