

## Sex and Gender Issues in Cardiovascular Research

As we worked on completing our recently published volume on psychosocial stress and cardiovascular disease (CVD) in women, we realized an important feature of recent original scientific articles. Sex and gender seemed to be only marginally mentioned or even excluded from the analyses, and these factors were certainly not treated as primary factors in the prediction of health outcome (1).

We would therefore like to raise the issue of sex and gender in CVD and other medical conditions, as described in recent issues of *Psychosomatic Medicine*. A distinction between sex and gender is common in social sciences, but has largely been neglected in health sciences. Unlike sex, which is a biologically based variable, gender is a construct that has a wider scope and incorporates the effect of social norms and expectations for men and women in a given society. We found that both sex and gender were unsystematically represented, and we thought that this finding may have consequences for scientific evaluation and interpretation.

We screened recent articles published in *Psychosomatic Medicine* (2014: issues 1–9; 2015: issues 1–2). We found that the pattern of sex representation was unpredictable. Some authors (7/24), who had aimed at investigating sex differences, designed the study group accordingly (1/24), whereas others (5/24) had only mentioned sex as possible modifier of outcome in multivariate analyses. Most articles presented the relative proportion of men and women in table or text (23/24), but 14 of 24 had avoided discussing the impact of sex (or gender) as a risk factor. With the recent emphasis on research in women's health, we found that surprising.

### RISK FACTORS AND EPIDEMIOLOGY

Although still disproportionately rare, the issue of sex is nowadays more often investigated than a few decades ago. As an example of the importance of sex- and gender-related differences in psychosomatic and behavioral medicine, we refer to research on stress and CVD (2). In contrast to common beliefs, heart attacks occur almost as frequently in women as in men, but at an older age and with clinical manifestations that differ between younger, premenopausal, and older postmenopausal women (3). Before menopause, women are relatively protected by their endogenous sex hormones. However, those rather few women who do get CVD at an earlier age (<50 years) do have a higher mortality and a worse long-term prognosis than men of the same age (3). This important high-risk group deserves increased attention, in particular if high risk is due to a sex-biased allocation of medical care. Swedish population-based registries have confirmed the adverse prognosis in women versus men with CVD (4).

### MECHANISMS OF SEX DIFFERENCES

Women with clinical CVD more often have “clean” coronary arteries on angiography (3). Microvascular ischemic coronary disease resulting from endothelial dysfunction, which is not detected on clinical coronary angiography, has been suggested as an explanation (5). Modulation of vessel wall architecture and its change by immune and autonomic functions may play a crucial role. The relative importance of the immune as well as clotting systems differs substantially between men and women (6).

Another mechanism concerns silent ischemia: it has been reported that women with heart disease, who are younger than 50 years and are still menstruating, react with more silent ischemia to laboratory stressors compared with men. An increased (silent) ischemic response to mental stress is also a possible underlying mechanism for the poor prognosis in younger women (7).

### PREVENTION AND INTERVENTION

Cardiology has produced powerful preventive drugs and other strong technological innovations, such as drug-eluting stents. These have led to better patient health, through a range of clinical outcomes, from prolonged survival and reduced rates of recurrent cardiac events, to improved health-related quality of life. It is now time to “set the stage” for the potential power of the psychosocial/behavioral interventions (9).

To disentangle sex- and gender-related needs and provide tools for stress-reducing interventions in men and women, we have, in addition to the sophisticated view of scientists, also included the views of therapists and of patients in our research projects and clinical work. In this way, sex- and gender-related issues were identified in almost every CVD aspect: cardiovascular risk profile, psychobiological mechanisms, and psychosocial/behavioral intervention programs.

In the June 2015 issue of *Psychosomatic Medicine*, a further possible mechanism was observed (8). Pelletier et al. identified psychosocial characteristics of gender in patients with heart disease. Fifty percent of female patients had a more masculine gender score, and 16% of male patients had a more feminine gender score. In multivariate analysis that included both gender and sex, feminine gender score, but not female sex, was associated with heart disease risk factors.

It follows that sex and/or gender should be included in virtually all investigative CVD models, particularly in those with implications for prevention and intervention.

In conclusion, sex remains an important factor, which must not be forgotten in *Psychosomatic Medicine*—or elsewhere in the health and medical sciences. We suggest that all study groups, addressed in *Psychosomatic Medicine*, are characterized by their sex and that sex is considered a risk factor as any other.

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