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Scientific Excellence in Applying Sex- and Gender-Sensitive Methods in Biomedical and Health Research

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Abstract

Despite regulations, the attention paid to sex and gender in biomedical and health research is far from optimal. Researchers often recognize the importance of incorporating sex and gender issues in general but fail to see the applicability to their own research. This can have severe consequences and impedes gender equity in healthcare. More hands-on approaches are needed that stimulate scientists to integrate sex and gender aspects into their research. The present work is based on the contents of a workshop developed by the authors that serves as such a hands-on method. It aims at familiarizing a broad range of scientists in the field of biomedical and health research with the basics of conducting sex- and gender-sensitive research. In addition to clarifying concepts, it serves to provide a general introduction to sex- and gender-sensitive methods. To this end, challenges in pitfalls conducting sex- and gender-sensitive research, originally identified in the social sciences, are translated to the practice of biomedical and health research. Implications and applicability to all areas of biomedical and health research are shown by providing illustrative examples. Finally, a tool is presented that allows for the detection of sex and gender bias throughout all phases of the research process and shows how this bias can be overcome through sex- and gender-sensitive (1) relevance checking, (2) literature search, (3) formulation of research questions and hypotheses, (4) research methods and sample, (5) data analysis and interpretation, (6) reporting, and (7) conclusions and recommendations.

Introduction

Little by little, sex and gender in research are getting the attention they deserve. In North America as well as in Europe, research and research policy organizations are making sure that the gap left open by industry, universities, and researchers is starting to fill. Regulations and policies should ensure that enough women are included in trials, that research designs account for possible sex differences, and that sex- and gender-specific results are reported.[1–3] Still, the efforts to incorporate sex and gender in research seem to be minimal. Women are included in trials if required, but the subsequent data analyses still are sex and gender insensitive.[4,5] The role of sex and gender is, often mandatorily, considered but poorly understood and "very weakly addressed."[6] This causes the rate of change to be very slow in spite of legislation and accountability frameworks.[7] However, to profit from the health advantages that sex- and gender-sensitive research can offer, as well as to avoid harm, this type of research needs to be conducted carefully, regularly, and to the full extent.[8]

It is often a lack of expertise and experience with sex and gender issues that leads to failure to address them in research. Evaluating the integration of sex and gender into their latest research programs, the European Commission (EC) concludes: "There is a lack of ideas on practical ways of integrating gender into research. [...] Some project proposals automatically dismiss the relevance of gender to the research topic or instruments used, without any analysis of whether it might be relevant."[6] Even a willing researcher is no guarantee for success, however. Of all Swedish public health researchers who believed their research to be gender sensitive, only a fifth conducted research that could be labeled as such.[9] It, therefore, happens that although researchers in the field of biomedical and health research acknowledge the added value that a sex and gender dimension could bring to their research, the lack of familiarity and practice with the topic holds them back.

Scientists educated in the field of gender studies have the expertise to see how sex and gender may play a role, but a majority of gender experts are in the social sciences. Articles

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by them often remain at a conceptual level. The distance to the practice of life science research is too great, and too few bridges between the two worlds exist. On the other hand, there is quite a body of literature from the fields of gender and life sciences alike that identifies the need to integrate the two lines of research, although, few move beyond descriptive or state-of-the-art articles. In addition, some excellent and detailed articles by gendered life scientists serve specific audiences.[10,11]

A consequence is that interested life science and health researchers cannot easily find ways and methods to incorporate sex and gender issues into their research. A general tool would have the advantage of broad applicability, but it is exactly this general level, in combination with a lack of familiarity with sex- and gender-sensitive research, that can make it very difficult for researchers to acknowledge that sensitivity to sex and gender is relevant to their own research as well.[6] It is, therefore, essential that general tools be accompanied by examples that show specific applications to different aspects of biomedical and health research.

