Vol 4 | Issue 1 | Pages 129-135

Annals of Public Health Reports
ISSN: 2642-4924

Review Article

DOI: 10.36959/856/507

Does Nature Have a Systematic Sex Bias: Prevalence, Mortality, and Trend of COVID-19

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Abstract

Background: The unprecedented outbreak of a contagious respiratory disease similar to pneumonia caused by a novel coronavirus termed COVID-19 has led to a pandemic claiming millions of lives worldwide. Potential vaccine candidates are underdevelopment to contain and mitigate the spread of global cases and deaths. Preliminary reports suggest that males and females are affected differentially in cases and deaths.

Objective: To study the statistical significance of sex and gender bias in COVID-19 infection and deaths across 75 selected countries in the world, specifically for the United States.

To summarize, the prevalence and incidence rates of this infectious disease globally segmented by developed, developing, and transitioning countries.

Methods: Data on sex are collected from the sex-disaggregated data tracker Global Health 50/50, University College London until September 21, 2020, UN COVID-19 and gender monitor, and CDC COVID data tracker. The hypothesis was tested using the binomial proportion test to be 50% within males and females for infection rate and mortality. Prevalence and Incidence rates by sex are illustrated graphically.

Results: Females in countries with transitioning and developed economies have a higher number of cases and deaths than males, but in developing countries, males have high mortality due to coronavirus. Also, men are at greater risk of worse outcomes if infected with the SARS-Cov-2 virus, including mortality. The differential effect of gender in death counts in the US is statistically significant, with reported p-values < 0.05. In the oldest US population (85+ years), female's death rate is higher due to the virus. Monthly deaths in the US was at its peak during March - April 2020 for both sexes.

Conclusion: Clinical researchers, health insurance planners can follow the suggested approach outlined here to target a specific population for inaugural vaccination and immunization. Although everyone should follow the CDC guidelines of prevention, it is recommended that the females strictly follow the CDC guidelines due to a higher rate of Covid-19 infection. Also, the effect of age is delineated to help vaccine administration priority.

Keywords

COVID-19 review, Coronavirus, SARS-Cov-2, Pandemic, Gender, Clinical trials, Sex, Mortality, Prevalence rate, Cancer, Demographics, P-Value, Statistical significance, Case fatality rate

Introduction

In late December 2019, clusters and community transmission of peculiar pneumonia cases arose in Wuhan, Hubei province of China [1]. It soon started spreading over hundreds of countries, and this 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) virus was declared a global pandemic in March. COVID-19, officially named by World Health Organization (WHO), has a total case count of 30,175,496 cases and 944,887 deaths as of September 22, 2020, according to John Hopkins's Coronavirus Resource Center [2]. The rapid spread of the disease at a pandemic speed can only end with the rapid development of vaccines and therapeutics. Potential vaccine candidates are under development from major

pharmaceutical companies and several universities around the world. To increase the impact of vaccine and therapeutic intervention and better inform the clinical researchers that sex and other critical demographics should be considered in designing clinical trials [3]; this research aimed to provide a lucid yet constructive and systematic summary of the significance of sex and the impact of COVID-19 on gender roles.

Often sex and gender are used interchangeably. Sex is a biological characteristic that defines males and females, and gender refers to the roles, behaviors, and activities that societies define for men and women [4]. Males and females differ at many biological levels starting from their DNA structure as males have XY chromosomes and females have XX chromosomes. In the case of an X-linked mutation, it will be expressed in half of the female cells and all the male cells; therefore, males have a higher rate of X-linked immunodeficiencies than females. Further, men and women have different reproductive organs and hormone levels. Gender roles differ by society, and they can impact how an individual is educated, seeks healthcare, or is exposed to certain infectious diseases. Both the biological and social roles of men and women play a role in the spread and impact of infectious diseases. Sex-based differences are prominent in epidemiology, clinical manifestations, progression, course, and therapy of disease [5] with varying hormonal levels, the reproduction potential in women makes them more susceptible to many infectious diseases. For instance, there is rare evidence for intrauterine infection caused by vertical transmission or transplacental transmission in women who develop COVID-19 pneumonia during late pregnancy, but a single case of severe maternal presentation makes the possibility of vertical transmission [6,7] irrefutable. Currently, there is no evidence to believe that pregnant women are at increased risk of Covid-19 [8,9].

