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ADVANCES IN PEDIATRICS

The Need to Integrate Sex and Gender Differences into Pediatric Pedagogy

Janice L. Werbinski, MD, NCMP[a,*], Mary K. Rojek, PhD[b], Maria Demma I. Cabral, MD[c]

[a]Department of Obstetrics and Gynecology, Western Michigan University Homer Stryker MD School of Medicine, 1000 Oakland Drive, Kalamazoo, MI 49008-1284, USA; [b]Sex and Gender Health Collaborative, American Medical Women's Association, 1100 Woodfield Rd. #350, Schaumburg, IL 60173, USA; [c]Department of Pediatric and Adolescent Medicine, Western Michigan University Homer Stryker MD School of Medicine, 1000 Oakland Drive, Kalamazoo, MI 49008-1284, USA

Keywords

• Medical education • Sex and gender differences • Pediatric education
• Sex and gender based medicine

Key points

- Despite including women in research over the past 25 years, only a fraction of that research has been translated into curricula for medical students, residents, or practicing physicians.
- Tens of thousands of articles document that diseases and conditions differ between women and men, boys and girls, in terms of biology, prevention, clinical signs, therapeutic approach, prognosis, and psychological and social impact.
- A 2001 Institute of Medicine report indicated that ''every cell has a sex,'' and knowledge of sex and gender differences would lead to improved clinical care for women and men.
- There are sex differences that begin with the fetus, and sex and gender differences throughout infancy, childhood, and adolescence that have implications for clinical care.
- Women/girls and men/boys are sometimes harmed when their unique presentation, metabolism, size, and reactions are not considered in their health care plan.

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*Corresponding author. 10073 Woodlawn Drive, Portage, MI 49002. *E-mail address:* dr.janwerbinski@gmail.com

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INTRODUCTION

Sex and gender based medicine (SGBM) is a lens or framework with which to consider sex and gender based differences between men/women and boys/girls. It applies to all patients. It is similar to the social determinants of health in that both sex and gender have an influence on health and illness. However, it also incorporates the social and cultural context that influences access to care, resources, opportunities, among other factors that affect health. Ignoring sex and gender can lead to bias in health care (often unconscious) and may harm patients.

SGBM evolved from the Women's Health Movement of the 1990s when research demonstrated that there were substantial differences in women's health compared with men's health that were relevant to all disciplines. SGBM emerged so that the similarities and differences between men and women would be explicitly considered to improve both women's and men's health. SGBM has progressed over the last 2 decades and has the potential to transform not only medicine, but also other interprofessional disciplines [1]. This article shows that the knowledge of sex and gender differences in adults also applies to the discipline of pediatrics.

EVERY CELL HAS A SEX AND EVERY PERSON HAS A GENDER

"Every cell has a sex," and all bodies are influenced by gender. *Sex* refers to a patient's biology, whereas *gender* refers to the sociocultural factors that influence both a patient's presentation and how society responds to an individual [2,3].

As a biological variable, sex refers to the patient's chromosomes, genes, hormones, and reproductive anatomy. Given that chromosomes and genes are present in all cells, and cells are influenced by hormones, every cell has a sex. Gender is a sociocultural variable that applies to the individual and to society. Individuals adopt roles, behaviors, and identities, and they express their gender. On a societal level, there are gendered expectations and opportunities that influence how individuals will and/or can express their gender. For example, access to a specific treatment may depend on a patient's sex and gender, which can influence insurance, ability to travel, childcare, socioeconomic status, a health provider's correct diagnosis, research conducted about the condition in the relevant population, and so forth.

SEX AND GENDER TERMINOLOGY

The appropriate terminology for sex is male/female/intersex, whereas for gender it is man/woman, boy/girl, masculine/feminine, cisgender/transgender, and other gendered expressions. Cisgender refers to gender expression and birth sex being congruent (most people), and transgender refers to gender expression differing from birth sex. Although sex and gender can be examined individually in terms of health, they also interact via epigenetic processes and may influence health [3]. Box 1 summarizes sex and gender terminology.

