SEX, GENDER & MEDICINE

TOWARDS EQUITY IN HEALTH

Edited by
Flavia Franconi, Elisa Manacorda

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PREFACE

by Elvira Marasco, Martina Rogato, Linda Laura Sabbadini

In this year when Italy presides over the G20, the W20, along with the delegates of 19 other countries, have discussed the topic of female empowerment. And for the first time there was talk of Health and Medicine and the aspect of gender, and how gender filters into nearly all other aspects of the study.

Gender Health and Medicine studies the impact of "gender", which includes variables such as environment, culture, socio-economic status and how these might affect males and females in different ways. The objective is to understand the various processes through which gender differences impact health and the development of other pathologies, in order to offer the best protection and care for every individual, male and female, thereby ending the gender discimination currently found in healthcare.

The W20 established the "Equity in Health" Commission to bridge the gap between people and politics, with actions geared at increasing the dissemination of and investment in effective strategies to address gender inequality in healthcare.

Professor Flavia Franconi, one of the first in Italy to address this issue, has been called to chair the Commission. Recently, Professor Franconi was nominated to the National Observatory which is dedicated to gender health. There is a lot of work to be done, but the Commission makes use of the finest Italian and international experts in the field. The result of their work is finally ready. Their objective, acting as experts of the field, is to submit their findings to the G20 leaders . It is an ambitious project, but we are certain that we are on the right path. A path which leads to the substantial improvement of the health of all the world's women.

AUTHORS

Elvira Marasco, *W20 Head of Delegation*
Martina Rogato, *W20 Sherpa*
Linda Laura Sabbadini, *W20 Chair*

INTRODUCTION

By Flavia Franconi, Elisa Manacorda

The Covid-19 pandemic has shined a light on a number of basic issues which, if not confronted in a timely manner, could threaten any type of “reopening”, especially as regards a return to normal for the healthcare system.

The long period we have spent with the virus has revealed some grave flaws in healthcare systems around the world. And so it seems necessary to make a global and collective effort to face and resolve these critical issues; beginning from the important topic of biomedical research investment all the way to the patient’s bed.
As far as Italy is concerned, reconstructing the healthcare system in a post-Covid era while integrating various social health factors (poverty, education levels, etc.), now also means including gender.

Sex and gender are often used interchangeably, but they are not, in fact, synonyms. Generally speaking, sex is related to human biology. This takes into accounts the variables, such as genes and sex hormones, that play a fundamental role in determining the male and female phenotypes. Defining gender is more complicated, as can be seen by the vast number of available definitions, as it includes one’s socioeconomic status, income, education, lifestyle, environment, access to healthcare and other social aspects of health. Many of these aspects have been changing over time, and vary between countries and cultures.

It is, however, extremely difficult to separate sex and gender, as they interact with each other in a continuous multidimensional and complex way. So much so that some have proposed using the term “sex-and-gender medicine”, which recognizes the signifigance of both the biological and socio-cultural-economic context.

The Covid-19 pandemic and subsequent lockdown impacted health in a gender-specific way. Morbidity and lethality were shown to be higher in men, but the consequences of the lockdown were more difficult for women, especially in terms of increased poverty, the risk of unemployment, the impact on family life, gender violence, and so on. Moreover, anti-covid-19 vaccine studies did not encompass pregnant women. This demonstrates how the gender division continues to pervade medicine.

But this gender bias in medicine did not begin with the pandemic; it has deep roots. Many errors in diagnosis, in therapy and the outcomes of many diseases can be attributed to the lack of basic research on female animals, and on women in clinical studies. Even today, as indicated by many surveys, only a miniscule part of clinical studies (less than 5%) include sex and gender as analitical variables. This impedes proper care and prevention and perpetes healthcare inequality among women.

This is why, on the occasion of the Italian-led G20, within Women20 Italy - the association that since the Australian 2014 summit has had as its aim the promotion of gender issues in various areas, from work to the environment to digital inclusion - we have created the "Equity in Health" Commission, which includes some of the most noted and globally recognized experts in sex-and-gender medicine. The Commission's objective is to stimulate reflection on the topic of sex-and-gender medicine and to examine how it represents the key to health equality for both women and men.

In this publication, Commission experts describe the numerous findings in the differences between men and women in differing areas of study. From basic research to cardiology and oncology, they explain how implementing a gender-based approach for prevention, diagnosis and care can become a driving force for healthcare equality for every man and woman of every country.

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1. SEX AND GENDER-BASED ANALYSIS

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Sex and gender-based analysis (SGBA) is a reflexive process that involves examining and consciously acknowledging the assumptions and preconceptions that are brought into research and practice, and that therefore shape the outcome for girls, boys, women, men and gender-diverse people [1,2]. There is significant evidence to demonstrate that sex (biological) and gender (social) differences between women, men, girls, boys, and gender-diverse people contribute to differences in their health as well as the treatments they receive [2-4]. A well-executed sex and gender-based analysis will identify ways in which sex and gender influence health and will point to corrective action to ensure that benefits are optimized across all groups.

Sex and gender

The terms sex and gender do not mean the same thing and should not be used interchangeably [5]. As illustrated in Figure 1, *Sex* refers to a set of biological attributes in humans and animals.

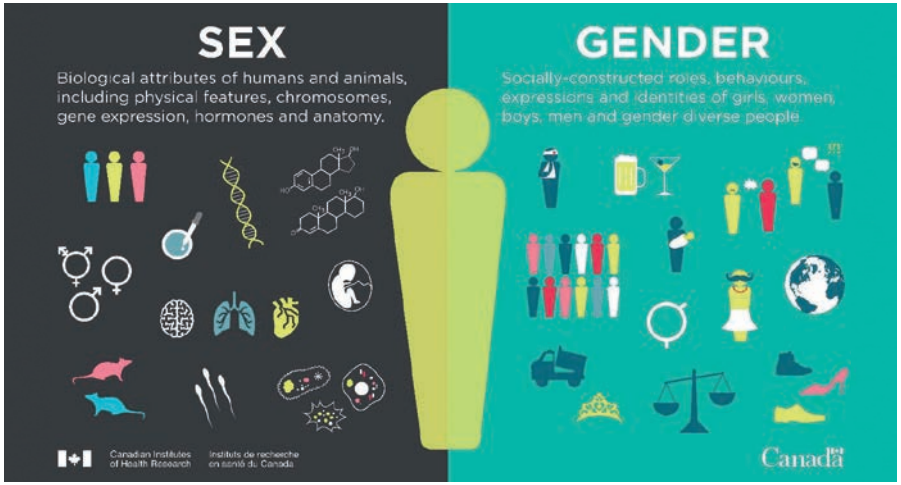

FIGURE 1
What is sex? What is gender? [1]

It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female, male or intersex, while acknowledging the variation in biological attributes that comprise sex and how those attributes are expressed. *Gender* refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Dimensions of gender include gender identity, gender roles, gender relations and institutionalized gender. Gender is not confined to a binary (girl/woman, boy/man) nor is it static; it exists along a continuum and can change over time. Generally, gender identity can be distinguished from sex assigned at birth by inquiring how an individual self-identifies along the gender spectrum.

An analytical process

As SGBA is an analytical process that systematically examines how sex-based and gender-based phenomena affect outcomes, the questions posed and the ways of addressing differences will vary depending on the topic of interest. For instance, a sex-based analysis of the heart might ask whether female (XX chromosomal complement) and male (XY chromosomal complement) cardiac cells behave the same way under healthy and diseased conditions. When both types of cells are included in basic science research, the two cell populations can be studied and compared. If differences are detected, the next step would be to elucidate the mechanism underlying the sex differences. Are differences due to sex chromosomes, hormones, physiology or anatomy? As understanding deepens, the approaches and treatment to the same condition may reasonably vary to address root causes.

Sex and gender-based approach

A sex and gender-based approach to a human patient might start by recording the patient's sex assigned at birth and their current gender identity [6]. Thoughtful reflection could be given to whether the presentation of symptoms is expected to be the same in individuals with different sex and gender characteristics. Might the same diagnostic tests have different sensitivities or normal threshold values, based on sex or gender groupings? Might gendered norms affect the rapidity and effectiveness of seeking access to care? Could gender stereotypes influence how treatments are delivered? Might different doses of medications be required based on sex? What gender biases might be embedded in the systems and algorithms of care or the development of therapies, affording disadvantages to one group or the other? How might we mitigate gender biased decision-making processes and their associated negative effects on outcomes? Might programs and policies be better tailored to rectify inequities? The answers to all these questions is what constitutes a reflexive and productive SGBA.

Health determinants

Ultimately, the purpose of SGBA is to promote rigorous science that considers sex and gender and therefore has the potential to expand our understanding and optimization of health determinants for all people. More recently, however, in countries such as Canada [1], a "plus" has been added to sex and gender-based analysis (e.g. SGBA PLUS) to acknowledge that many other identity factors such as race/ethnicity, socioeconomic status, disability, sexual orientation, migration status, age and geography interact with sex and/or gender to contribute to exposures to various risk factors, disease courses and outcomes (Figure 2). Applying SGBA PLUS brings these considerations into focus and can help formulate health research and gender medicine policies and programs that are relevant to the diversity of the populations.

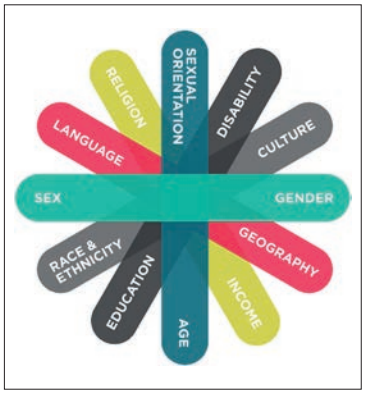

FIGURE 2

Some of the identity factors considered in SGBA PLUS (adapted from Women and Gender Equality Canada – Gender-based Analysis Plus).

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2. SEX AND GENDER BASED MEDICINE: PRECLINICAL RESEARCH

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In preclinical research, scientists test their ideas for new pharmacological and medical prevention strategies in laboratory experiments (cell culture, isolated organs) or animals. Unfortunately, in many biomedical fields, the stratification between male and female cells is lacking in nearly all cellular studies [1]. Furthermore, the majority of preclinical studies use only males or do not report the sex of the animals, and the same occurs in some clinical studies [2,3]. Despite several international organizations encouraging sex-gender studies, research with a gender perspective presents a high degree of complexity and many methodological questions, the majority of which are still neglected. However, it is a basic fact that sex and gender apply to all vertebrates and humans and that sexual dimorphism varies in the species and the strains of animals [4,5].

