PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mediation of Smoking-Associated Postoperative Mortality by perioperative complications in Veterans undergoing Elective Surgery: Data from Veterans Affairs Surgical Quality Improvement Program (VASQIP)
AUTHORS	Singh, Jasvinder; Hawn, Mary; Campagna, Elizabeth; Henderson, William; Richman, Joshua; Houston, Thomas

VERSION 1 - REVIEW

REVIEWER	David Warner Professor of Anesthesiology Mayo Clinic US No conflicts
REVIEW RETURNED	09-Dec-2012

THE STUDY	No supplemental documents provided
GENERAL COMMENTS	General Comments This is an interesting and valuable analysis using a well-characterized dataset. The mediational analysis is accomplished using standard techniques and is well-described, although I am curious about the notation in Table 4 that the proportion mediated is “unstable” – is this a critique of the general method, or a description of something specific to this analysis? One interesting result of this analysis that deserves comment is that the three potential mediators of the association between smoking status and increased mortality in fact are responsible for a relatively minor proportion of the relationship in adjusted analysis. Could you please mention 1) what other mediators you speculate might be involved, and 2) further make the point that the difference between adjusted and unadjusted analysis suggests that smoking is a marker for several other factors that determine outcome (only some of which you likely measured). You already state this to some extent but I think the point that smoking status should alert practitioners to other factors which may need to be addressed is important. The related point that you could make in the conclusion is that any observational study that examines the relationship between smoking status and outcomes must recognize that smoking status can be associated with a wide range of other factors that may be causal. Finally, it would be helpful to provide a table classifying causes of death in both smokers and inonsmokers, including the absolute mortality rates for each, as well as the absolute rates for each of the three complications as well as the composite outcome. Specific Comments

	P7, l36ff – I'm not sure I agree with this rationale. Smoking could never have a "direct" effect, unless somehow the smoke constituents had some direct toxic effect. It would seem that smoking must always have an effect on mortality via some mediator (i.e., smoking-related pathology), so the question is not whether there is a "direct" effect, but rather what might mediate increases in mortality risk (e.g., events related to the chronic underlying diseases associated with smoking vs. these three particular postoperative events). I would think that regardless the approach is to 1) intervene to stop smoking, and 2) treat to the best of our ability the smoking-related pathology. P8, l27 – again conceptually I think you are trying to determine what proportion of mortality can be associated with the particular putative mediators you examined…. P11, l12 – there are many variables available in this dataset – please justify why you chose these particular adjustor variables. P12, l16 – careful with terminology – would rather use "association of smoking" rather than "effect" so as not to imply causal relationship….I understand that this may be how Baron and Kenny put it, but given that there are a large number of unmeasured potential confounders that may also be important , I would be cautious…. P12, l44 – please be more precise than "significantly smaller" P14, l55 – refer to table 4 here P16, l12 – but statistically I doubt if there is a significant difference between the coefficients for 6 month and 1 year mortality. P16, l18 – wording of "attenuated significantly"? P16, l25 – include a few refs here P16, l32 – grammer P16, l51 – but presumably such attention was paid to both smokers and non-smokers, correct? Similar arguments could be made for patients with pulmonary disease. And cardiac factors were an important cause of mortality according to your analysis – it's just that it didn't matter much whether they smoked or not… P17, l8 – I agree, but reference. P17, l12 – For example do you think that smoking status causes "upcoding" of ASA status? And in following line, again be careful about "direct" effects – hard to see how there could be effects apart from the "lifetime exposure" to smoking. I think this is a better way of looking at this (the way that you do in the following paragraph). Can you further explain the notation in table 4 that the proportions are "unstable"?