Box 1: Sex and gender terminology

	Sex	Gender
Variable type	Biological variable	Sociocultural variable
Terms	Female, male, intersex	Woman/man Girl/boy Feminine/masculine Cisgender/transgender Other
Components	Chromosomes, genes, hormones, organs	Roles, behaviors, identities, expressions, opportunities, expectations
Levels	Organism, organ, cell	Both individual and societal

WHAT SEX AND GENDER BASED HEALTH IS NOT

Most casual observers of SGBM incorrectly confuse sexuality with gender. *Sexuality* refers to heterosexual, lesbian, gay, bisexual, asexual, and pansexual. It refers to sexual attractions, identities, and practices. *Gender identity* refers to how individuals see themselves as a man or a woman. The term *queer* refers to a chosen identity adopted by those who reject the binary distinctions regarding both sexuality and gender. Although sexuality is relevant to health, it is not the same as gender [3].

IMPLICIT BIAS IN PRACTICE

Health care providers already consider sex and gender in their practices, but they often do so unknowingly. They make assumptions about patients and interpret symptoms based on preconceived ideas about how a patient presents [4]. For example, pain is often interpreted differently in men and women. A stoic man may be assumed to be legitimately experiencing pain, whereas a stoic woman may be assumed to be experiencing little pain. Alternatively, a man complaining of severe pain will be assumed to be in great distress, whereas a woman complaining of severe pain may be interpreted as being emotional or responding to stress in her life. Such implicit bias can lead to inappropriate treatment. When that is coupled with limited research on sex and gender differences in health, it can lead to suboptimal care and outcomes [3].

SEX AND GENDER BASED HEALTH

The study and practice of sex and gender differences is referred to as sex and gender based health (SGBH). SGBH denotes that it is interprofessional and includes medicine, whereas SGBM applies solely to medicine. SGBH focuses on biological sex and sociocultural gender. It requires recognizing that every person has a sex and a gender, and both influence health. The basic differences between XX and XY must be researched and appreciated, and the health implications of the interrelationship between the two must be understood.

From the embryo to the grave, sex and gender have undeniable effects on a person's health. Diseases and conditions differ between women and men in terms of biology, prevention, clinical signs, therapeutic approach, prognosis, and psychological and social impact. Traditional medical textbooks and curricula still tend to approach health and diseases from a standard perspective largely based on research performed on male animals, cells which do not denote sex of source, and the 70-kg human man [5–7].

THE SEX AND GENDER BASED HEALTH DIFFERENCES MOVEMENT

The roots of studying sex differences between women and men are in the women's health movement [1]. In 1990, Congress passed the Women's Health Equity Act (WHEA), establishing the Office of Research on Women's Health (ORWH) at the National Institutes of Health (NIH), to ensure the inclusion of women in all NIH-funded research where appropriate. Before this time, the Food and Drug Administration (FDA) had banned the participation of women of childbearing age in clinical research. Since passage of the WHEA, and despite nearly 30 years of research that finally included women, outcomes are often not reported by sex. The lack of reporting by sex leaves outcomes in the less-studied sex (women) invisible, while muddying the data about outcomes in men. Only a small fraction of sex-specific research has been translated into curricula for medical students, residents, or practicing physicians [7,8].

The Women's Health Movement was inspired in large part by 2 momentous and pivotal research revelations:

1. The *Physicians' Health Study* of 1989 [9], showed that daily aspirin decreased the risk of a first heart attack in male physicians. More than 20,000 male physicians (but no women) were included in the study. Arguably, this became more infamous for its exclusion of women than its epidemiologic findings.
2. Results from the *Women's Health Initiative*, which had been launched in 1991, clearly showed that there were existing common medical practices that harmed some women [10,11]. For instance, hormone replacement therapy was discovered to be harmful to some women's cardiac health. Subsequent research has shown that coronary artery disease differs in women compared with men in terms of pathogenesis, symptoms, and prognosis [12].

