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CASE REPORT

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Biological sex and Covid-19: Science *versus* ideology

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ABSTRACT

In humans, the Covid-19 disease is caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). The virus spread in December 2019 in Wuhan/China, and via unrestricted travel, quickly reached other continents. On 12th March 2020, the WHO classed Covid-19 as a global pandemic. In many cases, Covid-19 symptoms begin as a respiratory infection. If not defended against, the virus spreads from the lungs to attack other vital organs, including the brain. Covid-19 causes a serious infection in mostly elderly people (over 65 years old), and displays a sex difference upon victims, with older men over twice as likely to die compared to same-age women. Here, we provide an evolutionary explanation and contextualize this biological phenomenon against the cultural backdrop of the "gender wars". We focus on the triadic relation between the brain, immunity, and hormones in men vs. women, with reference to the Autism Spectrum Disorder (ADS)-relationship.

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Introduction

In mammals, males and females have evolved different functions during sexual reproduction. Males contribute sperm for the fertilization of eggs, whereas females – the choosier sex – provide eggs, become pregnant, and give birth to offspring that represents the next generation. Immunity systems affect mate choice, and male versus female immune systems react differently to pathogens. The development of this sexual differentiation starts during fetal development when the unborn infant's brain is shaped by sex-specific steroid hormones [1]. After birth, the central nervous system (brain and spinal column) and the endocrine (hormones) and immune systems continue operating interdependently throughout our lives. Importantly, these three "organ level-systems" are mechanistically distinct in males and females, leading to sex-differentiated behavior and disease outcomes [2].

To develop a cure against the Covid-19-disease, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [3] (Figure 1), the genetics that underpin the triadic relationship between brain, immunity and hormones in men vs. women needs researching. However, despite the obvious necessity, this type of biomedical investigation is just not being done. Unfortunately, for the majority of the world's population, a minute, elite network of misguided and highly vocal left-wing liberals grandstand in the Global North, claiming that biomedical sex differences research is bigoted and divisive. This unsubstantiated criticism has resulted in urgently needed science being routinely under-funded and neglected. As a result, researchers turn a blind eye when they discover sex differences.

Women have a stronger immune system compared to men

Scientific endeavor has been aware of the differences in immunity for hundreds of years. When it comes to respiratory tract infections it is well documented that boys and men tend to have poorer outcomes. It is widely accepted that girls and women are expected to survive famine and pandemics better than males. During the 18th century, Swedish famine, baby boys suffered greater mortality rates and today, despite vaccines and modern medical science, male infants remain more vulnerable. The 1918 'H1N1 influenza A virus' infected about a third of the world's population causing a pandemic, known as Spanish Flu. Young males, who were otherwise fit, died at far higher rates compared to same-age women. Between 1918–20, Spanish Flu killed about 20 to 50 million people, the majority of which were young men in their 20s and 30s. At this time, prior to the discovery of penicillin and the use of the contraceptive pill, the world's nations didn't have the aging populations that exist today. Instead, people under the age of 25 represented the largest demographic group and consequently suffered the greatest loss from Spanish Flu.

Sex differences-research was once a routine element of biomedicine. But since the 1970s, biomedical research has been dragged into the culture wars between liberalism and conservatism. Acquired Immune Deficiency Syndrome (AIDS) was identified in the 1980s. Women are more vulnerable to contracting HIV-viruses, which cause this disease, and more likely to develop AIDS. The 1980s were a time of idealism and idolatry of sex equality; accordingly, sex differences in HIV infection rates were not studied. Scientists who publicized their discoveries of differences between the sexes or differences between ethnic

