Global Spine Journal
2023, Vol. 13(1) 242–253

DOI: 10.1177/21925682221110127
journals.sagepub.com/home/gsj

The Risk of Adverse Events in Smokers Undergoing Spinal Fusion: A Systematic Review and Meta-Analysis

Ravi S. Nunna, MD[1], Darius Ansari, MD[2], Philip B. Ostrov, MD[2], Joseph R. Dettori, PhD[3], Periklis Godolias, MD[4], Michael Ortiz-Torres, MD[1], Elias Elias, MD[5], Max Gruber, BS[6], Rod J. Oskouian, MD[4], and Jens R. Chapman, MD[4]

Abstract

Study Design: Systematic review and meta-analysis.

Objectives: Determine if tobacco use is associated with increased risk of postoperative adverse events within 90 days in patients undergoing spinal fusion surgery.

Methods: Databases were queried to identify cohort studies that directly compared smokers with non-smokers and provided the absolute number of adverse events and the population at risk. Data quality was evaluated using the Quality in Prognosis Studies tool. Risk ratios (RR) and 95% confidence intervals were calculated and compared between studies. The grading of recommendation, assessment, development and evaluation (GRADE) criteria were used to assess the strength of the evidence.

Results: Seventeen studies assessing 37 897 participants met the inclusion criteria. Of these, 10 031 (26.5%) were smokers and 27 866 (73.5%) were nonsmokers. The mean age for the study population was 58 years, and 45% were males. Smoking was not associated with increased risk of one or more major adverse events within 90 days following spine surgery (seven studies, pooled RR 1.13, 95% CI [.75-1.71], I2 = 41%). However, smoking was significantly associated with one or more major adverse events in ≤2 level fusion (three studies, pooled RR 2.46, 95% CI [1.18-5.12], I2 = 0%), but not in fusions of ≥3 levels (four studies, pooled RR .87, 95% CI [.70-1.08], I2 = 0%). Additionally, there was no statistically significant association between smoking and any adverse event, nor increased reoperation risk due to adverse events.

Conclusions: In this meta-analysis, tobacco use was not associated with a statistically significant increased risk of adverse events within 90 days in patients undergoing spinal fusion surgery. Our results are limited by the variable reporting methodology for both complication rates as well as smoking incidence between the included individual studies.

Keywords
fusion, smoking, nicotine, adverse, complications

Introduction

The use of tobacco products is widespread globally and is considered one of the most significant public health threats by the World Health Organization, killing more than eight million annually.[1] The harmful health effects from nicotine and other toxins are far-reaching and multi-organ dependent, causing both local as well as systemic microtrauma secondary to a myriad of inflammatory mechanisms.[2]

[1] Department of Neurosurgery, University of Missouri, Columbia, MO, USA
[2] Department of Neurosurgery, University of Illinois at Chicago, Chicago, IL, USA
[3] Spectrum Research, Inc, Tacoma, WA, USA
[4] Swedish Neuroscience Institute, Seattle, WA, USA
[5] Department of Neurosurgery, University of Texas-Southwestern, Dallas, TX, USA
[6] Elson S. Floyd College of Medicine, Spokane, WA, USA

Corresponding Author:
Ravi Nunna, Department of Neurosurgery, University of Missouri Health Care, 1 Hospital Dr, Columbia, MO 65212, USA.
Email: ravisnunna@gmail.com

Smoking increases the risk of various adverse surgical outcomes, including mortality, infection, and poor wound healing.[3-6] Tobacco smoking status has been previously associated with poor outcomes after spine surgery in particular, including increased rates of nonunion,[7] adjacent segment disease,[8,9] reoperation,[9] and postoperative disability.[10] The process by which smoking may result in such adverse events has been proposed to be secondary to osteoporotic degeneration and decreased disc tissue perfusion; however, the full mechanism has yet to be elucidated.[11,12] This has led most spine surgeons to strongly adhere to smoking cessation protocols, which most commonly consist of smoking cessation for at least 4 weeks prior to surgery.[8] In a similar fashion, most hospitals and surgery centers will consent patients for nicotine testing the morning of surgery in order to determine if it is safe to proceed with the procedure.

While there is well-documented evidence that smoking confers deleterious effects on spine surgery outcomes,[7,10,13,14] the scope and magnitude of adverse events remain controversial.[15-17] Most compiled evidence is derived from retrospective cohort studies. The purpose of this meta-analysis is to determine if tobacco use is associated with an increased risk of adverse events within a 90 days period after cervical or thoracolumbar fusion surgery.

Methods

Protocol and Registration

This work was registered with PROSPERO (CRD42021255534).[18] The study was conducted following the framework outlined by the Cochrane Prognosis Methods Group[19,20] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[21]

Identification of Studies

Multiple databases were searched including MEDLINE (PubMed), EMBASE (Ovid), Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from inception to April 30, 2021. Supplementary Table S1 in the supplemental material describes the search strategy. In addition to the electronic searches, reference lists of systematic reviews and included studies were reviewed for additional articles. The search was restricted to articles published in English.

Assessment of Eligibility

The titles and abstracts were screened independently by two of the authors to identify articles for full-text review. Citations were retrieved if deemed appropriate for inclusion by at least one of those authors. Each full-text article was independently reviewed for eligibility by the same two authors. Any disagreements were resolved by consensus.

Pre-established criteria were used to determine eligibility for inclusion and exclusion of full-text articles based on PECOT (patient population of interest, exposure, comparator, outcome, and timing), Table 1. The corresponding article's authors' definition of current smoking status was accepted. However, in cases where a study presented data for current, former, and never smokers, 'current' smokers were defined as those smoking within one year prior to surgery and non-smokers as those who quit one year prior to surgery. Adverse events within 90 days were classified as "major" or "minor", Table 2. "Major" adverse events were classified as perioperative events producing a detrimental effect and requiring significant further intervention, such as revision surgery. By contrast, "minor" adverse events were defined as any other perioperative events producing transient detrimental effect and not requiring significant further intervention.

Only cohort studies that directly compared smokers with non-smokers and provided the absolute number of adverse events and the population at risk were included. Prognostic studies that looked at several risk factors for adverse events that included smoking in a multivariate analysis but did not list the number of adverse events or the population at risk were excluded.

Data Abstraction and Data Management

Date from each study was extracted into an Excel spreadsheet (Microsoft, Redmond, WA). Data included: author last name, publication year, study design, country, sample size, population characteristics, data source, location and levels of fusion, surgical approach, follow-up time, and adverse events.

Table 1. Inclusion and exclusion criteria.

PECOT	Inclusion	Exclusion
Population	Adult (≥18 years) undergoing spinal fusion (single-level or multi-level; cervical or thoracolumbar)	Cancer, infection, trauma
Exposure	Smoking tobacco (current, defined as smoking within 1 year prior to surgery)	Smokeless tobacco Ex-smokers
Comparison	Non-current smokers	
Outcomes	Adverse events (major and minor)	Transfusion, blood loss
Time	≤90 days	

Table 2. Minor and major adverse events.

