Which are the factors affecting Coronavirus SARS-CoV-2 and/or related Covid-19 disease on which we can leverage to reduce the impact of epidemics in the future?

Field: Science Input

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Abstract

Following the tremendous worldwide impact of novel Coronavirus SARS-CoV-2, it becomes essential to identify the factors affecting both the virus biology and its clinical expression in humans, leveraging, wherever possible, on any of such factors to minimize the probability of recurrence of a wide epidemic spreading, either decreasing the infection rate or mitigating the symptoms.

This report seeks to identify the factors influencing Covid-19 outcome, particularly those that can be influenced or controlled, such as immune system mechanisms, comorbidities, age and sex, environment, genetic, and social factors.

Glossary

- AhR — Aryl hydrocarbon receptor
- ARDS — Acute respiratory distress syndrome
- Covid-19 — Coronavirus disease 2019
- SARS-CoV-2 — Severe acute respiratory syndrome coronavirus 2

The immune system response to SARS-CoV-2

The principal characteristic of SARS-CoV-2 infection is a uniquely inappropriate inflammatory response. The reduced innate defenses coupled with exuberant inflammatory activation are likely the defining features of Covid-19. Figure 1 shows how the Covid-19 drives a lower antiviral response compared with other respiratory viruses [1].

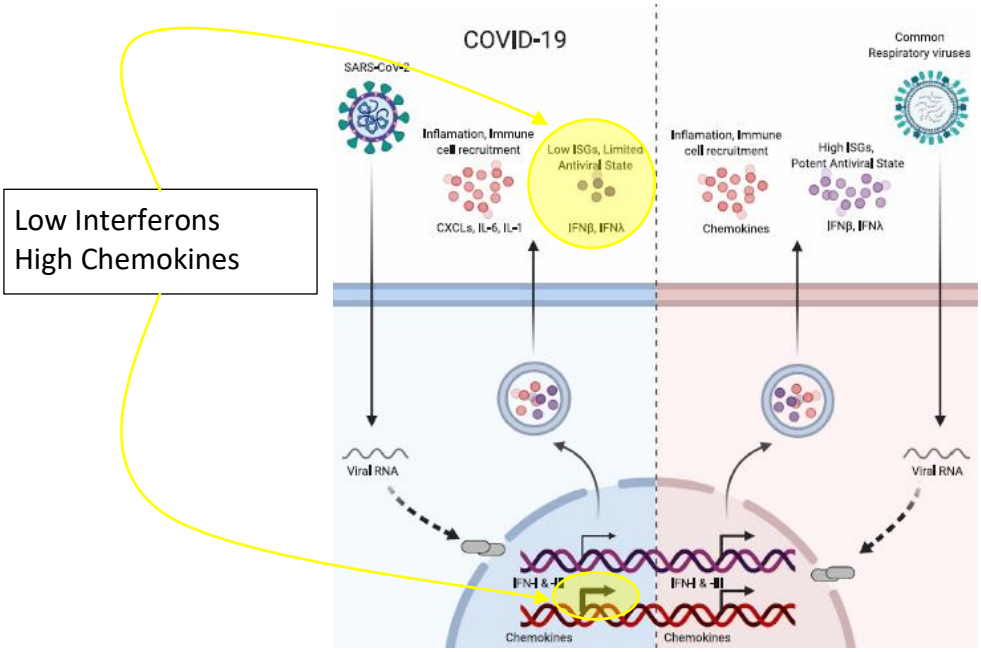

Figure 1. Comparison of inflammatory response between common respiratory viruses and SARS-CoV-2 [1]. SARS-CoV-2 infection (left) drives a lower antiviral response marked by low levels of IFN-I and IFN-III (signaling proteins made and released in response to the presence of viruses) and elevated chemokine (other signaling proteins) expression.

Because a waning immune response would enable sustained viral replication, these findings may explain why serious cases of Covid-19 more frequently occur in individuals with comorbidities [1], [3].

