© JLS 2020 J Life Science, 12(1-2): 12-19 (2020)
PRINT: ISSN 0975-1270 ONLINE: ISSN 2456-6306 DOI: 10.31901/24566306.2020/12.1-2.253

Sexual Dimorphism in the Susceptibility to Infections: "Being a Male is a Risk Factor" for SARS-Cov-2 Infection

Sudip Datta Banik

Department of Human Ecology, Cinvestav del IPN, Merida, Yucatan, Mexico

KEYWORDS COVID-19. Male. Female. Sex Difference. Evolution

ABSTRACT Sex difference in the susceptibility to infections by pathogens such as virus, bacteria, fungi and protozoa is reported by the scientists from medicine, epidemiology, immunology, molecular biology, and human genetics. Presently we are facing COVID-19 pandemic and higher prevalence of the disease is observed in men compared to women. The present essay is based on some previous reports from the fields of research mentioned above. Sexual dimorphism is a product of organic evolution and natural selection. Sex differences in size and shape are favorable for the females with higher plasticity than males. Differential intensity and prevalence of COVID-19 in men and women can be studied in the human ecological perspective that may associate demographic, biological, socio-cultural, and behavioral factors.

INTRODUCTION

COVID-19 Outbreak

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019 and number of confirmed cases reached 4,098,017 globally till 12th May 2020 (From the website of World Health Organization or WHO <https://covid19.who.int/> Retrieved on 12 May 2020). The highest number of confirmed cases was recorded in the United States of America (U.S.) (1,298,287), followed by the Russian Federation (232,243), Spain (227,436), the United Kingdom (U.K.) (223,064), Italy (219,814), Germany (170,508), Turkey (139,771), France (137,491), Brazil (162,699), and Iran (110,767): the countries where more than 100,000 cases have been confirmed. In China, number of confirmed cases reported was 84,451, followed by India (70,756), Canada (69,156), Peru (67,307), and Belgium (53,449). COVID-19 confirmed cases ranging between 20,000 and 50,000 were recorded in several countries including Ireland, Sweden, Portugal, Ecuador, Switzerland, Mexico, and Netherlands. Relatively lower number of cases (total: 32,953) were reported from the 46 African countries that included 7,572 cases from South Africa (information available up to 5 May 2020). A few African countries (Algeria, Cameroon, Ghana, Guinea, Ivory Coast, Nigeria, and Senegal) reported number of cases between 1,000 and 5,000 (WHO 2020a). The pathogenesis of COVID-19 is known (Rothan and Byrareddy 2020).

The number of deaths due to COVID-19 has reached 283,272 globally (From the website of WHO <https://covid19.who.int/> Retrieved on 12 May 2020) (Fig. 1). The highest number of deaths was reported from the U.S. (78,652), followed by the U.K., Italy, Spain, France, and Brazil. Total number of deaths crossed 10,000 in these countries. There were several other countries where death tolls recorded were more than 1,000 but below 10,000 that include Belgium, Germany, Iran, Netherlands and others (Fig. 2). Huge data are available on the official websites of WHO and Centers for Disease Control and Prevention (CDC) where country-wise daily updates are given on confirmed cases, recovered and deaths in COVID-19. In this public health issue, severe socio-economic disruption is a serious concern.

In most of the countries, outbreak of COVID-19 shows similar pattern that number of confirmed cases and deaths sharply increased in March and April this year. For example, the patterns in the U.S. and Mexico were similar (Figs. 3a and 3b). In the U.S., the pandemic started in the third week of January with 7 confirmed cases in that month. On 29 February, number of accumulated cases was 62. By 15 and 31 March, the accumulated numbers crossed 1,714 and 140,640 respectively. By 15 and 30 April, the numbers crossed 578,268 and 1,003,974 respectively. Until 12 May the total number of confirmed COVID-19 cases in the country was 1,298,287 (Fig. 3a) (From<https://

Address for correspondence:
Department of Human Ecology,
Centro de Investigación y de Estudios Avanzados del IPN (Cinvestav),
Km 6, Antigua Carretera a Progreso.
Merida, Yucatan, Mexico. Postal Code: 97310
E-mail: dattabanik@cinvestav.mx