Therefore, biological differences between the sexes should be considered across the entire range of research, starting from the pre-analytic conditions embodying research in genetics, epigenetics [6], developmental biology, biochemistry, physiology, pharmacology, toxicology, and epidemiology as well as the social sciences adopting all available technologies including omics [6]. In addition, all age stages should be included as biological and social factors are age-dependent, including pre-natal life, because it is recognized that sex differences start in utero [7,8]. In fact, most of the female and male animals used in biomedical research analyses are young. This choice makes experimental results difficult to translate to older populations that may predominate. Longitudinal studies are needed to understand gender differences over the course of life, including the different stages of female life. In addition, the importance of the phases of the estrous or menstrual cycle should not be forgotten and should be indicated in the methods section.

The inclusion of the female sex in preclinical research (XX cells, female animals, organs, and tissues from female donors) and the analysis of data by sex can help to solve, at least in part, the problem of non-reproducibility and gender bias found in preclinical biomedical research. Hence the importance of paying particular attention to methodological issues. Many studies tend to simply compare males and females on a range of health indicators. This is not enough, however, as it is necessary to use more sophisticated experimental designs, redefine old methods and develop new ones to produce new measures to study the influence of sex -gender on health. While some papers focus on methodological issues in sex-gender research [3,9–11], they simply describe differences between males and females and the origin of these differences (the role of hormones, for example) [12], or they discuss animal models of diseases and problems that research on sex-gender encounters after sampling [3,9–11] while neglecting pre-analytical issues, which also include environmental influences. Indeed, pre-analytic procedures can be a source of several errors [13] affecting the predictive value of all analyses. Pre-analytic variations (study design, compliance of the investigated subjects, compliance of the technical staff in adherence to protocols, choice of utilized specimens, sample collection, and processing) are of special interest in sex-gender research, as they could be sex-gender dependent. When creating an experimental design involving the analysis of sex-gender differences, there are specific criteria that should be taken into account to avoid errors in the results and their interpretation [14]:

1. What to do before sample collection as regards animal handling, fasting, stress, restraint, analgesia and anesthesia, dosing, diet, and so on.
2. What to do during sample collection: the choice of the appropriate time of collection; dimension of collection tubes; blood, organ and tissue sampling; collection technique; amount of blood, organ, and tissue; and so on.
3. What to do after sample collection: separation methods, storage time, temperature,etc. The creation of the research team, which should include both men and women, who should discuss the analysis and interpretation of the results obtained. There is indeed evidence that indicates a sex-specific interpretation of the data may create systematic errors.

To overcome gender bias, it is necessary to carry out more studies comparing the two sexes and to incorporate a sex-gender approach throughout the research process. This goes beyond the simple enrollment of both sexes and would improve the goals of personalized and translational medicine [15,16]. Furthermore, the awareness of the differences and similarities between males and females can improve the prevention, efficacy, safety, and appropriateness of the treatments [17,18].
Journal editors should promote the inclusion of participant sex-gender information and/or samples collected in the “Materials and Methods” sections. It is important that

results not showing statistically significant sex-gender differences are also disclosed in order to avoid conducting redundant studies.

As sex affects how an individual will respond to or metabolize a particular drug, it is clear that male and female animals and organs, male and female animal cells, and organelles should be used to screen for drugs, devices, and procedures to provide gender-based medicine that could lead to new therapeutic approaches and strategies that could improve the appropriateness and safety of the therapy.

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3. SEX AND GENDER-BASED ADDICTION

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Addictions or substance use disorders (SUDs) are severe mental disorders characterized by an irrepressible desire for psychoactive substances and, despite the knowledge of their devasting consequences, people with SUDs are unable to think of anything other than obtaining, using, and recovering from these substances [1]. The substances more frequently responsible for addiction comprise legal drugs such as alcohol and tobacco, and illegal drugs like cannabis, opioids, amphetamine-type substances, cocaine, hallucinogens, and other less known substances. Some medications approved for the treatment of mental or physical disorders may also be responsible for SUDs (e.g., benzodiazepines). In addition to psychoactive substances, certain behaviors such as gambling and internet games may induce addictive disorders with symptoms and signs comparable to SUDs [1].

Consequences

Addictions destroy the lives of both people with SUDs and their families [2]. The social and medical consequences of addictions are related to the specific characteristics and toxicity of each substance. Consequences include : the risk of car accidents related to alcohol use, due to its sedative effects; the route of administration of substances; the risk of infections by human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) with heroin and other injectable drugs; and toxicity of the other compounds assumed with psychoactive substances, such as the risk of cancer due to the cancerogenic substances inhaled with nicotine [2]. Psychoactive substances may be harmful even for people who do not use them; for instance, involvement in car accidents caused by people under the effects of these substances. Considering together the harmful effects induced both to those who use, as well as those who do not use, these substances, alcohol is the most harmful psychoactive drug, with heroin and crack cocaine (smoked) following in second and third places [3].

Globally, it has been estimated that in 2016, alcohol was responsible for almost 100 million disability-adjusted life-years (DALYs, a measure that combines burden caused by both premature mortality and disability) while all other psychoactive substances for almost 32 million DALYs. Accordingly, alcohol accounted for around three-quarters (76%) of all substance-use-attributable DALYs. The main causes of alcohol related DALYs included injuries, cardiovascular diseases, and cancers . Those of the other substance-related DALYs comprised cancers, cirrhosis driven by HCV, and HIV. Similar patterns for deaths were observed with almost 3 million deaths attributed to alcohol use and almost 500.000 deaths attributed to other substances [4,5].

Epidemiology

Addictions are amongst the most prevalent mental disorders, with more than 175 million estimated cases worldwide [5]. Alcohol use disorder (AUD) is the most prevalent SUD (more than 107 million estimated cases, more than 60% of all estimated cases of SUDs), followed by opioid use disorders (more than 40 million cases, 23% of SUDs), cannabis use disorders (almost 18 million cases, 10% of SUDs), amphetamine use disorders (more than 7 million cases, 4% of SUDs), and cocaine use disorders (more than 5 million cases, almost 3% of SUDs) [5].

Treatments

SUDs are chronic diseases characterized by long periods of large use of psychoactive substances alternating with periods of abstinence or moderate use of these substances [2]. According to the different period, people with SUDs may require treatment for acute intoxication and/or withdrawal syndrome, and/or chronic treatment to achieve and maintain abstinence or at least reduce consumption of the psychoactive substance [2].

Intoxication and withdrawal may be life-threatening conditions requiring prompt admission to an emergency department. To give an idea of the frequency of hospitalizations for emergencies due to psychoactive substances, in the United States (US) there are almost 5 million alcohol-related visits to Emergency Departments per year [2]. Antidotes are available for the treatment of intoxication of certain substances (e.g., naloxone for heroin intoxication) but not for others (e.g., alcohol). Effective medications are also available for the treatment of withdrawal syndrome of certain substances (e.g., benzodiazepines for alcohol withdrawal syndrome) [2].
Medical treatment to help people with SUDs achieve abstinence or reduce consumption of substances comprises behavioral interventions, support groups (e.g., Alcoholics Anonymous), and medications [2]. The combination of non-pharmacological and pharmacological interventions with the attendance of self-help group meetings contributes towards improving the efficacy of treatment. Behavioral interventions

comprise motivational interviewing, cognitive behavioral therapy, and contingency management [2]. For certain substances, effective medications have been approved by the main international regulatory agencies such as the Food and Drug Administration (FDA), European Medication Agency (EMA) and Australian Therapeutic Goods Administration (TGA). These medications comprise acamprosate, disulfiram, naltrexone and nalmefene for AUD; naltrexone, methadone and buprenorphine for heroin use disorder ; and nicotine replacement therapy, bupropion, and varenicline for nicotine use disorder. No medication is currently available for the treatment of other SUDs.

Priority problems

Although SUDs are historically more prevalent among men than women, their prevalence among women is still relevant. Worldwide in 2016 , almost 30 million and 10 million women suffered from AUD and opioid use disorder, respectively [5]. In addition, gender differences in SUDs are narrowing as the use of psychoactive substances among women has become more similar to those of men [6].

SUDs are usually underdiagnosed and undertreated. Recent studies evaluated that less than 10% of people with actual AUD received any kind of treatment [6] and less than 2% received specific medications for AUD [8]. Compared to men, lower rates of women receive SUD treatments [7], with pregnant women being less likely to receive SUD treatment than non-pregnant women [8]. Conversely, pregnant women should be considered a special population with regards to prioritizing addiction treatment access due to the risks of fetal alcohol syndrome and/or other substances-related consequences in their children.

Numerous barriers to SUD treatment exist, including a lack of sufficient well-trained health care providers with expertise in addiction and the stigma around SUDs. Women usually experience more severe barriers to SUDs treatment than men for several reasons, including responsibility towards their children. Additionally, medications used in the treatment of SUDs have been studied almost exclusively in men (see Figure 1), and these medications are contraindicated during pregnancy because of the complete lack of any evidence among pregnant women [6,8].

Finally, most people are not aware of the sex-specific risks related to the use of psychoactive substances. For instance, the majority of women attending breast screening programmes are not aware that alcohol consumption is a risk factor for breast cancer, the most common cancer worldwide [9].

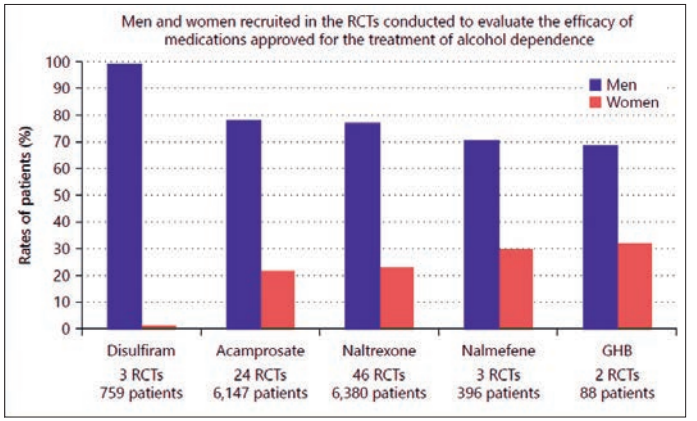

FIGURE 1

Figure 1 of the paper Agabio et al., Efficacy of Medications Approved for the Treatment of Alcohol Dependence and Alcohol Withdrawal Syndrome in Female Patients: A Descriptive Review. Eur Addict Res. 2016b;22(1):1-16.

RECOMMENDATIONS

1. Training in addiction should be increased and ameliorated among health care providers ranging from nurses to specialists in addiction.
2. Proper preventive programs should be developed to increase the knowledge that SUDs are mental disorders, that effective treatments exist, and to increase awareness of the risks related to use of these substances.
3. Appropriate numbers of men and women should be recruited by the studies conducted to evaluate the effectiveness and safety of treatments for SUDs. The results of the studies should also be provided separately for men and women.
4. Services for the treatment of SUDs should take into account the specific needs of men and women with SUDs to reduce barriers to treatment. For instance, as women would prefer to receive treatment for SUDs in sex-and gender-segregated settings, with facilities for childcare(McCrady et al., 2020), services for women with SUDs should offer these facilities.
5. Studies to evaluate the effectiveness and safety of treatment for SUDs among pregnant women should be considered a priority.

