

## ***‘Epidemiology is the Science of Sex and Age Breakdown’***

***Medicine, pharmacology, and molecular research should glue to what is a truism of public health and statistics.***

The confrontation of the ‘pros’ against the ‘const’ around the issue of two sexes or more developed now into a fight of different political positions and started to endanger the health and medical care of women. Because of the confusion around the two items ‘sex and gender,’ a ‘climate of fear and reticence evolved,’ such as ‘scientists have been warned of studying sex differences by colleagues’. Previously, neuroscience, psychology, immunology, and cancer scientists mainly studied men and male animals. Results obtained from male animal studies have often been considered valid for both sexes; however, health risks might significantly differ between women and men (1).

### Health and medical care for women is in danger

A publication in Nature in 2019 (2562) suggested observing sex and gender to improve science (2). As an example of the importance of observing the differences in genetic and hormonal conditions between the two biological sexes, immunotherapy is one example of the imminent necessity to observe the biological difference between males and females. In addition, physiology, neuroendocrine, behavioral, and metabolic systems heavily react differently between the two biological sexes a person is being born as.

### ‘Sex is a social construct’

All this goes back to the concept that ‘the biological age is a social construct (3). Suzanna Kessler and Wendy McKenna (1978) (2521) stated ‘that a world of two “sexes” is a result of the socially shared, taken-for-granted methods which members use to construct reality.’ After the ‘woke’ ideology came up, the different ‘sexes’ turned out to be listed as LGBTQ+. For those who don’t know: the letters stand for ‘lesbian, gay, bisexual, transgender, queer, and several other conditions. When asking what is to be understood about the ‘woke’ ideology, the answer changes depending on who you ask,’ as a commentator on the USA ABC television said. Being woke is to fight against social inequalities such as racial injustice and sexism’ and oppose those who deny LGBT rights (according to Wikipedia).

### Sex determination

Present-day humans evolved from mammals, which got the chance to conquer the world about 66 million years ago when an asteroid about 10 km wide with a speed about 50,000 miles per hour hit the planet, eradicating about three-quarters of the world's species, including the dinosaurs, giving rise to the Age of Mammals (4). Mammals are either females or males. The sex chromosomes of females are XX, whereas those of males are XY. Males and females evolve from one single ‘bipotential’ gonad (5). The Y chromosome initiates the male-specific testes, penis, and ultimately male-specific genetic and hormonal setting. In the absence of a Y

chromosome, under the influence of the XX chromosome, the ovaries and the female appearance develop (6).

### Deviation from the normal

Something that could go wrong during the development of the fetus caused some problems in 1843 (2386) in Salisbury, Connecticut, USA. Before the American Civil War (1860-1865) (2403-2408), one of the parties was the Whigs, who opposed the Democrats. At that time, only men were allowed to vote, but a certain Levi Suydam insisted on his right to support the Whigs, even though he appeared more female than male, to which he strongly objected. A doctor was called to decide about the sex of the twenty-three-year-old Suydam and declared him to be a man because of his penis. The Whigs party won the election at Salisbury with a majority of one vote. After the vote, however, the doctor realized that the physical appearance of Levi was more female than male, in that she regularly menstruated and had a vagina. Whether the election results were turned over is unknown (7). The anecdote is an amusing example of the fact that besides men and women, as a third possibility, 'intersex' must be taken into consideration.

### Intersex

Referring to biological sexes, including male and female, and disorders of sex development (DSD), intersex is expressed as a 'genetic lesion' basically resulting in 'gonadal dysgenesis to ovotestis' and 'genital phenotypes with mild hypospadias or clitoromegaly to ambiguous genitalia' (6). There are several different expressions of genetic lesions. A person might look like a female but somehow has a male-typical anatomy, which is not easily recognized by appearance. Born as a girl, the clitoris might be pretty significant; it might be that the opening of the vagina is missing. A person born as a boy might have a tiny penis, and the scrotum might be divided and formed like labia (8). The prevalence of intersex in the population varies due to the criteria used ranging from 1:100 to 1:4.500 (2), or 1.7% to 0.018% (9).

### Sex chromosomes and diseases

The definition of DSD, including 'congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical,' includes several pathological conditions that are now recognized as 'intersex' by clinicians. Sex chromosome abnormalities, such as the Turner syndrome in females having only one X (X0), or the Klinefelter syndrome, caused by an additional X (XXY) chromosome in boys, or the 46,XY situation in males where each cell has one X and one Y chromosome displaying genitalia not clearly being male or female (10). The latter genital disorder, however, is extremely rare, with 1:10.000 live births. The abnormal hormonal late-onset adrenal hyperplasia is sometimes also included in DSD. A more restricted definition of intersex suggested in 2002 referred to chromosomal sex inconsistent with phenotypic sex (2, 6, 9).

