Sex/Gender-Specific Medicine in Clinical Areas

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Preface

In the era of COVID-19, over 50% of the world's population has been vaccinated. However, I wondered whether the effect of COVID vaccination is equally effective for a man with 185 cm height/110 kg weight and a woman with 145 cm/40 kg. Maybe the effect will be different in terms of pharmacokinetics and pharmacodynamics, which are affected by sex factors such as total body water or fat composition. In addition, the side effects after vaccination were reported to be different depending on sex/gender. For example, the anaphylaxis rate of COVID-19 vaccination was 2.85 times higher in females than in males in South Korea suggesting the difference in immune mechanism. While physicians tend to agree that children are not miniature adults, few recognize that women are not simply smaller than men. Until recently, women and men had been considered to be the same except for reproductive organs. In the 1980s and 1990s, the realization that medicine as a whole—including the diagnosis and treatment of diseases—is male-centered which led to a focus on women's health such as endocrine and reproductive systems. With new studies of sex/gender differences in diabetes, cardiovascular diseases, and dementia, sex/gender became recognized as an important biological variable. Although many researchers and clinicians believe that sex differences are already well understood, experts point out that even where females and males are included in a study in equal numbers, data are frequently not analyzed according to sex. As a result, medical studies tend to present an "average" for each disease—an average that may not accurately describe either females or males. This issue is very important because studies that fail to disaggregate and analyze data by sex miss specific disease mechanisms and treatments for women, men, and non-binary people. This is a big loss for the research field as well as clinical settings. Nowadays, it has become clear that estrogen receptors (ERs) have widespread effects in numerous cells throughout the body, not just in reproductive organs. This means that differences between females and males in estrogen levels impact all kinds of cells in our body beyond the reproductive system. The testosterone and androgen receptor might be similar, which had been less focused so far. In light of these findings, researchers began to actively investigate conditions where the disease incidence is higher in one sex, or where clinical manifestation is different between women and men even in cases where the disease incidence is similar. In addition, recently physicians need to pay more attention to non-

binary people, and lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) individuals who experience higher rates of health disparities.

While I have been a gastroenterologist for 31 years, I first encountered the concept of "Gendered Innovation" or "Sex/Gender-Specific Medicine" in 2014 when I joined the GI Workshop cosponsored by Stanford University, National Science Foundation, and Korea Foundation of Women's Science and Technology Associations (KOFWST). The workshop was held at Stanford University and colorectal cancer (CRC) was one of the topics in this workshop. In particular, the sex/gender-specific aspect of CRC was very impressive and attractive as a research topic. The incidences of gastrointestinal (GI) cancers such as esophageal, gastric, colorectal, and hepatocellular carcinoma are higher in males compared to females, suggesting the protective role of estrogen in the GI cancers. Sex difference of GI cancers has two aspects between sexual dimorphism (biological differences in hormones and genes) and gender differences (non-biological differences in societal attitudes and behavior). It is the opposite in the case of functional gastrointestinal disorders (FGID). FGIDs, such as functional dyspepsia and irritable bowel syndrome, are more common in women than in men and are related to sociocultural factors such as stress, which tend to differ by gender. Various mechanisms of FGID have been proposed, such as disturbed gastroduodenal motility and visceral hypersensitivity. Women with FGID more commonly have visceral hypersensitivity and are more strongly influenced by the brain-gut axis. Physiological mediators such as ghrelin and transient receptor potential vanilloid-1 (TRPV1) play a significant role in the pathophysiological mechanism of functional dyspepsia in men, but factors related to the brain-gut axis, such as depression and anxiety, play a larger role in women. Women and men frequently are presented with different symptoms of FGID and respond differently to treatment. These differences can be caused by the effects of sex hormones or genetic predispositions on disease mechanisms (i.e., pathophysiology) and by sociocultural factors related to gender. The publication of *Sex/Gender-Specific Medicine in the Gastrointestinal Diseases* by Springer in 2022 causes an impact on Korean Academic Society, and there was a kind recommendation to apply this sex/gender-specific medicine to various clinical areas in addition to GI area. Thus, I tried to find Korean experts who have interests in sex/gender-specific medicine in each area. Finally, this book highlights the sex/gender differences in the diseases of human body such as cardiology, GI (adults and pediatric area), endocrinology, pulmonology, rheumatology, infection, general surgery, orthopedic surgery, psychiatrics, neurology such as dementia, stroke, parkinsonism, and Alzheimer's disease in the aspect of basic and clinical field, dermatology, ophthalmology, ENT, physical medicine and rehabilitation, emergency medicine, anesthesia, dentistry, clinical pharmacology, and nutrition. All of these chapters clearly show that studies must integrate both sex and gender analysis into the research design and analyze how sex and gender interact with each other. I hope this

book is helpful or even inspiring for medical students, trainees such as interns, residents, and fellows, medical boards of each field, and basic researchers. Finally, this book could contribute to precision medicine and tailored therapy which I hope will benefit all of the world.

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Acknowledgments

There are many individuals to thank without whom this book would not have seen the light of day. First, I would like to thank Dr. Heisook Lee, the President of Korea Center for Gendered Innovations in Science and Technology Research (GISTeR) and Prof. Kyu-Chang Wang, the President of National Academy of Medicine of Korea. They provided an opportunity to edit a Korean book entitled *Sex/Gender-Specific Medicine in Clinical Areas*. They gave me many opportunities of presentations regarding sex/gender-specific medicine at the Academic Symposium and Nature Forum, which was very helpful for spreading the word about *Sex/Gender-Specific Medicine* in South Korea. Next, Prof. Hee Young Paik suggested to open the "Research Center for Sex- and Gender-Specific Medicine" at Seoul National University Bundang Hospital in 2023, which was regarded as a success in this research in South Korea. It is expected to grow and play a vital role as a platform of communication abroad in the future. Prof. Londa Schiebinger from Stanford University gave me kind and accurate comments regarding Chap. 1 "Why Is Sex/Gender-Specific Medicine Important?"

I would like to thank 40 Korean co-authors of this book from various medical fields. Most of them told me that they learned a lot during their writing this chapter. I guess they will play an important role in stimulating the interests of researchers and clinicians worldwide in terms of "Sex/Gender-Specific Medicine." In addition, I would like to thank my colleagues and students who performed research regarding sex/gender-specific medicine in gastroenterology. Definitely, the quality of this book was upgraded by Ji Hyun Park who played the role of manuscript editor very well. She worked immensely hard even when she is very busy as a mother of two adorable kids.

Lastly, I would like to thank my husband Seyoung Im, and two daughters Chaerin Im and Jane Im. They are proud of the publication of this book and helped me a lot in various aspects. In addition, I would like to show my sincere gratitude to my mother Jung Sook Chun, who is 92 years old. She took care of my two daughters since they were babies. Without their help, I would not have been able to continue my research until now.

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Introduction

Sex/gender-specific medicine is defined as the practice of medicine based on the understanding that (sex-based) biological and (gender-based) socioeconomic and cultural environments are important in men and women for prevention, screening, diagnosis, and treatment of diseases. Sex/gender-specific medicine is fundamental in precision medicine and tailored therapy. Therefore, the variables must be seriously considered in medical education and practice as well as in research models ranging from human participants, animals, and cells. Three kinds of estrogen receptors (ERs) that have been cloned sequentially (ERα in 1985, ERβ in 1996 and G-protein coupled estrogen receptor 1 [GPER1] in 2012) showed widespread different effects in numerous cells throughout the body. Sometimes, these ERs play a different role in one disease. For example, ERα provokes diffuse type of gastric cancer, but ERβ seems to play a preventive role in the intestinal type of gastric cancer. These different roles in the specific diseases in each organ could be further clarified, thus explaining the pathogenesis and helping the development of specific treatment depending on sex and gender. In this book, co-authors and I have tried to cover sex/gender-specific medicine in various clinical areas to highlight how sex and/or gender influence the course of diseases and how these factors should be considered in the diagnoses and therapies of each disease.

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Contents

Part I

Why Is Sex/Gender-Specific Medicine Needed?

1 Why Is Sex/Gender-Specific Medicine Important?

Nayoung Kim

Abstract

Sex/gender-specific medicine investigates the differences between men and women in relation to disease diagnosis and treatment. These differences result from (sex-based) biological and (gender-based) socioeconomic and cultural environments. Sex refers to the biological attributes that distinguish male, female, and/or intersex according to functions that derive from the chromosomal complement, reproductive organs, or specific hormones or environmental factors that affect the expression of phenotypic traits in sexually reproducing organisms. Gender refers to sociocultural norms, identities, and relations that shape human attitudes, behaviors, and health. Both sex and gender intersect with other social categories, such as age, socioeconomic status, sexual orientation, and ethnicity. Taking sex and gender into account is important in relation to the future of personalized medicine. In addition, recently, physicians need to pay more attention to non-binary people and lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) individuals who experience higher rates of health disparities. This chapter tries to introduce research details across several medical specialties to highlight how sex and/or gender or non-binary influence the course of diseases and how these factors should be taken into consideration in diagnoses and therapies of diseases.

