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Mediation of Mortality by perioperative complications in Smokers undergoing Surgery: An analysis of Veterans Affairs Surgical Quality Improvement Program (VASQIP)

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."

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Article Summary

1) **Article Focus** -

- We aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery.
- We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality.

2) **Key Messages** -

- Pulmonary complications, followed by cardiovascular and surgical site infection complications were mediators of smoking-associated 6-month and 1-year mortality after elective knee or hip replacement surgery.
- Preoperative smoking counseling and implementation of smoking cessation programs should be done prior to an elective surgery such as knee/hip replacement.
- Early treatment of complications that mediate postoperative 1-year mortality may help to reduce risk of dying after an elective surgery.

3) **Strengths and Limitations -**

Strengths:

- Use of prospectively, collected national data in the largest integrated health care system in the U.S.
- Outcomes and complications had been defined using standardized definitions and validated by nurse abstractors

Limitations:

- Findings may not be generalizable to women and non-veteran U.S. population, since our sample included primarily men, representative of U.S. veterans.
- The current smoker variable is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association.
- Smoking status may change over time and the current study could not take that into account, since ongoing smoking status data are not available.
- Mediation assumes no unmeasured variables and despite accounting for all the important variables to the best of our capability with the given data, residual confounding is possible.

ABSTRACT

Objective: To assess the mediation of smoking-associated post-operative mortality by post-operative complications.

Design: Observational Cohort Study

Setting: Using data from the Veterans Affairs Surgical Quality Improvement Program, a quality assurance program for major surgical procedures in the VA healthcare system, we assessed the association of current smoking at the time of the surgery with 6-month and 1-year mortality.

Primary and Secondary Outcome Measures: Using mediation analyses, we calculated the relative contribution of each smoking-associated complication to smoking-associated postoperative mortality, both unadjusted and adjusted for age, race/ethnicity, work relative value unit of the operation, surgeon specialty, American Society of Anesthesiologists class, and year of surgery. Smoking-associated complications included surgical site infection, cardiovascular complications (myocardial infarction, cardiac arrest, and/or stroke), and pulmonary complications (pneumonia, failure to wean, and/or re-intubation).

Results: There were 186,632 never-smokers and 135,741 current smokers. The association of smoking and mortality was mediated by smoking-related complications with varying effects. In unadjusted analyses, the proportions of mediation of smoking to 6-month mortality explained by the complications were as follows: SSI, 22%; cardiovascular complications, 12%; and pulmonary complications, 89%. In adjusted analyses, the percents mediated by each complication were as follows: SSI, 2%; cardiovascular complications, 4%; and pulmonary complications, 22%. In adjusted analyses for 1-year mortality, respective percents mediated were 2%, 3% and 16%.

Conclusions: Pulmonary complications, followed by cardiovascular and SSI complications were mediators of smoking-associated 6-month and 1-year mortality. Interventions targeting smoking cessation and prevention and early treatment of pulmonary complications has the likelihood of reducing post-operative mortality after elective surgery.

Trial Registration: Not applicable, not an interventional study

INTRODUCTION

Smoking is the leading cause of preventable death in the U.S. (1, 2). While the prevalence of smoking in the U.S. has decreased (3), smoking is still highly prevalent with a recent national survey showing between 10-26% prevalence in most U.S. states (4). The prevalence of smoking in veterans using Veterans Affairs (VA) health care is even higher, at 30% (5). Smoking has detrimental effects on cardiovascular and lung health, and is linked to increased risk of surgical complications. Specifically, smokers undergoing surgery have a higher risk of several postoperative complications including wound infections, pneumonia, and mortality (6, 7). Smoking is a modifiable risk factor (8-10). Preoperative smoking cessation is associated with decreased postoperative wound complications and total complications (11).

While smoking-related postoperative morbidity is important, smoking is also associated with increased post-operative mortality (12-14). There are several proposed mechanisms of increased mortality in the perioperative period for smokers, including higher risk of cardiac (12, 13) and pulmonary complications (14). To our knowledge, no previous studies have assessed to what degree the increased smoking-associated postoperative mortality is mediated by specific complications associated with smoking. This has important consequences for designing interventions to improve outcomes. If the effect of smoking on mortality were direct, then the only method to improve smoking-related outcomes would be smoking cessation. Alternatively, if smoking were 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 direct actions to reduce pulmonary complications among smokers may be an alternative method for improving the mortality outcome.

We have recently demonstrated that smoking was associated with both postoperative surgical site infections (SSI) and pulmonary complications in a large cohort of veterans who underwent surgery in VA medical facilities and that mortality was also increased in this cohort

(15). These data are collected prospectively and systematically as part of the National VA Surgical Quality Improvement Program (VASQIP) (16) (17).

In this study we aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery. Conceptually, “mediation” occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events (18). As an example, this study explored the link between smoking and postoperative morbidity and mortality. We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality. This was done in two steps, i.e., once a link was established between smoking and adverse outcomes, we investigated whether the effect was directly due to smoking itself or whether it acts through a mediator, in this case, smoking-associated complication.

METHODS

Ethical Approval, Study Funding and Data sharing

The study was approved by the Institutional Review Boards at the VA Medical Centers (Birmingham, AL, Bedford, MA, Boston, MA and Seattle, WA), the University of Colorado, and by the Surgical Quality Data Use Group of VA Patient Care Services in VA Central Office, Washington, DC (as needed for studies using data from this dataset). All analyses used SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). This material is the result of work supported with VA Investigator-Initiated Research (IIR) IAB 06-038-2. Additionally, Dr. Singh's time was protected by research grants from the National Institute of Aging, National Cancer Institute and Agency for Health Quality and Research Center for Education and Research on Therapeutics (CERTs). We are committed to sharing the data with colleagues after an ethics committee approval and in accordance with VA data privacy and data security rules.

Study Sample

We used data from the VASQIP, a system-wide initiative instituted in 1994 to improve the quality of surgical care through prospective collection and reporting of comparative risk-adjusted post-operative outcomes of major surgeries requiring general, spinal, or epidural anesthesia(19). The abstracted data are >99% complete with >96% inter-observer agreement(17). We requested all cases in major procedure groups defined by CPT codes within each of the 8 surgical subspecialties (general, vascular, orthopedic, thoracic, otolaryngology, urology, neurosurgery, and plastic surgery) for the years 2002-2008. This produced a sample of roughly 60-70% of all non-cardiac operations in the VASQIP database for those years (n=507,545). We selected the first operation for each patient greater than or equal to 19 years of age, resulting in 412,511 unique patients. We excluded 17,202 patients coded as having emergency operations, since we wanted to focus on elective surgeries. We also excluded 1,515 patients who were coded as a current smoker but who had 0 pack-years (an

inconsistency) or were missing the current smoker variable. Since our focus was current smoking, we excluded 71,421 prior smokers leaving a total of 322,373 patients for analysis.

Independent Measure: Current Smoking

Smoking status was assessed using two variables. Patients are queried at the time of elective surgery if they have smoked cigarettes in the year prior to admission (yes/no) and regarding amount of smoking (pack years = the number of packs smoked per day multiplied by the number of years the patient smoked), documented in patients' medical records. Never-smokers were patients who had no smoking in the prior year and zero (or missing) pack years. Current smokers were those who responded "yes" to smoking in the year prior to admission and had pack years not equal to zero.

Dependent Measure: Mortality

Mortality was assessed at 6-months and at 1-year. The VASQIP nurses collect 30-day postoperative vital status for all patients assessed in the VASQIP program. Once every 6 months, the VASQIP database is passed through the VA administrative vitals file to obtain data on long-term postoperative mortality beyond 30 days after surgery.

Mediation Variables: 30-day Outcomes for Complications

All complications of interest were assessed 30-days after elective surgery. Specifically, the outcomes included: (1) SSI; (2) Cardiovascular complication, defined as occurrence of myocardial infarction (MI), cardiac arrest, and/or stroke; (3) Pulmonary complication, defined as occurrence of pneumonia, failure to wean, and/or re-intubation; and (4) Overall composite outcome, defined as the occurrence of SSI, cardiovascular and/or pulmonary complication. All outcomes have standard definitions in VASQIP and are extracted and validated for each patient

by an independent nurse abstractor at each VA site for the 30-day period after the surgery (16, 17).

Covariates: Patient, Surgeon, and Procedural Characteristics

Patient characteristics including age, race/ethnicity, American Society of Anesthesiologists (ASA) class, year of surgery, work relative value unit (RVU) for the operation, and wound classification were extracted. ASA class is a validated measure of peri-operative mortality and immediate post-operative morbidity, categorized into five classifications (20, 21) (class I, normal healthy patient; class II, patient with mild systemic disease (with no functional limitation); class III, patient with severe systemic disease (with some functional limitation); class IV, patient with severe systemic disease that is a constant threat to life; class V, moribund patient). Work RVU (a measure of procedure duration and complexity) and surgeon subspecialty were collected by chart review.

Statistical Analyses

Summary statistics were calculated for clinical and demographic characteristics. Mediation analysis was done without and with controlling for covariates that could potentially confound the relationship. Univariable and multivariable-adjusted logistic regression analyses were used to compute coefficients for association of smoking and mortality, smoking and major complications (SSI, pulmonary, cardiovascular or composite) and major complications and mortality, to assess mediation effect of complications on the relationship between smoking and mortality. In multivariable analyses, we adjusted for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year at each step of the mediation analysis. Wound classification was additionally adjusted for in the model when assessing the mediation effect of SSI.

The conceptual framework of “mediation” indicates that mediation occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events

(18). The classic exposition of statistical mediation analysis was given by Baron and Kenny in 1986 (18). The mediating relationship was conceived in causal terms, so while it was recognized that the statistical models cannot establish causality, the causal interpretation of the posited relationships must be plausible. The precondition was that the independent variable (smoking) is statistically significantly associated with the dependent variable (e.g. 6-month mortality). The total effect of smoking on mortality was denoted by the path "c" in figure 1 representing the effect of smoking on mortality without adjustment for the potential mediator. Baron and Kenny outlined three steps for a formal mediation analysis using regression, which can be explained with reference to figure 1 in the context of the relationship between smoking and 6-month mortality with the putative mediating effect of pulmonary complications. The first step was to establish that there is a significant association between the independent variable (smoking) and the potential mediator (pulmonary complications) corresponding to the path coefficient "a" in figure 1. The second step was to establish that the potential mediator (pulmonary complications) is associated with the dependent variable (6-month mortality), while controlling for the independent variable (smoking), corresponding to the path coefficient "b". 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' ". Less technically, if 1) smoking was related to both pulmonary complications and mortality, 2) pulmonary complications were related to mortality, and 3) the relationship between smoking and mortality was significantly smaller when controlling for pulmonary complications, then there was a significant amount of mediation by pulmonary complications.

