encyclopedia

Entry

COVID-19: Gender and Outcomes

Alfonso Ilardi

Department of Internal Medicine, Inmates Ward, "Antonio Cardarelli" Hospital, Via A. Cardarelli, 9, 80131 Naples, Italy; alfonso.ilardi@aocardarelli.it

Definition: The existence of differences in susceptibility to SARS-CoV-2 infection between males and females in both incidence and outcomes is well documented in the scientific literature. These differences, which are still underestimated, may have important implications in terms of prevention, diagnosis, and treatment of COVID-19, with significant prognostic consequences. The greater severity of the infection observed in males, even more so if they are elderly, would seem, according to current knowledge, to be due to multiple influences: immunological and endocrinological, but also genetic and behavioral.

Keywords: immunosenescence; coronavirus; Angiotensin Converting Enzyme 2 (ACE2); dendritic cells; estradiol

1. Introduction

Since the outbreak of the current pandemic, it has been clear that the severity of infection was greater in older people, depending on the burden of comorbidities [1], and most likely related to the decay of immune functions, referred to as immunosenescence, which occurs as the physiological aging process advances. The latter is characterized by a progressive failure of innate and especially acquired immunity, secondary to the decreased availability of naïve peripheral T and B cells, which tend to be gradually depleted by repeated microbiological exposure throughout life [2].This depletion is accompanied by the expansion of some memory cell subsets, which leads to a significant imbalance in the relationship with naïve cells. The result is a reduced availability of cells oriented towards immune responses to new pathogens and an increased susceptibility to infection [3,4].

Another widely recognized aspect of the aging process is theprofound structural changes that occur to the rib cage (stiffening from calcification and kyphosis from osteoporosis), reducing its compliance and impairing the complete emptying of the lungs at expiration with an increase in residual volume. There is also an increase in the size of the distal airspaces due to the loss of supporting tissue and a progressive reduction in the strength of the respiratory muscles. These effects reduce the reserve capacity of the whole system, increasing the vulnerability to functional failure in situations of increased ventilatory demand [5].

The aforementioned issues do not discount the weight of comorbidities on the severity of the infection. In the cohort of patients evaluated by Grasselli and co-workers, about 1550 subjects were admitted to the Intensive Care Unit (ICU), and at least one comorbidity was recorded in 68% of cases [6].

A lower percentage (23.7%) was reported in Guan's study of 1099 patients. However, in this cohort, the infection was classified as severe in only 173 patients [7].

The data on the type of preexisting disorder is also of significance. Case fatality is highest in patients with defined comorbidities, such as cardiovascular disease, diabetes mellitus, hypertension, chronic respiratory disease, and cancer [8]. Of these, hypertension is the most common in patients with COVID-19 and hypertensive patients have a higher disease severity and admission rate to the ICU than those with normal blood pressure [6,9].

check for updates

Citation: Ilardi, A. COVID-19: Gender and Outcomes. *Encyclopedia* **2022**, *2*, 864–872. https://doi.org/10.3390/encyclopedia2020056

Academic Editors: Stephen Bustin and Raffaele Barretta

Received: 6 March 2022
Accepted: 16 April 2022
Published: 22 April 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Therefore, since hypertension has a higher prevalence in males than in females, at least until the onset of menopause [10], the possible link between hypertension and the severity of COVID-19 should also be investigated. According to some authors, it should be attributable to endothelial dysfunction, which preexists with the infection but promotes its progression through a state of hypercoagulability, and to dysregulation of the Renin-Angiotensin System (RAS). The latter would be favored by downregulation of the ACE2 enzyme, on the surface of pneumocytes, with reduced production of Ang 1-7 and an increase of the pro-oxidative and pro-inflammatory actions of Ang II [11].

However, even irrespective of age and comorbidities, the greater severity of infection observed in males, makes this subset at higher risk for admission to the ICU [6,12], as well as having a higher mortality rate [13,14].

This was also supported by Peckam's meta-analysis, which selected 107 studies from all over the world with a total of 3,111,714 patients. The analysis shows that males and females are at equivalent risk of infection, with males being associated with the development of severe disease as measured by admission to the ICU [15].

Although the current epidemiological situation is in constant evolution, the trend does not seem to have changed substantially.

In England, the majority of deaths in COVID-19 patients (99%), from March 2020 to April 2021, occurred in adults aged 45 years and older, and from this threshold age, most deaths were in males [16].

In Italy, the most recent data provided by the National Institute of Health document that the number of positive swabs is higher in females between the ages of 20 and 55. Conversely, the incidence curves of hospital admissions, including those in the ICU, begin to differ after the age of 40, with a greater slope in males than in females [17].

