Scolaro JA, Schenker ML, Yannascoli S, and et al. Cigarette Smoking Increases Complications Following Fracture A Systematic Review. J Bone Joint Surg Am. 2014; 96:674-81.

Design: Systematic Review and meta-analysis of prospective and retrospective cohort studies
Date: 5-28-15 LM

Study Question: To assess the association between smoking and the development of fracture nonunion, fracture-healing time, and soft-tissue recovery in patients following operative treatment of long-bone fractures.

Comparison Framework:

- **Patients:** Adults with long bone fractures managed both operatively and nonoperatively
- **Exposure:** Smoking
- **Non-exposure:** Non-smoking
- **Outcomes:** Failure of fracture healing (fracture nonunion, fracture healing time)
- **Study types:** prospective and retrospective cohort studies

Study selection:

- Databases searched included MEDLINE, Embase, and Cochrane through March 2012. Only published English-language studies were reviewed.
- Two review authors independently screened articles by title and abstract for trial inclusion utilizing predetermined eligibility criteria and resolved any disagreements by consensus with the 2 senior authors.
- Inclusion criteria were (1) a level of evidence of I, II, or III; (2) a patient population with an age of at least eighteen years; (3) a study group size of at least fifteen patients; (4) long bone or long-bone periarticular fractures; (5) cigarette smoking status as a patient characteristic; and (6) documentation of complications (delayed union, nonunion, wound complication, and/or infection).
- Studies were excluded if they (1) did not meet the above inclusion criteria, (2) were not performed on human subjects, (3) did not involve a long bone or contained a pool of data that included non-long-bone fractures, (4) did not specify the number of smokers in the study population, or (5) did not specify the type of complication observed.
- Two of the authors assessed the methodological quality of the studies. The studies were evaluated on several criteria: description of the study population, sampling, measurement, data analysis, and result interpretation. No summary score was generated.
- The primary outcome was the assessment of the risk of nonunion in any long bone following a fracture in smokers compared with nonsmokers. Sensitivity analyses were performed involving nonunions in general, tibial nonunions only, and nonunions in patients with an open fracture. The definition of nonunion varied among the primary studies and included delayed healing at 20 weeks, 6 months, 9 months, one year, and 2 years, and the need for revision surgery for fracture repair.

- The time to union was assessed as a secondary outcome when reported in the primary studies as frequency-weighted means and group weighted standard deviations. This analysis was performed for all fractures, tibial fractures, and open fractures.
- Soft-tissue complication data were extracted for superficial and deep infections of postoperative and traumatic wounds.
- Forest plots were used to assess study heterogeneity and to provide summary estimates. A funnel plot and the Eggers intercept were used to assess publication bias resulting from small-study effects. Because of study heterogeneity, a random-effects model was utilized. A sensitivity analysis according to the level of evidence was performed to determine if higher levels of evidence could reveal significant differences that had not been identified initially.

Results:

- Overall 19 studies were included, seven prospective and twelve retrospective cohort studies. These included 6374 fractures in 6356 patients, 1446 smokers and 4910 nonsmokers. Nine studies evaluated fractures of the tibia, three of the femur or hip, three of the ankle, one of the humerus, and 3 of multiple long bones. Six studies evaluated open fractures only.
- The quality analysis revealed that study populations were well described in 13 of the studies. The remaining 6 studies did not adequately describe patient comorbidities that are known to contribute to increased fracture-healing complications.
- Eleven studies adjusted for potential confounding factors with use of multivariate logistic regression.
- All studies were rated as Level II or Level III for level of evidence for prognostic studies. Level II includes retrospective studies, and lesser quality prospective studies. Level III includes case-control studies. Seven studies in this review were Level II and 12 were Level III.
- When the nonunion rate and healing time were evaluated according to the level of evidence of the studies, the weighted cumulative OR of nonunion and frequency-weighted mean healing time in smokers compared with nonsmokers did not differ significantly between studies that provided Level-II and Level-III evidence.
- Ten studies with 1221 any log-bone fractures showed that there was a significant difference in the nonunion rate following all acute fractures between smokers and nonsmokers. Smoking exposure was associated with a cumulative odds ratio (OR) of 2.32 (95% CI = 1.76 to 3.06) for developing a nonunion. The overall risk of long-bone fracture nonunion was 12% (95% CI = 8% to 17%) higher in smokers.
- In the 8 studies that evaluated fracture healing times in any log bones, the mean healing time was 24.1 weeks (95% CI=17.3 to 30.9 weeks) for nonsmokers compared with 30.2 weeks (95% CI = 22.7 to 37.7 weeks) for smokers.
- Seven studies with 925 fractures showed the effect of smoking on the nonunion rate of just tibial fractures. A significant difference in the rate of tibial fracture nonunion was found between smokers and nonsmokers. The cumulative OR of developing a tibial nonunion with smoking exposure was 2.16 (95% CI=1.55 to 3.01). The risk of tibial fracture nonunion was 12% (95% CI=7% to 18%) higher in smokers.