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4. SEX AND GENDER-BASED DIFFERENCES IN ONCOLOGY

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Growing epidemiological evidence shows that several differences between men and women are detectable in incidence, progression and response to therapies of various cancers in non-reproductive organs. In general, males have higher incidence and worse outcomes than females [1]. Indeed, different pathogenetic mechanisms have been proposed and partially elucidated from cell level to clinical studies, likely depending on the combined effects of genetic, epigenetic and environmental factors [2,3]. Thus, in the era of precision and personalized medicine, an improved comprehension of factors and connections underlying these differences will improve cancer prevention, treatment and outcomes for all individuals, while considering the possible health-related differences overall the gender spectrum.

Looking at some examples of different cancer susceptibility and outcome associated with sex and/or gender, among many others we can highlight colorectal cancer, bladder cancer and melanoma as tumors displaying important disparities:

Colorectal cancer

Colorectal cancer, the third most common neoplasia in the world, shows a significantly higher incidence in men compared to women with sex hormones being one of the underlying factors . In fact, female sex hormonal factors, specifically estrogen, seem to be protective factor as suggested by the increased risk of colon cancer in older women, and by a 40% reduction of colorectal cancer risk in postmenopausal women undergoing hormone replacement therapy. In addition, recent studies have reported that males have a higher risk of developing CRC due to the action of testosterone and that the measurement of serum-unbound testosterone has been suggested as a novel biomarker.

It is also interesting to note that women appear more prone than men to right-sided colon cancer. Associated with the different localization are different molecular markers, such as microsatellite instability (MSI) and BRAF mutation in females and chromosomal instability and mutation in TP53 and APC oncosuppressor genes in males. In addition, the distance from the terminal part of the intestine of right sided tumors can cause more frequent false negative results in the standard screening for fecal occult blood test [4]. Finally, recent data produced by a German study run on

186.000 patients (46% women and 54% men), among a number of gender biases, evidenced some difficulties in performing a complete colonoscopy in women due to the longer female transverse colon and reduced associated diameter and medical devices whose suitability was validated on men. Besides all these differences, socio-cultural specificities, such as dietary factors, should be considered [5].

Bladder cancer

A gender discrepancy also exists in incidence and outcome of bladder cancer. Men have a threefold higher risk of developing this cancer, which is the fourth most common in men and the seventeenth in women worldwide. Although less frequent in women, epidemiological studies show that women typically present more advanced and aggressive diseases, who in turn suffer worse outcomes. This can be partly explained by a longer delay to get a diagnosis. Often, one of the first signs of this tumor is the appearance of blood in the urine. Since the same symptom can be associated with infections of the urinary tract, which is very frequent in women, they are typically given multiple courses of antibiotics before being diagnosed. This delay can have consequences on prognosis and quality of life [6]. In addition, recent data demonstrated a sexual dimorphism in the tumor immune microenvironment, as indicated by a difference in the expression level of some representative immune regulatory genes, indicative of a female exhausted immune scene [7]. It is interesting to note that the incidence of this disease is now decreasing in men, whereas it is significantly growing in women, possibly because of the direct association of this tumor with smoking, a behavior steadily growing in women in the last decades. Indeed, smokers have a 5-fold higher risk of developing bladder cancer.

Cutaneous melanoma

Cutaneous melanoma, the most aggressive skin cancer, shows significant differences related to ethnicity, age and even more to sex and gender. Worldwide, the incidence is higher in men than in women. Although male/female incidence ratios differ greatly across continents, the female survival advantage has been very consistently reported and gender remains an independent prognostic indicator after adjustment for thickness and body sites [8]. Questions remain as to how much of melanoma development and progression can be attributed to gender specific behaviors or to biological intrinsic differences. Lifestyle plays a role , with ultraviolet rays being an important risk factor combined with women's increased interests in tanning. In addition, men are less probable to engage in prevention or in self-detecting their melanoma lesions. This is due to the different anatomic localization: primary melanomas are frequently found on the backside of the torso in males and on the legs in females. A key reason is represented by the differences in tumor–host interaction. In fact, females have stronger immune responses in comparison to males. Interestingly, a different mutational burden has been reported, with men accumulating more mutations than women. However, the presence of mutations proved beneficial to the female's overall survival, possibly because of the functional pressure of the more efficient female immune system [9].

During the last few years, treatments of melanoma in advanced phases have shown relevant improvement by the introduction of new therapeutic approaches, including target and immunological therapies. Different effectiveness has been demonstrated for immunotherapy, in particular for immune checkpoint inhibitors, sex predictive and responses being lower in female patients [10]. The proposed explanation is that women are less able to mount an efficient host antitumor response due to a sex-specific immune selection during tumor development. This leads to a depletion of the more immunogenic abnormal peptides, which in turn influences the availability of peptides capable of driving effective response to immune checkpoint inhibitor therapy. [11].

Closing remarks

In conclusion, many accumulating data support the relevance of considering sex and gender for selecting the best therapeutic options for each person. Further studies will be required to more clearly define the molecular mechanisms which specifically underlie the anticancer immune response in men and women in order to actually reach tailored therapeutic actions.

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5. SEX AND GENDER IN CARDIOVASCULAR DISEASE

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Knowledge and understanding of Sex and Gender (S&G) differences in cardiovascular disease (CVD) phenotypes is rapidly increasing[1-5]. Nevertheless, significant data gaps need to be closed.

Among young adults, the number of acute coronary symptoms (ACS) is decreasing in men but not in women. Several reasons for this phenomenon were identified: first the pathophysiology of ACS is sex-dependent and current prevention strategies address mainly the atherosclerotic form of disease that occurs earlier and more frequently in men. Women have more non-obstructive coronary artery disease which is less well covered by our guidelines than the atherosclerotic type of disease. They have more endothelial dysfunction, coronary artery spasms or spontaneous coronary artery dissections (SCAD). The mixed pathophysiology of ACS in women leads to an inhomogeneous spectrum of symptoms which makes it more difficult to recognize the syndrome by the environment, by the patient, by physicians and emergency doctors. Thus, women frequently receive emergency treatment later than men.

Hypertension develops differently during the lifetimes of women and men . Women have a lower prevalence in younger age and a higher one in older age. Low grade hypertension has been associated with a higher relative risk for CAD in women compared to men and grade I hypertension was recently identified as a risk factor for ACS in women but not in men. This is not yet reflected in the prevention guidelines.

In heart failure, risk factors like hypertension and diabetes play a greater role in women. The sex-specific interaction of vascular and myocardial function in hypertension described above as well as sex differences in myocardial metabolism may contribute to the fact that women and men differ in the clinical manifestations of HF.

Stress-induced cardiomyopathy affects postmenopausal women in 90% of cases. Sex differences in the brain have been identified as a possible pathophysiological mechanism. However, why the disease affects mainly postmenopausal women has not yet been clarified. Recently, it was shown that emotional stress in general leads to a stronger activation of neuronal activity in the brain of women than in men, and that this induces activation of the immune system in a sex-specific manner and that this is linked to myocardial ischemia preponderantly in women[6].

Biological sex as determinant of CVD outcomes

Some of the sex differences in cardiovascular phenotypes can be explained by biological mechanisms at the gene, cellular- and organ level. Sex-specific effects of sex chromosome complement leads to sex differences in gene expression and cellular function. The X chromosome was neglected in the first GWAS studies and only few polymorphisms were detected. However, more recently, an increasing number of relevant SNP was found on this gene and associated with phenotypes. Cellular function, for example, in cardiomyocytes, neurons, fibroblasts, endothelial and immune cells, depends on sex[6,7]. Organ function and inter-organ crosstalk depends on sex as regards cardiac function, cardiometabolic disorders and brain-heart interaction[8]. Thus, more basic research on sex in CVD is needed.

Gender as determinant of CVD

A substantial amount of differences in cardiovascular phenotypes can be explained by sociocultural, i.e. gender mechanisms. Recent investigations aimed at rendering gender measurable and using it as a single variable, like sex, in multivariate models in clinical studies and retrospective dataset analyses. This makes it possible to detect the impact of gender, of cv phenotypes and to describe the interaction of sex and gender. New methodologies and approaches to assess gender retrospectively and prospectively in cardiovascular studies are required to analyze the impact of sex and gender on CVD prevention, diagnosis, treatments and outcomes.

Sex and gender differences in cardiovascular prevention, management, and outcomes

Sex and gender differences in cardiovascular prevention, management and therapies have been neglected over the years. The weight of classical risk factors such as hypertension is different in women and men. Women exhibit some non-classical risk factors like mental stress, hormonal stress and inflammatory diseases that predispose them to ACS which are not part of the classical risk profile and lead to a later start of prevention measures. Accordingly, women's CVD risk factors are still undertreated and their cardiovascular protection is incomplete [9,10]. A number of cardiovascular drugs have recently been shown to exert different effects in women and men or to be

overdosed in women. The use of implantable cardioverter defibrillators in women is based on studies overrepresenting the male population Consequently, life-saving devices are underused in women.

Precision medicine aims to make predictions on outcomes and suggestions for treatments based on CVD risk markers. To obtain a comprehensive picture of the patient, biological sex and gender should be introduced as a biomarker in precision medicine. This can only be achieved if evidence-based studies measuring the effects of sex and gender will become available. Failure to report sex and gender, as it frequently occurs in cv studies will decelerate medical-technological progress for all individuals and will result in avoidable complications of therapy. The neglect of sex and gender is a major drawback for novel fields such as precision and nanomedicine.

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PROMINENT DATA GAPS

1. Lack of sex- and gender-disaggregated data for disease related morbidity and mortality, in public databases and public health reporting
2. Lack of sex- and gender-disaggregated data in basic research and pharmacology
3. Lack of sex- and gender-disaggregated data on therapy outcomes

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6. SEX AND GENDER-BASED DIFFERENCES IN CHRONIC KIDNEY DISEASE

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On average, men have larger kidneys than women [1] and women have lower absolute glomerular filtration rate (GFR) [2] (the test used to check how well the kidneys are working), on the range of 15-25% [3,4] lower than that of men . Because measuring GFR is laborious and expensive, in epidemiological studies as well as in the clinic we often estimate GFR (eGFR) through equations that use sex, serum/plasma creatinine and occasionally body weight. These equations underestimate kidney function in women to a larger extent than in men[5], in part because of standardizing eGFR by a constant body surface area of 1.73 m^2 regardless of sex [6]. This has implications on two aspects of medicine: our understanding of the burden of the chronic kidney disease (CKD) epidemic and potential risks of drug overdosing, the most-commonly reported adverse drug reaction for women in society.

CKD encompasses a variety of etiologies that result in persistent, progressive and irreversible abnormalities of kidney structure or function. CKD is currently one of the top ten contributors to death worldwide [12,13], being suffered by more 850 million people. The increase of the CKD epidemics in the recent decades possibly relates to the aging of society and the growth of non-communicable diseases, which are in turn its main risk factors. CKD leads to adverse outcomes including kidney failure, infections, cardiovascular disease and death. Fortunately, CKD can be treated, but because CKD is poorly represented in health promotion and public awareness campaigns, many persons remain unaware of their condition and are left untreated.