To this end, we developed a workshop, Scientific Excellence and Sexy Research. The workshop aimed at familiarizing scientists in the field of biomedical and health research with the basics of conducting sex- and gender-sensitive research. The workshop was based on previous work and experience by the authors and a literature study focusing on key publications.[12–16] It aimed at finding a middle course between introducing general concepts that are of relevance to a wide variety of biomedical and health researchers, on the one hand, and the illustration of those concepts with specific examples, on the other, which allows all participants to acknowledge the relevance of such concepts to their own field of research. This article is an account and elaboration of the contents of the workshop and aims at conveying the importance of conducting sex- and gender-sensitive research to a larger audience of biomedical and health researchers. After clarifying terminology, we illustrate why and how sex and gender are relevant in biomedical and health research. Next, the shortcomings of sex- and gender-insensitive research are discussed by identifying common pitfalls. To make the knowledge on sex and gender issues applicable to one's own research, a step-by-step plan for sex- and gender-sensitive research is presented that synchronizes sex- and gender-sensitive actions with the phases of the research process.

Clarifying Concepts

For conceptual clarity, it is important to distinguish between the terms sex and gender. Scientists in the field of gender speak of sex when they refer to male/female differences attributed to biological characteristics, such as chromosomes, physiology, and anatomy, as well as processes at molecular and cellular levels.[17–19] Sex is a characteristic, usually dimorphic and related to the XX or XY genotype, although a range of exceptions of people who are chromosomically different exists. Gender, on the other hand, refers to the social and cultural influences that lead to differences between women and men. It is a process and a continuum: people may develop a strong or less strong gender identity and may adhere to perceived gender roles to a different extent. As an example: only women can give birth to children (sex difference), but it is not biologically determined if the man or the woman should raise these children (gender roles). The definition of the words implies that the term, sex, can be applied to biological male-female differences in both humans and animals but that the sociocultural term, gender, will almost exclusively be used for human beings. Unfortunately, the terms sex and gender are sometimes used interchangeably in the medical literature. To avoid confusion,[20] we use them distinctively in this article. We prefer the term, sex- and gender-sensitive research, which is used to indicate research that takes into account the full array of possible influences of both sex and gender on all phases and aspects of the research.

Why Conduct Sex- and Gender-Sensitive Research?

Sex and gender can have a profound influence on health and illness throughout the life span.[12] In order to ensure optimal healthcare for both men and women, the differences and similarities of their health needs should be considered in biomedical and health research and subsequently translated to clinical practice. Wieringa et al.[21] argue that the clinical relevance of sex and gender is 3-fold. First, sex and gender can help explain the differences in etiology and prognosis of diseases. Even if a condition predominantly affects one sex, it is exactly the differences between men and women that can lead us toward identifying the mechanisms responsible for the condition, which facilitates the development of (new) treatments. Second, sex and gender can modify the outcomes of diagnostic procedures and of preventive and treatment interventions. This effect modification will only come to the fore if carefully designed studies are analyzed by sex.[8] Third, the differences in health perception and practices of women and men may cause differences in health outcomes—a gender issue.

In addition to its clinical relevance, conducting sex- and gender-sensitive research can improve the scientific quality of a study. In many cases, it is plainly unscientific to leave out half the population or fail to do subgroup analysis and thereby miss out on valuable information. Thus, the EC made the integration of a sex and gender dimension a criterion of scientific quality in the evaluation of proposals for their research programs.[2] Furthermore, paying attention to possible sex differences and gender effects in research is an innovative enterprise, and its more precise results allow the researcher to get an edge on colleagues in the field. Last, because of its medical and social consequences, a sex and gender bias in medical research has ethical implications.[22] Increasing the quality and quantity of evidence on the effect of sex and gender on health outcomes and healthcare leads to better targeting of medical care at the individual level and, thus, to a better chance at improved health. Socially, the aim of ensuring gender equity in healthcare necessitates consideration of relevant differences in healthcare policy, including the conduct of clinical research.

Sex Differences and Gender Effects in Health and Disease

Sex differences and gender effects are relevant throughout biomedical and health research. Some examples in which sex differences plays a role include:

- Sex differences in the development of the pulmonary system are visible *in utero*. It has been demonstrated that the lungs of the female fetus mature more rapidly, and surfactant production begins earlier than in male fetuses.