More recent research has shown that the cardiac symptoms that are more typical in women can also occur in some men. This knowledge may help to improve clinical care not only for women at risk, but also for men [13]. This research led to the understanding that women (and men) are sometimes actually harmed when their unique presentation, metabolism, size, and reactions are not considered. There are known differences in pharmacokinetics and pharmacodynamics that matter. Whether a cell contains an XX or XY chromosome may have an impact on everything from phenotype to regulation of metabolism to the gut microbiome [10,14].

Since the 1990 WHEA legislation, a succession of events has moved us toward considering sex and gender differences in research, education, legislation, and publication. Table 1 depicts a timeline chronicling this activity.

Lay women have also become aware that women's health issues have received inadequate attention. Advocates have published books, articles, and opinion editorials about "*miss-diagnoses*" and the harm women have experienced. Maya Dusenbery's 2018 book, *Doing Harm: The Truth About How Bad Medicine and Lazy Science Leave Women Dismissed, Misdiagnosed, and Sick* [15], attempts to bring this issue to public attention. The Coalition for Women's Health Equity, a program of Hadassah, advocates for gender equity in medical prevention, research, funding, and quality of care, and raises awareness about how health inequities adversely affect women and families throughout the United States [16].

More recent legislative action has seen the introduction of the "Research 4 All Act of 2015" requiring the inclusion of both male and female cells, tissues, and animals in all human and pharmaceutical research, ordering the disaggregation of data analysis by sex, and mandating that sex differences be examined and analyzed [17]. It also directs the NIH to update its guidelines about the inclusion of women and minorities in research. Although this bill was introduced in the House of Representatives on a bipartisan basis in 2015, at the time of this writing, it has not been given a vote.

WHAT DOES THIS HAVE TO DO WITH PEDIATRICS?

It is the responsibility of the health care system to provide care to all populations equally, and it is the responsibility of doctors and doctors in training to be exposed to the health care needs of all populations. Medical training should include children as a special population. The specialty of Pediatrics was first proposed by Abraham Jacobi, who became the first president of the American Pediatric Society in 1888. Jacobi advocated for doctors to consider differences in metabolism, dosages, and therapeutics when treating children [18].

The phrase "children are not just small adults" [19] was coined, and yet it was another 45 years before the American Board of Pediatrics became a certifying body of the American Board of Medical Specialties. It is now known that there are many differences in health between men and women as well as between boys and girls. Just as it has come to be accepted that there are differences between children and adults, it must also be acknowledged that there are differences between boys and girls.

FETAL DEVELOPMENT AND HORMONES: A REVIEW OF HUMAN EMBRYOLOGY

Complex mechanisms are responsible for the development of the phenotypic differences between male and female humans from an undifferentiated zygote. It has long been recognized that testicular determination is initiated with the expression of the SRY (Sex Determining Region) gene on the Y chromosome. Once testes are developed, they begin to produce testosterone and

Table 1
Sex and gender timeline

Year	Research	Clinical	Legislation: national and international initiatives	Educational
1985	US Public Health Service task force finds exclusion of women from research negatively impacts women's health			
1990	The Society for Women's Health Research is founded		WHEA passed, establishing the ORWH at NIH	Publication of *Women's Health Issues* journal
1991	Women's Health Initiative is funded and launched in 1991		Office of Women's Health is established at US Department of Health & Human Service	
1992				Publication of the first issue of *Journal of Women's Health*
1993	NIH Revitalization Act requires that women be included in all research			The Advanced Curriculum on Women's Health is created by the AMWA
1994			Office of Women's Health is established at the FDA	
1995			National Centers of Excellence in Women's Health are funded	The Council on Graduate Medical Education calls for expanded education in women's health beyond reproductive health
1996				Publication of *Women's Health in the Curriculum: A Resource Guide for Faculty* The American College of Women's Health Physicians is founded
1998				Publication of *Textbook of Women's Health* by Dr Lila Wallis

