Sex is a Biological Trait of Medical Significance

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ABSTRACT

In the midst of society's questioning of the gender binary, the American College of Pediatricians (ACPeds) is concerned that the field of medicine risks denying the reality of biological sex. Sex is a dimorphic, innate trait defined in relation to an organism's biological role in reproduction. In humans, primary sex determination occurs at fertilization and is directed by a complement of sex determining genes on the X and Y chromosomes. This genetic signature is present in every nucleated somatic cell and is not altered by drugs or surgical interventions. Sex differences arise from at least four different genetic mechanisms, in addition to the actions of sex hormones and environmental influences. Consideration of these innate differences is critical to the practice of good medicine and to the development of sound public policy for children and adults alike.

Introduction

The National Institutes of Health urges scientists and physicians to include sex as a biological variable in all aspects of healthcare.[1] Although incompletely understood, the reality of sexual dimorphism and its importance to health has been documented for decades.[2] In recent years, however, the medical field has become heavily influenced by society's questioning of the gender binary.[3,4] Increasingly, physicians such as Dr. Deanna Adkins, Associate Professor of Pediatrics at Duke University School of Medicine and Director of Duke Child and Adolescent Gender Care, teach that "It is counter to medical science to use chromosomes, hormones, internal reproductive organs, external genitalia or secondary sex characteristics to override gender identity for purposes of classifying someone as male or female."[5] A corollary to this ideological claim is that no one can know whether individuals are male or female unless the individuals in question make it known. Accordingly, pediatricians have been cautioned against "assigning a sex" to newborns for fear that this could conflict with the infants' self-declared gender identity later in childhood.[6]

These claims belie the physical, biological fact that sex is not a state of mind that one can "identify" into or out of at will. Pediatricians do not "assign" an infant's sex; they announce it based upon the physical reality of the infant's body before them. This growing movement to deny the physical reality of sexual dimorphism requires a dangerous dismissal of both science and medical ethics, one that will cause severe harm to individuals and society at large if embraced.

Sex and gender are not synonyms

Although often used interchangeably, the terms sex and gender are not synonyms. According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), gender is defined as the "lived role" of male or female, resulting from the interaction of cultural and psychological factors with a person's biological constitution.[7] Gender identity is defined similarly as "a category of social identity" that is determined by the interaction of cultural, psychological and biological factors.[7] Incongruent gender

identities may come to align with biological sex across the lifespan; during childhood, adolescence, and adulthood. In other words, gender dysphoria (which prior to 2013 was classified as gender identity disorder) can desist.[8,9,10] Clearly, gender identity, resting largely upon a psychological comfort or discomfort with one's biological sex, is neither innate nor immutable and does not in any way determine biological sex.

Human sex is a dimorphic innate and immutable trait determined at fertilization

Medicine has long defined sex as a biological trait that distinguishes living things as being male or female based on the complement of sex chromosomes, the presence of distinctive reproductive organs and unambiguous genitalia.[2] This definition is not arbitrary. In the life sciences, sex is defined according to whether an organism is structured to donate or receive genetic material during the reproductive process. Organisms that donate genetic material are classified as male; those that receive genetic material are classified as female. Human beings, as do all mammals, reproduce sexually. By definition, such a reproductive system is a binary system. It requires the cooperation of two distinct sets of reproductive organs that give rise to and facilitate the union of two distinct gametes, sperm and ovum, to conceive an offspring. The term male designates members of the species who have reproductive organs structured to produce sperm and to deliver this to female members of the species. The term female designates the members of the species who have reproductive organs structured to produce ova, receive sperm, then gestate and give birth to a conceived offspring. Defining sex according to how an organism is innately structured to participate in the reproduction of the species is a stable and universally applicable definition that allows the consistent differentiation of males from females even when individuals exhibit behaviors that are not culturally typical of males or females.[11]

Primary sex determination in humans occurs at fertilization and is dependent upon the zygote's two sex chromosomes, or more specifically, upon the presence or absence of genetic material normally present on a Y chromosome. Barring genetic disorders, females contain two X chromosomes in every nucleated somatic cell, and males possess an X and a Y chromosome in every nucleated somatic cell.[12,13] Interventions that alter a person's sexual appearance do not alter the person's genetic code. Therefore, sex does not change. Administering sex hormones and other drugs can alter appearance and physiology to varying degrees, but these chemicals do not change biological sex. No amount of medical intervention can "transition" any person from one sex to the other.

