



## 1 **Abstract**

2 **Background:** Emerging evidence from China suggests that coronavirus disease  
3 2019 (COVID-19) is deadlier for infected men than women with a 2.8 percent fatality  
4 rate being reported in Chinese men versus 1.7 percent in women. Further, sex-  
5 disaggregated data for COVID-19 in several European countries show a similar  
6 number of cases between the sexes, but more severe outcomes in aged men. Case  
7 fatality is highest in men with pre-existing cardiovascular conditions. The  
8 mechanisms accounting for the reduced case fatality rate in women are currently  
9 unclear but may offer potential to develop novel risk stratification tools and  
10 therapeutic options for women and men.

11 **Content:** The present review summarizes latest clinical and epidemiological  
12 evidence for gender and sex differences in COVID-19 from Europe and China. We  
13 discuss potential sex-specific mechanisms modulating the course of disease, such  
14 as hormone-regulated expression of genes encoding for the severe acute respiratory  
15 syndrome coronavirus 2 (SARS-CoV2) entry receptors angiotensin converting  
16 enzyme (ACE)-2 receptor and TMPRSS2 as well as sex hormone-driven innate and  
17 adaptive immune responses and immunoaging. Finally, we elucidate the impact of  
18 gender-specific lifestyle, health behaviour, psychological stress, and socioeconomic  
19 conditions on COVID-19 and discuss sex specific aspects of antiviral therapies.

20 **Conclusion:** The sex and gender disparities observed in COVID-19 vulnerability  
21 emphasize the need to better understand the impact of sex and gender on incidence  
22 and case fatality of the disease and to tailor treatment according to sex and gender.  
23 The ongoing and planned prophylactic and therapeutic treatment studies must  
24 include prospective sex- and gender sensitive analyses.

1 **Keywords:** Gender; Sex; COVID-19; Renin angiotensin aldosterone system;  
2 Immune system

3 **List of abbreviations**

- 4 Androgen receptors (ARs)
- 5 Acute respiratory distress syndrome (ARDS)
- 6 Angiotensin converting enzyme (ACE) 2
- 7 Angiotensin receptor blockers (ARBs)
- 8 Angiotensin II receptor (AT2R)
- 9 Chronic low-grade inflammatory phenotype (CLIP)
- 10 Coronavirus disease 2019 (COVID-19),
- 11 Dendritic cells (DCs)
- 12 Highly active antiretroviral therapy (HAART)
- 13 Heart failure with preserved ejection fraction (HFpEF)
- 14 Heart rate-corrected QT (QTc) interval
- 15 Heat shock proteins (HSPs)
- 16 Helper T cell type 1 (Th1)
- 17 Hepatitis B virus (HBV)
- 18 Hepatitis C virus (HCV)
- 19 Herpes simplex virus (HSV)
- 20 High density lipoprotein (HDL)
- 21 Human immunodeficiency virus (HIV)
- 22 Intensive care unit (ICU)
- 23 Neutral endopeptidase (NEP)
- 24 Postmenopausal hormone replacement therapy [HRT
- 25 Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)
- 26 Trivalent inactivated influenza virus (TIV)
- 27 Toll-like receptor (TLR)
- 28 Renin angiotensin aldosterone system (RAAS)
- 29 World Health Organization (WHO)

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## 1 Introduction

2 In December 2019, a novel  $\beta$ -coronavirus, now designated SARS-CoV2 (severe  
3 acute respiratory syndrome coronavirus 2), was identified as the cause of an  
4 outbreak of acute respiratory illness in Wuhan City, China (1). SARS-CoV2 causes  
5 severe respiratory disease, termed coronavirus disease 2019 (COVID-19), which  
6 represents its most frequent lethal complication. Since its outbreak, SARS-CoV2 has  
7 spread to 196 countries and has been declared a pandemic by the World Health  
8 Organization (WHO) on March 11<sup>th</sup> 2020 (2, 3). It has caused over 2 million  
9 confirmed infections with over 130'000 deaths worldwide (as of April 15<sup>th</sup>, 2020), of  
10 which two thirds have occurred in Europe (4). To date, no specific antiviral treatment  
11 for SARS-CoV2 exists, but a number of investigational agents are currently being  
12 explored including Remdesivir, Lopinavir-ritonavir, a combined protease inhibitor,  
13 chloroquine/hydroxychloroquine, colchicine, and Tocilizumab, an IL-6 inhibitor (5).  
14 The worldwide case fatality rate of 3.4% of COVID-19 now exceeds that from  
15 seasonal influenza (2). Death results from acute respiratory distress syndrome  
16 (ARDS), acute respiratory failure, coagulopathy, septic shock, and metabolic  
17 acidosis (6). Cardiovascular complications of COVID-19 comprise arrhythmias, acute  
18 cardiac injury, and shock, and have been reported in 7-17% of hospitalized patients  
19 (7). In Italy, the estimated case fatality rate was 7.2% (8), while it was 0.9% in South  
20 Korea (3) and 2.3% in China (6). Case fatality is highest in those aged >80 years  
21 (14.8% in China, 20.2% in Italy) and in patients with pre-existing conditions including  
22 cardiovascular disease, diabetes mellitus, chronic respiratory disease, hypertension,  
23 and cancer (6, 9). Among all comorbidities, cardiovascular disease in the elderly was  
24 most consistently associated with adverse outcomes, as a case fatality rate of 10.5%  
25 has been reported in this high risk population (6).

## 1 **Sex Differences in COVID-19 Epidemiology and Case Fatality**

2 First reports from China have pointed to a sex imbalance with regard to  
3 detected cases and case fatality rate of COVID-19 (1, 10, 11). However, to date only  
4 few reports have addressed the sex disproportion in COVID-19 incidence and  
5 disease course and a thorough analysis of underlying causes is currently lacking  
6 (12-15). As the disease has spread across multiple continents, the *Global Health*  
7 *50/50 research initiative* presented an impressive overview of sex-disaggregated  
8 data from countries worldwide clearly demonstrating similar numbers of cases in  
9 women and men, but an increased case fatality in men (16) **(Figure 1)**.  
10 Nevertheless, sex-disaggregated data are still not provided by all countries, the  
11 interaction of sex and age is usually not visible in the public databases, and number  
12 of cases and case fatality vary significantly by region. To obtain a detailed European  
13 view and to cover these aspects, we collected latest epidemiological data (as of April  
14 1<sup>st</sup>) on confirmed COVID-19 cases in Italy, China, Spain, France, Germany and  
15 Switzerland (17-22) across multiple disease metrics including recently published  
16 hospitalisation and intensive care (ICU) admission data. Similar to global statistics,  
17 these reports show no major sex differences in the absolute number of confirmed  
18 COVID-19 cases in those countries where sex-disaggregated data were available  
19 **(Figure 2)**. However, equal absolute numbers of cases in women and men may  
20 point towards a higher incidence in men in the older age groups (i.e. *proportions* of  
21 COVID-19 diagnosed older men among men in that age group) since older men are  
22 fewer in absolute numbers than older women due to their lower life expectancy. In  
23 fact, reports from Switzerland and Germany have recently reported incidence rates  
24 (cases per 100,000 inhabitants by age and sex), which confirm an increased disease  
25 incidence in men >60 years, (21, 22). In detail, the disease incidence in men per