Keywords

Sex · Gender · Medicine · Pain · COVID-19
Gender dysphoria · LGBTQ+

1.1 Introduction

Along with age, sex/gender is a crucial area of focus in medicine. Sex differences arise from chromosomal, genetic, anatomical, reproductive, and physiological factors, while gender differences pertain to variations in social and cultural roles [1] (Fig. 1.1). The demarcation between sex and gender could sometimes be difficult due to their close correlation—for instance, biological aspects can influence social dynamics and vice versa [1]. Nowadays, intersex or intergender area becomes clear [2]. Thus, sex/gender-specific medicine deals with differences among male, intersex, and female/men, women, non-binary, and other gender-diverse people in relation to disease diagnosis and treatment [2]. Despite the common misconception that sex/gender differences have been adequately characterized for all diseases of inter-

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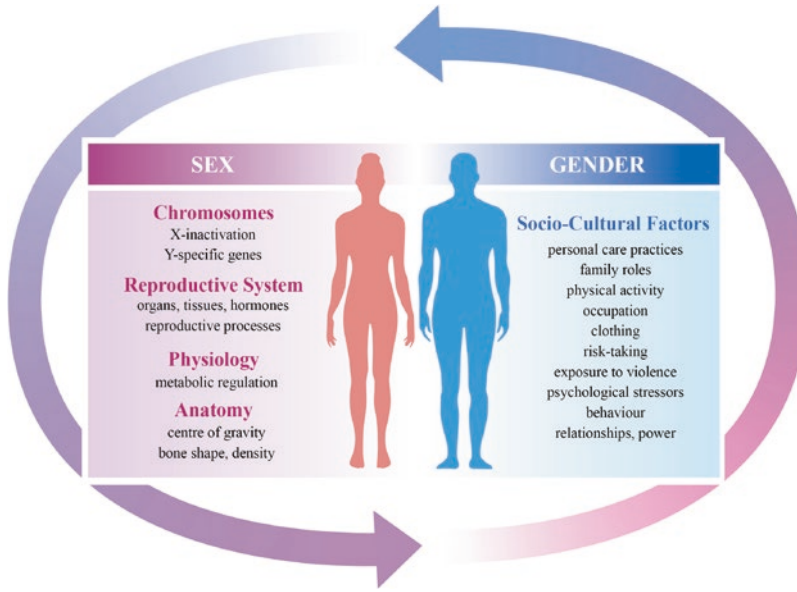

Fig. 1.1 The distinction between sex and gender. Although often used interchangeably, sex and gender can usefully be distinguished from one another. Sex refers to those characteristics that are rooted in biological differences between male and female bodies, including chromosomal, genetic, anatomical, reproductive, and physiological traits. On the other hand, gender relates to the social and cultural aspects of masculinity and femininity. Sex and gender are distinct concepts, but there is a significant interaction between them, with aspects of biology influencing social dynamics and vice versa. Although sex and gender are often thought of as dichotomous variables that neatly divide people into males/men and females/women, in fact, such classifications are not as clear and unambiguous as we tend to assume. (Adapted from Ritz et al. [1])

est, the reality is that research on most diseases has not been sufficiently analyzed for sex- and/or gender-specific disease mechanisms or treatments. Consequently, traditional medical school textbooks described some type of "average" knowledge for each disease which may not be true for men, women, or non-binary people. Furthermore, even we know that non-binary people is increasing, it was difficult to insert this concept into Fig. 1.1. It is the author's limitation to compare males/females and men/women in this chapter in spite of the importance of lesbian, gay, bisexual, transgender, and queer or questioning (LGBTQ+) individuals.

More recent studies have demonstrated that estrogen receptors (ERs) exist throughout the body and exert a wide range of effects [3] (Fig. 1.2). Therefore, differences in estrogen levels between males and females have implications that extend beyond the reproductive system. These findings have prompted researchers to actively investigate conditions for which there is either a significant sex/gender or clinically meaningful difference between males and females. Some notable examples include brain development, cardiovascular disease, osteoporosis, stem cell research, pain, and recently COVID-19.

The term "sex/gender-specific medicine" may be unfamiliar to many doctors in the world, including South Korea. Doctors frequently search online to see whether the term "sex/gender-specific medicine" is related to LGBTQ+ individuals. It is right that "sex/gender-specific medicine" needs to include non-binary individuals and LGBTQ+. However, it is the author's limitation that this chapter mainly discusses the male/female and men/women without enough introduction about intersex/binary gender. So far, sex/gender-specific medicine is a component of precision medicine that has become the focus of research in recent years. This review presents a history of sex/gender-specific medicine and discusses its definition, its importance, and examples in various clinical fields, including COVID-19.

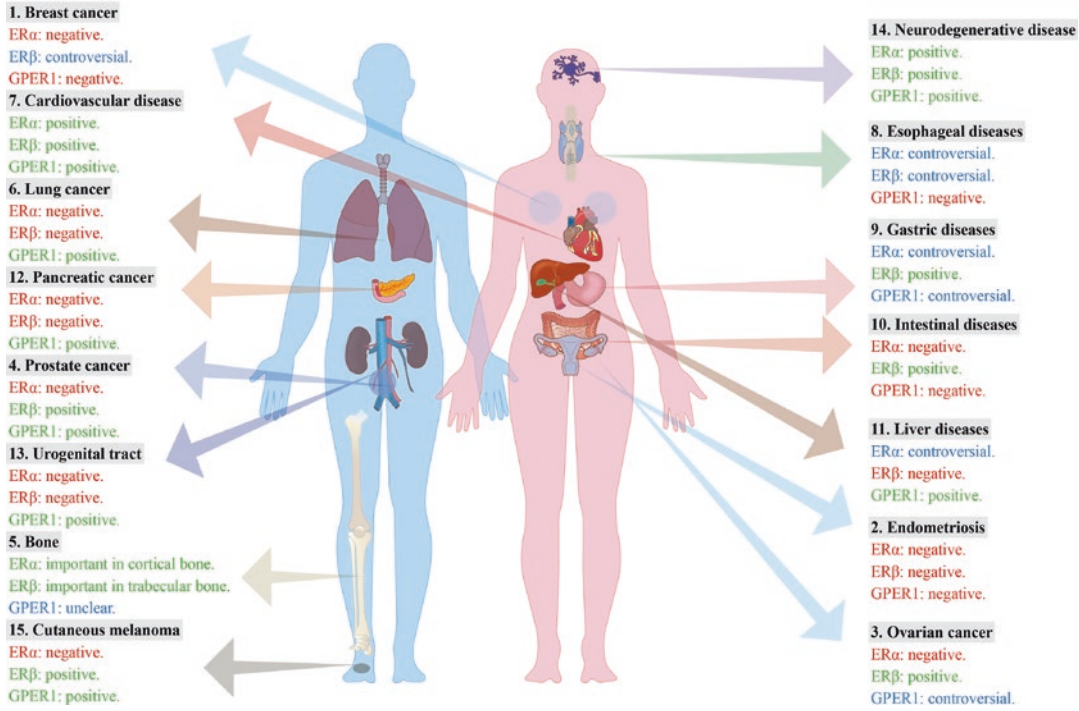

Fig. 1.2 The multifaceted role of estrogen receptors (ERs) in various diseases. (Adapted from Chen et al. [3])

The issue of sex/gender-specific medicine related to LBGTQ+ and gender dysphoria will be also covered although it is not enough.