Controlling the abnormal inflammatory response to SARS-CoV-2 may be as important as targeting the virus. Figure 2 represents the chronology of events during SARS-CoV-2 infection in the lung. The active replication and release of the virus cause an inflammatory form of programmed cell death, and release damage-associated molecules. This triggers the generation of pro-inflammatory proteins, which in turn attract white blood cells and T cells to the site of infection, promoting further inflammation and establishing a pro-inflammatory feedback loop. In a flawed immune response (Figure 2, left side), this may cause an overproduction of pro-inflammatory proteins, which eventually damages the lung architecture. The resulting inflammatory proteins loop affects other organs, leading to multi-organ damage. Alternatively, in a healthy immune response (Figure 2, right side), the inflammation attracts virus-specific T cells to the site of infection, where they can eliminate the infected cells before the virus spreads. Neutralizing antibodies can block the viral infection, while white cells recognize neutralized viruses and death cells and clear them by phagocytosis. Altogether, these processes lead to clearance of the virus and minimal lung damage, resulting in recovery [5].

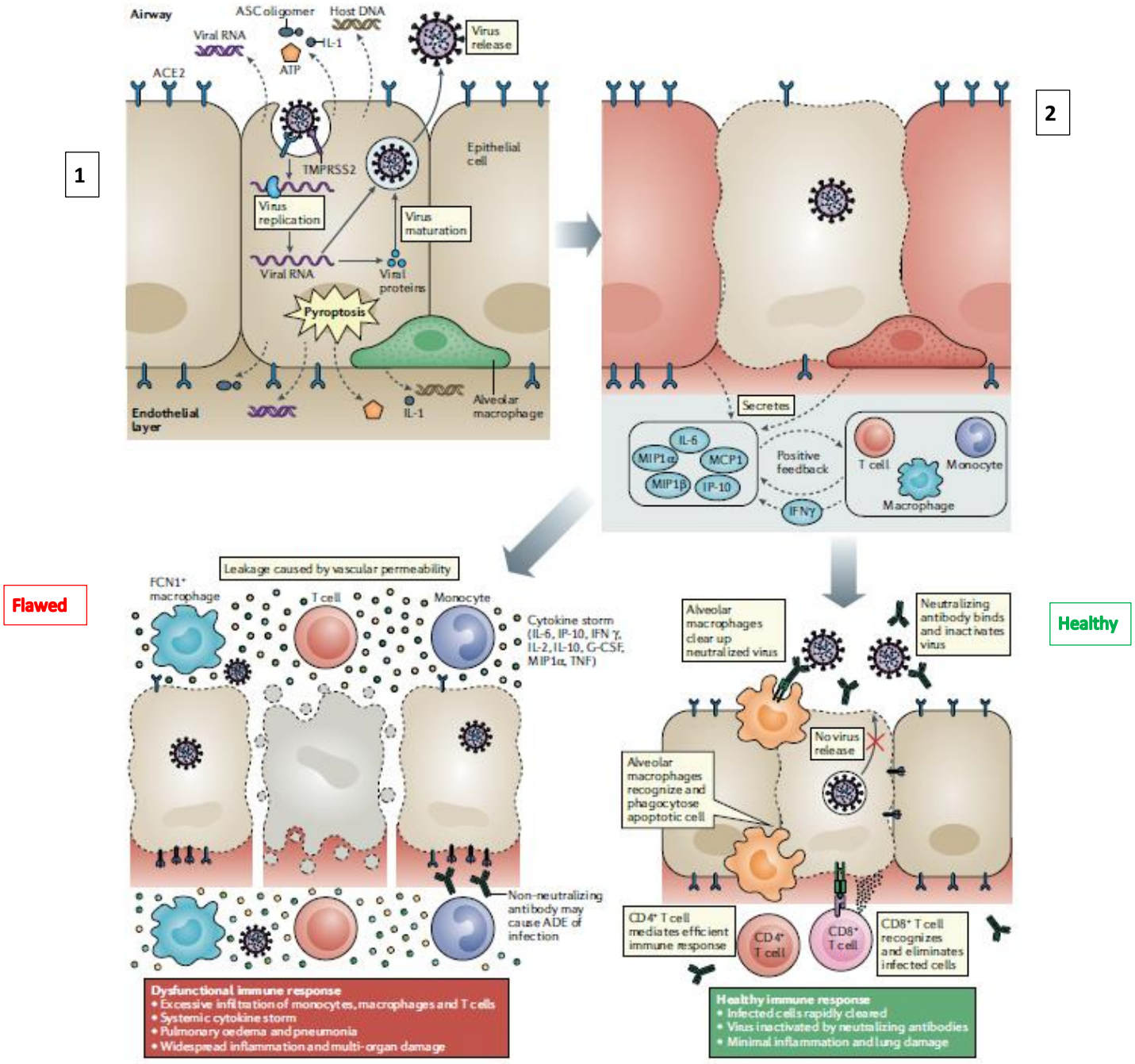

Figure 2. Chronology of events during SARS-CoV-2 infection [5].

(1) Virus replication and release cause cell death and release of damage-associated molecules (1).

(2) The production of pro-inflammatory proteins establishes an inflammatory feedback loop, which attract white blood cells and T cells.

Left: flawed immune response: overproduction of pro-inflammatory proteins and multi-organ damage.

Right: health immune response: immune system block the viral infection, minimal lung damage and recovery.

Genetics: the human perspective

There is a considerable heterogeneity in immunological parameters between individuals, and most of them are determined by non-heritable factors; for example, antibody responses to seasonal flu vaccines in adults have no detectable heritable component. In addition, some of these parameters become more variable with age, suggesting the cumulative influence of environmental exposure. This highlights the largely reactive and adaptive nature of the immune system in healthy individuals [4].

Genetics: the viral perspective