1999		Publication of *Guide to Preventive Cardiology for Women* by Dr Lori Mosca		
2000	NIH ORWH Building Interdisciplinary Research Careers in Women's Health grants program is established for faculty in women's health and sex differences research		National Community Centers of Excellence in Women's Health is funded	Women's Health Core Competencies are developed by Association of Professors of Gynecology and Obstetrics to create women's health curriculum Publication of *Academic Medicine* special issue on sex, gender, & women's health in medical education
2001	Institute of Medicine (IOM) report published: ''Exploring the Biological Contributions to Human Health: Does Sex Matter?''	US Government Accountability Office (GAO) report: 80% of market-withdrawn drugs show adverse effects in women		
2002	Women's Health Initiative study on hormone replacement therapy halted due to breast/cardiac adverse events			
2004				Publication of *Principles of Gender-Specific Medicine* by Dr Marianne Legato
2005	Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) concludes that sex differences are essential to the study of toxicology	Aspirin is found to decrease risk of stroke but not first myocardial infarction (MI) in women		
2006	Founding of the Foundation for Gender-Specific Medicine and the Organization for the Study of Sex Differences			

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Table 1
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Year	Research	Clinical	Legislation: national and international initiatives	Educational
2007	Advancing Novel Science in Women's Health Research grant established		National Centers of Excellence in Women's Health is defunded	Laura W. Bush Institute for Women's Health is established at TTUHSC
2010	IOM report finds lack of reporting and analysis of research data by sex		Women's Health Office Act establishes Offices of Women's Health in 5 federal agencies	Publication of *Biology of Sex Differences* Journal
2011	FDA releases guidance on the role of sex difference in determining safety and effectiveness of medical devices	Publication of Update: Guidelines for the Prevention of Cardiovascular Disease in Women		Division of Sex and Gender in Emergency Medicine is established at Warren Alpert Medical School, Brown University
2012	ApoEε4 in Alzheimer disease found to cause changes in brain activity in healthy adult women but not in men			The Sex & Gender Women's Health Collaborative is established More publications: *Sex and Gender Aspects in Clinical Medicine; Handbook of Clinical Gender Medicine; Sex and Gender Differences in Pharmacology* Mayo Clinic conference: *Embedding Sex and Gender Health Differences into Medical Curricula*
2013		Zolpidem: First drug designated for different dosing in women by the FDA		

2014	FDA releases guidelines for sex-specific patient enrollment and reporting for medical device applications	Research for All Act introduced in Congress for equity in basic and clinical research	
2015	NIH dictates that all federally funded cellular and animal research must include both sexes of cells and animals		First Sex and Gender Medical Education Summit held at the Mayo Clinic
2016			Publication of textbook *Sex and Gender in Acute Care Medicine* Publication of new journal *Gender and the Genome*
2017			Publication of third edition of *Principles of Gender-Specific Medicine* by Dr Legato
2018			First Sex and Gender Health Education Summit held at the University of Utah

Adapted from: American Medical Women's Association. SGBH timeline. 2018. Available at: https://www.amwa-doc.org/sghc/sgbh-timeline. Accessed November 13, 2018; with permission.

Anti-Mullerian Hormone, which lead to the development of the typical male phenotype through the mesonephric (Wolffian) ductal system. If testes do not develop, no testosterone is produced, and female internal and external phenotype develops through the paramesonephric (Mullerian) ductal system. Although female somatic sex does not depend on endocrine activity, androgenic steroids will lead to irreversible downstream expression of the male phenotype. Thus, without testosterone, the resulting embryo develops, by default, the female phenotype [20].

Uniparental disomy is the situation in which 2 copies of a chromosome come from the same parent. When a deletion occurs on the long arm of chromosome 15, if the 2 X's come from the mother, the offspring develops Prader-Willi syndrome. When the identical deletion is contributed by the father, the child has Angelman syndrome. These genetic conditions have very recognizable, yet drastically different resulting phenotypes. Indeed, this phenomenon would suggest that even each chromosome has a sex, likely due to methylation patterns specific to the mother's or the father's chromosomes [21].