1.2 History of Sex/Gender-Specific Medicine

The existence of pediatrics as a distinct specialty reflects the fact that children are not miniature versions of adults. However, the awareness that "women are not smaller versions of men" is more recent. In the 1980s and 1990s, interest emerged in female health based on the recognition that medicine as a whole—including the diagnosis and treatment of diseases—had been male-focused. While women's medicine focuses on the endocrine and reproductive systems, sex/gender-specific medicine focuses on differences through the body. Diabetes and cardiovascular diseases served as early examples. In addition, the increasing recognition of the relevance of gender roles for various diseases [4] led to the coinage of the term "gender medicine." Finally, the term "sex/gender-specific medicine" was established to encompass both biological and sociocultural aspects in the 2000s. The potential role of estrogen in these and other diseases has attracted interest among researchers since females and males show very different epidemiological patterns until menopause but became similar patterns thereafter. Estrogen, a steroid hormone, was first identified as a substance that controls the development and growth of human reproductive organs. However, subsequent research has shown that the role of estrogen and estrogen receptors (ERs) is not limited to the reproductive organs—instead, they are involved in physiological and pathological processes in the cardiovascular, gastrointestinal (GI), skeletal, and neuroendocrine systems [5]. Research on estrogen entered a new phase, with a broader focus, after the discovery of two different types of receptors (ERα and ERβ) in 1996. In addition, research on chromosomes has sparked interest in chromosomal factors relevant to sex/gender differences, beyond the initial focus on sex hormones. The X chromosome contains approximately 1100 genes, but the Y chromosome only

about 100 genes. This explains why female mice (with two X chromosomes) are more likely to develop systemic lupus erythematosus, multiple sclerosis, and experimental autoimmune encephalitis than male mice (with one X and one Y chromosome). Loss of the Y chromosome in neutrophils, which occurs due to aging, genetic factors, and cigarette smoking, is one reason why males are at a higher risk of developing heart disease as they become aged [6].

1.3 What Is Sex/Gender-Specific Medicine?

Sex/gender-specific medicine investigates the differences between men, women, and nonbinary people in relation to disease screening, diagnosis, and treatment. It focuses on integrating relevant findings into clinical practice [7]. Differences between males and females have been analyzed in the incidence, symptoms, morbidity, and mortality of various diseases [8], making sex/gender-specific medicine important for tailored treatments. To debunk a common misconception that sex/gender-specific medicine is limited to women's health, it examines differences between males/men and females/women in diseases and their pathophysiology, which is the basis of precision medicine. Furthermore, the knowledge should be in detail and have clinical implications in various medical fields. This could begin from sincere interests of many researches in medicine from basic to clinical areas.

Actually, the annual number of articles publishes in PubMed on sex/gender differences and medical conditions are rapidly increasing. A search in the PubMed database revealed a total of 20,944 publications, the first of them as early as 1966 [9]. While until the mid-1980s no more than ten articles were published each year, dozens of articles were published each year during the late 1980s, and the annual numbers steadily grew to over a hundred during the early 1990s, a few hundred during the 2000s, and over 1000 during the early 2010s, reaching approximately 2000 and more articles per year in recent years [9]. However, most of the literature revolves around sex/gender differences in the prevalence or incidence of medical conditions, and only few publications acknowledge sex/gender-specific medicine in guidelines or approach to treatment or intervention of the same medical conditions among males and females. Furthermore, even fewer studies deal with policy or prevention strategies related to these sex/gender-specific differences [9]. However, a similar upward trend has also been observed in the numbers of such studies regarding treatment/intervention guidelines or policy/prevention. That is, the first articles were only published during the late 1970s and early 1980s, respectively, and the highest annual publication rates became approximately 600 and 400, respectively. Of note, a significant proportion of these articles call for action, namely, converting the evidence for gender differences in health status and comorbidities into actual guidelines and treatments, as well as preventive strategies and health policy which is adapted to each sex/gender, rather than proposing or studying those gender-oriented guidelines, strategies, and policies [9]. Altogether, these trends suggest an increasing interest in studying differences in the occurrence and severity of health conditions among males and females. Following the slow initial accumulation of evidence and more rapid accumulation in recent years, sex/gender-specific guidelines for treatment or intervention programs have begun to emerge, as well as prevention strategies and health policies that consider each gender disease pair specifically [9]. There appears to be a fundamental understanding and recognition of the importance of formulating guidelines for treatments and medical policies based on the cumulative information. The publications of the guidelines and the policies are expected to increase in the near future.

1.4 Incorporation of Sex/Gender-Specific Medicine Into Education

In the long run, medical education and clinical practice should incorporate sex/gender-specific medicine to improve health indicators. To pursue this aim, Western countries, such as the United

States, Germany, and Sweden, have incorporated sex/gender-specific medicine into clinical training programs for medical students and graduate students. Experiences of education on sex/gender-specific medicine in the United States, Germany, and other European countries have been reported in reviews, summits, and surveys [10]. For instance, *Sex and Gender Aspects in Clinical Medicine* [11], written by Professors Sabine Oertelt-Prigione and Vera Regitz-Zagrpek in 2012, summarized knowledge regarding sex/gender-specific medicine in circulatory, respiratory, digestive, kidney, and autoimmune diseases, as well as endocrinology, hematology, neurology, clinical pharmacology, and pharmacokinetics.

From 2017, a sex/gender-specific medicine course was opened for graduate students in translational medicine at Seoul National University School of Medicine in South Korea [7]. Before attending the classes, faculty members and students who took the course were unfamiliar with sex/gender-specific medicine, but by the end of the semester they became motivated to apply sex/gender-specific medicine to their clinical research. This experience was described in an article entitled "Experiences with a graduate course on sex and gender medicine in Korea" [12], which received considerable global attention. A book titled *Sex/Gender-Specific Medicine in the Gastrointestinal Diseases* [13] also summarized relevant research with the aim of serving as an example for scholars in other clinical fields. In addition, from 2018, sex/gender-specific medicine has been offered as an elective subject for second-year medical students at the Seoul National University College of Medicine. Korea University College of Medicine also opened this lecture for the premedical students in 2022. Right now, several medical schools in South Korea have interests in this education regarding sex/gender-specific medicine. In addition, from 2021, Seoul National University College of Medicine offered lecture entitled "LGBTQ + medicine" as an elective subject for second-year medical students. The experience of incorporation of sex/gender-specific medicine into education suggested that effective curricula require the development of further educational materials, case studies, and reports about clinical experiences and studies [7, 9].

1.5 The Importance of Sex/Gender-Specific Medicine

The ultimate reason why sex/gender-specific medicine is important is that it helps treat patients [11]. So far, sex/gender-specific descriptions are uncommon in published papers and textbooks on various diseases. However, men and women often exhibit different symptoms of the same disease due to the effects of sex hormones or genetic traits on the pathophysiology (i.e., the disease mechanism). The sociocultural context also influences the incidence of diseases. Naturally, most of researchers found that systematic research is needed to accurately understand diseases in each sex.

Diseases with noteworthy sex/gender differences include myocardial infarction, heart failure, rheumatic disease, and autoimmune diseases. For instance, because myocardial infarction has traditionally been seen more frequently in males, female patients who present with atypical symptoms (such as pectus excavatum soreness or chest tightness) instead of chest pain have often been misdiagnosed as having gastroesophageal reflux disease or neurosis. This, in turn, has resulted in delayed treatment and poor outcomes. Even though the incidence of coronary syndrome was found to increase in women with stress, exercise stress testing found to have low sensitivity in female patients. In contrast, sudden ischemic death is markedly more common in men. Women predominate among patients with rheumatoid arthritis, with a 2–3:1 ratio of women to men, and women tend to evaluate their pain as more severe than men do, reflecting greater disease activity. Comorbidities in patients with rheumatoid arthritis also show considerable sex/gender differences; for instance, women more frequently have depression, thyroid disorders, and fibromyalgia, whereas cardiovascular diseases are more common in men. Another example is furnished by prediabetes. Glucose intolerance develops quickly in women, whereas in men fasting blood sugar gradually

rises in the early stages. The cardiovascular comorbidities of diabetes also present noteworthy differences between men and women.

Experts in these fields may be familiar with the aforementioned facts, but this information may be new for students, interns, and residents who do not have extensive experience with these diseases. Deep familiarity with these differences between women and men can assist in diagnosis and treatment, highlighting the need for in-depth research on these differences in the field of sex/gender-specific medicine.

1.6 Examples of Sex/Gender-Specific Medicine in Clinical Areas

Clinicians' reactions to sex/gender-specific medicine can be summarized in two ways: "this is nothing new, as the prevalence and symptoms of diseases have already been described separately for men and women." This might reflect the clinicians' belief that there is no need for sex/gender-specific medicine as a field because it has already been encompassed by existing advances in medicine. Another reaction is that "what is it? I have no idea." These misconceptions could be rebutted by reviewing the differences between males/men and females/women in diseases with obvious sex/gender differences, reinterpreting these distinctions in terms of (a) hormonal and chromosomal differences and (b) gender differences and presenting detailed clinical examples. Although COVID-19 has recently erupted and spread, there were noticeable differences between males and females. This section presents a selection of representative diseases with evident sex/gender differences and briefly introduces the sex/gender differences of COVID-19.