Drug dosage and efficacy
Drug prescriptions are universal and dosages disregard the morphological and hemodynamical differences in the kidneys of men and women [7]. Underestimation of kidney function in women possibly results in infra-therapeutic dosages and low efficacy for drugs that require strict dose adjustment. Further, drugs that are excreted unmetabolized in the urine tend to be cleared more slowly in women [8], such as for example gabapentin, pregabalin, digoxin, methotrexate, cephalosporins or vancomycin [8-11]. Being aware of these differences may prompt the prescription of lower dosages of these medications based on GFR in women to avoid adverse effects.

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CKD prevalence
In large population-based studies, CKD appears to be more common among women (average population prevalence 10.4%) than men (11.8%) [12,14]. This increased prevalence among women may be explained by the overestimation of kidney function in women explained above. Some etiologies of CKD are sex specific; for example, autoimmune kidney diseases such as lupus and pyelonephritis are more common causes of CKD in women, but hypertension or glomerulosclerosis are more common causes of CKD among men [6]. Complications during pregnancy, such as pre-eclampsia and other hypertensive disorders pose additional risk for women developing CKD later in life [15]. Men with CKD often develop low anabolic drive, in part attributed to testosterone deficiency, which increases the risk of muscle catabolism, cachexia and frailty [16].

CKD progression
Despite a higher CKD prevalence in women, the progression of CKD (i.e. the speed at which the kidney function is lost) is more rapid in men [6,17-19], and as a consequence more men than women initiate kidney replacement therapy (i.e. maintenance dialysis or transplantation) every year [20]. Several hypotheses have been proposed to explain this disparity in CKD progression [6,21], which can broadly be summarized into biological and non-biological factors. Biological factors include the different comorbidity burdens between sexes [22] (although this may be the result of differences in lifestyle habits) and affects of sex steroids on nephrons [23-25]. Non-biological factors may involve socioeconomic/cultural barriers such as lower disease awareness among women [26], lower surveillance/monitoring rates [27] and disparities in healthcare access [28], which in some health systems result in late or no initiation of kidney replacement therapy among women [29].

Treatment differences
Reports globally suggest that women are less likely to receive kidney transplants [6] even though they donate kidneys more often and despite similar survival benefits from transplantation [6], which may suggest gender inequalities. Elderly women more often choose conservative care [30], possibly because more elderly women than men live alone and lack a caregiver. Upon commencement of hemodialysis, women appear less likely to receive arteriovenous fistulas31, the preferred choice of vascular access for the dialysis exchange, in part because of the debunked myth [32] that smaller vascular diameters make positioning these devices more difficult in women. Other potential treatment differences such as dialysis overdose or larger amounts of erythropoietin-stimulating agents among women have been attributed to extrapolating men's observations to women [33,34].

Within this panorama, recent studies suggest that women on dialysis have higher hospitalization rates and report lower quality of life, higher symptom burden and greater symptom severity than men [6].

Closing remarks

A better understanding of sex and gender differences in CKD is needed to provide mechanistic clues into susceptibility and resilience to disease onset and progression, while uncovering the socioeconomic and cultural barriers that contribute to health disparities between the sexes. Investigating mechanical devices not only in men but also in women will prevent inaccurate assumptions that can limit a woman's access to new interventions. Furthermore, awareness of sex differences in body surface area, pharmacokinetics and pharmacodynamics will aid in avoiding risk of overdosing in women with CKD. Ultimately, these studies will lead to the discovery of new drug targets and avoid missed opportunities for sex-specific therapeutics to treat CKD [22].

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7. SEX AND GENDER DIFFERENCES IN DIABETES AND OBESITY: FROM PATHOPHYSIOLOGY TO PREVENTION AND PERSONALIZED THERAPY

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The alarming rise of obesity and type 2 diabetes mellitus, namely "diabesity", and associated complications go along with mounting evidence of clinically important sex and gender differences. Type 2 diabetes mellitus and associated complications come along with reduced quality of life and life expectancy. One's sex is a fundamental biological factor, which plays a key role in regulation of glucose, lipid and energy homeostasis in health and causes vulnerability to cardiometabolic risk factors, as well as manifestation, clinical picture, and management of diabesity.

Severity of injury differs in a sex-specific way regarding various comorbidities, especially reproduction, sexuality, cardiovascular and renal disease as well as cognitive and psychiatric disorders. Pregnancy is a vulnerable period, both maternal obesity and diabetes impact the health of future generations in a sex-dimorphic way. Therefore, care during obese and diabetic pregnancy demands special attention.

Culture and psychosocial factors also impact the development and progression of diabetes and coping in a gender-dimorphic way. Overall, women with diabetes bear greater increases of cardiovascular risk, myocardial infarction, and stroke mortality than men, compared with nondiabetic subjects. Diabetic women on dialysis also show higher risk of renal complications and comparable mortality rates. Diabetes appears to attenuate the protective female effect in the development of cardiovascular diseases and nephropathy. Therefore, early diagnosis and optimal therapy is essential and biological factors, including age and sex as well as psychosocial factors and gender issues, should be considered. However, up to now, sex and gender have had no impact in most clinical guidelines and decisions.

Nevertheless, side effects of drugs as well as choices and preferences of and adherence to therapies differ between men and women. Antihyperglycemic drugs differ in regard to their risk of cardiorenal complications, hypoglycemia, effects on weight and possible associations to risk of fractures and certain cancers. Metformin is the first choice for both men and women and appears to be particularly effective in women with previous gestational diabetes and obese men and women. Overall, women have higher risk of hypoglycemia on insulin therapy. Due to higher risk of stigmatisation of obese women, weight loss is even more important for women, favouring SGLT2 inhibitors or GLP-1 analogues. Overall, women seem to have lower success of antihyperglycemic therapies despite suffering more from drug side effects. Most clinical studies still include more men than women and do not stratify data analysis by sex. Taking into account sex and gender in diabetes management could contribute to more personalized better care in the future.

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8. SEX DIFFERENCES OF THE IMMUNE SYSTEM

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The immune system is a silent orchestra in which an enormous number of instruments (i.e. cells, antibodies, mediators such as cytokines, among others) contribute to the two major goals of immunity, namely to fight infections and to maintain tolerance to harmless stimuli. When the first goal fails, infections take place; while when tolerance breaks down, allergies and autoimmune diseases are found. Our immune response to external agents is based on two arms, namely the innate and acquired immunity, which have numerous ways of interacting . Innate immunity is the first to respond when viruses or bacteria enter our body and is the most ancient type of immunity, being shared with very simple organisms. On the other hand, acquired immunity is a more refined way to respond and is based on T cells and B cells which produce antibodies. Memory is a key feature of immunity and protects us should we encounter a pathogenic agent more than once .

Men and women show a series of differences when it comes to their immune system. In fact, some data show that women are more resistant to infections than men , in particular that they develop less aggressive complications and recover more quickly, as illustrated recently by COVID-19. In fact, the male and female reaction to the virus is different, with a stronger response from women and with 6/10 cases of Covid-19 infection in male subjects. There are many hypotheses on this aspect, such as the different expression of the molecule which allows the body to be invaded by the virus, the ACE2 protein, whose gene is located on the X chromosome, one of the sexual chromosomes in double copy in females. Moreover, females tend to have a better response to many vaccines.

It is fascinating to speculate that the evolutionary explanation for the differences between sexes rests in the fact that women of child-bearing age must be protected and must protect their offspring through placental transfer of antibodies against infections which represented the predominant causes of death for many centuries. In the same perspective of offspring protection, in the placenta, at the very interface between mother and fetus, there are mechanisms of protection against fetal loss caused by maternal inflammatory diseases. Women have a stronger immune response against viruses and bacteria, but also produce higher levels of autoantibodies to infections and vaccines. Moreover, some cells of the immune system (called dendritic cells and lymphocytes) work more efficiently in female subjects. Relevant to the sex differences of immunity, all functions are influenced by sex hormones (especially estrogens modulating the reproductive cycle in women), nutrition and the gut microbial environment, and by genetic factors linked to the two X chromosomes that characterize females.
The other side of a stronger immune system in female patients is related to the higher risk of developing systemic autoimmune rheumatic diseases that can affect women in up to 80-90% of cases, as observed for Systemic Lupus Erythematosus and Rheumatoid Arthritis, and different mechanisms may cause this observation. First, as stated earlier,sex hormones, in particular estrogens, act on the immune system. From a clinical perspective, most autoimmune diseases improve during pregnancy and change their manifestations with menopause when estrogen levels decrease. Second, females and males have different intestinal microbial systems (the gut microbiota), due to several environmental factors such as nutrition and hormones. There is also emerging evidence for sex differences in response to cancer immunotherapy.

In conclusion, the study of sex differences in the immune system has an enormous potential to allow a better definition of the mechanisms leading to autoimmune diseases and infections, thus proving instrumental to a personalized approach to complex diseases. Immunology represents a frontier in the perspective of gender medicine.

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9. METHODS FOR SEX, GENDER, AND INTERSECTIONAL ANALYSIS IN HEALTH & BIOMEDICINE

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Improving women's health and understanding sex differences in health and biomedicine requires state-of-the art methods. The methods reported here were developed by the European Expert Group, Gendered Innovations, from 2018 to 2020 to support European research under Horizon Europe.

Analyzing Sex

The European Commission[1], the U.S. National Institutes of Health[2], and the Canadian Institutes of Health Research[3] all require "sex as a biological variable" as a requirement of funding. The idea is that if taxpayer money is to be used, the research should benefit all across the whole of society, not just a privileged few.

The method shown below highlights that analyzing sex is important to each phase of the research process and details some critical steps for each phase[4].

How is analyzing sex crucial to getting research right? Take the example of stem cell research. Why might the sex of the cell be relevant? Stem cell therapies hold great promise for treatments for debilitating diseases, such as Parkinson's disease and muscular dystrophy, although few are currently in use. Oddly enough, most research today is still done in males.