Parental manipulation of postnatal survival is a deplorable example of using sex difference knowledge in utero to orchestrate the "desired" sex of offspring by using selective abortion or infanticide. Studies show that 9% of the world's cultures still adhere to this practice. In 97% of those countries, the male offspring is considered more desirable. These are clear examples of societal misogyny [22].

SEX DIFFERENCES IN THE BRAIN

Several sex-specific genes not dependent on sex steroids are expressed differently in male and female human brains. Structural sex differences in the brain begin to become recognizable by age 2. There are also differences in adult male and female brains. The size and shape of some areas of the corpus callosum are larger in women. The fascicles connecting each hemisphere internally are larger in men [23]. Certain hypothalamic nuclei are larger in men, and the gonadotropin feedback response to estradiol differs by sex. Even at the cellular level (dendrites, axons, astrocytes, microglia, and synapses), differences between male and female brains have been identified [23].

SEX AND GENDER DIFFERENCES IN ADULTS

There are tens of thousands of articles that document sex and gender differences in adults. German researchers have developed a comprehensive library [24] of these differences. The Sex and Gender Health Collaborative website [25] is a resource to access current research information about sex and gender differences in adults across disciplines. The Laura W. Bush Institute for Women's Health [26] developed a journal article search tool, which is available at https://www.sexandgenderhealth.org/resources.html. Table 2 provides a representative list highlighting a few of the differences between the 2 sexes in adults, presented by organ system and discipline.

Table 2
Sample sex and gender differences in adults by organ system and discipline

Organ system and discipline	Adult sex and gender differences
Cardiovascular	Women are more likely to have ''atypical'' (ie, unlike men's) symptoms of *heart attacks* and *strokes* than men [27]. Women who suffer *MI* are more likely to show *no* blockage in the heart arteries (coronary microvascular dysfunction) [28]. Women <50 y old have 24% higher mortality from *MI* than men of the same age [29]. Women are less likely than men to receive cardiopulmonary resuscitation when experiencing a *heart attack* [30]. Women are referred 3 times less frequently for catheter ablation of *atrial fibrillation* [31].
Gastrointestinal	Women *metabolize alcohol* more slowly than men, leading to more cognitive impairment, motor vehicle accidents, and liver disease [32]. When undergoing surgery for presumed *appendicitis*, men show more severe pathologic condition [33]. Incidence of *Crohn disease* varies by sex and age (higher in women age 25–29 and >35, but higher in men >45) [34].
Immunology	Women are twice as likely to contract *human immunodeficiency virus* from intercourse than men [35]. In the 2014 *Ebola* outbreak in Liberia, 75% of the people who contracted the virus were women [36]. *Myasthenia gravis* is more prevalent in women <40 y old, but more prevalent in men from ages 40 to 70 [37]. Women require only half of the men's dose of *vaccine* to be protected from the flu [38].
Musculoskeletal	Women have different outcomes resulting from military-related *extremity trauma* [39]. A man is more likely to die the year following an *osteoporotic hip fracture* than a woman [40]. Women runners are twice as likely to suffer from *patellofemoral pain syndrome* [41]. Women have a higher risk of *osteoarthritis* [42].
Neurology	Women are 20% to 30% less likely to receive tissue plasminogen activator for treatment of *acute stroke* [43]. *Aspirin* prevents *stroke* but not primary MI in women, whereas it prevents MI but not stroke in men [44]. Women have higher incidence (and differing manifestations) of *concussion* given the same level of impact [45]. Premenopausal oophorectomy is associated with a 70% increased risk of *Alzheimer disease* [46]. Women >65 y old are more likely to develop *Alzheimer disease* due to increased likelihood of having the APOE E4 gene [47]. *Parkinson's disease* is more common in men, but women have more highly disabling complications and less chance of receiving effective treatment [48].