As a result, female newborns have increased airflow rates compared with male newborns and are less likely to develop respiratory distress syndrome.[21,23]

- Healthy women produce three times as much growth hormone (GH) as men do yet have the same levels of insulin-like growth factor-I (IGF-I), suggesting a lower responsivity. GH-deficient women thus require higher doses of therapeutic recombinant human GH (rhGH) to achieve the same treatment effect as GH-deficient men.[24,25] Also, the changes in body composition induced by rhGH therapy are more pronounced in men than in women.[26]
- The incidence and location of gastric cancer vary by sex. Male/female incidence ratios are generally 1.5–2.5:1 but differ according to cancer location.[27] Whereas gastric cancer in women develops mostly in the lower part of the stomach (distal gastric cancer), it develops in the upper part of the stomach (proximal gastric cancer) in the majority of men. The reasons for the sex differences in location are still unknown.[28] Although gendered lifestyle factors (smoking, drinking, nutrition) contribute partially to the development of gastric cancer, it has been suggested that the relationship between smoking and alcohol and gastric cancer is mediated by sex.[29,30] Infection with the *Helicobacter pylori* bacterium, a proposed risk factor for gastric cancer, is also suggested to have a differential impact on the development of gastric cancer in males and females.[30,31] Because etiology, underlying biological processes, and clinical outcomes are hypothesized to be different in proximal and distal gastric cancer, this will have therapeutic implications.[32]

Although some tend to believe that for some areas of life science research a sex and gender dimension is taken sufficiently into account when paying attention to sex differences, it is a mistake to use sex as a proxy for gender.[7] Attention to gender effects might require different analyses than those needed for dealing with sex differences. Whereas sex is essentially biological, gender is a lens used to analyze factors that extend to behavioral, social, societal, and sometimes even political levels. To make sure an analysis includes the relevant factors that together account for gender effects can, therefore, be a wholly different enterprise. The potential impact of gender effects on health is highly significant because behaviors, power relations, and environments (among others) all have an impact on health but can differ between men and women. Some examples include:

- Gender influences environmental factors. In occupational health research, job segregation by sex can lead to differential exposure rates to different occupational hazards, such as toxic chemicals, ergonomic demands, accident risk, and psychosocial stressors.[33,34]
- Gender mediates risk perception. Men and women express different levels of concern about the same risks, attribute different meanings to them, and also perceive different risks.[35] It therefore cannot be assumed that men's and women's perception and fear of diseases, treatment, and health outcomes are the same, which is likely to have consequences for health-promoting and help-seeking behavior and noncompliance rates.
- Men make less use of health services than women, particularly in primary care. A common explanation of men's lower frequency of health service use is cultural norms with regard to masculinity and the expectation that men be strong and not show weakness.[36] Less frequent doctor-patient contact of men compared with women could lead to underdetection of certain conditions, such as osteoporosis, which because of its frequent occurrence in women, is underdiagnosed in men anyway.

Some scientists have objected to the distinction between sex and gender, fearing that a focus on the one might lead to ignorance of the other[9] or that they will be seen in hierarchical order. To avoid this, the potential roles of both sex and gender, as well as their interplay, should always be considered. In fact, it is infrequent that only sex or only gender plays a role. In general, sex and gender work together in influencing health and health outcomes. Krieger states: "Not only can gender relations influence expression—and interpretation—of biological traits, but also sex-linked biological characteristics can, in some cases, contribute to or amplify gender differentials in health."[13] To illustrate:

- Sex plays a role in the acquisition of HIV/AIDS through biological and physiological factors that make male-to-female compared with female-to-male transmission more likely in unprotected vaginal intercourse. At the same time, a gender power imbalance may lead to a lesser ability of the woman compared with the man to negotiate condom use.[13] Female injection drug users have also been shown to have a higher risk of acquiring an HIV infection than their male counterparts because of gender differences in injecting practices related to sharing and cleaning behaviors.[38]
- The risk of hypospadias, a urethral birth defect in males, is increased by maternal exposure to certain toxins. Because exposure to such agents is highest among hairdressers, gender influences the risk of exposure through the gender segregation of the workforce.[13]