Nevertheless, baseline characteristics like sex, gender, and age should be considered in COVID-19 research. In this research work, we discuss and statistically prove that the global outbreak is modified by sex, gender, and age. To better inform clinicians and health planners, this detailed study on the association of demographics is deemed necessary. The rest of the article includes sections i) Materials and Methods, which has the data collection and statistical methods used for analysis; ii) Results where the findings from multiple data sources are illustrated in tabular and graphical forms; iii) Discussion section elaborates the findings and data-driven reasoning and justifications are provided.

Materials and Methods

Data were collected from the different sources for assessing the gender- bias in infection rate and mortality due to the Coronavirus in the United States population: Global Health 50/50. COVID-19 Sex-disaggregated Data Tracker (https://globalhealth5050.org/the-sex-gender-and-covid-19-project/) updated upto September 21, 2020. United Nations COVID-19 and gender monitor (https://data.unwomen.org/COVID19) provided the sex-specific data and further supplemented by the Centers for Disease Control and Prevention (CDC) COVID Data Tracker (https://covid.cdc.gov/covid-data-tracker/#demographics).

Binomial proportion test of significance assessed the following hypotheses: a) Is sex a highly significant factor in determining its differential effect in COVID cases and deaths globally?; b) Are females in developing countries less prone to infection?; c) Are monthly deaths in the US are statistically significant?

No adjustment for multiple comparisons was made since we are drawing inferences at each country level.

Daily Case Incidence rate (IR) and prevalence (P) as of September 23, 2020, for the first six most affected countries (USA, India, Brazil, Colombia, Peru, Mexico) and three recovered countries (China, South Korea, Italy) are obtained.

Results

The data from Global 50/50 consists of 275 countries, of which only 27% have reported sex-disaggregated data, and 18% can be categorized as having reported partial data with either death percentage or case percentage. According to three economies based on the United Nations' World Economic Situation and Prospectus (WESP) [10], the countries are segregated within three economies. Transitioning economies like Russia, Belarus, developed economies like New Zealand, Japan, Singapore have none to partial sex-disaggregated data on Covid-19, while developing countries like India, China, and South Korea have reported data on both the cases and deaths. Table 1 shows that females have a higher number of cases in transitioning and developed economies, while in developing countries, males have a higher number of cases.

Table 2 and Table 3 categorize countries by statistical significance (highly significant, significant, and not significant) Covid-19 cases and deaths by sex and by type of world economy. United States, India, China, European countries like France and Sweden, irrespective of their economic dissimilarity, have noteworthy sex differences, and are statistically significant.

Table 4a presents the countries with a larger number of female cases and deaths, and Table 4b has low female cases. There is hardly any difference in infection rates among males and females in developed countries.

Figure 1 shows a higher female case prevalence in the US, Italy, South Korea, and Brazil. Death prevalence is consistent-

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Accepted: December 17, 2020

Published online: December 19, 2020

Citation: Srivastava N, Bhattacharyya A, Seth A, et al. (2020) Does Nature Have a Systematic Sex Bias: Prevalence, Mortality, and Trend of COVID-19. Ann Public Health Reports 4(1):129-135

Table 1: Sex bias in Covid-19 Cases and Death according to the type of World Economies for selected 75 countries.

Economy Type	**Total # of countries with Sex Data[1]**	**Infection**		**Death**	
		Higher Male	**Higher Female**	**Higher Male**	**Higher Female**
Transitioning	6	2	4	6	0
Developing	42	36	6	41	1
Developed	27*	6	20	19	8
Total	75	44	30	66	9

*Germany is excluded from the infection data as it has equal percentage of cases in males and females, therefore total number of countries does not add up to 27

Table 2: Countries with levels of significance and economy type in Cases among 75 selected countries.