1.6.1 Cardiovascular Diseases

Cardiovascular diseases were the first for which sex/gender differences were identified and have been widely discussed. Even though these diseases are serious (for instance, myocardial infarction has a very high fatality rate), angina pectoris and myocardial infarction were infrequently diagnosed in females who visited emergency rooms or outpatient departments due to chest pain. This mistakenly leads to the belief that the diseases occur only in males. Japanese cardiologist Noro shared his experiences and emphasized this point at the 2016 academic conference of the Korea Federation of Women's Science and Technology Associations. Subsequent research has demonstrated that differences in vascular structure between males and females are a crucial reason for the differing symptoms of angina pectoris. In males, a crack occurs as a thrombus forms in the coronary arteries, with a significant aftermath, whereas in females microvascular changes progress over a long period. Recent studies have shown that differences in sex hormones, the gut microbiome, and the immune response affect the development of cardio-metabolic diseases [14] (Fig. 1.3), potentially explaining the differences between males and females in heart disease [14] (Fig. 1.4). Several review articles support these explanations [15, 16].

According to a new hypothesis, the Y chromosome in males contributes to the differences between males and females in heart disease [6]. Defective clonal hematopoiesis in neutrophils can alter the blood coagulation system, with a particularly strong impact on the coronary artery. Interest in this hypothesis has surged in light of several recent reports [17]. Decades ago, scientists discovered that some males do not have the Y chromosome in their immune cells and that the Y chromosome shrinks with age. For example, the Y chromosome is lost in some white blood cells in approximately 40% of males aged 70 years old and 53% of males aged 73 years old. To determine the impact of Y chromosome reduction on health, a study removed two-thirds of the Y chromosome in mouse myelocytes using the CRISPR-Cas9 enzyme and transplanted them into mice [6]. Mice transplanted with bone marrow lacking the Y chromosome developed cardiovascular disease with scarring on the heart [6]. However, mice transplanted with normal bone marrow did not experience this problem, and

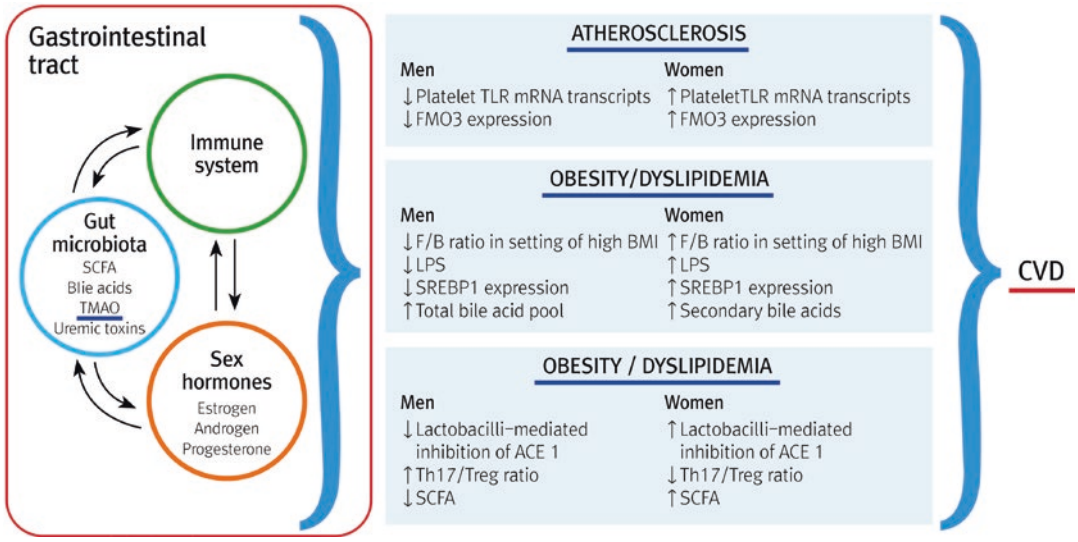

Fig. 1.3 Interconnections between the immune system, gut microbiota, and sex hormones as the possible mechanisms by which gut microbiota mediate the sex differences in the cardiovascular disease risk. *SCFA* short-chain fatty acids, *TMAO* trimethylamine N-oxide, *TLR* toll-like receptor, *FMO3* flavin monooxygenase 3, *TH17* T-helper 17, *CVD* cardiovascular disease. (Adapted from Maffei et al. [14])

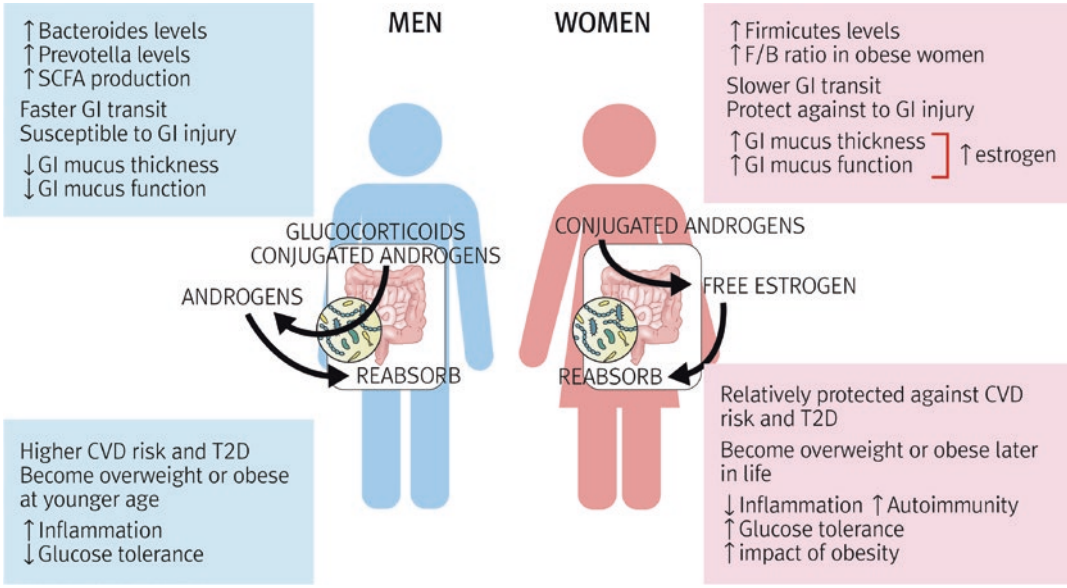

Fig. 1.4 Sex/gender differences in the cardio-metabolic diseases and the gut microbiome. *SCFA* short-chain fatty acids, *GI* gastrointestinal, *F/B* firmicutes/bacteroidetes, *CVD* cardiovascular disease. (Adapted from Maffei et al. [14])

60% survived after 2 years (vs. only 40% of mice transplanted with bone marrow without the Y chromosome) [6]. A study aiming to identify the effect of Y chromosome loss on the human body tracked the health records of males registered in the British Biobank. Those who had more immune cells without the Y chromosome at the time of enrollment had a higher risk of developing cardiovascular disease 12 years later than those who did not. Males in whom 40% or more immune cells were lacking the Y chromosome had a 31% higher risk of death from cardiovascu-

lar disease and a 3.48 times higher risk of cardiovascular disease [6]. A mechanism was discovered wherein immune cells without the Y chromosome enter cardiomyocytes and secrete a substance that signals infection. When this signal substance was blocked with an antibody in mice, the damage due to Y chromosome loss decreased [6]. Another explanation for the high frequency of heart disease in males is their low level of female hormones, which have a cardioprotective effect. These topics are expected to be the focus of active research in the future—both in terms of basic science and, potentially, drug development.