Minor adverse events	Major adverse events
C5 palsy	Cardiac arrest
Delirium	Coma
Durotomy	Cerebral vascular accident/stroke
DVT	Death
Dysphagia	Hardware malposition/ failure
Hematoma	Hepatic encephalopathy
Ileus	Meningitis
Nerve injury	Myocardial infarction
Pleural effusion	Pulmonary embolism
Pneumonia	Pericardial effusion
Pulmonary edema	Readmission (30-day)
Urinary tract infection	Re-intubation
Wound complications (Superficial, deep or organ space infection; dehiscence)	Renal failure
	Reoperation (unplanned)
	Seizure
	Sepsis
	Septic joint
	Septic shock
	Vessel injury
	Ventilator (prolonged)

Adverse events were not extracted as "zero" unless explicitly listed as such in the study report.

Assessment of Methodological Quality of Individual Studies

The risk of bias from these observational studies was determined using the "Quality in Prognosis Studies" (QUIPS) tool.[22] QUIPS evaluates six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis, and reporting, Supplementary Material Supplementary Table S2. Studies were judged as "good quality" when the majority of criteria were met (little or no risk of bias); "fair quality" if most criteria were met (some flaws in the study with an associated risk of bias); "poor quality" if either most criteria were not met, or if significant flaws relating to critical aspects of study design were present.[23] The same authors who extracted the data independently assessed the risk of bias and quality, and disagreements were resolved through consensus.

Data Synthesis

A meta-analysis was conducted when at least two studies reported similar adverse events. Results were pooled for specific major adverse events and those with one or more major and one or more minor adverse events via the Mantel-Haenszel method using a random-effects model. Risk ratios (RR) and 95% confidence intervals were calculated. All data analysis and presentation were performed using Review Manager 5. Heterogeneity was inspected by examining forest plots and subsequently quantified using the I2 statistic from the Chi-squared test for heterogeneity (I2 < 40, low heterogeneity; I2 ≥ 75% considerable heterogeneity). Stratified analyses were conducted to investigate whether effects varied by surgical location (cervical or thoracolumbar) or the number of segments fused (≤2 or >3 levels) when data was available. Procedures involving >3 segments of fusion were considered to be of higher complexity than those involving ≤2 levels, therefore this stratified analysis was performed in-line with the majority of screened studies reporting length of segmental instrumentation. The risk of bias due to missing results was examined qualitatively, given the relatively few studies in the meta-analyses. Sensitivity analyses were performed to investigate whether study quality influenced effect estimates by repeating the analyses excluding studies deemed poor quality.

The strength of evidence was evaluated using the GRADE working group criteria to assess evidence regarding prognostic factors.[24] According to GRADE, a body of observational evidence for questions of prognosis begins as high certainty in the evidence. The evidence can be downgraded due to the risk of bias, imprecision, inconsistency, indirectness, and publication bias. Upgrading also applies when estimates of associations between prognostic factors and outcome are robust. The strength of evidence was assigned an overall grade of high, moderate, low, or very low by evaluating and weighing the combined results of the above domains, Supplementary Material Supplementary Table S3.

Results

Study Selection

The search identified 6060 citations. A total of 5727 titles/abstracts were screened and, after removing 333 duplicates, 33 full texts were evaluated for study inclusion. Seventeen studies[15,16,25-39] assessing 37 897 participants met inclusion criteria, Figure 1. Articles excluded at full-text review and reason for exclusion are listed in Supplementary Material, Supplementary Table S4.

Study Characteristics

Fourteen studies (82%) were conducted in the United States[15,16,25-30,32-34,36,38,39] one in Australia,[35] one in Germany[31] and one in Austria.[37] Of the 37 897 participants, 10 031 (26.5%) were smokers and 27 866 (73.5%) were nonsmokers. The mean age for the study population was 58 years, and 45% were males. Four studies assessed the effect of smoking on adverse events in the cervical spine,[28,32,36,38] ten in the thoracolumbar spine,[16,25-27,30,31,33-35,37] and three in both the cervical and thoracolumbar spine.[15,29,39] In nine studies, the approach was only posterior,[16,25-29,31,33,37] in three only anterior,[35,36,38] and in five, a mix of posterior and/or

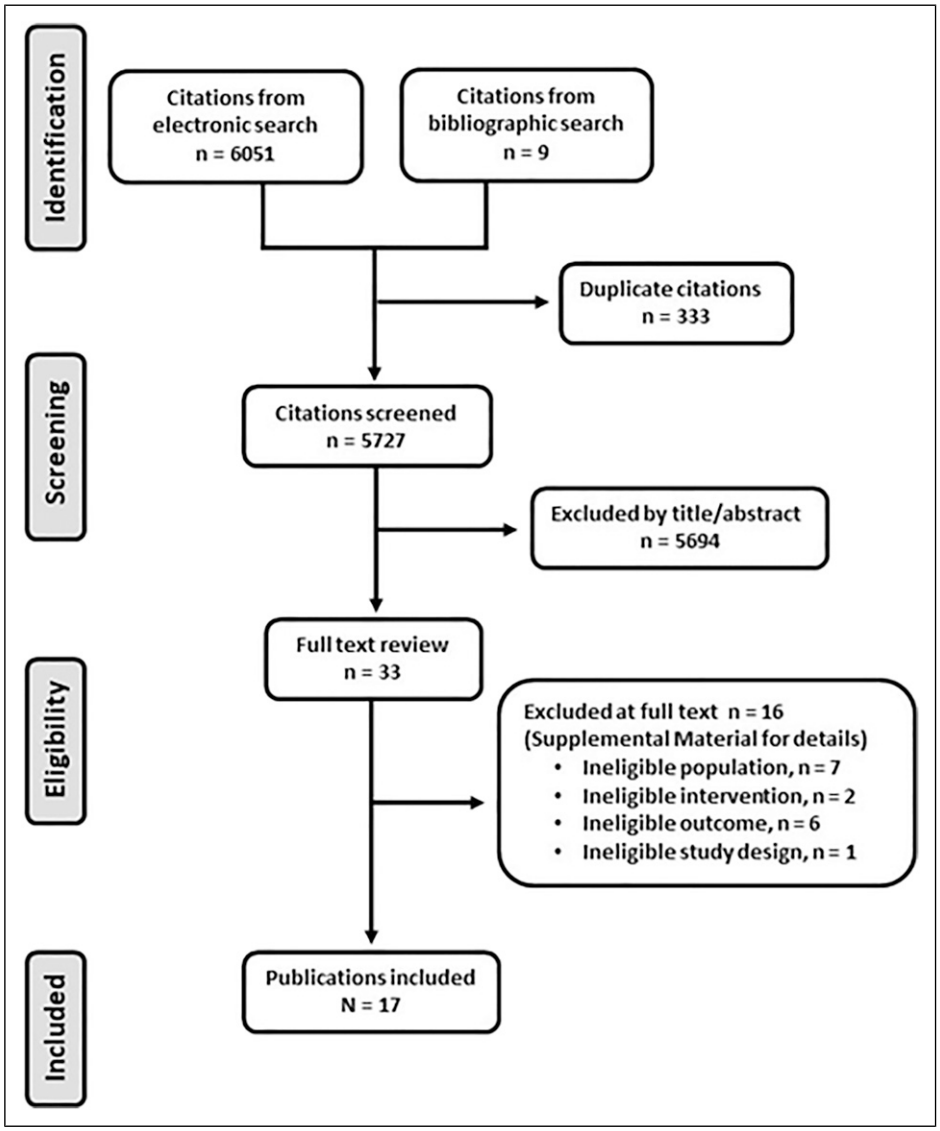

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flowchart outlining the search and review process used to identify and select articles for inclusion in this systematic review.

anterior and/or combination of both approaches.[15,30,32,34,39] The number of levels fused varied between 1 and 23, Table 3.