Highly Significant Cases (p-value < 0.005) P < 0.005	**Significant Cases p-value ϵ [0.005-0.05] 0.005 < p < = 0.05**	**Not significant Cases (p-value > 0.05)**
Transitioning countries		
Bosnia and Herzegovina, Kyrgyzstan	North Macedonia	Moldova, Albania, Ukraine,
Developing countries		
Cambodia, Nepal, Pakistan, Uganda, Bangladesh, Afghanistan, Maldives, Malawi, Mongolia, Bhutan, Burkina Faso, India, Kenya, Liberia, Guatemala, Haiti Iran, Philippines, Thailand, Panama Costa Rica, Morocco, Myanmar, Israel, Mexico, Argentina, China, Dominican Republic, Indonesia, Turkey, Peru, Ecuador, Chile, Colombia	N/A	Cabo Verde, Vietnam, Eswatini, Tunisia, South Korea, Jamaica, South Africa
Developed countries		
Greece, Czech Republic, Austria, Germany, Switzerland, France Italy, Denmark, Romania, Spain, Sweden, Netherlands, Wales, United States	N/A	England Australia, Finland, Slovenia Switzerland Estonia, France, Italy, Denmark Romania, Spain, Canada, Portugal Northern Ireland, Belgium, Netherlands Scotland, Wales

Table 3: Countries with levels of significance in Deaths among 75 selected countries.

Highly Significant Deaths (p-value < 0.005) P < 0.005	**Significant Deaths p-value ϵ [0.005-0.05] 0.005 < p < = 0.05**	**Not significant Deaths (p-value > 0.05)**
Transitioning countries		
Bosnia and Herzegovina, North Macedonia, Albania, Kyrgyzstan, Ukraine	N/A	Moldova
Developing countries		

Nepal, Pakistan, Bangladesh, China, India, Afghanistan, Iran Thailand, Malawi, Burkina Faso, Guatemala, Haiti Philippines, Panama, Costa Rica Morocco, Argentina, Peru Mexico, Dominican Republic, Indonesia, Turkey, Tunisia, South Africa, Kenya, Ecuador, Chile, Colombia	Uganda, Liberia, Israel, Eswatini	Maldives, Myanmar, Cabo Verde, Vietnam, South Korea, Jamaica
Developed countries		
Greece, Czech Republic, Austria, Germany, Switzerland, France Italy, Denmark, Romania, Spain, Sweden, Netherlands, Wales, United States, England	N/A	Latvia, Luxembourg, Norway, Australia, Finland, Slovenia, Belgium, Estonia, Canada, Portugal, Northern Ireland, Scotland

Table 4a: Countries with significantly higher female cases among 75 selected countries.

Transitioning countries	Developing countries	Developed countries
Albania, Kyrgyzstan, Ukraine, Moldova	Tunisia, South Korea, South Africa, Jamaica	Australia, England, Finland, Slovenia, Switzerland, United States, Estonia, France, Italy, Denmark, Romania, Spain, Canada, Portugal, Northern Ireland, Sweden, Belgium, Netherlands, Scotland, Wales
Countries with a Higher Percentage of Female Deaths		
N/A	Vietnam	Australia, Belgium, Canada, Estonia, Finland, Ireland, Scotland, Slovenia

Table 4b: Countries with a significantly lower proportion of female cases among 75 selected countries.