REVIEWER	Paulo Vitoria, PhD Health Sciences Faculty - Medical Department Universidade da Beira Interior Portugal
REVIEW RETURNED	19-Dec-2012

THE STUDY	Participants are divided in two groups: current smokers and never-smokers. Never-smokers were patients who had no smoking in the prior year and zero (or missing) pack years. Does this operationalization allow the classification of "never smokers"? Why not to use "no-smokers"
RESULTS & CONCLUSIONS	Table 1 - why not to present a test of significance in the table to better assess the differences reported?
GENERAL COMMENTS	Nice paper. Iwould like to congratulate the authors. The title… I'm not comfortable with this title. The main variables are

	mortality, and perioperative complications and smoking. And the title suggests that the object of analysis is the program and not the veterans. I would suggest a more direct title (Mediation of smoking-associated post-operative mortality by postoperative complications in VASQIP veterans undergoing surgery).

REVIEWER	Uyen-Sa D. T. Nguyen, DSc, MPH Research Assistant Professor Boston University School of Medicine Clinical Epidemiology Research & Training Unit USA
REVIEW RETURNED	03-Jan-2013

THE STUDY	The mediation analysis by the authors is very important and very clinically relevant. My understanding of Barron and Kenny's approach to mediation analysis in their classic original papers was that for linear regression, i.e., estimating of effect on an additive scale. Although Mackinnon and Dwyer, as cited by the authors, suggested a method of transforming the betas when using logistic regression for dichotomous mediators or outcomes, (i.e., standardizing the regression coefficients from logistic regression) prior to estimating mediation, it would be helpful to a reader to see the authors present a brief illustration. For example, the authors could present both unstandardized and standardized coefficients in their tables and results section, and illustrate with an example of how they applied Mackinnon and Dwyer's method to standardize a coefficient and how they estimated direct and indirect effect using these standardized coefficients. As currently presented, it was difficult to understand why the unstandardized estimates of total, direct and indirect effects in the tables and Figure do not quite add up, as was of proportions mediated. While providing estimates of mediating effect from the coefficients of logistic regression analyses and testing whether these coefficients statistically differ from 0 may inform whether mediation may occur statistically, it may not translate as intuitively to the size of direct or indirect effects from estimates of Odds Ratios (by exponentiating these coefficients). However, this may just be my own subjective opinion as I am more familiar with techniques from current approaches as advocated by Vanderweele et al. (Am J Epidemiol 2010;172:1339-1348) and Lange et al. (Am J Epidemiol 2012;176:190-195) on the multiplicative scale as used in logistic regression. Furthermore, these techniques by Vanderweele and Lange touch on issues of counterfactual framework and causal inference, which may be helpful in the context of mediation analysis, especially of confounders of smoking and mediator, and of mediator and mortality that need to be adjusted.
RESULTS & CONCLUSIONS	Again, I may have misunderstood the formulae as presented on pages 12 (lines 49-54), and page 13 (lines 8-14) and how that translate to the data presented in Tables 2, 3, 4 and Figure# 1 for estimating total, direct, and indirect effect. Thus, given my difficulty in understanding whether the analytic approach taken was appropriate, my ability to interpret the validity of the results is somewhat limited. In addition, I may have missed it but I think mortality in the current study needs to be presented in the results, i.e., what is the incidence of mortality overall and by smoking status?

	Also, whether estimating proportion mediated is appropriate needs to be addressed if mortality is a common outcome in the context of using logistic regression.
GENERAL COMMENTS	It may be helpful to have an epidemiologist with substantial experience in mediation analysis review this manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: David Warner
Professor of Anesthesiology
Mayo Clinic
US

No conflicts

General Comments
This is an interesting and valuable analysis using a well-characterized dataset. The mediational analysis is accomplished using standard techniques and is well-described, although I am curious about the notation in Table 4 that the proportion mediated is “unstable” – is this a critique of the general method, or a description of something specific to this analysis?
Response: The legend reads that the proportion mediated is unstable since this limitation relates to the general method of mediation analysis. Though succinct and theoretically informative, the proportion mediated is influenced by sample size, coefficient estimates, and distribution of the outcomes/predictors1 (continuous vs. binary). For our study, sample size is not an issue; however all our variables are dichotomous and we have small standardized coefficient estimates.