1 100,000 Swiss inhabitants in the age groups of 60-69 years, 70-79 years and 80+  
2 years was 267, 281 and 477, respectively, as of March 30<sup>th</sup>. The numbers reported  
3 in men exceeded the ones reported in women by 74, 87 and 108 per 100,000 Swiss  
4 inhabitants, respectively. In Germany, relative differences between men and women  
5 were similar to Switzerland, but at a lower level, with the incidence in Germany being  
6 one third of that in Switzerland. It is notable, however, that the number of confirmed  
7 cases and therefore also the incidence depends largely on testing strategy in  
8 countries and regions.

9 Novel data on disease course and severity show 50% more hospitalized men than  
10 women (**Figure 2**). Notably, although the overall number of confirmed COVID-19  
11 cases across all age groups is currently sex balanced in Switzerland, the  
12 hospitalizations in men exceeds the one observed in women by 1.5-fold. A similar  
13 gender distribution in hospitalisation rates is observed in France. This imbalance  
14 supports a higher susceptibility of men to develop severe respiratory disease  
15 following SARS-CoV2 infection, leading to more hospital admissions. While the  
16 number of ICU admissions of men and women are currently unknown in Switzerland,  
17 in France and in the Lombardy region (Italy) the number of men receiving ICU care is  
18 3-fold and 4-fold higher than the number of women (23). The latter might be  
19 indicative of gender differences in COVID-19 disease severity, however, gender  
20 inequity in ICU admission policies may also play a role.

21 Significant differences in the male to female COVID-19 case fatality ratio can  
22 be observed between European countries. The latter may also reflect the age-sex  
23 mix of cases by country as well as national testing strategies, besides case fatality.  
24 Nevertheless, case fatality rates reported in China, Italy, Spain, France, Germany  
25 and Switzerland are relatively homogenous and range between 1.7-1.8. This

1 supports the view that a consistent biological phenomenon is operating, accounting  
2 for the higher case fatality in men, independent of country-specific demographics  
3 and testing strategies (**Figure 2**) (17-19, 21, 22). In addition, pooled data comprising  
4 227,219 confirmed cases and 14,364 deaths suggest that the male to female case  
5 fatality ratio is consistently elevated through all age groups and may even be most  
6 pronounced at middle age (**Figure 3**). The latter is a novel observation which further  
7 supports the notion that age as well as gender-specific behaviour and/or biological  
8 variables interact in COVID-19 disease vulnerability. However, more data are  
9 needed to confirm an interaction between age and sex in COVID-19 case fatality.

10

### 11 **Sex Differences in ACE2 and TMPRSS2 Regulation**

12 To enter cells, SARS-Cov-2 binds to the angiotensin converting enzyme  
13 (ACE) 2 receptor and the cellular serine protease TMPRSS2 for priming (24). ACE2  
14 is a membrane-bound protein and is expressed in multiple tissues including the  
15 cardiovascular system, adipose tissue, gut and kidneys, the central nervous system,  
16 and in the lungs (25). The cell-associated form of ACE2 is required for SARS-CoV  
17 virus entry into target cells (26). ACE2 is cleared from the cells by the  
18 metalloproteases ADAM10 and ADAM17 (26, 27). Some reports indicate that  
19 circulating levels of ACE2 are higher in healthy and diabetic men as well as in men  
20 with renal disease as compared to women (43). Others found no sex difference but  
21 reported higher ACE2 serum activity in older compared to younger women (28). In  
22 patients with type 1 diabetes, circulating ACE2 activity increases with increasing  
23 vascular tone and in the presence of microvascular or macrovascular atherosclerotic  
24 disease (29). Soluble ACE2 is enzymatically active and has modest inhibitory effects

1 on viral infection efficiency (30). However, these data are not yet coherent and the  
2 link between circulating ACE2 and COVID-19 is not clear.

3 ACE2 plays a crucial role in the renin angiotensin aldosterone system (RAAS)  
4 as it opposes the vasoconstrictor actions of angiotensin II by converting angiotensin  
5 II to vasodilatory Angiotensin 1-7 in different organs. ACE2 regulates the cellular  
6 biology of cardiomyocytes, cardiac fibroblasts, and coronary endothelial cells in both  
7 heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved  
8 ejection fraction (HFpEF) models and after experimental myocardial infarction (31,  
9 32). Therefore, increasing ACE2 activity was considered a potential therapeutic  
10 option for COVID-19 (33). However, a previous report suggests that high protein  
11 expression of ACE2 receptor in specific organs was associated with organ failure in  
12 patients infected by SARS in 2002/2003 (34), while 35% of myocardial tissue  
13 samples of patients who died from SARS showed a reduced myocardial ACE2  
14 protein expression along with viral RNA (35). A loss of ACE2 function through  
15 endocytosis and activation of proteolytic cleavage following SARS-CoV-2 binding  
16 has recently been described and could reconcile these apparently contradictory  
17 findings (25).

18 In the lung, ACE2 is primarily expressed in bronchial transient secretory cells  
19 or type II alveolar cells (36). Experimental evidence derived from murine and rat  
20 models suggests a protective role of ACE2 activators in vascular remodeling during  
21 pulmonary hypertension, in allergic airway inflammation associated with asthma, and  
22 in the reduction of pulmonary fibrosis (37, 38). Further, ACE2 activation improved  
23 pulmonary endothelial function in a rat model of pulmonary hypertension via the  
24 endothelial nitric oxide synthase (eNOS) pathway and seems to play an important  
25 role in smoking-induced lung injury (39). Indeed, the latter was associated with a



1 significant reduction of ACE2 expression in lung tissue which was reversed by  
2 Losartan treatment (40). These preclinical studies suggest a protective role and a  
3 potential therapeutic use of ACE2 in a variety of pulmonary diseases. It is however  
4 currently unclear whether the role of ACE2 in pulmonary pathologies differs by sex.  
5 In addition to the above mentioned studies, ACE inhibitors and angiotensin receptor  
6 blockers (ARBs) have been reported to upregulate ACE2 expression in different  
7 organs in humans (41-43) and experimental animals (44), whereas no effect of ACE  
8 inhibitors or ARBs on ACE2 activity was found in other reports (32). The interaction  
9 between COVID-19 and ACE inhibitors or ARBs in patients with heart disease was  
10 recently reviewed (45). This topic is out of the scope of the present review which  
11 focuses on sex differences.