1.6.2 Brain Diseases, Pain, and COVID-19 Infection

Sex/gender differences in brain diseases, including dementia, stroke, and depression, may also be relatively familiar to clinicians and researchers. Relevant sex differences may have accumulated over humankind's evolutionary history, while gender differences arising from the differing roles between men and women interact with sex differences. Sex differences exist in human cognitive abilities, regional brain structure [18], and function [19]. Research using functional magnetic resonance imaging (fMRI) has demonstrated that different cerebral areas are primarily activated in men and women, with corresponding differences in behavior patterns [20] (Fig. 1.5). Based on the mental rotation technique with a two-dimensional or three-dimensional image [20], Binet found very clear differences between the capacities of men and women [20] (Fig. 1.5). Men and women performed in a relatively characteristic manner—for instance, men were faster and made fewer mistakes—and also used different regions of the brain during this exercise [20]. The frontal and temporal lobes tended to be activated in women, whereas the parietal lobe was activated in men [20] (Fig. 1.5). Thus, each sex tended to use a distinct strategy to solve the task [20]. Common psychiatric disorders also show sex/gender differences in the frequency of development and the age at which symptoms appear [21] (Fig. 1.6). One hypothesis of the sex/gender differences of psychiatric disorders or brain diseases is sex/gender differences of gut microbiome depending on age. Figure 1.7 shows the correlations among sex hormone levels

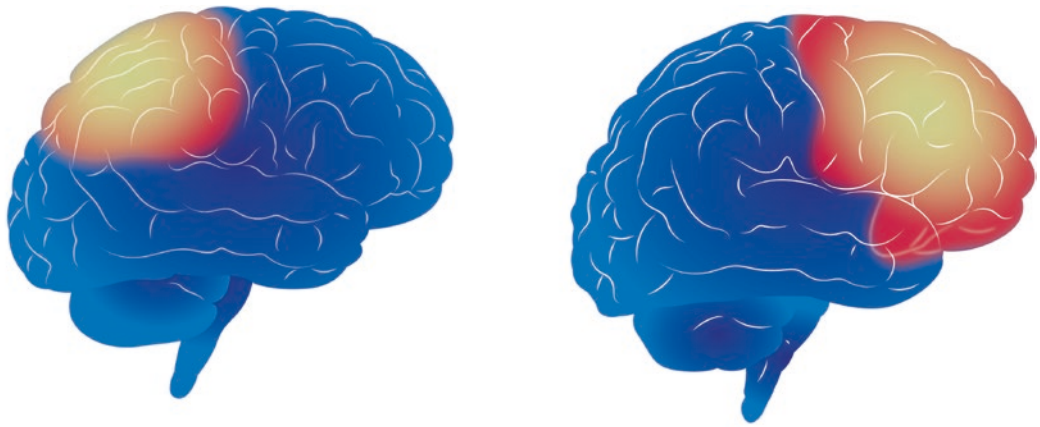

Fig. 1.5 Clear differences between the capacities of men and women in a type of exercise. Women tend to activate the frontal and temporal lobes, while men activate the parietal lobe which indicate that both sexes have their own strategy to solve the task. (Adapted from Binet [20])

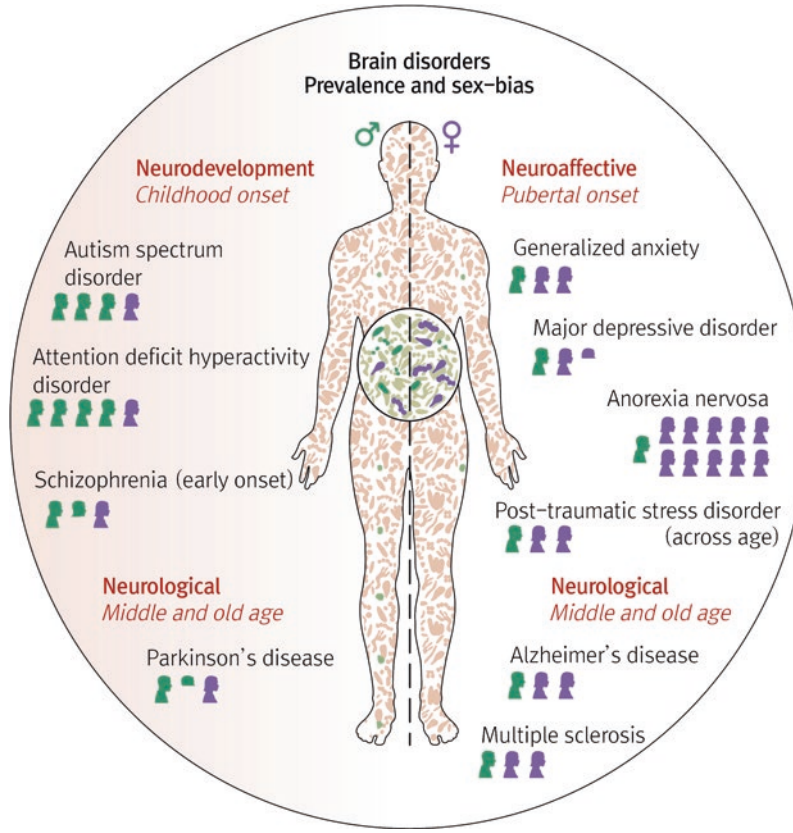

Fig. 1.6 Sex bias in several brain disorders and their likely onset. (Adapted from Jaggar et al. [21])

according to age, changes in the gut microbiome, and changes in neurological readouts across lifespan in men and women [21].

Pain also shows clear sex/gender differences. Women are more sensitive to pain than men, and this is also true in animals. Although most patients with chronic pain are women, the preclinical literature regarding pain processing and the pathophysiology of chronic pain has historically been derived overwhelmingly from the study of male rodents [22]. Interestingly, male animals show a clear effect of analgesic administration and a distinct response to manipulation during experiments [22] (Fig. 1.8). Microglial cells, which are closely associated with pain, exhibit differences in shape and function between males (Fig. 1.9a) and females [23] (Fig. 1.9b). Specifically, microglia have a larger soma and more reactivity in physiological conditions in males than in females [23]. Microglia in males have more pro-inflammatory responses, higher migration capacity, and enhanced MHCI, MHCII, and P2Y12 constitutive expression [23] (Fig. 1.9a). In contrast, microglia in females have a higher phagocytic capacity and higher expression levels of cell repair and inflammatory control genes, such as *P2Y12* purinergic receptor type Y, subtype 12 [23] (Fig. 1.9b). Another interesting report suggested that microglial cell signaling and neuron interactions are essential for chronic pain sensitivity only in males. For example, mechanical hypersensitivity after nerve injury was improved by inhibiting microglia in male mice, but not in female mice, suggesting that microglia are important as a chronic pain circuit only in males [24] (Fig. 1.10a, b). Interesting finding was that when female mice were lacking T cells they still became hypersensitive to the fine hairs, but the mechanism now seemed to occur through microglia [25] (Fig. 1.11). In females lacking T cells, blocking the activity of microglia prevented this pain response, just as it did in males. And when the researchers transferred T

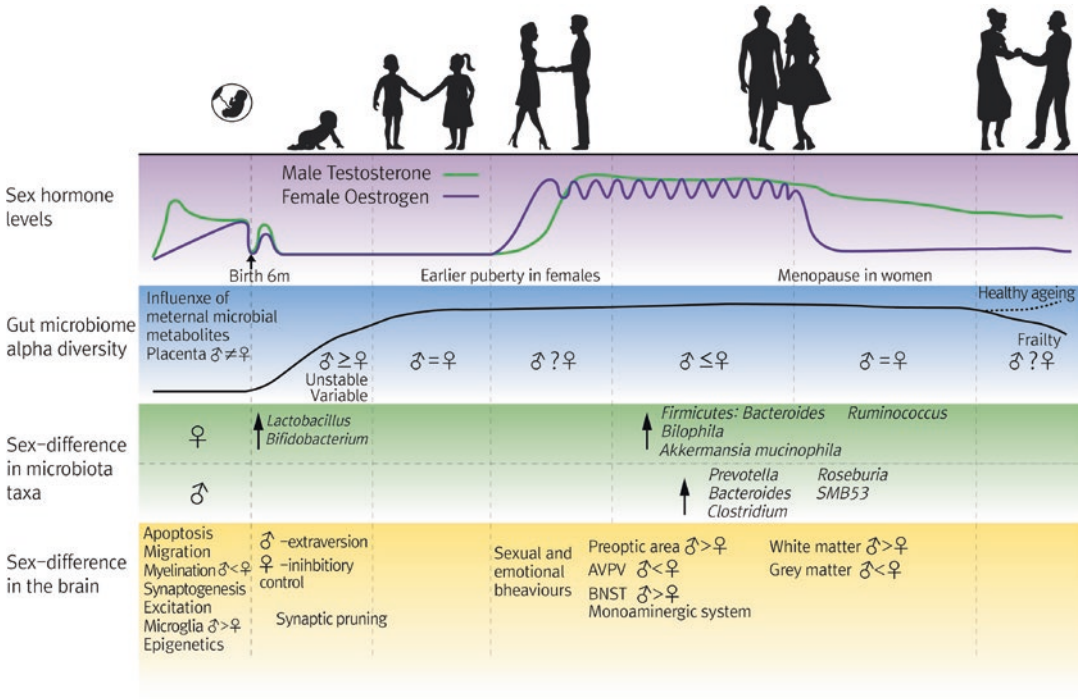

Fig. 1.7 An overview of sex differences in sex hormonal levels, gut microbiome profiles, and neurological readouts across lifespan. (Adapted from Jaggar et al. [21])

