



MIND THE GAP: FACING SEX BIAS IN BIOMEDICAL RESEARCH

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Over the years, an “androcentric” bias has dominated biomedical research with male subjects and animals being overrepresented in (pre)clinical studies [1]. Indeed, for decades, medical textbooks have defined the “70-kg man” as the default human model for studying human physiology [2]. As a consequence, women have been largely excluded from biomedical research over the years. There are, of course, many biological similarities between the two sexes that prompted this simplification. However, there are multiple layers of variation between males and females. Sex differences begin at the genetic level where a chromosomal composition of XX in females and XY in males orchestrates changes on the anatomical and physiological features of each sex [3]. Besides genetics, hormonal factors are also crucial to differentiate between males and females [4]. Such hormonal differences are responsible for the development and maturation of the reproductive system, as well as specific behavioural and cognitive traits in each sex [4]. On an organismal level, women generally have lower muscle mass, higher body fat mass, and lower blood pressure compared to men [3]. Collectively, genetic, endocrine, and physiological variation between the two sexes can affect their disease risks, illness patterns, symptoms, and even treatment efficiency.

History and state-of-the-art

The underrepresentation of women in biomedical studies has been present for a long time. “Hundred years ago, medicine was a men’s domain. In discourse, the representation in research and textbooks was just men. This does not mean they all thought females were inferior, it was just an ignorance for the differences between the male and female body”, says Sabine Oertelt-Prigione, professor of sex- and gender-sensitive medicine at the Radboudumc. “A huge pullback was the thalidomide crisis in the ‘70’s, where babies were born with malformations after their mother had taken thalidomide during pregnancy. This led to a reaction by regulatory agencies that wanted to protect unborn babies, so they excluded women from clinical trials.” In the ‘90’s, researchers realised that sex differences have a larger impact on healthcare than previously thought [5, 6]. “What happened is that women were permitted to participate in clinical trials again, and we have seen an uptake ever since”, notes Oertelt-Prigione. Yet, a 2019 analysis observed clear sex bias in clinical studies from Pubmed and Clinicaltrials.gov [7]. Strikingly, the analysis only found a small increase in the number of female participants over the period of 1966 until 2018 [7]. In another study, phase I trials were found to have more sex bias than phase II and III trials [6]. Thus, women are still underrepresented in early drug development, which could lead to sex differences being unnoticed until later stages of clinical development.

“20 to 25 years ago, people started looking at sex differences incidentally, but there was no systematic integration”, says Oertelt-Prigione. “Considering that sex was perceived as an emancipatory political statement rather than a content analysis, when I tell people ‘well, I work in sex- and gender-sensitive healthcare’, they start telling me the number of female professors they have in their institution, which is very important but not the point.” The last five years, things are coming together. First, there is an accumulation of knowledge that convinces more people to look into sex differences. Second, funding bodies mandate that researchers consider sex differences in their studies. The National Institutes of Health expects researchers to



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include sex as a variable in research design, analysis, and reporting [8]. If researchers do not incorporate sex in their study, they need to explain why not [8]. The Canadian Institute of Health has also commenced such regulations since 2010 and has become stricter over the years [9]. Likewise, the European Commission has mandated to include sex via the Horizon 2020 program [10]. “This does not mean everybody does it [integrating sex in biomedical research] systematically and perfectly, but it encourages researchers to think about whether their study has a sex dimension.” Lastly, as Oertelt-Prigione explains, publishing about sex differences in journals and even high-profile journals is increasingly possible. “At this point, it becomes a

virtuous cycle where agencies want it, there is more knowledge, and you can get it published decently. So, the process is kind of encouraging itself."

Why is this an issue?

Sex differences are evident in many pathological conditions such as diabetes, Alzheimer's, and cardiovascular diseases [11]. For example, compared to men, women suffering from coronary artery disease are older and usually do not experience an obstruction in large blood vessels at the same rates [11, 12]. Differences in pathophysiology and symptomatology between the two sexes can complicate proper identification as well as treatment of major chronic diseases [11]. Thus, establishing sex-specific guidelines for the diagnosis and prevention of such diseases is urgent. Perhaps one of the most dangerous consequences of the exclusion of females from clinical trials involves sex-specific responses to therapy [13]. "We are giving a drug to somebody, and we would like to know whether it is as efficacious in females as in males, and, of course, if it shows the same side effects in both [sexes]", mentions Oertelt-Prigione. Not only therapy efficacy but also treatment-related side effects can be different in males and females prescribed the same medication [13]. The one-size-fits-all norm often applied in medicine has led to the overmedication of women and is associated with increased adverse drug reactions in women [14]. Oertelt-Prigione notes, "There are some cases where drug dosages have been adapted but were still as efficacious and without side effects. Notable examples are the use of certain sleep medications and even chemotherapeutics." A systematic analysis performed in 2016 reported that about half of the drugs (307), most frequently prescribed in the USA, are associated with sex-specific adverse reactions [15]. These differences are mainly attributed to sex-based differences in pharmacokinetics and pharmacodynamics [13]. Therefore, the exclusion of females and ignorance of sex-based differences in (pre)clinical research can have detrimental effects on women's health. Oertelt-Prigione concludes, "This is a field where we expect substantial progress in the next years and potentially even different types of medications for men and women. Coming to the future, we can adapt our therapies to tailor the medication to whoever the individual taking it is."