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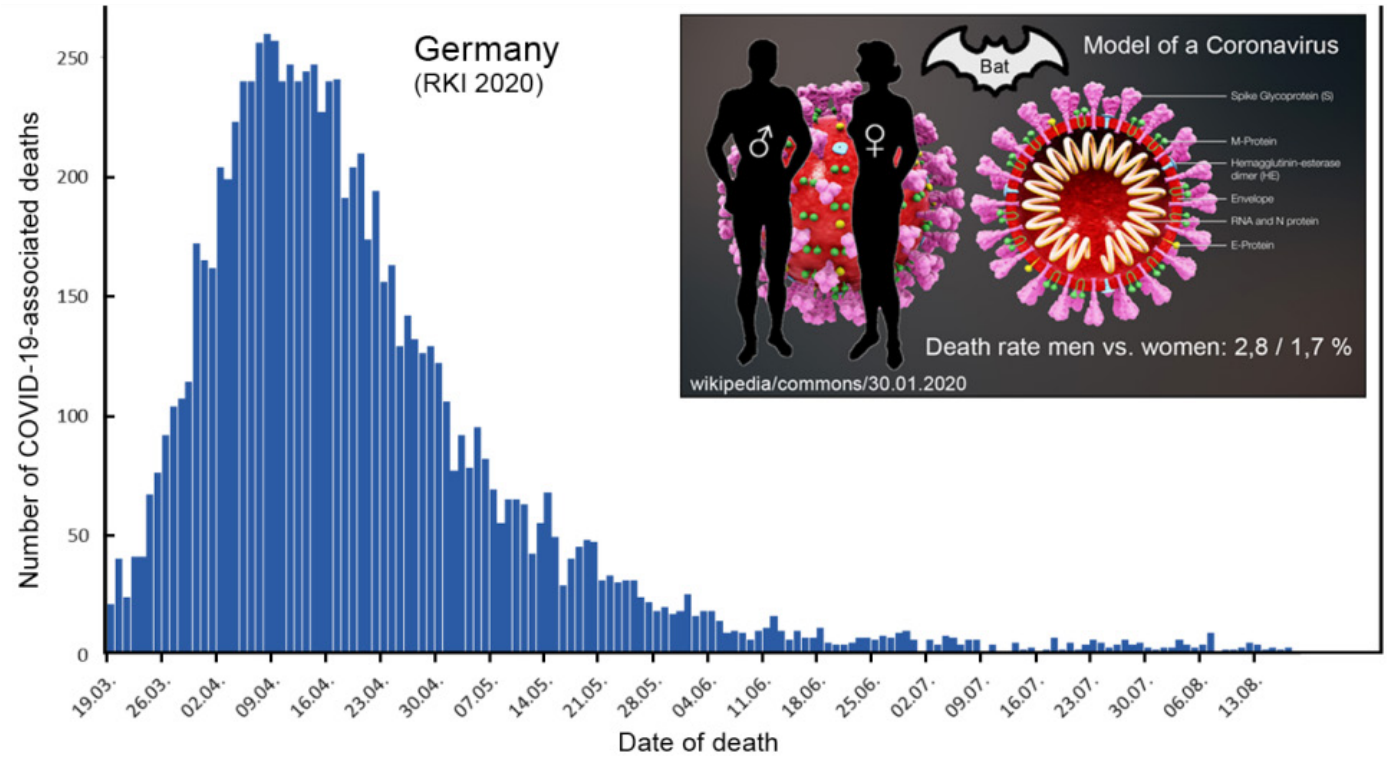

Figure 1: The coronavirus-pandemic in Germany, according to official statistics published by the Robert Koch Institut, Berlin. The inset shows the structure of a coronavirus, a bat (source of the zoonotic transmission to humans), and the gender-specific death rate, as determined in China (April 2020).

groups were accused of sexism and racism. Any science that exposed difference was dropped. A direct consequence is that, today, sex differences research in neurology is largely ignored, and studies on between sex-diversity, as well as the biology of the female protective effect in neurological inflammation, remains consciously under-reported.