12       There is increasing evidence that sex and sex hormones affect many  
13 components of the circulating as well as tissue-based RAAS including ACE2 (46-48),  
14 (49, 50) (Figure 4). Down regulation of angiotensin II receptor type 1 (AT1R) by  
15 estrogens, and regulation of renin activity by estrogens have been described and  
16 reviewed elsewhere (51, 52). More recently, it was shown that estrogen modulates the  
17 local RAAS in human atrial myocardium via downregulation of ACE and  
18 simultaneous upregulation of ACE2, AT2R and MAS expression levels (53). The  
19 ACE2/Ang1-7/Mas receptor axis appears to be of greater relevance in women than  
20 in men (47). Indeed, genes coding for ACE2 and angiotensin II receptor 2 (AT2R)  
21 are located on the X-chromosome suggesting a potential for higher expression in  
22 women (54). Nevertheless, reports from a number of preclinical studies agree that  
23 ACE2 is frequently higher expressed in males than in females, mainly under  
24 pathological conditions (47, 50, 55).

1           In addition to sex chromosome complement, sex hormones promote opposite  
2 effects on ACE and ACE2 activity, cardiac hypertrophy and contractility in  
3 spontaneously hypertensive rats (56). Ovariectomy led to increased ACE2 activity in  
4 females, whereas in males, orchiectomy decreased ACE2 activity. In agreement with  
5 these data, ovariectomy increased ACE2 expression in the female kidney, and  
6 adipose tissue, and estradiol replacement reduced ACE2 expression (46). Thus,  
7 testosterone seems to maintain high ACE2 levels in the heart and kidney whereas  
8 estrogen reduces ACE2 expression in these organs. Based on these data, we must  
9 assume that a significant interaction between sex hormones and ACE2 expression  
10 exists.

11           In humans, several clinical trials highlight the relevance of sex differences in  
12 the RAAS. In fact, a recent prospective cohort study indicates that women require  
13 lower doses of ACE inhibitors for heart failure treatment than men (57). Also, the  
14 neprilysin (NEP) inhibitor sacubitril, which degrades angiotensin peptides, in  
15 combination with valsartan, has recently been shown to exert beneficial effects in  
16 women with HFpEF, but less so in men (58). Unfortunately, specific mechanisms  
17 accounting for this difference have not been reported in these studies. A higher  
18 tissue expression of ACE2 has been observed in Asian men as compared to women  
19 (59, 60), while in our own unpublished investigation in tissue samples from patients  
20 with aortic valve stenosis, ACE2 was upregulated 4-5 fold in the myocardium of men  
21 as compared to their female counterparts. In contrast, no sex difference in ACE2  
22 expression was seen in control hearts (61). Whether these sex differences in ACE2  
23 regulation are of clinical relevance remains to be determined.

24           The second protein, necessary for SARS-CoV2 invasion into cells, the cell-  
25 surface serine protease TMPRSS2 is predominantly expressed in prostate

1 epithelium, in high-grade prostate cancers, and in the majority of human prostate  
2 cancer metastases (62, 63). Although TMPRSS2 is expressed several fold higher in  
3 the prostate relative to any other human tissue, the serine protease has also been  
4 detected in airway epithelia where its normal physiologic function remains unknown  
5 (64). TMPRSS2 transcription is regulated by androgenic ligands and an androgen  
6 receptor binding element in the promoter (65). Notably, recurrent gene fusions of the  
7 5' untranslated region of TMPRSS2 to the transcription factor ERG is the most  
8 frequent genomic alteration in early- and late-stage prostate cancer and results in  
9 overexpression of ERG. The latter is present in both early- and late-stage prostate  
10 cancer (65). However, it is currently unclear under which conditions the fusion  
11 protein is generated, whether TMPRSS2 is also regulated by oestrogen, and  
12 whether it plays a role in COVID-19. The involvement of TMPRSS2 in viral S protein  
13 priming might explain, at least in part, the higher case fatality seen in males affected  
14 by COVID-19. Accordingly, a TMPRSS2 inhibitor has recently been shown to block  
15 entry of the virus in vitro and might become a therapeutic strategy for antiviral  
16 intervention (24). Whether previous prostate cancer and anti-androgenic treatment  
17 might affect virus entry and the course of disease is currently unknown (65).

18

## 19 **Sex Differences in Immune Responses to Viruses**

20 Females and males differ in their susceptibility and response to viral  
21 infections, leading to sex differences in incidence and disease severity (66). For  
22 infectious diseases caused by viruses, there are numerous and diverse ways in  
23 which sex and gender can impact differential susceptibility between males and  
24 females. For example, human studies reveal that females have over 40% less  
25 human immunodeficiency virus (HIV) RNA in circulation than males. Despite having

1 less circulating HIV RNA than males, females who are matched with males on their  
2 HIV RNA loads have a 1.6-fold higher risk of developing AIDS (67). Although  
3 exposure to influenza A viruses is often higher in males, fatality following exposure to  
4 pathogenic influenza A viruses is reportedly higher in females (68). In contrast, the  
5 prevalence of serum hepatitis B virus (HBV) surface antigen, HBV DNA titers, and  
6 development of hepatocellular carcinoma is higher in males than females (69-71).

7       The innate recognition and response to viruses as well as downstream  
8 adaptive immune responses during viral infections differ between females and  
9 males. The number and activity of innate immune cells, including monocytes,  
10 macrophages, and dendritic cells (DCs) as well as inflammatory immune responses  
11 in general are higher in females than in males. (72-74). Toll-like receptor (TLR) 7 is a  
12 pattern recognition receptor in the endosomes of several immune cells, including  
13 plasmacytoid DCs and B cells, and is used to detect single stranded RNA viruses,  
14 including coronaviruses. The TLR7 gene, encoded on the X chromosome, may  
15 escape X inactivation resulting in higher expression levels of TLR7 in females when  
16 compared to males (75-77). Exposure of peripheral blood mononuclear cells  
17 (PBMCs) to TLR7 ligands in vitro causes higher production of interferon- $\alpha$  (IFN $\alpha$ ) in  
18 cells from females than from males (78); and plasmacytoid DCs (pDCs) from  
19 females and female mice have higher basal levels of IFN regulatory factor 5 (IRF5)  
20 and IFN $\alpha$  production following TLR7 ligand stimulation (79). Immune responses to  
21 viruses can vary with changes in sex hormone concentrations naturally observed  
22 over the menstrual cycle, following contraception, after menopause and during  
23 hormone replacement therapy (HRT) as well as during pregnancy (80).

