

Title: Prevalence of Current Smoking and Association with Adverse Outcome in Hospitalized COVID-19 Patients: A Systematic Review and Meta-Analysis

Running head. Smoking and COVID-19

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Funding. No funding was provided for this study.

Conflict of Interest statement. None

Abstract

Background: The purpose of this study was to examine the prevalence and effects of current smoking on adverse outcomes among hospitalized COVID-19 patients.

Methods: We performed a systematic review of the literature (PubMed) for studies published until April 25. Studies were included into the analysis if they satisfied all of the following criteria: 1. To present hospitalized patients with COVID-19. 2. To classify patients into less and more severe disease, irrespective of the severity definition (defined as “adverse outcome”). 3. To present data on the smoking status, separately for each severity classification. We identified 18 (from a total of 1398) relevant studies. Pooled current smoking prevalence was compared with the gender-adjusted, population-based expected prevalence by calculating Prevalence Odds Ratio (POR). The association between current, compared to non-current and former, smoking and adverse outcome was examined by calculating Odds Ratio (OR). All analyses were performed using random-effects meta-analysis.

Results: Among 6515 patients, 440 of whom were current smokers, the pooled prevalence of current smoking was 6.8% (95%CI: 4.8-9.1%) and the POR was 0.21 (95%CI: 0.16-0.26, $P < 0.001$). In Chinese studies only, the POR was 0.20 (95%CI: 0.16-0.25, $P < 0.001$). Current smokers were more likely to have an adverse outcome compared to non-current smokers (OR:

1.53, 95%CI: 1.06-2.20, P = 0.022). However, they were less likely to have an adverse outcome compared to former smokers (OR: 0.42, 95%CI: 0.27-0.74, P = 0.003).

Conclusion: An unexpectedly low prevalence of current smoking, , approximately 1/5th the population smoking prevalence, was observed among hospitalized patients with COVID-19. Hospitalized current smokers had higher odds compared to non-current smokers but lower odds compared to former smokers for an adverse outcome. The possibility that nicotine may have a protective effect in COVID-19 which is masked by smoking-related toxicity and by the abrupt cessation of nicotine intake when smokers are hospitalized should be explored.

Keywords. SARS-CoV-2; COVID-19; inflammation; smoking; nicotine; hospitalization; adverse outcome

Introduction

Smoking is a risk factor for respiratory infections [1]. Until recently, smoking was presented as a risk factor for COVID-19 mainly through media reports and opinion pieces. The main assumption was that the gender differences in vulnerability to COVID-19 and mortality may be due to the increased prevalence of smoking among Chinese men compared to women [2-3]. However, clinical and epidemiological data were lacking. A recent study of 78 COVID-19 patients found that smoking was associated with 14-fold higher odds for disease progression [4]. However, the association was weak and with a wide 95%CI since only 5 smoking patients were included, of whom 3 progressed to severe disease. An analysis of 5 case series from China

reported that current smokers had a statistically insignificant increase in the odds of progressing towards severe COVID-19 [5]. However, another systematic review reported that adverse outcome was more likely in smokers than non-smokers [6].

Smoking is an established risk factor for a variety of diseases, including cardiovascular disease and COPD. These are also risk factors for severe COVID-19 and adverse outcomes [7]. While this would imply an over-representation of smokers among COVID-19 patients, a recent meta-analysis of 13 studies of hospitalized COVID-19 patients in China found an unexpectedly low prevalence of smoking, approximately 1/4th the population smoking prevalence, was found [8]. To further explore this issue, we performed a systematic review of case series presenting data on the smoking status of hospitalized COVID-19 patients in order to:

1. Calculate the pooled prevalence of smoking among hospitalized COVID-19 patients and compare it with the expected prevalence based on population smoking rates.
2. Examine the association between current, compared to non-current and former, smoking and adverse outcome in COVID-19.