The glymphatic system is a sexually dimorphic part of the brain. It works differently in males and females and is the location of our innate immune mechanism. It is a scandalous situation that, despite centuries of observations evidencing male and female neuroimmune systems respond differently to infections, we are no closer to understanding why some people's immune system easily fights off Covid-19 infection, caused by air-borne virus particles. Conversely, other people within the same population, experience a severer inflammatory response causing critical immune failure and death.

If within sex differences-research on male/female dimorphism in neuroimmunity and neuroendocrinology were conducted we could discover why some men exposed to SARS-CoV-2-viruses do not develop Covid-19. Moreover, within sex-neurodiversity research could reveal why Covid-19 kills some women, while for other females the infection is mild or asymptomatic. The spread of the Covid-19-pandemic in Germany started in February 2020, reached a peak of ca. 260 death-cases per day related to this viral infection in March/April, thereafter declined (Figure 1), and increased again (Oct/Nov). This serious disease has affected different groups (sex/age/ethnicity) differently and, because of the dogma of "political correctness", medical science has been woefully unprepared.

For decades, the World Health Organization (WHO) have put "political correctness" before health and declined to gather sex differences-data from their global vaccination campaigns and disease interventions. A direct result of the gaps in research on sex and geographic/ethnic differences to disease susceptibility is that thousands of people have fallen victim to Covid-19. These lives very possibly could have been saved, had sex differences-research not been stymied for the last sixty years.

Gender ideology versus scientific facts

Over the past years, the fatuous idea that men and women are not distinct, evolved versions within the same bio species *Homo sapiens* having different reproductive functions, became very popular within the framework of the so called "gender-movement", which we interpret here as a political ideology. Within the framework of this social-constructivist world view, humans are believed to be a sexually "fluid" species: As a result, the alleged population-level "fluid continuum between the sexes" has been given cultural credence. People with gender dysphoria equal a minority group requiring support and protection. Despite a rise in recent years, cases are exceedingly rare, equating to approximately 0.04% per 100,000 of a population. It is estimated that 0.6 % of North America's adult population experience some form of gender dysphoria [4]. However, a number of prominent women neurologists and journalists have cynically damaged sex and gender research by writing best-selling books that appeal to liberal progressives and fanatical gender war-activists by promoting the falsehood that male and female brains are "the same". Knowingly misleading the public to make a buck is a dangerous and selfish game. At the start of the pandemic, sex-specific vulnerabilities expert Professor Geary emphasized, *"Activists have set back research on sex differences, including biomedical research, by decades"* [5].

Today, activists continue to promote the dogma of a "biological sameness between people", especially in terms of brain function, because they fear studies on differences will invite discrimination and empower the so-called "Alt-right". The cruel irony being that recognizing and protecting 'difference' and neurodiversity is the raison d' être of social equality and parity.

Families have been devastated by the premature deaths of relatives. We have learned the hard way that males and the BAME (Black, Asian & Minority Ethnic) community are more vulnerable to Covid-19 [6]. In Britain and America, the majority of Covid-19 fatalities have been in Black, Asian, Hispanic, Ethnic and First Nation communities [7]. In contrast, people with white body skin (Caucasians) are, on average, more resistant to this viral disease. Spurious cultural and social explanations have been touted. For example, BAME and males have been wrongly blamed for causing their higher mortality rate via the accusation they have failed to wash their hands adequately. False social explanations for biological differences will only cost more lives. There is hope the enlightened *woke* community, who are not intimidated by difference, will champion sex and ethnic neurodiversity and campaign for a long-overdue revival in gender-specific biomedical research.

If we look for comparative evidence from other animals, we can see the female survival advantage in immune response is evident throughout the natural world. In species as diverse as the Sea urchin, the Fruit fly, the garden warbler and the macaque monkey the female exhibits a larger protective effect. Humans inherited this ancient sex-bias via evolutionary processes [8]. Animal studies on respiratory infections tend to replicate the sex difference seen in humans. Severe Acute Respiratory Syndrome – SARS coronavirus (SARS-CoV) was first identified in 2003. SARS belongs to the same family of RNA viruses as Covid-19 and influenza, Ebola, rabies, hepatitis and measles. RNA viruses cause diseases in mammals and birds and commonly inflame the respiratory system.