24       With regard to adaptive immune responses, females generally exhibit greater  
25 humoral and cell-mediated immune responses to antigenic stimulation, vaccination,

1 and infection than do males (81). Both basal levels of immunoglobulin (82) as well as  
2 antibody responses are consistently higher in females than in males (83). In humans,  
3 global analysis of B cell gene expression signatures reveals that the majority of  
4 genes differentially expressed between the sexes are significantly upregulated in B  
5 cells from adult females compared with males (84). Clinical studies reveal that males  
6 have lower CD3+ and CD4+ cell counts, CD4+:CD8+ cell ratios, and helper T cell  
7 type 1 (Th1) responses than females (85-88). Females also exhibit higher cytotoxic T  
8 cell activity along with upregulated expression of antiviral and proinflammatory  
9 genes, many of which have estrogen response elements in their promoters (89).

10 Sex steroids, particularly testosterone (T), estradiol (E2), and progesterone  
11 (P4), influence the functioning of immune cells. Sex steroids alter the functioning of  
12 immune cells by binding to specific receptors, which are expressed in various  
13 lymphoid tissue cells as well as in circulating lymphocytes, macrophages, and  
14 dendritic cells (90). The binding of sex steroids to their respective steroid receptors  
15 directly influences cell signaling pathways, including NF- $\kappa$ B, cJun, and interferon  
16 regulatory factor (IRF) 1, resulting in differential production of cytokines and  
17 chemokines (90). Although direct effects of gonadal steroids cause many sex  
18 differences in immune function, some sex differences might be caused by the  
19 inherent imbalance in the expression of genes encoded on the X and Y  
20 chromosomes (91). Polymorphisms or variability in sex chromosomal genes as well  
21 as in autosomal genes that encode for immunological proteins can also contribute to  
22 sex differences in immune responses (92).

23 Sex differences in immune response in cardiac tissues also depend on age.  
24 We have recently shown that females develop stronger chronic immune reactions in  
25 the myocardium with old age (93). Aging is associated with the development of a

1 chronic low-grade inflammatory phenotype (CLIP) (94). Such CLIP may be induced  
2 by chronic viral infections, among others. Cellular senescence may also contribute to  
3 CLIP as senescent cells circulate in the tissues through the body. They secrete a  
4 variety of pro-inflammatory mediators, stimulating CLIP. Furthermore, factors as  
5 smoking, decreased production of sex steroids, and accumulation of adipose tissue  
6 may also contribute to CLIP.

7

## 8 **Gender-Related Risk Factors and Impact**

9 When considering differentials in incidence and case fatality between males and  
10 females we must also consider how sex intersects with gender to influence  
11 vulnerability. Gender is defined as the social and cultural norms, roles, attributes and  
12 behaviors that a society considers appropriate for men and women or boys and girls  
13 (95). Evidence suggests that the current COVID-19 pandemic has both primary and  
14 secondary effects related to sex and gender. Primary effects include differences  
15 between males/men and females/women in incidence and case fatality, while  
16 secondary effects include differences in social and economic consequences as a  
17 result of the pandemic, including risk of domestic violence (96, 97), economic and  
18 job insecurity, and increased domestic workload (15).

19 Preliminary data indicate an association between co-morbidities, such as  
20 chronic lung disease, hypertension, and cardiovascular disease, and severity of  
21 COVID-19 (16). Worldwide, these morbidities are higher among men than women  
22 (98), except for older age groups. Gender differences in risk behaviors, such as  
23 smoking and drinking, may be contributing to the gender gaps in mortality of such  
24 non-communicable diseases (13). Smoking and drinking rates are higher among  
25 men than women worldwide. Such behaviors are associated with the risk of

1 developing co-morbidities (16). These behaviors are linked to gender norms related  
2 to what is considered appropriate behaviors and activities for men and women (99).  
3 Other gendered norms and behaviors which may be contributing to a higher  
4 incidence among men include lower rates of hand washing, which is a recognized  
5 preventative measure, and delayed healthcare seeking (16). Evidence from China  
6 suggests that patients whose diagnoses were delayed were at greater risk of dying  
7 (100). In this regard, greater system delays between onset of symptoms and  
8 initiation of treatment have been described in women with cardiovascular disease  
9 (101), however, no data on prehospital delays in COVID-19 are currently available.  
10 Thus, it is currently unknown whether potential gender differences in prehospital  
11 delays imposes disadvantages on women. Other gendered differences which place  
12 women and men at differential risk of infection and/or mortality include rejection of  
13 social isolation, social obligations, psychological stress, low quality of life, and low  
14 socioeconomic status amongst COVID-19 (13). A careful analysis of a patient's  
15 history including traditional cardiovascular risk factors, socioeconomic status,  
16 menopausal status, age at menopause, number of pregnancies, pregnancy-related  
17 complications, fertility treatments, postmenopausal HRT, hormonal contraception,  
18 history of breast or prostate cancer and aromatase inhibitors/anti-androgenic  
19 treatments will be essential to discover mechanisms accounting for the gender  
20 disparities in COVID-19.

21 Women's roles as caregivers – both within the health system and at home –  
22 may place them at increased risk of infection. Approximately 70% of health and  
23 social care workforce worldwide are women (102), including frontline healthcare  
24 workers. Women are also more likely to care for children or other relatives who are ill  
25 (15). Overall, more research is needed to understand how sex and gender, and the

1 intersection of sex and gender, is causing differential outcomes and effects related to  
2 COVID-19 among and between men and women. In particular, there is a need to  
3 evaluate the influence of such gender variables on disease manifestation and  
4 outcomes.

5

## 6 **Sex Differences in COVID-19 Treatment Approaches**

7 Vaccines are the best prophylactic treatment for infectious diseases as they provide  
8 immunity and protection prior to infection. Sex and gender impact vaccine  
9 acceptance, responses, and outcomes. Females are often less likely to accept  
10 vaccines, but once vaccinated, develop higher antibody responses (i.e., primary  
11 correlate of protection) and report more adverse reactions to vaccines than males  
12 **(Table 1)** (81). For example, after vaccination against influenza, yellow fever, rubella,  
13 measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox, and dengue  
14 viruses, protective antibody responses are twice as high in adult females as  
15 compared with males (81). Data from inactivated influenza vaccines indicate that  
16 adult (18-45 years of age) females develop greater IL-6 and antibody responses than  
17 males, with diminished differences between the sexes among aged individuals (65+  
18 years of age) (103). Reduced male-female differences in immune responses to the  
19 monovalent 2009 H1N1 vaccine among aged individuals is partly due to reproductive  
20 senescence in females, in which higher circulating estradiol concentrations in  
21 females are associated with greater antibody responses to the vaccine (103).

