

Explaining the gender disparities in SARS-Cov 2 infection and Covid-19 Disease in Malawi

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Global Covid-19 data show that there is higher morbidity and mortality among males compared to females¹⁻³. Why, is this the case, and what needs to be done to save lives? Alternatively is this a situation where the observed status is only good for reporting but not worth interventions?

Lessons from demography

Anyone who has studied demography and life expectancy numbers will not be surprised when they see higher mortality numbers for men compared to women (<https://ourworldindata.org/why-do-women-live-longer-than-men>). Of course this has not always been so as death rates were previously higher among women compared to males. Women now live longer almost in all countries; for instance Russia where there is a difference of 10 years amongst males and females. Talking about Russia, life expectancy was 29.6 in 1845, and over the course of the next 175 years, it is expected to have increased to 72.3 years.

Yes, lifestyle (discussed later) has a lot to play but even among neonates, males die more than females. It is not relatively the same amongst under-fives, suggesting it cannot just be lifestyle (<https://ourworldindata.org/grapher/child-mortality-by-sex>). After all, what lifestyle do male neonates have that would be different from their female counterparts? Unless of course if parents give differential attention between male and female neonates. While this is possible there is doubt that this can have an impact and in any case, sociological studies point to parental son preference (https://www.stopvaw.org/harmful_practices_son_preference) which would ordinarily give them an advantage over females as males may receive better parental attention compared to girls. Luckily, such overwhelming son preference over daughters is changing in some settings⁴. The observation leads to the ubiquitous answer medical students fall on when stuck with a difficult clinical question. One throws in genetics. In 9 out of 10 instances, genetics does not fail you at the final year medical school examination.

Genetics^{5,6}

The distribution and expression of receptors influence the route of virus infection. In the case of SARS-Cov 2 there is evidence that the Angiotensin-converting enzyme-2 (ACE 2), encoded by ACE 2 gene is the receptor for SARS-CoV 2, the virus responsible for Covid-19. An *in vitro* study demonstrated the positive correlation of ACE 2 expression and SARS-CoV infection. Now what has this got to do with males? In a study on the expression level and pattern of human ACE 2 using a single-cell RNA-sequencing (RNA-seq), analysis indicated that (Asian) males had higher expression of ACE 2 than females. Further, the expression

of ACE 2 in human lungs was highly expressed in males compared to females.

Immunology⁷⁻¹⁰

A well-regulated immune response following an infection is vital if the host should not be further harmed due to either a sub-optimal immune response or an uncontrolled hyper response. This is where immunological checkpoints come in. For instance, the inhibitory CD200 receptor (CD200R) is key in balancing the immune system during microbial infection by stimulating and controlling hyperimmune mediated responses. CD200R is found in myeloid receptors and expressed on granulocytes, macrophages, and dendritic cells (DCs). It also expressed on other immune cells such as T-cells, B-cells, and natural killer cells (NK cells). A review which looked at the association between sex difference and immune responses concluded that sex-based immunological differences contribute to variations in the susceptibility to infectious diseases and responses to vaccines.

Certain immunological differences between males and females are present throughout life, while others are expressed only after puberty and before reproductive senescence. This suggests that both genes and hormones are involved. And competing with genetics as the clever examination answers for medical students (when stuck as to what may cause a clinical syndrome, after thinking about genetics), presently, is the microbiome. Environmental exposures influencing the microbiome are thought to have sex-dependent effects on immune function. As a disclaimer, we are not proposing oestrogen hormonal therapy to save male lives during the current pandemic.

Harmful Lifestyles

The following lifestyles are known to be life-limiting in diverse situations: excessive alcohol intake, smoking, poor diets and poor health seeking behaviours. Men, for a diverse reasons are at greater risk of participating in these risk behaviours than females. In the 2009 Malawi STEPs survey the proportion of males versus females who were reported as tobacco smokers, were 25 % and 3% respectively. A Spanish study reported that women had more responsible attitude toward the Covid-19 pandemic than men¹¹. Women are likely to embrace preventive measures such as frequent hand washing, face masking, and adherence to stay at home orders. Men may be underserved by the health system just as they may not actively access care, thereby putting their lives at risk^{12,13}.