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Table 2
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Organ system and discipline	Adult sex and gender differences
Oncology	A man is more likely to die following a diagnosis of *breast cancer* [49]. Women have higher levels of DNA in their *mitochondria* [50]. More than 70% of *oropharyngeal cancer* in men is associated with the human papilloma virus (HPV), whereas 98% of cervical cancer in women is associated with HPV [51]. *Lung cancer* is the leading cancer killer of women [53]. Women with *lung cancer* are more likely to be non-smokers than men with lung cancer [54].
Psychiatry	Women are more likely to attempt *suicide*, but men are more likely to be successful at it [55]. *Depression* is twice as common in women [56]. Office *depression screening tests* often omit common questions that would identify depression in men (anger, violence, substance abuse) [56]. Men are diagnosed with *Schizophrenia* more often, and at an earlier age than women [57].
Pulmonary	40% of women have exacerbation of *asthma* symptoms premenstrually [58]. Women with chronic obstructive pulmonary disease (*COPD*) report greater breathlessness and depression than men, largely due to anatomically smaller airway lumen and thicker airway walls [59]. Women who smoke are up to 70% more likely to develop *COPD* than men who smoke [52].
Pharmacology	Women reach maximum blood levels of *Zolpidem* 8 h after dose (45% greater than in men), leading to impaired driving [60]. In 2013, the FDA *revised the dosage* recommendation of Zolpidem to one-half for women due to impaired driving [61]. *Adverse drug reactions* are 60% more frequent in women than men [62]. In a 2011 GAO audit, 80% of *drugs withdrawn* from the market in a 10-year period were due to side effects in women [63].
Radiology	In the Emergency Department, women are more likely than men to have a diagnostic procedure that includes *radiation* [64]. Women are more susceptible to the *dangers of radiation* (eg, breast cancer) than men [64]. Women are more likely than men to develop *cancer* associated with ionizing radiation [65].

WHAT IS KNOWN ABOUT SEX DIFFERENCES IN PEDIATRICS?

Using a basic search tool developed by the Laura W. Bush Institute for Women's Health [66], a PubMed search of information related to sex and gender differences in children and adolescents detected more than 9000 articles. Unfortunately, these results are not organized in a way that can be easily categorized by disease or organ. There is no organized reference available yet that addresses pediatric and adolescent sex and gender differences. However,

there are several textbooks, journal special editions, and popular books published that categorize and organize research in adults into structured study references.

To emphasize the need to recognize such differences in pediatrics, a case of fever without source (FWS) is presented in Box 2. Knowing sex differences in urinary tract infections (UTI) will allow for prompt diagnosis and management, preventing severe complications such as septicemia.

More conditions showing sex and gender differences in embryology, fertilization, preterm infants, infancy, childhood, and adolescents are presented in Tables 3 and 4, as found using the sex and gender specific health PubMed search tool [66].

Box 2: Pediatric case of fever without source

Case presentation	
Pertinent medical history:	11-month-old female infant with 3-d history of fever
Medications:	None, except vitamin D and omega-3 in formula
Relevant vital signs:	Blood pressure: 100/70; heart rate: 130 bpm; O_2 saturation 98%; rectal temperature: 39.5°C
Laboratory tests:	Catheterized urine shows positive nitrites and >20 white blood cells per high-power field
Physical examination:	Crying but consolable The rest of the examination is unremarkable
Assessment/ testing:	FWS in female infant <2 y old with leukocytosis in catheterized urine sample
Discussion:	FWS is more commonly due to UTI in girls and women, as compared with boys and men (unless uncircumcised or with ureteral reflux). The most sensitive predictors of UTI in febrile girls: 1. White race 2. Age <12 mo 3. Fever >39°C 4. Fever >2 d 5. Absence of other sources of fever These risk factors have been validated as a screening tool and were adapted by the American Academy of Pediatrics [67].
Conclusion:	FWS in children <2 y of age is more commonly found in girls (8%–9%) than boys (3%–4%) [68]. Vesicoureteral reflux and *Escherichia coli* have been found to be more prevalent in girls compared with boys in children <18 y old [68].

Adapted from Canares T, Franco M, Lazarus G. Special populations. In: McGregor AJ, Choo E, Becker B, editors. Sex and gender in acute care medicine. Cambridge (Unite Kingdom): Cambridge University Press; 2016. p. 193–215; with permission.