Arithmetically, the indirect effect is equal to the product of coefficients a*b and the total effect (c), is equal to the indirect effect (a*b) plus the remaining direct effect (c'), thus: c=a*b +c', so c'=c-a*b. Clearly, as the indirect effect through the mediator gets larger, the residual direct effect must decrease, implying that a larger part of the effect is via the mediator. The more the direct effect is diminished, the greater part of the effect is mediated. In our work, the

independent, dependent, and mediator variable were all dichotomous. For this situation, logisitic regression was used and coefficients must then be standardized to the same scale prior to comparison and statistical testing as presented by MacKinnon and Dwyer (22). When using logistic regression, unlike in multiple regression, a*b+c' only approximated c. In this work, we reported the proportion of the effect mediated as (a*b)/(a*b+c'), or the indirect effect divided by the total effect. 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.

RESULTS

There were 186,632 never-smokers and 135,741 current smokers. The mean age was 63 years for never smokers and 58 years for current smokers. 95% were men and 63% were White (race/ethnicity missing in 19%) (**Table 1**). Diabetes was less common among current smokers compared to never smokers, but COPD, dyspnea, and alcohol consumption were more common. Other characteristics were similar between the two groups (Table 1).

Mediation Analyses for 6-month and 1-year mortality

Unstandardized coefficients were calculated without (unadjusted; **Table 2**) and with (adjusted; **Table 3**) potential confounders using regression analyses**.** Variances for computing standardized coefficients are footnoted. The unadjusted coefficients were highest between smoking and pulmonary complications (coefficient a =0.46), and between pulmonary complication and 6-month mortality, controlling for smoking was (coefficient b =2.90) among all complications (**Table 2**); similar observations were made for pulmonary complications and 1-year mortality. In general unadjusted coefficients were higher than adjusted coefficients.

Table 3 provides coefficients for the mediation analyses controlling for confounding from age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year for 6-month and 1-year mortality. Mediation analysis for SSI additionally controlled for wound classification. The coefficients for the path from smoking to 6- and 12-month mortality when considering the mediation factor of SSI were 0.39 and 0.45 (coefficient c). Again as an example, the coefficient between smoking and pulmonary complications was 0.48 (coefficient a), between pulmonary complication and 6-month mortality controlling for smoking was 2.17 (coefficient b), and that between smoking and 6-month mortality controlling for pulmonary complication was 0.32 (coefficient c'). The association between smoking and 6-month mortality was significantly mediated by pulmonary complication (22%). For 6-month mortality, adjusted coefficients between smoking and complications were highest for pulmonary complications (0.48), followed

by composite outcome (0.29), SSI (0.19) and cardiovascular complications (0.19) (coefficient a). Adjusted coefficients were highest for pulmonary followed by cardiovascular, composite and SSI complications for association with 6-month mortality, controlling for smoking (coefficient b). The proportion of mediation of smoking to 6-month mortality explained by the complications in adjusted analyses was 16% for the composite outcome, while the proportions were lower for SSI (2%) and cardiovascular complications (4%) (**Table 4**).

Similar patterns were noted for mediation of smoking and 1-year mortality for adjusted coefficients (**Table 3**). In the adjusted models, the proportion of mediation of smoking to 1-year mortality explained by the complications in adjusted analyses was 16% for pulmonary complications, 11% for composite complications, 3% for cardiovascular complications and 2% for SSI (**Table 4**).

DISCUSSION

In this analysis of prospectively collected data in a national sample of non-cardiac elective surgeries at VA facilities, we found that increased 6-month and 1-year smoking-associated mortality was mediated by pulmonary complications and to a lesser extent cardiovascular complications and surgical site infections. Not unexpectedly, the proportion of smoking-mortality association mediated by these peri-operative complications was greater for 6-month mortality compared to that for 1-year mortality. The proportion mediated by complications also attenuated significantly between adjusted and unadjusted analyses, as expected. These observations are novel and have important implications for targeting interventions for patients undergoing elective surgery.

That smoking is associated with increased mortality after elective surgical procedures is well known. This study examined a critical question, i.e., is this increased mortality mediated by the postoperative complications seen more commonly in smokers than in non-smokers? The evidence presented here confirms that these postoperative complications mediated significant proportion of increased mortality risk, and that this varies by the type of complication. Pulmonary complications explained the most variation in this increased risk, as compared to cardiovascular complications or surgical site infections. Our findings suggest pulmonary complications are far more important contributors to the smoking-mortality association than the cardiovascular complications. There has been significant emphasis placed on pre-operative cardiac risk assessment for non-cardiac surgery (24). Consensus statements on cardiac risk stratification including who should undergo screening and revascularization and management of patients with implanted cardiac stents have been developed and widely disseminated (25-27). Perhaps this focus and attention on identifying and intervening on cardiac risk has mitigated effects of smoking related cardiovascular events on mortality. Similar attention has not been given to pre-operative risk stratification for post-operative pulmonary events. These events

occur more frequently than cardiovascular events and lead to substantial post-operative mortality (28-33).

Perioperative complications associated with smoking mediated a high proportion of the association of smoking and mortality before adjustment. But the proportion mediation was greatly attenuated after adjustment. This suggests that a major part of the mediation effect was contained in variables we adjusted for, including ASA class. In addition, some of the association of smoking and subsequent mortality is related to lifetime exposure to smoking, and not the direct effect 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 effect of smoking on mortality is a lifetime exposure effect, and part due to immediate complications, such as pulmonary complications. The first goal should always be to get smokers to quit prior to surgery. But acknowledging that not all smokers will quit prior to their surgery, the surgical staff should be especially vigilant of pulmonary complications, as our data clearly demonstrates them to mediate mortality. Careful monitoring of adherence to pneumonia prevention guidelines in postoperative period as well as early diagnosis and management may lead to reduction in mortality. Far more importantly, preventive pre-operative evaluation and optimization of pulmonary health in addition to implementation of preoperative smoking cessation programs in patients undergoing elective surgery have the likelihood of reducing the increased mortality risk. Consensus statements on pulmonary risk assessment and patients who should be referred for intervention are strongly needed.

We found that attributable risk of SSI to smoking-related mortality was lower than that for pulmonary and cardiovascular complications. SSIs constitute the most common infection, accounting for 38% of all infections (6). In addition, SSIs are associated with significant

increases in hospital stay,(6) making them one of the most costly post-operative complications.(6, 34). SSIs are the third most common nosocomial infection overall, representing 14% of all hospital acquired infections. Thus even though their contribution to mortality is lower, their common prevalence and the ability to institute measures to prevent them make them suitable targets for interventions.

Our study has several limitations. It is possible that findings may not be generalizable to women, since our sample included primarily men, representative of U.S. veterans. These findings may not be generalizable to non-veterans; however, it is unlikely that the pathway of smoking-associated mortality risk differs by veteran status. The current smoker variable in VASQIP is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association. Thus, these results are conservative estimates of these associations. Another limitation is that smoking status may change over time and current study design and analyses did not take that into account. Mediation assumes no unmeasured variables; this is of course not true as we can never account for all omitted factors. We accounted for all the important variables to the best of our capability with the given data.

In conclusion, this study found that a high proportion of association between smoking and post-operative 6-month and 1-year mortality is mediated by postoperative complications, especially pulmonary complications. Future efforts at reducing post-operative mortality should be aimed at pre-operative risk identification and intervention. Efforts directed at pulmonary risk stratification, surveillance and prevention for pulmonary and other complications in smokers undergoing elective surgery may likely impact mortality in current smokers undergoing elective surgical procedures.

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TABLES AND FIGURES

Table 1. Patient characteristics by smoking status (Column percents unless noted otherwise)

Characteristic		Never Smoked (n=186,632)	Current Smoker (n=135,741)
Smoking Pack Years, mean (SD)		N/A	48.8 (32.6)
Demographics			
Age, mean (SD)		63.1 (13.7)	57.6 (11.0)
Sex	Female	5.1%	4.1%
	Male	94.9%	95.9%
Race/Ethnicity	White	62.3%	63.1%
	Black	12.3%	14.9%
	Hispanic	5.3%	2.7%
	Other/Unknown	20.2%	19.3%
Comorbidities			
Diabetes		20.2%	14.6%
Congestive heart failure		1.2%	1.0%
History of severe COPD		7.0%	18.4%
Dyspnea		8.4%	15.4%
Chronic Corticosteroid use		1.7%	1.7%
Renal failure/Dialysis		0.7%	0.5%
CVA/Stroke		5.9%	6.6%
Transient ischemic attacks		2.9%	3.6%

Functional health status	Independent	93.5%	94.8%
	Partially dependent	5.2%	4.6%
	Totally dependent	1.3%	0.6%
>10% loss body weight in past 6 months		1.8%	3.4%
Disseminated cancer		1.0%	1.3%
Open wound/wound infection		3.2%	4.3%
DNR status		0.9%	0.6%
Alcohol > 2 drinks/day		4.3%	14.6%
Operative Characteristics			
Anesthesia technique	General	79.4%	84.8%
	Epidural/Spinal	15.6%	10.9%
	Local/Monitored	5.1%	4.2%
ASA classification	1	4.4%	1.6%
	2	35.8%	33.4%
	3	53.8%	58.2%
	4/5	6.1%	6.8%
Admission status	Outpatient	51.0%	47.1%
	Inpatient	49.0%	52.9%
Specialty of Surgeon	General Surgery	39.3%	35.3%
	Neurosurgery	5.4%	7.9%
	Orthopedic Surgery	29.6%	21.9%
	Otolaryngology	1.1%	1.3%
	Plastic Surgery	0.6%	0.6%
	Thoracic Surgery	1.7%	5.6%
	Urology	15.6%	13.1%

	Cardiovascular Surgery	6.3%	13.8%
	Other	0.4%	0.4%
Wound Classification	Clean	70.0%	70.8%
	Clean/contaminated	27.3%	26.2%
	Contaminated	1.6%	1.6%
	Infected	1.2%	1.4%
Work RVU (mean, SD)		14.1 (7.1)	14.8 (7.8)
Operation time, hours (mean, SD)		1.9 (1.4)	2.1 (1.6)

All p-value are less than 0.001 with the exception of steriod use, for which was 0.581

N/A, not applicable; SD, standard deviation; RUV, relative value units; ASA, American Society of Anesthesiologists; DNR, Do not resuscitate; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident

Table 2. Unadjusted coefficients[a] and their 95% confidence intervals

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.12	0.08-0.15	0.37	0.33-0.41	0.89	0.81-0.96	0.10	0.07-0.14
	Cardiovascular complications	0.12	0.08-0.15	0.15	0.05-0.24	2.70	2.60-2.80	0.11	0.07-0.15
	Pulmonary complications	0.12	0.08-0.15	0.46	0.42-0.51	2.90	2.85-2.95	0.01	-0.02-0.05
	Composite outcome	0.12	0.08-0.15	0.39	0.36-0.42	2.21	2.17-2.25	0.02	-0.02-0.05
1-year mortality[c]	Surgical site infection	0.20	0.17-0.23	0.37	0.33-0.41	0.83	0.76-0.89	0.19	0.16-0.22
	Cardiovascular complications	0.20	0.17-0.23	0.15	0.05-0.24	2.42	2.32-2.52	0.20	0.17-0.23
	Pulmonary complications	0.20	0.17-0.23	0.46	0.42-0.51	2.60	2.57-2.64	0.13	0.10-0.17
	Composite outcome	0.20	0.17-0.23	0.39	0.36-0.42	1.91	1.88-1.95	0.13	0.10-0.16

c=direct path from smoking to mortality

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite)

b= path from complication (SSI etc.) to mortality controlling for smoking

c' = path from smoking to mortality controlling for complication (SSI etc.)