22 For treatment of COVID-19, a number of investigational agents are currently  
23 being explored including Remdesivir, Lopinavir-ritonavir, a combined protease  
24 inhibitor, chloroquine/hydroxychloroquine, colchicine, and Tocilizumab, an IL-6  
25 inhibitor (5). Although some of these compounds have shown promise in inhibiting



1 the growth of SARS-CoV2 *in vitro* (5, 104-106) and *in vivo* (8, 107), their 'off-label'  
2 use carries the risk of adverse side-effects such as cardiac arrhythmias and sudden  
3 cardiac death (108, 109). In particular chloroquine and hydroxychloroquine, both  
4 antimalarial agents inhibiting the cell entry of SARS-CoV2 by under-glycosylation of  
5 ACE2 receptors (104, 105), are known to trigger life-threatening polymorphic  
6 ventricular tachycardia (Torsades de Pointes) by prolonging the heart rate-corrected  
7 QT (QTc) interval (109, 110). Previous reports indicate that women are more prone  
8 to develop drug-induced Torsades de Pointes than men, with 65-75% of drug-  
9 induced Torsades de Pointes occurring in women (111). Indeed, there are  
10 substantial sex differences in the electrocardiographic pattern of ventricular  
11 repolarization with a longer QTc interval at baseline being observed in women (48,  
12 111, 112). Protective effects of testosterone have been suggested to account for the  
13 shorter QTc interval and the reduced incidence of drug induced Torsades de Pointes  
14 in men. However, mechanisms underlying these differences are not fully understood.  
15 In addition, experimental and clinical studies have shown that chloroquine exerts  
16 different effects on adrenocortical function in female and male rats (113) and  
17 depresses testosterone secretion and sperm count in men (114). The latter is of  
18 particular interest in the treatment of COVID-19 as the expression of TMPRSS2, a  
19 protein that primes SARS-CoV-2 entry into cells, is upregulated by androgens (115).  
20 The latter has been suggested to account for the higher mortality seen in men  
21 affected by COVID-19. However, whether anti-androgenic treatment might affect  
22 virus entry and the course of disease is currently unknown.

23 Further, there is evidence that women encounter more often adverse drug  
24 reactions to antiviral treatment than men (**Table 1**). In addition, pharmacokinetics  
25 and treatment responses to antiretroviral therapy with Ritonavir and Lopinavir differ

1 between males and females (116). In fact, higher plasma concentrations of ritonavir  
 2 and a higher total cholesterol:high density lipoprotein (HDL) ratio have been reported  
 3 in girls (116, 117), while an atazanavir plus ritonavir regimen was associated with a  
 4 higher risk of virologic failure in women as compared to men (106).

5 The current off-label use of anti-inflammatory drugs, such as colchicine, for  
 6 the reduction of excessive inflammation caused by SARS-CoV2 is also notable. The  
 7 COLCORONA trial has just started recruiting patients with COVID-19 and will  
 8 determine whether short term treatment with colchicine reduces the rate of death  
 9 and lung complications related to COVID-19  
 10 (<https://clinicaltrials.gov/ct2/show/NCT04322682>). The drug has recently regained  
 11 popularity when it was shown that colchicine reduced the risk of ischemic  
 12 cardiovascular events in patients with a recent myocardial infarction (118). However,  
 13 while the primary efficacy composite endpoint was reduced by colchicine in the total  
 14 cohort and in men, a subgroup analysis pointed to a lower efficacy in women (118).  
 15 Also, previous experimental work in rats reports a higher acute oral toxicity of  
 16 colchicine in females as compared to males with female rats being two times more  
 17 susceptible to the lethal effects of colchicine than male rats (119). Thus, a sex-  
 18 specific analysis in the COLCORONA trial will be essential in order to take these  
 19 differences into account.

20 Taken together, these data emphasize the importance to consider the effect of  
 21 age, reproductive status, and exogenous hormonal manipulation when antiviral and  
 22 other treatment strategies are applied to COVID-19 patients.

<b>Virus</b>	<b>Antiviral drug/vaccine</b>	<b>Sex-specific features</b>	<b>Comments</b>	<b>References</b>
HIV	HAART	M < F	CD4+ T cell count; adverse reactions; fat accumulation;	(120-126)

			drug concentration; virus clearance; hepatitis	
	HAART	M > F	Fat loss; survival	(121, 127)
HSV-2	HSV-2 gD vaccine	M < F	Humoral immune responses; cell-mediated immune responses; vaccine efficacy	(128-130)
	Acyclovir	M < F	Frequency of prescription; adverse reaction	(131, 132)
	Acyclovir	M > F	Reduction of virus shedding	(132)
HBV	HBV vaccine	M < F	Humoral immune responses	(133-136)
HCV	pegylated interferon alpha/ribavirin	M < F	Adverse reaction; sustained virologic response <sup>2</sup>	(137-139)
Seasonal Influenza viruses	TIV vaccine	M < F	Humoral immune responses; adverse reactions	(140-143)
	Oseltamivir	M < F	Drug clearance and metabolism <sup>3</sup>	(144)
	Oseltamivir	M > F	Alleviation of symptoms; reduction of viral load	(145)
	Zanamivir	M = F	Alleviation of symptoms; reduction of viral load	(145)

**Table 1:** Sex differences in adverse reactions, immune responses, and efficacy of vaccines and antiviral drugs in humans<sup>1</sup>. <sup>1</sup>Abbreviations: HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; TIV, trivalent inactivated influenza virus. <sup>2</sup>premenopausal females only, <sup>3</sup>tested in neonates only.

## Conclusion

The sex and gender disparities observed in COVID-19 vulnerability emphasize the need to understand the impact of sex and gender on incidence and case fatality of the disease and to tailor treatment according to sex and gender. Experiences from past outbreaks and pandemics have clearly shown the importance of incorporating a sex and gender analysis into preparedness and response efforts of health interventions (68, 146-149). Policies and public health efforts, however, have not yet addressed the gendered impacts of disease epidemics, outbreaks, or pandemics.

1 Some countries have not disaggregated data by sex and age the way other countries  
2 have. In conclusion, governments in all countries should disaggregate and analyze  
3 data for sex and age differences. Furthermore, as prophylactic and therapeutic  
4 treatment studies begin, inclusion of sex- and gender analyses in their protocols  
5 must occur.

6

## 7 **Figure legends**

8 **Figure 1:** Sex-disaggregated data of confirmed COVID-19 cases and deaths  
9 provided by Global Health 50%50 data tracker as of April 2<sup>nd</sup>, 2020 (16).

10

11 **Figure 2:** Male to female ratios of COVID-19 cases, hospitalizations, intensive care  
12 unit (ICU) admissions, deaths, and case-fatality rates in European countries and  
13 China as of April 2<sup>nd</sup>, 2020. \*absolute numbers are provided. Sex-disaggregated data  
14 were not available for all indicators.