The aim of this entry is to explore the above gender-correlated differences, with particular focus on risk factors that are thought to have the greatest impact on important clinical outcomes.

2. Risk Factors

The observed differences between the sexes may have different assumptions: behavioral, endocrinological, immunological, as well as genetic. These factors have come more strongly to the attention of the scientific community since the pandemic SARS, which originated in China in 2002. Over the years it has become clear that their knowledge and management can provide useful contributions both in terms of preventive strategies and the identification of potential therapeutic targets. This last aspect is even more important if framed within the context of gender-orientedpharmacology, which highlights and defines the differences in the efficacy and safety of drugs according to gender.

2.1. Behavioural Factors

The adoption of healthy lifestyles by females is considered to be one of the contributing factors. For example, in this subgroup, there is lower consumption of cigarettes and alcohol [18].

However, it should be emphasized, especially with regard to smoking status, that its impact on the two sexes varies between countries. Developed countries have a higher prevalence of female smokers than developing countries, while the prevalence of male smokers tends to be more or less similar [19].However, among non-daily smokers, women have lower cigarette consumption and nicotine dependence [20].

At the same time, significant differences were observed among females and males in the perception of illness in terms of both severity and compliance. As reported in a survey involving 21,649 subjects from eight different countries (Australia, Austria, France, Germany, Italy, New Zealand, UK and USA), this perception, which appears less relevant in young people, tends to increase with age, although males with symptoms of illness are more likely to adhere to containment measures (interpersonal distance, hand washing, and correct use of personal protective equipment) [21].

Significant differences also emerged between the two sexes in their responses to stress triggered by lockdown and prolonged restriction actions. The study by Salfi and coworkers demonstrates, within the Italian population, a different temporal pattern of sleep disturbances and mental health status during the pandemic. Although the scores recorded in females were higher than males over time, especially at the beginning of the lockdown, the gender gap progressively narrowed. In the long term, women seemed to be more resilient than men, showing a tendency to improve in terms of anxiety, depression, and insomnia [22].

The different responses would be due to the emergence of two different reactive patterns: a fight-or-flight pattern in males and a tend-and-befriend pattern in females [23]. The latter can further explain the greater acceptance by females of the rules and restrictions imposed by the health emergency.

On the other hand, increased levels of perceived stress in males may also have significant effects on immune-mediated responses. In fact, it is known that under conditions of chronic stress, the cytotoxic action of Natural Killer cells is reduced, with suppression of the lymphocyte proliferative response and attenuation of humoral responses [24].

A further observationofthe gap between the two sexes, disadvantaging the females in this case, can be observed in the under-60 age group and is related to the characteristics of the working pattern. The direct care of the sick members of the family, who are often elderly, as well as the care of children, especially those of school age, could represent a source of increased exposure to infection in females, a relationship, moreover, already suggested by Monto about twenty years ago [25].

Moreover, in this age group, women are highly represented in the health professions, especially among nurses and the risk of respiratory infections among health care workers is also well described [26].

Indeed, it is estimated that women currently represent more than 70% of the global health workforce, and this representation rises to 90% in the nursing professions [27].

2.2. Endocrine and Immunological Factors

The interfering effect of immunological and hormonal factors on susceptibility to infection and its progression is a complex study area.

First of all, we must consider the potential role of androgens as a restraining factor in the cytokine response, with higher levels of TNF-α and IL1-β seen in androgen-deficient males [28].

In this regard, it has been demonstrated that androgens suppress the activity of transcription factors (NF-kB) by increasing the expression of peroxisome proliferator-activated receptor (PPAR) in T cells [29].

However, suppressing the cytokine response should make younger males more vulnerable. This hypothesis is disproved by available epidemiological data [17].

Alternatively, overexpression of the integral membrane glycoprotein Angiotensin Converting Enzyme 2 (ACE2), which acts as a gateway for coronavirus, might be considered [30].

This function is related to its binding with the viral Spike-protein, which protrudes from the surface, causing the virus to take on a crown-like appearance. The key role of ACE2 has been widely confirmed by several studies, which have also shown that the affinity of the Spike-protein of the new coronavirus is higher than that of the Spike-protein of SARS-CoV [31].

The enzyme, like its counterpart, the Angiotensin Converting Enzyme (ACE), plays an essential role in modulating sodium balance and vasoconstriction and is highly expressed not only in the lungs but also in other organs [32]. Particularly in the lungs, more than 80% of the cells expressing this metalloproteinase on the surface are type II pneumocytes, explaining the increased vulnerability of the lower respiratory tract to infection [33].

