Competing Interests

The author declares no competing interests.

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In Reply:

We thank Dr. Yu *et al.*, and Dr. Pace for their interest in our meta-regression analysis of the relationship of duration of exposure to the risk of nitrous oxide (N_2O)–induced postoperative nausea and vomiting.[1]

Among the trials included in our meta-analysis, almost all delivered between 60 and 70% N_2O to their treatment arms. Only two small studies (Mraovic *et al.* [2008] who administered either 50 or 70% N_2O, and Sengupta and Plantevin [1988] who administered 33% N_2O) varied this. Therefore, the possibility of a concentration–response relationship was not investigated by us. We considered that patient age and sex were important confounding covariates to include in our analysis, but did not consider there to be sufficient data to allow us to investigate type of surgery as an additional covariate. The influence of type of surgery on postoperative nausea and vomiting risk is still debated, and a rationale for a differential effect of nitrous oxide in specific surgeries is unclear.[2] Statistical authorities have cautioned against the dangers of increased Type 1 error from excessive zeal in seeking relationships between variables and endpoints due to the *post hoc* nature of meta-regression analyses.[3]

Dr. Pace has taken the trouble to check our findings against the data in table 1 in our article. In addressing his letter, we have found typographical errors in table 1 we overlooked at proofreading. The data for the treatment and control arms in the study by Bloomfield *et al.* (1997) are reversed in table 1 in the article, but not in our database. This explains Dr. Pace's finding that some meta-regression models produce nonsignificant results for the primary endpoint we studied using the data in this table. We sincerely apologize for the confusion this has caused. The correct data, as indicated in the accompanying Erratum, are as follows.

Bloomfield (1997): Non-N_2O Group 12/60 (20); N_2O Group 26/59 (44)
Eger (1990): Non-N_2O Group 63/137 (46)
Myles (2007): Non-N_2O Group 102/1,015 (10)

Our Microsoft Excel and STATA 12.0 database did not contain this error. The results for statistical significance in our article are correct, and the point estimate for the study by Bloomfield *et al.* (risk ratio = 2.2) is correctly indicated in figures 2 and 3.[1] We conducted meta-regression using the method of moments of Der Simonian and Laird. The relationship of duration of exposure to the risk of nitrous oxide-induced postoperative nausea and vomiting remains statistically significant ($P < 0.05$) if any of the alternative models available in STATA 12.0 are used instead. These are the residual maximum likelihood method (with or without the Knapp–Hartung modification, which reduces false positive findings),[4] or with the empirical Bayesian method (for which the Knapp–Hartung modification is unnecessary).[5]

Higgins and Thompson have written on the limitations of meta-regression that increase the risk of Type 1 error, which we have minimized in our analysis by applying random effects analysis and avoiding *post hoc* "data dredging" of multiple covariates.[3] As the primary covariate of interest in our study, time was prespecified, which they recommend. Our meta-regression was not secondary to the overall meta-analysis shown in figure 3. Higgins and Thompson discussed the potential problem of "aggregation" or "ecological" bias when averages of patient characteristics in each trial (*i.e.*, time, in our study) are used as covariates, about which Dr. Pace has expressed concern. However, given the wide range of duration of nitrous oxide exposure and of magnitude of the treatment effect across the 29 studies in our review, we believe it unlikely that the relationship we have found is spurious, particularly when the findings of the several large, adequately powered trials on this subject, and our alternative mechanistic hypothesis, are considered.

Competing Interests

The authors declare no competing interests.

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ERRATUM

Nitrous Oxide–related Postoperative Nausea and Vomiting Depends on Duration of Exposure: Erratum

In the article beginning on page 1137 of the May 2014 issue, typographic data errors exist in table 1, in the two right-most columns. The correct data are as follows:

Table 1. List of Eligible Included Studies

	Anesthetic				PONV/*n* (% Incidence)	
First Author and Ref	Non-N_2O Group	N_2O Group	Type of Surgery	Duration (min)	Non-N_2O Group	N_2O Group
Eger[34]	Iso ± Fent	N_2O-Iso ± Fent	Various	178	63/137 (46)	64/133 (48)
Bloomfield[42]	Iso-Alfent	N_2O-Iso-Alfent	Extraabdominal	139	12/60 (20)	26/59 (44)
Myles[46]	Various	N_2O-Various	Major surgery	222	102/1,015 (10)	229/997 (23)

Alfent = alfentanil; DC = day case/ambulatory surgery; Des = desflurane; Enf = enflurane; Fent = fentanyl; Iso = isoflurane; Morph = morphine; N_2O = nitrous oxide; PONV = postoperative nausea and vomiting; Prop = propofol; Remi = remifentanil; Sevo = sevoflurane; Sufent = sufentanil.

Reference

Peyton PJ, Wu CY: Nitrous oxide–related postoperative nausea and vomiting depends on duration of exposure. Anesthesiology 2014; 120:1137–45