According to recent findings [9], [10], a mutated variant of SARS-CoV-2 is circulating throughout Europe and the US, which might be responsible of a higher infectivity and stability of the virus. This tiny mutation would markedly increase the number of the so-called "spike" proteins, which allow the virus to bind to and infect cells. Typically, viruses acquire small genetic changes as they reproduce and spread, but such changes rarely impact fitness or ability to compete; instead, this SARS-CoV-2 mutation, lacking in the earliest regional outbreaks, seems now dominating in much of the world.

Pathogenesis

Both the viral particle and the exaggerated immune response play an important role in the pathogenesis of Covid-19. An overproduction of small proteins, called cytokines, is the major responsible for the severe progression of the disease and the organ damage. The clinical course of the disease is variable, and asymptomatic course is likely higher than expected. The disease progress with various symptoms, such as fever, cough, dyspnea, malaise, myalgia, taste and smell dysfunctions, diarrhea, and headache. Severe cases progress to acute respiratory distress syndrome (ARDS) and death [3].

Patients with comorbidities have poorer clinical outcomes and greater disease severity than those without. A greater number of comorbidities also correlated with poorer clinical outcomes [2].

Prevention

Occupational, residential, dietary and environmental exposures to mixtures of synthetic chemicals have a strong relationship with the increase of chronic diseases. Pollution is the largest environmental cause of disease and premature death in the world today [16].

The link between environment and immunity is particularly intriguing; there is an association between pollution and immunotoxicity, such as allergies and autoimmune diseases. Among the interactions between the environment and the immune system, the aryl hydrocarbon receptor (AhR) plays an interesting role [6] [17]. Different environmental factors activate AhR, and this is expressed in different immune cells, thus integrating the effects of the environment and metabolism on the immune response, by regulating its gene expression [14] [15]. A recent study suggests that AhR (Aryl Hydrocarbon Receptor) pathway plays a role in the pathogenesis of Covid-19, by regulating the immune system and the response to pollutants. Once into cells, coronaviruses would activate the AhRs, resulting in a "Systemic AhR Activation Syndrome" which culminates in multiple organ injuries,

and even in death. Activation of AhRs may lead to diverse reactions depending on time after infection, health status, hormonal balance, age, gender, and environmental factors as well. [13].

