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Letter to the Editor

Does active smoking worsen Covid-19?

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ABSTRACT

Probably it does.

Letter

It was with great interest that we read the recent meta-analysis of 5 studies conducted in China in which Lippi et al conclude that active smoking is not associated with severity of coronavirus disease 2019 (Covid-19), with an odds ratio (OR) of 1.69 (95% CI, 0.41-6.42) [1]. This conclusion has been publicized in society, conveying the idea that smoking is not a risk factor for developing severe Covid-19. From a historical perspective, Lippi et al's conclusion has intriguing parallelisms with a long-standing, scientific battle already settled.

In 1951, Doll & Hill launched the British Doctors' Study with the aim of prospectively resolving the controversy surrounding the causal relationship between active smoking and cancer [2]. This herculean effort was justified, since strong evidence had emerged in earlier years, although previous case-control studies did not bear out causal inferences [3]. The lack of prospective data impeded a consensus among the medical community and, among the most illustrious skeptics was Ronald Fisher, father of frequentist statistics [4]. The British Doctors' Study was one of the most protracted studies in the history of medicine. The latest paper was signed by Richard Doll in 2004, shortly before his demise at the age of 92 [5]. However, in the 50s, when the study began, most of the Western adult population smoked and the yearly mortality rate was tremendous. Jerome Cornfield did not want to wait that long and, in 1951, applied Bayesian statistics for the first time to reveal the causal association between smoking and cancer [6]. It was a novel way to analyze health data, hastening by several decades the proof that smoking impacts the incidence of lung cancer and its mortality using frequentist analyses, as Sharon McGrayne so judiciously states in the book "The Theory that Would Not Die" [7].

Therefore, we have done nothing more than to perceive a troubling parallelism while reading the results of Lippi et al, categorically denying that active smoking worsens the course of Covid-19 [1]. Beyond public health considerations, the authors must know that the conclusions they reach do no derive from their data, which is a classic example of the well-known "absence of evidence is not evidence of absence" error [8]. Under the frequentist paradigm, Lippi's meta-analysis must be interpreted as an inconclusive outcome. According to the null hypothesis significance testing framework, if H0 is not rejected, judgment should basically be suspended.

In contrast and as Jerome Cornfield proved [6], Bayesian analyses address inference about research questions more directly and intuitively [9]. Consequently, they can be a more fitting option for meta-analysis based on just a few studies, as in this case, as they are better able to resolve the problem of inter-study heterogeneity [10]. In particular, Bayesian models estimate the probability of the parameters directly, bearing in mind the available data, which is not what the frequentist confidence interval pursues [11].

Smoking damages the airway and fosters the development of COPD and worsens outcomes during the course of bronchial infections [12]. Therefore, as Cornfield did decades ago [6] to establish a direct estimate of the probability that active smoking worsens Covid-19, we have reanalyzed Lippi et al's data using a Bayesian random-effects model performed by the R bayesmeta package [10]. The model assumes a normal prior (with mean 0, no effect in the logarithmic odds ratio scale,

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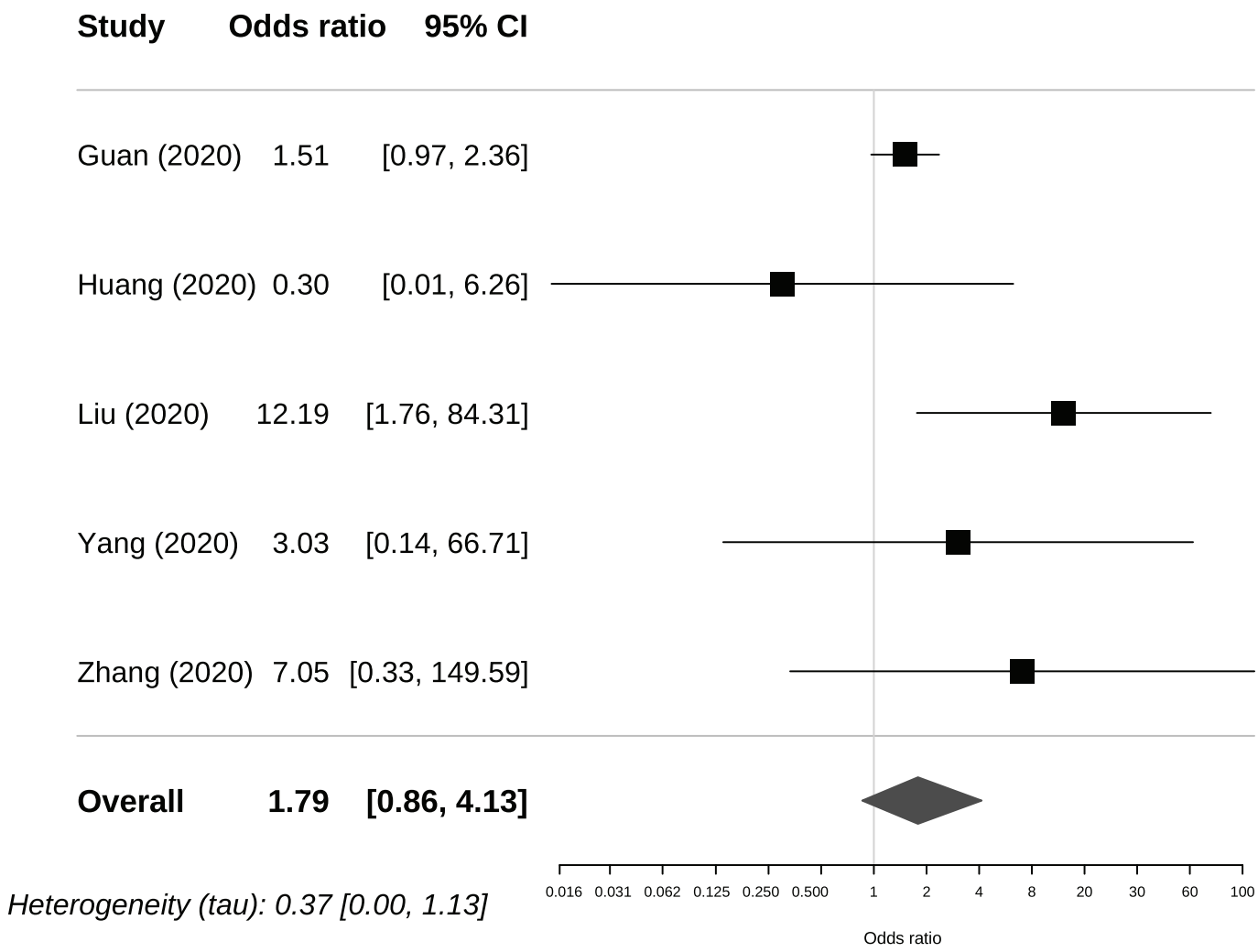

