The seXY side of COVID-19: what is behind female protection?

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SUMMARY

Gender distribution of COVID-19 is unbalanced. Higher mortality rates are reported in men (60-70% deaths in men). We briefly point out *pros* and *cons* elements for underlying mechanisms. We believe this can offer a point of reflection for further investigations.

Keywords: SARS-CoV-2, COVID-19, gender, female

Sir,
SARS-CoV-2 pandemic concerns more than 1 900 000 people as of April 16, 2020. Gender distribution of COVID-19 is unbalanced. Higher mortality rates are reported in men (60-70% deaths in men). This, first observed in China, is now confirmed in other countries, *i.e.* Italy, actually burdened by high mortality rate (13%). We briefly point out *pros* and *cons* elements for underlying mechanisms.

"Sexual dimorphism in immunity"
Pro: constitutive differences in immune system between males and females have long been studied. Women seem to mount a stronger immune response (immunoglobulines, protecting them by virus-induced damage, occurring in the first place), but with lower proinflammatory cytokine release (thus protecting them by immune-mediated damage, occurring at a later time). In particular, men resulted to have an increased type 1 cytokine production (IFN-γ, IL-2) [1].
Cons: contrasting data from different studies.

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Immunomodulatory effects of sex hormones
Pro: Robinson proved efficacy of high 17β-estradiol levels against Influenza A in mice by reducing proinflammatory response [2]. Kramer found a correlation between low 17β-estradiol levels and increased CD16 expression (consequently, proinflammatory cytokines) [3]. Other studies suggest a protective role of estrogens.
Cons: the gender-related difference of mortality and clinical severity is present in all age groups, also in post-menopausal women (with estrogen depletion, opposite results would be expected).

Smoking
Pro: male smokers are 2 to 22 times more numerous than female smokers. Smoking is related to higher expression of angiotensin-converting enzyme 2 (ACE2), the receptor SARS-CoV-2 uses to enter the host cells. Smoking is also associated with a higher risk of other respiratory infections.
Cons: to date, it is not reported a significant difference in severe clinical course between smokers and non-smokers.

Diabetes
Pro: men have higher mean/median glycemia than women. Diabetes is a risk factor for adverse outcome in Influenza, SARS and MERS by promoting immune dysregulation. It is the second

more frequent comorbidity in hospitalized patients with COVID-19 [4].
Cons: to date, a defined relationship between clinical severity and diabetes has not been established. Type 2 diabetes is often associated with metabolic syndrome and aromatase enzymes producing estrogen by fat deposits would have a protective role.

Social role
Pro: women are more prone to looking after the family and this might have played a sort of social limitation before going into lock down.
Cons: in Hubei province, 90% of healthcare-workers were women and 2/3 of deaths occurred in men anyway [5].

Conflict of interest
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