The key action of ACE2 is the conversion of the octapeptide Ang II to its metabolite Angiotensin-(1–7), which performs opposite actions to those of Angiotensin II, a molecule with vasopressive, profibrotic, and proliferative properties [34].

However, the interaction of the virus with ACE2 may favor its downregulation with a loss of enzyme function. The higher concentration of the enzyme at the alveolar cell surface, observed in males, suggests that the downregulation phenomenon mentioned above is more extensive and potentially unbalancing; i.e., the increased production of Ang II and subsequent over-stimulation of the AT1 receptor (AT1R) could contribute to additional or worsening lung damage in this subgroup of patients. Indeed, it has been suggested that the loss of ACE2 activity may result, via the AT1R, in an increase in vascular permeability with the destruction of the alveolar barrier and the extravasal collection of inflammatory cells [35].

Conversely, high concentrations of estradiol reduce ACE2 expression in the lungs, with opposite effects in the presence of decreased levels [36,37].

Additional to these observations is the finding that estrogens affect the expression of the AT1R and ACE, promoting the concurrent decrease in plasma renin activity [38]. The reduced concentration of AT1R could, therefore, exert a dampening effect on lung damage in women.

A further issue for discussion is the possible imbalance between the enzyme bound to the plasma membrane and the soluble form (sACE2), which is released into the circulation through the action of tumor necrosis factor-alpha convertase (ADAM17). It could be assumed that an increased circulating fraction reduces the compensatory power of ACE2. Since males exhibit higher plasma concentrations of sACE2 relative to children and women [39], the greater severity of the disease in males should be secondary to an accentuation of the pathogenic sequences triggered by the infection [40].

However, Yang and coworkers' study reported that, in patients with higher circulating levels of the enzyme ectodomain, the outcome improved, suggesting a protective effect of sACE2 against acute lung injury [41].

From this perspective, it could be assumed that sACE2, acting as a decoy for the coronavirus, prevents the downregulation of the cell surface enzyme and subsequent over-stimulation of the AT1R [42].

The different immunological reactivity detectable in the two sexes is more accurately defined. Indeed, females are more likely to develop a vigorous immunological response following an infection, in both innate and acquired immunity [43]. From an evolutionary viewpoint, this high level of responsiveness increases their survival and hence the reproductive capacity of the species [33]. This is supported by the observation in animal studies that infections tend to occur more severely in the middle-aged than in the young and old [43].

The above differences should be related to the estrogenic effects mediated by specific receptors (e.g., ERα), which promote gene transcription after interaction with an appropriate ligand [44]. It has been established that signals triggered by ERα activation are involved in the differentiation of various subsets of dendritic cells (DCs), which are essential for the activation of specific naïve T cells and their subsequent differentiation into effector T cells [45].

In addition to the classical DCs (cDCs), which specialize in antigen processing and presentation, there are monocyte-derived CD11b+ inflammatory/migratory DCs, which display many of the characteristics of cDCs, Langerhans cells, and plasmacytoid DCs (pDCs). CDCs, with their distinctive dendritic appearance, are specialized in antigen processing and presentation. In contrast, pDCs have a spherical shape, have no phagocytic functions, and are unable to present exogenous antigens to CD4+ T cells [45].

They are activated by specific pattern recognition receptors (PRRs).Among these receptors is Toll-Like-Receptor 7 (TLR-7), an endosomal innate immune sensor, which recognizes single-stranded RNA sequences, including the coronavirus genome [33].

These cells are also able to produce large amounts of type I Interferons (IFN) in response to viral infections [45,46], although all nucleated cells can in fact produce type I IFN. The signals triggered by these mediators induce transient lymphopenia, which is due to the rapid migration of lymphocytes into secondary lymphoid organs [47].

However, the production and release time of these compounds can be critical for protection, because a possible slowdown can have negative inflammatory effects. In this regard, the reaction can be regarded as more timely and quantitatively more intense in females [43].

2.3. Genetic Factors

A genetic hypothesis has been advanced to overcome the traditional estrogen/androgen hormone dichotomy and to support the differences in immunological reactivity. Such an assumption makes possible an extension of the differences between the sexes to a broader age range [48].

In mammals, females carry a pair of X chromosomes in their somatic cells, each of which consists of 154 Mb, about three times the 59 Mb of the Y chromosome. To balance the dosage of genes carried by the X chromosome between males and females, one of the two X chromosomes is randomly inactivated in female embryos, and DNA methylation is one of the factors contributing to gene silencing on the inactivated X chromosome [49].