AhR pathway seems to be a way through which several pathogenic agents can act, as represented in Figure 3. Long-term exposure to, for example, thousand chemicals in mixtures, mostly fossil fuel derivatives, exposure to particle matters, metals, ultraviolet (UV)-B radiation, ionizing radiation and lifestyle contribute to immunodeficiency observed in the contemporary pandemic [6].

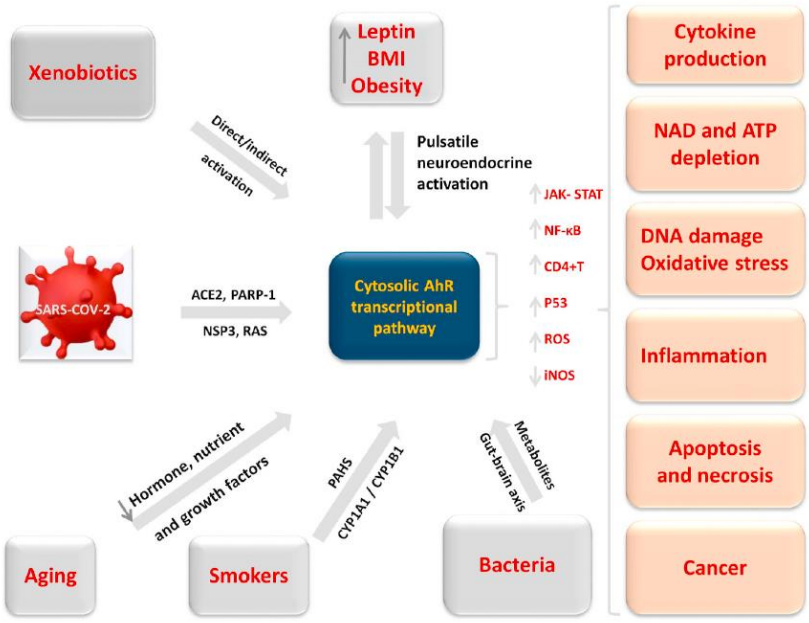

Figure 3. Xenobiotics, viruses, bacteria, obesity and aging acting through AhR pathway [6].

Impact of sex and gender

Compared to women, men infected with the Covid-19 have more severe disease and a higher mortality; this indicates that sex is an important driver of risk of mortality and response to the Covid-19 pandemic.

Figure 4 compares the proportion of deaths among confirmed cases in women and man [11].