Disorders of sex development (DSD) are disorders - not additional sexes

Disorders of sex development (DSD), commonly referred to as intersex conditions, are maladies in which normal sexual differentiation and function are disrupted. Some argue that DSD demonstrate the existence of more than two sexes.[4,14,15] However, DSD do not represent additional reproductive organs, gonads or gametes. Therefore, by definition, DSD do not constitute additional sexes. Human sex is a binary, not a spectrum. In reality, DSD are rare congenital disorders affecting 0.02% of the population in which either genitalia are ambiguous in appearance, or an individual's sexual appearance fails to match what would be expected given the person's sex chromosomes.[16,17] Reflecting the disordered nature of these conditions, all DSD are associated with impaired fertility.[18]

Genetics is the primary driver of sex differences

Genes found on the sex chromosomes underlie the developmental origin of many differences between males and females. Sex hormones, which are ultimately determined by these genes, are the second most impactful factor. Fluctuations of sex hormones exert significant effects during the prenatal period in males, during the reproductive years in females, and during puberty and following midlife in both sexes.[2]

There are at least four genetic mechanisms that contribute to sex differences.[19] The first mechanism involves sex chromosome effects. Genes present on the Y chromosome influence male development and

function in multiple organs within and beyond the reproductive system. Among females, randomized inactivation of half of their X chromosomes exerts a genetic influence males do not experience. For example, randomized X chromosome inactivation protects females against X-linked recessive diseases like Hemophilia A and Duchenne Muscular Dystrophy, which is why these disorders predominantly affect boys and men rather than females.[20] A second mechanism involves sex-dependent genetic liability thresholds. The male predominance of pyloric stenosis in infants (a thickening of the pylorus muscle that prevents the stomach from emptying into the small intestine) falls into this category.[19] Two additional genetic mechanisms underlying sexual dimorphism include gene-by-environment interactions and sex-differential gene expression.[19] Regarding the latter, at least 6500 shared genes have been identified that are expressed differently in males and females.[21]

In 2001, the Institute of Medicine (IOM) concluded that the genetics of sex contributes significantly to males and females having different propensities for diseases, sex-dependent responses to pain, drugs and toxins, sex differentiated cognitive and emotional processes, sex variation in behavior and more. The Institute found that sex differentiated genetics and sex hormones are the two major reasons diseases that affect both sexes often have different frequencies, presentations, and responses to treatments in males and females. Therefore, the Institute posited that different preventative, diagnostic, and treatment approaches might be required to provide optimal outcomes for males and females.[2] The remainder of this position paper will highlight some of the sex differences that have been identified in the fields of neuroscience, pharmacology, cardiovascular health, and sports medicine in the decades since this landmark IOM review was published.

Sex differences in neuroscience

While male and female brains are more similar than they are different, the influence of sex on the brain has been demonstrated "at every level of neuroscience from the behaving human to the ion channel."[22] At least a decade of neuroscience research has found varying degrees of sexual dimorphism in the structure and function of the brain across the lifespan. [23] In fact, sex differences have been identified among all major brain parameters, including:

> higher rates of cerebral blood flow, higher percentage of gray matter tissue, and higher interhemispheric connectivity in females, compared with higher percentage of white matter and greater intrahemispheric connectivity as well as higher glucose metabolism in limbic regions in males. Many of these differences are present in childhood, but they become more prominent with adolescence, perhaps linked to [the action of sex hormones during] puberty.[24]

More recently, sex differences in neural connectivity were also demonstrated throughout the prenatal period.[25] These foundational brain differences appear to translate into differences in cognitive processing, visual processing, auditory processing, social skills and more.[26,27] For example, males do better with spatial processing and motor speed tasks. In contrast, females outperform males in memory and social cognition tasks.[24]

Some attribute the superiority of females in social cognition tasks solely to enculturation. However, a study of 102 neonates disproved this hypothesis. One day old male and female newborns were tested to see if they would exhibit a difference in the length of time spent staring at a picture of a face versus a twirling mobile. Male newborns exhibited a stronger interest in the mechanical object, whereas the female newborns showed a stronger interest in the face, which represents a social object. Since one-day-old neonates have not been "enculturated," these results clearly demonstrate that sex differences in social behavior are at least in part innate.[28]