Due to the randomness of this inactivation, some cells will have an active X chromosome of maternal origin and others a paternal chromosome [50].

However, about 15% of X-linked genes escape X-inactivation in women [49]. TLR7, encoded on the X chromosome, is one of the molecules able to escape the inactivation process, and this allows females to carry higher amounts of this receptor [51].

Consequently, its level of activity in pDCs results in higher IFNα production in females than in males after stimulation [33].

Such an observation is particularly attractive when one considers that coronavirus (SARS-CoV-1) is a weak IFN inducer due to its ability to inhibit TLR7-mediated signals. This would suggest that inhibition of antiviral responses in females is reduced [52].

In addition, early activation of IFN release may improve the protection of the host against the cytokine storm that in males is associated with later secretion of these mediators [43].

As a link between innate and adaptive immunity, it is interesting to highlight that IFNα release results in up-regulation of TLR7 receptors onendosomal compartmentsof naïve B lymphocytes. This up-regulation allows immediate expansion and differentiation of B cells, with the production of IgM and inflammatory cytokines. Therefore, in females, which produce more TLR7, antibody production will be more pronounced [33].

On the male side, androgens are reported to inhibit B-cell lymphopoiesis; indeed, gonadectomy in male mice activates B-cell lymphopoiesis in the bone marrow, an effect that can be reversed by the administration of testosterone [53]. This effect would be achieved both directly, through androgen receptors, and indirectly, through the upregulation of TGFβ production by marrow stromal cells, which suppresses B-lymphopoietic activity [54].

A recent study reported the presence of neutralizing autoantibodies (immunoglobulin G) against at least one type I IFN in patients with life-threatening COVID-19 (101/987, 10.2%): against IFN-α (36 patients), against interferon-ω (13 patients), or against both (52 patients). Instead, neutralizing autoantibodies were absent in asymptomatic individuals and in patients with mild SARS-CoV-2 infection [55]. Among patients with severe SARS-CoV-2 related pneumonia and anti-IFNs antibodies, males were highly predominant (95/101, 94%).

Additionallysignificant is the observation that the prevalence of these Abs tends to increase with age, although they were detected from 25 to 87 years old [55].This may account for the increased vulnerability to infection described in the elderly, regardless of comorbidities.

Post-Transcriptional Gene Regulation

In post-transcriptional gene regulation, a pivotal position is currently assigned to small non-coding RNA molecules of about 22 nucleotides in length, called microRNAs (miRNAs, miRs) [56].

It is estimated that up to 4% of the entire genome encodes about 400 miRs, which in turn are involved in the regulation of about 1/3 of the whole genome [57].This regulation is

achieved by binding to complementary sequences within the 3′untranslated region (UTR) of the target mRNA, with a blockade of translation or rapid mRNA degradation [58].

These small molecules are involved in a number of biological processes, from apoptosis to tumorigenesis and, as reported, in the regulation of immune responses [59].

One of the first studies to highlight this relationship showed that miR-146 is a negative regulator of signals mediated by Toll-like Receptors [60]—signals that are known to be activated by the recognition of specific molecular patterns, associated with pathogenic microorganisms (PAMPs: pathogen-associated molecular patterns), or released from damaged tissues (DAMPs: damage-associated molecular patterns) [61].

It was subsequently established that IFNβ inhibits replication of the hepatitis C virus in the human hepatoma cell line Huh7 by inducing miRNAs that target the viral genome [62].

Since about a hundred miRs are encoded by the X chromosome but only four are encoded by the Y chromosome [63], it is easily predictable that these molecules are differentially expressed in both sexes, promoting different susceptibilities to infectious and autoimmune diseases.

This difference in expression could be further enhanced by estrogen receptors as transcription factors that regulate the genesis of miRs [64].

3. Conclusions

The availability of sex-disaggregated data during the current pandemic has opened a wide window on the existing gaps between males and females in both incidence and fatality rates. These differences can be ascribed to several factors.