[a] all coefficients were unstandardized and rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking') = 3.30, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.32, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.34, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.54

[c] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking') = 3.33, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.34, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.36, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.47, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.49

Table 3. Adjusted coefficients[a] and their 95% confidence intervals controlling for confounding

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.39	0.35-0.44	0.19	0.14-0.24	0.45	0.37-0.53	0.39	0.35-0.43
	Cardiovascular complications	0.38	0.34-0.42	0.19	0.08-0.30	2.00	1.89-2.12	0.38	0.34-0.42
	Pulmonary complications	0.38	0.34-0.42	0.48	0.43-0.54	2.17	2.11-2.23	0.32	0.27-0.36
	Composite outcome	0.38	0.34-0.42	0.29	0.25-0.32	1.71	1.66-1.76	0.33	0.28-0.37
1-year mortality[c]	Surgical site infection	0.45	0.42-0.49	0.19	0.14-0.24	0.44	0.37-0.51	0.45	0.41-0.48
	Cardiovascular complications	0.44	0.40-0.47	0.19	0.08-0.30	1.77	1.66-1.88	0.44	0.40-0.47
	Pulmonary complications	0.44	0.40-0.47	0.48	0.43-0.54	1.90	1.85-1.96	0.39	0.36-0.43

Composite outcome	0.44	0.40-0.47	0.29	0.25-0.32	1.44	1.40-1.48	0.40	0.36-0.44

c=direct path from smoking to mortality controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite) controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

b= path from complication (SSI etc.) to mortality controlling for smoking, age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

c' = path from smoking to mortality controlling for complication (SSI etc.), age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

[a] all coefficients were unstandardized and were rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking [SSI]') = 3.44, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.43, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.44,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.45, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.53

[c] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking [SSI]') = 3.49, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.48, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.49,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.49, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.52, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.54

Table 4. Proportion of mediation of smoking to mortality association explained by each complication in unadjusted and adjusted

Outcome	Mediator	Proportion Mediation Unadjusted for covariates	Proportion Mediation Adjusted for covariates
6-month mortality	Surgical site infection	22.2%	2.0%
	Cardiovascular complications	12.2%	3.8%
	Pulmonary complications	88.9%	21.6%
	Composite outcome	86.4%	15.7%
1-year mortality	Surgical site infection	12.6%	1.7%
	Cardiovascular complications	6.5%	3.0%
	Pulmonary complications	42.7%	16.2%
	Composite outcome	40.8%	11.3%

The proportion mediated has been shown to be unstable and should be interpreted with caution. Coefficient values (magnitude and significance) should be the main proponent in assessing mediation

Figure 1. Path diagram of the relations among the three standardized variables and standardized coefficients of paths

Figure legend:

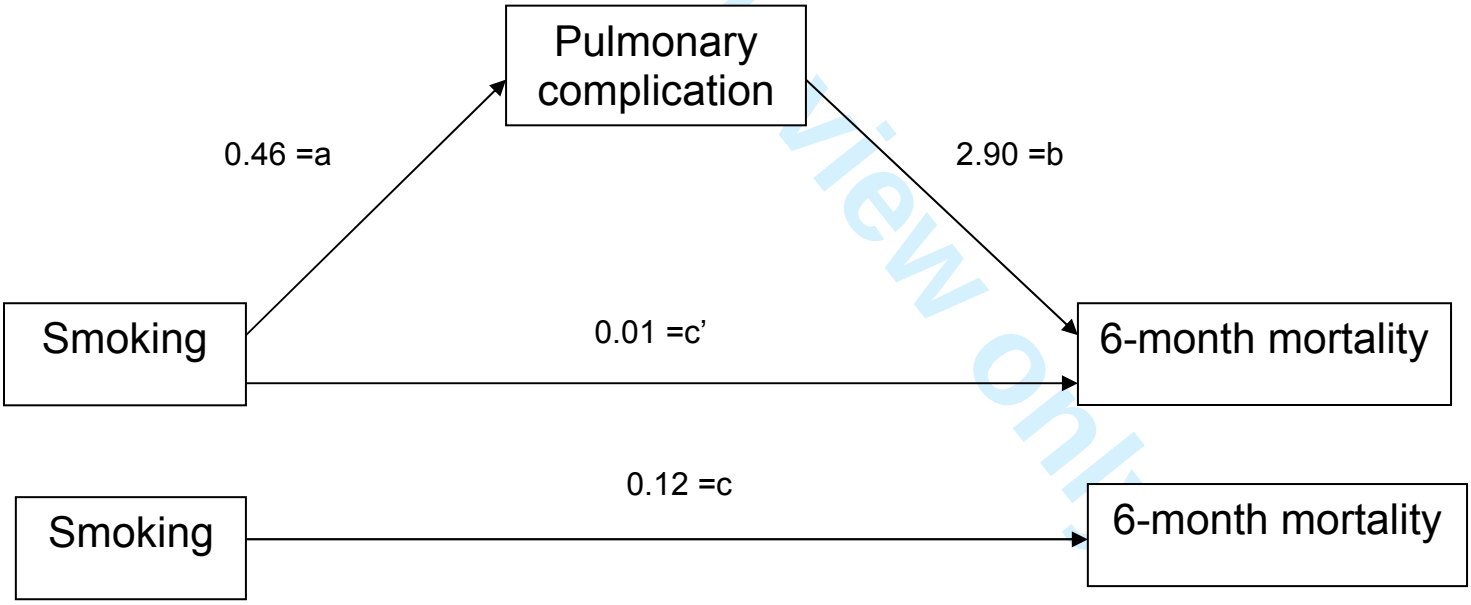
a= regression coefficient for path from smoking to pulmonary complication

b= regression coefficient for path from pulmonary complication to 6-month mortality, controlling for smoking

c'= regression coefficient for path from smoking to 6-month mortality, controlling for pulmonary complication

c= regression coefficient for direct path from smoking to 6-month mortality

Smoking is the independent variable, pulmonary complication the mediator and 6-month mortality dependent variable. a, b, c and c' are coefficients from logistic regression analyses.



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Mediation of Smoking-Associated Postoperative Mortality by perioperative complications in Veterans undergoing Elective Surgery: Data from Veterans Affairs Surgical Quality Improvement Program (VASQIP)

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Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."

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Running Title: Mediators of Mortality in Smokers Undergoing Arthroplasty

Article Summary

1) **Article Focus** -

- We aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery.
- We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality.

2) **Key Messages** -

- Pulmonary complications, followed by cardiovascular and surgical site infection complications were mediators of smoking-associated 6-month and 1-year mortality after elective knee or hip replacement surgery.
- Preoperative smoking counseling and implementation of smoking cessation programs should be done prior to an elective surgery such as knee/hip replacement.
- Early treatment of complications that mediate postoperative 1-year mortality may help to reduce risk of dying after an elective surgery.

3) **Strengths and Limitations -**

Strengths:

- Use of prospectively, collected national data in the largest integrated health care system in the U.S.

- Outcomes and complications had been defined using standardized definitions and validated by nurse abstractors

Limitations:

- Findings may not be generalizable to women and non-veteran U.S. population, since our sample included primarily men, representative of U.S. veterans.
- The current smoker variable is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association.
- Smoking status may change over time and the current study could not take that into account, since ongoing smoking status data are not available.
- Mediation assumes no unmeasured variables and despite accounting for all the important variables to the best of our capability with the given data, residual confounding is possible.

ABSTRACT

Objective: To assess the mediation of smoking-associated post-operative mortality by post-operative complications.

Design: Observational Cohort Study

Setting: Using data from the Veterans Affairs Surgical Quality Improvement Program, a quality assurance program for major surgical procedures in the VA healthcare system, we assessed the association of current smoking at the time of the surgery with 6-month and 1-year mortality.

Primary and Secondary Outcome Measures: Using mediation analyses, we calculated the relative contribution of each smoking-associated complication to smoking-associated postoperative mortality, both unadjusted and adjusted for age, race/ethnicity, work relative value unit of the operation, surgeon specialty, American Society of Anesthesiologists class, and year of surgery. Smoking-associated complications included surgical site infection, cardiovascular complications (myocardial infarction, cardiac arrest, and/or stroke), and pulmonary complications (pneumonia, failure to wean, and/or re-intubation).

Results: There were 186,632 never-smokers and 135,741 current smokers. The association of smoking and mortality was mediated by smoking-related complications with varying effects. In unadjusted analyses, the proportions of mediation of smoking to 6-month mortality explained by the complications were as follows: SSI, 22%; cardiovascular complications, 12%; and pulmonary complications, 89%. In adjusted analyses, the percents mediated by each complication were as follows: SSI, 2%; cardiovascular complications, 4%; and pulmonary complications, 22%. In adjusted analyses for 1-year mortality, respective percents mediated were 2%, 3% and 16%.

Conclusions: Pulmonary complications, followed by cardiovascular and SSI complications were mediators of smoking-associated 6-month and 1-year mortality. Interventions targeting smoking cessation and prevention and early treatment of pulmonary complications has the likelihood of reducing post-operative mortality after elective surgery.

INTRODUCTION

Smoking is the leading cause of preventable death in the U.S. (1, 2). While the prevalence of smoking in the U.S. has decreased (3), smoking is still highly prevalent with a recent national survey showing between 10-26% prevalence in most U.S. states (4). The prevalence of smoking in veterans using Veterans Affairs (VA) health care is even higher, at 30% (5). Smoking has detrimental effects on cardiovascular and lung health, and is linked to increased risk of surgical complications. Specifically, smokers undergoing surgery have a higher risk of several postoperative complications including wound infections, pneumonia, and mortality (6, 7). Smoking is a modifiable risk factor (8-10). Preoperative smoking cessation is associated with decreased postoperative wound complications and total complications (11).

While smoking-related postoperative morbidity is important, smoking is also associated with increased post-operative mortality (12-14). There are several proposed mechanisms of increased mortality in the perioperative period for smokers, including higher risk of cardiac (12, 13) and pulmonary complications (14). To our knowledge, no previous studies have assessed to what degree the increased smoking-associated postoperative mortality is mediated by specific complications associated with smoking. This has important consequences for designing interventions to improve outcomes. 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.