Methods

A systematic search of the literature (PubMed) was performed for studies published until April 25 using the terms "[SARS-CoV-2 OR COVID-19 OR 2019-nCoV] AND [Clinical OR Mortality OR Outcome]" in the title or the abstract. Studies were included into the analysis if they satisfied all of the following criteria:

1. To present hospitalized patients with COVID-19.

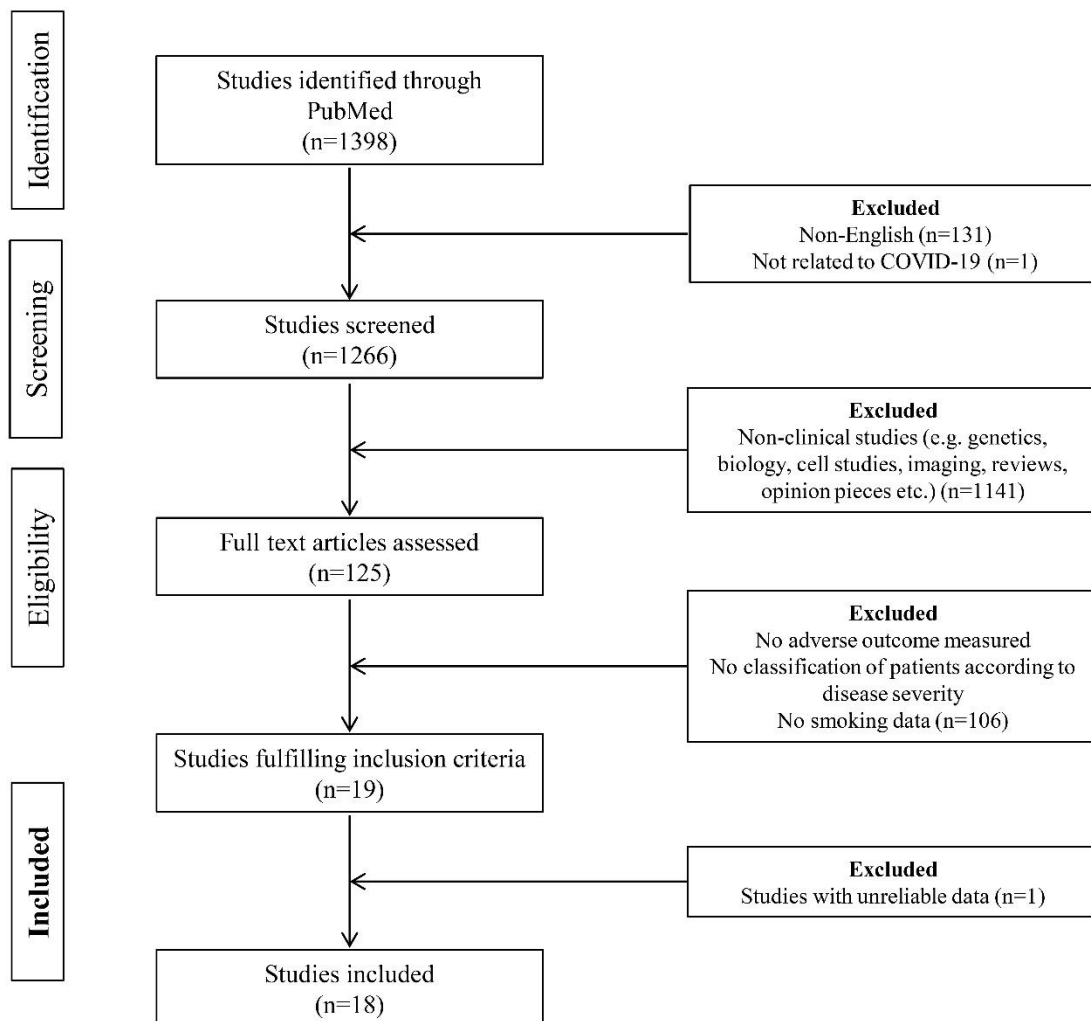
2. To classify patients according to disease severity (less and more severe disease), irrespective of the definition of severity.

3. To present data on the smoking status, separately for each severity classification.

Out of a total of 1398 studies, 19 studies fulfilling the above-mentioned criteria were found [9-27]. One study was excluded because of unreliable data [27]. Thus, 18 studies were included.