- First, it is well-documented that there are differences in lifestyle between sexes, with lower alcohol and tobacco consumption in women. Moreover, significant differences have been also reported in response to the stress imposed by the pandemic and lockdown. Females demonstrated greater adherence to non-pharmacological prevention measures (interpersonal distance, hand washing, correct use of personal protective equipment) than males but they also showed greater resilience, lower levels of anxiety, depression and insomnia triggered by lockdown.
- Second, differences have been observed in terms of immunological reactivity. The latter could be influenced by the patient's hormonal profile, which favors – in the male sex – an increased expression of ACE2 on the surface of the alveolar cells. This molecule, acting as receptor for the viral spike-protein, is internalized following interaction with its ligand. Internalization would lead to an imbalance in ACE-controlled activities, i.e., increased Ang II production with overstimulation of AT1R. This results in an increased vascular permeability and overflow of inflammatory cells.
- Finally, in addition to the above-mentioned differences, specific genetic interferences have a significant modulating role. Due to the different gene load carried by the X and Y chromosomes, in order to ensure balancing, one of the two X chromosomes is randomly inactivated in female embryos. However, about 15% of X-linked genes escape this random inactivation process (e.g., the gene encoding for TLR7). Therefore, in females there is a greater production of INFs with positive effects both on the production of inflammatory cytokines and on B-cells expansion. It has been recently reported that patients with life-threatening COVID-19 have neutralized antibodies against at least one type I IFN; among patients with IFNs antibodies, males are largely predominant. Genetic interference may be further accentuated by the post-transcriptional control exerted by the so-called miRNAs, which are encoded in large numbers by the X chromosome but in very low amounts by the Y chromosome.

Adequate knowledge of these multiple differences may allow a more comprehensive investigation of their origins, identifying possible therapeutic targets and selecting the most effective preventive strategies.

Funding: This research received no external funding.

Acknowledgments: Many thanks to Ciro Rosario Ilardi for helpful suggestions.

Conflicts of Interest: The author declare no conflict of interest.

References

1. Ya'Qoub, L.; Elgendy, I.Y.; Pepine, C.J. Sex and Gender Differences in COVID-19: More to be learned! *Am. Heart J. Plus Cardiol. Res. Pract.* **2021**, *3*, 100011. [CrossRef]
2. Aiello, A.; Farzaneh, F.; Candore, G.; Caruso, C.; Davinelli, S.; Gambino, C.M.; Ligotti, M.E.; Zareian, N.; Accardi, G. Immunosenescence and Its Hallmarks: How to Oppose Aging Strategically? A Review of Potential Options for Therapeutic Intervention. *Front. Immunol.* **2019**, *10*, 2247. [CrossRef]
3. Farber, D.; Yudanin, N.; Restifo, N. Human memory T cells: Generation, compartmentalization and homeostasis. *Nat. Rev. Immunol.* **2014**, *14*, 24–35. [CrossRef]
4. Nikolich-Zugich, J.; Rudd, B.D. Immune memory and aging: An infinite or finite resource? *Curr. Opin. Immunol.* **2010**, *22*, 535–540. [CrossRef]
5. Sharma, G.; Goodwin, J. Effect of aging on respiratory system physiology and immunology. *Clin. Interv. Aging* **2006**, *1*, 253–260. [CrossRef]
6. Grasselli, G.; Zangrillo, A.; Zanella, A. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *JAMA* **2020**, *323*, 1574–1581. [CrossRef]