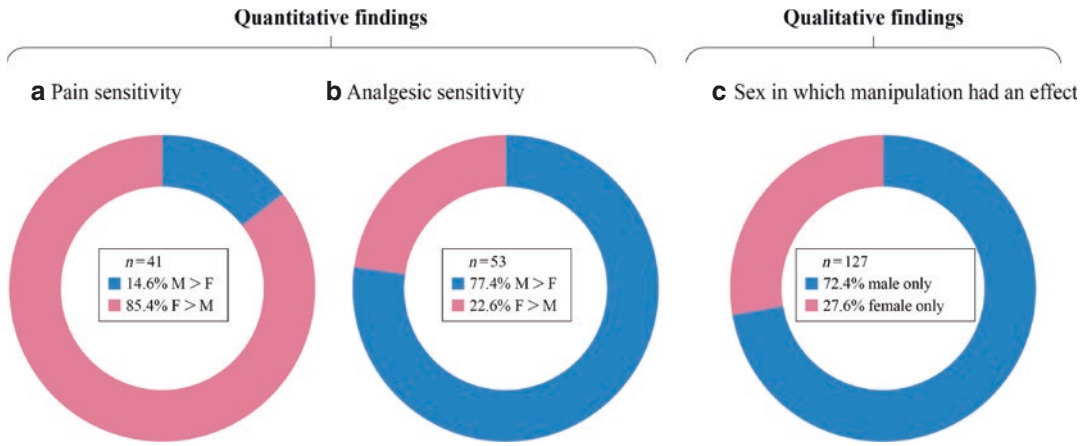

Fig. 1.8 (**a**) Of the 41 findings of quantitative sex differences in pain sensitivity, 85.4% reported female mice or rats to be more sensitive than male mice or rats. (**b**) Of the 53 findings of quantitative sex differences in analgesic sensitivity, 77.4% reported male mice or rats to be more sensitive than female mice or rats. (**c**) Of the 127 findings of qualitative sex differences, 72.4% reported statistically significant effects of the experimental manipulation in male mice or rats only

cells back to female mice that were lacking them, the animals stopped using microglia in nerve injury pain [25]. That is, females who lack T cells, or who are pregnant, switch to the pathway observed in males [25]. Similarly, when males are lacking testosterone, they switch to the pain response through T cells seen in females [25] (Fig. 1.11). These results strongly suggest that the approach for chronic pain therapeutics should be different depending

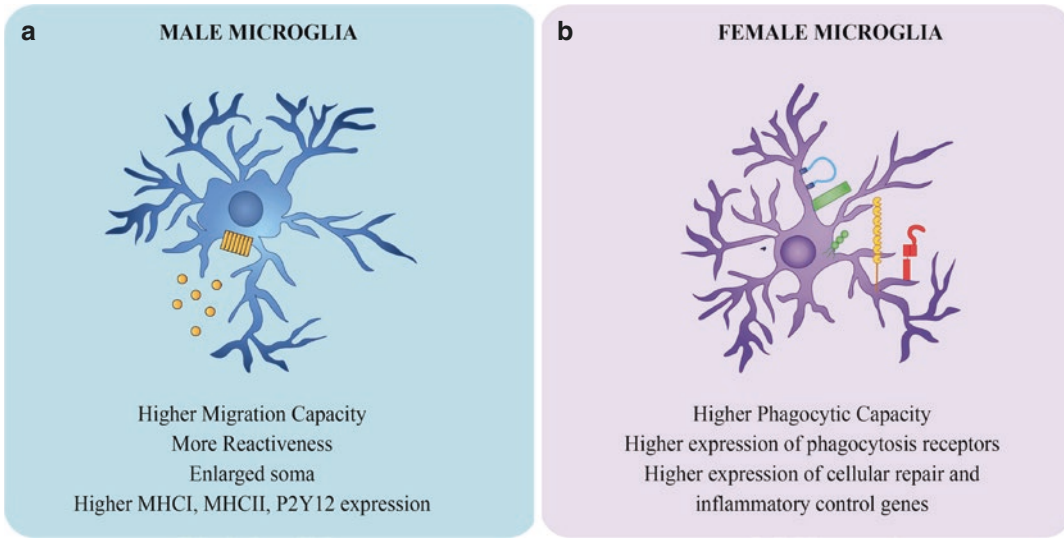

Fig. 1.9 Physiological sex differences in male and female microglia. (**a**) Male microglia have an enlarged soma and more reactiveness in physiological conditions than female microglia. These cells have more pro-inflammatory responses, higher migration capacity, and enhanced MHCI, MHCII, and P2Y12 constitutive expression; (**b**) female microglia, on the other hand, have a higher phagocytic capacity and higher gene expression of cell repair and inflammatory control genes. *P2Y12* purinergic receptor type Y, subtype 12. (Adapted from Yanguas-Casás [23])

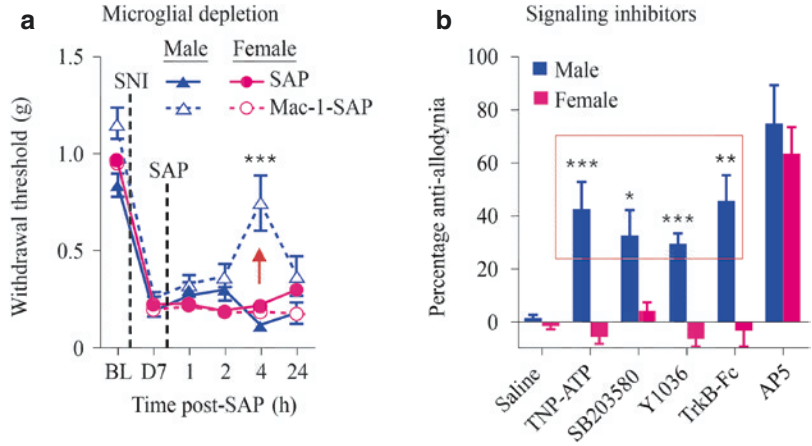

Fig. 1.10 Mechanical allodynia after nerve injury is reversed by microglial inhibition in male but not in female mice. (**a**) Reversal of established SNI-induced mechanical allodynia by intrathecal minocycline (MCL) in male but not in female mice. (**a**) Symbols represent mean ± SEM 50% withdrawal threshold from von Frey filaments before surgery (BL), 7 days after surgery (pre-injection, D7), and 10–120 min postinjection of minocycline. (**b**) Intrathecal administration of the P2X inhibitor, TNP-ATP; the p38 MAPK inhibitor, SB203580; the NGF/BDNF inhibitor, Y1036; or the BDNF-sequestering fusion protein, TrkB-Fc, all block SNI-induced allodynia in male but not in female mice. The NMDA receptor antagonist, APV, blocks allodynia equally in both sexes. Bars represent mean ± SEM percentage of maximal anti-allodynia. $*p < 0.05$, $**p < 0.005$, $***p < 0.001$. (Adapted from Sorge [24])

on sex. However, a meta-analysis of animal experiments on pain showed that the studies had been conducted primarily in males but this difference became narrower recently [22] (Fig. 1.12). Taken together in the clinical trials for pain drug development, the success rate will increase if clinical trials are tested separately by sex [25].

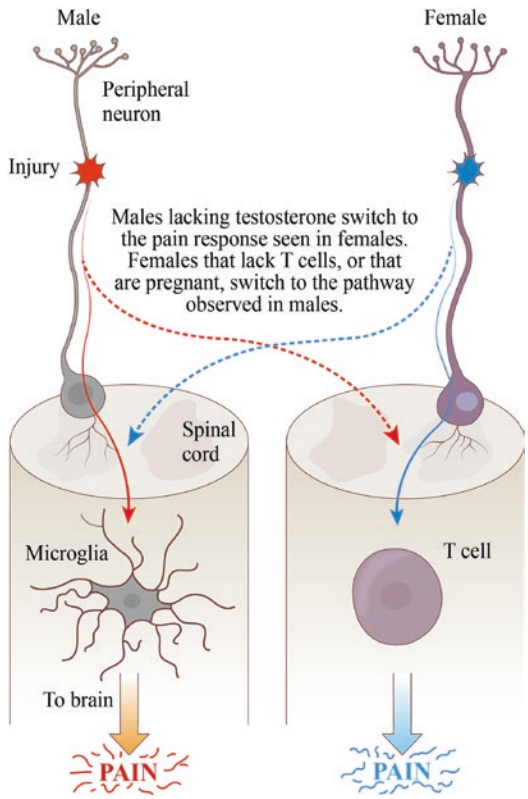

Fig. 1.11 The main pathway of chronic pain is microglia in male mice and T lymphocyte in female mice. However, females who lack T cells, or who are pregnant, switch to the pathway observed in males, and when males are lacking testosterone, they switch to the pain response through T cells seen in females. (Adapted from Dance [25])

1.6.3 Gastrointestinal Diseases

Functional gastrointestinal disorders (FGIDs), such as gastroesophageal reflux disease, functional dyspepsia, and irritable bowel syndrome, are more prevalent among women. Stress plays a particularly significant role in these diseases. Women are more susceptible to stress, making it very important to consider gender differences in treatment. The brain–gut axis, which is influenced by gender, regulates visceral hypersensitivity and mobility. These play key roles in the mechanism of FGIDs, further highlighting the relevance of gender. However, defining gender and reflecting it in research may be challenging because sociocultural conditions in terms of the role of gender are continuously changing in time and place. In contrast, GI cancers, such as esophageal cancer, gastric cancer (GC), and colorectal cancer (CRC), are twice as prevalent in males as in females. Hepatic fibrosis commonly progresses after hepatitis B or C infection in males but rarely in females. This sex difference of GI cancers is found to be related with sex hormones.