The PRISMA flow diagram is presented in the **Figure 1**.

Figure 1. PRISMA flow diagram.



Most studies were from China (n=15), while 2 studies presented patients from USA and 1 from South Korea. Four of the studies recorded separately current and former smokers [9,13,21,22] and were used to examine the association between current, compared with former, smoking and adverse outcome. All other studies reported the smoking status as “smoking” or “history of smoking” and may have included former smokers.

A cross-sectional analysis was performed. One study presented both outpatients and hospitalized patients [21]; data on hospitalized patients only were included. When former smokers were not separately presented, all patients with a positive smoking history were classified as current smokers. When presented separately, former smokers were included in the non-current smoking group.

Pooled prevalence of current smoking was calculated. Smoking prevalence in each study was compared with the expected prevalence based on gender-specific population smoking rates by estimating the prevalence odds ratio (POR) [28]. The population smoking rates used to calculate the expected proportion of smokers in each study were (males and females, respectively): 50.5% and 2.1% for China [29], 15.6% and 12.0% in USA [30] and 35.8% and 6.5% in South Korea [31].

The association between current (vs. non-current) smoking and adverse outcome was performed by calculating odds ratio (OR). Additionally, the association between current smoking (vs. former smoking) and adverse outcome was calculated for the studies which presented separately data for former smokers; never smokers were excluded from the analysis. All analyses were performed with random-effects meta-analyses using MetaXL v5.3.

Results

The characteristics of the studies included in this analysis are presented in **Table 1**. Published studies included 6515 hospitalized patients of whom 440 were current smokers. Adverse outcomes ranged from non-specific “severe” to specific definitions based on clinical criteria, or death (**Table 2**).

Table 1. Characteristics of the studies analyzed

	Hospitalized cases N	Males %	Females %	Hospitalized smokers n	Hospitalized smokers Pooled prevalence %	Expected smokers %	Country
Guan et al. ⁹	1085	58.1%	41.9%	137	12.6 (10.6-14.6)	30.2%	China
Chen et al. ¹⁰	274	62.4%	37.6%	12	5.4 (2.4-8.3)	32.3%	China
Zhou et al. ¹¹	191	62.3%	37.7%	11	5.8 (2.5-9.1)	32.3%	China
Mo et al. ¹²	155	55.5%	44.5%	6	3.9 (0.9-6.9)	29.0%	China
Zhang et al. ¹³	140	50.7%	49.3%	2	1.4 (0.0-3.3)	26.6%	China
Wan et al. ¹⁴	135	53.3%	46.7%	9	6.7 (2.5-10.9)	27.9%	China
Liu et al. ¹⁵	78	50.0%	50.0%	5	6.4 (0.1-11.8)	26.3%	China
Huang et al. ¹⁶	41	73.2%	26.8%	3	7.3 (0.0-15.3)	37.5%	China
Zhang, Cai et al. ¹⁷	645	50.9%	49.1%	41	6.4 (4.6-8.5)	26.7%	China
Shi et al. ¹⁸	474	53.2%	46.8%	40	8.4 (6.1-11.3)	27.8%	China
Yang, Yu et al. ¹⁹	52	67.3%	32.7%	2	3.8 (0.5-13.2)	34.7%	China
Kim et al. ²⁰	27	53.6%	46.4%	5	18.5 (6.3-38.1)	22.2%	S. Korea
CDC ²¹ (1)	1494			27	1.8 (1.2-2.6)	13.7%	USA
Li et al. ²²	544	51.3%	48.7%	41	7.5 (5.4-10.1)	26.9%	China
Wang et al. ²³	125	56.8%	43.2%	16	12.8 (7.5-20.0)	29.6%	China
Feng et al. ²⁴	454	56.9%	43.1%	44	9.7 (7.1-12.8)	29.7%	China
Ji et al. ²⁵	208	56.3%	43.8%	19	9.2 (5.6-13.9)	29.3%	China
Goyal et al. ²⁶	393	60.6%	39.4%	20	5.1 (3.1-7.8)	14.2%	USA
Total	6515			440	6.8 (4.8-9.1)		

(1) No data on gender were reported.