One interesting result of this analysis that deserves comment is that the three potential mediators of the association between smoking status and increased mortality in fact are responsible for a relatively minor proportion of the relationship in adjusted analysis. Could you please mention 1) what other mediators you speculate might be involved, and 2) further make the point that the difference between adjusted and unadjusted analysis suggests that smoking is a marker for several other factors that determine outcome (only some of which you likely measured). You already state this to some extent but I think the point that smoking status should alert practitioners to other factors which may need to be addressed is important. The related point that you could make in the conclusion is that any observational study that examines the relationship between smoking status and outcomes must recognize that smoking status can be associated with a wide range of other factors that may be causal.
Response: We agree with the reviewer. We added a paragraph to the discussion related to these excellent points made by the reviewer.

“The proportion mediated by each of three complications was attenuated by adjustment for age, race/ethnicity, work RVU, surgeon specialty and ASA class, indicating that these factors may have contributed to mortality outcome. In addition, other factors that we did not measure in this study such as other smoking-related diseases such as cancer, COPD etc. may have contributed. Additionally, as is common in observational studies such as ours, smoking status may be a marker for unmeasured variables that may be causal. Thus, smoking status should alert clinicians to other factors, which may need to be addressed preoperatively.”

Finally, it would be helpful to provide a table classifying causes of death in both smokers and in nonsmokers, including the absolute mortality rates for each, as well as the absolute rates for each of the three complications as well as the composite outcome.

Response: As requested, we have added a new table 2. Unfortunately, we do not have information related to the cause of death, which is listed a study limitation.

Postoperative Outcome Never Smoked (n=186,632) Current Smoker (n=135,741)
Surgical site infection 2.4 3.4
Vascular 0.5 0.5
Cerebral vascular accident/Stroke 0.2 0.3
Myocardial infarction 0.3 0.3
Pulmonary 2.0 3.1
Reintubation for respiratory or cardiac failure 0.9 1.6
Pneumonia 1.2 1.9
Failure to wean > 48 hours 0.8 1.4
Composite 4.5 6.5
Death within 6 months* 3.5 3.9
Death within 1 year* 5.3 6.4
Results presented as column-%
* Never: N=186,305; Current: N=135,561

Specific Comments
P7, l36ff – I'm not sure I agree with this rationale. Smoking could never have a "direct" effect, unless somehow the smoke constituents had some direct toxic effect. It would seem that smoking must always have an effect on mortality via some mediator (i.e., smoking-related pathology), so the question is not whether there is a "direct" effect, but rather what might mediate increases in mortality risk (e.g., events related to the chronic underlying diseases associated with smoking vs. these three particular postoperative events). I would think that regardless the approach is to 1) intervene to stop smoking, and 2) treat to the best of our ability the smoking-related pathology.
Response: We have edited this as suggested.
"If the effect of smoking on mortality were direct (direct toxic effects on health; low likelihood), then the only effective method to improve smoking-related outcomes would be smoking cessation. Alternatively, to the extent that smoking is related to mortality through an increase in pulmonary complications among smokers, then the effect of smoking is said to act through the mediating factor of pulmonary complications. Such a result would suggest that interventions to reduce pulmonary complications among smokers may be an additional strategy for improving the mortality outcome."

P8, l27 – again conceptually I think you are trying to determine what proportion of mortality can be associated with the particular putative mediators you examined….
Response: We have edited this as suggested.
"This was done in two steps: we first established a link between smoking and adverse outcomes, and we then investigated and quantified the proportion of the observed association appearing to act through a particular and plausible mediator, in this case, smoking-associated complication."

P11, l12 – there are many variables available in this dataset – please justify why you chose these particular adjustor variables.
Response: The reasons to choose these variables were that we wanted to choose key known patient-related factors that are predictors of mortality, including age, race and ASA class. In addition, we selected work RVU and surgeon specialty since these may indicate the complexity of surgery, which may also predict mortality.
"These variables were chosen based on previous literature of association of these factors with mortality or because they represented the complexity of the surgery."