Study Quality

Four studies were judged as good-quality,[16,27,34,39] five as fair-quality[15,25,29,32,35] and eight as poor-quality studies.[26,28,30,31,33,36-38] The concerns about bias in the studies were primarily related to three domains: outcome measurement, lack of control for confounding, and high or uncertain study attrition.

Adverse Events

Any Major Adverse Events. Smoking was not associated with increased risk of one or more major adverse events within 90 days following spine surgery (seven studies, pooled RR 1.13, 95% CI .75-1.71, I2 = 41%) Figure 2 (Strength of Evidence, MODERATE, Supplementary Table S5). This lack of association was seen both in the cervical spine (four studies,[28,32,36,38] pooled RR 1.36, 95% CI [.69-2.68], I2 = 62%) and the thoracolumbar spine (three studies,[16,33,35] pooled RR .84, 95% CI [.50-1.42], I2 = 0%), Figure 2, and both in the posterior (three studies,[16,28,33] pooled RR .88, 95% CI [.41-2.36], I2 = 15%) and anterior approaches (three studies,[35,36,38] pooled RR .89, 95% CI [.71-1.13], I2 = 0%), Figure 3. However, smoking was significantly associated with one or more major adverse events in ≤2 level fusion (three studies,[32,33,35] pooled RR 2.46, 95% CI [1.18-5.12], I2 = 0%), but not in fusions of ≥3 levels (four studies,[16,28,36,38] pooled RR .87, 95% CI [.70-1.08], I2 = 0%); subgroup difference, P = .008, Figure 4. In the sensitivity analysis, smoking was not

Table 3. Characteristics of included studies.

Author (year)	Country	n (S vs NS) Mean Age % Males	Spine Region Levels Fused Approach	Condition Procedure	Graft Material (S vs NS)	Study Quality
Bydon 2014	USA	50 vs 231 59 vs 59 years 42% vs 45%	Thoracolumbar 2 levels posterior	Degenerative spine disease PLF with instrumentation	Autograft 72% vs 76% Allograft 54% vs 53% BMP 56% vs 54%	Fair
De la Garza 2017	USA	217 vs 1151 53 vs 59 years 29% vs 29%	Thoracolumbar 1-13+ levels posterior	Adult spinal deformity PLF with instrumentation	NR	Good
Dinizo 2021	USA	79 vs 961 46 years all pts NR	Thoracolumbar 4 levels, mean=10 posterior	Adult spinal deformity Posterior fusion	NR	Poor
Echt 2018	USA	271 vs 1417 65 vs 59 years 36% vs 37%	Thoracolumbar 1 level posterior	Spondylolisthesis PLF, PLIF or TLIF	NR	Good
Elsamadicy 2017	USA	124 vs 715 60 vs 63 years 45% vs 38%	Cervical, thoracolumbar ≥3 levels Posterior 42% Anterior 20%	Adult spinal deformity NR	NR	Fair
Eubanks 2011	USA	41 vs 117 55 vs 63 years 66% vs 56%	Cervical ≥2 levels, (mean = 4) posterior	NR Posterior fusion with autograft, lateral mass screw and rod instrumentation	Autograft 100% all pts	Poor
Fisahn 2017	USA	13 vs 43 65 years all pts 63% all pts	Cervical, thoracolumbar ≥8 level posterior	Adult spinal deformity Posterior fusion	NR	Fair
Goyal 2020	USA	52 vs 220 58 vs 54 years 36% vs 37%	Thoracolumbar 1-3 levels (75% 1-level) Posterior (66%), ant + post (34%)	Spondylolisthesis (77%), scoliosis (16%), stenosis (7%) PLF, PLF+ALIF, or TLIF	NR	Poor
Hermann 2016	Germany	16 vs 34 48 vs 58 years 46%	Thoracolumbar 1 level posterior	Spondylodesis PLIF, TLIF	Autograft 100% all pts allograft added in a few cases	Poor
Lau 2014	USA	40 vs 120 53 years all pts 58% all pts	Cervical 1-3 levels (1 level = 74%) Anterior (74%), ant + post (27%)	Radiculopathy, myelopathy Anterior corpectomy and plating	Allograft (%NR)	Fair
Macki 2017	USA	28 vs 82 54 vs 61 years 54% vs 37%	Thoracolumbar 1-4 levels (1 level = 37%, 2=35%, 3=18%, 4 = 10%) posterior	Degenerative spine disease Posterolateral instrumented fusion	BMP (100%)	Poor
Park 2017	USA	1147 vs 4133 58 years all pts 44% all pts	Thoracolumbar 1 level anterior, posterior, combined (%NR)	NR ALIF, PLF, TLIF, combined	NR	Good
Phan 2018	Australia	23 vs 114 57 vs 53 years 46% vs 57%	Thoracolumbar ≥1 level (1 level = 72%) anterior	DDD (73%), spondylolisthesis (13%), failed fusion (4%), ASD (4%), scoliosis (5%) ALIF	iFactor (100%)	Fair

(continued)

Table 3. (continued)

Author (year)	Country	n (S vs NS) Mean Age % Males	Spine Region Levels Fused Approach	Condition Procedure	Graft Material (S vs NS)	Study Quality
Purvis 2017	USA	7847 vs 18 022 50 vs 55 years 59% vs 57%	Cervical ≥2 levels (2-3 = 89%) anterior	NR ACDF	NR	Poor
Senker 2021	Austria	49 vs 138 53 vs 68 years 37% vs 39%	Thoracolumbar Level NR Posterior	Degenerative lumbar disease MIS PLF or TLIF	NR	Poor
Smith 2020	USA	8 vs 125 61 years all pts 38% all pts	Cervical Mean 8 levels Anterior	Adult spinal deformity		Poor
Wilson 2020	USA	26 vs 244 55 vs 57 years 46% vs 32%	Cervical, thoracolumbar 3-23 levels posterior (77%), ant + post (23%)	Adult spinal deformity NR	NR	Good

NR, not reported; NS, nonsmoking; S, smoking.

associated with an increased risk of one or more major adverse events when four poor-quality studies were excluded, Supplementary Figure S1.

Any Adverse Events (Major or Minor). There was no significant association between smoking and any adverse events (one or more major or minor adverse events) within 90 days following spine surgery (six studies,[16,25,26,36,38,39] pooled RR .99, 95% CI [.77-1.29], I2 = 65%), Figure 5 (Strength of Evidence, LOW, Supplementary Table S2). There were no differences in the subgroup analyses stratifying by surgical location or approach (Supplemental Material, Supplementary Figures S2 and S3) or when omitting three poor-quality studies in the sensitivity analysis, Supplementary Figure S4.