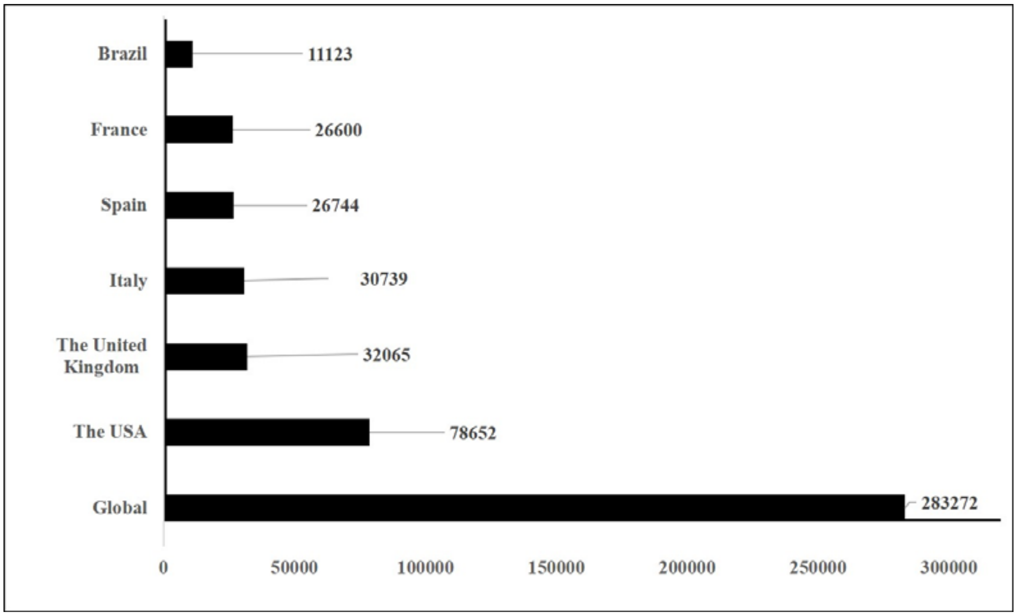

Fig.1. Number of death toll due to COVID-19 (global and the countries with more than 10,000 cases)
Source: https://covid19.who.int/ (Retrieved on 12 May 2020)

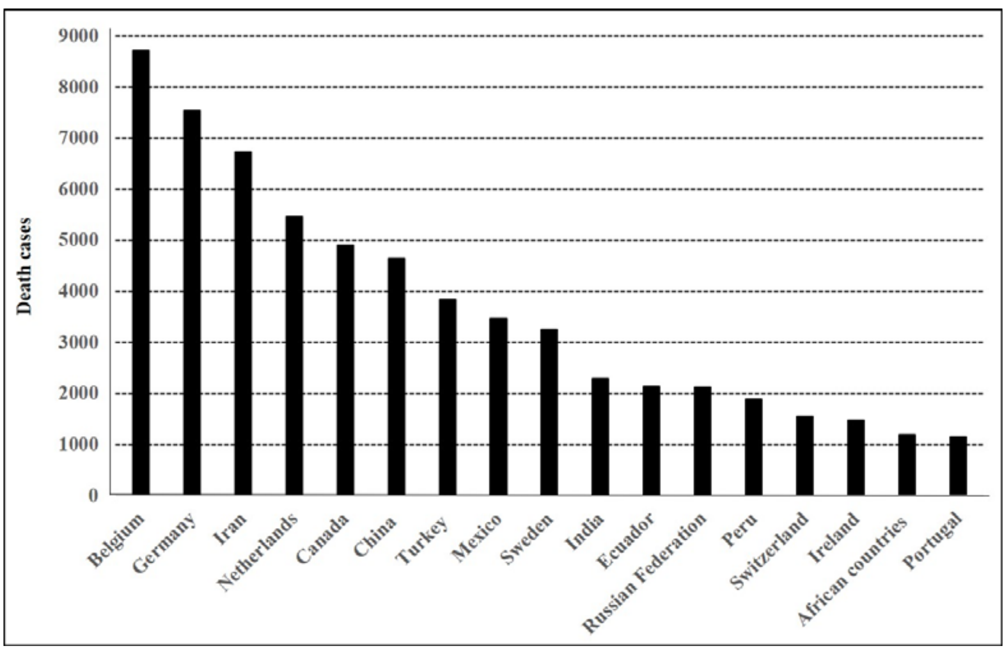

Fig. 2. COVID-19 death toll in the countries with between 1,000 and less than 10,000 cases
Source: https://covid19.who.int/ (Retrieved on 12 May 2020)