P12, l16 – careful with terminology – would rather use "association of smoking" rather than "effect" so

as not to imply causal relationship….I understand that this may be how Baron and Kenny put it, but given that there are a large number of unmeasured potential confounders that may also be important , I would be cautious….
Response: We have edited this as suggested.
“The total effect of smoking on mortality was denoted by the path “c” in figure 1 representing the association of smoking on mortality without adjustment for the potential mediator.”

Discussion: “. In addition, some of the association of smoking and subsequent mortality is related to lifetime exposure to smoking, and not the association of smoking on perioperative complications. This may be related to occurrence of major lifetime complications from smoking, for example, COPD, coronary artery disease, various cancers and stroke, which can all contribute to postoperative mortality.”

“We did find that even after adjustment, smoking-related pulmonary complications mediated over 15% of the association of smoking and postoperative mortality. Thus, part of the association of smoking on mortality is due to a lifetime exposure, as shown previously (38, 39),”

P12, l44 – please be more precise than “significantly smaller”
Response: We have edited this as suggested.
“Less technically, if 1) smoking was related to both pulmonary complications and mortality, 2) pulmonary complications were related to mortality, and 3) the magnitude of the relationship between smoking and mortality decreased by a statistically significant amount when controlling for pulmonary complications, then there was a significant amount of mediation by pulmonary complications.”

P14, l55 – refer to table 4 here
Response: We have made this edit as suggested.
“The association between smoking and 6-month mortality was significantly mediated by pulmonary complication (22%) (Table 4).”

P16, l12 – but statistically I doubt if there is a significant difference between the coefficients for 6 month and 1 year mortality.
Response: We have made an edit as suggested, since this was not statistically tested.
“Not unexpectedly, estimates of the proportion of smoking-related mortality mediated by each peri-operative complication were all numerically larger for 6-month mortality compared to that for 1-year mortality, although this was not tested statistically.”

P16, l18 – wording of “attenuated significantly”?
Response: We have edited this as suggested.
“The proportion mediated by complications also decreased considerably between adjusted and unadjusted analyses, as expected.”

P16, l25 – include a few refs here
Response: We have added more references as suggested.
“That smoking is associated with increased mortality after elective surgical procedures is well known 2,3. Preoperative period has been proposed a “window of opportunity” and a “teachable moment” to help patients quit smoking 4,5.”

P16, l32 – grammer
Response: We have corrected this as suggested.
“The evidence presented here confirmed that a significant proportion of smoking-related mortality is mediated bythese postoperative complications, and that the proportion mediated varied by the type of complication.”

P16, l51 – but presumably such attention was paid to both smokers and non-smokers, correct? Similar arguments could be made for patients with pulmonary disease. And cardiac factors were an important cause of mortality according to your analysis – it's just that it didn't matter much whether they smoked or not…
Response: We believe that, in general, due to close attention to preoperative optimization of cardiac risk, the cardiac risk may have been greatly attenuated, and the attenuation would be expected more in smokers than in non-smokers, since the risk is higher in smokers.

"Perhaps this focus and attention on identifying and intervening on cardiac risk has mitigated the associations of smoking related cardiovascular events with mortality, in both smokers and never smokers."

P17, l8 – I agree, but reference.
Response: We have added more references as suggested.
"Thus, part of the effect of smoking on mortality is a lifetime exposure effect as shown previously 6,7, and part due to immediate complications, such as pulmonary complications."

P17, l12 – For example do you think that smoking status causes "upcoding" of ASA status? And in following line, again be careful about "direct" effects – hard to see how there could be effects apart from the "lifetime exposure" to smoking. I think this is a better way of looking at this (the way that you do in the following paragraph).
Response: We agree that smoking-related illnesses may have contributed to higher ASA status in smokers. We have modified the statements related to direct effects, as suggested.