Elwood Jensen first established the existence of ERs in 1958 by demonstrating that female reproductive tissue can take up estrogen by binding to proteins [26], suggesting that estrogen bond receptors can stimulate gene transcription after migrating to the nucleus proteins [27]. In

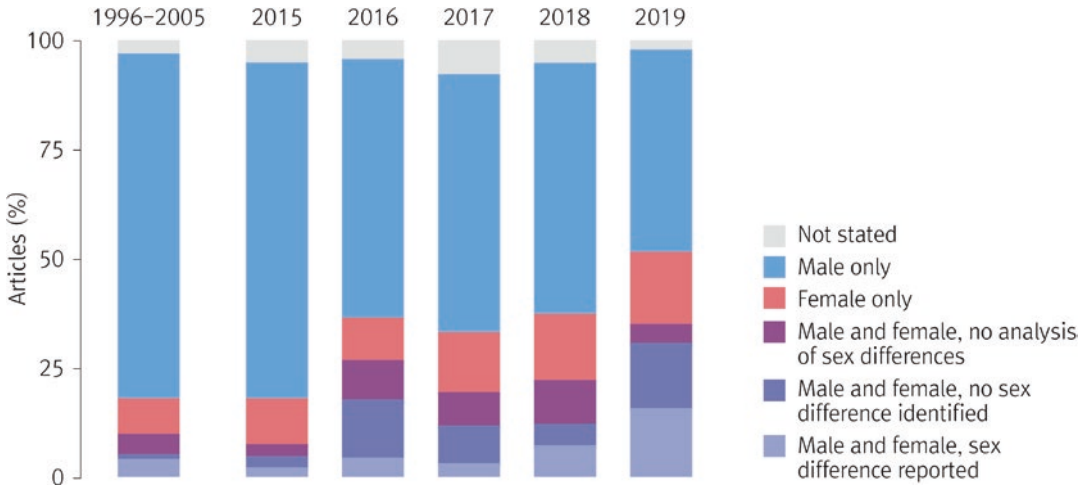

Fig. 1.12 Analysis of the selection and reporting of animals in the academic journal *PAIN*. (Adapted from Mogil [22])

1985, the first human ER, termed ERα, was cloned [28]. Subsequently, ERβ (or ERβ1) was discovered by Kuiper et al. in 1996 [29]. ERα and ERβ are highly homologous nuclear ERs (nERs), isolated using traditional biochemical approaches [3]. After ERβ was discovered, many studies have demonstrated that ERs exist throughout the body and exert a wide range of effects (Fig. 1.2). Androgen receptors (ARs) were also found to be involved in cancer mechanisms in nonreproductive tissues. AR overexpression appears to promote carcinogenesis and is related to lymph node metastasis and a poor prognosis [30, 31]. AR positivity in neoplastic tissue in the stomach is independently associated with a lower survival rate of GC, although relationships to other clinical and pathological factors have not been found [30, 32, 33].

CRC is more prevalent among males than among females, potentially because ERβ inhibits colon cancer [34, 35]. However, the incidence of CRC in females rises following menopause. GC is also more common in males than in females, with a 2:1 ratio [36], but not in males in all age groups [37, 38]. Research should incorporate a variety of perspectives to clarify potential explanations for the male predominance of GC, especially, after 40s. Tumor microenvironmental factors should be comprehensively analyzed, as well as genetic factors related to X and Y chromosomes, differences in sex hormones, lifestyle factors including smoking and alcohol drinking, *Helicobacter pylori* (*H. pylori*) infection, and the gut microbiome. Known risk factors of GC, such as *H. pylori* infection, alcohol consumption, and smoking, may contribute to a higher incidence in males [39, 40], but these factors do not fully explain the difference. Studies have shown that the rate of ER positivity in GC was not substantially different between males and females [40, 41]. However, undifferentiated adenocarcinoma was found to occur more frequently than differentiated adenocarcinoma in AR-positive patients [41]. Subsequent studies have shown associations between ER status and cancer stage in GC [42, 43]. Furthermore, ER expression was linked to diffuse-type GC and a lower disease-free survival rate [44]. Recently, there was a Korean study which showed tumorigenic mechanisms of estrogen and *H. pylori* cytotoxin-associated gene A in estrogen receptor α-positive diffuse-type gastric adenocarcinoma [45]. It nicely explained why there is a high prevalence of stomach cancer in females than in males in the age below 40s.

1.6.4 Sex Issues in Cell Line Studies and Hormone Issues in Cancer Therapies

Many in vitro studies have not reported the sex of experimental cells, tissues, or animals, leading to issues in replication studies. Taylor et al. discovered that only 45 studies (23.6%) out of 191 which had been published in prestigious academic journals on cardiovascular diseases mentioned cell sex in 2011 [46]. Even in the studies that indicated cell sex, 68.9% of studies used only male cells [46]. This situation is similar in other fields. Shah et al. conducted a random analysis of 100 studies published in the *American Journal of Physiology-Cell Physiology* in 2013 and found that only 25% of them indicated cell sex [47]. This was also the case for well-known cell banks worldwide (e.g., American Type Culture Collection, European Collection of Authenticated Cell Cultures, and Japanese Collection of Research Bioresources). Among the best-selling human cell lines worldwide in 2013, 20% did not indicate sex. The percentages were even higher for mice and rats (92% and 83%, respectively) [48].

Analyses using big data or prospective data are expected to play a crucial role in elucidating the role of sex/gender differences in the development of cancer. However, many clinical studies have not considered sex as a meaningful factor and did not even collect data on factors related to sex hormone exposure. In addition, numerous clinical trials reflecting efforts to integrate conventional medicine with nanomedicine have failed. Experts think that one reason for these failures is that those studies did not consider sex/gender in different physiological stages [49]. From this analysis, Hajipour et al. emphasized the need to consider sex and physiology [49].

In research on homeostasis in cancer stroma and organs, the regulation of angiogenesis or inflammation by sex hormones is expected to be an important foundation for understanding sex/gender differences in cancer progression. Furthermore, as anticancer therapy based on immune checkpoint inhibitors gains traction, understanding how the immune system differs between sexes/genders will become essential for establishing this type of therapy as a core treatment approach for cancers with frequent genetic mutations. The use of programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitor agents has been reported to improve the survival period of patients with lung cancer, melanoma, or stomach cancer. Our group recently published a study on different treatment mechanisms of colon cancer between male and female in mice [50]. This research showed the benefit of estrogen in the inhibition of MC38 colon cancer cell line growth by down-regulating PD-L1 expression and regulating tumor-associated cell populations in male mice [50]. These findings suggest that pretreatment of estrogen might improve the response of colon cancer to anti PD-L1 therapy in male patients with metastasis or advanced stage. However, very limited research is investigating the role of sex hormones in the immune response to cancer. Likewise, although estrogen and androgens may impact the mechanism, treatment, and prognosis of cancers, research on this topic is scarce.