Wound Adverse Events. Smoking tended to be associated with more frequent wound adverse events, though this observed association was not statistically significant (nine studies,[15,16,25,27,29,31,33,35,39] pooled RR 1.43, 95% CI [.95-2.16], I2 = 14%), Figure 6 (Strength of Evidence, MODERATE, Supplementary Table S2). There were no differences in subgroup analyses stratifying by surgical location or number of segments fused, Supplementary Figures S5 and S6. The results were unchanged in the sensitivity analysis when two poor-quality studies were omitted, Supplementary Figure S7.

Reoperation due to Adverse Events. Smoking tended to be associated with increased reoperation risk, though the association failed to reach statistical significance (seven studies,[16,28,30,32-34,36] pooled RR 1.37, 95% CI [.98-1.91], I2 = 18%), Figure 7 (Strength of Evidence, LOW, Supplementary Table S2). There were no differences in subgroup analyses stratifying by surgical location or number of segments fused, Supplementary Figures S8 and S9. The results were unchanged in the sensitivity analysis when four poor-quality studies were omitted, Supplementary Figure S10.

Individual Major Adverse Events. Individual major adverse events rarely occurred across studies ranging from .1 to 6.1 per 1000 patients. There were no differences in the frequency of any individual major adverse events between those who did and did not smoke, Table 4.

Discussion

Despite a detailed understanding of its long-term deleterious effects, tobacco use remains the most common cause of preventable morbidity in the United States.[40] Cigarette smoking has been linked with higher rates of complications, delayed recovery time, and poorer functional outcomes in surgical patients.[4] The known impacts of tobacco use on normal physiological functions such as inflammation have resulted in widespread efforts to curb its use.[40,41] The increasing population of spine surgical patients both in recent times and in the projected future renders the consideration of

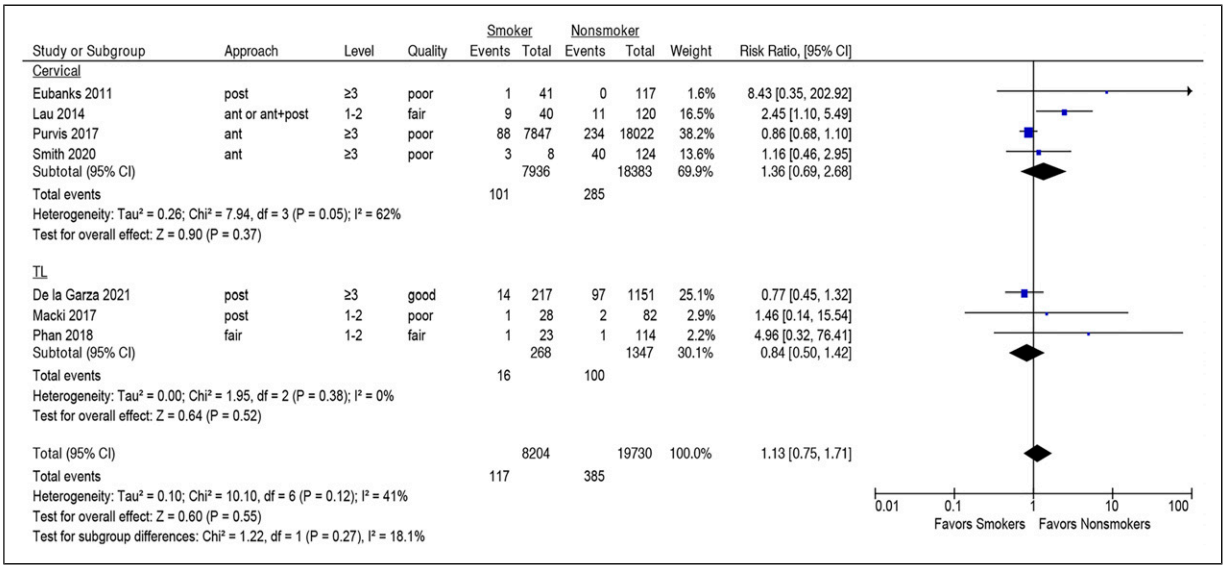

Figure 2. Association between smoking and risk of one or more adverse events within 90 days following spine surgery.

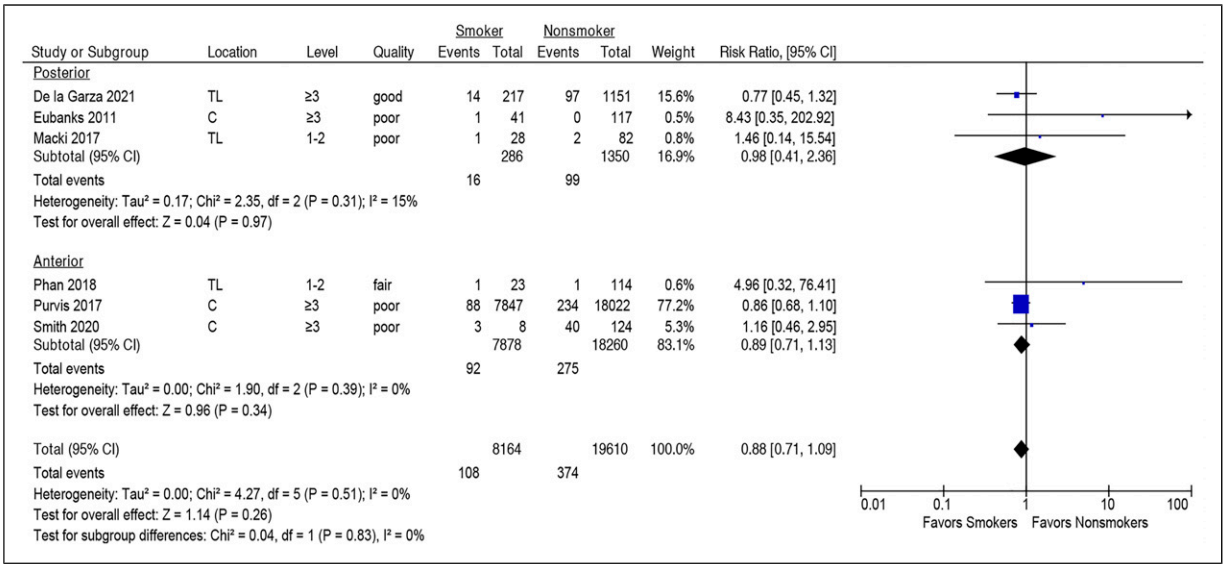

Figure 3. Association between smoking and risk of one or more adverse events within 90 days following spine surgery as compared between posterior and anterior approaches.

tobacco exposure especially relevant. Although the relationship between preoperative smoking and postoperative complications has been studied extensively in the context of bony fusion,[7] abdominal surgery,[42] and surgical patients in general,[43] to our knowledge, our systematic review and meta-analysis is the first to compare smokers to non-smokers in spinal fusion surgery directly and to quantify the relative risk differences for individual and aggregates of complications between these groups. We sought to understand (1) the specific complications associated with smoking in individuals undergoing spinal fusion, as well as (2) the degree to which the risks for these complications differed.