"Methods: Last, when controlling for the mediator (pulmonary complications) the "direct effect" of the independent variable (smoking) on the dependent variable (6-month mortality) corresponds to the coefficient "c' ". We interpret the 'direct effect' to be the 'lifetime exposure' of smoking."

"Discussion: In addition, some of the association of smoking and subsequent mortality is related to lifetime exposure to smoking (direct effect), and not the association of smoking on perioperative complications (indirect effect through pulmonary complications)."

Can you further explain the notation in table 4 that the proportions are "unstable"?
Response: We have edited this as suggested.
"Because the proportion mediated is a ratio statistic, its estimated value is sensitive to variation in point estimates of the regression coefficients from which it is derived; it should therefore be interpreted with caution. Coefficient values (magnitude and significance) should be the main proponent in assessing mediation."

Reviewer: Paulo Vitoria, PhD
Health Sciences Faculty - Medical Department
Universidade da Beira Interior
Portugal

Participants are divided in two groups: current smokers and never-smokers.
Never-smokers were patients who had no smoking in the prior year and zero (or missing) pack years. Does this operationalization allow the classification of "never smokers"? Why not to use "no-smokers"
Response: We followed the same terminology and algorithm as in the published literature related to smoking research. Never-smoker is preferred term, since it indicates both current and past non-smoking status, as opposed to non-smokers, which is conventionally interpreted as 'not a current

smoker'.

Table 1 - why not to present a test of significance in the table to better assess the differences reported?
Response: P-values are already included in the footnote, and all p-values were <0.001 with the exception of steroid use, for which was 0.581.

Nice paper. I would like to congratulate the authors.
The title… I'm not comfortable with this title. The main variables are mortality, and perioperative complications and smoking. And the title suggests that the object of analysis is the program and not the veterans. I would suggest a more direct title (Mediation of smoking-associated post-operative mortality by postoperative
complications in VASQIP veterans undergoing surgery).
Response: We have modified the title as suggested.
"Mediation of Smoking-Associated Postoperative Mortality by perioperative complications in Veterans undergoing Elective Surgery: Data from Veterans Affairs Surgical Quality Improvement Program (VASQIP)"

Reviewer: Uyen-Sa D. T. Nguyen, DSc, MPH
Research Assistant Professor
Boston University School of Medicine
Clinical Epidemiology Research & Training Unit
USA

The mediation analysis by the authors is very important and very clinically relevant. My understanding of Barron and Kenny's approach to mediation analysis in their classic original papers was that for linear regression, i.e., estimating of effect on an additive scale. Although Mackinnon and Dwyer, as cited by the authors, suggested a method of transforming the betas when using logistic regression for dichotomous mediators or outcomes, (i.e., standardizing the regression coefficients from logistic regression) prior to estimating mediation, it would be helpful to a reader to see the authors present a brief illustration. For example, the authors could present both unstandardized and standardized coefficients in their tables and results section, and illustrate with an example of how they applied Mackinnon and Dwyer's method to standardize a coefficient and how they estimated direct and indirect effect using these standardized coefficients. As currently presented, it was difficult to understand why the unstandardized estimates of total, direct and indirect effects in the tables and Figure do not quite add up, as was of proportions mediated.
Response: We have modified the methods to clarify this, please see below. We have clarified the methods to emphasize that in this context they do not need to 'add up' but that the unstandardized coefficients are retained due to their greater interpretability.

"The statistical significance of the mediated, or indirect, effect was determined by testing whether the product a*b is statistically different from zero. The standard approximate test was due to the work of Sobel, and presented by Baron and Kenny (18). Subsequent work, notably by Shrout and Bolger (23) note that the Sobel test can be overly conservative for small samples but also that this ceases to be a concern when the sample size is greater than 1,000. The much larger sample size of this study suggested that the Sobel test was adequate in this context.
To evaluate the importance of the mediation it can be informative to calculate the proportion of the effect due to mediation as the indirect effect divided by the total effect as a*b/c. In our work, the independent, dependent, and mediator variable were all dichotomous. In this context where logistic regression is used a*b+c' may only approximate c, so we followed the methods of MacKinnon and Dwyer (22) and calculated the proportion of the effect due to mediation using coefficients

standardized to the same scale. We present only the unstandardized coefficients because they are more interpretable within the context of the individual regression models."