We have recently demonstrated that smoking was associated with both postoperative surgical site infections (SSI) and pulmonary complications in a large cohort of veterans who underwent surgery in VA medical facilities and that mortality was also increased in this cohort

(15). These data are collected prospectively and systematically as part of the National VA Surgical Quality Improvement Program (VASQIP) (16) (17).

In this study we aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery. Conceptually, “mediation” occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events (18). As an example, this study explored the link between smoking and postoperative morbidity and mortality. We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality. 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.

METHODS

Ethical Approval, Study Funding and Data sharing

The study was approved by the Institutional Review Boards at the VA Medical Centers (Birmingham, AL, Bedford, MA, Boston, MA and Seattle, WA), the University of Colorado, and by the Surgical Quality Data Use Group of VA Patient Care Services in VA Central Office, Washington, DC (as needed for studies using data from this dataset). All analyses used SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). This material is the result of work supported with VA Investigator-Initiated Research (IIR) IAB 06-038-2. Additionally, Dr. Singh's time was protected by research grants from the National Institute of Aging, National Cancer Institute and Agency for Health Quality and Research Center for Education and Research on Therapeutics (CERTs). We are committed to sharing the data with colleagues after an ethics committee approval and in accordance with VA data privacy and data security rules.

Study Sample

We used data from the VASQIP, a system-wide initiative instituted in 1994 to improve the quality of surgical care through prospective collection and reporting of comparative risk-adjusted post-operative outcomes of major surgeries requiring general, spinal, or epidural anesthesia(19). The abstracted data are >99% complete with >96% inter-observer agreement(17). We requested all cases in major procedure groups defined by CPT codes within each of the 8 surgical subspecialties (general, vascular, orthopedic, thoracic, otolaryngology, urology, neurosurgery, and plastic surgery) for the years 2002-2008. This produced a sample of roughly 60-70% of all non-cardiac operations in the VASQIP database for those years (n=507,545). We selected the first operation for each patient greater than or equal to 19 years of age, resulting in 412,511 unique patients. We excluded 17,202 patients coded as having emergency operations, since we wanted to focus on elective surgeries. We also excluded 1,515 patients who were coded as a current smoker but who had 0 pack-years (an

inconsistency) or were missing the current smoker variable. Since our focus was current smoking, we excluded 71,421 prior smokers leaving a total of 322,373 patients for analysis.

Independent Measure: Current Smoking

Smoking status was assessed using two variables. Patients are queried at the time of elective surgery if they have smoked cigarettes in the year prior to admission (yes/no) and regarding amount of smoking (pack years = the number of packs smoked per day multiplied by the number of years the patient smoked), documented in patients' medical records. Never-smokers were patients who had no smoking in the prior year and zero (or missing) pack years. Current smokers were those who responded "yes" to smoking in the year prior to admission and had pack years not equal to zero.

Dependent Measure: Mortality

Mortality was assessed at 6-months and at 1-year. The VASQIP nurses collect 30-day postoperative vital status for all patients assessed in the VASQIP program. Once every 6 months, the VASQIP database is passed through the VA administrative vitals file to obtain data on long-term postoperative mortality beyond 30 days after surgery.

Mediation Variables: 30-day Outcomes for Complications

All complications of interest were assessed 30-days after elective surgery. Specifically, the outcomes included: (1) SSI; (2) Cardiovascular complication, defined as occurrence of myocardial infarction (MI), cardiac arrest, and/or stroke; (3) Pulmonary complication, defined as occurrence of pneumonia, failure to wean, and/or re-intubation; and (4) Overall composite outcome, defined as the occurrence of SSI, cardiovascular and/or pulmonary complication. All outcomes have standard definitions in VASQIP and are extracted and validated for each patient

by an independent nurse abstractor at each VA site for the 30-day period after the surgery (16, 17).

Covariates: Patient, Surgeon, and Procedural Characteristics

Patient characteristics including age, race/ethnicity, American Society of Anesthesiologists (ASA) class, year of surgery, work relative value unit (RVU) for the operation, and wound classification were extracted. ASA class is a validated measure of peri-operative mortality and immediate post-operative morbidity, categorized into five classifications (20, 21) (class I, normal healthy patient; class II, patient with mild systemic disease (with no functional limitation); class III, patient with severe systemic disease (with some functional limitation); class IV, patient with severe systemic disease that is a constant threat to life; class V, moribund patient). Work RVU (a measure of procedure duration and complexity) and surgeon subspecialty were collected by chart review. These variables were chosen based on previous literature of association of these factors with mortality or because they represented the complexity of the surgery.

Statistical Analyses

Summary statistics were calculated for clinical and demographic characteristics. Mediation analysis was done without and with controlling for covariates that could potentially confound the relationship. Univariable and multivariable-adjusted logistic regression analyses were used to compute coefficients for association of smoking and mortality, smoking and major complications (SSI, pulmonary, cardiovascular or composite) and major complications and mortality, to assess mediation effect of complications on the relationship between smoking and mortality. In multivariable analyses, we adjusted for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year at each step of the mediation analysis. Wound classification was additionally adjusted for in the model when assessing the mediation effect of SSI.

The conceptual framework of "mediation" indicates that mediation occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events (18). The classic exposition of statistical mediation analysis was given by Baron and Kenny in 1986 (18). The mediating relationship was conceived in causal terms, so while it was recognized that the statistical models cannot establish causality, the causal interpretation of the posited relationships must be plausible. The precondition was that the independent variable (smoking) is statistically significantly associated with the dependent variable (e.g. 6-month mortality). 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. Baron and Kenny outlined three steps for a formal mediation analysis using regression, which can be explained with reference to figure 1 in the context of the relationship between smoking and 6-month mortality with the putative mediating effect of pulmonary complications. The first step was to establish that there is a significant association between the independent variable (smoking) and the potential mediator (pulmonary complications) corresponding to the path coefficient "a" in figure 1. The second step was to establish that the potential mediator (pulmonary complications) is associated with the dependent variable (6-month mortality), while controlling for the independent variable (smoking), corresponding to the path coefficient "b". 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. 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.

Arithmetically, the indirect effect is equal to the product of coefficients a*b and the total effect (c), is equal to the indirect effect (a*b) plus the remaining direct effect (c'), thus: c=a*b +c', so c'=c-a*b. Clearly, as the indirect effect through the mediator gets larger, the residual direct effect must decrease, implying that a larger part of the effect is via the mediator. The more the direct effect is diminished, the greater part of the effect is mediated.

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.

RESULTS

There were 186,632 never-smokers and 135,741 current smokers. The mean age was 63 years for never smokers and 58 years for current smokers. 95% were men and 63% were White (race/ethnicity missing in 19%) (**Table 1**). Diabetes was less common among current smokers compared to never smokers, but COPD, dyspnea, and alcohol consumption were more common. Other characteristics were similar between the two groups (**Table 1**). Crude estimates of outcomes by smoking status us shown in **Table 2**.

Mediation Analyses for 6-month and 1-year mortality

Unstandardized coefficients were calculated without (unadjusted; **Table 3**) and with (adjusted; **Table 4**) potential confounders using regression analyses**.** Variances for computing standardized coefficients are footnoted. The unadjusted coefficients were highest between smoking and pulmonary complications (coefficient a =0.46), and between pulmonary complication and 6-month mortality, controlling for smoking was (coefficient b =2.90) among all complications (**Table 3**); similar observations were made for pulmonary complications and 1-year mortality. In general unadjusted coefficients were higher than adjusted coefficients.

Table 4 provides coefficients for the mediation analyses controlling for confounding from age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year for 6-month and 1-year mortality. Mediation analysis for SSI additionally controlled for wound classification. The coefficients for the path from smoking to 6- and 12-month mortality when considering the mediation factor of SSI were 0.39 and 0.45 (coefficient c). Again as an example, the coefficient between smoking and pulmonary complications was 0.48 (coefficient a), between pulmonary complication and 6-month mortality controlling for smoking was 2.17 (coefficient b), and that between smoking and 6-month mortality controlling for pulmonary complication was 0.32 (coefficient c'). The association between smoking and 6-month mortality was significantly mediated by pulmonary complication (22%) (**Table 5**). For 6-month mortality, adjusted

coefficients between smoking and complications were highest for pulmonary complications (0.48), followed by composite outcome (0.29), SSI (0.19) and cardiovascular complications (0.19) (coefficient a). Adjusted coefficients were highest for pulmonary followed by cardiovascular, composite and SSI complications for association with 6-month mortality, controlling for smoking (coefficient b). The proportion of mediation of smoking to 6-month mortality explained by the complications in adjusted analyses was 16% for the composite outcome, while the proportions were lower for SSI (2%) and cardiovascular complications (4%) (**Table 5**).

Similar patterns were noted for mediation of smoking and 1-year mortality for adjusted coefficients (**Table 4**). In the adjusted models, the proportion of mediation of smoking to 1-year mortality explained by the complications in adjusted analyses was 16% for pulmonary complications, 11% for composite complications, 3% for cardiovascular complications and 2% for SSI (**Table 5**).

DISCUSSION

In this analysis of prospectively collected data in a national sample of non-cardiac elective surgeries at VA facilities, we found that increased 6-month and 1-year smoking-associated mortality was mediated by pulmonary complications and to a lesser extent cardiovascular complications and surgical site infections. 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. The proportion mediated by complications also attenuated significantly between adjusted and unadjusted analyses, as expected. These observations are novel and have important implications for targeting interventions for patients undergoing elective surgery.

That smoking is associated with increased mortality after elective surgical procedures is well known (24, 25). Preoperative period has been proposed a “window of opportunity” and a “teachable moment” to help patients quit smoking (26, 27). This study examined a critical question, i.e., is this increased mortality mediated by the postoperative complications seen more commonly in smokers than in non-smokers? The evidence presented here confirmed that these postoperative complications mediated significant proportion of increased mortality risk, and that this varied by the type of complication. Pulmonary complications explained the most variation in this increased risk, as compared to cardiovascular complications or surgical site infections. Our findings suggest pulmonary complications are far more important contributors to the smoking-mortality association than the cardiovascular complications. There has been significant emphasis placed on pre-operative cardiac risk assessment for non-cardiac surgery (28). Consensus statements on cardiac risk stratification including who should undergo screening and revascularization and management of patients with implanted cardiac stents have been developed and widely disseminated (29-31). 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. Similar attention has not been given

to pre-operative risk stratification for post-operative pulmonary events. These events occur more frequently than cardiovascular events and lead to substantial post-operative mortality (32-37).

Perioperative complications associated with smoking mediated a high proportion of the association of smoking and mortality before adjustment. But the proportion mediation was greatly attenuated after adjustment. This suggests that a major part of the mediation effect was contained in variables we adjusted for, including ASA class. 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). 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), and part due to immediate complications, such as pulmonary complications. The first goal should always be to get smokers to quit prior to surgery. But acknowledging that not all smokers will quit prior to their surgery, the surgical staff should be especially vigilant of pulmonary complications, as our data clearly demonstrates them to mediate mortality. Careful monitoring of adherence to pneumonia prevention guidelines in postoperative period as well as early diagnosis and management may lead to reduction in mortality. Far more importantly, preventive pre-operative evaluation and optimization of pulmonary health in addition to implementation of preoperative smoking cessation programs in patients undergoing elective surgery have the likelihood of reducing the increased mortality risk. Consensus statements on pulmonary risk assessment and patients who should be referred for intervention are strongly needed.