### Gender and cisgender

Gender identity goes far beyond the anatomical and biological characteristics of males and females but 'encompasses social and environmental factors addressed as gender' (1). The

definition, according to Global Health, relates gender ‘to socially constructed norms that impose and determine roles, relationships, and positional power for all people across their lifetime’ (11). Formerly, everybody used ‘sex’ and ‘gender’ alternatively and was aware that each individual was born as either a boy or a girl, which nowadays is termed as ‘cisgender’ being either a ciswomen or a cisman (12). Individuals belonging to the cisgender as well as those belonging to the ‘society,’ differentiated as the LGBTQ+ gender (?), are exposed to the environment, such as lifestyle, nutritional habits, exercise, perceived stress, smoking, and alcohol consumption, and should be considered according to their sex but also to their gender in health, disease, and medicine (13).

### LGBTQ and politics

Especially in Western countries, the LGBTQ+ movement split the general public. It is not the sexual attraction towards the same sex which is a controversial issue. These human expressions have been known since ancient times. ‘Variability between individuals’... attracted to the.. ‘same sex.. could be even more important’ ... for medicine and public health ‘than that between’... opposite.. ‘sexes.’ Also, the habits of borne males to transfer themselves to appear as females (t = transfemales) don’t evoke public resistance unless participating in sportive events reserved for females and using legal means to invade the intimate rooms for females. Sexualization of children, even the very young ones, pedophilia, and repulsive behavior in public are phenomenons that are widely rejected. Both biological sex and the environment are undoubtedly important to be considered in health and diseases. This certainly not only involves ailments directly related to sexual activities, such as syphilis and AIDS but involves psychology and psychiatry when it comes to the uncertainty of children and young people whether they are content with their biological sex (1, 14).

### Universities and DEI

LGBTQ+ is embedded into the woke movement, which in Western universities is disguised as ‘diversity, equity, and inclusion (DEI)’ and of which its activists are the driving forces (15). As mentioned above, scientists are not very fond of examining the differences between males and females in health and disease. Those who are neglected are the females.

### A drug worked in men but not in women

The phenomenon is not restricted to women but to female mammals as long as they are used for laboratory animal experiments (16). In neuroscience, for instance, the relationship of studies with male- and female animals amounted to 5.5 to 1. If both sexes are included in the investigation, the differences between sexes are not analyzed. A recent comment in the science magazine Nature saw neglecting sex and gender in research as a public health risk (12). As a telling example, the drug ‘lecanemab’ was considered to significantly work against ‘cognitive’ decline for Alzheimer patients, unfortunately only for males but not for females (17). The standard treatments are based on studies made with men weighing about 70 kg (12). Also, pharmaceutical studies tend to use male animal models and cell cultures. Likewise, pre-clinical research is based mainly on men. It might be due to these circumstances that between 1997 and 2000, eight of ten medicaments were taken from the market because the health risk was greater for women than for

men (13). It should be self-understood that individually shaped medicine, using an immunological approach for nanomedicine and cancer vaccines, must be based on the biological sex of the patients (18).

#### Morbidity and mortality depend on age and sex

Not only the therapeutical approach but mortality and morbidity significantly depend not only on age but on sex as well. Cardiovascular diseases in middle-aged men are much more frequent compared to women, while females at that time are hit by cancer. The risk of dying earlier is higher for males because of their unhealthier lifestyle (12). In older age, both causes of death are similar. Among the ten leading causes of death in 2017, the USA did show obvious mortality differences. Injuries of 4.4% for females are lower compared to males with almost 8%. Alzheimer's and stroke exceed in females (13).

Even more apparent are sex differences for important, but not necessarily fatal, diseases. Painful and rather irritating diseases are much more frequent in females, such as arthritis, inflammatory gut diseases, migraine, and chronic fatigue syndrome. The same is true for eating disorders and anxiety. Except for type 1 diabetes mellitus, there are nine autoimmune diseases, so, for instance, systemic lupus erythematosus is significantly more common in women compared to men (13).

#### Immunoregulation differs between males and females

Recently, the results of an investigation into the immunoregulation of inflammatory diseases between the sexes were published. Age, circadian rhythms, diet, and BMI were considered, together with sex hormones, microbiota, and tissue-specific immunity. The study concluded that antiviral immunity, antitumoral immunity, and risk of asthma increased in females and decreased in males, and it confirmed the increased risk for autoimmune diseases in females (19).

The neglect to honor sex differences in health and diseases, resulting in the disadvantage for women, is aggravated by the male-dominated funding for research and prevention from the National Institute of Health. Male-dominated diseases and conditions got US\$ 7.3 BN compared to US\$ 5.6 BN for those females-dominated ones (12).

#### Conclusion

The reluctance to insist on the noticeable biological differences between males and females started to endanger women. Awareness of these differences must remain a priority in medical research, medical education, public health, and clinical practice. That doesn't contradict an overall acceptance of gender differences.

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