covid19.who.int/region/amro/country/us> Retrieved on 12 May 2020). Information on the differences in the prevalence of COVID-19 cases by age, sex, and ethnicity are not available in details from the countries. According to CDC (From <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html> Retrieved on 12 May 2020), COVID-19 infected cases by ethnicity in the U.S. showed that Native Hawaiians and Pacific Islanders were least affected (0.3%); then in the order of higher prevalence recorded among American Indians (1.1%), Asians (4.9%), miscellaneous groups (13.8%), Black African Americans (27.5%), and Whites (52.4%). In the U.S. population, almost 76.5% people are the White Americans, 13.4 percent Black Americans, 5.9 percent Asians, 1.3 percent Native Americans, 0.2 percent Pacific islanders, and others include 2.7 percent (From the United States Census Bureau page <https://www.census.gov/quickfacts/fact/table/US/PST045218> Retrieved on 12 May 2020).

Epidemiological data of COVID-19 in Mexico indicate that up to 12th May 2020, a total number of 44,995 confirmed cases have been reported, and 4,778 deaths. Of the total confirmed cases, 58.39 percent correspond to men and 41.61% to women (From the official website of the Federal Government of Mexico <https://coronavirus. gob.mx/datos/> Retrieved on 12 May 2020). In Mexico, first confirmed case of COVID-19 infection was diagnosed on 8th January 2020. There was a steep rise from 13 accumulated cases on 29th February to 2,495 cases on 31st March and 27,668 on 30th April (Fig. 3b).

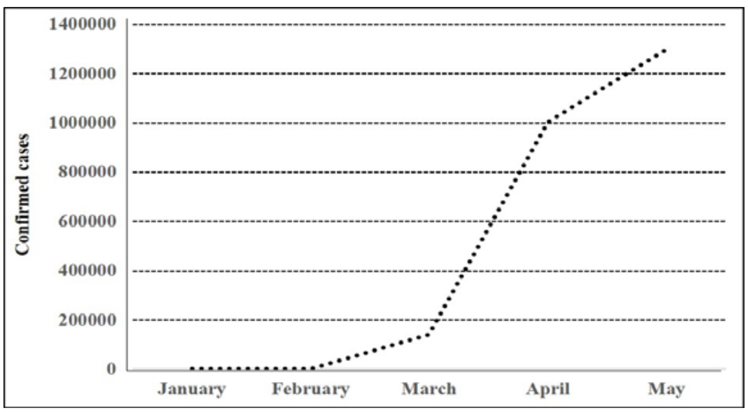

Fig. 3a. Outbreak of COVID-19 in the U.S.
Source: https://covid19.who.int/region/amro/country/us (Retrieved on 12 May 2020)

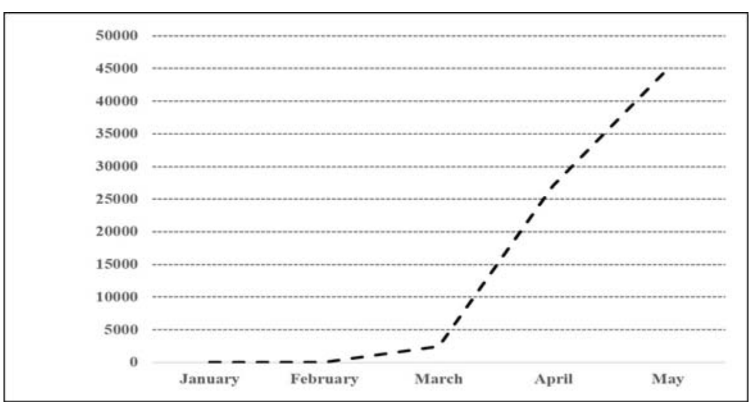

Fig. 3b. Outbreak of COVID-19 in Mexico
Source: https://coronavirus.gob.mx/datos/ (Retrieved on 12 May 2020)

Objectives

In this background, the objectives of the present study were:

1) To observe sexual dimorphism in the susceptibility to SARS-CoV-2 infection.
2) To explain the phenomenon of sex difference of SARS-CoV-2 infection in the light of epidemiology, molecular biology, and evolution.