But the above is not the whole story. While obesity and physical inactivity may result in bad clinical outcomes for

Covid-19, in Malawi women are more likely to be obese, more sedentary and high cholesterol levels. Yet, with such higher levels of obesity Malawian women seem just fine, at least in as far as SARS-Cov 2 is concerned.

Conclusions

Having explored why men are having worse outcomes compared to women, what should be the next step? The least we can do is to talk about it. Even when people have little to do to reverse the situation, not knowing could be worse. I doubt we can do much about genetics presently, although in future precision medicine, genetic manipulation will be possible widely. There are many modifiable actions that can influence one's immunity: diet, exercise, sleep and rest, reducing alcohol, stopping smoking, and yoga. Of course by the time one is infected with SARS-Cov 2, perhaps it is a little too late to engage these immune-modifying behaviours. Of course there is probably nothing wrong in trying or using the infection/disease as a cue to future positive behaviours. The higher male morbidity and mortality should make all of us review whether we are doing enough to save male lives; and for once, we will avoid victim blaming!

References

1. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;1–13.
2. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020;2019:2019–20.
3. Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission potential and severity of COVID-19 in South Korea. *Int J Infect Dis* [internet]. 2020;93:339–44. <https://doi.org/10.1016/j.ijid.2020.03.031>.
4. Claire Cain Miller, American Might No Longer Prefer Sons Over Daughters, *Y. Times* (Mar. 5, 2018), <https://www.nytimes.com/2018/03/05/upshot/americans-might-no-longer-prefer-sons-over-daughters.html>.
5. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCoV. *BioRxiv* [internet]. 2020;2020.01.26.919985. <https://doi.org/10.1101/2020.01.26.919985v1>.
6. Cao Y, Li L, Feng Z, Wan S, Huang P, Sun X, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* [internet]. 2020;6(1):4–7. <https://doi.org/10.1038/s41421-020-0147-1>.
7. Mhrshahi R, Barclay AN, Brown MH. Essential roles for Dok2 and RasGAP in CD200 receptor-mediated regulation of human myeloid cells. *J Immunol*. 2009;183(8):4879–86.
8. Karnam G, Rygiel TP, Raaben M, Grinwis GCM, Coenjaerts FE, Rensing ME, et al. CD200 receptor controls sex-specific TLR7 responses to viral infection. *PLoS Pathog*. 2012;8(5):1–8.
9. Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol*. 2016;16(10):626–38.
10. Ghazeeri G, Abdullah L, Abbas O. Immunological differences in women compared with men: overview and contributing factors. *Am J Reprod Immunol*. 2011;66(3):163–9.
11. De La Vega R, Barquín RR, Boros S, Szabo A. Could attitudes toward COVID-19 in Spain render men more vulnerable than women? *Prepr*. 2020. <https://doi.org/10.31234/osf.io/dyxqn>
12. Muula AS, Ngulube TJ, Siziya S, Makupe CM, Umar E, Prozesky HW, Wiysonge CS, Mataya RH. Gender distribution of adult patients on highly active antiretroviral therapy (HAART) in Southern Africa: a systematic review. *BMC Public Health*. 2007 Apr 25;7:63. doi: 10.1186/1471-2458-7-63.
13. Braitstein P, Boulle A, Nash D, Brinkhof MW, Dabis F, Laurent C, Schechter M, Tuboi SH, Sprinz E, Miotti P, Hosseinipour M, May M, Egger M, Bangsberg DR, Low N; Antiretroviral Therapy in Lower Income Countries (ART-LINC) study group. Gender and the use of antiretroviral treatment in resource-constrained settings: findings from a multicenter collaboration. *J Womens Health (Larchmt)*. 2008 Jan-Feb;17(1):47-55. doi: 10.1089/jwh.2007.0353.
14. Msyamboza KP, Ngwira B, Dzowela T, Mvula C, Kathyola D, Harries AD, Bowie C. The burden of selected chronic non-communicable diseases and their risk factors in Malawi: nationwide STEP survey. *PLoS One* 2011;6(5):e20316. doi: 10.1371/journal.pone.0020316. Epub 2011 May 23.