Nitrous Oxide–related Postoperative Nausea and Vomiting Depends on Duration of Exposure: More Questions than Answers

To the Editor:

We have read the recent article by Peyton and Wu[1] with great interest, which suggested nitrous oxide–related postoperative nausea and vomiting (PONV) was correlated with the length of time exposed to nitrous oxide. Their excellent meta-analysis on this important subject deserves applause. However, we would like to add some comments to emphasize a few important issues.

First, the concentrations of inhaled nitrous oxide were ignored in the current analysis, which may have a confounding influence on the relationship between the incidence of PONV and duration of exposure to nitrous oxide besides patient sex, age, and duration of anesthesia. In fact, several studies included in this meta-analysis observed different concentrations of inhaled nitrous oxide and showed that nitrous oxide increased the incidence of PONV in a dose-dependent manner.[2–4] Both duration of exposure to nitrous oxide and concentrations of inspired nitrous oxide may be significant covariates in the incidence of PONV. Therefore, it is necessary to rule out the influence of concentrations of inhaled nitrous oxide on PONV when determining whether duration of exposure to nitrous oxide was related to the incidence of PONV.

Second, the authors stratified studies based on duration of anesthesia and suggested that the effect of duration of anesthesia on nitrous oxide–induced PONV may instead simply reflect the invasiveness and magnitude of the surgery. However, the type of surgery *per se* may also be a confounding covariate. In this meta-analysis, more than one-third of the studies involved gynecologic surgery with or without laparoscopy, including a large sample study[5] in which up to 45.1% was gynecologic surgery. Duration of anesthesia in this type of surgery was usually no more than 1 to 2 h, while nongynecologic surgeries in remaining studies were almost more than 1 to 2 h except orthopedic surgery in two studies and day case/ambulatory surgery laparoscopy in one study less than 1 h. That is to say, a big difference exists in the types of surgery among groups stratified by duration of anesthesia. Although whether the type of surgery identified as a risk factor of PONV is still somewhat controversial, increased incidence of PONV has been demonstrated in the gynecologic, laparoscopic, and middle-ear surgeries.[6–8] Thus, the heterogeneity of the type of surgery may have tempered their conclusion.

Though this meta-analysis brings us closer to draw overall conclusion, it may only be regarded as an interim analysis toward reaching a final answer. Further studies are still needed to clarify the relationship between duration of exposure to nitrous oxide and the incidence of PONV.

Competing Interests

The authors declare no competing interests.

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Questioning a Relationship between Nitrous Oxide Duration of Exposure and Postoperative Nausea and Vomiting

To the Editor:

Peyton and Wu[1] have recently published a systematic review with meta-analysis that identified a relationship between the risk of postoperative nausea and vomiting within the first 24 h and the duration of the intraoperative exposure to nitrous oxide. Using data from over 10,000 patients in 29 randomized controlled trials of nitrous oxide administration (Peyton and Wu[1]; table 1),

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Table 1. Meta-analysis/Meta-regression of Nitrous Oxide Duration and PONV

Model	Effect Size	Method	R Package	Effect Size Estimate	95% CI	95% PI
Pairwise	OR	GLMM	metafor	1.23	0.96–1.59	0.44–3.42
Pairwise	RR	LME	metafor	1.14	0.94–1.38	0.58–2.24
Pairwise	RR	Higher order	metaLik	1.14	0.97–1.34	NA
Pairwise	RR	Bayesian	mmeta	1.14	0.86–1.52	NA
Regression (effect at 2 h)	OR	GLMM	metafor	1.10	0.84–1.44	0.49–2.48
Regression (effect at 2 h)	RR	LME	metafor	1.02	0.84–1.25	0.63–1.67

Bayesian = empirical Bayesian regression; GLMM = generalized linear mixed effects regression (conditional exact likelihood); higher order = higher order likelihood regression estimation; LME = linear mixed effects regression; NA = not available; OR = odds ratio; PI = prediction interval; PONV = postoperative nausea and vomiting; RR = risk ratio.

a meta-regression analysis found a statistically significant linear relationship between the increasing log risk ratio (RR) and increasing anesthesia/surgery duration with an estimated increased RR of 20% per hour of exposure after the first 45 min. They also reported a pairwise meta-analysis showing an increased RR of postoperative nausea and vomiting for nitrous oxide regardless of duration. I raise two concerns about their statistical analysis: (1) a failure to identify the claimed relationship using other meta-analytic models; and (2) the possibility of ecological (aggregation) bias.

Peyton and Wu performed their meta-analysis/meta-regression using the statistical software STATA 12 choosing a random effects analysis with inverse variance weighting (DerSimonian and Laird method of moments). Their original data were subjected to a secondary analysis using four alternative statistical approaches in the R statistical platform—namely (1) generalized linear mixed effects regression (conditional exact likelihood),[2] (2) linear mixed effects regression (restricted maximum likelihood estimation),[3] (3) higher order likelihood regression estimation,[4] and (4) empirical Bayesian regression (exact posterior inference).[5] All analyses were random effects or mixed effects models because of the considerable statistical heterogeneity; both RR and odds ratio effect sizes were used. Both a pairwise analysis and when possible a meta-regression was estimated by each statistical approach. Partial results are shown in table 1 with display of the effect size, 95% CI and 95% prediction interval. The 95% prediction interval estimated where 95% of true outcomes will fall in future studies. For meta-regression models, the effect size was predicted at 120 min. Full details of the data set, the statistical software, the function calls, and the statistical output are presented in Supplemental Digital Content 1, http://links.lww.com/ALN/B97.

No regression coefficient in any model reached statistical significance. For the pairwise comparisons, the RR effect sizes were 1.14 with the lower bounds of the 95% CI approaching the line of identity (table 1), similarly for the odds ratio effect size. For methods offering prediction intervals, future studies will have a wide range of values. For the regression predictions of the risk of postoperative nausea and vomiting at 120 min, effect sizes ranged from 1.02 to 1.19; the 95% CI extended widely across the line of identity. A sensitivity analysis of meta-analytic results using other statistical models has been recommended to explore the vulnerability of estimates to inherent assumptions.[6] In the data of Peyton and Wu, any effect of nitrous oxide is not sufficiently robust to show clear evidence of effect in alternative statistical methods.

Peyton and Wu used a study level covariate in their meta-regression. Specifically, RR was regressed on the mean or median anesthesia/surgery time for all patients reported in each randomized controlled trial. Thus, the average of the sample (nitrous oxide exposure in an randomized controlled trial) was assumed to provide inferences about the likelihood of the response of a patient at an individual level. Using a study-level covariate is of course acceptable when patients are randomly assigned to receive or not receive nitrous oxide. But patients were not randomized to receive nitrous oxide for varying durations—a function of the surgical procedure. This duration could vary widely in studies. For example, in one of the largest studies (Myles *et al.*),[7] the median anesthesia duration was 3.1 h with interquartile range (2.3 to 4.6); 25% of patients were exposed for less than 2.3 h and 25% were exposed for more than 4.6 h.

Stated formally, the correlation of aggregate quantities is not equal to the correlation of individual quantities. It is this assumption that constitutes the ecological fallacy/bias. This is not a hypothetical risk; "ecological bias rears its ugly head" in meta-regression.[8] Only by using individual patient data in meta-analysis and meta-regression can the possibility of ecological bias be excluded. Using individual patient data, it has been demonstrated that ecological bias can either conceal a real treatment interaction[8] or mistakenly indicate a clinically important treatment effect.[9]

There are clearly data to question the benevolence of nitrous oxide. But the case against nitrous oxide remains incompletely proved.

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.