Research on mice exposed to SARS-CoV showed sex-bias increases with age. Mature male mice were more susceptible to respiratory damage and vulnerable to developing the disease from a lighter viral exposure. They also exhibited a reduced immune response, taking longer than females to repel the disease [8].

Blocking testosterone in male mice had no impact. However, when diseased female mice were subjected to oophorectomy and their ovaries removed, their estrogen levels fell, and mortality increased [9].

The role of sex chromosomes and gender-specific brain architecture

Humans are characterized by a diploid genome (2 x 23 chromosomes), one of each is inherited from the mother and the father, respectively, during sexual reproduction. The so-called "sex chromosomes" (XX in females, XY in males) have been well characterized, but many questions are still open. The central nervous system (CNS) consists of the brain and the spinal cord and sexual dimorphism exists in the CNS. For example, the structural connectome of human male brains supports co-ordination and perception, whereas in contrast, in females it supports intuitive and analytical communication [10].

Sex differences in brain architecture are crucial to immunological responses. The X-sex chromosome is disproportionally loaded with genes used to build the brain and fight infection. Females have two X-sex chromosomes, although one of which is largely inactivated (Barr-body). Because they have, in contrast to men, two X chromosomes (of which one is fully active, whereas the second is to a large extent inactive), typical females have in theory twice the opportunity of recruiting effective genes from either of their X chromosomes to fight disease-causing microorganisms [11]. Women have an advanced immune response memory, enabling them to quickly fight diseases they were exposed to as children, and females commonly develop stronger immunity post vaccinations.

Males have an X and Y chromosome – it is the gender-specific Y that makes males "male". With only one X chromosome, males are singularly dependent on inheriting an effective X chromosome replete with immune defence genes. With half the genetic armoury of women, males are typically twice as vulnerable to infection. The male disadvantage doesn't end there. Testosterone is itself a further obstacle because it inhibits the immune system from recognizing infection and blocks it from fighting inflammation. Moreover, in certain circumstances, testosterone is itself carcinogenic and the cause of cardiovascular disease [12].

Conversely, the female hormone estrogen brings benefits to girls and women by turning the immune system on. Once a pathogenic invasion is identified by estrogen, it promotes an aggressive immune response to infection and inflammation. Estradiol is the most dominant of the four endogenous estrogen hormones. Both males and females need estradiol for healthy bone and brain function. However, estradiol-levels are much higher in females; this hormone is essential for fertility and menstruation.

Estradiol also provides a sex-specific neurobiological effect in women. The hippocampus is a sexually dimorphic part of the brain. When overall brain size is adjusted, it is bigger in females, and is responsible for sex differences in learning, memory and behavior. When post-menopausal women take hormone replacement therapy (HRT), within three months they experience a gray-matter increase in their hippocampus. This is evidence of sex differences in neuroplasticity, improved working memory and executive function for the older female [13]. Sex differences in brain disease and dementia are substantial and another seriously under-funded area of research, despite the globally growing population in older adults.

It is very probable that steroid hormone therapies are implicated in poor Covid-19 outcomes. Post-menopausal women's immunity is not bolstered by estrogens, and we know that older women are more vulnerable to Covid-19. It is therefore possible that estradiol-rich HRT could help women with early menopause and older women to better survive the pandemic. As age increases, the risk to Covid-19 for men rises substantially. Some older males take testosterone hormone replacement to raise their libido. Transgender males must take

testosterone therapy life-long to help sustain their artificial gender transition [4]. These groups are examples of people who should be warned: there is a risk artificial sex steroid hormone treatment could decrease their chances of survival during a Covid-19-epidemic.