Because of their interplay, it is not always easy to distinguish between the roles of sex and gender. For example, bone mass development is related to body weight and exercise. The current thin ideal for girls and weightbearing exercises commonly performed by boys (gender) lead to a different weightbearing impact on the bones of females compared with males, contributing to differences in bone mass in males and females (sex). Also, it is fairly difficult to determine the relative influences of biological factors on the development of melanoma because of different social practices of men and women, for example, with regard to clothing styles and levels of sun exposure.[12]

Exploring Underlying Biological Mechanisms of Sex Differences

Sex- and gender-sensitive health research is most easily associated with the detection of health differences between men and women, for example, through epidemiology or clinical outcomes. It is also because this step is perhaps most obvious that in recent years, considerable attention has been given to the differences and similarities between females and males at the societal level, on the one hand, and at the level of the whole organism, on the other.[12] The scope of sex- and gender-sensitive research has historically been limited. But although it might have been most clear-cut to explain sex

differences by focusing on the reproductive system, the role of sex hormones have to be considered outside of their reproductive functions. Their influence has been major in some nonreproductive health matters, such as cardiovascular disease, asthma, and osteoporosis.[21,23,37,39] Indeed, to be able to provide tailored and adequate healthcare to men and women alike, researchers must begin to "see women's entire bodies as different from men's."[40] It is necessary to start exploring the precise mechanisms and explanations that can account for the sex differences in patterns, course, and treatment response that are revealed at the population level. For example, the NIH Office of Research on Women's Health (ORWH)[41] lists the need for studies of chromosomal, genetic, gonadal, and phenotypic sex *in vitro* or in animal models, the need for systemic and cellular modeling of biological pathways and systems related to women's health, and the need for mapping etiological mechanisms that can shed a light on sex differences in cellular, tissue/organ, physiological, and immune responses to environmental and infectious agents. Even—or exactly—at these levels we may not presume men and women to be the same. "Every cell has a sex. Whether a cell contains an XX or an XY chromosome may have an impact on everything from regulation of gene expression in a cell line to the efficacy or toxicity of a pharmaceutical in living human."[42]

Genomics and pharmacogenomics enable new approaches to identify research populations according to biological variables, such as the rates of drug metabolism and other genetic differences in metabolism that are likely to interact with sex.[21] More pharmacogenomic research is needed that addresses such issues as the role of sex chromosomal differences on pharmacokinetics, the mechanisms of sex effects on gene expression, and the genetic, molecular, and cellular basis of action of pharmacological agents that are known to have differential effects in men and women.[41] Even at this level, the influence of gender should not be dismissed. Gender roles can, for example, determine dietary habits, smoking, and alcohol consumption, and thereby influence the environment to which genetic factors might respond differently.[43]

Ignoring Sex and Gender

To protect the potentially childbearing woman and in the belief that accepted the male as a model for the human species (which, at the same time, meant that the complicated hormonal cycles could be ignored), sex and gender have been ignored in biomedical and health research for a very long time.[44,45] Even today, it appears that the standard way of doing research is sex and gender insensitive. Paying attention to sex and gender in research counts as something extra, which might or might not be taken into consideration, depending on time, budget, and good will of the researcher. Even something as basic as the collection of sex-disaggregated statistics is not routine. Because old habits die hard, sex- and gender-insensitive ways of doing research are passed on to a new generation of scientists. To be able to avoid sex and gender bias, researchers will have to act.

In her book on nonsexist research methods, Eichler[14] identifies common pitfalls related to sex and gender issues that may bias research, with less reliability and validity as a result. Although the book was written from the perspective of the social sciences and although the pitfalls are closely related and, therefore, not always conceptually distinguishable from each other, the problems she identifies are (still) very relevant for biomedical and health research. Clearly, if healthcare and health policies are based on research that has significant reliability and validity problems, the consequences can be major. To increase awareness, we discuss three of these main pitfalls: overgeneralization, sex and gender insensitivity, and double standards.