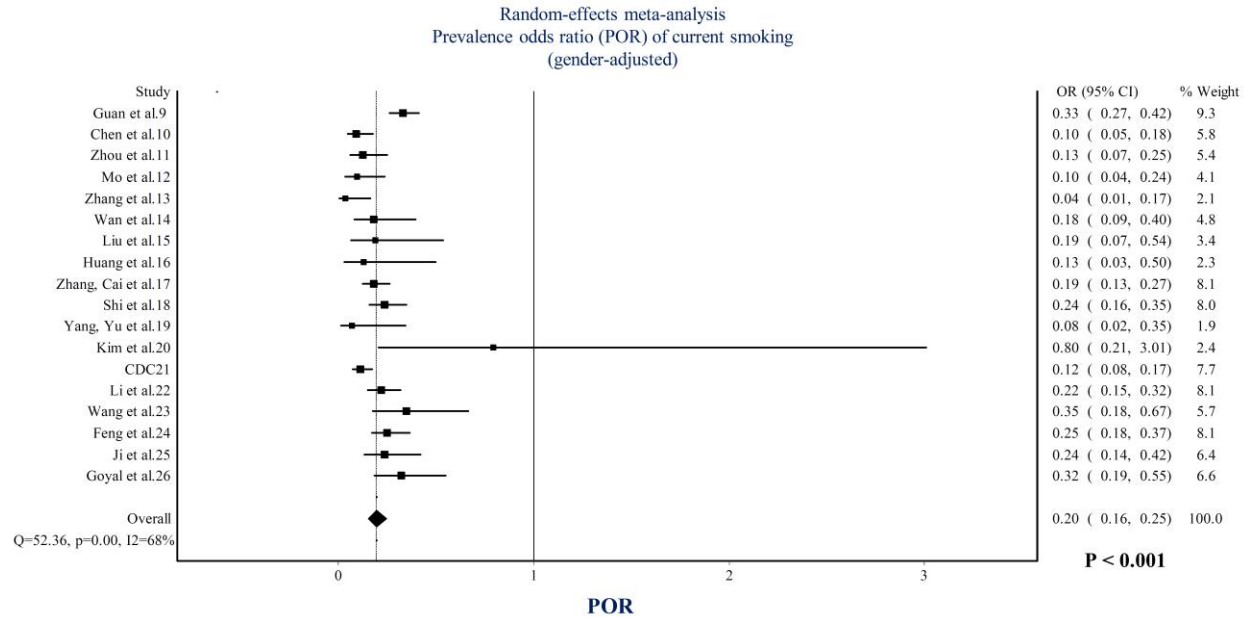
Hospitalized cases refer to number of patients for whom smoking data were available.

Table 2. Definition of disease severity.