Transitioning countries	Developing countries	Developed countries
Bosnia and Herzegovina, Kazakhstan, North Macedonia,	Cambodia, Nepal, Pakistan, Uganda, Bangladesh, Afghanistan, Maldives, Malawi, Mongolia, Bhutan, Burkina Faso, India, Kenya, Liberia, Guatemala, Haiti, Iran Philippines, Thailand, Panama, Costa Rica, Morocco, Myanmar, Israel, Mexico, Argentina, China, Dominican Republic, Indonesia, Turkey, Cabo Verde, Vietnam, Peru, Ecuador, Chile, Colombia	Greece, Czech Republic, Austria, Latvia, Luxembourg, Norway, Germany

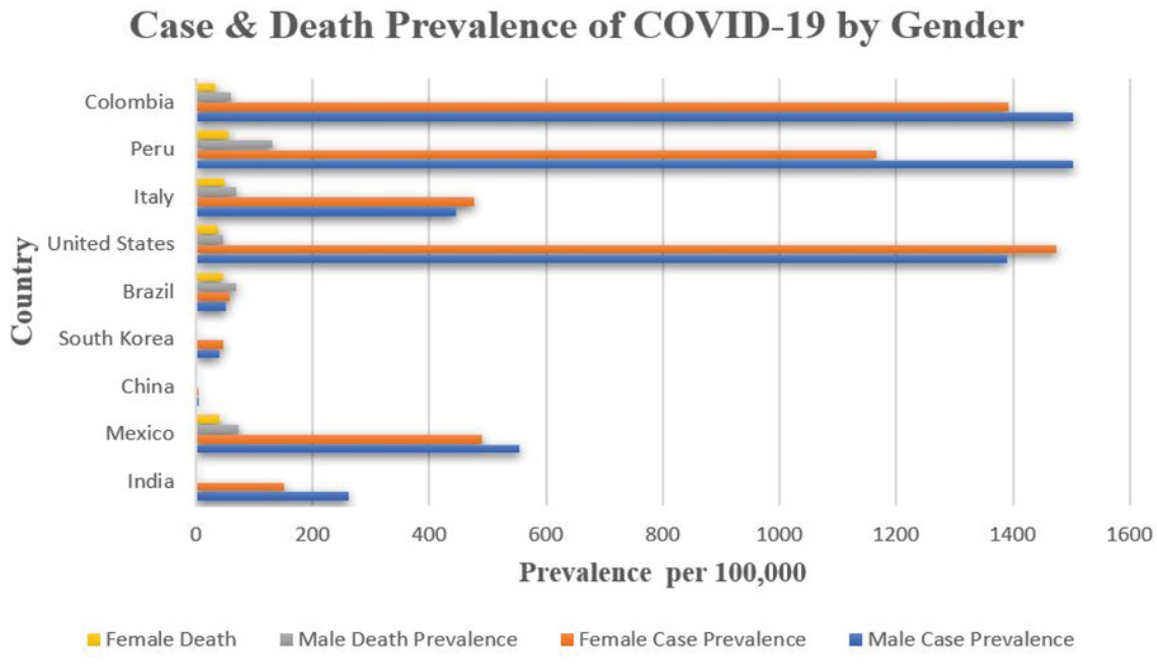

Figure 1: Covid-19 death and case prevalence by gender for nine countries.