METHODOLOGY

The adopted methodology was to review the information of COVID-19 available in different official websites, recently published articles on COVID-19 and other publications related to evolution of sexual dimorphism among humans. This essay addresses in general, a perspective of human sexual dimorphism in immune response, taking the current COVID-19 epidemic as its starting point, based on some available reports and reviews (Ghosh and Klein 2017; Jaillon et al. 2019; Klein and Flanagan 2016; Libert et al. 2010).

OBSERVATIONS AND DISCUSSION

Gender Bias in Covid-19

Are Men More Susceptible to Getting or Dying from COVID-19?

High prevalence of COVID-19 positive cases among males is not an isolated case since epidemiological data from other diseases have shown that males are more susceptible to infections by various pathogens. Reports from 50 countries (From <http://globalhealth5050.org/covid19/> Retrieved on 12 May 2020) have also shown higher prevalence of COVID-19 confirmed cases among male patients. A pattern of sex difference in the prevalence is shown in Figure 4. Higher prevalence of COVID-19 confirmed cases in male patients (>50%) was reported from 22 countries.

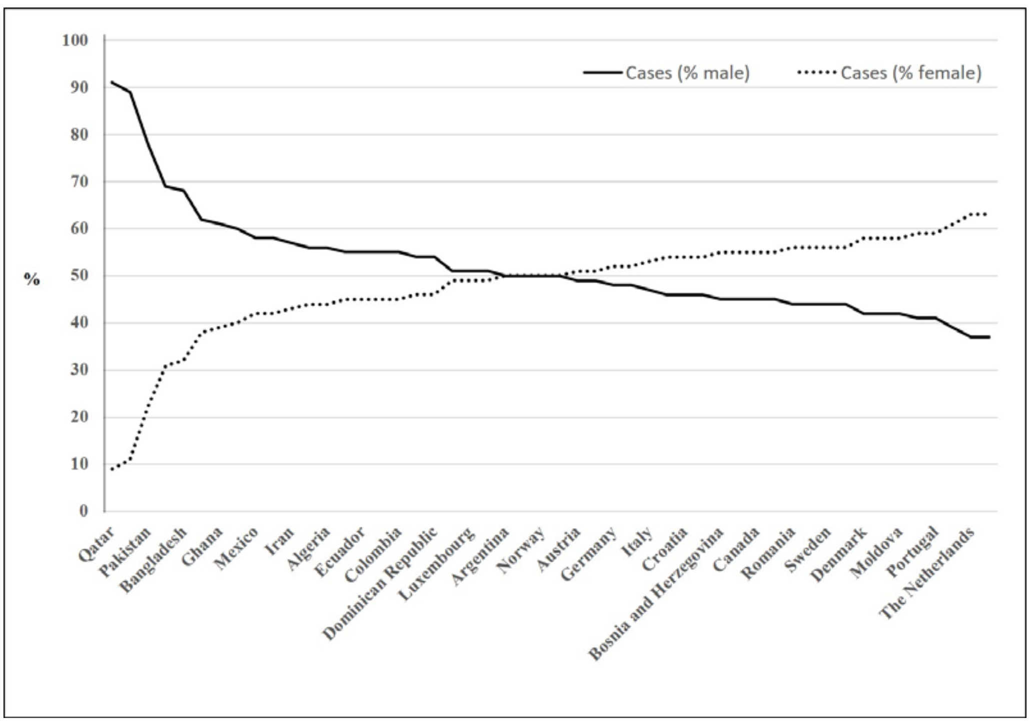

Fig. 4. Sex difference of COVID-19 confirmed cases in some countries
Source: http://globalhealth5050.org/covid19/ (Retrieved on 12 May 2020)

Mean value of prevalence in men (61%) was higher than in women (39%). Equal prevalence (50%) in male and female individuals was reported from Argentina, Australia, Norway, and Iceland. Higher rates of confirmed COVID-19 cases in female patients (>50%) compared to males (<50%) were recorded in 24 countries (mean values among females 56% and males 44%). Similar reports of greater number of COVID-19 cases in men than women are available from other countries including Iran (Nikpouraghdam et al. 2020) and China (Chen et al. 2020).