1.6.5 COVID-19 Infection

The Global Health 50/50 research institute has published a comprehensive analysis of sex/gender differences in COVID-19 (rates of testing, confirmed cases, severe illness, deaths, and vaccinations). More women received COVID-19 tests, and severe cases and deaths were more frequent in males [17, 51] (Fig. 1.13). Gender-related factors, such as smoking, alcohol use, and the underlying diseases, might contribute to these differences. Another striking difference is that male prevalence ranges from approximately 55 [52–54] to 67% [55, 56] and up to approximately 75% [57, 58], depending on the country, disease severity, and method of diagnosis [9]. Overall, the male-to-female ratio was 2.7:1 [59], which is quite similar to the ratio detected in the outburst of Middle East respiratory syndrome coronavirus (MERS-Cov) in 2012 [9]. For these reasons, the experts think

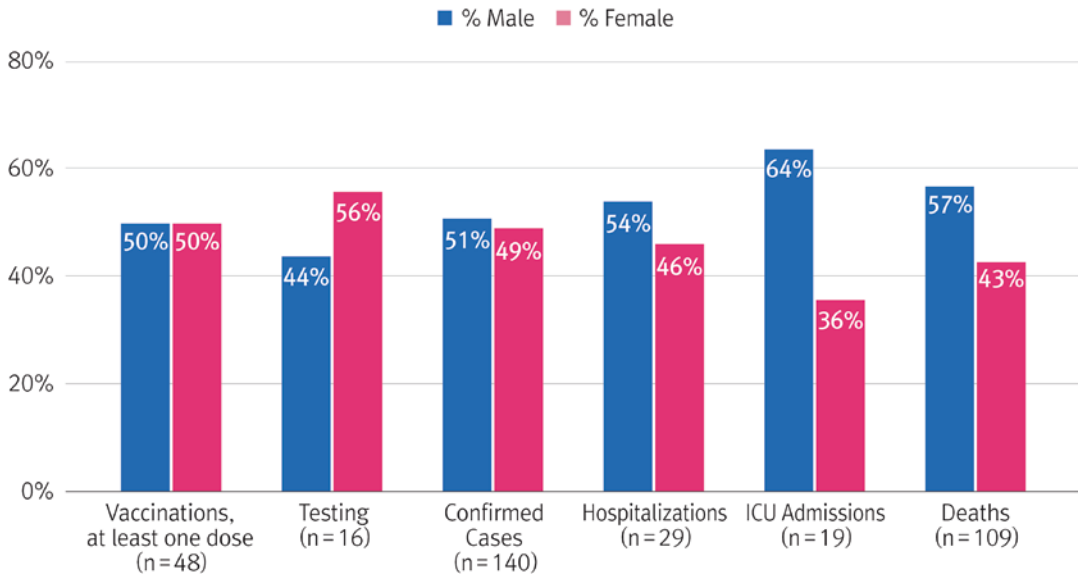

Fig. 1.13 Sex differences along the COVID-19 clinical pathway, September 2022. (Adapted from Global Health 50/50 [17])

that there might be a sex/gender predisposition to COVID-19, with males more prone to being affected [60]. The reduced susceptibility of females to viral infections could be attributed to enhanced innate and adaptive immune responses in females driven by chromosome X and sex hormones [61]. In addition, lower density (or expression level) of angiotensin-converting enzyme 2 (ACE-2), which is the entry receptor for the COVID-19 virus, was found in the lungs of females compared to males [62]. Furthermore, smoking habits and their effects on increased airway expression of ACE-2 could be a reason [63, 64]. However, as only a few studies have provided precise data stratified by age group and sex [65], thus, it becomes a major hurdle to the evidence-based decision-making and policy design [66]. Regardless of susceptibility, there seem to be sex/gender differences in mortality from and vulnerability to the disease [67, 68]. Males were more prone to higher severity and mortality, independent of age [66]. The mortality in males was particularly high among severely ill (or worse) patients and those who need management in intensive care units [57, 69] and when they were under invasive mechanical ventilation [68]. Furthermore, patients with refractory COVID-19 were also more likely to be males, and male sex also was predicted to lead to poorer treatment efficacy compared to female [70]. In addition, indirect effects of COVID-19 also exhibited sex/gender differences. For example, women in the hardest-hit areas of China reported significantly higher posttraumatic stress symptoms (PTSS), compared to men, during the COVID-19 outbreak [71]. Naturally, most of the research to date has focused on adults and the elderly, who are more prone to and affected by the disease. In general, children are less affected [72, 73] and tend to have a milder clinical course, yet the reported proportion of male children is approximately 55% or higher than female children [74–76]. Data on children and adolescent patients with COVID-19 have just begun to accumulate [76, 77].

Although data on sex/gender differences are limited and have not yet been integrated into guidelines and recommendations for disease screening, management, and public policy, evidence for the consideration of sex/gender differences has already emerged [9]. For example, exploration of serial intervals, which refers to the time interval from symptom onset of a primary case (infecting) to that of a secondary case (infected), by regression models has accounted for sex/gender-specific differences [78]. Nevertheless, to date, the international and national responses of countries dealing with the COVID-19 pandemic have neither considered nor addressed sex/gender differences such as "gender norms, roles, and relations that influence women's and men's differential vulnerability to infection, exposure to pathogens, and treatment received" [67]. Moreover, these factors may also differ among different groups of women and men, based on age, ethnicity/race, etc., and therefore should also be considered and integrated into guidelines and health policies [9].

1.7 Health Disparities for LGBTQ+

Emerging research reveals that LGBTQ+ individuals experience higher rates of health disparities [79–81]. These disparities may be driven, in part, by medical providers' biases and lack of knowledge in healthcare settings [79–82]. There has been a tectonic shift in the field of transgender healthcare since 2007, but little is known about how medical, nursing, or dental students are trained to identify and reduce the effects of their own biases toward LGBTQ+ individuals. Over the past decade, the number of people referring to gender identity clinics has rapidly increased [83]. This raises several questions, especially concerning the frequency of gender-affirming treatments with irreversible effects and regret from such interventions [83]. In addition, there is a report regarding the increase of children and adolescents experiencing gender dysphoria.

1.7.1 Gender Dysphoria in Children and Adolescents

Gender dysphoria is defined as an apparent incongruence between assigned sex and experi-

enced gender. Scholars across the world are attempting to develop guidelines for a universal approach for children and adolescents experiencing gender dysphoria [84]. Recent studies have highlighted the importance of the biopsychosocial model as a holistic template for gender dysphoria. Youth with gender dysphoria often evince emotional and behavioral problems resulting from the stress of being marginalized and being forced to inhabit a body that does not match their experienced gender [84]. The assessment processes for young people with gender dysphoria are complex, and child/adolescent psychiatrists must contemplate numerous crucial factors regarding gender identity and possible psychopathologies [84]. Transgender mental and medical healthcare is a long-lasting process during which not only the child/adolescent with gender incongruence but also their parents/family need to be counseled in making choices about their social, medical, and legal transitions [85]. Therefore, an individualized approach by an experienced team is necessary. Taken together, new strategies are needed to assess and mitigate implicit bias toward children and adolescents experiencing gender dysphoria.

1.7.2 The Prevalence of LGBTQ+ from the Literature

The term "transgender" broadly includes people whose gender identity differs from their birth assigned sex, such as trans men, trans women, and intersex individuals born with an ambiguous reproductive anatomy that does not match the typical definitions of binary males or females. Most of the data were based on the American or European population and have pertained primarily to Caucasian people. Canada was the first country to collate and publish data on gender diversity from a national census [86]. According to Canada's 2021 census population report, 100,815 people (0.33% of the population older than 15) were identified as transgender (59,460) or non-binary (41,355) [86]. In addition, it has been estimated that there are 1.4 million transgender individuals (0.6% of adults) in the United States. Due to cultural differences and social stigma, there has been limited research or data related to sexual minorities in Asian countries, especially the transgender population [87]. In Asia, transgender individuals are prone to be hidden than other population groups because their trans status is not always obvious and does not have to be disclosed [88]. Transgender people began to appear as a population in the Korean community in the early 1990s when people sought to change their gender on their legal documents after undergoing gender-affirming surgery [89]. However, there has been lack of information of the social and health disparities faced by transgender people living in South Korea. It is mainly due to the lack of comprehensive epidemiologic data of transgender population and data related to gender identity [90]. Thus, previous literature on health disparities among transgender individuals in Korea relied mostly on web-based surveys in which participants were recruited via various forms of media [91–93]. Recently, there was a pilot study for development of a gender variable model for Health Research in Korea from online survey of 3000 adults in 2022 [94]. Surprisingly, participants identified themselves as men (45.6%) and women (43.9%), and 10.5% selected that they are other gender [94]. It means that relatively high percentage of Koreans think that they are non-binary. It needs to be confirmed by further research.

To determine the disease burden and incidence, set healthcare priorities and goals, advocate for healthcare and treatment programs, and evaluate the impacts of interventions at the population level, it is necessary to identify the denominator of at-risk individuals [95]. According to reports, transgender individuals had limited access to care, higher risk of mental health problems, suicide, violence, discrimination, poverty, and HIV than the general population [96, 97]. Sense of alienation causes psychological distress and increases the likelihood of engaging in risky behaviors and having poor health outcomes [98]. It is therefore important to support these individuals to reduce healthcare disparities.