Table 3
Sample sex and gender differences in infants and children

Stages	Pediatric sex and gender differences
Conception, embryo, and fetus	The maternal oviduct can influence which sperm, X or Y, is successful at penetrating the ovum. This is known as ''*Cryptic Female Choice*'' [20].
	Toxins or stress in men can result in decreased *viability* of their Y, but not X, spermatozoa [20].
	Embryonic viability, after a catastrophic event (eg, 9/11, earthquakes), more male embryos die in utero [20].
	Famine and severe stress during the first trimester are more likely to cause future *addiction* problems *in male* offspring, but *schizophrenia in female* offspring [20].
	Female fetal lungs produce more surfactants at an earlier time than male fetal lungs, making *respiratory distress syndrome* more prevalent in preterm male infants [20].
	Cardiovascular system birth defects in male embryos are more likely to be coarctation, single ventricle, or hypoplastic left ventricle, but in female embryos, atrioventricular septal defects, tricuspid atresia, or truncus arteriosus are more prevalent [20].
Preterm infants	Male preterm babies are at higher risk than female preterm babies for *later adverse respiratory illness* [20].
	In low-birth-weight infants, *causation of preterm birth in male infants* is more likely due to abruptio placenta, UTI, or maternal hemorrhage, but in female infants, preeclampsia or intrauterine growth restriction is more likely the cause [20].
	Preterm hyperglycemic female babies have higher *insulin secretion levels* than preterm hyperglycemic male babies [69].
Infants and children	When supplemented with fish oil, male infants showed greater increase in *insulin-like growth factor* than female infants [70].
	Female, but not male, offspring are protected from *maternal hypertension-induced sensitization of angiotensin II* in pregnancy [71].
	Autism diagnostic guidelines reflect boys' lower functional levels and may lead to missed diagnoses in girls [72].
	Boys under age 12 have higher *pain tolerance* than girls [73].
	Boys under age 12 are more likely than girls to experience *major depression* [74].
	Severity of most *infectious diseases* is higher in boys due to sex hormone effect on T cells [75].
	Before puberty, *asthma* is 16% greater in boys, but in adulthood, it is 62% greater in women [76].
	In children under age 2, girls are twice as likely as boys to have UTI as the cause of FWS [67].
	Developmental dysplasia of the hip is 4 times more common in girls [77].
	In families with *multiple childhood cancer* cases, girls predominate [78].

WHERE TO GO WHEN YOU WANT TO KNOW

There is a growing list of resources available to those who are interested in finding information about sex and gender differences. The NIH ORWH has a 3-part Continuing Medical Education course that delivers this content and assesses one's knowledge in the field [101]. ORWH also maintains a

Table 4
Sample sex and gender differences in adolescents by organ system and discipline