Global data from 36 countries (From <http://globalhealth5050.org/covid19/> Retrieved on 12 May 2020) reveal that male-to-female ratio of death in COVID-19 is ranging from lowest 1.0 (Pakistan, Canada, Iran) to highest 3.2 (Greece) and other countries in between (for example, 1.8 in Italy, Spain, and Belgium). The values from 1.4 to 1.7 have been recorded in many countries including Germany, South Africa, Argentina, Peru, Mexico, China, and Ecuador. Reports on deaths due to COVID-19 from Spain (Total: 26,621, males 57%, updated on 10.5.2020) (From< https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_ 101_COVID-19.pdf> Retrieved on 12 May 2020), and Italy (Total: 27,995, males 61%, last update on 7th May 2020) (From< https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_7_maggio.pdf,> Retrieved on 8 May 2020), showed higher numbers in males compared to females. A systematic review and meta-analysis of 13 articles published in 2020 from China (total 3,027 patients) also reported similar trends of higher prevalence of death among men (Zheng et al. 2020). People with some chronic diseases like diabetes, cardiovascular and respiratory disorders and of advanced age were more vulnerable than young individuals in this pandemic (Jayawardena et al. 2020; Yang et al. 2020). Smoking was reported to be significantly associated with severity of the disease (Garufi et al. 2020; Zheng et al. 2020).

Sex Differences in the Susceptibility to Infections

The pandemic caused by the etiological agent SARS-CoV-2 is an RNA (ribonucleic acid) virus. According to the official data, it has been observed that males present higher number of positive cases compared to the cases reported among females. Recent studies reported male-to-female ratio 1.93:1 (Nikpouraghdam et al. 2020). Previous reports indicate that males are more susceptible to different infections by pathogens such as virus, compared to females, which has been studied in other mammals, birds, and reptiles. A study reported male mice were more susceptible to SARS-CoV infection compared to age matched females (Channappanavar et al. 2017). Females showed stronger immune response than males. Studies reported that intensity and prevalence of viral infections were higher in men, however, disease outcome might be worse in women (Klein 2012). Behavioral factors are also responsible for the exposure to virus. For example, women are at greater risk of HIV and gonorrhea infections from sexual intercourse with an infected partner than men. Therefore, social and cultural contexts are also intimately associated with epidemiological issues.

But what is known until now? Epidemiological studies have shown that there is a greater susceptibility and mortality to viral diseases among males, from infancy to adulthood compared to females. Evidence so far shows that females develop a much stronger innate and adaptive immune response than males. In general, females have been shown to be less susceptible to infections caused by some bacteria, viruses, parasites, and fungi such as *Staphylococcus* spp., *Mycobacterium tuberculosis*, parainfluenza virus, hepatitis B, *Entamoeba histolytica*, and *Aspergillus fumigatus*. In case of virus, a wide variety of studies have been reported, such as HIV, vesicular stomatitis virus (VSV), hantavirus, influenza virus (H1N1), and hepatitis C virus, among others. Diseases caused by these pathogens have become highly relevant due to their importance in public health.

Due to its importance in the field of health, studies in immunology, cell biology and genetics have been developed in order to understand the causes and mechanisms underlying the differential effects of viral infections in male and female. The main differences of disease susceptibility between genders are due to genetic factors caused by the sex chromosomes, epigenetic factors, sex hormones (estrogens, progesterone, and androgens), extragonadal factors and the reduction of genetic dose due to the inactivation of X and Y chromosomes (Libert et al. 2010).

According to what has been reported so far, sex chromosomes have important roles in the immune response, since several genes related to the immune response are associated with the X chromosome (Klein and Flanagan 2016). In addition, several genetic factors, linked to the X chromosome have been found to be responsible for the hyper-response of immune system in female. However, despite presenting advantages in the response to pathogens, women have disadvantages due to the high prevalence in autoimmune diseases compared to men, in addition to being more likely to develop some types of cancer in children and adults. Gender bias regarding genetic polymorphisms in relation to the autoimmune diseases are also reported. Sex-related genetic and immunological differences contribute to systemic lupus erythematosus (SLE), a well-known chronic inflammatory autoimmune disease (Weckerle and Niewold 2011).