15

16 **Figure 3:** Male predominance in COVID-19 case-fatality (deaths divided by  
17 confirmed cases) in Italy, Spain, Germany and Switzerland by age. A male to female  
18 mortality ratio of 1 would reflect gender balance, the red bars reflect male  
19 predominance. Pooled data from Italy as of March 30th 2020, Spain as of March  
20 31st 2020, Germany as of April 1st 2020, and Switzerland as of March 31st 2020.

21

22 **Figure 4:** Oestrogen and sex regulate components of the renin-angiotensin-  
23 aldosterone-system (RAAS). Oestrogen-regulated pathways are depicted in green.  
24 AT2R, angiotensin II type 2 receptor; ACE2, angiotensin converting enzyme 2; NEP,  
25 neutral endopeptidase Neprilysin.

1

**2 Figure 5: Sexual dimorphism in TMPRSS2-mediated SARS-CoV2 host cell****3 entry.** Androgen receptors (ARs) are activated via heat shock proteins (HSPs)

4 release in response to changes in intracellular testosterone concentration. ARs are

5 then phosphorylated and translocated as homodimers into the nucleus, prompting

6 transcriptional activation of *TMPRSS2* and translation of the TMPRSS2 protein

7 (150). At the cell membrane, TMPRSS2 facilitates viral entry and spread into the

8 host cell by activating the spike proteins (24).

9

**10 Declarations****11 Ethics approval and consent to participate**

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**25 Authors' contributions**

1 HKN analyzed and interpreted the patient data regarding COVID-19 case fatality and  
2 mortality, CG and VRZ were major contributors in designing and writing the  
3 manuscript, SLK wrote the paragraphs on sex differences in antiviral treatment and  
4 immune responses, and RM wrote the paragraph on gender-related risk factors and  
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36

# Figure 1

GH5050 COVID-19 sex-disaggregated data tracker : GH5050 COVID-19 data tracker

Prepared by Global Health 50/50

Last updated: 01/04/2020. Data reported from last available date of sex-disaggregated reporting based on the 35 countries with the highest number of confirmed cases