Multisystem inflammatory syndrome: boys vs. girls

So far, infants, juveniles and adolescents have been the groups least affected by Covid-19. However, small populations of children have contracted Multisystem Inflammatory Syndrome (MIS-C). Symptoms typically include abdominal pain, fever and a rash. MIS-C appears symptomatic of previous (and possibly non-symptomatic) Covid-19 infection and caused by a delay in immune response. Studies have shown that boys are more vulnerable to MIS-C, making up well-over 60 % of infected children [14].

The X chromosome carries lots of genes known as 'Toll-like receptors' (TLR) and because TLR drive the T cell (or T lymphocyte) response, they are integral to our immunity. Studies on four boys who became very unwell with Covid-19, so much so that one of them died has revealed that the gene TLR7 is a key player in fighting the virus. TLR7 recognizes single-stranded RNA viruses – like those causing Covid-19 – and once activated, TLR7 triggers the production of signaling proteins known as interferon's. These proteins are essential in defending against viral infections, including Covid-19. The virus, which recombines during multiplication in eukaryotic host cells, is not mutating at a fast rate to improve its "survival". However, it does put up a fight and Covid-19 attacks the crucial cells producing interferon's.

With only one X chromosome in their genome, the four boys were reliant on the TLR7 genes to protect them. Tragically, their TLR7 gene was deleterious and didn't recognize the Covid-19 invasion quickly enough so that their immune system was unable to produce sufficient interferon. In the fight against Covid-19, administering interferon therapeutically is now being trialed.

Neuro-inflammation influences the progression of diseases and syndromes. In airborne viral infections, such as Covid-19, the noses' olfactory immune system must protect the brain and central nervous system from encephalitis or meningitis. Females have an advanced olfactory system and superior sensitivity to smell. Sensory neurons extend from the nasal passage to the brain. They differ from most other types of central nervous system neurons because they can regenerate, once an infection is cleared. A noted symptom of Covid-19 is, in addition to its well-known respiratory infection and possibly negative impact on the brain, the loss of taste and smell (anosmia). This indicates that in some people Covid-19 attacks the central nervous system, destroying olfactory sensory neurons. Most people who lost their taste and smell after catching Covid-19 got it back a few weeks later after their olfactory immune system had fought the infection and protected the brain from inflammation. A study on Covid-19 chemosensory impairment has found symptoms of loss of taste and smell is significantly more common amongst women compared to men [15].

The public has been told the most common symptoms of COVID-19 are fever, tiredness, and a dry cough. However, it is possible these symptoms may be typical of infected males, and females with male-type brains, because it is these people who have most needed medical intervention bringing their symptoms to the attention of clinicians.

Autism spectrum disorder, the male brain and Covid-19

The *American Psychiatric Association* characterized "Autism Spectrum Conditions" (ASC) as a "developmental disorder" that causes in patients the following symptoms: difficulties with interactions in groups, repetitive behaviors, and other behavioral problems related to the person's capability to integrate in school classes etc. Male and female ASC have different brain architecture to neurotypicals. People suffering from ASC display features associated with abnormal T cell and microglia cell activation [16-18]. Microglia are central nervous system shape-shifting immune cells; they are quick to converge at injury or infection. In the fight against Covid-19, we rely on the impact our microglia bring. As well providing immunity, microglia brings about brain and spinal cord maintenance. Males, and females with ASC, have greater numbers of microglia in the cerebellum and cerebral cortex than neurotypicals. Microglia also cause sex difference outcomes to the developing foetus.

Microglia are essential to early brain development, and masculinization of brain and behavior. In addition, they are implicated in the development of brain areas that control reproductive behavior. Across the lifespan, microglia's neuro-immune function continues to differentiate between males and females. It is very likely that microglia plays a significant role in sexual dimorphism, including in the noted sex differences in psychiatric illnesses [19].

Due to the unique duality of microglia cells in neuro-masculinisation and responding to inflammation they may contribute to the sex difference in vulnerability of males developing neuro-disorders, including autism. Individuals with raised microglia-levels might also have heightened vulnerability to Covid-19. Brain damage has been noted in some patients recovering from Covid-19 with an increase in grey matter in sexually dimorphic brain regions, including the hippocampus and olfactory system [20].