Wound Complications

Surprisingly, in the present analysis, smokers undergoing fusion were not associated with a statistically significant higher risk for developing wound-related complications when compared to non-smokers. Further, upon aggregating studies based on location (ie, cervical and thoracolumbar vs thoracolumbar alone), surgery location was not found to be an effect modifier of smoking on risk for wound complications. Smoking induces chronic inflammation and impairs normal wound healing processes, among other negative impacts on overall health.[44] It is hypothesized that surgical site organ trauma in the setting of

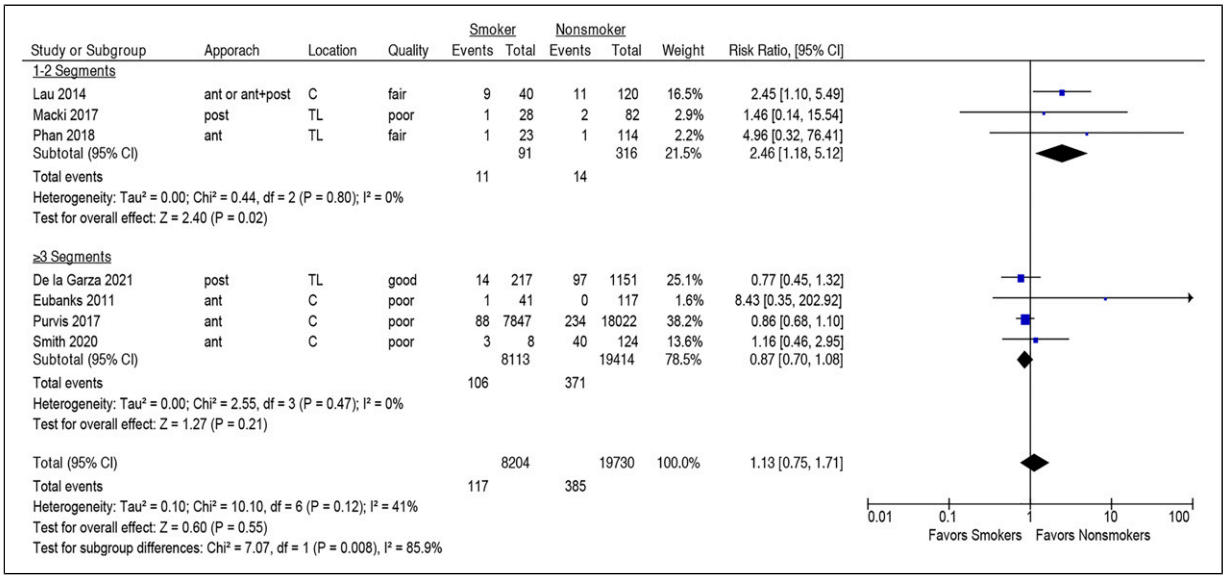

Figure 4. Subgroup analysis of the association of smoking and risk of one or more adverse events within 90 days following spine surgery between ≤2 level and ≥3 level fusions.

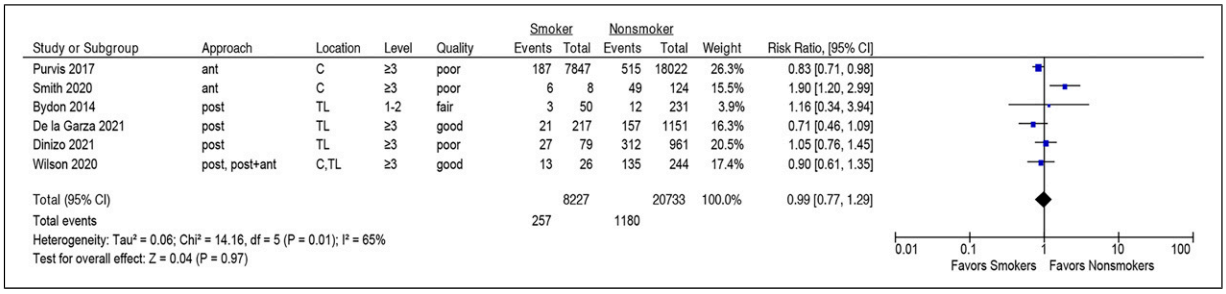

Figure 5. Association between smoking and risk of any adverse event within 90 days following spine surgery.

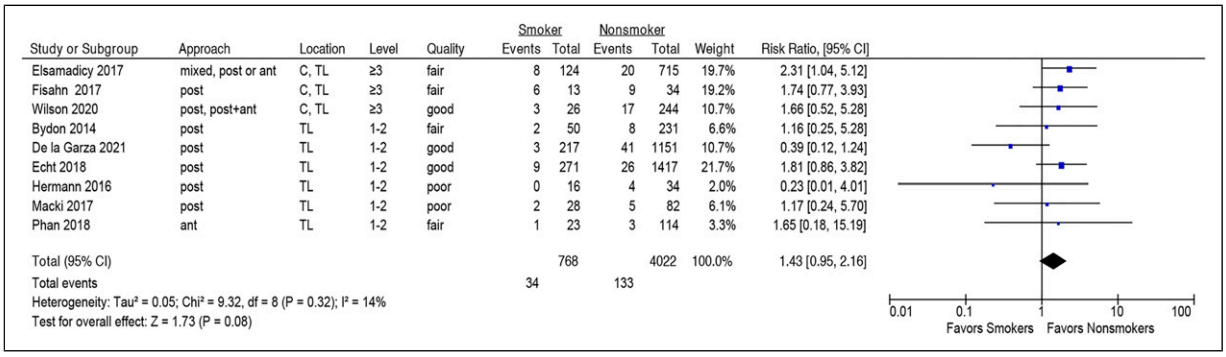

Figure 6. Association between smoking and risk of wound adverse events following spine surgery.

tobacco-induced damage may impart additional risk for perioperative complications.[4] Studies have shown that smokers have impaired immune function with increased risk of infection,[45] as well as a decreased rate of collagen production,[46] both of which negatively influence the wound healing process. It has been suggested that the deleterious effect of smoking cessation is at least partially reversible, including the associated wound-healing complications.[47] In the present meta-analysis, only the study by Elsamadicy et al demonstrated a significant difference in smokers vs non-smokers regarding wound-related complications, and overall heterogeneity was low (I2 = 14%, Figure 6).

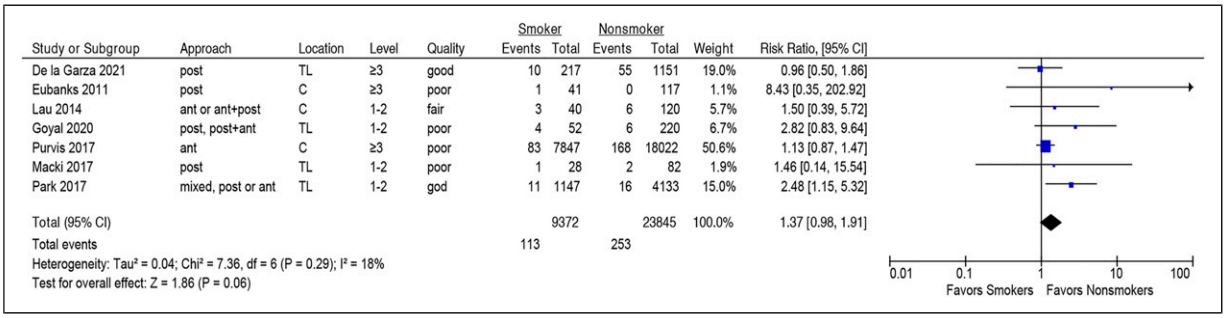

Figure 7. Association between smoking and risk of reoperation.