Taking sex into account will be important when it comes to advancing basic knowledge. Research has documented potential sex differences in the therapeutic capacity of stem cells. Muscle-derived stem cells, for example, show variability in proliferation and differentiation. Researchers found that XX cells show a higher regenerative capacity than XY cells[5]. This may constitute an important clinical finding, but requires further investigation. Researchers should consider all combinations of donor/recipient sex

[1] *European Commission (EC), Gendered Innovations 2: How Inclusive Analysis Contributes to Research and Innovation, eds. Londa Schiebinger and Ineke Klinge (Luxembourg: Publications Office of the European Union, 2020).*
[2] *Arnegard M.E., Whitten L.A., Hunter C., Clayton J.A. Sex as a biological variable: a 5-year progress report and call to action. Journal of Women's Health. 2020 Jun 1;29(6):858-64.*
[3] *Haverfield J., Tannenbaum C. A 10-year longitudinal evaluation of science policy interventions to promote sex and gender in health research. Health research policy and systems. 2021 19(94):1-12.*
[4] *EC, Gendered Innovations 2; also available at: Gendered Innovations: General Methods: http://genderedinnovations.stanford.edu/methods/sex.html*
[5] *http://genderedinnovations.stanford.edu/case-studies/stem_cells.html#tabs-2*

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ANALISING SEX

Enhances all phases of research

	IDENTIFY PROBLEM	DESIGN RESEARCH	COLLECT DATA	ANALYZE	DISSEMINATE
1	Sex may play a role in all studies involving humans or non-human animals	Sex may serve as a direct explanatory factor or act as a potential modulator for associations between other factors; drawing a causal diagram helps make underlying assumptions explicit (see e.g. Buckley et al., 2017)	Consider how to collect information on intersex subjects and hermaphrodite animals	Examine overlaps between and variation between groups of different sexes (see, e.g., Maney et al., 2016)	Report the sex of your subject even in single-sex studies
2	Perform a literature review to identify how sex may be of relevance to your study (Moerman et al., 2009)	In experimental studies, consider factorial designs to reduce the sample size required for sex-based comparisons	Includes adequate numbers of females and males and, where relevant, intersex or hermaphrodites of different configurations in research samples	Consider the sources of any sex difference observed, including the role of environmental, genetic, hormonal or anthropometric factors	Report the sex distribution of the cells, animals, or human subjects
3	Consider whether sex is a covariate, confounder or explanatory variable	Consider how sex should be conceptualized in data collection; does your research concern physiological, hormonal, anthropometric, or biomechanical aspects? (Tannenbaum et al., 2019)	Record information on factors da intersect whit sex (e.g. age, life-style, socioeconomic status)	When examining sex differences, adjust for possible intersecting and confounding factors (e.g. age). Overlooking confounding factors may result in overemphasising sex differences	Report how information on sex was obtained
4	Consider what sex-related characteristics are of relevance to your study (e.g. genetic, physiological, hormonal, anthropometric, biomechanical, injury thresholds, levels of pain tolerance, etc.)	In longitudinal research, consider how reproductive history may influence the cohort under investigation; will, e.g., data acquisition be impacted if females get pregnant during the study?	In experiments, consider how the sex of the researcher may impact research outcomes (Chapman et al., 2018)	In longitudinal studies examine how observed sex variations evolve over time	Disaggregate reports results by sex
5	Consider how sex-related factors interact with gender, ethnicity, age, socioeconomic status, lifestyle etc.		In survey research, questions about gender should not be used as a proxy for birth sex	Analyze how observed sex differences may vary by factors such as age, ethnicity, socioeconomic status	Ensure that sex variations are properly visualized in the tables, figures and conclusions
6	Consider what opportunities have been missed in the past as a result of failing to analyse sex		In product and systems design, data collection should pay careful attention to anthropometric biomechanical and physiological factors that vary by sex (Tannenbaum et al., 2019; Jingwen et al., 2012)		Avoid overemphasising sex differences. Are observed sex differences of practical significance? (Maney et al., 2016; Ribbon et al., 2014)
7					Report all results: positive negative and inconclusive
8					Consider following the SAGER publication guidelines (Heidari et al., 2016)

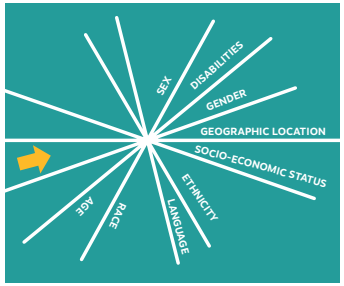
interaction before ruling out sex as a variable. This type of donor/recipient analysis has also been important in human organ transplant.
The effects of sex, however, may also vary by type of stem cell used, type of disease treated, and hormonal and environmental factors, plus their intersections. It is complicated, but research that takes these factors into account leads to better outcomes.

Analyzing Gender

Sex refers to biological characteristics[6]. Gender, by contrast, refers to sociocultural attitudes, behaviors, and identities[7]. It is also important to analyze gender through all phases of research (see below)[8].And, importantly, sex and gender interact[9], as seen through the example of chronic pain[10].
Pain has both biological aspects, for example, sex differences in electrical, ischemic, thermal, pressure, and muscle pain sensitivity. Pain also has cultural aspects in how people report pain, and how physicians understand and treat pain in patients. Gender identity may influence a person's willingness to report pain. Gender norms in many cultures expect men to be strong and resolute, which means that men may be less willing to express pain than women. This, of course, will vary by ethnicity and other social factors. In addition, gender relations means that the gender expectations of physicians in relation to gendered behaviors of patients may influence what treatments are prescribed.
Clinicians often perceive women's pain to be psychological; consequently, women receive more non-specific diagnoses, wait longer for treatment, and receive more antidepressants and fewer painkillers than men.

Intersectional Approaches

Finally, it is also important to consider intersectionality. Intersectionality describes overlapping or intersecting factors related to sex, gender, age, ethnicity, socioeconomic status, sexuality, geographic location, disabilities, etc. that impact health outcomes[11].



[6] http://genderedinnovations.stanford.edu/terms/gender.html
[7] http://genderedinnovations.stanford.edu/terms/gender.html
[8] EC, Gendered Innovations 2; also available at: Gendered Innovations: General Methods: http://genderedinnovations.stanford.edu/methods/gender.html
[9] http://genderedinnovations.stanford.edu/methods/intersect.html
[10] EC, Gendered Innovations 2; also available at: http://genderedinnovations.stanford.edu/case-studies/pain.html#tabs-2
[11] http://genderedinnovations.stanford.edu/methods/intersect.html

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ANALYZING GENDER

Enhances all phases of research

	IDENTIFY PROBLEM	DESIGN RESEARCH	COLLECT DATA	ANALYZE	DISSEMINATE
1	Gender may play a role in all studies involving humans (Tannenbaum et al., 2019)	Consider how to involve diverse groups of research subject/end-users in the project life-cycle to ensure inclusive solutions	Collect data across gender characteristics (e.g. gender norms, gender identities, and gender relations) and intersecting factors	Conduct analysis of relevant factors related to gender norms, gender identity and gender relations (Nielsen et al., forthcoming)	Report sample characteristics by gender, sex and relevant intersecting variables
2	Perform literature searches with adequate terms for "gender" and "sex" (Oertelt-Prigione et al., 2010)	Consider which methods (qualitive and quantitative) are suited for examining the gender dimensions of relevance to your project	In survey research use the two-step approach to collect data on gender identity and birth sex (Deutsch et al., 2013). Ensure that all participants feel safe disclosing their gender identity	When using existing data, consider the cultural or institutional context in which the data were generated for potential gender biases	Report how information on gender identity was obtained
3	Consider the project's relevance in relation to different gender identities, norms and relations	Use appropriate sample size for gender comparison (Sell, 2017)	Ensure equal access for women, man and gender-diverse individuals. Is oversampling needed to ensure a sufficient number of gender-diverse participants? (Vaughan, 2017)	Examine similarities between groups (i.e. men, women, and gender-diverse individuals) and variations within groups (Hyde, 2005)	Disaggregate reported results by sex and gender
4	Consider relevant factors intersect with gender (age, socio-economic status, ethnicity etc.)	When measuring gender in survey research, ensure that your instrument has been psychometrically validated in the target population (Steenkamp & Baumgartner, 1998)	Consider how gender relations between researchers and participants may impact data collection (Chapman et al., 2018)	Examine how observed differences between women, men and gender-diverse individuals relate to gender norms and relations	Report all results: positive, negative, and inconclusive
5	Reflect upon your own gender assumptions in relations to the project	Inspect your analytical concepts, categories, and theoretical models for misguided or stereotypical assumptions		Examine how observed gender differences vary by factors such as age, ethnicity, socioeconomic status	Ensure that gender variations are properly reported in tables, figures, and conclusions
6	Consider what opportunities may be missed by failing to analyse gender and intersecting factors	Consider the risk of stereotyping or excluding relevant groups		In longitudinal studies, examine how observed gender variations evolve over time	Avoid overemphasizing gender differences. Are the observed variations of practical significance? (Nelson, 2017)
7				Consider how gender norms, identities and relations intersect to shape people's experiences, opportunities and practices	Consider following the SAGER publication guidelines (Heidari et al., 2016)

We saw the importance of intersectionality already in the study of stem cells above. We also see this in the example of medical technologies, such as the pulse oximeter, so important during COVID, and other wearables, such as the Apple Watch, Fitbit, etc.

Pulse oximeters were first developed in Japan in 1972. We discovered in 1989, however, that they do not accurately report oxygen saturation levels in patients with darker skin. Why is that? Pulse oximeters measure oxygen saturation in the blood by shining infrared light through the finger to measure oxygen in the blood. The problem is that the device does not work well because both deoxyhemoglobin in the blood and melanin in skin absorb light.

An analysis of over 47,000 readings done in the U.S. in 2020 at the height of the pandemic found that oximeters misread blood gases 12 percent of the time in patients with darker skin compared to 4 percent of the time in patients with lighter skin. This means that patients may not get the supplemental oxygen needed to avoid damage to vital organs, such as heart, brain, lungs, and kidneys.

But what about sex? Is an intersectional analysis required? There may also be sex differences in pulse oximeter reading, but it has not been made a research priority and current findings are inconclusive. A 2007 study suggested that pulse oximeters do not work well for women or anyone with smaller fingers. The 2020 study of 47,000 patients also found a slight sex difference. If we analyze how skin tone intersects with sex, we see that women with darker skin are the most at risk.[12]
What is true for pulse oximeters is also true for consumer wearables. Apple Watch, Fitbit, or other wearables collect a wealth of health-related information, including oxygen levels, sleep heart rate, arrhythmia, etc. The problem with devices that use infrared, red, or green light signaling is that these signals interact with skin pigmentation, and accuracy may vary with skin tone. This means basic data collection may be flawed.
We could summarize other methods and examples. The European Commission Expert Group also developed methods for: analyzing gender in health & biomedicine, analyzing sex in biomedicine, analyzing sex in cells and tissues, analyzing sex in lab animal research, and analyzing gender and intersectionality in machine learning[13].