Overgeneralization

Overgeneralization takes place when only one sex is studied but the data are presented as if they were of general (rather than sex-specific) applicability. Overgeneralization can take many different forms, the most serious of which is overgeneral data interpretation. One sex is studied, but the results are interpreted as if they were applicable to both sexes. For example, the American Heart Association recommended aspirin therapy to high-risk adults to reduce the incidence of coronary heart disease based on a number of trials in which only 20% of the subjects studied were women. Recent sex-specific meta-analyses, however, showed that aspirin therapy reduces the risk of a myocardial infarction in men only, whereas the risk of an ischemic stroke is lowered only in women.[46] The recommendation should, therefore, only have applied to men and in fact was harmful to women because the use of aspirin increases the risk of bleeding events.

Overgeneralization can also pervade language, such as when sex-specific terms are used for purposes that are generic, for example, by using he or man when, in fact, both sexes are meant. A questionnaire might contain the following question: If a doctor tells you smoking is bad, do you believe him? Not only is it wrongly implied that a doctor is necessarily a man, thus reinforcing stereotypes, but also the answer might just be different if it said "her" because of different patient-doctor interactions.[47] Second, overgeneral language occurs when generic terms are used for all-male of all-female groups, for example, when the wording single parents is used to indicate a group of single mothers only. Such undifferentiated as humans, healthy volunteers, patients, consumers, and families should always be specified. Preferably, the title of a publication should reflect the sex composition of the research population. For an extensive guide on how to avoid sexist language, see the APA Publication Manual Task Force.[48]

Sex and gender insensitivity

Sex and gender insensitivity occurs when sex and gender are not addressed in the research, although they are related to the research content. This can take several forms. First, studies may fail to report the sex of the research subjects altogether. When it is not mentioned in the title or abstract, but closer scrutiny of text and tables allows us to determine the sex of the subjects, this is a form of overgeneralization. When there is no mention of sex at all in the article, however, it is impossible to even establish if overgeneralization took place. To date, multiple examples of such studies can be found in respected journals (e.g., a recent article in *JAMA* fails to mention the sex of the subjects completely[49]). This can easily be avoided by adhering to the rules for nonsexist language. Even if no human subjects are involved, the sex of research subjects in animal trials should be noted and since every cell has a sex, also the origin of the (cellular) material used.[18]

A second form of sex and gender insensitivity occurs when data are collected from both sexes, but the analysis ignores this.[4,5] Eichler states that this may "severely limit the utility of any findings and may, in fact, hide some of the most important aspects of a phenomenon."[14] As an example using information from Mickalide,[50] Figure 1 depicts the relationship between income and being overweight (defined as ≥20% above desirable body weight for height). The line for both sexes supports the widely acknowledged inverse relationship between income and being overweight. However, a sex-disaggregated analysis corrects this assumption, showing it to be the mean of two opposite trends for men and women. The only way to prevent such errors is to routinely analyze data by sex and only after it has shown to be empirically insignificant, collate the data.[14] Obviously, a sex-disaggregated analysis requires sufficient power because results might otherwise be misleading.[51]

In addition to the sex of the subject, a sex- and gender-sensitive study also considers the sex of the investigator and the different interactions that might stem from different subject-investigator combinations.[52] For example, it was found that pain tolerance of research participants rises with experimenters of the opposite sex and that having a female investigator increased pain intensity.[53] For animals, investigator effects have not been clearly identified but are believed to occur and could be related to differences in the way female and male researchers sound, smell, and handle the animals.[18] Although it will not always be possible to take the sex of the investigator into account in the study design, reporting should explicitly mention their sex in relevant cases, and possible effects should be considered,[14] especially when more than one researcher is involved.