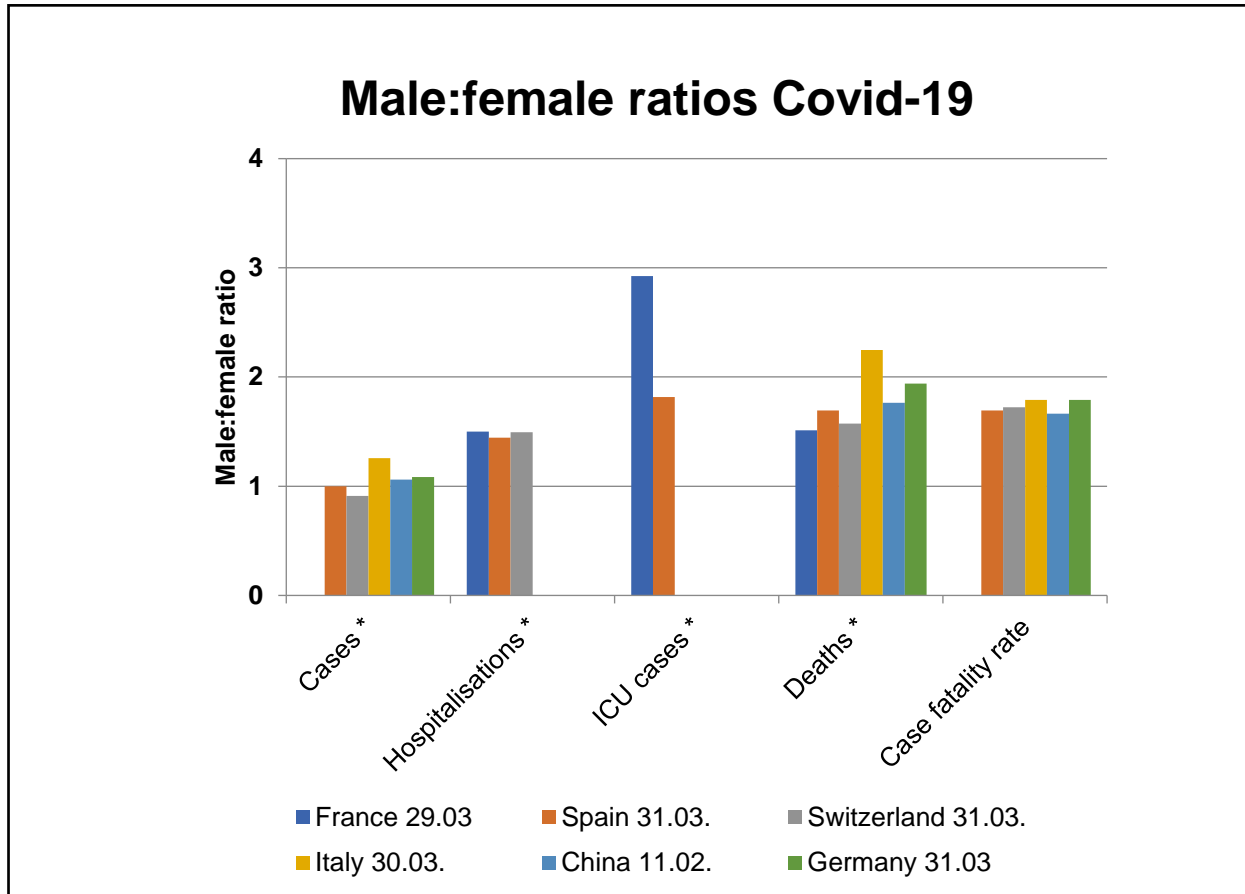


## COVID-19: Sex-disaggregated data tracker

Country	Date	Confirmed cases			Deaths			Proportion of deaths among confirmed cases			
		Total	% male	% female	Total	% male	% female	Total	Male	Female	Male:female ratio
USA	31/03	163,539	na	na	2860	na	na	1.7%	na	na	na
Italy	30/03	94,312	56%	44%	10026	69%	31%	10.6%	13.3%	7.4%	1.79
Germany	31/03	61,913	52%	48%	583	66%	34%	0.9%	1.2%	0.7%	1.77
China	28/02	55,924	51%	49%	2114	64%	36%	3.8%	4.7%	2.8%	1.68
Spain	30/03	46,885	50%	50%	2505	65%	35%	5.3%	6.9%	3.8%	1.82
UK	31/03	25,150	na	na	1789	na	na	7.1%	na	na	na
Switzerland	31/03	16,176	48%	52%	373	61%	39%	2.3%	2.9%	1.7%	1.70
Pakistan	31/03	15,709	na	na	25	na	na	0.2%	na	na	na
Iran	17/03	14,991	57%	43%	853	59%	41%	5.7%	5.9%	5.4%	1.09
Belgium	31/03	13,964	47%	52%	828	58%	41%	5.9%	7.2%	4.7%	1.53
The Netherlands	01/04	13,614	50%	50%	1173	61%	39%	8.6%	10.6%	6.6%	1.60
Turkey	31/03	13,531	na	na	214	na	na	1.6%	na	na	na
Austria	01/04	10,372	51%	49%	146	na	na	1.4%	na	na	na
South Korea	01/04	9,887	40%	60%	165	51%	49%	1.7%	2.1%	1.4%	1.56
Portugal	31/03	8,251	45%	54%	187	59%	41%	2.3%	3.0%	1.7%	1.79
Canada	31/03	7,708	51%	49%	89			1.2%	na	na	na
France	15/03	6,378	47%	53%	161	58%	42%	2.5%	3.1%	2.0%	1.55
Brazil	31/03	5,717	na	na	201	na	na	3.5%	na	na	na
Israel	01/04	5,591	na	na	21	na	na	0.4%	na	na	na
Norway	01/04	4,655	51.19%	49%	28	na	na	0.6%	na	na	na
Sweden	31/03	4,435	52.50%	48%	180	58%	42%	4.1%	4.5%	3.6%	1.27
Australia	01/04	4,325	51.40%	49%	20	na	na	0.5%	na	na	na

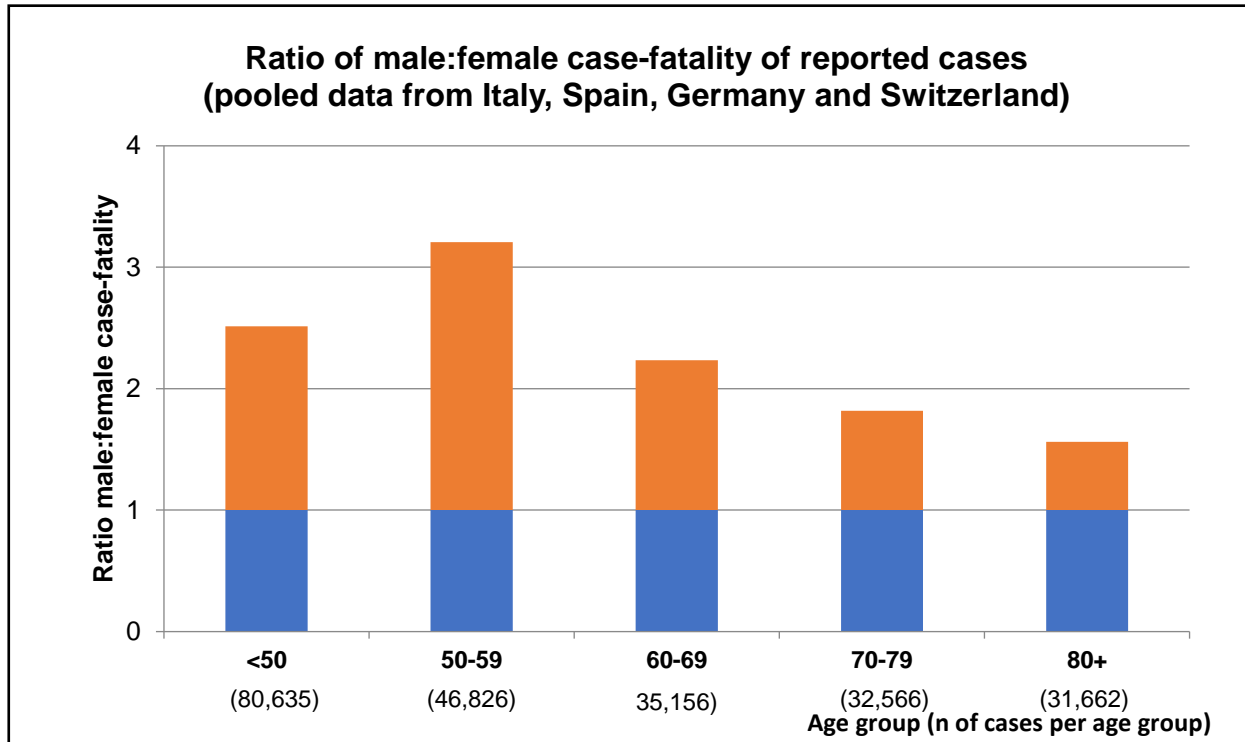
**Figure 1:** Sex-disaggregated data of confirmed COVID-19 cases and deaths provided by Global Health 50/50 data tracker (12).