[12] *Zou J, Schiebinger L. Ensuring that biomedical AI benefits diverse populations. EBioMedicine. 2021 (67):1-6.*
[13] *EC, Gendered Innovations 2.*

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RECOMMENDATIONS

Policy is one driver of innovation and can help health and medical researchers integrate sex, gender, and intersectional analysis into their research. Three pillars of the science infrastructure need to coordinate policies*:

1. *Funding agencies.* Funding agencies, especially publicly funded granting agencies, can ask applicants to explain how sex, gender, and intersectional analysis is relevant to their proposed research, or to justify that it is not. The European Commission is a leader here and requires this of all applicants to Horizon Europe. In the U.S., the National Institutes of Health requires sex analysis in all proposals; the Canadian Institutes of Health Research also encourage sex and gender analysis in all proposals.
2. *Editorial boards of peer-reviewed journals.* To guarantee excellence, editors of peer-reviewed journals can require sophisticated sex, gender, and intersectional analysis when selecting papers for publication. The Lancet adopted such guidelines in 2016 followed quickly by the International Committee of Medical Journal Editors. Numerous other medical journals have implemented the Sex and Gender Equity in Research (SAGER) guidelines**.
3. *Universities and research institutions.* To support research and to train the next generation, universities must integrate knowledge of sex, gender, and intersectional analysis into the curriculum. This is highly important-especially in medical schools. We need more progress in this area.

*** Tannenbaum C, Ellis RP, Eyssel F, Zou J, Schiebinger L.** Sex and gender analysis improves science and engineering. *Nature.* 2019 Nov. 575(7781):137-46. Policies for funding agencies, peer-reviewed journals, and university curricula can be found at: http://genderedinnovations.stanford.edu/policy_landing.html.

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10. LACK OF INTEGRATION OF SEX-BASED MEDICINE CAUSES INEQUALITIES IN HEALTHCARE

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Sex and gender (S&G) inequities in health are evident across the lifespan from birth to older age. Women's health is an unfinished agenda with large gaps and unmet needs persisting. Sex and gender is not systematically integrated into policy, programmes, education, training, research, data collection or analysis. Existing policies, for example in clinical trials, are not fully enforced[1].

Major diseases including cardiovascular disease, cancer and respiratory disease, account for nearly four-fifths of women's (and men's) deaths on the continent of Europe[2]. Mental health and neurological disorders are the third highest cause of death in the EU when stroke (which accounts for 35% of deaths from neurological disorders) is included. These include neurodegenerative disorders such as Parkinson's disease, Alzheimer's and other dementias and mental disorders including schizophrenia, depression, bipolar disorder, alcoholism, and drug abuse[3].

Large differences exist between men and women regarding prevention, disease development and progression, diagnosis, treatment, and care of various health conditions. Yet, there is a lack of comparable cross national health data that sufficiently disaggregates by factors, including sex and gender, age, and ethnicity. Robust age as well as sex and gender analysis of data is often lacking, resulting in gaps in evidence-based medicine and research, particularly for women and older people. To improve existing policy and practice, research design should include sex and gender, and research results should produce sex and age disaggregated data.

Pregnancy and breastfeeding

Innovation efforts are not always aligned to public health needs. For example, there is a certain knowledge gap in the treatment area of safe medicines used during pregnancy and breastfeeding. It is important to create awareness of the safe use of medicines, including vaccines during pregnancy and lactation, in the development of new initiatives and health tools to combat infectious diseases[4].
The IMI funded project Conception is addressing the lack of information on medicines during pregnancy and lactation for both women and their health care providers[5]. However, many women need to take medication during pregnancy to manage their health condition, so in some cases, avoiding or stopping medication use during pregnancy may be more harmful than taking a medication. As more women postpone pregnancy, the use of medicines during pregnancy is likely to increase. In its new Regulatory Science Strategy 2025, the European Medicines Agency (EMA[6]) has addressed various unmet medical needs for certain population groups such as pregnant and breastfeeding women and older people.

Ageing and dementias

One of the biggest challenges facing societies is maintaining health across the lifespan particularly considering an increasingly ageing population. Europe has the highest proportion of older women in the world. Women are on the forefront of ageing due to their greater longevity, their multiple caregiver and societal roles and their lower financial resources. Despite women's increased lifespan, their older years are disproportionately burdened by ill health. Women outlive men by more than five years, but the difference in healthy life expectancy is less than nine months.

Women are at the epicentre of the Alzheimer's crisis. In the EU, Alzheimer Europe estimates that close to 6 million women have dementia[7]. The proportion of women aged over 75 is expected to double by 2060 (from 5.5% to more than 10% of the total population). Given these trends and the strong impact of ageing on dementia risk, it is projected that the numbers of older women with dementia will increase substantially in the coming decades. There are women-specific risk factors for dementia, like pregnancy induced hypertension, and pre-eclampsia. Pre-eclampsia has been associated with higher risk for cardiovascular disease and cognitive impairment later in life. Hysterectomy and oestrogen loss after menopause may increase risk in women[8].

Progression of dementia is different between men and women. However, clinical data are rarely stratified by sex. Women experience the strain of caring for family members with dementia more acutely, reporting higher levels of stress, depression and anxiety symptoms as well as lower levels of quality of life[9].

Healthcare professional education

Apart from reproductive health, it is rare that sex and gender are considered in healthcare professional education curricula. Over the last ten years, the importance

[1] *European Institute of Women's Health (2018b) Right from the star conference. Available from eurohealth.ie/ report-21st-anniversary-expert-conference*
[2] *Eurostat 2017a*
[3] *Global Burden of Disease Study 2017 (EU-28)*
[4] *European Institute of Women's Health Policy Brief-Safety of Medicines in Pregnancy and Lactation (2018)*
[5] *European InsWtitute of Women's Health (2018b) Right from the star conference. Available from eurohealth.ie/ report-21st-anniversary-expert-conference*
[6] *https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy*
[7] *Alzheimer's Disease International (2015). Women and Dementia, a Global Research Review. Alzheimer's Disease International: London, UK.*
[8] *European Institute of Women's Health-Women and Dementia in Europe 2019*
[9] *European Institute of Women's Health-Women and Dementia in Europe 2019*

of sex and gender in medical healthcare research and treatment of medical conditions has been increasingly recognised. However, the need for integration of this knowledge into healthcare professional education curriculum remains a challenge[10].

Acknowledging the impact of sex and gender differences in medicine increases the quality of health care provision. A patient-centred evidence-based sex and gender perspective is required throughout healthcare professional curricula including all levels of undergraduate, graduate, and continuous education for medical, nursing and pharmacy, as well as all allied healthcare workers. Incorporating information generated from the growing discipline of sex and gender-based medicine in educational and training programmes improves access to high quality health care and, thereby, improves patient outcomes.

Final considerations

Leadership and commitment is needed to ensure sex and gender are included as part of the health care continuum from research to implementation of treatment and care for better health outcomes. This will require changes in governance that integrate, for example, women's lifelong needs into health policies and intersectoral action. Policy makers must listen to and engage with women in expressing their unmet health needs across the life course and their experiences, good and bad, with the health system. An example of a governmental commitment to women's health is Ireland. Women's health is included in the Programme for Government. The Minister for Health at the Department of Health established the Women's Health Task Force in 2019 and allocated a budget to initiate a radical listening exercise to hear diverse women's experience of the health system response to their needs and, based on their feedback, to produce a Women's Health Action Plan[11].

The translation of sex and gender differences into biomedical and health research, as well as regulatory and healthcare practice is essential to reduce the impact of health inequities on women. There must be an investment in a life-course approach to health promotion and disease prevention at critical points from preconception to childhood through older age which incorporates the impact of the social determinants of health to ensure equity of opportunities for women and men in all policies to foster a healthy lifestyle.

[10] *European Institute of Women's Health Policy Brief-Sex and Gender in Health Professional Education*
[11] *Department of Health Ireland-Women's Health Task Force, https://www.gov.ie/en/campaigns/-womens-health/*

RECOMMENDATIONS

1. Move from the description of sex differences to a more systematic approach of implementation into regulatory and clinical practice for the benefit of patients.
2. Cross-national collection of data must be disaggregated by sex, gender, and age, to target health policy and programmes based on different population group's needs.
3. Robust post-marketing data for pregnant women should be collected and common rules for pregnancy exposure registries should be developed.
4. Integrate sex and gender into healthcare professional education.
5. Prioritise sex and gender considerations in all European funding mechanisms, evaluations and assessments, including the EU 4 Health Programme and Horizon Europe.

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11. HOW TO MEASURE GENDER IN CLINICAL STUDIES

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Sex (biology) and gender (social construct) do make a difference when it comes to health of citizens.
Health is defined by the World Health Organization (WHO) as *"A state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity"*.

Therefore, incorporating gender and sex in health research is desirable and this approach fits the need of delivering personalized and tailored solutions to health problems in the era of precision medicine.
Identifying sex- and gender-related modifiable factors that shape health and disease is extremely useful to develop new solutions to health problems. The COVID-19 pandemic has raised these aspects of healthcare even more strikingly. While differences in health status and outcomes have been predominantly attributed to biological sex, it is now increasingly recognized that sociocultural gender influences the risk of developing certain diseases, presentation of symptoms, severity of illness, response to drugs or non-pharmacological interventions, and even how one seeks health care.

A lack of method
When considering gender in the evaluation of clinical findings, the first hurdle for clinical researchers to cross originates from the lack of a standardized method to measure the complexities of all that gender encompasses. Gender is, in fact, a complex construct which includes at least four dimensions: gender identity, relations, roles, and institutionalized gender (see Table below).

DIMENSIONS OF GENDER	DEFINITION	EXAMPLES
IDENTITY	How an individual self-identifies, including how they behave, express their gender, and are perceived by other people	• Stress • Personality traits • Anxiety and depression • Self-reported gender identity (e.g., woman, man, non-binary)
RELATIONS	How individuals interact with and are treated by other people based on their perceived and/or expressed gender identity	• Marital or relationship status • Social support • Family or local network (i.e., social capital) • Experiences of gender-based violence • Experience with healthcare providers (e.g., use of gender inclusive language)
ROLE	Social expectations and norms typically associated with a given gender	• Household responsibilities • Family caregiver or parental responsibilities • Occupation or employment status • Primary earner status
INSTITUTIONALIZED GENDER	The way power, resources, and opportunities are distributed in society based on gender	• Wage gap • Education level • Retirement eligibilities

A researcher can decide to explore the role of the gender-related factors (i.e., any individual characteristic that falls under any of these 4 domains) in health depending on the original research question that needs a response. The databases of clinical studies which include all clinical and sociodemographic data of patients with a certain disease can be utilized to generate new sex- and gender-sensitive evidence.
Commonly a researcher can deal with already collected data (i.e., retrospective analysis of data) or can decide to design a new study which includes the collection of gender-related factors among the variables of interest (i.e., prospective new collection of new gender-related data)
(Figure 1).