Table 4. Individual adverse events.

Adverse Events	Number of Studies	Smoking Risk per 1000 (n/N)	Non-Smoking Risk per 1000 (n/N)	Pooled RR, M-H, Random, 95% CI
Cardiac arrest	2[a,b]	1.74 (14/8064)	1.77 (34/19 173)	1.02 (.55-1.90)
Coma	2[a,b]	.0 (0/8064)	.10 (2/19,173)	1.16 (.12-11.15)
Stroke	3[a,b,c]	.85 (7/8188)	1.36 (27/19 888)	.78 (.34-1.80)
Death	5[a,b,d,e,f]	2.08 (17/8183)	2.90 (57/19 654)	1.16 (.41-3.31)
Hardware failure	3[c,g,h]	14.63 (3/205)	4.20 (4/952)	3.44 (.72 - 16.46)
MI	6[a,b,c,d,f,h]	.84 (7/8324)	2.16 (44/20 375)	.59 (.28-1.24)
PE	5[a,b,c,f,i]	1.21 (10/8262)	3.23 (65/20 106)	.64 (.24-1.71)
Reintubation	3[a,b,h]	6.66 (54/8104)	1.71 (33/19 293)	3.29 (.53-20.26)
Renal failure	3[a,b,h]	.37 (3/8104)	.52 (10/19 293)	1.05 (.33-3.39)
Sepsis	4[a,b,c,h]	2.62 (22/8405)	4.42 (93/21 039)	.84 (.37-1.91)
Septic shock	2[a,b]	1.61 (13/8064)	1.36 (26/19 173)	1.44 (.72-2.90)
Prolonged ventilation	2[a,b]	6.08 (49/8064)	6.00 (115/19 173)	1.15 (.82-1.61)

[a]De la Garza Ramos R, Goodwin CR, Qadi M, et al. Impact of Smoking on 30-day Morbidity and Mortality in Adult Spinal Deformity Surgery. Spine (Phila Pa 1976) 2017;42(7):465-470.
[b]urvis TE, Rodriguez HJ, Ahmed AK, et al. Impact of smoking on postoperative complications after anterior cervical discectomy and fusion. J Clin Neurosci 2017; 38:106-110.
[c]Elsamadicy AA, Adogwa O, Sergesketter A, et al. Reduced Impact of Smoking Status on 30-Day Complication and Readmission Rates After Elective Spinal Fusion (≥3 Levels) for Adult Spine Deformity: A Single Institutional Study of 839 Patients. World Neurosurg 2017;107:233-238.
[d]Bydon M, De la Garza-Ramos R, Abt NB, et al. Impact of smoking on complication and pseudarthrosis rates after single- and 2-level posterolateral fusion of the lumbar spine. Spine (Phila Pa 1976) 2014;39(21):1765-1770.
[e]Phan K, Fadhil M, Chang N, Giang G, Gragnaniello C, Mobbs RJ. Effect of Smoking Status on Successful Arthrodesis, Clinical Outcome, and Complications After Anterior Lumbar Interbody Fusion (ALIF). World Neurosurg 2018;110:e998-e1003.
[f]Senker W, Stefanits H, Gmeiner M, Trutschnig W, Radl C, Gruber A. The influence of smoking in minimally invasive spinal fusion surgery. Open Med (Wars) 2021;16(1):198-206.
[g]Eubanks JD, Thorpe SW, Cheruvu VK, Braly BA, Kang JD. Does smoking influence fusion rates in posterior cervical arthrodesis with lateral mass instrumentation? Clin Orthop Relat Res 2011;469(3):696-701.
[h]Lau D, Chou D, Ziewacz JE, Mummaneni PV. The effects of smoking on perioperative outcomes and pseudarthrosis following anterior cervical corpectomy: Clinical article. J Neurosurg Spine 2014;21(4):547-558.
[i]Macki M, Syeda S, Rajjoub KR, et al. The Effect of Smoking Status on Successful Arthrodesis After Lumbar Instrumentation Supplemented with rhBMP-2. World Neurosurg 2017;97:459-464.

Reoperation

Although most studies reporting reoperation rates tended to show higher rates of reoperation in smokers than non-smokers, the overall effect failed to reach significance (RR 1.37, 95% CI 0.98 to 1.91). Similarly, stratification by region of spinal surgery (ie, cervical vs thoracolumbar) and overall number of levels operated upon lacked statistical significance. Importantly, even though the pooled analysis did not reach significance, the included studies, by and large, showed little heterogeneity in their tendency to report smaller proportions of reoperations in non-smokers (I2 = 18%, Figure 7).

Several studies have evaluated smoking on reoperation in spine surgery and other surgical disciplines. Reoperation, in the short term, may commonly be attributed to occurrences of complications such as wound infections, dehiscence, implant malposition, or other acute findings that necessitate surgical exploration.[48,49] At longer follow-up, in addition to the reasons described above, factors such as the development of secondary instability, adjacent segment disease, deformity, or

pseudarthrosis may necessitate revision procedures.[48] For example, the impact of smoking on pseudoarthrosis rates following spinal fusion at months to years of follow-up has been well documented.[7] It is plausible that any mechanisms by which smoking predisposes patients to any of the above or alternative causes of reoperation would manifest themselves in a significant association between smoking and reoperation. Intriguingly, such a relationship was not evident in our meta-analysis, although this may be due to sample size limitations.

Any Major or Minor Adverse Events

Preoperative smoking has been implicated as a predictor of adverse outcomes in disciplines such as abdominal surgery,[50] cosmetic procedures,[51] thoracic surgery,[52] and several other surgical fields.[53] Published meta-analyses comparing perioperative outcomes between smokers and non-smokers in the surgical literature suggest that the drivers of increased complication rates in smokers are pulmonary, infectious, or cardiovascular complications.[53] Interestingly, the influence of smoking is not well-defined in every surgical discipline, especially when considering complications other than wound disruption/dehiscence or surgical site infection. Systematic reviews of the head and neck surgery literature, for example, have suggested that tobacco smoking carries a negative impact on perioperative outcomes. However, depending on the specific research methodology and inclusion criteria, statistically significant associations often cannot be established.[54,55] In our analysis, we similarly did not find significant associations between major or minor adverse events with smoking status, even when considering individual events, such as pulmonary complications. Notably, surveillance methodology for specific postoperative adverse events is highly variable between studies, with inconsistent reporting of screening strategies, definitions of complications, or unspecified follow-up.

