Sex bias in clinical trials in gastroenterology and hepatology

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Biological sex bias in clinical trials is a common issue in various medical fields, including gastroenterology and hepatology. Without sex parity and increased attention to sex-specific analyses, the translation of trial results into real-world clinical practice remains suboptimal with unpredictable consequences for patient care.

Biological sex (throughout the article, 'sex' is used as a shorthand for biological sex, acknowledging that sex and gender are distinct) influences and modifies the development of health and disease[1]. Epidemiology, clinical presentation and response to therapy of many gastrointestinal and liver diseases are different in women from men owing to a sex-specific genetic, hormonal and immune background. For example, autoimmune hepatitis is more frequent and potentially severe in women, whereas the relationship is inverse for viral hepatitis and liver and oesophageal cancers[2]. Nevertheless, in real-world practice, a sex-specific approach in clinical decision-making is mostly overlooked or not even considered.

A better understanding of the factors responsible for sex bias in clinical trials would help on the path towards sex-specific medicine in the field of gastroenterology and hepatology.

Two major issues to address are sex disparity in the trial population and the lack of sex-specific analyses of trial results. A report including 107 clinical trials in the USA found that 72% of these trials did not include the variable 'sex' in the results[3]. The lack of sex-specific analysis not only hampers the ability of the clinicians to correctly inform the individual patient (male or female) on prognosis but also increases the risk of drug-related adverse events. For instance, a hypothetical clinical trial assessing the safety and efficacy of a new drug for the treatment of nonalcoholic fatty liver disease (NAFLD) included 80 men and 20 women without a post hoc analysis according to biological sex. In such a trial, one cannot ascertain whether the drug profile was truly comparable in men and women. In real-world practice, on the other hand, the same dose and/or duration of treatment is prescribed to treat NAFLD in both sexes. The lack of a sex-specific approach could be potentially harmful as it is well established that the volume distribution and elimination rate of a given drug are frequently lower in women than in men owing to differences in hepatic and/or renal metabolism[4]. Not surprisingly, a study demonstrated that women who were treated with drugs approved by 'men-dominated' clinical trials were exposed to a higher risk of adverse events owing to an increased plasmatic concentration of the drug[4]. To further complicate this issue, the clinical phenotype of NAFLD and associated comorbidities, which can also affect drug safety and efficacy, vary according to biological sex[2]. As these confounders will further increase the probability of sex-related issues, they should be considered and appropriately addressed at the time of the design of a trial.

Yet, most clinical trials evaluating new drugs for NAFLD do not include any data on sex-specific responses[2]. Additionally, in the majority of these trials, sex-related outcomes are not even indicated[2]. These observations are particularly worrisome as NAFLD has now become the leading cause of liver-related death globally and is projected to increase. As biological sex influences the natural history and clinical presentation of NAFLD, a clear definition of sex-related outcomes, including sex-specific analyses in clinical trials, is paramount for the future treatment of these patients.

Hormonal changes occurring with ageing might affect the development of many gastrointestinal and liver diseases[2]. Thus, the combination of age and sex should be considered in patients recruited in clinical trials, particularly in women (that is, from menarche to reproductive years and menopause). On the other hand, drug companies want to set the most favourable and easy conditions to test drug safety and efficacy. Thus, women are generally disadvantaged in recruitment in clinical trials. On top of that, those of reproductive age are generally excluded owing to safety concerns about exposing potentially pregnant women to drugs and their potential teratogenic effects.

A study investigated the rates of recruitment of women in 20,020 clinical trials in the USA performed between 2000 and 2020 and found a marked sex disparity in many clinical trials[5]. As a result, patients included in clinical trials might not represent those seen in real-world clinical practice. A multivariate model showed that paediatric, cardiology and infectious diseases were

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associated with a particularly lower rate of female enrolment (adjusted relative difference: −20.5%, −18.7% and −18.5%, respectively)[5]. A less substantial association was found for trials in gastroenterology, although female participants were still under-represented by 12.8%, which is alarming given the high morbidity and mortality associated with gastrointestinal diseases in women[2,6].

Evidence indicates that biological sex affects pathogenesis, clinical presentation and response to treatments in inflammatory bowel disease (IBD)[6]. However, sex-specific data on clinical outcomes and response to therapy are mostly lacking in clinical trials. As we are now entering a new era of disease modification treatments for IBD, further efforts towards the role of biological sex in IBD are required to truly improve individual patient management[6].

Despite previous interventions from the National Institute of Health and the European Union to mitigate sex disparity in clinical trials[7], these results indicate the need for further efforts by both regulatory agencies and ethics committees. Investigators should also remember that clinical trials represent a privileged way of accessing the latest innovation in therapeutics. Thus, limiting the access of female or male patients is unfair and unethical.

Patient-reported outcomes (PROs) have emerged as important tools in patient-oriented medicine[8]. Indeed, PROs would allow a more comprehensive assessment of symptoms and quality of life than standard outcomes. In the setting of clinical trials, PROs are particularly helpful in evaluating outcomes that authentically mimic real-world conditions and challenges. Men and women report physical and psychological symptoms differently and therefore PROs can be profoundly different between sexes[8]. Addressing sex differences in PRO development and applications is therefore an additional issue to prevent sex bias and conduct well-balanced clinical trials.

As we have experienced during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, the risk of safety issues due to unaddressed sex bias in clinical trials might be particularly relevant for any drug evaluated by fast track[9]. Many vaccines and drugs for the prevention or treatment of the associated coronavirus disease 2019 (COVID-19) were commercialized without clear knowledge of the potential issues associated with biological sex. Current evidence, however, clearly indicates that the risk of adverse events after vaccination against SARS-CoV-2 was substantially higher in women than in men[10], which again underlines the importance of sex-specific analysis in clinical trials for drug approval. This sex-specific analysis would not only reduce the risk of adverse effects for the individual patient, but also the health-care costs associated with the development of drug-related adverse events.

Finally, investigators should consider that biological sex is only a part of the larger, multidimensional construct of gender. In fact, gender includes not only sexual characteristics of individuals (that is, biological sex) but also epigenetic differences resulting from psychology and physiology as well as social and cultural related factors (that is, exposure to risks or aggravating or protective conditions)[1]. The relationship between sex and gender further affects pathophysiology, clinical manifestations and response to treatment of many gastrointestinal and liver diseases. An example could be NAFLD for which gender-related factors such as dietary patterns, exercise and quality of life should be equally considered in the assessment of drug response[1]. Thus, as discussed for biological sex, attention to gender differences is also paramount to effectively mitigate the gender-related bias in clinical trials and not to exclude people affected by gender bias such as transgender patients.

In conclusion, although the awareness of the sex gap in clinical trials has increased, sex equity has yet to be achieved. As clinicians who have long known the importance of biological sex in clinical decision-making, we wonder why it has taken so long to acknowledge — and start to address — the sex bias in clinical trials. Certainly, in the constantly evolving field of gastroenterology and hepatology, additional efforts towards sex and gender-specific treatments are now expected from clinical investigators, drug companies and regulatory agencies. These joint efforts will reduce the sex and gender bias in clinical trials and ultimately help achieve the true goal of personalized medicine, that is, to ensure the best possible treatment for any individual, independent of sex and gender.

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Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
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