Fig. 1. Forest plot. The x axis is displayed in logarithmic scale.

and standard deviation 1) for the μ effect parameter. As for the heterogeneity parameter τ, we chose a half-Student-t prior with scale 0.5, as recommended in the literature [10]. The code and data are available upon request to the authors. Fig. 1 displays the forest plot. The Bayesian meta-analysis suggests that active smoking increases the severity of Covid-19 with an odds ratio of 1.79 (95% credible interval, 0.86-4.13). There is a 95% posterior probability of the disease following a worse course in a smoker versus a non-smoker; thus, Lippi et al's categorical conclusion based on the frequentist analysis does not hold up. Fig. 2 shows the distribution of log odds ratio that tilts broadly to the right of 0, revealing a deleterious effect of smoking on the evolution of Covid-19. This conclusion is more compatible with both the data available, as well as the impact of active smoking in patients with pneumonia and other infections [13,14]. Moreover, given the aggressiveness Covid-19 displays in the airway, it would be bizarre that it should be the only respiratory disease not affected by smoking. The discrepancy between the conclusion reached by Lippi et al and the true message contained in the data is a good example of the danger of misreading non-significant or inconclusive frequentist results [8]. Therefore, as in the 1950s, if you are a smoker, the Bayesian analysis provides you with yet another good reason to quit in times of Covid-19.

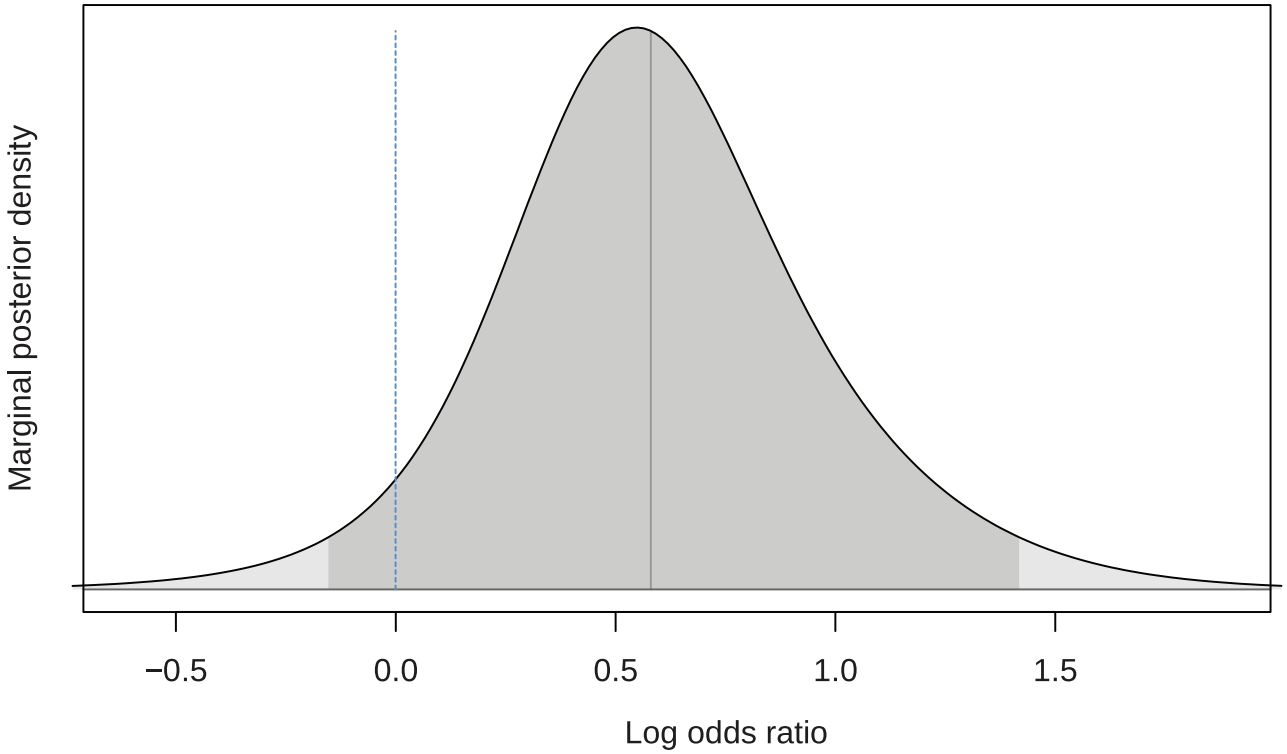

Fig. 2. Marginal density plot for the harmful effect of smoking (log odds ratio).

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