In our analysis of individuals undergoing spinal fusion procedures, there was overall no association between smoking status and the occurrence of any minor or major adverse events within 90 days. While we did identify a significant association between smoking and adverse events in fusions of $\leq$2 levels, this finding did not persist following a sensitivity analysis that excluded low-quality data. Because the effect of smoking has been studied in numerous individual articles in spine surgery and systematic reviews of studies in other fields, findings in the literature vary widely, from those demonstrating nonsignificant differences to those showing larger effect sizes.[39,50,51,53]

Strengths and Limitations

The present analysis has several strengths and limitations. While prior meta-analyses have examined the effect of smoking on complications in surgery in general, we performed the first comprehensive systematic review of the spine-specific surgical literature and identified all papers in the English language reporting complications as stratified by smoking status, thereby permitting us to calculate risk differences and quantify effect sizes of smoking on specific complications. The advantage of limiting our scope to spine surgery is reflected in the relatively small degree of heterogeneity in our primary findings. Aggregation of these studies allowed us to perform several subgroup analyses for certain complications as stratified by spinal segment or levels operated upon, and appraisal for quality of evidence permitted sensitivity analyses to exclude low-quality data.

Limitations of this analysis include its reliance upon retrospective studies, which may affect the number and types of reported complications based on the respective authors' definitions and screening criteria. Although we defined "current smoking" as smoking within a year whenever the data was available, in the vast majority of cases, we relied upon the authors of the original articles for their definitions of current vs non-smoker, in the case of individuals who had quit smoking. Similarly, we were unable to explore a dose-response relationship between the extent of cigarette smoking and the effect on complication rates if any such relationship exists. The same goes for alternate delivery modalities for nicotine intake, such as patches, gum and vaping devices Transparent and consistent definitions of current smoking status, abstinence, and reporting for specific complications are necessary for future cohort studies to examine outcomes more clearly in this population.

Conclusion

In this meta-analysis, smokers undergoing spinal fusion procedures in general were not at greater risk for most complications within a 90-day period compared to non-smokers. Our results are limited by the variable reporting methodology for both complication rates as well as smoking incidence between the included individual studies. Further cohort studies directed at this point should clearly define nonsmoking status as well as rates of specific complications experienced in those undergoing spinal fusion procedures.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Ravi S. Nunna https://orcid.org/0000-0003-2516-5445
Darius Ansari https://orcid.org/0000-0003-2516-6894
Philip B. Ostrov https://orcid.org/0000-0002-5121-6587
Joseph R. Dettori https://orcid.org/0000-0002-0216-8363
Elias Elias https://orcid.org/0000-0003-0339-3666

Supplemental Material

Supplemental material for this article is available online.

References

1. WHO report on the global tobacco epidemic 2021: Addressing new and emerging products. WHO report on the global tobacco epidemic. 8th ed. Geneva, Switzerland: World Health Organization; 2021.
2. U.S. Department of Health and Human Services. *The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
3. Yoshikawa R, Katada J. Effects of active smoking on postoperative outcomes in hospitalised patients undergoing elective surgery: A retrospective analysis of an administrative claims database in Japan. *BMJ Open*. 2019;9:e029913. doi:10.1136/bmjopen-2019-029913
4. Gronkjaer M, Eliasen M, Skov-Ettrup LS, et al. Preoperative smoking status and postoperative complications: A systematic review and meta-analysis. *Ann Surg*. 2014;259:52-71. doi:10.1097/SLA.0b013e3182911913
5. Lindstrom D, Sadr Azodi O, Wladis A, et al. Effects of a perioperative smoking cessation intervention on postoperative complications: A randomized trial. *Ann Surg*. 2008;248:739-745. doi:10.1097/SLA.0b013e3181889d0d
6. Kean J. The effects of smoking on the wound healing process. *J Wound Care*. 2010;19:5-8. doi:10.12968/jowc.2010.19.1.46092
7. Nunna RS, Ostrov PB, Ansari D, et al. The risk of nonunion in smokers revisited: A systematic review and meta-analysis. *Global Spine J*. 2021;12:526-539. doi:10.1177/21925682211046899
8. Berman D, Oren JH, Bendo J, Spivak J. The effect of smoking on spinal fusion. *Int J Spine Surg*. 2017;11:29.
9. Lee JC, Lee SH, Peters C, Riew KD. Adjacent segment pathology requiring reoperation after anterior cervical arthrodesis: The influence of smoking, sex, and number of operated levels. *Spine (Phila Pa 1976)*. 2015;40:E571-577. doi:10.1097/BRS.0000000000000846
10. Sanden B, Forsyth P, Michaelsson K. Smokers show less improvement than non-smokers two years after surgery for lumbar spinal stenosis: A study of 4555 patients from the Swedish spine register. *Spine (Phila Pa 1976)*. 2011;36:1059-1064. doi:10.1097/BRS.0b013e3181e92b36
11. Battié MC, Videman T, Gill K, et al. 1991 Volvo award in clinical sciences. Smoking and lumbar intervertebral disc degeneration: An MRI study of identical twins. *Spine (Phila Pa 1976)*. 1991;16:1015-1021.
12. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int*. 2001;68:259-270. doi:10.1007/BF02390832
13. Andersen T, Christensen FB, Laursen M, Hoy K, Hansen ES, Bunger C. Smoking as a predictor of negative outcome in lumbar spinal fusion. *Spine (Phila Pa 1976)*. 2001;26:2623-2628.
14. Kusin DJ, Ahn UM, Ahn NU. The effect of smoking on spinal cord healing following surgical treatment of cervical myelopathy. *Spine (Phila Pa 1976)*. 2015;40:1391-1396.
15. Elsamadicy AA, Adogwa O, Sergesketter A, et al. Reduced impact of smoking status on 30-day complication and readmission rates after elective spinal fusion (≥3 levels) for adult spine deformity: A single institutional study of 839 patients. *World Neurosurg*. 2017;107:233-238.
16. De la Garza Ramos R, Goodwin CR, Qadi M, et al. Impact of smoking on 30-day morbidity and mortality in adult spinal deformity surgery. *Spine (Phila Pa 1976)*. 2017;42:465-470.
17. Seicean A, Seicean S, Alan N, et al. Effect of smoking on the perioperative outcomes of patients who undergo elective spine surgery. *Spine (Phila Pa 1976)*. 2013;38:1294-1302.
18. Nunna R, Dettori JR, Devine J, et al. The risk of complications after spinal fusion in smokers: A systematic review and meta-analysis. PROSPERO 2021 CRD42021231462. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021255534
19. Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: A framework for researching clinical outcomes. *BMJ*. 2013;346:e5595.
20. Moons KG, Hooft L, Williams K, Hayden JA, Damen JA, Riley RD. Implementing systematic reviews of prognosis studies in cochrane. *Cochrane Database Syst Rev*. 2018;10:ED000129.
21. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *J Clin Epidemiol*. 2009;62:e1-e34.
22. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med*. 2013;158:280-286.
23. Scottish Intercollegiate Guidelines Network. *Scottish Intercollegiate Guidelines Network: Rating a Quality of Cohort Studies. Methodology Checklist 3: Cohort Studies*. https://www.sign.ac.uk/what-we-do/methodology/checklists/. Accessed January 14, 2021.
24. Foroutan F, Guyatt G, Zuk V, et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: Rating certainty in identification of groups of patients with different absolute risks. *J Clin Epidemiol*. 2020;121:62-70.
25. Bydon M, De la Garza-Ramos R, Abt NB, et al. Impact of smoking on complication and pseudarthrosis rates after single- and 2-level posterolateral fusion of the lumbar spine. *Spine (Phila Pa 1976)*. 2014;39:1765-1770.
26. Dinizo M, Dolgalev I, Passias PG, Errico TJ, Raman T. Complications after adult spinal deformity surgeries: All are not created equal. *Int J Spine Surg*. 2021;15:137-143.
27. Echt M, De la Garza Ramos R, Nakhla J, et al. The effect of cigarette smoking on wound complications after single-level posterolateral and interbody fusion for spondylolisthesis. *World Neurosurg*. 2018;116:e824-e829.