Differential actions of sex steroids in men and women influencing the functions of immune cells are also known. Sexual dimorphism in the immune response occurs from embryonic development and is maintained throughout the life of an individual due to the actions caused by the presence of gonadal hormones such as estrogen and testosterone. Studies under controlled conditions demonstrate that the levels of these hormones differentially alter the expression of genes involved in the innate and adaptive immune response. However, the studies are complicated by the impacts of non-biological factors such as social behavior, habitat, and diet.

Sexual dimorphism in the adaptive immune response has been reported (Jaillon et al. 2019). The innate immune response is the first line of defense response against infections of any virus and Pattern Recognition Receptors (PRRs) that are expressed by cells of the innate immune system show sex difference. Some toll-like receptors (TLR), such as TLR3, TLR7, TLR8 can recognize viral components like dsRNA, ssRNA. The PRRs are of great interest; among them TLR signaling pathways leading to type I interferon (IFN) secretion stand out, where it has been observed that females present around 10 times higher expression of TLR than males. Higher expression of TLR 7 (which mainly recognizes RNA fragments) has been observed in females, in contrast TLR 4 (which recognizes bacterial lipopolysaccharide or LPS) expression is higher in males (Libert et al. 2010). Higher expression of antiviral and pro-inflammatory genes and increased cytotoxic activity of T cells have been observed in females. In humans, particularly lower number of CD4+ cells (cluster of differentiation 4) and lower ratio of CD4+: CD8+ have been observed in males compared to females. Based on the situation we are currently experiencing due to the COVID-19 pandemic and due to the higher prevalence among males, epidemiological data may open a field for the study of immunological differences at the genetic, cellular, and biochemical levels, expressed in both sexes in order to have a better understanding of the immune response to the pathogen SARS-CoV-2.

Sexual Dimorphism: A Product of Evolution

Sexual dimorphism is a product of organic evolution and natural selection. There are ontogenetic factors that cause morphological differences between sexes. The variability of these ontogenetic processes leads to the existence of sexual dimorphism associated with size as an evolutionary response to various factors that include territoriality, competition and the distribution of resources (Smith 1999). Patterns of change in size and shape in humans in terms of body proportion and body composition during gestation to birth and to adulthood, large and complex brain can be explained by evolution and the interactions between genetic and environmental factors (Frayer and Wolpoff 1985). Different scientists had proposed hypotheses explaining sex differences in size and shape (for example, height and body fatness demonstrated by the somatotypes). Intra- and inter-sexual differences are evident through reproductive success (Berns 2013). Sexual dimorphism in humans therefore, ranges from molecular to morphological levels that are socially and culturally defined. Sexual selection, preference of healthy and attractive mates influences female fecundity. Differences in primary and secondary sexual characteristics, size, shape, complexion, behavior, socioeconomic and cultural factors influence sexual selection and enhance competition between peers of same and opposite sex.

Reduction of sexual dimorphism through evolution is evident from differential anatomical dimensions of the fossil remains of our male and female ancestors. Plethora of reports are available on sex differences in size, robustness, roughness, muscular insertions of bones in skeleton, paleo diet, infections, and diseases (Turbón 2006). Fossil remains of Australopithecines (between 4 and 1 million years ago) evidenced sex differences in size and body weight. Males were taller and heavier (approximately 140 cm and 40 kg respectively) in comparison with female peers (115 cm and 30 kg respectively) (Arsuaga et al. 2000; Reno et al. 2003; Turbón 2006). However, species level differences were reported from different regions. From genus Homo onward (*Homo habilis*, *Homo erectus* and others: 2 to 0.2 million years ago), sex difference of size (between 10 and 20% across populations) was becoming like our recent species (*Homo sapiens sapiens*) that varies with genetic, socioeconomic backgrounds and differential nutritional status in men and women. Further reduction of sexual dimorphism (6.3%) had been observed in advanced species like *Homo neanderthalensis* (300,000 to 28,000 years ago approximately). *Homo sapiens* appeared (150,000 years ago approximately) with much reduced sexual dimorphism in size (average height of males 170 cm, females 160 cm) that was nearly 5.9 percent (Larsen 2003). Reduction of sexual dimorphism in size and shape; lower height and higher body fatness in women are the products of human evolution that can be interpreted as "adaptive canalization" where larger sized sex has less plasticity and fitness compared to smaller sized sex (Berns 2013; Fairbairn 2005). Smaller size of females with broad pelvis, wide birth canal and higher adiposity in gluteofemoral region help in the protection of fetus and delivery of offspring. Therefore, sexual dimorphism resulted through evolution is favorable for the females with higher plasticity than males.

