Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Obesity Research & Clinical Practice 14 (2020) 293–294

Contents lists available at ScienceDirect

Obesity Research & Clinical Practice

journal homepage: www.elsevier.com/locate/orcp

Covid-19: Spiking a focus on men's health

For decades, a persistently higher reported prevalence of, and poorer outcomes from, chronic disease between men and women has been reported [1]. Recent events have also drawn into focus the sex differential in health outcomes for acute infectious disease. Compared to women, men with COVID-19 are more likely to have severe disease (56% vs 44%), require admission to intensive care (71% vs 29%) and die (69% vs 31%) [2]. Men also have significantly higher mortality from SARS and MERS and sepsis of any cause [3].

Some plausible, and some wildly speculative, explanations for the sex-related differences in outcomes after infection with SARS-COV-2 have been proposed. Higher rates of smoking among men is an implausible explanation because it has been shown to be protective of unfavourable COVID-19 outcomes. A role for testosterone in susceptibility to severe infection with SARS-COV-2 has been proposed because androgen receptor activation increases transcription of the Transmembrane Protease Serine 2 (TMPRSS2) which is considered necessary for cellular up take of SARS-COV-2 [4]. Angiotensin-Converting Enzyme 2 (ACE2) also participates in the mechanism of cellular uptake of SARS-COV-2 (and SARS-COV-1) by a mechanism dependent on TMPRSS2. The ACE2 gene is located on the X chromosome, and ACE2 activity is generally higher in females than males (20,608,988). However, at least in mice, the oestrogen receptor signalling pathway appears to diminish the severity of SARS-COV-1 [5]. Another possible explanation is the men have poorer health to start with.

The paper by Hernández–Garduñoy in this issue of the Journal shows that among a cohort of the Mexican population selected for none or a single chronic disease, of those diagnosed with COVID-19, 58.7% were males and 41.3% were female. The strength of the work is that males and females were analysed separately. Comparing males and females 50% vs 37%, 10.4% vs 9.4%, and 14% vs 8.3%, respectively, were hospitalised, admitted to ICU, or died. In multivariate analyses the presence of obesity, diabetes, hypertension were predictors of increasing risk, smoking was protective of risk in both men and women and chronic renal failure was predictive of risk in women only. Although the prevalence of obesity was the same in men and women each of the other factors was more prevalent in men as illustrated in the Table below showing reformatted data from the manuscript.

	Men (%)	Women (%)
Diabetes	23.4	18
Hypertension	24	22.8
CVD	1.9	1.5
Smoking	12.5	5.7
Chronic renal failure	1.4	1.3

Significant limitations to the data are the classification of disease state or risk factor by self-report only, the absence of any estimate of severity, medication use and laboratory measures of glucose, lipids, sex steroids, or other parameters. Therefore, co-morbidities may have been underreported and the notion that severity was more prominent in men can be conjectured on the balance of probability but not confirmed. Nevertheless, these data suggest an association between greater prevalence (and perhaps severity) of diabetes and hypertension and the poorer COVID-19 related outcomes in men as compared to women. And they support the notion smoking cannot explain the sex-based differences in COVID-19 outcomes.

What then of testosterone? While not measured in this study, the co-morbidities that are associated with greatest risk of poor outcomes in those infected with COVID-19 are more frequent with increasing age and these in turn are also associated with lower serum testosterone concentrations in men [6]. Further, men who smoke tend to have higher testosterone levels than those who do not [6]. Men with cardiovascular disease [7] and diabetes [8] have higher concentrations of ACE2 which may mediate increased risk [9].

Whatever the interplay of TMPRSS2, ACE2 and changes in sex steroids in the severity and outcome of COVID-19, it seems unlikely that testosterone is primarily responsible but reflects changes in sex steroid physiology that are secondary to the chronic diseases that disproportionately affect men. This returns the focus to the iniquitous states of health between men and women, and the need for research on the reasons for sex related disparities in disease. The temptation to distil men's health down to a single chromosome, testosterone, or misconceived stereotypes about gender is best avoided.

Conflicts of interest

The authors have no conflicts of interest in relation to this work.

References

[1] The L. Raising the profile of men's health. Lancet 2019;394:1779.
[2] Galbadage T, Peterson BM, Awada J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. Front Med (Lausanne) 2020;7:348.
[3] Walter LA, McGregor AJ. Sex- and gender-specific observations and implications for COVID-19. West J Emerg Med 2020;21:507–9.
[4] Komukai K, Mochizuki S, Yoshimura M. Gender and the renin-angiotensin-aldosterone system. Fundam Clin Pharmacol 2010;24:687–98.
[5] Channappanavar R, Fett C, Mack M, et al. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol 2017;198:4046–53.
[6] Shi Z, Araujo AB, Martin S, et al. Longitudinal changes in testosterone over five years in community-dwelling men. J Clin Endocrinol Metab 2013;98:3289–97.
[7] Sama IE, Ravera A, Santema BT, et al. Circulating plasma concentrations of angiotensin-converting enzyme 2 in men and women with heart failure and effects of renin-angiotensin-aldosterone inhibitors. Eur Heart J 2020;41:1810–7.

https://doi.org/10.1016/j.orcp.2020.08.004

[8] Underwood PC, Adler GK. The renin angiotensin aldosterone system and insulin resistance in humans. Curr Hypertens Rep 2013;15:59–70.
[9] Hernández-Garduño E. Obesity is the comorbidity more strongly associated for Covid-19 in Mexico. A case-control study. Obes Res Clin Pract 2020;14:375–9.

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