	Definition of adverse outcome
Guan et al. ⁹	Composite end point of admission to an intensive care unit, the use of mechanical ventilation, or death. Mild vs. Severe disease
Chen et al. ¹⁰	Death
Zhou et al. ¹¹	Death
Mo et al. ¹²	Refractory disease, defined as not fulfilling the following criteria: (i) obvious alleviation of respiratory symptoms (eg. cough, chest distress and breath shortness) after treatment; (ii) maintenance of normal body temperature for ≥ 3 days without the use of corticosteroid or antipyretics; (iii) improvement in radiological abnormalities on chest CT or X-ray after treatment; (iv) a hospital stay of ≤ 10 days.
Zhang et al. ¹³	Severe disease, designated when the patients had one of the following criteria: (a) respiratory distress with respiratory frequency ≥ 30 /min; (b) pulse oximeter oxygen saturation $\leq 93\%$ at rest; and (c) oxygenation index (artery partial pressure of oxygen/inspired oxygen fraction, PaO ₂ / FiO ₂) ≤ 300 mm Hg.
Wan et al. ¹⁴	Severe disease, defined as having: respiratory distress, RR ≥ 30 beats/minute in a resting state, a mean oxygen saturation of $\leq 93\%$, and an arterial blood oxygen partial pressure (PaO ₂)/oxygen concentration (FiO ₂) ≤ 300 mmHg. Critical cases were also included, defined as: having respiratory failure and requiring mechanical ventilation, the occurrence of shock, and the combined failure of other organs that required intensive care unit (ICU) monitoring and treatment.
Liu et al. ¹⁵	Disease progression, defined as: common-type disease changed to severe- or critical-type, or death; severe-type changed to critical-type or death; critical-type progressed to death.
Huang et al. ¹⁶	ICU care.
Zhang, Cai et al. ¹⁷	Pneumonia, diagnosed based on imaging findings (abnormal imaging findings).
Shi et al. ¹⁸	Occurrence of death or severe cases
Yang, Yu et al. ¹⁹	Death
Kim et al. ²⁰	Oxygen administration in mask or nasal cannula
CDC ²¹ (1)	ICU Admission Not hospitalized vs. hospitalized
Li et al. ²²	Severe disease
Wang et al. ²³	Critical patients
Feng et al. ²⁴	Severe, defined as respiratory distress or respiratory rate ≥ 30 per min or oxygen saturation on room air at rest $\leq 93\%$ or partial pressure of oxygen in arterial blood / fraction of inspired oxygen ≤ 300 mmHg Critical, defined as respiratory failure and mechanical ventilation or shock or other organ dysfunction needing intensive care unit treatment.
Ji et al. ²⁵	Progression to severe disease, defined as respiratory rate ≥ 30 breaths/min or resting oxygen saturation $\leq 93\%$ or PaO ₂ /FiO ₂ ≤ 300 mmHg or requirement of mechanical ventilation or worsening lung CT.
Goyal et al. ²⁶	Invasive mechanical ventilation

The random-effects pooled prevalence of current smoking was 6.8% (95% CI 4.8-9.1%). The POR, displayed in **Figure 1**, was 0.20 (95% CI: 0.16-0.25, $P < 0.001$) with substantial heterogeneity being observed ($I^2 = 68\%$). Current smokers were more likely than non-current smokers to experience an adverse outcome (OR: 1.53, 95% CI: 1.06-2.20, $P = 0.022$), with moderate heterogeneity being observed ($I^2 = 43\%$, **Figure 2**). Compared to former smokers, current smokers were less likely to experience an adverse outcome (OR: 0.42, 95% CI: 0.24-0.74, $P = 0.003$), with no heterogeneity being observed ($I^2 = 0\%$, **Figure 3**)

Figure 1. Prevalence odds ratio (POR) of current smoking among hospitalized COVID-19 patients.



Discussion

The main finding of this systematic review was the unusually low prevalence of current smoking among hospitalized COVID-19 patients, with approximately 1/5th the expected smoking prevalence based on gender-adjusted population smoking rates. Additionally, current smokers had higher odds for adverse outcome compared with non-current smokers. In contrast, lower odds of adverse outcome were observed in current compared to former smokers.

An important limitation is that the analysis was unadjusted for confounding factors, such as age and comorbidities, which appear to be associated with higher risk for an adverse outcome in COVID-19 [32]. Sociodemographic factors may also be associated with reduced access of

smokers to hospital care. Older age is usually associated with reduced current smoking and increased former smoking prevalence, which could explain the lower odds for adverse outcome in current compared with former smokers. However, prevalence of smoking in China is high even in older age groups, > 50% in smoking males aged 60-69 years and > 40% in those > 70 years [33]. Thus, age cannot fully explain the low prevalence observed herein. The possibility for inaccurate recording, false-reporting or inability to report the smoking status due to critical condition, as well as the lack of an objective assessment of the smoking status should also be considered. Still, the findings that smokers are under-represented by approximately 4-fold could be explained only by extensive under-reporting of the current smoking status.