Sex chromosome and sex hormone effects also contribute to sex differences in mental illness.[26] For example, neurodevelopmental disorders, including autism, attention deficit disorder, schizophrenia and others, disproportionately affect males.[29,30,31] In contrast, females have twice the lifetime rates of depression and most anxiety disorders.[32,33]

In the case of substance use disorders, females more rapidly advance from use to dependence, report more severe impairment in domains such as employment, social/family and medical functioning, and suffer from higher rates of co-occurring psychiatric disorders.[34] This is explained at least in part by metabolic sex differences. For example, alcohol intake in women typically results in higher blood alcohol levels compared with men after the consumption of equal volumes. This is because the bioavailability of alcohol, due to differences in volume of distribution and gastric alcohol dehydrogenase activity, is greater in women than in men.[34,35]

Sex differences in pharmacology

Many medications are also metabolized differently between the sexes due to biological variance in body size, sex hormone levels, metabolic enzyme activity, absorption, distribution volumes and elimination.[35] Differences in body fat and organ blood flow have been implicated in the faster onset of action and prolonged duration of neuromuscular blockade in women as compared to men.[36] Differences in body fat and protein binding between the sexes explain the sex-related pharmacokinetic differences in the distribution of diazepam.[36] Sex differences in the kidney, including rates of glomerular filtration, tubular secretion and tubular reabsorption, result in a renal clearance that is generally higher in men which causes differences between the sexes in response to several medications including fentanyl.[36]

Additional examples of specific drug variances between the sexes are many and beyond the scope of this paper. However, an analysis of data from the Adverse Events Reporting System and similar resources found that women not only experience more adverse medication events than men but also experience adverse events of a more serious nature.[36] The most widely reported sex difference in this regard is the higher risk in females for drug-induced long QT syndrome, with two-thirds of all cases of the fatal torsades de pointe arrhythmia occurring in females. This is due to women's unique electrophysiology which normally produces a longer QT interval than that of men.[37] Clearly, knowledge of these differences is crucial to designing and implementing optimal medical treatment plans. Therefore, FDA regulations and guidance are in place to ensure that both sexes are represented in all phases of clinical trials and that medical products are labeled to alert physicians and patients to sex differences in drug responses.[38]

Sex differences in cardiovascular health

"Cardiovascular diseases occur and progress differently in the two sexes, because biological factors differing between the sexes have sex-specific protective and harmful effects."[39] For example, it has long been recognized that males and females have significantly different risks in regard to arrhythmias. Following atrial fibrillation (afib), for example, females face a higher mortality risk, experience more symptoms, and have higher rates of recurrence following ablation. Females also experience higher rates of afib-related stroke and greater mortality rates following stroke.[37]

However, apart from arrhythmias, females face an overall lower risk of stroke than males before menopause and a higher risk of stroke following menopause.[39,40,41] The effect of estrogen on cardiovascular tissue contributes to this overall decreased risk in pre-menopausal women, but hormone replacement therapy after menopause does not mitigate the increased risk to women at this stage of life. Therefore, both hormonal and sex chromosome differences appear to contribute to the difference in stroke risk between males and females.[39,40,41]

Finally, in both sexes, 80% of the risk of suffering an acute myocardial infarction (MI) is accounted for by obesity, hypertension, dyslipidemia, smoking and diabetes.[37] However, in females, diabetes is associated with a six-fold elevated risk of coronary artery disease (CAD) as compared to only a three-fold increased risk among males with diabetes.[37] Additionally, diabetic females with CAD face a three-fold increased risk of heart failure, whereas diabetic males have only a minimally elevated risk of heart failure.[37] When matched for age, young females with CAD have worse outcomes than young males with CAD.[37] In the midst of an MI, almost half of all females do not report chest pain. Instead, females often present with shortness of breath, fatigue, sleep disturbances, indigestion, and anxiety. Because of this, timely diagnosis of MI in females is often delayed.[37] In addition, the standard stress test has a lower specificity and sensitivity in women. The preferred diagnostic modality for CAD in females is stress echocardiography.[37]

Sex differences in sports medicine

Long-term research on elite athletes has consistently shown that when matched for training, males outperform females in regard to speed and strength.[42] Though predominantly related to hormones, these differences are also the result of sex-differential gene expression. Studies have identified over 3,000 genes that are differentially expressed in male and female skeletal muscle, contributing to the difference in skeletal muscle fiber-type composition and resulting in a difference between the sexes in skeletal muscle fatigue recovery and endurance testing. These findings are consistent with animal studies that find force generation and relaxation are faster during fatigue in male muscle fibers as compared to female fibers, whereas endurance is higher and recovery is quicker in female muscle fibers versus male fibers.[43]