In this background, sexual dimorphism in the susceptibility to infections can be studied in human ecological perspective, as a problem of human biology (molecular to morphological levels) and behavior that appears in the species *Homo sapiens sapiens*. Differential social, economic and behavioral factors are also important that might be studied in both biological and social anthropological perspectives. In general, lifestyle habits of men like higher smoking, alcohol consumption and other behavioral aspects compared to women vary in different societies.

Sex-ratio (often used as female to male ratio or FMR) is an important demographic index that exhibits differential status of men and women in a society and interprets social and cultural issues from anthropological point of view (Agnihotri 2000). Sex-ratio at birth involves differential neonatal death that has biological as well as social factors like sex selective abortion and female neonaticide. Studies reported that sex-ratio among infants below two years of age and in preschool children are the indicators of several social, economic and cultural issues including girl-child mortality (low FMR) (Agnihotri 2000). Girl children show earlier puberty and maturity in physical growth and development than male peers. Sex-ratio of working population also indicates differential participation of men and women in the occupation. Sex-ratio among people over 65 years of age indicates higher number of women than men. Female life expectancy is higher than male (WHO 2020b). Therefore, sex-ratio, morbidity and mortality in infectious diseases across the world can show a clear picture of sexual dimorphism (WHO 2019).

CONCLUSION

Epidemiology of any disease, sexual dimorphism of pathogenesis, intensity and prevalence of viral infections can be studied in human ecological perspectives, in the light of organic evolution. The COVID-19 pandemic is not an exception. Associated biological, social-cultural, demographic, and economic factors are important to consider for an integrated research. Scientists from different disciplines will join hands together to fight against the infection. Comorbidities like cardiovascular and respiratory disorders, obesity and diabetes are the serious risk factors for COVID-19 that are related to age, sex, ethnicity, genetic backgrounds, lifestyle habits, other psychosocial and economic aspects in different populations. In this outbreak of a novel coronavirus disease (COVID-19), immediate nutrition intervention programs at community levels are required to enhance immunity. Macro and micronutrient supplementation, proper care for health and hygiene, particularly for the underprivileged communities across the world are important.

ACKNOWLEDGEMENTS

The author thankfully acknowledges the useful discussion with Mr. Román Espinal Palomino

(Ecologist), Mr. Jorge Gabriel Barceló Lugo (Bioarchaeologist), review and insightful comments of Dr. Sujay Chattopadhyay (A scientist in the research area of bacterial comparative genomics and molecular evolution) and Mr. Rudradeep Datta Banik (a student of medicine and surgery) that substantially helped to develop the manuscript.

REFERENCES

Agnihotri SB 2000. *Sex-Ratio Patterns in Eastern Indian Population – A Fresh Exploration*. New Delhi: Sage Pub.

Arsuaga JL, Carretero J, Lorenzo CG, Martínez I, Bermudez de Castro J, Carnonell E 1997. Size variation in Middle Pleistocene Humans. *Science,* 227(5329): 1086-1088.

Berns CM 2013. The Evolution of Sexual Dimorphism: Understanding Mechanisms of Sexual Shape Differences. Intech Open Science Open Minds, Chapter 1. From <http://dx.doi.org/10.5772/55154> (Retrieved on 1 May 2020).

Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S 2017. Sex-based differences in susceptibility to SARS-CoV infection. *J Immunol*, 198(10): 4046-4053.

Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al. 2020. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. *Lancet,* 395: 507-513.

Fairbairn DJ 2005. Allometry for sexual size dimorphism: Testing two hypotheses for Rensch's rule in the water strider *Aquarius remigis*. *Am Nat*, 166(4): S69-S84.