Sex and gender insensitivity in research can have great consequences for establishing criteria and protocols for diagnosis or treatment of conditions. For example, although the exercise stress test is less accurate in women than in men, it has long been used to detect heart abnormalities in both sexes. Likewise, it took researchers and medical specialists some time to determine that balloon angioplasty, a procedure in which narrowed blood vessels are widened by means of inserting and inflating a balloon in the vessel, required different balloon sizes for men and women.[54] Sex and gender sensitivity is essential in pharmacological research as well, where sex differences in weight, size, body composition, and cell metabolism influence the required dose.

Double standards

When the same or identical situations, traits, or behaviors are treated or evaluated differently on the basis of a person's sex, double standards are being used. Detection is difficult because double standards are often presented in an indirect manner, as is the case when behaviors or situations are labeled differently for different sexes. For example, when women and men experience the same symptoms of heart disease, women's symptoms are three times more likely to be attributed to emotional rather than physical causes.[54] When their cardiovascular symptoms are recognized, women are also less likely than men to receive treatment.[39]

Double standards are present not only in clinical practice but in research as well. Different instruments, methods, or requirements are sometimes used for men and women when there is no indication that this is biologically or socially necessary.[14] For example, although paternal drug exposure could lead to fetal harm, contraceptive requirements for entry into clinical trials focus on women only.[55] Prudence is also called for when gathering demographic data of research participants, for example, when the socioeconomic status of a child is measured in terms of education of the father or male guardian, and only in his absence, by the education of the mother or

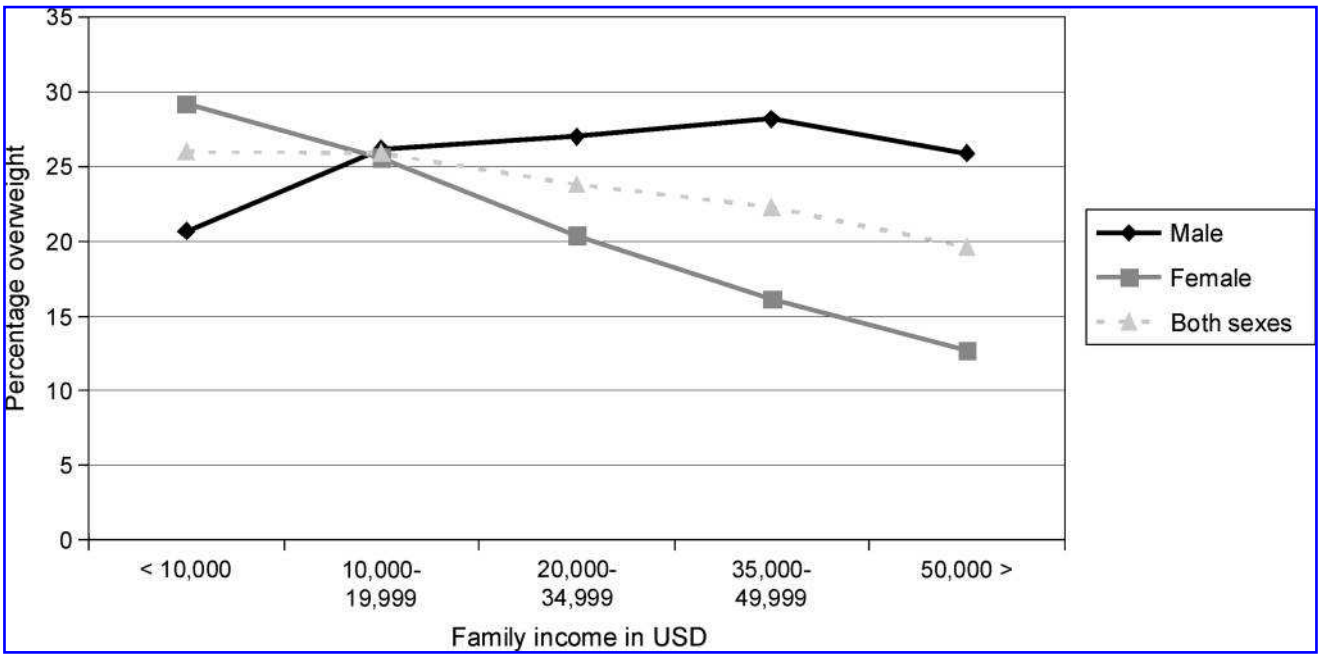

FIG. 1. The relationship between family income and being overweight.

female guardian. Double standards can play a role in data interpretation as well, when identical responses are coded differentially according to sex.

