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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Caution is needed on the effect of altitude on the pathogenesis of SAR-CoV-2 virus☆

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Arias-Reyes and colleagues (Arias-Reyes et al., 2020) recently discussed the intriguing hypothesis that living at high altitude may be protective with regard to SAR-CoV-2 infection. They provide indications of lower severity and reduced prevalence of the COVID-19 pandemic in exemplary high altitude regions (Tibet, Bolivia and Ecuador) and provide suggestions on how environmental factors associated with high altitude may mechanistically – directly by UV-radiation, or indirectly via physiological adaptations of the angiotensin converting enzyme (ACE) systems – effectuate protection from viral infection and spreading.

As this effect of high altitude on SAR-CoV-2 pathogenesis is not *a-priori* expected, we would like to comment on viral spreading and the consequences of respiratory/lung infections at altitude.

It should first be highlighted that the robustness of the global epidemiological data on COVID-19 at present is doubtful, given that data collection in many parts of the world currently is limited by access to and actual performance of diagnostic tests. Also, to date (5.5.2020) no deaths due to SAR-CoV-2 have been reported in several countries, including other high altitude countries like Nepal and Bhutan, but also many low altitude countries, such as for example a number of Caribbean / Pacific islands (https://www.worldometers.info/coronavirus/#countries, accessed 5.5.2020). We thus argue that potential effects of high altitude on SAR-CoV-2 infection rates and pathogenesis based on the current data situation has to be regarded with caution.

Independent of the COVID-19 pandemic, available data convincingly indicate that residence at moderate and higher altitudes is associated with lower mortality from cardiovascular diseases and certain types of cancer (Burtscher, 2014; Burtscher, 2016; Faeh et al., 2009). In contrast, living at higher elevations may adversely affect mortality from respiratory diseases, with some indications also pointing to negative consequences on lower respiratory tract infections and disease progression (Burtscher, 2014). It is, however, difficult to dissect the causal factors attributed to these altitude-conferred benefits, as living in high altitude involves a multitude of adaptations and altered conditions. The most obvious factors differing from life in lowlands at comparable latitudes are changes in temperature, altered exposure to radiation and of course hypoxia due to reduced barometric pressure. Additionally, socio-economic conditions and various life-style factors may deviate in comparison to residence at lower altitudes.

By themselves or in combination, these factors will directly affect pathogens or influence human susceptibility or resistance on various levels (Fig. 1). (i) On a structural level, living at high altitudes may influence population density, access to commodities, clinical care and the “social distancing”. (ii) Behaviorally, people will adapt to for example weather conditions and radiation by appropriate clothing, housing, etc. High-altitude residence is also associated with higher levels of physical activity (Burtscher, 2016) and lower obesity prevalence (Millet et al., 2016), known as a major risk factor in COVID-19 patients (Sattar et al.); (iii) On the molecular level, these conditions result in physiological adaptations at acute or chronic altitude exposure and may entail genetic adaptations after generations of high-altitude residence.

While in the study of Arias-Reyes and colleagues (Arias-Reyes et al., 2020) structural components important for viral spreading, like

☆ Comment on the recent publication of Arias-Reyes et al. 2020: Does the pathogenesis of SAR-CoV-2 virus decrease at high-altitude?

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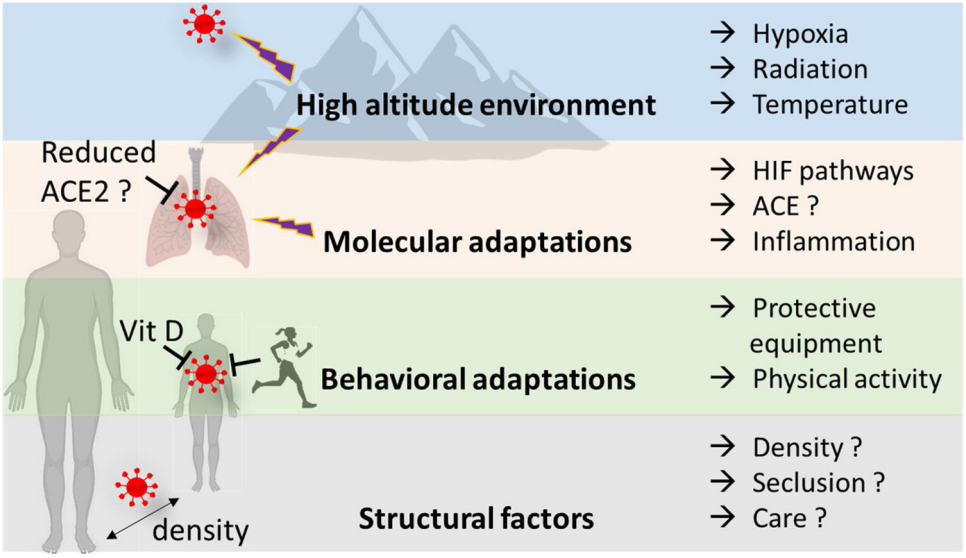

