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Sex and gender approach in epidemiology and public health research

Eliana Ferroni[1], Anna Ruggieri[2], Lilia Biscaglia[3], Cristina Mangia[4]

[1] Epidemiological Service, Azienda Zero of the Veneto Region, Padua, Italy; [2] Center for Gender Specific Medicine, Italian National Institute of Health, Rome, Italy; [3] Health Promotion Unit, Health Department of Lazio Region, Rome, Italy; [4] CNR ISAC - Institute of Atmospheric Sciences and Climate, Lecce, Italy

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Epidemiological research played an important role in bringing out the differences between men and women in the disease's development, symptoms and prognosis, as well as in reactions to drugs and in the access to health care services. Nonetheless, many researchers continue to overlook these differences, either by neglecting them, presenting neutral data, or by merely stratifying by sex a neutral data in an analysis without any gender approach. Moreover, the frequent misunderstanding between sex and gender dimensions in studies where the two terms have been used interchangeably, affects the relevance of these two variables, with implications for prevention measures, health promotion and treatments.[1,2]

Presenting study data stratified by sex is appropriate, but not sufficient. A paradigm shift is needed to take gender and sex differences into account when setting up the study design. This action requires a combination of medical, epidemiological and sociological expertise to better understand the impact of the socio-cultural gender dimension on the health status of men and women. First of all, it is important to develop the right research hypotheses, identifying the most appropriate tools for evaluating them. A sex/gender approach should be applied also when collecting data through questionnaires or surveys, including all variables related to gender. Furthermore, when presenting results stratified by age class, it is important to consider not only age groups more representative of working life, but also those related to hormonal and metabolic changes, which greatly contribute to the increased risk of age-related chronic diseases.[3]

This new approach in health care is fundamental: evaluating any sex and gender difference through appropriate epidemiological research, helps reaching the so-called 'precision medicine'. The Italian Association of Epidemiology (AIE) embraced this change of views, and in 2020 a specific working group was created, with the aim of dealing specifically with sex/gender, health and medicine, promoting the gender approach in all areas of epidemiological research.[4] This working group includes professionals with different scientific profiles and expertise; several topics are discussed in depth, in particular environmental epidemiology, prevention strategies, and vaccine effectiveness and safety.

In environmental and occupational epidemiology, it is important to distinguish between the biological and physiological characteristics that determine 'sex' and those associated with culture-related roles and behaviours linked to culture and social conditioning that define 'gender'.

Accounting for this difference contributes not only to a better interpretation of each gender's place in the environmental health paradigm, but also to an understanding of whether or not there are environmental risks associated with exposure to certain substances by one gender and not by the other.

The pathways through which gender and sex may shape exposure and susceptibility to the same toxic are different. If the gender dimension is relevant in defining exposure and the concentration-exposure pathway, the biological dimension is relevant in the exposure-effective-dose-effect pathway, which, in turn, may be influenced by gender differences in disease recognition and access to care. For the same exposure, men and women may respond differently due to differences in body size and composition, absorption and metabolism of toxicants, and different hormonal influences. Thus, the choice of biomarkers may be decisive in risk assessment. Differences in socio-cultural roles between men and women may influence disease exposure, recognition and treatment. For example, the use of costume jewellery or cosmetics in girls or the greater amount of time boys spend playing outdoors exposes boys and girls to different possible contaminants. Just as in exposure assessment, it is also not possible to overlook how men and women are engaged in paid and unpaid work differently.[5,6]

In environmental epidemiology, gender bias also exists in the identification of health outcomes to be targeted. An example is represented by breast cancer. Although scientific evidence is growing on a possible risk association between exposure to certain atmospheric pollutants and breast cancer[7], in most environmental studies conducted in Italy this disease is not included among those usually considered related to air pollution.