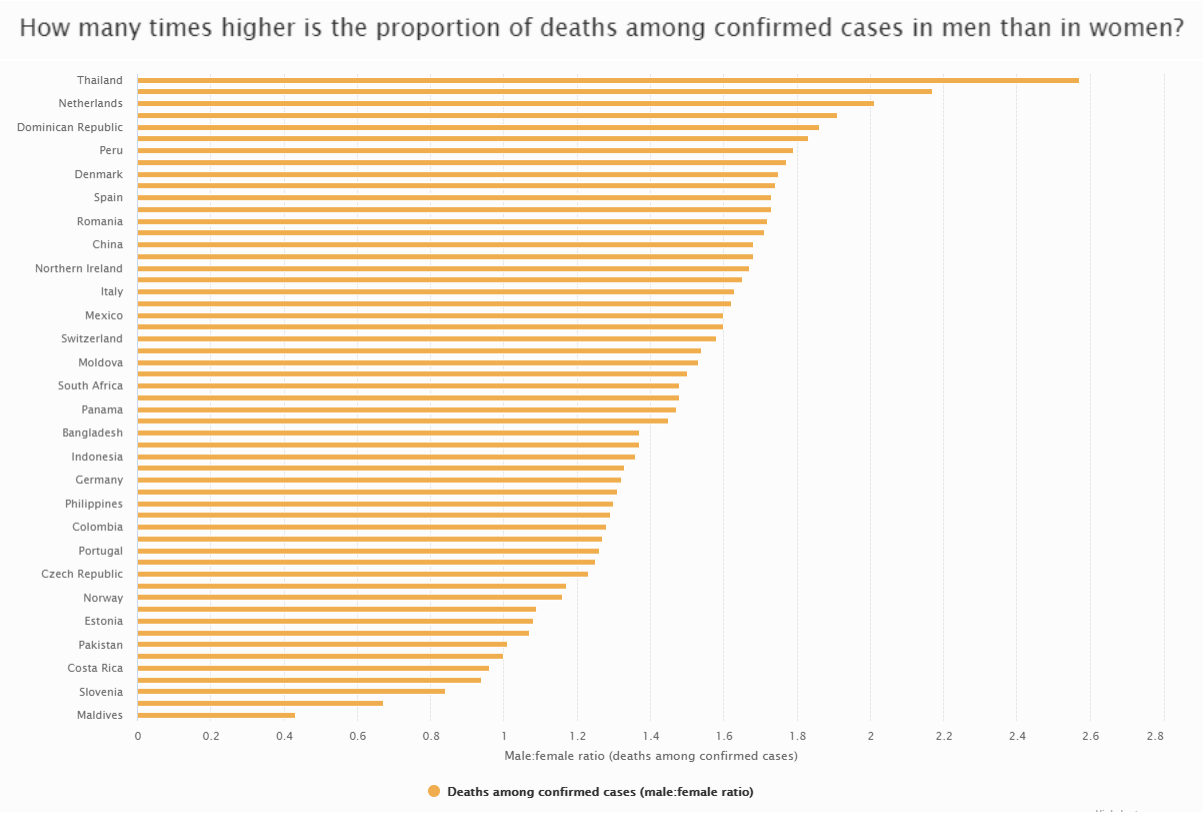

Figure 4. Proportion of Covid-19 deaths among confirmed cases in women and man [11].

To develop a better understanding of the true biological differences in disease propagation and adverse outcomes, sex-disaggregated data are essential for understanding the distributions of risk, infection, and disease in the population and the extent to which sex affects clinical outcomes. In a case's series from China, 75% of the Covid-19 deaths were among men. A report on 3,200 Covid-19–related deaths from Italy also showed higher deaths for men compared to women across all age groups, with women accounting for only 29.4% of these deaths. Overall, women dying from Covid-19 infection were older than men were (median age: 82 vs. 79 years for women vs. men, respectively). Among the nine deaths of patients younger than 40 years, eight were men. Besides comorbidities, the occurrence of other gender-related risk factors should be investigated to tailor proper treatments accordingly. Despite experiences from past outbreaks and pandemics have clearly shown the importance of incorporating a sex and gender analysis, public health efforts have not yet fully addressed this topic [7], [8].

Vulnerability to Covid-19

The impact of Covid-19 mortality in different world regions has been simulated through a standardized vulnerability index calculated from the Covid-19 death rates and the 2020 age and sex structures. As reported in Figure 5, there are considerable variations in vulnerability to Covid-19 because of the demographic structures of the different countries. When compared to younger countries in Sub-Saharan Africa, the vulnerability to Covid-19 mortality is 17 times higher in several industrialized countries of East Asia and Europe data shows.

There is a high correlation (r^2= 0.44) between demographic vulnerability to Covid-19 mortality and current Covid-19 death rates [12].