We found that the attributable risk of SSI to smoking-related mortality was lower than that for pulmonary and cardiovascular complications. SSIs constitute the most common infection, accounting for 38% of all infections (6). In addition, SSIs are associated with significant increases in hospital stay,(6) making them one of the most costly post-operative complications.(6, 40). SSIs are the third most common nosocomial infection overall, representing 14% of all hospital acquired infections. Thus even though their contribution to mortality is lower, their common prevalence and the ability to institute measures to prevent them make them suitable targets for interventions.

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.

Our study has several limitations. It is possible that findings may not be generalizable to women, since our sample included primarily men, representative of U.S. veterans. These findings may not be generalizable to non-veterans; however, it is unlikely that the pathway of smoking-associated mortality risk differs by veteran status. The current smoker variable in VASQIP is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association. Thus, these results are conservative estimates of these associations. Another limitation is that smoking status may change over time and current study design and analyses did not take that into account. Mediation assumes no unmeasured variables; this is of course not true as we can never account for all omitted factors. We accounted for all the important variables to the best of our capability with the given data. Another limitation of the mediation analysis is that the proportion mediated is influenced by

sample size, coefficient estimates, and distribution of the outcomes/predictors and since our variables were dichotomous and we have small standardized coefficient estimates.[1] Cause of death was not available to us, so these details could not be provided for smokers and never smokers.

In conclusion, this study found that a high proportion of association between smoking and post-operative 6-month and 1-year mortality is mediated by postoperative complications, especially pulmonary complications. Future efforts at reducing post-operative mortality should be aimed at pre-operative risk identification and intervention. Efforts directed at pulmonary risk stratification, surveillance and prevention for pulmonary and other complications in smokers undergoing elective surgery may likely impact mortality in current smokers undergoing elective surgical procedures.

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TABLES AND FIGURES

Table 1. Patient characteristics by smoking status* (Column percents unless noted otherwise)

Characteristic		Never Smoked (n=186,632)	Current Smoker (n=135,741)
Smoking Pack Years, mean (SD)		N/A	48.8 (32.6)
Demographics			
Age, mean (SD)		63.1 (13.7)	57.6 (11.0)
Sex	Female	5.1%	4.1%
	Male	94.9%	95.9%
Race/Ethnicity	White	62.3%	63.1%
	Black	12.3%	14.9%
	Hispanic	5.3%	2.7%
	Other/Unknown	20.2%	19.3%
Comorbidities			
Diabetes		20.2%	14.6%
Congestive heart failure		1.2%	1.0%
History of severe COPD		7.0%	18.4%
Dyspnea		8.4%	15.4%
Chronic Corticosteroid use		1.7%	1.7%
Renal failure/Dialysis		0.7%	0.5%
CVA/Stroke		5.9%	6.6%
Transient ischemic attacks		2.9%	3.6%

Functional health status	Independent	93.5%	94.8%
	Partially dependent	5.2%	4.6%
	Totally dependent	1.3%	0.6%
>10% loss body weight in past 6 months		1.8%	3.4%
Disseminated cancer		1.0%	1.3%
Open wound/wound infection		3.2%	4.3%
DNR status		0.9%	0.6%
Alcohol > 2 drinks/day		4.3%	14.6%
Operative Characteristics			
Anesthesia technique	General	79.4%	84.8%
	Epidural/Spinal	15.6%	10.9%
	Local/Monitored	5.1%	4.2%
ASA classification	1	4.4%	1.6%
	2	35.8%	33.4%
	3	53.8%	58.2%
	4/5	6.1%	6.8%
Admission status	Outpatient	51.0%	47.1%
	Inpatient	49.0%	52.9%
Specialty of Surgeon	General Surgery	39.3%	35.3%
	Neurosurgery	5.4%	7.9%
	Orthopedic Surgery	29.6%	21.9%
	Otolaryngology	1.1%	1.3%
	Plastic Surgery	0.6%	0.6%
	Thoracic Surgery	1.7%	5.6%
	Urology	15.6%	13.1%

	Cardiovascular Surgery	6.3%	13.8%
	Other	0.4%	0.4%
Wound Classification	Clean	70.0%	70.8%
	Clean/contaminated	27.3%	26.2%
	Contaminated	1.6%	1.6%
	Infected	1.2%	1.4%
Work RVU (mean, SD)		14.1 (7.1)	14.8 (7.8)
Operation time, hours (mean, SD)		1.9 (1.4)	2.1 (1.6)

***All p-value are < 0.001 with the exception of steroid use, for which was 0.581**

N/A, not applicable; SD, standard deviation; RUV, relative value units; ASA, American Society of Anesthesiologists; DNR, Do not resuscitate; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident

Table 2. Frequency of Outcomes by Smoking status

Postoperative Outcome	Never Smoked (n=186,632)	Current Smoker (n=135,741)
Surgical site infection	2.4	3.4
Vascular complications	0.5	0.5
Cerebral vascular accident/Stroke	0.2	0.3
Myocardial infarction	0.3	0.3
Pulmonary complications	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 outcome	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

Table 3. Unadjusted coefficients[a] and their 95% confidence intervals

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.12	0.08-0.15	0.37	0.33-0.41	0.89	0.81-0.96	0.10	0.07-0.14
	Cardiovascular complications	0.12	0.08-0.15	0.15	0.05-0.24	2.70	2.60-2.80	0.11	0.07-0.15
	Pulmonary complications	0.12	0.08-0.15	0.46	0.42-0.51	2.90	2.85-2.95	0.01	-0.02-0.05
	Composite outcome	0.12	0.08-0.15	0.39	0.36-0.42	2.21	2.17-2.25	0.02	-0.02-0.05
1-year mortality[c]	Surgical site infection	0.20	0.17-0.23	0.37	0.33-0.41	0.83	0.76-0.89	0.19	0.16-0.22
	Cardiovascular complications	0.20	0.17-0.23	0.15	0.05-0.24	2.42	2.32-2.52	0.20	0.17-0.23
	Pulmonary complications	0.20	0.17-0.23	0.46	0.42-0.51	2.60	2.57-2.64	0.13	0.10-0.17
	Composite outcome	0.20	0.17-0.23	0.39	0.36-0.42	1.91	1.88-1.95	0.13	0.10-0.16

c=direct path from smoking to mortality

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite)

b= path from complication (SSI etc.) to mortality controlling for smoking

c' = path from smoking to mortality controlling for complication (SSI etc.)

[a] all coefficients were unstandardized and rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking') = 3.30, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.32, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.34, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.54

[c]Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking') = 3.33, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.34, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.36, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.47, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.49

Table 4. Adjusted coefficients[a] and their 95% confidence intervals controlling for confounding

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.39	0.35-0.44	0.19	0.14-0.24	0.45	0.37-0.53	0.39	0.35-0.43
	Cardiovascular complications	0.38	0.34-0.42	0.19	0.08-0.30	2.00	1.89-2.12	0.38	0.34-0.42
	Pulmonary complications	0.38	0.34-0.42	0.48	0.43-0.54	2.17	2.11-2.23	0.32	0.27-0.36
	Composite outcome	0.38	0.34-0.42	0.29	0.25-0.32	1.71	1.66-1.76	0.33	0.28-0.37
1-year mortality[c]	Surgical site infection	0.45	0.42-0.49	0.19	0.14-0.24	0.44	0.37-0.51	0.45	0.41-0.48
	Cardiovascular complications	0.44	0.40-0.47	0.19	0.08-0.30	1.77	1.66-1.88	0.44	0.40-0.47
	Pulmonary complications	0.44	0.40-0.47	0.48	0.43-0.54	1.90	1.85-1.96	0.39	0.36-0.43
	Composite outcome	0.44	0.40-0.47	0.29	0.25-0.32	1.44	1.40-1.48	0.40	0.36-0.44

c=direct path from smoking to mortality controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite) controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

b= path from complication (SSI etc.) to mortality controlling for smoking, age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

c' = path from smoking to mortality controlling for complication (SSI etc.), age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

[a] all coefficients were unstandardized and were rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking [SSI]') = 3.44, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.43, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.44,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.45, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.53

[c] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking [SSI]') = 3.49, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.48, var (SSI) =

0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.49,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.49, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.52, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.54

Table 5. Proportion of mediation of smoking to mortality association explained by each complication in unadjusted and adjusted models

Outcome	Mediator	Proportion Mediation Unadjusted for covariates	Proportion Mediation Adjusted for covariates
6-month mortality	Surgical site infection	22.2%	2.0%
	Cardiovascular complications	12.2%	3.8%
	Pulmonary complications	88.9%	21.6%
	Composite outcome	86.4%	15.7%
1-year mortality	Surgical site infection	12.6%	1.7%
	Cardiovascular complications	6.5%	3.0%
	Pulmonary complications	42.7%	16.2%
	Composite outcome	40.8%	11.3%

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

Figure 1. Path diagram of the relations among the three standardized variables and standardized coefficients of paths

Figure legend:

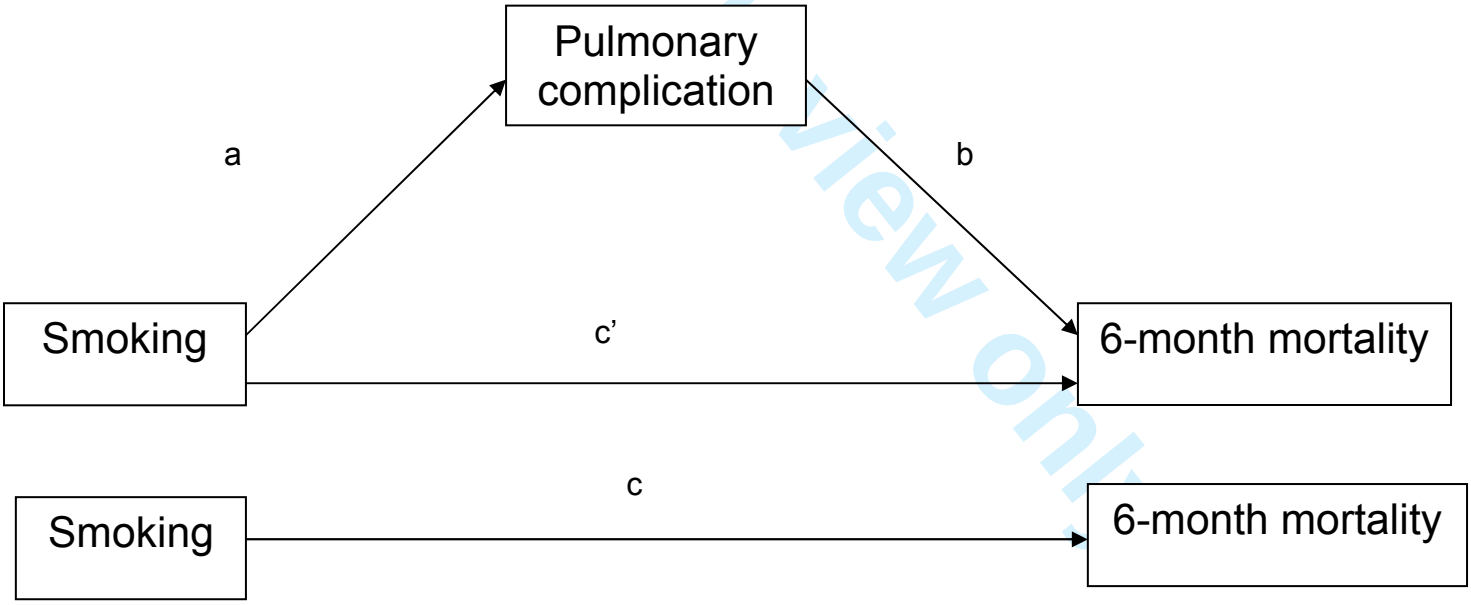
a= regression coefficient for path from smoking to pulmonary complication

