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COMMENTARY

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Why do we treat women as if they were men? Rethinking sex and gender in biomedical research and healthcare

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Abstract
Modern medicine largely relies on a male-default model, incorrectly assuming that findings from male bodies can be universally generalized. This paradigm results in structural biases that lead to diagnostic delays, inadequate treatments, and inequitable health outcomes for women. Although sex involves biological attributes and gender reflects sociocultural roles, both dimensions are frequently overlooked in research design and data interpretation. Significant differences exist at cellular levels and in disease manifestations, yet studies often fail to provide sex-stratified analyses, obscuring unique symptoms and mechanisms. Furthermore, women face higher risks of adverse drug reactions because pharmacological guidelines often ignore sex-specific metabolic profiles. Moving toward precision healthcare requires structural changes, such as mandatory sex-disaggregated reporting and the integration of gender-responsive variables. Ultimately, acknowledging that women are not simply smaller versions of men is a scientific necessity for ensuring an accurate and inclusive healthcare system.

Key words
- sex
- gender
- gender-sensitive medicine
- precision medicine
- health equity
- biomedical research

INTRODUCTION

Despite decades of scientific progress and growing awareness of biological diversity, modern medicine still largely relies on a model historically derived from male bodies. From preclinical research to clinical trials and therapeutic guidelines, the assumption that findings obtained in male organisms can be generalized to women continues to shape biomedical science and healthcare delivery. This paradigm has important consequences: it contributes to diagnostic delays, inadequate treatments, differential adverse drug reactions, and ultimately inequitable health outcomes.

The question "Why do we treat women as if they were men?" is therefore not rhetorical, but reflects a structural limitation embedded in research design, data interpretation, and clinical practice. While *sex* refers to biological attributes such as chromosomes, reproductive organs, and hormonal profiles, *gender* encompasses sociocultural roles and exposures that influence health. These dimensions interact across the life course and should be systematically integrated into research and care [1]. Yet, historically, women have been underrepresented or insufficiently analyzed, resulting in a knowledge base that does not fully capture sex- and gender-specific determinants of health.

This commentary examines the origins of this bias, its consequences across the research continuum, and the need to integrate sex and gender considerations into preclinical, clinical, and pharmacological studies, highlighting opportunities for more equitable and effective healthcare.

HISTORICAL ROOTS OF THE MALE DEFAULT MODEL

The male body has long been considered the default in biomedical research. Early physiological, pharmacokinetic, and toxicological studies were predominantly conducted in male animals and participants. This imbalance was driven by concerns about hormonal variability, potential pregnancy risks, and the perceived complexity of female biology, leading to the systematic exclusion of women from many trials until the late twentieth century [2].

The effects of this bias persist. Many clinical guidelines still rely on evidence derived mainly from male populations. Even when women are included, results are often not stratified by sex, obscuring important differences in disease mechanisms, symptom presentation, and treatment responses. This lack of disaggregated analysis reinforces the assumption of uniform applicability.

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In addition, gender-related factors – such as occupational exposure, caregiving roles, healthcare access, and sociocultural norms – are rarely incorporated into study design. As a result, the interaction between biological and social determinants remains insufficiently explored.

SEX DIFFERENCES IN PRECLINICAL RESEARCH

Sex differences emerge at cellular and molecular levels and influence fundamental biological processes. Cells from female and male organisms differ in chromosomal composition, gene expression, epigenetic regulation, and metabolism. These differences persist even in vitro, independent of circulating hormones.

For example, female cells often show greater resilience to stressors such as oxidative stress, metabolic challenges, and inflammation, supported by stronger antioxidant responses, more efficient mitochondrial function, and activation of cytoprotective mechanisms like autophagy [3]. In contrast, male cells may be more prone to apoptosis under similar conditions, with differences reported in mitochondrial dynamics, reactive oxygen species production, and DNA repair capacity [3].

Despite this evidence, preclinical studies frequently fail to report the sex of cells or animal models, limiting reproducibility and potentially leading to incomplete conclusions [4]. Considering sex as a biological variable is essential to improve translational relevance.

SEX AND GENDER IN CLINICAL RESEARCH

Clinical research also reflects the legacy of the male default model. Women remain underrepresented in many trials, particularly in early phases and in areas such as cardiovascular, neurological, and pharmacological research. Even when participation is balanced, sex-disaggregated analyses are not consistently performed [2].

This gap is especially relevant in conditions that present differently in women. Cardiovascular disease, for instance, often manifests with atypical symptoms, contributing to underdiagnosis and delayed treatment [5]. Autoimmune diseases – more common in women – have historically received less attention despite their significant burden [6]. Differences in pain perception, immune responses, and metabolism further influence disease progression and treatment outcomes.

Gender-related factors add a further layer of complexity. Differences in environmental exposures, access to care, and social determinants – such as caregiving roles and socioeconomic status – affect disease risk, adherence, and recovery. Ignoring these aspects limits the effectiveness of clinical interventions and contributes to persistent disparities.