In non-autistic people the male and female brains are sexually dimorphic, whereas in ASC-patients, both males and females have brains shaped with pronounced male-specific architecture. Women with ASC have brains that look similar to typical male brains and men with ASC have brains shaped like extreme male brains. ASC males and females are prone to exhibit atypical immune responses. They tend to experience syndrome or disease comorbidity, have an elevated likelihood of autoimmune disorders, and a heightened propensity to contract illnesses. Mothers of children with autism have been found to carry higher than average deleterious genes [21], and mothers of children with neurological disorders carry higher mutational levels than fathers [22].

Neurodiverse people are experiencing the pandemic differently. Women with ASC typically have impaired immunity while carrying disproportionately high genetic mutations. It is highly probable ASC females will be more susceptible to a poor Covid-19 outcome than ASC males.

Copy number variation (CNV) is the term given to a phenomenon where genes or whole stretches of the genome are copied and repeated. Instead of a normal individual having two copies of a gene, these humans may have three, or four or many more. CNV is implicated in elevated disease risk. Mothers of ASC offspring have higher CNV than fathers, and people with autism have increased CNV; over 70 % of them are inherited from their mothers [23].

In COVID-19 physiopathology, one of the main inflammation mechanisms is the "cytokine storm". In this pro-inflammatory condition, there tends also to be a reduction in lymphocyte B and T cells response, and an individual's immune system overproduces cytokines causing damage to the cardiac and pulmonary systems.

People with ASD have abnormal cytokine levels in their body fluids. Levels of pro-inflammatory and T cell driven cytokines are elevated in ASC cerebrospinal fluid and plasma [24]. The genetics of ASD causes immune deregulation, such as the increase of inflammatory cytokines. It is highly probable that ASC could be as much of a risk-factor for a poor Covid-19 outcome as the commonly cited comorbidities of diabetes, hypertension, cardiovascular and coronary diseases, and obesity. ASC runs in families, and mothers and sisters of males and females with ASC are very likely to have impaired immune systems. Furthermore, women on the spectrum are likely to be especially vulnerable because they carry greater mutation loads [22]. Worryingly, a high percentage of ASC females are under-diagnosed, and therefore these people are likely to be unaware of the risk they are facing.

A greater focus on the female and male brain and the extreme male brain theory of autism [25] will help medical science identify and protect those with ASC while also protecting the public at large from Covid-19. Women who are behaviorally atypical, particularly in traditional female sex/gender roles surrounding dating, parenting and family life, may carry a greater burden of deleterious genes [26]. High numbers of people with autism report gender dysphoria, and ASC people are disproportionately represented amongst the Trans community [27]. ASC individuals, with impaired immunity undertaking gender re-assignment and hormone therapy are at increased risk to Covid-19, especially as they age.

Conclusions

The SARS-CoV-2-virus spread in December 2019 in Wuhan/China, and soon reached other countries via unrestricted travel of millions of people. Therefore, on March 12, 2020, the WHO classified Covid-19 a global pandemic, which achieved its peak in April/May, and thereafter declined; and increased again in October/November (Seasonality, see ref [3]). Around one in every five elderly people who are infected with Covid-19 develops difficulty in breathing and require hospital care. Lives could be saved if only science could effectively identify and protect the "1 in 5". Sociologists and liberal activists have been forced to face the sex difference in immunity to Covid-19. The hard-wired biological sex differences in cognition between girls and boys (or men and women) that leads to gender-specific disease outcomes represents the torched epicenter of the culture war. Gender- and Trans-activists have been especially hostile towards the female/male brain theory of autism [25]. Now, in a strange twist of fate, to survive in the "Covid-19 world", they may become dependent on the very area of science that has, until now, so offended their political sensibilities.

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