Circadian misalignment and cardiovascular risk

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Current opinion is that the increased risk of obesity, hypertension, cardiovascular disease (CVD), and type 2 diabetes mellitus (DM2) in circadian misalignment is multifactorial, with physiologic, social,

psychologic, sleep, and eating patterns all likely contributing. The data so far indicate circadian misalignment is robustly associated with increased obesity and cardiovascular events in women, with a dose-response relationship for the latter.

There is a weaker association between shift work and DM2 and metabolic syndrome in women and conflicting data regarding shift work and hypertension. The differences and disparities in conclusions are a result of numerous confounders, including methodological differences in studies, the definition of shift work, human behaviors, and sleep deprivation. Prospective and longitudinal studies are needed to address the limitations of the current body of literature. In addition, experimental and interventional studies are needed to address optimal interventions and treatments for circadian misalignment.

It seems termination of shift work reverses or attenuates some of adverse consequences. Also, behavioral modifications regarding the timing of eating, diet, weight loss, sleep patterns, and light exposure have been proposed as possible interventions. Pharmacologic agents such as melatonin, stimulants, and hypnotics have also been studied as potential treatments for shift work disorder. However, it is unclear if these interventions have any effect on diminishing the deleterious effects observed with circadian misalignment. These concepts may play a role in future treatment strategies.

An article in *Cardiovascular Innovations and Applications* is part of a special issue on Women's Cardiovascular Health guest edited by Gladys P. Velarde. Recent decades have witnessed great progress in the treatment of cardiovascular disease (CVD). Due to improved therapies, preventive strategies and increased public awareness, CVD (stroke, heart failure, ischemic heart disease, peripheral arterial disease and congenital heart disease) mortality has been on the decline over this span of time for both genders. Unfortunately, the decline has been less prominent for

women, especially women of color.

Once viewed as a man's disease, CVD remains the leading cause of mortality for women in the United States and is responsible for a third of all deaths of women worldwide and half of all deaths of women over 50 years of age in developing countries. In the United States, CVD far outpaces all other causes of death, including all forms of cancer combined. The statistics are sobering with about one female death in the United States every 80 seconds from CVD. That represents close to 400,000 deaths per year according to the more recent statistics.

Of these, more than one quarter of a million women will die this year from ischemic heart disease (IHD) which includes obstructive and non-obstructive coronary disease, and about 64 percent of women who die suddenly of IHD have no prior symptoms. Despite a significant number of females with known CVD and increased awareness among women of heart disease as their major health threat, a substantial proportion of women (46 percent as per the most recent American Heart Association survey) remain unaware of their cardiovascular risk and continue to fail to recognize its significance.

This lack of awareness is more profound (over 60 percent unaware) among women in higher-risk groups, racial and ethnic minorities, and has changed little in decades.

Poorly understood sex/gender differences in pathobiologic mechanisms, clinical presentation, management and application of diagnostic and therapeutic and preventive strategies have contributed to this gap. A critically important factor has been the underrepresentation of women in CVD research to date. In fact, only one-third of CVD clinical trials report sex-specific results despite The Food and Drug Administration regulations requiring sex stratification data, as well as the National Institute of Health recommendations of increased inclusion of women in

clinical trials.

This makes it difficult for researchers and clinicians to draw accurate conclusions about sex differences in mechanisms of disease, accuracy of specific diagnostic modalities and risks or benefits of a particular drug or device for the treatment of women with CVD. Furthermore, physicians and other healthcare providers continue to underestimate women's cardiovascular risk, in part because of utilization of traditional approaches which can lead to over-testing or inappropriate risk assessment without accurate differentiating who is truly at risk and inadequate use of preventive therapies for women.

More information: Tracy Ashby et al. Circadian Misalignment and Cardiovascular Risk, *Cardiovascular Innovations and Applications* (2019). DOI: 10.15212/CVIA.2017.0070