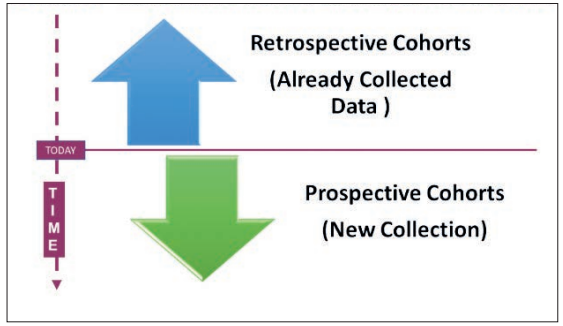

FIGURE 1
Clinical Scientist - which database to use for answering a research question

Going Fwd

For a retrospective evaluation of the effect of gender on clinical and patient-relevant outcome **(retrospective studies)**, a first obstacle is that the gender-related variables are only barely collected in clinical studies and even when they are available, they are neglected as potential determinants of health outcomes, mainly for a lack of awareness and knowledge on their importance. Therefore, the GOING-FWD (Gender Outcomes International Group: to Further Well-being Development) transatlantic network (https://www.mcgill.ca/going-fwd4gender/), funded by the GENDER-NET Plus Initiative specifically set up to promote equity in health, has developed a 5-step methodology for guiding researchers in approaching gender-variables in retrospective cohorts [1].

Briefly:

- Step 1 (Identification of Gender-related Variables): Based on the gender framework of the Women's Health Research Network (i.e., gender identity, gender role, gender relations and institutionalized gender), and available literature for certain diseases, an optimal "wish-list" of gender-related variables/factors was created and discussed by experts.
- Step 2 (definition of outcomes): Data dictionaries were screened for clinical and patient-relevant outcomes, using the International Consortium for Health Outcome Measurement framework.
- Step 3 (building of feasible final list): a cross-validation between variables per database and the 'wish-list' was performed.
- Step 4 (retrospective data harmonization): The harmonization potential of variables was evaluated.
- Step 5 (definition of data structure and analysis): The following analytic strategies were identified: (1) local analysis of data not transferable followed by a meta-analysis combining study-level estimates; (2) centrally performed federated analysis of data, with the individual-level participant data remaining on local servers; (3) synthesizing the data locally and performing a pooled analysis on the synthetic data and (4) central analysis of pooled transferable data.

Practical examples of the application of such methodology have been published [2-3]; for example, individuals with characteristics typically ascribed to women had poorer cardiovascular health and higher risk of heart disease, independent of biological sex and the magnitude of gender impact varied by country (Canada vs Austria), suggesting how much gender is country and culturally specific [3].

For designing a new study with a prospective collection of gender (prospective cohorts), the GOING-FWD investigators also provided general recommendations [4]. First, review the literature and determine whether gender-related variables are relevant to the research question and hypothesis. During the literature review, expand your perspective beyond biology to reflect on how psychosocial factors may influence health outcomes and consider the multidimensionality of gender. Then, decide which gender-related variables should be collected. Consider working with patient partners and/or interdisciplinary research teams to develop the list of relevant variables as well as the measurement instruments.

Once researchers have accessibility to gender-related variables in clinical datasets, they may want to focus their inquiries on a single dimension, or measure variables across multiple dimensions.

Data managing

How to handle the data in the analysis?

1) Option A - *Combining all the gender-related variables into a composite measure of gender (the gender score).*

Recently, through a Pan-Canadian collaboration of a multi-disciplinary team of scientists, a comprehensive list of gender-related variables was established and collected in the setting of premature cardiovascular disease. Constructed with the aim of exploring the impact of gender on the clinical outcomes of young patients with acute coronary syndrome, the GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond) Gender Score (GPGS) (http://www.cihr-irsc.gc.ca/e/50529.html) was developed [5]. The GPGS measures a comprehensive group of gender-related factors and offers a *pragmatic means to explore the relationship between sex, gender and health outcomes.* The authors used the GPGS in patients with premature and established cardiovascular disease and showed that gender factors, independent of biological sex, emerged as powerful predictors of risk factor acquisition (e.g., diabetes, hypertension etc) and of one-year adverse health outcomes (i.e., recurrence of heart attack [6-7]. Most significantly, those who exhibited a score most traditionally ascribed to women's identity and roles in society were more likely to have a recurrent cardiac event within the first year. While these results have important direct implications for expanding

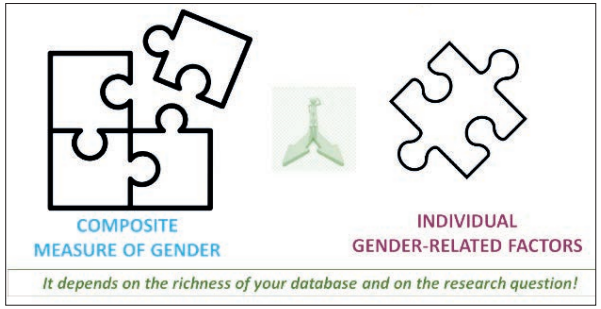

FIGURE 2
Clinical Scientist - Options on how to deal with gender related factors

the measurement of gender determinants of health to other populations, they may also identify novel determinants of health care costs that could be averted.

The methodology of GENESIS-PRAXY was also applied to and validated in a German retrospective cohort, the Berlin Aging Study II [8]. Nine variables contributed to a gender score: chronic stress, marital status, risk-taking behaviour, personality attributes (i.e., agreeableness, neuroticism, extraversion, loneliness, conscientiousness), and level of education. Of note, regardless of sex, characteristics traditionally ascribed to women were associated with lower levels of cortisol, hand grip strength and life satisfaction.
In conclusion, it may be helpful to reduce multiple gender-related variables into a composite gender score in studies where many variables will be explored.

2) Option B - *Assess the effect of a gender domain or of individual gender-related factors on the outcome of interest*
For example, country-level data on SARS-CoV-2 cases and mortality due to COVID-19 may only include sex. However, you can use a measure of institutionalized gender – the Gender Inequality Index (http://hdr.undp.org/en/content/gender-inequality-index-gii) – to investigate whether observed sex differences in SARS-CoV-2 cases were associated with gender. Countries with a higher Gender Inequality Index (i.e., higher inequality which favored men over women) had a higher male to female ratio of positive SARS-CoV-2 cases (i.e., more males tested positive) [9]. This suggests that gender plays a role in observed sex differences, even though only sex-disaggregated data were available.
Another example, in three US cross-sectional survey populations, seven gender-related variables resulted relevant to health: caregiver strain, work strain, independence, risk-taking, emotional intelligence, social support, and discrimination. Specific analyses adjusted for age, ethnicity, income, education, sex assigned at birth, and self-reported gender identity, identified associations between these gender-related variables and self-rated general health, physical and mental health, and health-risk behaviors [10].

Closing remarks

The choice of which gender-related variables to integrate and how to handle the analysis should be guided by the conceptual framework, research question and hypothesis of the study.
In conclusion, exploring the effect of gender in clinical studies is informative and can boost innovative solutions in health to improve the outcome of all, women, men and gender-diverse people.

SEX, GENDER& MEDICINE
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RECOMMENDATIONS

1. Increase international funding resources for promoting sex and gender-based clinical research
2. Increase the awareness and the knowledge on the importance of sex- and gender-based data through the dissemination of already available methods for measuring gender to scientific community
3. Campaigns to inform on the added value to collect and screen for gender-related characteristics as part of the clinical consultation to guide the decision-making of clinicians.
4. Guarantee high-quality and equitable evidence to guide healthcare providers in their daily work
5. Development of feasible and pragmatic tools for assessing gender in the routine clinical assessment.

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SEX, GENDER& MEDICINE
TOWARDS EQUITY IN HEALTH

12. SEX AND GENDER IN SAFETY AND QUALITY IN HEALTHCARE

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There is a longstanding assumption that clinical care, and the evidence underpinning that care, is sex and gender neutral. However, both historic and current biases in research have led to substantial data blindness and bias. Despite established policies from many funders and journals, publications do not routinely sex and/or gender disaggregate research outcomes [1]. Even when they do, authors seldom provide a meaningful comparison of sex and gender differences [2] to inform future guidelines and health care planning.

Women, particularly those who are pregnant or breastfeeding, and gender diverse people are systematically excluded or hidden in research. Due to a variety of individual and trial-specific factors, women continue to be underrepresented in clinical trial research, including for health conditions that affect both women and men, such as stroke [3].

The lack of sex- and gender-specific data, and under-representation of women in clinical trials, are safety and quality issues leading to poor health outcomes and, sometimes, harm. Quality and safety frameworks emphasize the principles of being centered around consumers and evidence [4], which should include a sex and gender

lens. Here we demonstrate this through two case studies and recommendations for the future.

Case study 1 – Cardiovascular Disease

Cardiovascular disease (CVD, mainly coronary heart disease and stroke) is the leading cause of death for men and women worldwide. However, research shows that women do not always fit the classical model of CVD, which has historically been informed by research primarily conducted with men. Women are currently at a greater risk of being misdiagnosed, due to symptom presentation that differs from men, which can delay life-saving treatment. They are also systematically undertreated in both general practice and hospital settings [5]. These differences are due to a combination of factors including biological differences, behavioral differences, data and evidence gaps, and conscious and unconscious gender-based biases from both clinicians and the community. The consequence of this is a greater proportion of preventable deaths and ill-health in women, compared with men, which should be regarded and acted upon as a patient safety issue.

Case study 2 – Hip replacements

Total hip replacement is a common orthopedic procedure. While these devices are available in different sizes, they are assumed to be sex and gender neutral with sex and gender considerations not incorporated into fundamental research and the same models used in men and women. There are, however, known differences in anatomy, physiology and biomechanics of, for example, gait, weight bearing and sexual intercourse, between women and men [6]. Consequences are now becoming clear, with women having a higher risk of failure (damage requiring replacement) compared with men, as well as higher rates of adverse reactions, dislocations, loosening and required revisions [7,8]. Gender biases also impact these poorer outcomes for women, for example surgeon reluctance to discuss sexual intercourse with their patients, and women being less likely than men to initiate conversation about how their hip replacement may impact sexual activity [6].

Opportunities to bridge the evidence to care gap

Product regulation

Currently there are no consistent requirements from regulators (such as the US Food and Drug Administration or Australian Therapeutic Goods Administration) for companies to specifically investigate sex or gender differences when submitting applications for product registration. To prevent safety issues with clinical use, regulators should require new products, including biosimilars, to present safety data disaggregated by sex and/or gender, and demonstrate that products are equally safe and effective for all [9] Additionally, registry data disaggregated by sex/gender is critical for continuous monitoring of post market safety.

Clinical guidelines

There is growing evidence demonstrating that sex and gender influences health and disease. However, while this research gap is improving, sex and gender is rarely incorporated into the evidence reviews and clinical guidelines that underpin care practices and decisions. For example a review of Canadian clinical practice guidelines found that only 35% of guidelines included sex-specific screening, diagnosis or management considerations [10]. It is critical to close this translation gap between research and practice so as to improve the quality and safety of healthcare. A structured framework for sex-specific guidelines has been proposed, which includes a critical implementation point of ensuring any changes to recommendations due to sex and gender are adequately communicated, with explanations, to clinical audiences [11].