Organ system and discipline	Adolescent sex and gender differences
Cardiovascular	Pubertal boys have a stronger *cardiovascular response* to caffeine than girls [79].
Gastrointestinal	Pubertal girls, when challenged with indomethacin, are more susceptible than boys to inflammatory bowel syndrome, ulcerative colitis, and celiac disease [80].
	Boys are more likely than girls to develop *Helicobacter pylori* and its related outcomes [81].
Endocrinology	Girls exhibit a greater *insulinemic response* to meals than boys despite similar glycemic responses [82].
Immunology	*Immunization response,* girls require only half the dose of influenza vaccine for the same response [83].
	Autoimmune disease may be more prevalent in girls due to testosterone downregulation of a cytokine known as *BAFF* [84].
	Eligible boys are less likely than girls to receive the *HPV vaccine* [85].
Musculoskeletal	Female athletes sustain more *concussions* and have more severe symptoms [86].
	Anterior cruciate ligament injury is up to 8 times more prevalent in female adolescent athletes [87].
	Patellofemoral pain and instability in adolescents are more prevalent in girls [88].
	Adolescent idiopathic *scoliosis* is twice as common in girls [89].
	Ankle sprains and bunions are more prevalent in adolescent girls [90].
	The *female athlete triad* (athlete energy imbalance) is also found in boys. Both can result in hypothalamic hypogonadism, osteoporosis, and fatigue [91]
Neurology	*Catamenial epilepsy,* up to 70% of girls with epilepsy have exacerbations premenstrually [92].
	Migraine, but not other severe headaches, is more prevalent in girls after puberty [93].
Psychiatry	Adolescent girls are more likely than boys to benefit from *suicide prevention programs* [94].
	Although 60% of adolescents are exposed to traumatic events, more girls than boys develop related *posttraumatic stress disorder* [95].
	Depressive symptoms in boys are associated with long-term cortisol concentration in hair, whereas *anxiety symptoms* in girls are associated with hypothalamic-pituitary-adrenal axis hypoactivity [82].
	Watching television increases *self-esteem* in white boys, but decreases it in white girls and black girls and boys [96].
	Adolescent girls are more susceptible to *addiction* to cannabis than boys [97].
	Substance abuse in sports in adolescents is more likely to be diuretics in girls (30% vs 14%) and anabolic steroids in boys (20% vs 11%) [98].
Respiratory	Adolescent girls with *cystic fibrosis* have worse prognosis and lower median survival [99].
	Globally, predominance of *allergic rhinitis* in boys changes to predominance in women after adolescence [100].

website that contains policy statements, research guidelines, and notices of webinars and other educational programs [102]. The Laura W. Bush Institute of Women's Health at Texas Tech University Health Sciences Center (TTUHSC) has many educational resources that are now open access for educators and students. These resources include a slide library, case studies, the PubMed search tool, learning modules, and a wide collection of resources to educate about sex and gender-specific management of various conditions [26]. They have begun to use these materials to weave SGBM knowledge into all 4 years of medical education at TTUHSC. It is also being integrated into the curricula of other medical schools. It is important to note that this does not require adding a new department or division. It only requires some faculty development and adding this knowledge to already existing curricula.

The Sex and Gender Health Collaborative, an initiative of the American Medical Women's Association (AMWA), hosts a digital library that contains many resources, including teaching tools, clinical cases, and marketing materials for researchers, educators, students, and residents [25]. Dr Alyson McGregor's edited textbook for emergency physicians, *Sex and Gender in Acute Care Medicine*, has a chapter addressing pediatric patients [64]. *Sex and Why* is an Internet site hosted by Dr Jeannette Wolf, who created a Jeopardy Game with Sex and Gender Difference topics. The game was a joint project with The Society for Academic Emergency Medicine (SAEM) Sex and Gender in Emergency Medicine's Interest Group, the Academy of Inclusion and Diversity in Emergency Medicine, and The Academy of Women in Academic Emergency Medicine [103]. Dr Marianne Legato, considered the "Mother of the Sex and Gender Based Medicine Movement," has published the third edition of her textbook, *Principles of Gender-Specific Medicine: Gender in the Genomic Era* [20] and is also editor of the journal, *Gender and the Genome* [104].

WHAT CAN YOU DO RIGHT NOW?

The minimum that should be done in any educational experience, be it a lecture, team-based learning, clinical case, or journal article, is to ask 2 simple questions:

1. How would this appear in the other sex?
2. Were women/girls included in this study, and were the results reported by sex?

This alone will go a long way to advance the field of sex and gender medicine and ultimately improve the health and health care of all.

FUTURE IMPLICATIONS

We are beginning to realize that there is a growing inventory of sex and gender research available to pediatricians, but there appears to be a wide gap between research and clinical application. With the recent NIH recognition that this information is necessary for evidence-based personalized patient care, the field of pediatrics should integrate sex and gender knowledge into education and practice. The pediatric field stands to benefit immeasurably when this knowledge is

applied in research, evaluation, documentation, and health care delivery. In the meantime, the least we must do as educators and clinicians is to begin to recognize that these differences exist. Just as we once recognized that children were not small adults, it is time to recognize that girls are not the same as boys. Our children's health depends on it.

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