- In 6 studies, the mean healing time for tibial fractures was 32.0 weeks (95% CI=23.2 to 41.0 weeks) in smokers compared with 25.1 weeks (95% CI=16.4 to 33.9 weeks) in nonsmokers.
- Four studies with 658 fractures showed the effect of smoking on the nonunion rate of open fractures. A significant difference in the rate of open fracture nonunion was found between smokers and nonsmokers. The cumulative OR of developing a nonunion of an open fracture with smoking exposure was 1.95 (95% CI=1.3 to 2.9. The risk of open fracture nonunion was 9% (95% CI=3% to 16%) higher in smokers.
- In three studies, the mean healing time for open fractures was 37.2 weeks (95% CI=26.8 to 47.6 weeks) in smokers compared with 29.1 weeks (95% CI=9.4 to 48.8 weeks) in nonsmokers.
- Three studies with 4796 fractures evaluated superficial infections in smokers. The superficial infection rate was 7% in smokers compared with 4% in nonsmokers. The cumulative OR of developing a superficial infection with smoking exposure was 1.38 (95% C= 0.91 to 2.07).

Authors' conclusions:

- The results of this review show that cigarette smoking is associated with an increased nonunion rate of long bone fractures overall, tibial fractures, and open fractures, with nonsignificant trends toward prolonged healing time and increased risk of wound infection.
- The results of this systematic review show a nonsignificant trend toward increased wound infections was observed in smokers with either open fracture wounds or postoperative wounds from orthopaedic long-bone fracture surgery.
- The data indicates that cigarette smoking affects soft-tissue structure, local blood flow, and is believed to retard bone-healing, and potentially places operative wounds and soft-tissue flap coverage at higher risk of infection.
- The inclusion of retrospective cohort studies introduces inherent risks of bias, confounding, and associations that are not improved by study aggregation or statistical analysis. One weakness of the review was the inability to account for patient comorbidities as these were not recorded or controlled for in most of the studies evaluated, but they have known effects on bone and soft-tissue healing.
- To best account for the inherent differences in the data obtained in the included studies, a random-effects model was chosen to account for the fact that the true effect of smoking would have varied among the studies on the basis of uncontrolled variables.
- The quality analysis of the presented data in the studies selected for inclusion in the review revealed that publication bias did exist in the studies evaluating tibial nonunion.
- Since tissue hemodynamics return to near-control levels when nicotine is withheld for two weeks, a role for smoking cessation therapy in the perioperative period may be warranted.
- Smoking presents substantial risks to patients with a fracture, and these potential risks need to be discussed both at the time of injury and when considering surgical fixation.

- Future prospective clinical studies are needed to clarify whether the effects of smoking and nicotine are dose-dependent.

Comments:

- Even though retrospective cohort studies can introduce higher risks of bias than randomized controlled trials, one cannot evaluate the topic of this review between smokers and nonsmokers using a randomized controlled trial. The consistency of the evidence across all 19 studies implicating a significantly higher risk of nonunions of long bone fractures among smokers compared to nonsmokers imparts rather impressive evidence.
- Nicotine levels, which represent one of the few quantitative methods to assess smoking are difficult to obtain and were not reported in the included studies. Patients were often classified simply as ‘‘smokers’’ or ‘‘nonsmokers,’’ which did not take into account the frequency, duration, or intensity of an individual’s smoking and can lead to misclassification of the exposure.
- No universal definitions of the outcomes of nonunion and infection were used across the studies, and this can lead to misclassification of the outcome.
- Individual study quality and risk of bias was not known for each of the included studies, making it difficult to determine the quality of evidence and interpret the results, thus decreasing the level of confidence in the findings.

Assessment:

- An adequate systematic review and meta-analysis which supports good evidence that smoking significantly increases the risk of nonunion of long bone fractures overall, tibial fractures, and open fractures compared to nonsmokers in patients following operative treatment of long-bone fractures.