The way in which results are phrased in reporting may also lead to double standards. The combination man and wife, for example, designates the man by his sex but the woman by her marital status.[48] Another example is that medical literature often speaks of atypical symptoms when discussing women's symptoms signaling a heart attack; by the implication that his symptoms are typical, the man is taken as a norm.[21] Double standards also occur when women are routinely described in the passive mode and men in the active mode. These gender stereotypes are reinforced even at the level of the cell: biology has created the image of the passive egg cell waiting for the competing, active sperm to fertilize it, although given the life expectancy of both sex cells, it happens more often that sperm cells are waiting for the egg cell to come.[56]

Considering Sex and Gender in all Research Phases

The pitfalls described can apply to all kinds of research practices. Although their detection might require some diligence, there is almost no study involving humans or animals to which they are not relevant. Some research phases are more prone to being influenced by certain pitfalls, however, and throughout the research process, other sex- and gender-insensitive practices might occur.

A step-by-step plan is offered here that indicates the main sex and gender issues to consider in each stage of research. The checklist is based on the early Gender Impact Assessment (GIA) protocol developed in 2001 as a short tool to analyse the sex and gender sensitivity of European research projects.[17] It was completed and extended by including important issues identified in the literature since. The step-by-step plan helps to identify where sex and gender issues can be of relevance in research projects. It can be used while writing a research proposal or during the research process to monitor the implementation of a sex and gender dimension along the way. It can also serve as a tool for reviewing a peer's research.

Step 1. Relevance Check

Sex and gender are most likely of relevance to a study when:

- The project involves human subjects.
- The project uses human cells, tissues, or other specimens or animal tissues or cells that serve as a model for human biology or physiology.
- The project aims at modifying, changing, or developing (health) policies that have a direct or indirect impact on human beings.
- It is expected that humans will be confronted with the effects of this research in daily life.
- Gender and sex differences on this research topic have already been documented in the literature.

In all instances, sex or gender or both then deserve further consideration until proven otherwise. The only possible exceptions are conditions that are unique to one sex. For conditions that occur in both sexes, looking for sex differences might give clues to the responsible mechanisms of action, especially when they are much more prevalent in one of the sexes.

Step 2. Literature Search

The design, results, and discussion of prior studies and existing literature will often give indications about the nature, scope, and direction of sex differences and gender effects and identify areas that still need to be explored. Moreover, gathering information about to what extent sex and gender have been taken into account in past research gives us material for comparison and allows us to assess the quality of our current efforts to include sex and gender. Our efforts to include sex and gender are adequate when we include differences that were identified as relevant before. If there are known differences that we fail to address in our current study, relevant aspects are missed. This might be because a lack of resources, but such decisions have to be substantiated. If our research addresses or identifies new, undocumented sex or gender differences, it is innovative. Sex and gender differences remain to be studied when they have not been documented to date, and are not addressed in our current research. This should be noted in the discussion or recommendations.

It may take some practice to develop a search strategy that identifies the full range of sex and gender differences that have been documented. The most straightforward method is to combine the name of a condition or biomedical research topic with MeSH terms, such as sex factors and sex characteristics, or text words, such as gender differences and sex differences. For a more extensive search strategy, see the article by Wieringa et al.[21] In basic life sciences research, it might be more rewarding to use search terms signaling sex-specific features on, for example, the cellular or hormonal level (e.g., estrogen receptors), which are dependent on the field of research.

Step 3. Research Questions and Hypotheses

Research questions and hypotheses should indicate how sex and gender can be of relevance.