Obvious anatomical musculoskeletal differences also exist between the sexes. For instance, men's larger and denser bones result in taller stature as well as a larger fulcrum which provides greater leverage for muscular limb power to be exerted in jumping, throwing and other explosive power activities.[44] Even at birth, the average male is heavier and longer (taller) than the average female, and this advantage for most athletics continues, when controlled for Tanner Stage of puberty, throughout life. Differences in the bone mass of the axial skeleton are present prior to puberty, with boys having thicker vertebral bodies than girls of the same height, weight, and age.[45]

The predominant influence affecting male versus female athletic performance is hormonal, particularly during puberty. The sex hormone testosterone plays an important role in regulating bone mass, fat distribution, muscle mass and strength, and the production of red blood cells leading to higher circulating hemoglobin. After puberty, male circulating testosterone concentrations are 15 times greater than those of females at any age. The result is a clear male advantage in regard to muscle mass, strength and circulating hemoglobin levels even after adjusting for sex differences in height and weight.[44]

On average, females have 50-60% of male's upper arm muscle cross-sectional area and 65-70% of male's thigh muscle cross-sectional area with a comparable reduction in strength. Young males have on average a skeletal muscle mass over 12kg greater than age‑matched females at any given body weight. While numerous genes and environmental factors such as physical activity and diet contribute to muscle mass, the major cause of the sex difference in muscle mass and strength is the difference in circulating testosterone. Taken together, these discrepancies render females, on average, unable to compete effectively against males in power‑based or endurance‑based sports.[44]

These sex-based differences also influence the risk for and type of injuries athletes experience. For instance, stress fractures involving the long bones of the legs in runners are more frequent in females. Male athletes are far less susceptible due to their larger and denser bones.[46] Abundant data also demonstrates that female athletes are particularly vulnerable to anterior cruciate ligament (ACL) rupture resulting in the incidence of non-contact ACL injuries being 2 to 8 times higher in females compared with males who participate in basketball, soccer, team handball, netball, and alpine skiing.[46]

Conclusion

Sex is defined according to the specific role of a member of a species in the process of reproduction, whether a member is structurally organized to produce the egg or to contribute the sperm. Among humans, sex is a dimorphic, innate and immutable trait established at fertilization by sex determining genes located on the X and Y chromosomes. This sexual dimorphism is genetically programmed and is present in every nucleated somatic cell of the body; sex does not and cannot change. The presence or absence of a Y chromosome correlates with a person's definitive sex phenotype in 99.98% of all people.

The 0.02% of people with disorders of sex development (DSD), more commonly referred to as intersex conditions, represent males and females with congenital disorders affecting the external genitalia and/or reproductive organs among other systems. These rare DSD conditions are frequently associated with reduced fertility reflecting the fact that they are biological disorders not additional sexes. Individuals with gender dysphoria are distinct from individuals with DSD conditions and yet self-identify as something other than their biological sex. Individuals with DSDs may require medical and/or policy accommodations depending upon their specific diagnosis.

Sex differences are real and arise from at least four different genetic mechanisms, in addition to the actions of sex hormones and environmental influences. These biological sex differences impact all organ systems, affect the propensity to develop certain diseases, alter responses to drugs, toxins and pain, and also result in important physical, cognitive, emotional and behavioral differences. For these reasons, the NIH recognizes sex as a binary or dimorphic biological variable in research and medical practice.

Acknowledging the fact of inborn genetic sex differences is also crucial for creating public policies that will ensure the health and safety of children and adults alike. Genetics is the reason a male who self-identifies as female remains male, and explains why giving estrogen to a male does not transform him into a female. While it is true that a male who uses estrogen after puberty will lose muscle strength and impair other aspects of his physiology, he does not alter his genetics; he remains male at the cellular level in all body systems. Similarly, a female who self-identifies as male remains female, and giving her testosterone does not transform her into a male. In terms of genetics, she remains female at the cellular level. There is no scientific justification for allowing, let alone mandating, males access to female-specific spaces such as restrooms, homeless shelters, prisons and the like. Similarly, just as a female doping testosterone would be prohibited from competing against other females, so too should all males be barred from competing against females. The risk for harm to females from ignoring biological sex in these scenarios is both obvious and documented.

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