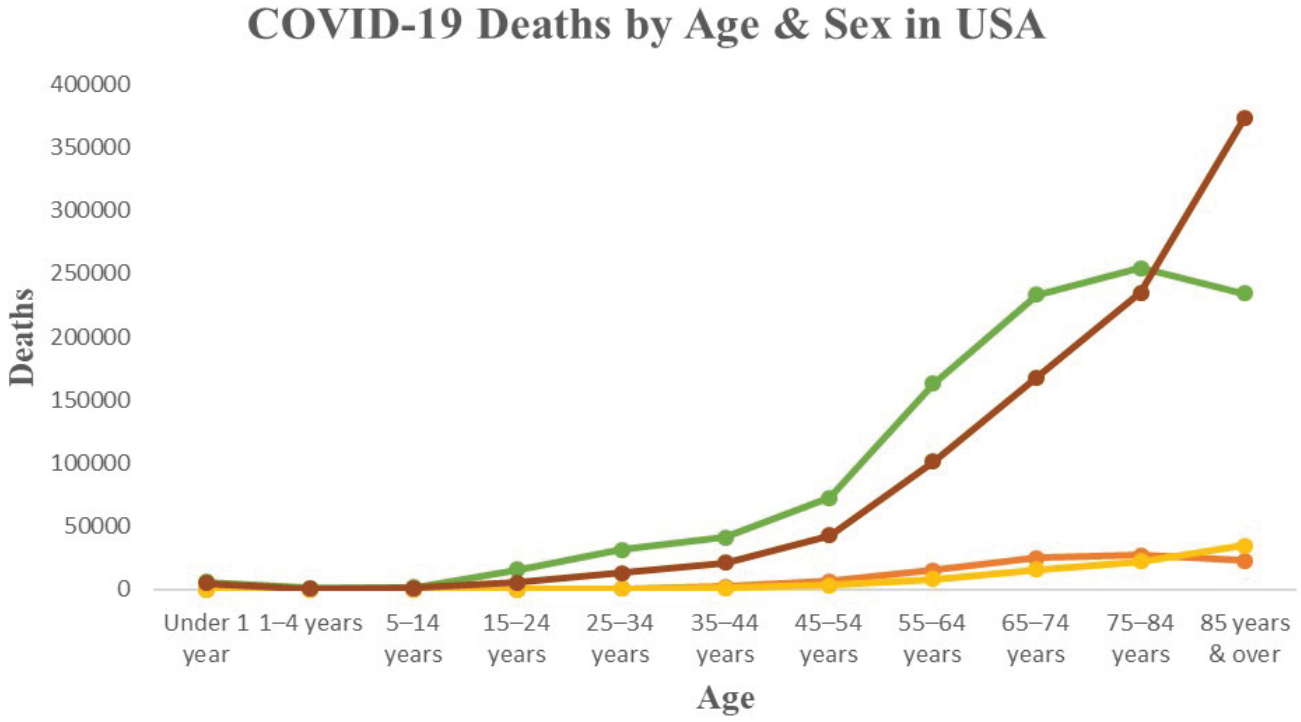

Figure 2: COVID-19 deaths in the USA by age and sex until September.