28. Eubanks JD, Thorpe SW, Cheruvu VK, Braly BA, Kang JD. Does smoking influence fusion rates in posterior cervical arthrodesis with lateral mass instrumentation? *Clin Orthop Relat Res*. 2011;469:696-701.
29. Fisahn C, Jeyamohan S, Norvell DC, et al. Association between allogeneic blood transfusion and postoperative infection in major spine surgery. *Clin Spine Surg*. 2017;30:E988-E992.
30. Goyal DKC, Divi SN, Bowles DR, et al. How does smoking influence patient-reported outcomes in patients after lumbar fusion? *Clin Spine Surg*. 2020;34:E45-E50.
31. Hermann PC, Webler M, Bornemann R, et al. Influence of smoking on spinal fusion after spondylodesis surgery: A comparative clinical study. *Technol Health Care*. 2016;24:737-744.
32. Lau D, Chou D, Ziewacz JE, Mummaneni PV. The effects of smoking on perioperative outcomes and pseudarthrosis following anterior cervical corpectomy: Clinical article. *J Neurosurg Spine*. 2014;21:547-558.
33. Macki M, Syeda S, Rajjoub KR, et al. The effect of smoking status on successful arthrodesis after lumbar instrumentation supplemented with rhBMP-2. *World Neurosurg*. 2017;97:459-464.
34. Park JH, Li G, Kim M. Incidence and risk factors of postoperative hematoma requiring reoperation in single-level lumbar fusion surgery. *Spine (Phila Pa 1976)*. 2017;42:428-436.
35. Phan K, Fadhil M, Chang N, Giang G, Gragnaniello C, Mobbs RJ. Effect of smoking status on successful arthrodesis, clinical outcome, and complications after anterior lumbar interbody fusion (ALIF). *World Neurosurg*. 2018;110:e998-e1003.
36. Purvis TE, Rodriguez HJ, Ahmed AK, et al. Impact of smoking on postoperative complications after anterior cervical discectomy and fusion. *J Clin Neurosci*. 2017;38:106-110.
37. Senker W, Stefanits H, Gmeiner M, Trutschnig W, Radl C, Gruber A. The influence of smoking in minimally invasive spinal fusion surgery. *Open Med (Wars)*. 2021;16:198-206.
38. Smith JS, Buell TJ, Shaffrey CI, et al. Prospective multicenter assessment of complication rates associated with adult cervical deformity surgery in 133 patients with minimum 1-year follow-up. *J Neurosurg Spine*. 2020;33:1-13.
39. Wilson JRF, Jiang F, Badhiwala JH, et al. The effect of tobacco smoking on adverse events following adult complex deformity surgery: Analysis of 270 patients from the prospective, multicenter Scoli-RISK-1 study. *Spine*. 2020;45:32-37. doi:10.1097/BRS.0000000000003200
40. Cokkinides V, Bandi P, McMahon C, Jemal A, Glynn T, Ward E. Tobacco control in the United States–recent progress and opportunities. *CA Cancer J Clin*. 2009;59:352-365. doi:10.3322/caac.20037
41. Rom O, Avezov K, Aizenbud D, Reznick AZ. Cigarette smoking and inflammation revisited. *Respir Physiol Neurobiol*. 2013;187:5-10. doi:10.1016/j.resp.2013.01.013
42. Myers K, Hajek P, Hinds C, McRobbie H. Stopping smoking shortly before surgery and postoperative complications: A systematic review and meta-analysis. *Arch Intern Med*. 2011;171:983-989. doi:10.1001/archinternmed.2011.97
43. Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: A systematic review and meta-analysis. *Arch Surg*. 2012;147:373-383. doi:10.1001/archsurg.2012.5
44. Niemann B, Rohrbach S, Miller MR, Newby DE, Fuster V, Kovacic JC. Oxidative stress and cardiovascular risk: Obesity, diabetes, smoking, and pollution: Part 3 of a 3-part series. *J Am Coll Cardiol*. 2017;70:230-251. doi:10.1016/j.jacc.2017.05.043
45. Mehta H, Nazzal K, Sadikot RT. Cigarette smoking and innate immunity. *Inflamm Res*. 2008;57:497-503. doi:10.1007/s00011-008-8078-6
46. Chrysanthopoulou A, Mitroulis I, Apostolidou E, et al. Neutrophil extracellular traps promote differentiation and function of fibroblasts. *J Pathol*. 2014;233:294-307. doi:10.1002/path.4359
47. Mills E, Eyawo O, Lockhart I, Kelly S, Wu P, Ebbert JO. Smoking cessation reduces postoperative complications: A systematic review and meta-analysis. *Am J Med*. 2011;124:144-154. doi:10.1016/j.amjmed.2010.09.013
48. Irmola TM, Hakkinen A, Jarvenpaa S, Marttinen I, Vihtonen K, Neva M. Reoperation rates following instrumented lumbar spine fusion. *Spine (Phila Pa 1976)*. 2018;43:295-301. doi:10.1097/BRS.0000000000002291
49. Ansari D, Deslaurier JT, Patel S, Chapman JR, Oskouian RJ. Predictors of extended hospitalization and early reoperation after elective lumbar disc arthroplasty. *World Neurosurg*. 2021;154:e797-e805. doi:10.1016/j.wneu.2021.08.016
50. Chow A, Neville A, Kolozsvari N. Smoking in bariatric surgery: A systematic review. *Surg Endosc*. 2021;35:3047-3066. doi:10.1007/s00464-020-07669-3
51. Kaoutzanis C, Winocour J, Gupta V, et al. The effect of smoking in the cosmetic surgery population: Analysis of 129, 007 patients. *Aesthet Surg J*. 2019;39:109-119. doi:10.1093/asj/sjy088
52. Lugg ST, Kerr A, Kadiri S, et al. Protocol for a feasibility study of smoking cessation in the surgical pathway before major lung surgery: Project MURRAY. *BMJ Open*. 2020;10:e036568.
53. Schmid M, Sood A, Campbell L, et al. Impact of smoking on perioperative outcomes after major surgery. *Am J Surg*. 2015;210:221-229. doi:10.1016/j.amjsurg.2014.12.045
54. Lassig AA, Yueh B, Joseph AM. The effect of smoking on perioperative complications in head and neck oncologic surgery. *Laryngoscope*. 2012;122:1800-1808. doi:10.1002/lary.23308
55. Crippen MM, Patel N, Filimonov A, et al. Association of smoking tobacco with complications in head and neck microvascular reconstructive surgery. *JAMA Facial Plast Surg*. 2019;21:20-26. doi:10.1001/jamafacial.2018.1176