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Understanding Vasovagal Syncope: A Role for Sex and Gender

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Vasovagal syncope (VVS) is a common and frequently distressing problem. About 40% of people faint at least once in their life, and at least 20% of adults faint more than once.[1] VVS affects all ages and both sexes. It is known that there are multiple pathophysiological mechanisms underlying vasovagal syncope ranging from decreased cardiac venous return,[2] active arteriolar vasodilation due to a loss of sympathetic tone, to differential catecholamine release.[3] To date, it has been difficult to show the clear benefits of pharmacological therapies for VVS in well-designed randomized clinical trials.[4,5] VVS has shown a strong familial clustering,[6] but it has been difficult to show a strong genetic basis underlying VVS.[7]

A recent genetic association study in VVS took a slightly different approach. Instead of just looking at the overall cohort of 160 participants, the investigators probed 12 distinct candidate genes by sex.[8] There was no significant association for 9 of the 12 candidate genes. In the serotonin 5-HT1A receptor gene (*HTR1A*), the presence of a G allele was associated with syncope in male (GG 77% vs. CC 9%), but not in female participants. The *SLC6A4* gene for the serotonin reuptake transporter promoter L alleles were associated with decreased syncope in males, but increased syncope in females. LL males had a 25% likelihood of syncope, while LL females had a 75% likelihood of syncope. The catecholamine O-methyltransferase gene (*COMT*) A allele was associated with decreased syncope in males (15% vs. 50%), but increased syncope in females (73% vs. 52%). Importantly, these relationships might have been overlooked if only a global analysis was performed.

In this issue of *Clinical Autonomic Research*, Ghariq and colleagues report their experience from their high-volume tilt testing laboratory.[9] Overall, the proportions of men and women

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with a positive tilt table test were not different, when corrected for age. However, the difference became apparent when looking at tilt test provocation. Women were less likely than men to have a positive drug-free tilt table test (odds ratio = 0.54), but were more likely to have a positive tilt table test in the setting of nitroglycerin provocation. These data suggest that there might be different sex-based pathophysiological substrates to positive tilt table testing in males and females.These insights would be missed in their entirety if sex-specific analyses were not planned and performed.

The importance of sex and gender in clinical research, and in understanding our clinical care, has become increasingly clear.[10] This has led to initiatives from national funding agencies to encourage (https://orwh.od.nih.gov/sex-gender/sexgender-influences-health-and-disease), and in some cases dictate, sex and gender-based analyses in clinical research (https://www.cihrirsc-igh-isfh.ca/).

While the terms are often erroneously used interchangeably, sex and gender refer to distinct concepts. Sex refers to an objective biological component, defined by the genetic dotation since the time of conception, and manifesting in cellular, molecular and hormonal differences. So far, sex cannot be changed. The concept of gender, however, is less clear but has gained prominence in the last decades. Gender identity is a subjective assessment of how an individual perceives and presents themselves; it has to do with the social, emotional, environmental, cultural, and behavioral factors that influence a person's self-identity. Gender identity can be very fluid; an individual could self-identify with one or multiple genders, which could also change over time. While the assessment of gender is evolving and can be challenging (e.g., there are currently more than 50 different terms to refer to different gender identities), a simple starting point would be to ask research participants about both their objective biological sex at birth (i.e., as indicated on their birth certificate), and, also, how they define themselves in terms of gender identity.

Aside from political correctness, this is relevant because gender roles could impact cardiovascular health. For instance, a feminine gender, independent of the objective biological sex, appears to be associated with an increased risk of recurrent acute coronary syndrome.[11] And a recent paper by Bernier and colleagues might point to differential effects of sex and gender in patients with syncope.[12] Using administrative data of patients presenting to hospital with syncope in Alberta, Canada, the investigators found that women had lower mortality rates than men. However, women were more likely to present to the emergency department than men. The survival advantage observed in women in this study likely reflects both biological differences between males and females, as well as gender-related social/emotional factors that resulted in earlier presentation to medical attention.

So, moving forward, it appears that collecting information on sex and gender in clinical research projects may provide interesting scientific information. Ideally, outcome data should be reported both in toto, and also stratified by sex (for biological variables) and, if possible, for gender (for psychosocial or cultural variables).

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