7. Guan, W.J.; Ni, Z.Y.; Hu, Y.; Liang, W.H.; Qu, C.Q.; He, J.X.; Liu, L.; Shan, H.; Lei, C.L.; Hui, D.S.C.; et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N. Engl. J. Med.* **2020**, *382*, 1708–1720. [CrossRef]
8. Onder, G.; Rezza, G.; Brusaferro, S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* **2020**, *323*, 1775–1776. [CrossRef]
9. Wang, D.; Hu, B.; Hu, C.; Zhu, F.; Liu, X.; Zhang, J.; Wang, B.; Xiang, H.; Cheng, Z.; Xiong, Y.; et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* **2020**, *323*, 1061–1069. [CrossRef]
10. Ramirez, L.A.; Sullivan, J.C. Sex Differences in Hypertension: Where We Have Been and Where We Are Going. *Am. J. Hypertens.* **2018**, *31*, 1247–1254. [CrossRef]
11. Muhamad, S.-A.; Ugusman, A.; Kumar, J.; Skiba, D.; Hamid, A.A.; Aminuddin, A. COVID-19 and Hypertension: The What, the Why, and the How. *Front. Physiol.* **2021**, *12*, 665064. [CrossRef]
12. Alkhouli, M.; Nanjundappa, A.; Annie, F.; Bates, M.C.; Bhatt, D.L. Sex differences in case fatality rate of COVID-19: Insights from a multinational registry. *Mayo Clin. Proc.* **2020**, *95*, 1613–1620. [CrossRef]
13. Iaccarino, G.; Grassi, G.; Borghi, C.; Carugo, S.; Fallo, F.; Ferri, C.; Giannattasio, C.; Grassi, D.; Letizia, C.; Mancusi, C.; et al. Gender differences in predictors of intensive care units admission among COVID-19 patients: The results of the SARS-RAS study of the Italian Society of Hypertension. *PLoS ONE* **2020**, *15*, e0237297. [CrossRef]
14. Su, W.; Qiu, Z.; Zhou, L.; Hou, J.; Wang, Y.; Huang, F.; Zhang, Y.; Jia, Y.; Zhou, J.; Liu, D.; et al. Sex differences in clinical characteristics and risk factors for mortality among severe patients with COVID-19: A retrospective study. *Aging* **2020**, *12*, 18833–18843. [CrossRef]
15. Peckham, H.; de Gruijter, N.M.; Raine, C.; Radziszewska, A.; Ciurtin, C.; Wedderburn, L.R.; Rosser, E.C.; Webb, K.; Deakin, C.T. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat. Commun.* **2020**, *11*, 6317. [CrossRef]
16. Scientific Advisory Group for Emergencies and Department of Health and Social Care. Direct and Indirect Health Impacts of COVID-19 in England. 2021; Published 17 September 2021. Available online: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1018698/S1373_Direct_and_Indirect_Health_Impacts_of_C19_Detailed_Paper_.pdf. (accessed on 25 January 2022).
17. CovidStat INFN—Datidell'ISS. Available online: https://covid19.infn.it/iss/ (accessed on 25 January 2022).
18. Bwire, G.M. Coronavirus: Why Men are More Vulnerable to COVID-19 Than Women? *SNCompr. Clin. Med.* **2020**, *2*, 874–876. [CrossRef]
19. Ng, M.; Freeman, M.K.; Fleming, T.D.; Robinson, M.; Dwyer-Lindgren, L.; Thomson, B.; Wollum, A.; Sanman, E.; Wulf, S.; Lopez, A.D.; et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. *JAMA* **2014**, *311*, 183–192. [CrossRef]
20. Allen, A.M.; Scheuermann, T.S.; Nollen, N.; Hatsukami, D.; Ahluwalia, J.S. Gender Differences in Smoking Behavior and Dependence Motives Among Daily and Nondaily Smokers. *Nicotine Tob. Res.* **2016**, *18*, 1408–1413.
21. Galasso, V.; Pons, V.; Profeta, P.; Becher, M.; Brouard, S.; Foucault, M. Gender differences in COVID-19 attitudes and behavior: Panel evidence from eight countries. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 27285–27291. [CrossRef]
22. Salfi, F.; Lauriola, M.; Amicucci, G.; Corigliano, D.; Viselli, L.; Tempesta, D.; Ferrara, M. Gender-related time course of sleep disturbances and psychological symptoms during the COVID-19 lockdown: A longitudinal study on the Italian population. *Neurobiol. Stress* **2020**, *13*, 100259.
23. Taylor, S.E.; Klein, L.C.; Lewis, B.P.; Gruenewald, T.L.; Gurung, R.A.; Updegraff, J.A. Biobehavioral responses to stress in females: Tend-and-befriend, not fight-or-flight. *Psychol. Rev.* **2000**, *107*, 411. [CrossRef] [PubMed]