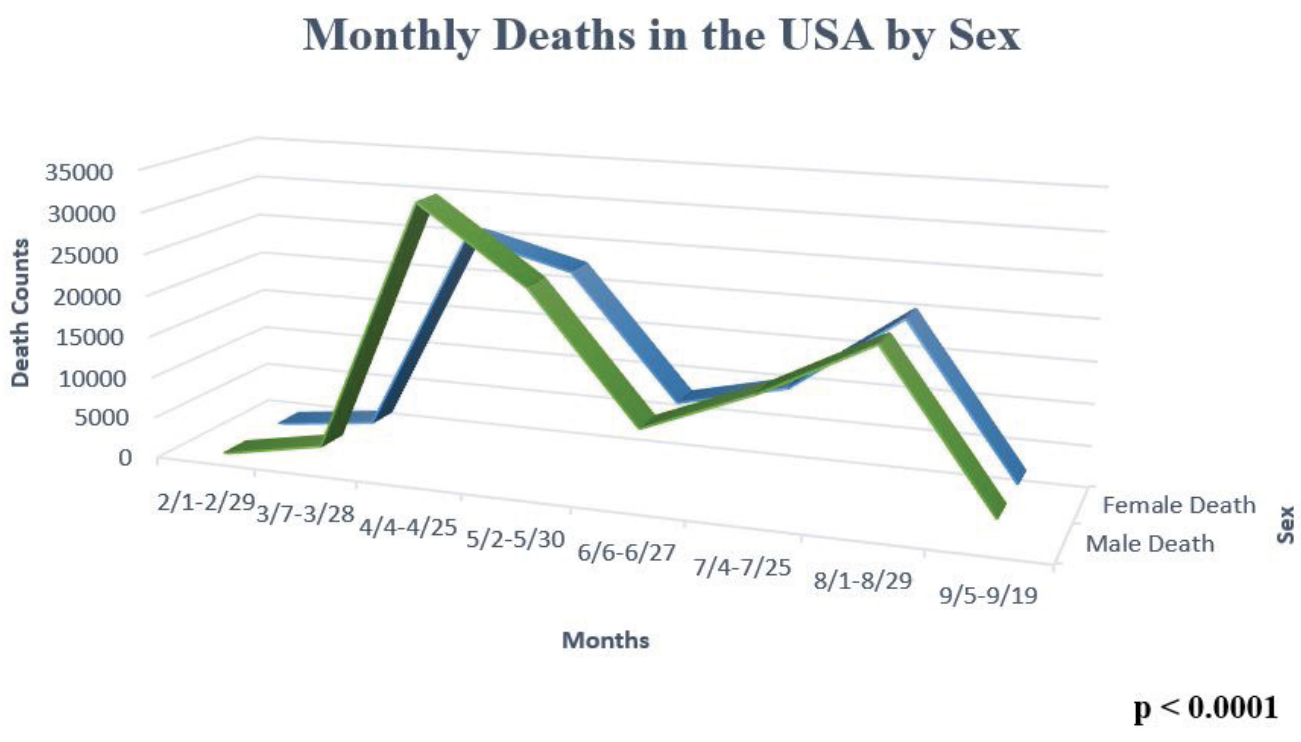

Figure 3: Time lag of US Covid-19 cases by sex ($p < 0.001$).

ly higher for males across countries. Figure 2 concentrates on the sex distribution by age for the US, with female mortality increasing after (85+ years). There is not much difference in Covid-19 related deaths between males and females.

Finally, Figure 3 shows the monthly deaths by sex in the US with a peak in March-April. Though the monthly deaths taper off in September, the presence of death lag behind surging infections may be a reason, but researchers anticipate a rising trend with the onset of fall and winter season in addition to the flu season. As of September 28, the daily incidence rates are 2.4 and 6.07 per 1000,000 for the USA and India.

