Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Considerations on the article De Bernardis, E., & Busà, L. (2020). A putative role for the tobacco mosaic virus in smokers' resistance to COVID-19 *Medical Hypotheses*, 110153

We were very interested in the article published by De Bernardis and Busà about a putative role for the tobacco mosaic virus in smokers' resistance to COVID- 19 [1]. However, we wish to point out, on our opinion, some issues regarding the study. Regarding the first citation of the article [2], by virtue of which De Bernardis and Busà declare "smokers' resistance to COVID-19", the authors, Landoni et al., themselves, referred about issues regarding their own study, such as, possible "selection biases", putative "high mortality rate of smokers infected by SARS-CoV-2" (that the authors subjectively declare "unlikely" without giving out any scientific data to justify such a declaration), and most of all, they state: "poor collection of medical history details in an emergency situation might have contributed to our findings. This might also apply to other published studies included in our systematic review.". Here again, the authors subjectively declined this bias stating "we have no reason to assume that missing patients would have a different rate of smoking versus non-smoking, and have no reason to believe inaccurate reporting by health care workers", going against their own judgement on the accuracy of their medical history collection. Interestingly, many authors, such as Patanavanich et al., indeed evidenced the "objective difficulty of having accurate medical history collection and thus underassessment of smoking especially in the difficult conditions present in overwhelmed health systems among COVID patients". "Thus", they concluded, "it is highly likely that many smokers were misclassified as non-smokers, which would bias the risk estimate toward the null" [3]. Moreover, other authors such as Jason Sheltzer [4] and Lion Shahab [5], reviewing the article of Farsalinos et al. on smoking and hospitalisation for COVID-19, [6], evidenced how difficult or quite impossible it was to register accurately the smoking status at hospitalisation of severely ill or dying patients. Cited studies registered only heavy smokers with an incredible - and useless - cut-off of 30 pack-years, such as the WHO conducted survey by Chen et al., mentioned by the authors. In fact, there were also many situations that, according to the reviewers, could have underpinned an artefactual association: 1) *reverse causation* (i.e. smokers with severe symptoms may stop smoking before admission to hospital and therefore be counted as non-smokers; alternatively, people presenting with COVID-19 may be less likely to admit to being current smokers); 2) *self-selection* (smokers with COVID-19 may be less likely to present to hospital, either because they have died or they self-treat in the community, e.g. because of lack of access to funds, given that smoking has a strong negative association with socio-economic position) and 3) *cohort effects* (smoking prevalence declines with age and older people are more likely to be hospitalised if they are infected).

De Bernardis and colleague, based on this, on our opinion, debatable article, state as follows: "it has been suggested that tobacco smoking might confer some protection against the SARS-CoV-2 infection, at least in its initial phases" [1].

This statement has been taken for granted even if many studies have opposite outcomes. For instance, Zhao and co-workers [7] studied the impact of COPD and smoking history on the severity of COVID 19. They reported in seven studies the relationship between active smoking and the severity of COVID-19. The pooled OR showed that smoking increases the risk of severe COVID-19 (fixed effects model; OR = 1.98; 95% CI: 1.29–3.05) by around two-folds. The same result is published by Berlin et al. who confirm that smoking is a risk factor for progression of COVID-19, with smokers having 1.91 times the odds of progression in COVID-19 severity than never smokers. The authors point out also that smoking behavior is characterized by inhalation and by repetitive hand-to-mouth movements which are strongly advised against to reduce viral contamination. Public health interventions, such as lockdown, may increase the exposure of family members to second-hand smoke [8]. A very recent publication by Shivani Mathur Gaiha and colleagues studied the association between youth smoking, Electronic Cigarette (e-cig) use, and Coronavirus Disease 2019, by means of an online national survey of adolescents and young adults (n = 4,351) aged 13–24 years conducted in May 2020. Multivariable logistic regression assessed relationships among COVID-19 related symptoms, testing, and diagnosis and cigarettes only, e-cigarettes only and dual use, sociodemographic factors, obesity, and complying with shelter-in-place. Ever-users of cigarettes only were 3.9 times (95% CI: 1.43–10.86) more likely to get COVID-19 tested. COVID-19 diagnosis was *five times more likely* among ever-users of e-cigarettes only (95% confidence interval [CI]: 1.82–13.96), *seven times more likely* among ever-dual-users (that is e-cig users who smoke also conventional cigarettes) (95% CI: 1.98–24.55), and *6.8 times more likely* among past 30-day dual-users (95% CI: 2.40e19.55). Testing *was nine times more likely* among past 30-day dual-users (95% CI: 5.43–15.47) and 2.6 times more likely among past 30-day e-cigarette only users (95% CI: 1.33–4.87). Symptoms were *4.7 times more likely* among past 30-day dual-users (95% CI: 3.07–7.16). The authors concluded that COVID-19 is associated with youth use of e-cigarettes only and dual use of e-cigarettes and cigarettes. For adolescents and young adults the results show that electronic cigarette use and dual use of electronic cigarettes and cigarettes are significant underlying risk factors for coronavirus disease 2019 [9]. Our study group already published data on old and new issues about tobacco smoking and COVID-19 pandemic [10]. Meta-analyses confirmed higher prevalence of comorbidities, many of which are tobacco-related diseases, in patients with severe COVID-19 reporting an OR = 2.25 (95% CI: 1.49–3.39) for developing severe Covid-19 among patients with a smoking history. Some authors, noticing that reported smoking prevalence among hospitalized patients was substantially below smoking prevalence in the corresponding populations, speculated a protective role of nicotine. However, it is likely that low prevalence among hospitalized patients are partially due to many smokers misclassified as non-smokers. In another published review, V. Zagà et al. [11] evidenced from articles dealing with 1,099 cases in China of Covid-19 disease, that 32% of