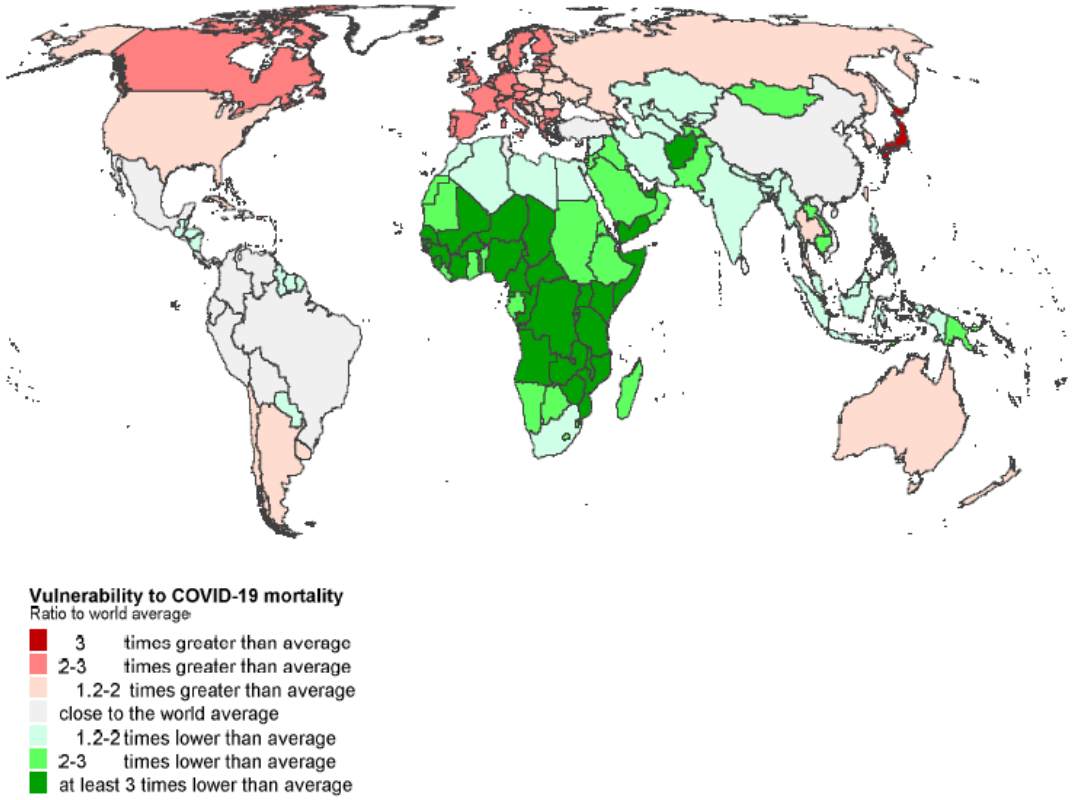

Figure 5. Vulnerability to Covid-19 in different countries [12].

Conclusion

While Covid-19 presents similarities with other common respiratory diseases, yet it affects the human body in a very particular way with an exuberant production of inflammatory cytokines, which promote a pro-inflammatory feedback loop. The response in a flawed immune system leads to multi-organ damage, while a health immune system is able to block the viral infection and inflammation. Many factor interplay for the outcome, most of which are somehow connected to the immune system, such as the environment pollution.

There are indications that Covid-19 shares same pathogenic mechanisms with environmental-related diseases such as type II diabetes and cancers. Thus, it could be extremely valuable to fully understand the impact that environmental chemicals have on the immune system, the mechanisms underlying these effects, and how they might be mitigated.

These elements suggest that the best strategy in the long-term for the prevention of both viral infections and chronic diseases is to promote a healthy immune response.

While age and sex have a clear correlation with Covid-19, there are indications that other factors such as environmental pollutants, gender, geography and diet may all have a role. Upon deeper knowledge and understanding of these factors, different solutions may become available to minimize the consequences of epidemics in the future, such as the development of dietary supplements able to optimize the response to the infections, or the reduction of those pollutants known to weaken the immune system.

The clinical course is variable; older male adults, those with comorbidities have a more severe disease course. Asymptomatic people are more common than expected; while this aspect is positive because it would mean a reduced mortality and morbidity associated to the Covid-19, it makes more difficult tracking the affected population, and in general the epidemiologic investigation.

Finally, governments worldwide should be sensitized about the outmost importance of social distancing, large-scale screening, and effective sanitary systems to control the current pandemic in the short-term, and to invest in scientific research and share results with the community to develop effective countermeasures able to improve global health in the future.

[1] D. Blanco-Melo *et al.*, "Imbalanced Host Response to SARS-CoV-2 Drives Development of Covid-19," Cell, vol. 181, no. 5, pp. 1036-1045.e9, 28 2020, doi: 10.1016/j.cell.2020.04.026.

[2] W.-J. Guan *et al.*, "Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis," *Eur. Respir. J.*, vol. 55, no. 5, 2020, doi: 10.1183/13993003.00547-2020.