Figure 2



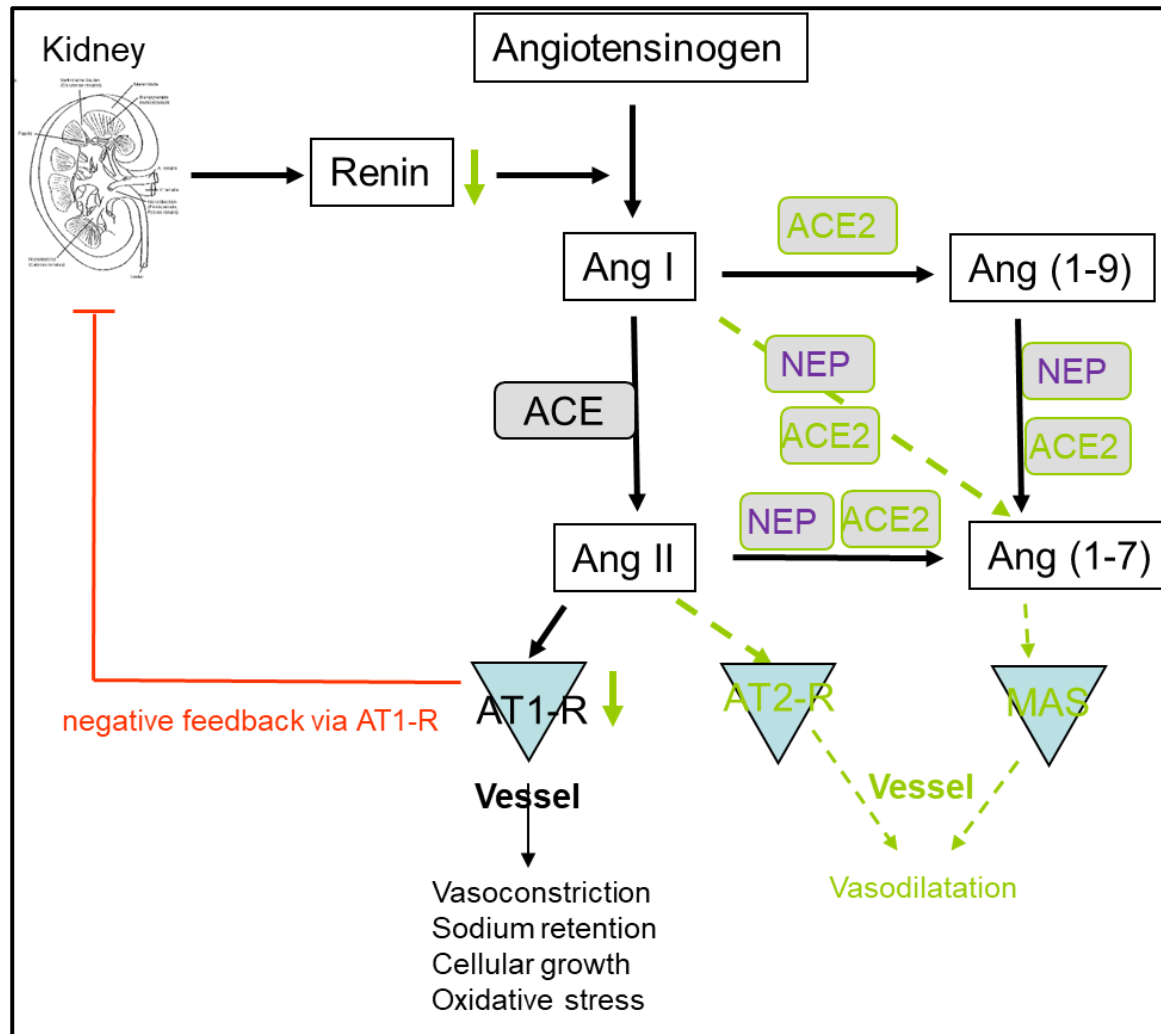
**Figure 2:** Male to female ratios of COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions, deaths, and case-fatality rates in European countries and China. \*absolute numbers are provided. Sex-disaggregated data were not available for all indicators.

**Figure 3**



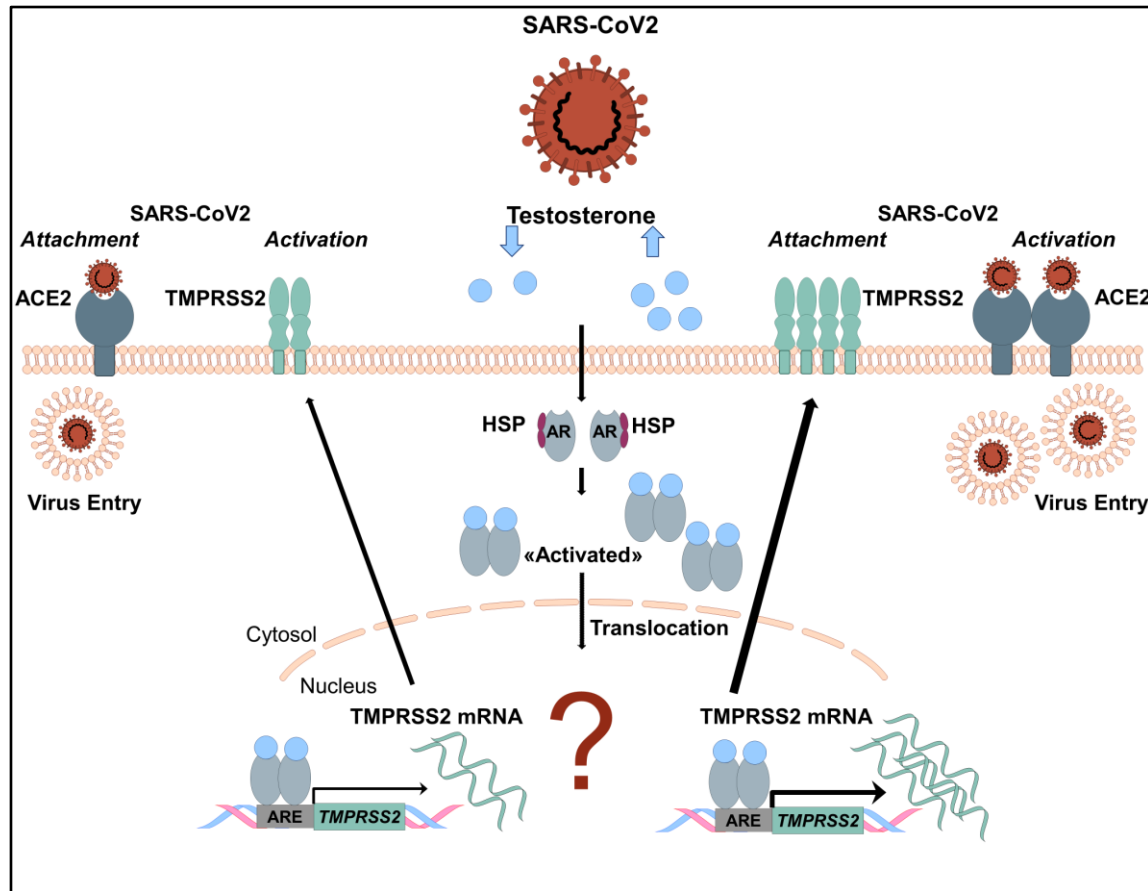
**Figure 3: Male predominance in COVID-19 case-fatality (deaths divided by confirmed cases) in Italy, Spain, Germany and Switzerland by age.** A male to female mortality ratio of 1 would reflect gender balance, the red bars reflect male predominance. Pooled data from Italy as of March 30<sup>th</sup> 2020, Spain as of March 31<sup>st</sup> 2020, Germany as of April 1<sup>st</sup> 2020, and Switzerland as of March 31<sup>st</sup> 2020.

**Figure 4**



**Figure 4:** Oestrogen and sex regulate components of the renin-angiotensin-aldosterone-system (RAAS). Oestrogen-regulated pathways are depicted in green. AT2R, angiotensin II type 2 receptor; ACE2, angiotensin converting enzyme 2; NEP, neutral endopeptidase Neprilysin.

**Figure 5**



**Figure 5.** Sexual dimorphism in TMPRSS2-mediated SARS-CoV2 host cell entry. Androgen receptors (ARs) are activated via heat shock proteins (HSPs) release in response to changes in intracellular testosterone concentration. ARs are then phosphorylated and translocated as homodimers into the nucleus, prompting transcriptional activation of TMPRSS2 and translation of the TMPRSS2 protein (141). At the cell membrane, TMPRSS2 facilitates viral entry and spread into the host cell by activating the spike proteins (19).