Protocolised care

Development and implementation of standard protocols and care pathways have great potential to reduce sex and gender-based disparities and improve safety, by not only translating the latest evidence into daily clinical practice, but also address individual level biases or assumption based on patient sex or gender. For example a trial of a 4-step protocol for ST elevation myocardial infarction care found that it reduced sex disparities in guideline directed medical therapy and door to balloon time [12]. Critically, after the implementation of this protocol, there were no significant differences between men and women in rates of any in-hospital adverse events. A core part of quality and safety initiatives in hospital settings should be ensuring sex and/or gender disaggregated routine evaluation of protocol usage, adherence and outcomes.

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13. W20 PERSPECTIVE

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The purpose of the Commission is to overcome discrimination in health, diseases, outcomes and treatments. The sex-gender gap is one of the most pronounces source of discrimination. To neglect it means to ignore at least one in two people, as women, according to the United Nations World Population Prospect 2019, are 49.58% of the world population. The sex-gender gap is linked to many factors: those biological (sex) and environmental, psycho-social, cultural, roles, relationships, and the relative power that people or societies generally attribute to women and men, irrespective of their genetic make-up (gender). Therefore, sex and gender are not interchangeable [1]. It is hard to separate sex and gender because they are multi-dimensional, entangled, and interactive [1]. Thus, many authors prefer to use sex- and gender-based medicine [2]. The low recruitment of women in clinical studies and of female animals in preclinical studies has also generated a lack of knowledge and this generates a scientific inequality bias. In this situation, physicians have to extrapolate medical recommendations to women and other gender identities from research conducted mainly on men. In other words, androcentrism is still prevailing in medicine. Despite mandates and recommendations, some surveys shows little progress in sex and gender research and application in the last decades [3,4].

In addition, the recent pandemic, which has disrupted everyone's life, has had "the task" of making everyone understand the importance of sex and gender in health and disease. In short, the importance of sex and gender in regards to Covid-19 is highlighted in the higher mortality of men and in the higher prevalence of long Covid -19 in women [5,6].

The differences in how men and women have dealt with the consequences of government limitations on movement by means of quarantines, lockdowns, social isolation, and transportation restrictions, created to combat Covid-19, are still being understood. For example, women are more likely to adopt preventive measures and experience more depression than men, while men experience more anxiety [7]. Nevertheless, despite the numerous sex-gender differences, women only represented around one-third of the participants in clinical trials for Covid-19. Without more women recruitment, the sex and gender gap remains.

The widespread closures of schools, workplaces and businesses left many people unemployed. The economic impacts are especially high in women because they generally have insecure jobs and live in poverty or risk falling into it. Furthermore, unpaid work among women continues to increase [8].

All previous observations lead to the conclusion that sex-and gender based medicine is needed to overcome the pandemic and to reach equity in health as it does not separate the right to health from other rights such as education, proper habitation, ethnicity, disability, community and working conditions, as stated by many authors (see chapter 1). The application of sex- and gender-based health and medicine requires a new organization of health care systems. We have arrived in a moment in which we must reimagine healthcare as Covid-19 has violently brought to the surface many problems such as the failure of primary and community care, the low financial support for prevention, and the exacerbation of inequalities. The highest price that has been paid has been by low income individuals, where women prevail.

In view of possible financial support through "Next Generation EU" and the Unites States Coronavirus Aid, Relief, and Economic Security (CARES) Act, it is time to:

Organize a universal sex-gender sensitive health system that is well interconnected with the welfare system united with the strategical contribution and vision of women and men

Gender-responsive services are required to combat the stigma associated with many diseases such as Covid-19; and psychiatric diseases (including addiction), which present numerous sex and gender differences (see chapter 3). Policy makers must listen to and engage with women and other gender identities as they express their unmet health needs across all areas of life (see chapter 10).

There is the need for more sex and gender data as there is currently a lack of sex-gender disaggregated data in both clinical and preclinical settings (see chapter 5). Data must have rigorous scientific value and sex and gender based analysis. To do this, it is necessary stratify data for sex and gender from the pre-analytical phase [9] and throughout all the research phases. In short, the appropriate numbers of men and women and male and female animals should be recruited, the design should be appropriate and the results should be stratified by sex. There is the need to find, or to verify, if men and women have the same reference value of diagnostic or therapeutic biomarkers through pilot experiments, as illustrated in chapter 6. It is hard to measure gender, as explained in chapter 11, for the lack of a standardized method to measure the complexities of all that gender encompasses. Intersectionality could help to find differences. Studies to evaluate the effectiveness and safety of treatments among pregnant women should be considered a priority; without forgetting screenings, such as that for gestational diabetes.

It should also be recognized that sex and gender studies could boost innovative solutions in drugs, medical devices and in the organization and management of sustainable health systems (see chapter 12). Obviously, sex and gender should be considered in drug and device approval processes.

Build innovative strategic plans to bridge the sex-gender gap through rigorous scientific data and incentives for investigators

Sex and gender research is more expensive both in terms of time and economic costs. The value of the researcher is assessed on the basis of scientific production (manuscripts and patents), therefore extended research on sex and gender slow down his/her career. The previous considerations highlight the need to provide both economic and career incentives for researchers who focus on this topic. Furthermore, the presence of incentives makes this issue more attractive by encouraging the approach of new and young researchers. Editorial boards of peer-reviewed journals could request sex, gender, and intersectional analysis when selecting papers for publication. Funding agencies, as suggested in chapter 9, should require sex, gender, and intersectional analysis. It is important to recall that sex and gender research and health are the pillars of personalized (see chapter 7) and holistic medicine (Franconi personal communications). The results of sex and gender research should be used in decision-making processes to promote gender equity in health.

Include gender sensitive approaches in the curricula of health professionals and promote appropriate career paths for women

Sex and gender are not systematically integrated into education and training (see chapter 10 and others). Universities should assure that sex and gender related issues become enclosed in medical curricula, or at least in medical and biomedical schools. A worldwide curriculum on sex- and gender- medicine should be developed and shared among G20 countries. Researchers and health professionals should be trained to focus on the person, on interactions and on biological aspects and environments. Looking at the gender distribution in high-level management positions in industry, academia and public services, one cannot escape the fact that men seem to be more represented than women. Therefore, strategies should be applied to close the gender gap, either through legislation or through raising awareness and training.

In the real world, however, the accumulation of small discriminations and specific

problems that men do not experience on their career paths, serve to block a woman's progression up the career. Daily concerns such as nursery school, school schedules related to mothers' working times, means of transport with timetables and routes adapted to the needs of women should be addressed. There is an evident need to ensure social supports and safe environments such as urban areas designed to consider the needs of everyone including women, boys and girls, the elderly and disabled, etc., as described in Kern L Feminist City: Claiming Space in a Man-Made World, (2020). Strategies should be applied to close the gender gap, either through legislation or through raising awareness and training in order to ensure equity.

Due to intrinsic characteristics (being both personalized and holistic*), the application of sex and gender based medicine is the main road to combat inequalities in health. It is also important to remember that application of sex-and gender medicine is not limited only to health and welfare systems but extends to all levels of politics.

** In 1936, Albert Einstein wrote that relativity and holism would play a key role in human thought (Einstein, A. (1936). Letter from Einstein to Smuts, June 24. Cambridge, UK: Cambridge University Library).*

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WOMEN 20

Women20 is a recent G20 dialogue process: agreed by the G20 at the 2014 summit in Australia, the goal of reducing the gender employment gap by 25% by 2025 ("25 by 25"), paved the way for inclusion of a new involvement group in the official sphere.

In October 2015, the first working meeting of Women 20 (W20) took place in Istanbul under the Turkish G20 presidency. Demands and measures were formulated to promote the economic participation of women in the G20 member states and to strengthen their economic power.

Since 2016, these lines of work have been continued in the G20 presidencies of China, Germany, Argentina, Japan and Saudi Arabia.

In 2021 the annual W20 Summit took place in Rome, Italy, on July 13-15. The three-e-day event brought together hundreds of leaders, experts and role models from across the world, to discuss the most pressing issues facing women's social, economic and political empowerment, and to deliver the W20's 2021 Communiqué to the G20 Leaders.

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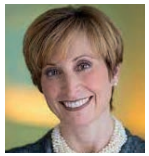

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SEX, GENDER& MEDICINE
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FONDAZIONE INTERNAZIONALE MENARINI

The Fondazione Internazionale Menarini is an association created in the 70s to promote and disseminate culture, science and medical education at all different levels and in multiple scientific fields.

Among the different instruments to achieve these goals, the organization of international congresses with a specific focus on medical disciplines is particularly relevant and appreciated.

During the course of its activities, approximately 600 international conferences have been organised in order to address innovative medical and biological issues as well as other topics of specific interest for the medical world in terms of widespread scientific implications and repercussions of a practical nature.
Another important cultural engagement of the Fondazione Internazionale Menarini is its editorial activity.

The Minuti s cience magazine (in collaboration with the U.S. publication American Family Physician) works alongside the Fondazione as a medical information journal. Delivered free of charge to 100,000 subscribing Italian physicians, Minuti offers updates on various diseases, disorders and treatment approaches.
In addition to the Science Edition, the Fondazione also publishes an Art Edition of Minuti, with the aim of helping keep the ancient tradition of the humanist physician and its readers' sensitivity to art and love for its myriad forms alive.

Since October, the Scientific and Artistic issues of the Minuti magazine are also available online in three languages (English, Spanish, Italian). Besides facilitating international distribution to a broader readership, the digital editions constitute an important step toward sustainable publishing.

Other paramount initiatives of the Fondazione Internazionale Menarini are the 'Coronavirus Library' and 'Dialogs Beyond Borders'.
The first is a space dedicated to an updated and selected list of the most pertinent articles chosen from the most notable international medical journals and magazines in the world regarding the current pandemic.
The most recent initiative, 'Dialogs Beyond Borders', is a series of brief interviews/ conversations with the most prominent people in the science field, who talk about their personal experiences while moderated by an experienced scientific journalist.

GALILEO SERVIZI EDITORIALI

Information, dissemination, communication, are the three keywords of Galileo servizi editoriali, a company founded in 2004 by scientific journalists and science communicators. Its editorial staff is made up of young journalists specialized in science and technology.

Galileo Servizi Editoriali's field of interest ranges from the medical-biological and technological-IT sectors, especially biotechnology, genetics, environmental protection, communication technologies, and focus on basic research in physics, chemistry, mathematics, space science.

Galileo Servizi Editoriali has divided its offer into 4 areas.

Journalism
We produce articles and surveys for the main Italian newspapers about science, health, the environment, technology and new media. Since 1997 we run the first Italian digital newspaper dedicated to science communication to the general public: *Galileo. Giornale di scienza* - galileonet.it.

Consultancy
We help institutions and companies in the science and technology sector to attract the interest of the media. We support research institutions to achieve greater visibility.

Formation
We train managers and employees of the public and private sector about science communication, health policy and technology. We run science journalism courses in Universities.

Communication
We design websites for associations of doctors and patients, organize exhibitions, events, conferences, and edit publications with an informative slant.

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