24. Dhabhar, F.S. Effects of stress on immune function: The good, the bad, and the beautiful. *Immunol. Res.* **2014**, *58*, 193–210. [CrossRef] [PubMed]
25. Monto, A.S. Epidemiology of viral respiratory infections. *Am. J. Med.* **2002**, *112*, 4S–12S. [CrossRef]
26. Menzies, D.; Joshi, R.; Pai, M. Risk of tuberculosis infection and disease associated with work in health care settings. *Int. J. Tuberc. Lung Dis.* **2007**, *11*, 593–605.
27. Shannon, G.; Minckas, N.; Tan, D.; Haghparast-Bidgoli, H.; Batura, N.; Mannell, J. Feminisation of the health workforce and wage conditions of health professions: An exploratory analysis. *Hum. Resour. Health* **2019**, *17*, 72. [CrossRef]
28. Ilardi, A.; Politi, C.; Ciarambino, T. COVID-19: Could sex and age be a risk factor? *Minerva Med.* **2020**. [CrossRef]
29. Klein, S.; Flanagan, K. Sex differences in immune responses. *Nat. Rev. Immunol.* **2016**, *16*, 626–638. [CrossRef]
30. Zhang, H.; Penninger, J.M.; Li, Y.; Zhong, N.; Slutsky, A.S. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Med.* **2020**, *46*, 586–590. [CrossRef]
31. Mercurio, I.; Tragni, V.; Busto, F.; De Grassi, A.; Pierri, C.L. Protein structure analysis of the interactions between SARS-CoV-2 spike protein and the human ACE2 receptor: From conformational changes to novel neutralizing antibodies. *Cell. Mol. Life Sci.* **2021**, *78*, 1501–1522. [CrossRef]
32. Hamming, I.; Timens, W.; Bulthuis, M.L.C.; Lely, A.T.; Navis, G.J.; van Goor, H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J. Pathol.* **2004**, *203*, 631–637. [CrossRef]
33. Gadi, N.; Wu, S.C.; Spihlman, A.P.; Moulton, V.R. What's Sex Got to Do With COVID-19? Gender-Based Differences in the Host Immune Response to Coronaviruses. *Front. Immunol.* **2020**, *11*, 2147. [CrossRef] [PubMed]
34. Turner, A.J.; Julian, A.; Hiscox, J.A.; Hooper, N.M. ACE2: From vasopeptidase to SARS virus receptor. *Trends Pharmacol. Sci.* **2004**, *25*, 291–294. [CrossRef] [PubMed]
35. Lambert, D.W.; Yarski, M.; Warner, F.J.; Thornhill, P.; Parkin, E.T.; Smith, A.I.; Hooper, N.M.; Turner, A.J. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). *J. Biol. Chem.* **2005**, *280*, 30113–30119. [CrossRef]
36. Pinna, G. Sex and COVID-19: A Protective Role for Reproductive Steroids. *Trends Endocrinol. Metab.* **2021**, *32*, 3–6. [CrossRef]
37. Baristaite, G.; Gurwitz, D. Estradiol reduces ACE2 and TMPRSS2 mRNA levels in A549 human lung epithelial cells. *Drug Dev. Res.* **2022**, 1–6. [CrossRef]
38. McGuire, B.B.; Watson, R.W.G.; Pérez-Barriocanal, F.; Fitzpatrick, J.M.; Docherty, N. Gender differences in the renin-angiotensin and nitric oxide systems: Relevance in the normal and diseased kidney. *Kidney Blood Press. Res.* **2007**, *30*, 67–80. [CrossRef]
39. Swärd, P.; Edsfeldt, A.; Reepalu, A.; Jehpsson, L.; Rosengren, B.E.; Karlsson, M.K. Age and sex differences in soluble ACE2 may give insights for COVID-19. *Crit. Care* **2020**, *24*, 221. [CrossRef]
40. Larouche-Lebel, É.; Loughran, K.A.; Oyama, M.A.; Solter, P.F.; Laughlin, D.S.; Sánchez, M.D.; Assenmacher, C.A.; Fox, P.R.; Fries, R.C. Plasma and tissue angiotensin converting enzyme 2 activity and plasma equilibrium concentrations of angiotensin peptides in dogs with heart disease. *J. Vet. Intern. Med.* **2019**, *33*, 1571–1584. [CrossRef]
41. Yang, P.; Gu, H.; Zhao, Z.; Wang, W.; Cao, B.; Lai, C.; Yang, X.; Zhang, L.; Duan, Y.; Zhang, S.; et al. Angiotensin-converting enzyme 2 (ACE2) mediates influenza H7N9 virus-induced acute lung injury. *Sci. Rep.* **2014**, *4*, 7027. [CrossRef]
42. Medina-Enríquez, M.M.; Lopez-León, S.; Carlos-Escalante, J.A.; Aponte-Torres, Z.; Cuapio, A.; Wegman-Ostrosky, T. ACE2: The molecular doorway to SARS-CoV-2. *Cell Biosci.* **2020**, *10*, 148. [CrossRef]
43. Channappanavar, R.; Fett, C.; Mack, M.; Ten Eyck, P.P.; Meyerholz, D.K.; Perlman, S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *J. Immunol.* **2017**, *198*, 4046–4053. [CrossRef]
44. Heldring, N.; Pike, A.; Andersson, S.; Matthews, J.; Cheng, G.; Hartman, J.; Tujague, M.; Strom, A.; Treuter, E.; Warner, M.; et al. Estrogen receptors: How do they signal and what are their targets. *Physiol. Rev.* **2007**, *87*, 905–931. [CrossRef] [PubMed]
45. Satpathy, A.; Wu, X.; Albring, J.; Murphy, K.M. Re(de)fining the dendritic cell lineage. *Nat. Immunol.* **2012**, *13*, 1145–1154. [CrossRef] [PubMed]
46. Gilliet, M.; Cao, W.; Liu, Y.J. Plasmacytoid dendritic cells: Sensing nucleic acids in viral infection and autoimmune diseases. *Nat. Rev. Immunol.* **2008**, *8*, 594–606. [CrossRef]
47. Kamphuis, E. Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. *Blood* **2006**, *108*, 3253–3261. [CrossRef]
48. Laffont, S.; Guéry, J.C. Deconstructing the sex bias in allergy and autoimmunity: From sex hormones and beyond. *Adv. Immunol.* **2019**, *142*, 35–64.
49. Hewagama, A. Role of X-Chromosome encoded miRNAs in Autoimmunity: Suppressing the suppressor and female predisposition. *Rheumatol. Curr. Res.* **2013**, *3*, 118. [CrossRef]
50. Fang, H.; Disteche, C.M.; Berletch, J.B. X Inactivation and Escape: Epigenetic and Structural Features. *Front. Cell Dev. Biol.* **2019**, *7*, 219. [CrossRef]
51. Souyris, M.; Mejía, J.E.; Chaumeil, J.; Guéry, J.-C. Female predisposition to TLR7-driven autoimmunity: Gene dosage and the escape from X chromosome inactivation. *Semin. Immunopathol.* **2019**, *41*, 153–164. [CrossRef]
52. Li, S.-W.; Wang, C.-Y.; Jou, Y.-J.; Huang, S.-H.; Hsiao, L.-H.; Wan, L.; Lin, Y.-J.; Kung, S.-H.; Lin, C.-W. SARS Coronavirus papain-like protease Inhibits the TLR7 signaling pathway through removing Lys63-linked polyubiquitination of TRAF3 and TRAF6. *Int. J. Mol. Sci.* **2016**, *17*, 678. [CrossRef]
53. GubbelsBupp, M.R.; Jorgensen, T.N. Androgen-Induced Immunosuppression. *Front. Immunol.* **2018**, *9*, 794. [CrossRef] [PubMed]

