

Competing Interests

The author declares no competing interests.

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References

1. Peyton PJ, Wu CY: Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. *ANESTHESIOLOGY* 2014; 120:1137–45
2. Stijnen T, Hamza TH, Ozdemir P: Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med* 2010; 29:3046–67
3. Viechtbauer W: Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36:1–48
4. Guolo A, Varin C: The R package metaLik for likelihood inference in meta-analysis. *J Stat Softw* 2012; 50:1–14
5. Luo S, Chen Y, Su X, Chu H: mmeta: An R package for multivariate meta-analysis. *J Stat Softw* 2014; 56:11
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009; 339:b2700
7. Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E; ENIGMA Trial Group: Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. *ANESTHESIOLOGY* 2007; 107:221–31
8. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI; Anti-Lymphocyte Antibody Induction Therapy Study Group: Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: Ecological bias rears its ugly head. *Stat Med* 2002; 21: 371–87
9. Riley RD, Lambert PC, Abo-Zaid G: Meta-analysis of individual participant data: Rationale, conduct, and reporting. *BMJ* 2010; 340:c221

(Accepted for publication August 21, 2014.)

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 (N₂O)–induced postoperative nausea and vomiting.¹

Among the trials included in our meta-analysis, almost all delivered between 60 and 70% N₂O to their treatment arms. Only two small studies (Mraovic *et al.* [2008] who administered either 50 or 70% N₂O, and Sengupta and Plantevin [1988] who administered 33% N₂O) 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-N₂O Group 12/60 (20); N₂O Group 26/59 (44)

Eger (1990): Non-N₂O Group 63/137 (46)

Myles (2007): Non-N₂O 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.

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The authors declare no competing interests.

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References

1. Peyton PJ, Wu CY: Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. *ANESTHESIOLOGY* 2014; 120:1137–45
2. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD,

Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR; Society for Ambulatory Anesthesia: Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014; 118:85–113

3. Thompson SG, Higgins JP: How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; 21:1559–73
4. Higgins JP, Thompson SG: Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004; 23:1663–82
5. Harbord RM, Higgins JPT: Meta-regression in stata. *Stata J* 2008; 8:493–519

(Accepted for publication August 21, 2014.)

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

First Author and Ref	Anesthetic		Type of Surgery	Duration (min)	PONV/h (% Incidence)	
	Non-N ₂ O Group	N ₂ O Group			Non-N ₂ O Group	N ₂ O Group
Eger ³⁴	Iso ± Fent	N ₂ O-Iso ± Fent	Various	178	63/137 (46)	64/133 (48)
Bloomfield ⁴²	Iso-Alfent	N ₂ O-Iso-Alfent	Extraabdominal	139	12/60 (20)	26/59 (44)
Myles ⁴⁶	Various	N ₂ O-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; N₂O = nitrous oxide; PONV = postoperative nausea and vomiting; Prop = propofol; Remi = remifentanyl; Sevo = sevoflurane; Sufent = sufentanyl.

Reference

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