Gender biases also exist in occupational epidemiology, where few studies have been conducted so far and thus there is still a lack of knowledge.[8,9]

Closely linked to the epidemiological aspects are the consequences in terms of prevention. An important critical issue in this area is represented by the mismatch often observed between epidemiological results and prevention policies: one example comes from osteoporosis. Many osteoporosis prevention campaigns continue to target women, considered to be more at risk because the hormone changes of the menopause directly affect bone density. This happens, despite several epidemiological studies have shown that although women are more at risk of falls and bone fractures with increasing age, men also develop osteoporosis, being at risk of fracture, with a higher mortality rate after a hip fracture than women.[10] Or it happens with the so-called 'bikini syndrome' or 'bikini medicine' for women, whereby pathologies in organs other than those of the reproductive-sexual sphere (breast-uterus-ovaries) are underestimated even when epidemiologically and prognostically more relevant. For example, cardiovascular diseases that represent the leading cause of female mortality and disability in developing countries have been traditionally considered a purely male disease, and for many years they have been under-estimated and under-recognized in women due to the differences in terms of clinical presentation.[11]

Gender stratification is also important for a careful reading of the population's health status. If a disease affects one sex more than the another, it may be appropriate to use different instruments to counteract its incidence. An important opportunity to overcome some of these biases is currently provided by the Italian National Prevention Plan (INPP) 2020-2025, approved in 2020 in the midst of the pandemic which recalls the need to decline health promotion and prevention interventions, paying attention to aspects related to sex and gender.[12]

The INPP 2020-2025 underlines the need for more efforts to reduce health inequalities, including those related to sex and gender. It identifies the gender approach as a strategic component of public health, recognizing the importance of biological and sociocultural differences related to sex and gender, with the aim of improving clinical appropriateness of prevention interventions and promote equality and equity in health. To reach this scope, the INPP 2020-2025 recommends all Italian Regions to provide community health and equity profiles, which constitute the strategic tool for regional/local planning of interventions, consistent with contextual data of an epidemiological, demographic, socio-economic, behavioural and organizational framework, allowing direct programming towards equity, also with respect to sex and gender.

Another important issue for the epidemiological research is the theme of vaccines. It is well known that men and women react differently to infections and vaccinations. Women are generally more immunoreactive and develop more intense vaccine responses, with antibody titers often double than those of men.[13] However, adverse reactions to vaccinations are more frequent and often more serious in women; nonetheless, this difference in the immune response has not so far been considered in the design or dosage of drugs and vaccines and this, together with the fact that for a long time women have not been included in clinical trials, may have led to inappropriate use of dosages and administration of drugs and vaccines in women.

In this regard, an American study, conducted on a sample of men and women undergoing seasonal flu vaccination with a full or half dose of vaccine, respectively, highlighted that women vaccinated with a half dose of anti-flu vaccine developed antibody titers equal to those obtained in men vaccinated with a full dose.[14] This study highlights the importance of examining the effects of vaccination separately in men and women, as a starting point for planning sex personalised vaccine administration.

Furthermore, there is evidence that the greater female immunoreactivity is associated with long lasting protection and/or greater efficacy of the vaccination itself. This was the case of the experimental vaccine with the glycoprotein of the herpes virus simplex-1, responsible for the transmission of genital herpes, which was found to protect women, but not men.[15] Since the evaluation of the results from clinical trials, which include either male and female individuals, is done without sex disaggregation of the data, that experimental herpes vaccine was not licensed; actually, the vaccine effectiveness in women would have been indirectly protective also for the male partners, being the herpes simplex-1 infection sexually transmitted.

Among the mechanisms that make women more immunoreactive to vaccination and more likely to receive protective efficacy, sex hormones play an important role, as they positively modulate the immune response in general and the specific humoral response to anti-flu vaccination. In addition to sex hormones, genetic factors, linked to the X/Y sex chromosomes, and epigenetic factors (methylation and microRNA), as well as microbiota composition, also contribute to the gender bias in the response to vaccines. Thus, it appears very important to promote and carry out studies aimed at identifying sex-specific molecular markers predictive of the response to vaccinations, in order to be able to adjust schedules and vaccination doses on the basis of the biological differences between man and woman. These studies, together with the analysis disaggregated by sex of the data obtained from clinical trials and post-marketing studies will help optimize vaccination campaigns and customize prevention and surveillance programs.

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Correspondence to
Eliana Ferroni
Epidemiological Service
Azienda Zero of the Veneto Region
email eliana.ferroni@azero.veneto.it