[3] R. Öztürk, Y. Taşova, and A. Ayaz, "Covid-19: pathogenesis, genetic polymorphism, clinical features and laboratory findings," Turk J Med Sci, vol. 50, no. SI-1, pp. 638–657, 21 2020, doi: 10.3906/sag-2005-287.

[4] P. Brodin et al., "Variation in the human immune system is largely driven by non-heritable influences," Cell, vol. 160, no. 1–2, pp. 37–47, Jan. 2015, doi: 10.1016/j.cell.2014.12.020.

[5] M. Z. Tay, C. M. Poh, L. Rénia, P. A. MacAry, and L. F. P. Ng, "The trinity of Covid-19: immunity, inflammation and intervention," Nat. Rev. Immunol., vol. 20, no. 6, pp. 363–374, 2020, doi: 10.1038/s41577-020-0311-8.

[6] A. Tsatsakis et al., "Covid-19, an opportunity to reevaluate the correlation between long-term effects of anthropogenic pollutants on viral epidemic/pandemic events and prevalence," Food Chem. Toxicol., vol. 141, p. 111418, Jul. 2020, doi: 10.1016/j.fct.2020.111418.

[7] G. Sharma, A. S. Volgman, and E. D. Michos, "Sex Differences in Mortality From Covid-19 Pandemic: Are Men Vulnerable and Women Protected?," JACC: Case Reports, May 2020, doi: 10.1016/j.jaccas.2020.04.027.

[8] C. Gebhard, V. Regitz-Zagrosek, H. K. Neuhauser, R. Morgan, and S. L. Klein, "Impact of sex and gender on Covid-19 outcomes in Europe," Biology of Sex Differences, vol. 11, no. 1, p. 29, May 2020, doi: 10.1186/s13293-020-00304-9.

[9] "Mutated coronavirus shows significant boost in infectivity." https://www.scripps.edu/news-and-events/press-room/2020/20200612-choe-farzan-coronavirus-spike-mutation.html (accessed Jul. 07, 2020).

[10] L. Zhang et al., "The D614G mutation in the SARS-CoV-2 spike protein reduces S1 shedding and increases infectivity," bioRxiv, Jun. 2020, doi: 10.1101/2020.06.12.148726.

[11] "COVID-19 sex-disaggregated data tracker – Global Health 50/50." https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/ (accessed Jul. 16, 2020).

[12] C. Z. Z. Guilmoto, "COVID-19 death rates by age and sex and the resulting mortality vulnerability of countries and regions in the world," Public and Global Health, preprint, May 2020. doi: 10.1101/2020.05.17.20097410.

[13] W. A. Turski, A. Wnorowski, G. N. Turski, C. A. Turski, and L. Turski, "AhR and IDO1 in pathogenesis of Covid-19 and the 'Systemic AhR Activation Syndrome:' Translational review and therapeutic perspectives," RNN, pp. 1–12, Jun. 2020, doi: 10.3233/RNN-201042.

[14] C. Gutiérrez-Vázquez and F. J. Quintana, "Regulation of the Immune Response by the Aryl Hydrocarbon Receptor," Immunity, vol. 48, no. 1, pp. 19–33, 16 2018, doi: 10.1016/j.immuni.2017.12.012.

[15] J. M. Kreitinger, C. A. Beamer, and D. M. Shepherd, "Environmental Immunology: Lessons

Learned from Exposure to a Select Panel of Immunotoxicants," J.I., vol. 196, no. 8, pp. 3217–3225, Apr. 2016, doi: 10.4049/jimmunol.1502149.

[16] P. J. Landrigan et al., "The Lancet Commission on pollution and health," The Lancet, vol. 391, no. 10119, pp. 462–512, Feb. 2018, doi: 10.1016/S0140-6736(17)32345-0.

[17] M. Veldhoen et al., "The aryl hydrocarbon receptor links T H 17-cell-mediated autoimmunity to environmental toxins," Nature, vol. 453, no. 7191, Art. no. 7191, May 2008, doi: 10.1038/nature06881.