b= regression coefficient for path from pulmonary complication to 6-month mortality, controlling for smoking

c'= regression coefficient for path from smoking to 6-month mortality, controlling for pulmonary complication

c= regression coefficient for direct path from smoking to 6-month mortality

Smoking is the independent variable, pulmonary complication the mediator and 6-month mortality dependent variable. a, b, c and c' are coefficients from logistic regression analyses.



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Mediation of Smoking-Associated Postoperative Mortality by perioperative complications in ~~Smokers~~ Veterans undergoing Elective Surgery: ~~An analysis of~~Data from Veterans Affairs Surgical Quality Improvement Program (VASQIP)

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Veterans Affairs Rheumatology Field Advisory Committee. Other authors declare no conflict of interest.

Each author certifies that his or her institution has approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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"The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."

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Running Title: Mediators of Mortality in Smokers Undergoing Arthroplasty

Article Summary

1) **Article Focus** -

- We aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery.
- We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality.

2) **Key Messages** -

- Pulmonary complications, followed by cardiovascular and surgical site infection complications were mediators of smoking-associated 6-month and 1-year mortality after elective knee or hip replacement surgery.
- Preoperative smoking counseling and implementation of smoking cessation programs should be done prior to an elective surgery such as knee/hip replacement.
- Early treatment of complications that mediate postoperative 1-year mortality may help to reduce risk of dying after an elective surgery.

3) **Strengths and Limitations -**

Strengths:

- Use of prospectively, collected national data in the largest integrated health care system in the U.S.

- Outcomes and complications had been defined using standardized definitions and validated by nurse abstractors

Limitations:

- Findings may not be generalizable to women and non-veteran U.S. population, since our sample included primarily men, representative of U.S. veterans.
- The current smoker variable is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association.
- Smoking status may change over time and the current study could not take that into account, since ongoing smoking status data are not available.
- Mediation assumes no unmeasured variables and despite accounting for all the important variables to the best of our capability with the given data, residual confounding is possible.

ABSTRACT

Objective: To assess the mediation of smoking-associated post-operative mortality by post-operative complications.

Design: Observational Cohort Study

Setting: Using data from the Veterans Affairs Surgical Quality Improvement Program, a quality assurance program for major surgical procedures in the VA healthcare system, we assessed the association of current smoking at the time of the surgery with 6-month and 1-year mortality.

Primary and Secondary Outcome Measures: Using mediation analyses, we calculated the relative contribution of each smoking-associated complication to smoking-associated postoperative mortality, both unadjusted and adjusted for age, race/ethnicity, work relative value unit of the operation, surgeon specialty, American Society of Anesthesiologists class, and year of surgery. Smoking-associated complications included surgical site infection, cardiovascular complications (myocardial infarction, cardiac arrest, and/or stroke), and pulmonary complications (pneumonia, failure to wean, and/or re-intubation).

Results: There were 186,632 never-smokers and 135,741 current smokers. The association of smoking and mortality was mediated by smoking-related complications with varying effects. In unadjusted analyses, the proportions of mediation of smoking to 6-month mortality explained by the complications were as follows: SSI, 22%; cardiovascular complications, 12%; and pulmonary complications, 89%. In adjusted analyses, the percents mediated by each complication were as follows: SSI, 2%; cardiovascular complications, 4%; and pulmonary complications, 22%. In adjusted analyses for 1-year mortality, respective percents mediated were 2%, 3% and 16%.

Conclusions: Pulmonary complications, followed by cardiovascular and SSI complications were mediators of smoking-associated 6-month and 1-year mortality. Interventions targeting smoking cessation and prevention and early treatment of pulmonary complications has the likelihood of reducing post-operative mortality after elective surgery.

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~~Trial Registration~~~~: Not applicable, not an interventional study~~

INTRODUCTION

Smoking is the leading cause of preventable death in the U.S. (1, 2). While the prevalence of smoking in the U.S. has decreased (3), smoking is still highly prevalent with a recent national survey showing between 10-26% prevalence in most U.S. states (4). The prevalence of smoking in veterans using Veterans Affairs (VA) health care is even higher, at 30% (5). Smoking has detrimental effects on cardiovascular and lung health, and is linked to increased risk of surgical complications. Specifically, smokers undergoing surgery have a higher risk of several postoperative complications including wound infections, pneumonia, and mortality (6, 7). Smoking is a modifiable risk factor (8-10). Preoperative smoking cessation is associated with decreased postoperative wound complications and total complications (11).

While smoking-related postoperative morbidity is important, smoking is also associated with increased post-operative mortality (12-14). There are several proposed mechanisms of increased mortality in the perioperative period for smokers, including higher risk of cardiac (12, 13) and pulmonary complications (14). To our knowledge, no previous studies have assessed to what degree the increased smoking-associated postoperative mortality is mediated by specific complications associated with smoking. This has important consequences for designing interventions to improve outcomes. 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 isAlternatively, if smoking were 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 direct actionsinterventions to reduce pulmonary complications among smokers may be an additional strategy alternative method for improving the mortality outcome.

We have recently demonstrated that smoking was associated with both postoperative surgical site infections (SSI) and pulmonary complications in a large cohort of veterans who

underwent surgery in VA medical facilities and that mortality was also increased in this cohort (15). These data are collected prospectively and systematically as part of the National VA Surgical Quality Improvement Program (VASQIP) (16) (17).

In this study we aimed to examine whether smoking-associated post-operative mortality is mediated through smoking-associated postoperative complications in patients who are current smokers at the time of their surgery. Conceptually, "mediation" occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events (18). As an example, this study explored the link between smoking and postoperative morbidity and mortality. We hypothesized that specific smoking-associated complications (SSI, pulmonary, cardiovascular) in the post-operative period in current smokers, mediate smoking-related 6-month and 1-year mortality. 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, ~~i.e., once a link was established between smoking and adverse outcomes, we investigated whether the effect was directly due to smoking itself or whether it acts through a mediator,~~ in this case, smoking-associated complication.

METHODS

Ethical Approval, Study Funding and Data sharing

The study was approved by the Institutional Review Boards at the VA Medical Centers (Birmingham, AL, Bedford, MA, Boston, MA and Seattle, WA), the University of Colorado, and by the Surgical Quality Data Use Group of VA Patient Care Services in VA Central Office, Washington, DC (as needed for studies using data from this dataset). All analyses used SAS version 9.2 (SAS Institute Inc., Cary, North Carolina). This material is the result of work supported with VA Investigator-Initiated Research (IIR) IAB 06-038-2. Additionally, Dr. Singh's time was protected by research grants from the National Institute of Aging, National Cancer Institute and Agency for Health Quality and Research Center for Education and Research on Therapeutics (CERTs). We are committed to sharing the data with colleagues after an ethics committee approval and in accordance with VA data privacy and data security rules.

Study Sample

We used data from the VASQIP, a system-wide initiative instituted in 1994 to improve the quality of surgical care through prospective collection and reporting of comparative risk-adjusted post-operative outcomes of major surgeries requiring general, spinal, or epidural anesthesia(19). The abstracted data are >99% complete with >96% inter-observer agreement(17). We requested all cases in major procedure groups defined by CPT codes within each of the 8 surgical subspecialties (general, vascular, orthopedic, thoracic, otolaryngology, urology, neurosurgery, and plastic surgery) for the years 2002-2008. This produced a sample of roughly 60-70% of all non-cardiac operations in the VASQIP database for those years (n=507,545). We selected the first operation for each patient greater than or equal to 19 years of age, resulting in 412,511 unique patients. We excluded 17,202 patients coded as having emergency operations, since we wanted to focus on elective surgeries. We also excluded 1,515 patients who were coded as a current smoker but who had 0 pack-years (an

inconsistency) or were missing the current smoker variable. Since our focus was current smoking, we excluded 71,421 prior smokers leaving a total of 322,373 patients for analysis.

Independent Measure: Current Smoking

Smoking status was assessed using two variables. Patients are queried at the time of elective surgery if they have smoked cigarettes in the year prior to admission (yes/no) and regarding amount of smoking (pack years = the number of packs smoked per day multiplied by the number of years the patient smoked), documented in patients' medical records. Never-smokers were patients who had no smoking in the prior year and zero (or missing) pack years. Current smokers were those who responded "yes" to smoking in the year prior to admission and had pack years not equal to zero.

Dependent Measure: Mortality

Mortality was assessed at 6-months and at 1-year. The VASQIP nurses collect 30-day postoperative vital status for all patients assessed in the VASQIP program. Once every 6 months, the VASQIP database is passed through the VA administrative vitals file to obtain data on long-term postoperative mortality beyond 30 days after surgery.

Mediation Variables: 30-day Outcomes for Complications

All complications of interest were assessed 30-days after elective surgery. Specifically, the outcomes included: (1) SSI; (2) Cardiovascular complication, defined as occurrence of myocardial infarction (MI), cardiac arrest, and/or stroke; (3) Pulmonary complication, defined as occurrence of pneumonia, failure to wean, and/or re-intubation; and (4) Overall composite outcome, defined as the occurrence of SSI, cardiovascular and/or pulmonary complication. All outcomes have standard definitions in VASQIP and are extracted and validated for each patient

by an independent nurse abstractor at each VA site for the 30-day period after the surgery (16, 17).

Covariates: Patient, Surgeon, and Procedural Characteristics

Patient characteristics including age, race/ethnicity, American Society of Anesthesiologists (ASA) class, year of surgery, work relative value unit (RVU) for the operation, and wound classification were extracted. ASA class is a validated measure of peri-operative mortality and immediate post-operative morbidity, categorized into five classifications (20, 21) (class I, normal healthy patient; class II, patient with mild systemic disease (with no functional limitation); class III, patient with severe systemic disease (with some functional limitation); class IV, patient with severe systemic disease that is a constant threat to life; class V, moribund patient). Work RVU (a measure of procedure duration and complexity) and surgeon subspecialty were collected by chart review. These variables were chosen based on previous literature of association of these factors with mortality or because they represented the complexity of the surgery.