LIFESTYLE AND NUTRITION

Lifestyle and nutritional recommendations are often perceived as gender-neutral, yet they are frequently based on evidence that does not adequately account for sex-specific biological differences or gender-related determinants. As in other areas of medicine, a "one-size-fits-all" approach prevails, potentially limiting the effectiveness of preventive strategies. Women and men exhibit distinct metabolic profiles, nutrient requirements, and physiological responses to dietary interventions [7]. For instance, hormonal fluctuations across the female life course, from menstrual cycles to postmenopause, significantly modulate energy metabolism, nutrient absorption, and needs for essential micronutrients like iron and calcium [8]. Furthermore, gendered social roles often dictate food choices (e.g., women tending toward vegetable-rich diets) [9], which in turn affect the risk of chronic disease such as type 2 diabetes and cardiovascular disease.

Failure to integrate both sex and gender perspectives into lifestyle medicine reflects the same structural bias observed in biomedical research more broadly. Incorporating sex-disaggregated data and gender-sensitive variables into nutritional science and prevention strategies is therefore essential to move beyond generalized recommendations and toward more precise and equitable approaches to health promotion.

PHARMACOLOGICAL IMPLICATIONS

Sex differences in pharmacokinetics and pharmacodynamics are well established [10]. Variations in body composition, gastric motility, enzyme activity, renal clearance, and hormonal regulation influence drug absorption, distribution, metabolism, and elimination. As a result, women may experience different efficacy profiles and a higher risk of adverse reactions. These concepts are important also when considering vaccine efficacy and safety. It is generally known that women develop stronger immune responses to vaccines and undergo more frequent and more severe adverse reactions [11, 12]. Consistent with drugs, also vaccines pharmacokinetics and pharmacodynamics differ by sex, females often experience higher serum concentrations of vaccine components due to lower body weight and differences in body composition; differences in body fat (higher in women) and muscle mass (higher in men) can impact the distribution of vaccines from the injection sites.

Historically, drug dosing recommendations have been based largely on male populations, contributing to inappropriate dosing and increased side effects in women. Differences in QT interval prolongation, sedation, and metabolism have been observed across multiple drug classes. Hormonal fluctuations during the menstrual cycle, pregnancy, and menopause can further modify responses, yet are rarely accounted for in trial design.

Achieving precision medicine requires integrating sex-specific pharmacological data, ensuring adequate female representation, and considering hormonal status.

THE ROLE OF RARE AND UNDERSTUDIED CONDITIONS

Bias also affects rare and understudied conditions. Many diseases with female predominance, particularly autoimmune and inflammatory disorders, remain insufficiently characterized. Limited data hinder diagnosis and delay therapeutic innovation. Women with rare dis-

eases often experience longer diagnostic pathways due to both biological complexity and systemic bias.

Studying these conditions offers valuable insight into sex-specific mechanisms, including immune regulation and hormonal signaling, with broader implications for common diseases.

FROM SEX-BLIND RESEARCH TO GENDER-RESPONSIVE MEDICINE

Moving beyond a sex-blind approach requires structural changes. Preclinical studies should include both female and male models and report sex clearly [2]. Clinical trials must ensure balanced recruitment and perform sex-disaggregated analyses, while pharmacological research should evaluate sex-specific responses.

Equally important is the integration of gender-related variables, including social determinants, occupational exposures, and healthcare access. Mixed-method approaches can better capture these interactions.

Regulatory agencies, funding bodies, and journals play a key role by requiring sex-disaggregated reporting and transparent methodologies. Education and training are also essential to improve awareness among researchers and clinicians.

IMPLICATIONS FOR CLINICAL PRACTICE

Integrating sex and gender into clinical practice improves diagnosis and treatment. Clinicians should consider sex-specific symptoms, risk factors, and responses. Laboratory reference ranges, imaging interpretation, and scoring systems may require adjustment [2].

Gender-sensitive approaches also enhance patient-centered care by accounting for social context, caregiving roles, and health behaviors, supporting more effective decision-making.

TOWARD EQUITABLE AND PRECISION HEALTHCARE

Incorporating sex and gender into research aligns with the goals of precision medicine. Recognizing biological and social diversity improves reproducibility, strengthens translational relevance, and supports equitable care.

Understanding both differences and similarities between women and men enables more accurate risk assessment, better prevention, and optimized treatments – benefiting all individuals.

CONCLUSIONS

The persistence of the male default model reflects historical practices, methodological limitations, and insufficient integration of sex and gender variables. Yet evidence clearly shows that these factors influence disease mechanisms, treatment responses, and outcomes.

Achieving equitable healthcare requires systematically incorporating sex and gender across all stages of research. This effort involves researchers, clinicians, institutions, and policymakers. Embracing biological diversity and social complexity will improve scientific rigor and patient care.

Recognizing that women are not simply smaller versions of men is both a matter of fairness and a scientific necessity. Integrating sex and gender into medicine is essential for a more accurate, inclusive, and effective healthcare system.

Conflict of interest statement

The Authors declare no conflicts of interest.

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