Fig. 1. Parameters of high altitude exposure and adaptations.
ACE2 - angiotensin converting enzyme 2, HIF – hypoxia inducible factor, Vit D – vitamin D.
See text for more information.

reduced density of population in higher altitudes (Cohen and Small, 1998), may be less relevant for La Paz and Lhasa, they certainly are of importance on a global level.

If confirmed, the reduced vulnerability of high-altitude inhabitants to viral infection in general and to SAR-CoV-2 specifically could be explained by a number of factors. As described by Arias-Reyes and colleagues, elevated levels of UV-light and other environmental parameters of high altitude might reduce survival of exposed viral particles. One could also argue that increased exposure to UV-B light at high altitude theoretically will lead to elevated vitamin D levels (Kimlin, 2008), which in turn could decrease viral infection susceptibility (Grant et al., 2020), although the potentially beneficial effects of vitamin D levels with regard to specifically SAR-CoV-2 has not yet been sufficiently explored.

Molecular high altitude adaptations, such as the potential reduction of ACE2, as pointed out by Arias-Reyes and colleagues (Arias-Reyes et al., 2020), may be relevant for coronavirus infections. It is, however, important to highlight that acute and chronic high altitude (homeostatic and developmental plasticity) adaptations may be fundamentally different to transgenerational adaptations. For example, while Tibetan highlanders have developed transgenerational adaptations to altitude that include for example a rather "normal" hemoglobin concentration, lowlanders exposed to high altitude exhibit increased hemoglobin values as a compensatory adaptation to hypoxia (Simonson et al., 2010). Thus, while the studies referred to by Arias-Reyes and colleagues (Arias-Reyes et al., 2020) clearly demonstrate individual adaptations of ACE2 in *in vitro* and animal models in response to chronic hypoxia, human studies (e.g. genetics) related to ACE2 are needed to confirm equivalent molecular long-term adaptations in high altitude populations.

Mechanistically, respiratory diseases, including such resulting from severe SAR-CoV-2 infection, may progress more seriously in altitude due to deleterious effects of radiation and reduced oxygen partial pressure that can cause pulmonary inflammation via alveolar hypoxia and inhibits lung fluid absorption and thus could contribute to the development of respiratory infections (Hwang et al., 2018). Climatic factors, like low temperature and humidity or frequent high-wind conditions may be involved in the negative development as well. Positive associations between altitude and mortality from chronic lower respiratory diseases and pneumonia were demonstrated (Hwang et al., 2018). Taken together high altitude conditions thus could also be relevant for acute respiratory distress syndrome and COVID-19 pneumonia resulting from SAR-CoV-2 infection.

Finally, even if the underlying viral infections are different, previous pandemics seem to not necessarily have exhibited more favorable progressions in high altitude populations, with some reports pointing even in the opposite direction. For example, during the pandemic 2009 influenza A (H1N1) virus pneumonia in Mexico, high altitude residence was linked to more adverse outcomes (Perez-Padilla et al., 2013). The later authors pointed out the detrimental effect of altitude-induced hypoxemia.

While we agree that all environmental factors – including altitude – are of interest for the analysis of the COVID-19 pandemic, we advocate caution in the interpretation of associations of high altitude residence with reduced severity of SAR-CoV-2 pathogenesis. In particular, it is paramount to be confident on comparability and completeness of diagnostic datasets on cases and mortality and to take into account biological, environmental and psycho-sociological factors.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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