- The research questions should reflect the sex(es) of the population under investigation. To preclude overgeneralization, terms that do not specify the sex, such as subjects or patients, should be avoided; use a specific term like female subjects instead. Furthermore, research questions should not assume that the research population is homogeneous if the results may differ for women and men.
- If it is not documented if and how sex differences and gender effects can influence the results, a separate question aimed at investigating this can have great added value. The inclusion of gender hypotheses allows for a description of the direction of the expected outcomes.
- Carefully phrased research questions and hypotheses should avoid setting males as a standard.

Step 4. Research Methods and Composition of Research Population

Methods should preferably be sex and gender sensitive and allow for gathering of sex-disaggregated data.

- Is it substantiated why women or men are included or excluded?
- Is it necessary or possible to collect sex-disaggregated data?
- Is it necessary to validate an instrument that is being developed for both sexes?

- Is the existing instrument being used validated for both sexes? If not, should it still be used for both sexes?

Step 5. Data Analysis and Interpretation

A study includes both men and women because it acknowledges that results of one sex might not apply to the other; there is a recognition that results might differ between the sexes. It logically follows that those potential differences should be investigated through a sex-disaggregated analysis. A joint analysis might hide opposing trends. Only if proven irrelevant, sex and gender can be left out.

- Sex can be included in a study in many different ways, and the choice will have a great impact on the analysis. Is it merely a prognostic factor or also an effect modifier?[57] Does it need to be controlled for, or will this obscure interesting findings? Does a certain research question or design call for sex-disaggregated models, or are dummy variables better suited?[58] Gender is less easy to reduce to variables that can be included in a statistical analysis, but its explanatory power can be enormous.
- To analyze sex differences using subgroup analyses, the statistical power must be large enough.

Sex- and gender-insensitive research may lower the quality of the data analysis and interpretation by, for example:

- Taking men as a norm.
- Pathologizing normal female biological processes, such as pregnancy or menopause.
- Reproducing existing stereotypes without scientific ground.

Step 6. Reporting

A sex- and gender-sensitive study does not guarantee sex- and gender-sensitive reports. Applying a gender lens during or after writing will reveal:

- If pitfalls were avoided.
- If sex or gender differences are visualized in the tables, figures, and conclusions.
- If it is considered whether the results will differently affect women and men, for example, in a clinical setting.
- If results and conclusions about gender and sex outcomes are reported even if the results indicated they did not have an impact. The underreporting of negative sex and gender findings is caused by the researcher and not the result of editorial decisions![44]

Step 7. Conclusions and Recommendations

A complete gender analysis ends with the formulation of recommendations and implications for clinical practice and future research.

- Is it necessary that future research on this topic further investigate the role of gender or sex?
- How can information on sex differences be translated into preventive, diagnostic, and therapeutic practice?
- How can the new knowledge about and understanding of biological sex differences and similarities most effectively be used to positively affect patient outcomes and improve health and healthcare?[12]

Conclusions

In the introduction to her book on nonsexist research methods, Eichler[14] begins by quoting a passage from Abbott's novel *Flatland*, in which entities living in a two-dimensional world cannot seem to grasp the notion of a third dimension. The two-dimensional world seems logical and complete as it is, and the characters cannot imagine the concept of and need for an additional dimension. We might be experiencing a similar situation in life sciences research, where biased research practices of long ago are carried on, and the added value of sex and gender is not always noticed. However, there is a whole new world to explore. Sex and gender differences are relevant to biomedical and health research in many ways, and it is a challenge for life science researchers to step out of their two-dimensional world by adding a sex and gender dimension to their research activities. Such a challenge was, for example, taken up by the EU-funded project GenderBasic, which resulted in 10 state-of-the-art reviews on integrating sex and gender aspects in methodologies of basic, clinical, and public health research.[59] More initiatives are needed to ensure research that is innovative and of high quality so that healthcare and policies based on the results will be better, fairer, and more effective.

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Disclosure Statement

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