Discussion

Significant sex differences in Covid-19 cases have been noted in various studies across the world [11]. As the sex- disaggregate data (37% of the confirmed cases, as of July 2020) started getting reported mostly in the developed economies with few exceptions, we considered data from countries over the world and the association of age and sex. Higher mortality risk for men became apparent during the first few months of the pandemic, especially in China [12]. Prevalence of COVID-19 in men and women in the USA and other case series from other parts of the world, death rates differed between males and females. The odds ratio of cases in males vs. females is 1.1; that of hospitalizations is 1.3, ICU admissions are 1.8, deaths are 1.4, so for every ten females, there are 11 male cases globally, based on Global Health analysis 50/50 data. Based on the above statistics, it is recommended that the researchers include sex and gender as important analytical variables in designing drug and vaccine clinical trails. It is evident that sex and gender have major roles in any kind of disease, and Covid-19 is no exception. SARS-CoV-2 infects host cells through Angiotensin-converting enzyme 2 (ACE2) receptors, leading to coronavirus disease (COVID-19)-related pneumonia, highly expressed in males and also causing acute myocardial injury and chronic damage to the cardiovascular system [13]. Heart diseases are more common in men than women due to frequent smoking (35%, 6%), alcohol consumption, and air-pollution prone work environment, so that ACE2 enzyme expression may be one of the biological evidence of high mortality in men. There are several biological evidences and theories for the high mortality in men. The frequent occurrence of endothelial dysfunction as a risk of cardiovascular disease in men with erectile dysfunction and type 2 diabetes, coagulopathy, highly expressed TNFSF13b (BAFF) cytokine proteins leading to increased inflammation and progression of COPD [14]. Females with higher expression of TLR7 and TLR8 genes active on both X-chromosomes, responsible for immune responses, whereas, in men, there is just a single copy. At the same time, gender differences and inequality have widened for women. One study [15], using single-cell sequencing, found that expression of ACE2 was more predominant in Asian men, which might be why the higher prevalence of COVID-19 in these Asian male patients than in women patients as compared to other ethnicities. A study with 140 patients with COVID-19 in China [16] found the sex distribution to be equal. In a study of critically ill patients [17], more men were affected (67%) than women. In the latest report [18] of 1099 patients with COVID-19 from 552 hospitals in 30 provinces in China, 58% were men. The data seem to indicate that there might be a sex predisposition to COVID-19, with men more prone to being affected [19]. It is noticeable that there is a striking disparity in the number of cases and deaths between females and males in developing countries. The trend of the low-case and death percentage in females is apparent in South-Asian countries where the women labor force is low (< = 25%) like Afghanistan (21.4%), Bangladesh (30.5%), Pakistan (20.3%), Yemen (7.7%), with data derived from World Bank [20]. The women from these countries are less in the workforce. Their attire may also confer an advantage in having a lower percentage of cases, despite the sex ratio to be 0.98:1.0 [21]. The high percentage of female positives in developing countries like South Korea (Republic of Korea) and South Africa are in the high-income and the upper-middle-income group as per United 'Nation's 2020 World Economic situation prospectus (WESP) [10] with the percentage of the woman labor force being 42.1% and 45.4% respectively than other developing economies. So, there is an imminent increase in virus exposure among working women in these countries. Also, the first study in South Korea did report the number of cases to be high in females, with mainly four clusters: of the church (first case, a woman), gym and fitness classes in Cheonan (all women) [22], hospital and pilgrimage [23]. Gender inequality has been further widened by this pandemic, with United Nations for Women reporting marginalized groups being more prone to death like Black women have 4.3%- and two-times higher mortality than white women in the United Kingdom and Brazil, respectively. Loss of working hours in Asia and Pacific, job losses in Europe and Central Asia, 80% of domestic workers, accommodation, and domestic sectors are evident more in women than men [24]. Globally, 70% of healthcare workers are females, with three times higher infection rates. Several instances of increased domestic violence due to social distancing and house confinement in Tunisia, New Zealand [25], and intensified unpaid care and domestic workloads, along with school closures, have imposed challenges in maintaining work-life balance [26].

There is also a constant gender bias in leadership positions, primarily in Asian-African countries, in minority groups, with women of color, be it in senior management business positions, political leadership, discrimination in equal pay, equal rights, or even household chores and a constant fight for gender equality (50/50) in all aspects. Interestingly, there is still hope in demolishing these stereotypes slowly but permanently when research shows that countries with political leadership as female presidents (women heads of states) like New Zealand, Finland, Bangladesh, Denmark, tend to have better public health metrics based on testing and number of positive cases, reproduction number (R_0) [27]. This study will help clinical researchers incorporate sex and gender appropriately while designing Covid-19 clinical trials and targeting age-sex specific populations for future vaccination programs, allocating medical resources. Investment in sex and age-segregated data collection should be prioritized.

Acknowledgments

This work was supported by the National Institute of Health grant P42 ES023716 to the principal investigator: Dr. S Srivastava, the National Institute of Health grants 1P50 AA024337 and 1P20 GM113226 to the principal investigator: Dr. Craig McClain, and 1P30ES030283 to the principal investigator Dr. C States. Dr. Rai, Wendell Cherry Chair in Clinical Trial Research, has also partially supported the research. Except for Dr. Rai, the funders had no role in study design, data collection, analysis, decision to publish, or manuscript preparation.

Author's Contribution

AB has contributed towards analysis, data collection, and

preparation of graphics, and writing the manuscript. NS conducted a preliminary analysis to identify data trends and understand the mechanism. AS and SNR have contributed with valuable comments, developing ideas, editing. All the authors have contributed to the final preparation of the manuscript.

Competing Interests

The authors declare no competing interests.

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DOI: 10.36959/856/508