Frayer D, Wolpoff M 1985. Sexual dimorphism. *Ann Rev Anthropol,* 14: 429-473.

Garufi G, Carbognin L, Orlandi A, Tortora G, Bria E 2020. Smoking Habit and Hospitalization for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)-Related Pneumonia: The Unsolved Paradox Behind the Evidence. Eur J Intern Med. doi: https://doi.org/10.1016/j.ejim.2020.04.042 (Journal Pre-proof) (Retrieved on 1 May 2020).

Ghosh S, Klein RS 2017. Sex drives dimorphic immune responses to viral infections. *J Immunol*, 198(5): 1782-1790.

Rothan HA, Byrareddy SN 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun*. https://doi.org/10.1016/j.jaut.2020.102433 (In Press).

Jaillon S, Berthenet K, Garlanda C 2019. Sexual dimorphism in innate immunity. *Clin Rev Allergy Immunol*, 56: 308-321.

Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P 2020. Enhancing Immunity in Viral Infections, with Special Emphasis on COVID-19: A Review. Diabetes Metab Syndr. From <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7161532/pdf/main.pdf> (Retrieved on 1 May 2020).

Klein SL 2012. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. *BioEssays*, 34(12): 1050-1059.

Klein SL, Flanagan KL 2016. Sex differences in immune responses. *Nat Rev Immunol*, 16: 626-638.

Larsen CS 2003. Equality for the Sexes in Human Evolution? Early Hominid Sexual Dimorphism and Implications for Mating Systems and Social Behavior. PNAS, 100(16): 9103-9104. From <http://www.pnas. org/content/100/16/9103> (Retrieved on 1 May 2020).

Libert C, Dejager L, Pinheiro I 2010. The X chromosome in immune functions: When a chromosome makes the difference. *Nat Rev Immunol*, 10: 594-604.

Nikpouraghdam M, Farahani AJ, Alishiri GH, Heydari S, Ebrahimnia M, Samadinia H et al. 2020. Epidemiological characteristics of Coronavirus Disease 2019 (COVID-19) patients in Iran: A single center study. *J Clin Virol*. doi: https://doi.org/10.1016/j.jcv.2020.104378

Reno Pl, Meindi RS, McCollum MA, Lovejoy O 2003. Sexual Dimorphism in *Australopithecus afarensis* was Similar to that of Modern Humans. PNAS, 100(16): 9404–9409. From <http://www.pnas.org/content/100/16/9404.full?sid=3a8d5b3a-bfd4-435a-a645-6a79150b24fc> (Retrieved on 1 May 2020).

Smith RJ 1999. Statistics of sexual size dimorphism. *J Hum Evol,* 36: 423–459.

Turbón D 2006. *La evolución humana.* Barcelona: Ariel Ciencia.

Weckerle CE, Niewold TB 2011. The unexplained female predominance of systemic lupus erythematosus: Clues from genetic and cytokine studies. *Clin Rev Allergy Immunol,* 40(1): 42-49.

WHO 2019. Life Expectancy and Causes of Death. World Heath Statistics 2019: Monitoring Health for the SDGs. World Health Organization, Geneva. From <https://www.who.int/gho/publications/world_ health_statistics/2019/EN_WHS_ 2019_ Main. pdf?ua=1> (Retrieved on 1 May 2020).

WHO 2020a. COVID-19: Situation Update for the WHO African Region. External Situation Report 10. WHO Regional Office for Africa. From <https://apps.who.int/iris/bitstream/handle/10665/331989/SITREP_COVID-19_WHOAFRO_20200506-eng.pdf.> (Retrieved on 12 May 2020).

WHO 2020b. Female Life Expectancy. Global Health Observatory. World Health Organization, Geneva. From <https://www.who.int/gho/women_and_health/mortality/situation_trends_life_expectancy/en/.> (Retrieved on 1 May 2020).

Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q et al. 2020. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. *Int J Infect Dis*, 94: 91-95.

Zheng Z, Peng F, Xu B, Zjao J, Liu H et al. 2020. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. *J Infection.* doi: https://doi.org/10.1016/j.jinf.2020.04.021.

Paper received for publication in May, 2020
Paper accepted for publication in May, 2020