54. Olsen, N.J.; Gu, X.; Kovacs, W.J. Bone marrow stromal cells mediate androgenic suppression of B lymphocyte development. *J. Clin. Investig.* **2001**, *108*, 1697–1704. [CrossRef] [PubMed]
55. Bastard, P.; Rosen, L.B.; Zhang, Q.; Michailidis, E.; Hoffmann, H.H.; Zhang, Y.; Dorgham, K.; Philippot, Q.; Rosain, J.; Béziat, V.; et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **2020**, *370*, eabd4585. [CrossRef] [PubMed]
56. Lewis, B.P.; Burge, C.B.; Bartel, D.P. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* **2005**, *120*, 15–20. [CrossRef]
57. Gu, S.; Jin, L.; Zhang, F.; Sarnow, P.; Kay, M.A. Biological basis for restriction of microRNA targets to the 3′ untranslated region in mammalian mRNAs. *Nat. Struct. Mol. Biol.* **2009**, *16*, 144–150. [CrossRef]
58. Moulton, V.R. Sex Hormones in Acquired Immunity and Autoimmune Disease. *Front. Immunol.* **2018**, *9*, 2279. [CrossRef]
59. Dai, R.; Phillips, R.A.; Zhang, Y.; Khan, D.; Crasta, O.; Ahmed, S.A. Suppression of LPS-induced Interferon-γ and nitric oxide in splenic lymphocytes by select estrogen-regulated microRNAs: A novel mechanism of immune modulation. *Blood* **2008**, *112*, 4591–4597. [CrossRef]
60. Taganov, K.D.; Boldin, M.P.; Chang, K.-J.; Baltimore, D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 12481–12486. [CrossRef]
61. Chen, G.Y.; Nuñez, G. Sterile inflammation: Sensing and reacting to damage. *Nat. Rev. Immunol.* **2010**, *10*, 826–837. [CrossRef]
62. Pedersen, I.M.; Cheng, G.; Wieland, S.; Volinia, S.; Croce, C.M.; Chisari, F.V.; David, M. Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature* **2007**, *449*, 919–922. [CrossRef]
63. Pérez-Cremades, D.; Mompeón, A.; Vidal-Gómez, X.; Hermenegildo, C.; Novella, S. Role of miRNA in the Regulatory Mechanisms of Estrogens in Cardiovascular Ageing. *Oxid. Med. Cell. Longev.* **2018**, *2018*. [CrossRef] [PubMed]
64. Castellano, L.; Giamas, G.; Jacob, J.; Coombes, R.C.; Lucchesi, W.; Thiruchelvam, P.; Barton, G.; Jiao, L.R.; Wait, R.; Waxman, J.; et al. The estrogen receptor-alpha-induced microRNA signature regulates itself and its transcriptional response. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 15732–15737. [CrossRef] [PubMed]