Statistical Analyses

Summary statistics were calculated for clinical and demographic characteristics. Mediation analysis was done without and with controlling for covariates that could potentially confound the relationship. Univariable and multivariable-adjusted logistic regression analyses were used to compute coefficients for association of smoking and mortality, smoking and major complications (SSI, pulmonary, cardiovascular or composite) and major complications and mortality, to assess mediation effect of complications on the relationship between smoking and mortality. In multivariable analyses, we adjusted for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year at each step of the mediation analysis. Wound classification was additionally adjusted for in the model when assessing the mediation effect of SSI.

The conceptual framework of "mediation" indicates that mediation occurs when a cause and its effect are linked through an intervening factor that is part of the causal chain of events (18). The classic exposition of statistical mediation analysis was given by Baron and Kenny in 1986 (18). The mediating relationship was conceived in causal terms, so while it was recognized that the statistical models cannot establish causality, the causal interpretation of the posited relationships must be plausible. The precondition was that the independent variable (smoking) is statistically significantly associated with the dependent variable (e.g. 6-month mortality). The total effect of smoking on mortality was denoted by the path "c" in figure 1 representing the ~~effect~~ association of smoking on mortality without adjustment for the potential mediator. Baron and Kenny outlined three steps for a formal mediation analysis using regression, which can be explained with reference to figure 1 in the context of the relationship between smoking and 6-month mortality with the putative mediating effect of pulmonary complications. The first step was to establish that there is a significant association between the independent variable (smoking) and the potential mediator (pulmonary complications) corresponding to the path coefficient "a" in figure 1. The second step was to establish that the potential mediator (pulmonary complications) is associated with the dependent variable (6-month mortality), while controlling for the independent variable (smoking), corresponding to the path coefficient "b". 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. 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 ~~the relationship between smoking and mortality was significantly smaller~~ when controlling for pulmonary complications, then there was a significant amount of mediation by pulmonary complications.

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Arithmetically, the indirect effect is equal to the product of coefficients a*b and the total effect (c), is equal to the indirect effect (a*b) plus the remaining direct effect (c'), thus: c=a*b +c', so c'=c-a*b. Clearly, as the indirect effect through the mediator gets larger, the residual direct effect must decrease, implying that a larger part of the effect is via the mediator. The more the direct effect is diminished, the greater part of the effect is mediated.

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.

~~In our work, the independent, dependent, and mediator variable were all dichotomous. For this situation, logisitic regression was used and coefficients must then be standardized to the same scale prior to comparison and statistical testing as presented by MacKinnon and Dwyer (22). When using logistic regression, unlike in multiple regression, a*b+c' only approximated c. In this work, we reported the proportion of the effect mediated as (a*b)/(a*b+c'), or the indirect effect divided by the total effect. 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.~~

RESULTS

There were 186,632 never-smokers and 135,741 current smokers. The mean age was 63 years for never smokers and 58 years for current smokers. 95% were men and 63% were White (race/ethnicity missing in 19%) (**Table 1**). Diabetes was less common among current smokers compared to never smokers, but COPD, dyspnea, and alcohol consumption were more common. Other characteristics were similar between the two groups (**Table 1**). Crude estimates of outcomes by smoking status us shown in **Table 2**.

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Mediation Analyses for 6-month and 1-year mortality

Unstandardized coefficients were calculated without (unadjusted; **Table 3~~2~~**) and with (adjusted; **Table 4~~3~~**) potential confounders using regression analyses**.** Variances for computing standardized coefficients are footnoted. The unadjusted coefficients were highest between smoking and pulmonary complications (coefficient a =0.46), and between pulmonary complication and 6-month mortality, controlling for smoking was (coefficient b =2.90) among all complications (**Table 3~~2~~**); similar observations were made for pulmonary complications and 1-year mortality. In general unadjusted coefficients were higher than adjusted coefficients.

Table 4~~3~~ provides coefficients for the mediation analyses controlling for confounding from age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year for 6-month and 1-year mortality. Mediation analysis for SSI additionally controlled for wound classification. The coefficients for the path from smoking to 6- and 12-month mortality when considering the mediation factor of SSI were 0.39 and 0.45 (coefficient c). Again as an example, the coefficient between smoking and pulmonary complications was 0.48 (coefficient a), between pulmonary complication and 6-month mortality controlling for smoking was 2.17 (coefficient b), and that between smoking and 6-month mortality controlling for pulmonary complication was 0.32 (coefficient c'). The association between smoking and 6-month mortality was significantly mediated by pulmonary complication (22%) (**Table 5**). For 6-month mortality, adjusted

coefficients between smoking and complications were highest for pulmonary complications (0.48), followed by composite outcome (0.29), SSI (0.19) and cardiovascular complications (0.19) (coefficient a). Adjusted coefficients were highest for pulmonary followed by cardiovascular, composite and SSI complications for association with 6-month mortality, controlling for smoking (coefficient b). The proportion of mediation of smoking to 6-month mortality explained by the complications in adjusted analyses was 16% for the composite outcome, while the proportions were lower for SSI (2%) and cardiovascular complications (4%) (**Table 54**).

Similar patterns were noted for mediation of smoking and 1-year mortality for adjusted coefficients (**Table ~~43~~**). In the adjusted models, the proportion of mediation of smoking to 1-year mortality explained by the complications in adjusted analyses was 16% for pulmonary complications, 11% for composite complications, 3% for cardiovascular complications and 2% for SSI (**Table 54**).

DISCUSSION

In this analysis of prospectively collected data in a national sample of non-cardiac elective surgeries at VA facilities, we found that increased 6-month and 1-year smoking-associated mortality was mediated by pulmonary complications and to a lesser extent cardiovascular complications and surgical site infections. Not unexpectedly, estimates of the proportion of smoking-related mortality mediated by each peri-operative complication were all numerically larger for~~the proportion of smoking-mortality association mediated by these peri-operative complications was greater for~~ 6-month mortality compared to that for 1-year mortality, although this was not tested statistically. The proportion mediated by complications also attenuated significantly between adjusted and unadjusted analyses, as expected. These observations are novel and have important implications for targeting interventions for patients undergoing elective surgery.

That smoking is associated with increased mortality after elective surgical procedures is well known (24, 25). Preoperative period has been proposed a "window of opportunity" and a "teachable moment" to help patients quit smoking (26, 27). This study examined a critical question, i.e., is this increased mortality mediated by the postoperative complications seen more commonly in smokers than in non-smokers? The evidence presented here confirmed~~s~~ that these postoperative complications mediated significant proportion of increased mortality risk, and that this varied~~s~~ by the type of complication. Pulmonary complications explained the most variation in this increased risk, as compared to cardiovascular complications or surgical site infections. Our findings suggest pulmonary complications are far more important contributors to the smoking-mortality association than the cardiovascular complications. There has been significant emphasis placed on pre-operative cardiac risk assessment for non-cardiac surgery (28). Consensus statements on cardiac risk stratification including who should undergo screening and revascularization and management of patients with implanted cardiac stents have been developed and widely disseminated (29-31). Perhaps this focus and attention on

identifying and intervening on cardiac risk has mitigated the association~~effect~~s of smoking related cardiovascular events ~~on~~ with mortality, in both smokers and never smokers. Similar attention has not been given to pre-operative risk stratification for post-operative pulmonary events. These events occur more frequently than cardiovascular events and lead to substantial post-operative mortality (32-37).

Perioperative complications associated with smoking mediated a high proportion of the association of smoking and mortality before adjustment. But the proportion mediation was greatly attenuated after adjustment. This suggests that a major part of the mediation effect was contained in variables we adjusted for, including ASA class. In addition, some of the association of smoking and subsequent mortality is related to lifetime exposure to smoking (direct effect), and not the ~~direct~~ association~~effect~~ of smoking on perioperative complications (indirect effect through pulmonary 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 ~~effect~~ association of smoking on mortality is due to a lifetime exposure ~~effect~~, as shown previously (38, 39), and part due to immediate complications, such as pulmonary complications. The first goal should always be to get smokers to quit prior to surgery. But acknowledging that not all smokers will quit prior to their surgery, the surgical staff should be especially vigilant of pulmonary complications, as our data clearly demonstrates them to mediate mortality. Careful monitoring of adherence to pneumonia prevention guidelines in postoperative period as well as early diagnosis and management may lead to reduction in mortality. Far more importantly, preventive pre-operative evaluation and optimization of pulmonary health in addition to implementation of preoperative smoking cessation programs in patients undergoing elective surgery have the likelihood of reducing the increased mortality risk. Consensus statements on

pulmonary risk assessment and patients who should be referred for intervention are strongly needed.

We found that the attributable risk of SSI to smoking-related mortality was lower than that for pulmonary and cardiovascular complications. SSIs constitute the most common infection, accounting for 38% of all infections (6). In addition, SSIs are associated with significant increases in hospital stay,(6) making them one of the most costly post-operative complications.(6, 40). SSIs are the third most common nosocomial infection overall, representing 14% of all hospital acquired infections. Thus even though their contribution to mortality is lower, their common prevalence and the ability to institute measures to prevent them make them suitable targets for interventions.

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.

Our study has several limitations. It is possible that findings may not be generalizable to women, since our sample included primarily men, representative of U.S. veterans. These findings may not be generalizable to non-veterans; however, it is unlikely that the pathway of smoking-associated mortality risk differs by veteran status. The current smoker variable in VASQIP is collected retrospectively from medical records, which could lead to misclassification bias and underestimation of the association. Thus, these results are conservative estimates of these associations. Another limitation is that smoking status may change over time and current study design and analyses did not take that into account. Mediation assumes no unmeasured variables; this is of course not true as we can never account for all omitted factors. We

accounted for all the important variables to the best of our capability with the given data. Another limitation of the mediation analysis is that the proportion mediated is influenced by sample size, coefficient estimates, and distribution of the outcomes/predictors and since our variables were dichotomous and we have small standardized coefficient estimates.[1] Cause of death was not available to us, so these details could not be provided for smokers and never smokers.

In conclusion, this study found that a high proportion of association between smoking and post-operative 6-month and 1-year mortality is mediated by postoperative complications, especially pulmonary complications. Future efforts at reducing post-operative mortality should be aimed at pre-operative risk identification and intervention. Efforts directed at pulmonary risk stratification, surveillance and prevention for pulmonary and other complications in smokers undergoing elective surgery may likely impact mortality in current smokers undergoing elective surgical procedures.