Low prevalence of current smokers among hospitalized COVID-19 patients has been observed in case series outside China too [21,26,34,35]. While it is highly unlikely for any other cigarette smoke compound to have any potential benefit, considering their toxic characteristics, some researchers have raised the possibility that these findings might imply a protective effect of nicotine [35-38]. It was recently reported that many of the clinical manifestations of COVID-19, including the cytokine storm, could be explained by a dysfunction of the nicotinic cholinergic system and hypothesized that nicotine could modulate the immune response by restoring the function of the cholinergic anti-inflammatory pathway [38]. While this would seemingly be in disagreement with the higher odds of adverse outcomes among hospitalized COVID-19 smokers, it should be emphasized that smokers experience abrupt cessation of nicotine intake after hospital admission and are unlikely to receive nicotine replacement therapies while hospitalized. As a result, the effects of nicotine will be rapidly weaned off within hours after admission. Therefore, the higher odds for adverse outcome in current smokers are not contradictory to the hypothesis that nicotine may be beneficial for COVID-19. Other factors such as smoking-related

comorbidities could also explain the higher odds for adverse outcome in hospitalized smokers. Thus, it is possible that COVID-19 severity and outcome may differ between smokers without and with smoking-related disease.

Severe COVID-19 appears to represent a hyper-inflammatory response that could correspond to dysregulation of the immune system and a failure to return to homeostasis after its activation to combat viral invasion. Elevated pro-inflammatory cytokines have been associated with worse prognosis in COVID-19 patients [11,39]. The cholinergic anti-inflammatory pathway has well-established immunomodulatory effects that are mediated mainly through the vagus nerve and alpha 7 nicotinic acetylcholine receptors present in a variety of cells such as macrophages and bronchial epithelial and endothelial cells [40-43]. Nicotine is an agonist of the nicotinic cholinergic system and has been shown to prevent acute respiratory distress syndrome, the hallmark of severe COVID-19, in animal models [44]. Therefore, nicotine intake could be the reason for the low prevalence of smokers among hospitalized COVID-19 patients. In fact, such effects could be masked by the well-established adverse effects of smoking. However, concerns have been recently raised about the effects of nicotine in up-regulating Angiotensin Converting Enzyme 2 (ACE2), which is used as a receptor by SARS-CoV-2 for cell entry [45,46]. These recent studies contradict previous findings that smoking and nicotine down-regulate ACE2 [47]. Moreover, up-regulation of ACE2 does not necessarily imply more fulminant disease. Similar concerns were raised early during the COVID-19 pandemic about the use of ACE-inhibitors and ARBs [48], but recent studies found either no adverse effect or even a protective effect associated with the use of these medications [34,49]. Children and young women, who usually experience mild COVID-19, were found to have higher levels of ACE2 than older people [50], an indication of the complexity of the renin-angiotensin-aldosterone axis.

In conclusion, this systematic review identify a low prevalence of current smoking among hospitalized COVID-19 patients, but higher odds of adverse outcome for current compared with non-current smokers. Smoking cannot be considered a protective measure against COVID-19 (or any other condition) due to associated risk for cardiovascular, respiratory and cancer morbidity and mortality. Thus, smokers should still be encouraged to quit. However, the possibility that nicotine may be protective against severe COVID-19 should be explored through laboratory and, eventually, clinical studies using pharmaceutical nicotine products.

Figure 2. Association between current (vs. non-current) smoking and adverse outcome.

