Dear Editor,
Please find enclosed the edited manuscript in Word format (file name: 5663-review.doc).

Title: Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. *(invited review article – author ID 00031835)*

Author: Theodore Lytras, Georgios Nikolopoulos, Stefanos Bonovas

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 5663

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(i) Regarding the proposed subgroup analysis of statins in observational studies by lipophilicity, we avoided to perform such an analysis because the available data from the included studies were scarce. In particular, we retrieved information to estimate the effect on colorectal cancer, by lipophilicity, in only 5 case-control studies (out of 19) and not in a single cohort study (out of 13). As a result, there is a significant potential for selective outcome reporting bias, which we cannot credibly evaluate and control for, in such an analysis.

(ii) The proposed subgroup analysis of statins in observational studies by tumor location, would similarly be prone to outcome reporting bias. We did, however, include such an analysis in the revised manuscript, as relevant data were available from 5 case-control studies (out of 19) and 6 cohort studies (out of 13). As noted in the manuscript, we found a statistically significant effect of statins on rectal cancer under a random-effects assumption (RR=0.78, 95% CI: 0.62–0.97), but we believe this result should be interpreted with great caution.

(iii) As suggested, we specifically addressed the role of socioeconomic status as a confounder in the observed effects of statins on colorectal cancer ("Discussion" section, page 18).

(iv) Regarding the proposed subanalysis for studies presenting results of long-term use of statins, beyond the follow-up periods in RCTs; indeed an analysis with longer follow-up would be expected to detect more colorectal cancer cases and thus have increased power to detect any statin effect. However, after the trial period ends, most trial patients usually receive open-label statin treatment. Thus any differences between the two arms may be blunted, and bias may be introduced in the result.

3 References and typesetting were corrected

Thank you again for considering our manuscript for publication in the *World Journal of Gastroenterology.*

Sincerely yours,

Theodore LYTRAS, MD, MPH
Department of Occupational and Industrial Hygiene
National School of Public Health
11521 Athens, Greece

Fax: +30-210-6412059
E-mail: thlytras@gmail.com