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EDITORIAL COMMENT

Gender Matters in Biological Research and Medical Practice*

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In recent years, the National Institutes of Health (NIH) has re-energized a focus on the importance of rigor and reproducibility in research, which includes blinding, randomization, replication, adequate sample size, and the importance of sex as a biological variable in experimental outcomes of preclinical, clinical, and population health studies (1,2). According to the NIH, both sex (biological characteristics) and gender (cultural attitudes and behaviors) "play a role in how health and disease processes differ among individuals, and consideration of these factors in research studies informs the development and testing of preventive and therapeutic interventions in both sexes." In recognition of the importance of these factors, the NIH released a *Guide* notice in June 2015 that highlighted the NIH expectation that sex and gender be factored into research designs, analyses, and reporting of results (3). Well ahead of the NIH, the Canadian Institutes of Health Research has explicitly called for sex and gender analysis in health research since 2010 (4), and the European Commission has done so since 2013 (5). Nonetheless, the role of gender and the interaction of gender with biological sex have generally been neglected in biomedical research.

Among the many biological and medical disciplines, cardiovascular researchers have been leaders in recognizing and investigating differences between men and women in epidemiology, pathophysiology, clinical manifestations, effects of therapy, and problems introduced in the diagnosis, treatment, and management of cardiovascular diseases by assumptions based on gender biases of clinicians, leading to differences in health outcomes (6–8). Yet, despite a vast and growing literature on differences between men and women in ischemic heart disease, heart failure, hypertension, and valvular heart disease (9), the relative contributions of biological sex versus sociocultural, gender-related variables remain largely unexplored. This arises in part from the fact that the research community has not sufficiently addressed how to study gender in biomedical research.

Sex analysis in research includes reporting the sex of the subject, analyzing data by sex, and reporting results and is increasingly the topic of intense research. Whereas biological sex differences are initiated by genes encoded on the sex chromosomes, all other factors (e.g., autosomal and mitochondrial genes) are believed to be equally inherited by males and females. However, many characteristics that are affected by biological sex are continuous and have overlapping distributions. For instance, men may be taller on average than women, but there is great overlap. Researchers understand well how to quantify sex variables in ways that allow for rigorous statistical analysis (10).

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Gender, by contrast, is less well understood in health research. In particular, we lack agreed-upon methods for measuring gender in ways that can be analyzed statistically. Hence, our excitement to read the paper by Pelletier et al. (11) in this issue of the *Journal*. The study used a composite measure of gender recently reported by the lead and senior authors of the paper, Roxanne Pelletier and Louise Pilote, to be associated with health-related quality of life (12) and risk factors in patients with premature

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acute coronary syndrome (ACS) in the GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond-Premature Acute Coronary Syndrome) cohort (13).

Gender, in their analyses, referred to sociocultural values and roles that shape expected behaviors of men and women. Social factors and behaviors often influence biology such that gender becomes a modifier of biology (or sex). Gender refers to cultural attitudes that are learned and vary by culture, historical era, ethnicity, socioeconomic status, geographic location, and other factors (the interaction between gender and ethnicity, for example, is important to take into account). Gendered attitudes and behaviors exist on a continuum, and both masculine and feminine behaviors may manifest in any one individual and change over the life course (gendered behaviors change from childhood to adolescence to adulthood and old age). Of course, gender does not necessarily match sex, which the Pelletier et al. study in this issue showed beautifully. Gender includes *gender identity* (how individuals and groups perceive and present themselves), *gender norms* (unspoken rules in the family, workplace, institutional, or global culture that influence individual attitudes and behaviors), and *gender relations* (the power relations between individuals of different gender identities) (14).

Gender is not one thing we measure in the course of a study, but a cascade of questions and factors governing research methods. First, when a study is designed, it is important to consider whether the investigators' assumptions about gender play a role in the selection of study subjects. Assumptions about the role of hormones or disease states, for example, may influence choices concerning which sex to test; an erroneous assumption in subject choice has consequences for the study as a whole, especially when sex is included as a biological variable (Gillian Einstein, personal communication, October 2015). For example, researchers may assume that testosterone is a male hormone only, even when changes in the brain due to testosterone administration are noted in females too. Such assumptions may lead to a decision to test the relationship between testosterone and aggression in males only (15). In this case, potentially important data concerning these relationships in females would be missed. Similarly, gendered assumptions about a particular disease state may influence the sex of study subjects. For example, researchers' assumption that breast cancer is a female disease has led to the development of female-only animal models, thus eliminating the opportunity to better understand breast cancer in males (16,17).

Second, researchers will want to consider the impact of social environmental factors (i.e., gender) on the health of the individual. We might call these the "biologic expressions of gender" (18). Lifestyle behaviors, such as smoking, a leading cause of cardiovascular disease and cancer; physical activity; dietary habits; alcohol consumption; and other well-known cardiovascular risk factors, differ significantly between men and women in the U.S. and other populations (19). Although these behaviors differ by racial/ethnic group, socioeconomic status, age, and other factors, men generally have higher smoking rates, are more physically active, consume fewer vegetables and fruits and more alcohol, etc.

Pelletier et al. (11) developed new methodology to analyze gender as a variable to understand the association between gender, sex, and cardiovascular risk factors among patients with premature ACS. Importantly, they found no sex differences (i.e., being a man or a woman did not predict accurately which patients were likely to relapse or die within 12 months from diagnosis). The team found, however, that gender mattered: patients received a gender-related score of between 1 and 100 points. Patients with a higher "femininity" score—regardless whether they were a man or a woman—were more likely to experience a recurrence of ACS. This study showed that a man with a high femininity score was more likely to suffer a recurrence, and a woman with a high masculinity score was not.

We see this as an innovative methodology. Although more and more studies are addressing the importance of gender factors in health, methods for *measuring* gender need further development. As the investigators concluded, "there exists no gold standard for gender." This is something that now needs to be developed.

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