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patients with a history of smoking (smokers and ex-smokers) at the time of hospitalization had a severe form of Covid-19 pneumonia, compared to 15% of non-smokers. In addition, 16% of patients with a history of smoking were then hospitalized in intensive care or died, compared to 5% of non-smokers.

The ACE-2 expression debate is also well clarified by the following studies:

Leung et al. is the first study to demonstrate increased ACE-2 expression in airways of current (but not former) smokers and those with COPD with higher expression in current smokers compared to former and never smokers (2.86 ± 0.92 in current smokers, 2.35 ± 0.57 in former smokers, and 2.27 ± 0.45 in never smokers, p = 6.16 × 10–2). These results are also consistent with previous observations in small animals wherein smoke exposure has been shown to up-regulate both the expression and activity of ACE-2 in the airways [12–14] Other authors such as Brake et al. demonstrated that smoking up-regulates angiotensin-converting enzyme-2 receptor [15].

Regarding the statement of De Bernardis et al. “So far, though, no data are available on the effects of pure nicotine on COVID-19” [1], it is worthy mentioning that Russo and co-workers studied the possible link between COVID and nicotine, suggesting that smoking, by means of nicotine, may promote cellular uptake mechanisms of SARS-CoV-2 through α7-nAChR signalling. A possible α7-nAChR down-stream mechanism may be the induction of phospho-Akt and phospho-p44/42 MAPK. This mechanism was hypothesised, partially, by Olds and Kabbani [12] on their schematic model explaining how nicotine exposure increases the risk of SARS-CoV-2 entry into lung cells. α7-nAChR is present both in neuronal and non-neuronal cells (i.e. lung, endothelial, lymphocyte); consequently, smoking may impact COVID-19 pathophysiology and clinical outcome in several organ systems [16]. Our study group evidenced that tobacco smoking seems to cause a dose-dependent upregulation of the angiotensin-converting- enzyme-2 (ACE-2), the virus cellular entry receptor, which could explain the higher risk of severe COVID-19 in smokers [11].

In the light of all these considerations, we are not quite convinced about the validity of the affirmation made by De Bernardis and Colleague about the “resistance of tobacco smokers to the SARSCoV-2 infection” [1], neither for infection, nor for progression and severity of COVID-19. This is the key hypothesis upon which the whole article dealing with a “putative role of the tobacco mosaic virus (TMV) in smokers’ resistance to COVID-19”, is constructed.

One last consideration is to be made on the statement of the authors regarding the TMV.

Li and co-workers studied (in pre-COVID-19 period) the invasion of TMV RNA in human epithelial carcinoma (HeLa) cells, and demonstrated endoplasmatic reticulum stress-related autophagy, notably initiated in cells after viral invasion. Since HMV is found in sputum and saliva specimens from cigarette smokers, as well as in cigarettes, while being absent in non-smokers, Li et al. concluded that “If a virus mutates into a form that is more easily spread between humans, it can cause a pandemic” [17]. We feel that, according to a dynamic of anthrophytosis, TMV, being a very mutable RNA virus, and already well represented in smoking human beings (who are 1,3 billion persons in the world, according to WHO 2020), is thus more likely to become a threat for human health, in case of mutation, rather than an ally against COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110251.

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Vincenzo Zagà[a], Daniel L. Amram[b,*], Giacomo Mangiaracina[c], Maria Sofia Cattaruzza[d]

[a] *Italian Society of Tobaccology, Italy*

[b] *Regional Representative for Tuscany of the Italian Society of Tobaccology, Italy*

[c] *President of the National Agency of Prevention, Italy*

[d] *Department of Public Health and Infectious Diseases, La Sapienza University of Rome, Vice-President of the Italian Society of Tobaccology, Italy*

E-mail address: daniellawrence.amram@gmail.com (D.L. Amram).

* Corresponding author.