Sex-(in)sensitive research fields

The incorporation of sex differences is not equal among the various biomedical fields. "Cardiology is probably the most advanced field in sex-specific research", says Oertelt-Prigione. "Realising there was a higher incidence of heart attacks in women due to different symptomatology or simply because the physician did not think women were having heart attacks, highlighted the importance of sex-based differences in cardiology". Indeed, research into cardiovascular diseases in women has led to the establishment of sex-specific guidelines for the risk, diagnosis, and treatment of such diseases [16]. For instance, special protocols for pregnancy and menopausal related risks are now being recommended in cardiology practice [16]. Yet, systematic analysis of articles published between 1966 and 2018 revealed a clear underrepresentation of female participants [7]. A negative sex bias, indicating male overrepresentation, was observed in multiple research fields, including that of HIV/AIDS, kidney diseases, and even cardiovascular diseases [7]. Oertelt-Prigione discusses, "There are fields that are a bit more advanced and fields that are lagging a bit behind. I would say that my impression is that there are fields where we know a lot, and still, nothing is happening. It is also true that in many fields sex-disaggregated data is lacking and, therefore, larger meta-analyses are difficult to conduct. As a consequence, we do not have a high enough level of evidence to include this knowledge into clinical guidelines."

Tools to support sex-sensitive research

Despite the advances made in the last years, integrating sex-based differences is still limited. Oertelt-Prigione explains, "There is some ignorance or lack of information about how to conduct sex-based analyses. Not that much because of bad intentions, but because of a lack of knowledge. Besides, there are more practical considerations, for example, the statistical analysis and instruments you use in your study. All these make implementation difficult". There are many ways to stimulate and guide researchers to consider sex-based differences in their studies. Oertelt-Prigione discusses, "I think there are different steps and levels depending on where people are. Initially, what you want is to raise awareness that there is a problem. That is what I do in a way by giving talks to the community. The second level is providing researchers with tools and experts to accompany them." Recruitment, randomisation, data collection, and data analysis can be optimised to include sex-specific differences [17]. Educating the scientific staff is also important to promote their involvement into sex-sensitive research. Oertelt-Prigione notes, "If you have a faculty where there is a person who likes the topic or has this as a research subject, it will pop up during the teaching. But if you do not have somebody that embodies this, or carries the torch for this, it does not automatically happen. I really hope that in the next ten years we will move from these single experiences to more of an institutionalised process, where it is simply requested to perform sex-sensitive studies, and there is a trained faculty who can teach this." On a global level, multiple guidelines and online training tools have been developed to help researchers add a sex dimension in their research [8, 9].

The challenges of gender in the clinic

Alongside sex, gender differences can also influence biomedical research. Sex and gender are two similar but different concepts. Sex is considered a biological component, defined by the sex chromosomes, hormones, and anatomy [8, 9, 18]. Gender is a broader term and comprises the social, environmental, cultural, and behavioural factors and choices that influence a person's self-identity and health [9, 18]. This includes gender identity, gender norms, and gender relations [9, 18]. "Historically, the two concepts have been mixed. People thought sex was a dirty word, so they used gender instead." According to Oertelt-Prigione, researchers and physicians became more aware of the fact that the concepts are not the same in the last 15-20 years. "They both have an impact on healthcare but in a different way. Gender especially impacts access to healthcare, perception of health and disease, preventive behaviour, and the way diagnosis might be offered to you." Thus, including gender is as important as the inclusion of sex. Currently, this remains a challenge. Oertelt-Prigione explains, "Gender is a concept that comes from social studies. The studies in social sciences are very different from medical studies, so we need to make sure gender is measurable with instruments that work for healthcare studies. The current challenge is to make gender more usable in medical research. The knowledge is present, but the methods on how to incorporate it must be clearer and more distinct."

Initiatives at the Radboudumc

As a professor in sex- and gender-sensitive medicine, Oertelt-Prigione is working with many people at the Radboud University and Radboudumc. She mentions some initiatives within the Radboudumc to introduce sex and gender in biomedical sciences. "In this coming year, we are working on a project where we are trying to find out how to combine an innovative topic as sex- and gender-sensitive research with innovative teaching methods." For the future, she is hoping that teaching about sex and gender in biomedical research becomes natural. "By building collaborative projects with many different clinical disciplines, we hope to engage them so that they will mention it themselves when they are teaching." Besides, there

are other initiatives within the research institute. These range from performing research into the topic to scientific student lunches with PhD candidates and Research Integrity Rounds about the topic. "The most important aspect over time is that people know where to find you. Every once in a while, people contact me with their questions. That means people start taking up what we have said and translate it into the work they are doing."

Conclusion

From the earliest days of medicine, sex and gender differences have not been thoroughly considered in biomedical research. As a result, few and slow advances have marked sex and gender-sensitive research and medical practice. Nevertheless, the research landscape has evolved in the last years, encouraging sex- and gender-based analyses in biomedical studies. Oertelt-Prigione concludes, "The climate is definitely changing, and ten years ago things were much trickier. Not to say that everything is perfect, but we are in a moment where there is more awareness and people are more accepting and more interested. We will definitely see a lot of new things coming up in the future."

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