While providing estimates of mediating effect from the coefficients of logistic regression analyses and testing whether these coefficients statistically differ from 0 may inform whether mediation may occur statistically, it may not translate as intuitively to the size of direct or indirect effects from estimates of Odds Ratios (by exponentiating these coefficients). However, this may just be my own subjective opinion as I am more familiar with techniques from current approaches as advocated by Vanderweele et al. (Am J Epidemiol 2010;172:1339-1348) and Lange et al. (Am J Epidemiol 2012;176:190-195) on the multiplicative scale as used in logistic regression.

Furthermore, these techniques by Vanderweele and Lange touch on issues of counterfactual framework and causal inference, which may be helpful in the context of mediation analysis, especially of confounders of smoking and mediator, and of mediator and mortality that need to be adjusted.
Response: We have modified the methods to clarify this (see response to the comment above). We agree that the causal analysis with counterfactuals in an interesting approach to mediation analysis. However, it is epistemologically contentious, especially within an observational study such as ours and it is our feeling that it would be even more difficult to explain to our target audience than the approach we have employed here which more closely follows the familiar Barron and Kenny strategy.

Again, I may have misunderstood the formulae as presented on pages 12 (lines 49-54), and page 13 (lines 8-14) and how that translate to the data presented in Tables 2, 3, 4 and Figure# 1 for estimating total, direct, and indirect effect. Thus, given my difficulty in understanding whether the analytic approach taken was appropriate, my ability to interpret the validity of the results is somewhat limited. In addition, I may have missed it but I think mortality in the current study needs to be presented in the results, i.e., what is the incidence of mortality overall and by smoking status? Also, whether estimating proportion mediated is appropriate needs to be addressed if mortality is a common outcome in the context of using logistic regression.
Response: We have modified the methods to clarify this, emphasizing that in this case with logistic regression a*b +c' may only approximate c, and clarifying that the standardized coefficients are only used for calculating the proportion of the effect due to mediation. We have added a table showing the frequency as suggested by the reviewer.

It may be helpful to have an epidemiologist with substantial experience in mediation analysis review this manuscript.

1. Mackinnon DP, Warsi G, Dwyer JH. A Simulation Study of Mediated Effect Measures. Multivariate behavioral research. Jan 1 1995;30(1):41.
2. Ashraf MN, Mortasawi A, Grayson AD, Oo AY. Effect of smoking status on mortality and morbidity following coronary artery bypass surgery. Thorac Cardiovasc Surg. Oct 2004;52(5):268-273.
3. Jones R, Nyawo B, Jamieson S, Clark S. Current smoking predicts increased operative mortality and morbidity after cardiac surgery in the elderly. Interact Cardiovasc Thorac Surg. Mar 2011;12(3):449-453.
4. Shi Y, Warner DO. Surgery as a teachable moment for smoking cessation. Anesthesiology. Jan 2010;112(1):102-107.
5. Warner DO. Helping surgical patients quit smoking: why, when, and how. Anesth Analg. Aug 2005;101(2):481-487, table of contents.
6. Gellert C, Schottker B, Holleczek B, Stegmaier C, Muller H, Brenner H. Using rate advancement periods for communicating the benefits of quitting smoking to older smokers. Tob Control. Sep 22 2012.
7. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P. Life-time history of

smoking and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. Int J Cancer. Dec 2 1991;49(6):816-822.

VERSION 2 – REVIEW

REVIEWER	David O. Warner, M.D. Professor of Anesthesiology College of Medicine, Mayo Clinic, USA No competing interests
REVIEW RETURNED	13-Feb-2013

GENERAL COMMENTS	The authors have done a good job in responding to my prior comments.