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TABLES AND FIGURES

Table 1. Patient characteristics by smoking status* (Column percents unless noted otherwise)

Characteristic		Never Smoked (n=186,632)	Current Smoker (n=135,741)
Smoking Pack Years, mean (SD)		N/A	48.8 (32.6)
Demographics			
Age, mean (SD)		63.1 (13.7)	57.6 (11.0)
Sex	Female	5.1%	4.1%
	Male	94.9%	95.9%
Race/Ethnicity	White	62.3%	63.1%
	Black	12.3%	14.9%
	Hispanic	5.3%	2.7%
	Other/Unknown	20.2%	19.3%
Comorbidities			
Diabetes		20.2%	14.6%
Congestive heart failure		1.2%	1.0%
History of severe COPD		7.0%	18.4%
Dyspnea		8.4%	15.4%
Chronic Corticosteroid use		1.7%	1.7%
Renal failure/Dialysis		0.7%	0.5%
CVA/Stroke		5.9%	6.6%
Transient ischemic attacks		2.9%	3.6%

Functional health status	Independent	93.5%	94.8%
	Partially dependent	5.2%	4.6%
	Totally dependent	1.3%	0.6%
>10% loss body weight in past 6 months		1.8%	3.4%
Disseminated cancer		1.0%	1.3%
Open wound/wound infection		3.2%	4.3%
DNR status		0.9%	0.6%
Alcohol > 2 drinks/day		4.3%	14.6%
Operative Characteristics			
Anesthesia technique	General	79.4%	84.8%
	Epidural/Spinal	15.6%	10.9%
	Local/Monitored	5.1%	4.2%
ASA classification	1	4.4%	1.6%
	2	35.8%	33.4%
	3	53.8%	58.2%
	4/5	6.1%	6.8%
Admission status	Outpatient	51.0%	47.1%
	Inpatient	49.0%	52.9%
Specialty of Surgeon	General Surgery	39.3%	35.3%
	Neurosurgery	5.4%	7.9%
	Orthopedic Surgery	29.6%	21.9%
	Otolaryngology	1.1%	1.3%
	Plastic Surgery	0.6%	0.6%
	Thoracic Surgery	1.7%	5.6%
	Urology	15.6%	13.1%

	Cardiovascular Surgery	6.3%	13.8%
	Other	0.4%	0.4%
Wound Classification	Clean	70.0%	70.8%
	Clean/contaminated	27.3%	26.2%
	Contaminated	1.6%	1.6%
	Infected	1.2%	1.4%
Work RVU (mean, SD)		14.1 (7.1)	14.8 (7.8)
Operation time, hours (mean, SD)		1.9 (1.4)	2.1 (1.6)

***All p-value are ~~less than~~< 0.001 with the exception of steroi~~i~~d use, for which was 0.581**

N/A, not applicable; SD, standard deviation; RUV, relative value units; ASA, American Society of Anesthesiologists; DNR, Do not resuscitate; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident

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Table 2. Frequency of Outcomes by Smoking status

Postoperative Outcome	Never Smoked (n=186,632)	Current Smoker (n=135,741)
Surgical site infection	2.4	3.4
Vascular complications	0.5	0.5
Cerebral vascular accident/Stroke	0.2	0.3
Myocardial infarction	0.3	0.3
Pulmonary complications	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 outcome	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

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Table 32. Unadjusted coefficients[a] and their 95% confidence intervals

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.12	0.08-0.15	0.37	0.33-0.41	0.89	0.81-0.96	0.10	0.07-0.14
	Cardiovascular complications	0.12	0.08-0.15	0.15	0.05-0.24	2.70	2.60-2.80	0.11	0.07-0.15
	Pulmonary complications	0.12	0.08-0.15	0.46	0.42-0.51	2.90	2.85-2.95	0.01	-0.02-0.05
	Composite outcome	0.12	0.08-0.15	0.39	0.36-0.42	2.21	2.17-2.25	0.02	-0.02-0.05
1-year mortality[c]	Surgical site infection	0.20	0.17-0.23	0.37	0.33-0.41	0.83	0.76-0.89	0.19	0.16-0.22
	Cardiovascular complications	0.20	0.17-0.23	0.15	0.05-0.24	2.42	2.32-2.52	0.20	0.17-0.23
	Pulmonary complications	0.20	0.17-0.23	0.46	0.42-0.51	2.60	2.57-2.64	0.13	0.10-0.17
	Composite outcome	0.20	0.17-0.23	0.39	0.36-0.42	1.91	1.88-1.95	0.13	0.10-0.16

c=direct path from smoking to mortality

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite)

b= path from complication (SSI etc.) to mortality controlling for smoking

c' = path from smoking to mortality controlling for complication (SSI etc.)

[a] all coefficients were unstandardized and rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking') = 3.30, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.32, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.34, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.54

[c]Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking') = 3.33, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.42, var (predicted Mortality|Smoking & SSI'') = 3.34, var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.31, var (predicted Mortality|Smoking & Cardiovascular'') = 3.36, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.50, var (predicted Mortality|Smoking & Pulmonary'') = 3.47, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.44, var (predicted Mortality|Smoking & Composite'') = 3.49

Table 43. Adjusted coefficients[a] and their 95% confidence intervals controlling for confounding

Outcome	Mediator	c	95% CI	a	95% CI	b	95% CI	c'	95% CI
6-month mortality[b]	Surgical site infection	0.39	0.35-0.44	0.19	0.14-0.24	0.45	0.37-0.53	0.39	0.35-0.43
	Cardiovascular complications	0.38	0.34-0.42	0.19	0.08-0.30	2.00	1.89-2.12	0.38	0.34-0.42
	Pulmonary complications	0.38	0.34-0.42	0.48	0.43-0.54	2.17	2.11-2.23	0.32	0.27-0.36
	Composite outcome	0.38	0.34-0.42	0.29	0.25-0.32	1.71	1.66-1.76	0.33	0.28-0.37
1-year mortality[c]	Surgical site infection	0.45	0.42-0.49	0.19	0.14-0.24	0.44	0.37-0.51	0.45	0.41-0.48
	Cardiovascular complications	0.44	0.40-0.47	0.19	0.08-0.30	1.77	1.66-1.88	0.44	0.40-0.47
	Pulmonary complications	0.44	0.40-0.47	0.48	0.43-0.54	1.90	1.85-1.96	0.39	0.36-0.43
	Composite outcome	0.44	0.40-0.47	0.29	0.25-0.32	1.44	1.40-1.48	0.40	0.36-0.44

c=direct path from smoking to mortality controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

a= path from smoking to complication (SSI, cardiovascular, pulmonary or composite) controlling for age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

b= path from complication (SSI etc.) to mortality controlling for smoking, age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

c' = path from smoking to mortality controlling for complication (SSI etc.), age, race/ethnicity, work RVU, surgeon specialty, ASA class, and year

[a] all coefficients were unstandardized and were rounded off to 2-digits after the decimal

[b] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.036, var(predicted Mortality|Smoking [SSI]') = 3.44, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.43, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.44,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.45, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.49, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.53

[c] Variances used to compute standardized coefficients (22): var (Smoking) = 0.975, var (Mortality) = 0.054, var(predicted Mortality|Smoking [SSI]') = 3.49, var(predicted Mortality|Smoking [Cardiovascular, Pulmonary, and Composite]') = 3.48, var (SSI) = 0.028, var (predicted SSI|Smoking') = 3.32, var (predicted Mortality|Smoking & SSI'') = 3.49,var (Cardiovascular) = 0.005, var (predicted Cardiovascular|Smoking') = 3.33, var (predicted Mortality|Smoking & Cardiovascular'') = 3.49, var (Pulmonary) = 0.024, var (predicted Pulmonary|Smoking') = 3.52, var (predicted Mortality|Smoking & Pulmonary'') = 3.52, var (Composite) = 0.051, var (predicted Composite|Smoking') = 3.37, var (predicted Mortality|Smoking & Composite'') = 3.54

Table 54. Proportion of mediation of smoking to mortality association explained by each complication in unadjusted and adjusted models

Outcome	Mediator	Proportion Mediation Unadjusted for covariates	Proportion Mediation Adjusted for covariates
6-month mortality	Surgical site infection	22.2%	2.0%
	Cardiovascular complications	12.2%	3.8%
	Pulmonary complications	88.9%	21.6%
	Composite outcome	86.4%	15.7%
1-year mortality	Surgical site infection	12.6%	1.7%
	Cardiovascular complications	6.5%	3.0%
	Pulmonary complications	42.7%	16.2%
	Composite outcome	40.8%	11.3%

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~~The proportion mediated has been shown to be~~

~~unstable and should be interpreted with caution~~. Coefficient values (magnitude and significance) should be the main proponent in assessing mediation

Figure 1. Path diagram of the relations among the three standardized variables and standardized coefficients of paths

Figure legend:

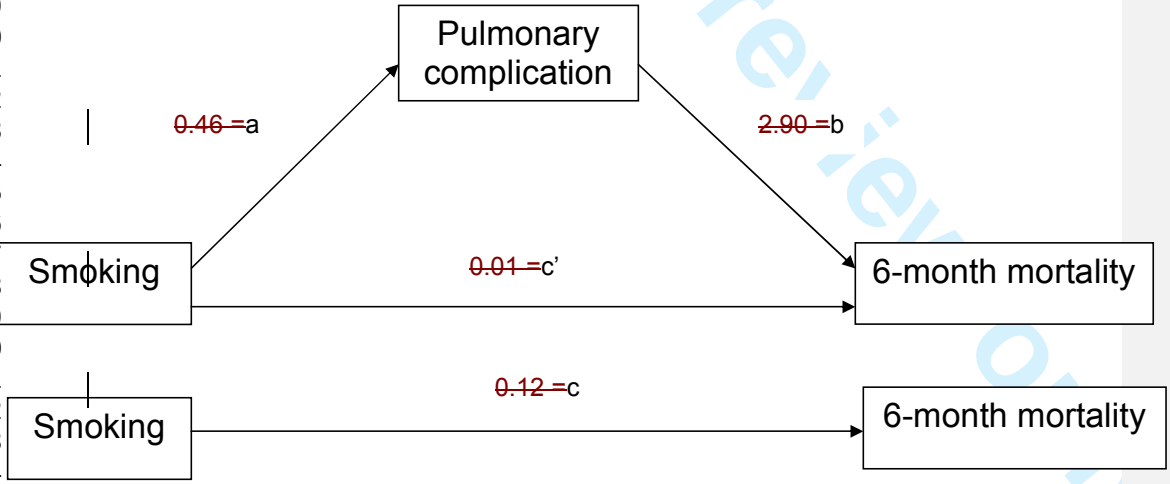
a= regression coefficient for path from smoking to pulmonary complication

b= regression coefficient for path from pulmonary complication to 6-month mortality, controlling for smoking

c'= regression coefficient for path from smoking to 6-month mortality, controlling for pulmonary complication

c= regression coefficient for direct path from smoking to 6-month mortality

Smoking is the independent variable, pulmonary complication the mediator and 6-month mortality dependent variable. a, b, c and c' are coefficients from logistic regression analyses.



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