

Competing Interests

The authors declare no competing interests.

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In Reply:

We appreciate the important comment by Moreault *et al.* on our article, “Protective Ventilation during Anesthesia: Is It Meaningful?”¹ We agree fully with the opinion that a low tidal volume should be based on ideal body weight to avoid harmful stress and strain to the lungs during anesthesia. This is even more important during one-lung ventilation. Ideally, the tidal volume should be adjusted to the size of the ventilated lung, but without a simple recording of lung volume, ideal body weight is a reasonable alternative. However, we also believe that an appropriate positive end-expiratory pressure is a prerequisite when using a low tidal volume, whatever the calculation method of ideal body weight. We find the method proposed by the authors commendable and indeed easy to remember as most anesthesiologists already are familiar with the method for calculating body mass index.

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Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II (ENIGMA II) Revisited: Patients Still Vomiting

To the Editor:

We read the secondary analysis of the Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II (ENIGMA II) trial for severe postoperative nausea and vomiting (PONV) with great interest.¹ Because PONV remains an often-cited risk in using nitrous oxide,² the investigation of methods to mitigate PONV using existing data generated from randomized controlled trials is an important undertaking. We wish to respond to this thorough reanalysis.

The authors used a retrospective propensity score approach to investigate the effects of antiemetic prophylaxis on the nitrous oxide and non-nitrous oxide arms. The well-recognized limitations of this approach were openly acknowledged in the publication, including the inability to control for hidden covariates and the need to truncate available data.³ In the abstract, the authors conclude that the emetogenic effects of nitrous oxide are near eliminated by the addition of antiemetics. However, the results from the propensity score-matched analysis do not seem to support this conclusion, as the nitrous/antiemetic group had statistically higher odds of PONV compared with the non-nitrous/nonantiemetic group. In addition, administration of antiemetic prophylaxis among participants who did not receive nitrous oxide counterintuitively increased the odds of PONV. Although various clinical and scientific reasons may be hypothesized to explain this phenomenon, perhaps the simplest hypothesis is the presence of hidden covariates. Therefore, it is our opinion that the conclusion of negating PONV with antiemetics when nitrous is used is not supported by the results of this retrospective analysis, and the use of propensity score matching in this instance may not have resulted in a balanced comparison.

In light of the aforementioned results, another statistic (risk ratio, 0.74 [95% CI, 0.63 to 0.84]; $P < 0.001$) is quoted in the report¹ to support the conclusion that PONV is not increased when antiemetics are used in conjunction with nitrous oxide. This risk ratio does not appear among the results generated by propensity score matching but appears to be the result of a subgroup analysis for the PONV outcome in the original ENIGMA II report for patients who received antiemetic prophylaxis.⁴ However, the lack of blinding of attending anesthesiologists to treatment allocation may have introduced selection bias into antiemetic prophylaxis, a possibility supported by the statistically significant difference in antiemetic administration between the nitrous and non-nitrous arms. If selection bias were present in antiemetic administration, the efficacy of this originally randomized subgroup analysis to equalize hidden covariates may have been compromised.⁵

Although this secondary analysis¹ of antiemetic prophylaxis on PONV has important limitations, we believe that

the authors' dose-effect analysis of nitrous oxide on PONV is very clinically relevant, although not emphasized in the abstract or report. The authors note in the report that nitrous oxide, when used for less than 2 h, did not seem to result in added PONV compared with the non-nitrous arm. This observation is congruent with existing literature,⁶ is a randomized comparison that carries with it the methodologic robustness of the original ENIGMA II trial, and has applicability in a wide variety of clinical settings. In closing, we thank the authors for their thorough reanalysis and presentation of the ENIGMA II data for the PONV outcome. This secondary analysis is revealing, but the conclusion that prophylaxis nearly eliminates PONV seems untenable.

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In Reply:

We thank Li *et al.* for these perspectives. We agree that nonrandomized studies have greater risk of bias and confounding, and the results may therefore be misleading. This certainly applies to studies using propensity-based

Table 1. The Incidence (%) and Relative Risk of Postoperative Nausea and Vomiting in Patients Receiving Nitrous Oxide for Major Surgery in the ENIGMA II Trial¹

	Nitrous Oxide (n = 3,483)	No Nitrous Oxide (n = 3,509)	Relative Risk (95% CI)	P Value
Overall	14.5%	10.8%	1.35 (1.19–1.53)	<0.001
Antiemetic prophylaxis				
No	16.6%	9.6%	1.75 (1.43–2.13)	<0.001
Yes	13.1%	11.7%	1.12 (0.95–1.32)	0.18

The risk estimate differed according to use of antiemetic prophylaxis; interaction *P* value 0.001.

ENIGMA II = Evaluation of Nitrous Oxide in the Gas Mixture for Anesthesia II.

methods. We would first like to point out that in their letter Li *et al.* state we used propensity score matching. In fact, we actually used inverse probability of treatment weighting. These are distinct methods (although both based on propensity scores) and estimate different quantities (effect of treatment overall *vs.* effect of treatment in the treated).

More importantly however, our comments regarding the risk mitigation associated with antiemetic prophylaxis in patients exposed to nitrous oxide were based not on the secondary analysis referred to by Li *et al.* but in a preplanned secondary analysis of the original large randomized trial.¹ Relevant, expanded details are provided in table 1. The emetogenic effect of nitrous oxide was less apparent in those who received prophylactic antiemetics before the end of surgery compared with those who did not. The interaction *P* value was 0.001, indicating that there was a statistically significant differential effect between these two subgroups. We acknowledge that use of antiemetic prophylaxis was left to the discretion of the attending anesthesiologist, but such use was more likely in those with more risk factors for postoperative nausea and vomiting (PONV; as we reported in our publication).² That is, there was a selection bias, but it would underestimate the protective effect of antiemetic prophylaxis because such use was higher in those with greater risk of PONV. We therefore stand by our conclusion that PONV prophylaxis near-eliminates the risk of nitrous oxide-induced severe PONV after major surgery.

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