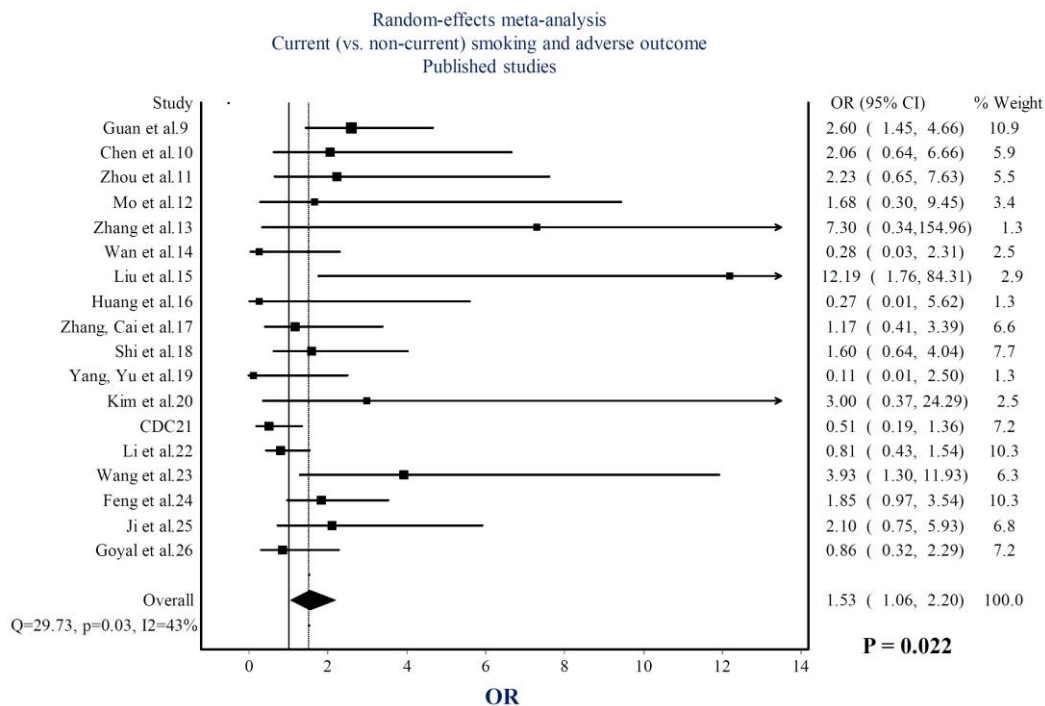
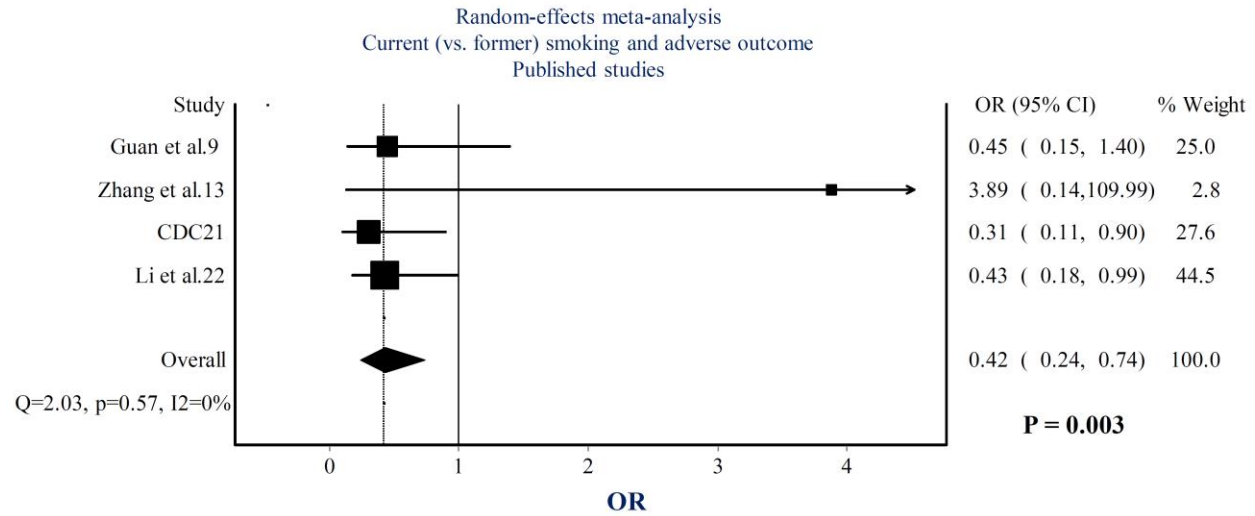


Figure 3. Association between current (compared to former) smoking and adverse outcome.

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