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## Invisible Gender in Medical Research

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Four decades ago, gender disparities research was uncommon. A quick search of Pubmed today reveals how far we have come, yielding 8391 published articles with either the term 'gender disparities' or 'gender differences' in the title. A similar search for disparities in transgender or gender minority populations, however, yielded only 67 articles with only a handful focused on conditions outside of mental and sexual health. This discordance exists because, until recently, our society has posited gender as binary—male or female—and we have viewed individuals and conducted our research with this paradigm.

The past two decades has ushered in a new and more nuanced societal understanding of gender—one where gender is a spectrum that includes traditional cisgender male and female identities (i.e., those whose gender identity matches their biological sex) but also individuals who identify themselves as transgender, gender-nonconforming/non-binary (neither exclusively of male or female gender identity), intersex (with dual male and female sex phenotypes indeterminate sex phenotype, or with mosaic genetics), agender (no gender identity), or one of many other non-cisgender classifications. The number of transgender individuals in the U.S. is currently estimated to be 1.4 million, with varying prevalence of 0.3% to 0.8% across the 50 states.<sup>1</sup>

Alarming, recent research has found that a transgender (i.e., any non-cisgender) individual is more likely to be poor, unemployed, or homeless. Rates of attempted suicide are much more common in transgender individuals (40% vs. 5%) as are rates of stress, depression, and intimate-partner violence.<sup>2</sup> Moreover, many transgender individuals avoid seeking medical care because of lack of health insurance or prior negative health encounters where they were not recognized as full human beings (e.g., intentionally not being addressed by their preferred name or gender pronouns, questioned for their gender identity choices, mocked for the effects of hormonal therapies on their bodies). In fact, 19% of transgender people have been refused treatment solely on the basis of their gender identity<sup>3</sup> and 23% have avoided care due to fear of discrimination against them.<sup>4</sup> Transgender people are also reluctant to reveal their bodies, especially if they have not fully transitioned with hormone and/or surgical treatments.

Against this backdrop, in this issue of *Circulation: Cardiovascular Quality and Outcomes*, Alzahrani and colleagues have leveraged the Behavioral Risk Factor Surveillance System

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(BRFSS) data from the Centers for Disease Control and Prevention (CDC) to compare the prevalence of myocardial infarction between transgender vs. cisgender individuals.<sup>5</sup> The BRFSS is a unique national dataset as it can be used to assess gender as a multilevel category, thereby avoiding assumptions of gender as only a binary choice of male vs. female. The investigators found that transgender males and females have higher rates of prior myocardial infarction than cisgender individuals (except when comparing transgender women vs. cisgender men), but that this relationship was particularly striking (nearly 5-fold higher odds) when comparing transgender men vs. cisgender women. These results were consistent after adjustment for a limited number of cardiovascular and lifestyle risk factors.

This article was notable in several respects. First, it reported on the health of transgender individuals as a separate gender group and the focus was not on mental or sexual health. This article remains one of only a handful of cardiovascular publications where gender was assessed as multiple levels and not assumed to be binary. Second, the authors leveraged a national dataset which collected information on gender identity through telephone interviews, which may be viewed as less threatening than in-person interviews where transgender identity may not be as willingly volunteered. And third, the authors found an important association for myocardial infarction risk among transgender individuals, especially among transgender men as compared with cisgender women. This report provides important insights, given conflicting reports from two recent studies, in which one similarly found a higher risk for myocardial infarction among transgender men vs. cisgender men and women and for transgender women vs. cisgender women but not for transgender women vs. cisgender men,<sup>6</sup> and the other found no increased risk for myocardial infarction among transgender individuals (although transgender women in this study had higher rates of venous thromboembolism as compared with cisgender men).<sup>7</sup>

No doubt, there are limitations with the methods and findings from this article. First, the nature of the BRFSS data makes this a cross-sectional study. As such, the association between transgender status and higher risk of myocardial infarction is hypothesis-generating at best, and causation cannot be inferred, especially since the authors were not able to establish whether the myocardial infarction occurred prior to the individual's recognition of their transgender identity.

Second, the authors had little information as to the reasons for a higher risk of myocardial infarction among transgender individuals. The BRFSS data does not collect data on use and duration of use of gender-affirming hormone therapy, nor the duration of time one has identified themselves as transgender. Although there are potential risks of myocardial infarction with both testosterone and estrogen hormone therapies in other contexts, the risks of testosterone in transgender men and estrogen in transgender women are not well understood. Because prior research has also found that a transgender person has a higher likelihood of suicide, depression, stress, unemployment, lack of insurance, and poverty—which are all well-known determinants of cardiovascular health—it is unclear whether transgender individuals in this study may have had higher risks for myocardial infarction due to these social determinants of health. Had the authors possessed information on duration of hormone affirming therapy, psychosocial and economic variables, and duration of transgender status, they may have been able to provide greater insights into potential

mechanisms by which transgender status increases risks for myocardial infarction. Long-term cohort studies with granular information on transgender status and treatments are critically needed, with an emphasis of not only delineating cardiovascular issues but also noncardiovascular risks and benefits.

And third, the authors categorized individuals who were non-binary (i.e., gender non-conforming) using an unvalidated formula. It was unclear what proportion of transgender men and women were actually non-binary. Non-binary identity refers to individuals who see themselves as neither exclusively of male or female gender identity or as a combination of both; therefore, non-binary individuals may not take gender-affirming hormones (testosterone or estrogen) and may instead choose hormone blockers (such as vantas or lupron for biological females to block the effects of estrogen). The risks for transgender individuals who take gender-affirming hormones vs. hormone blockers may differ if the majority of this risk is mediated by hormones rather than higher rates of stress, depression, and poverty found in the transgender population.

Nonetheless, Alzahrani and colleagues have continued an important dialogue on transgender health research. It is time that transgender individuals are not treated as second-class citizens. As researchers, we can start by doing something easy but transformative—we should avoid imposing the false dichotomy of asking patients to identify themselves as either male or female. Instead, we should provide, at a minimum, **five** gender categories for all patients: cisgender male, transgender male, cisgender female, transgender female, and other (e.g., non-binary). We should actively use the term ‘cisgender’ for those who do not view themselves as transgender. Doing so will normalize transgender identity and avoid putting the burden of ‘differentness’ on transgender peoples as if they are a deviation from the norm. And defining gender as more than a binary choice will allow us to gain deeper insights into whether transgender and non-binary individuals have higher risks for certain outcomes regardless of whether gender is the independent variable of interest. Being intentional about classifying gender as multiple categories will passively generate volumes of research data for cisgender, transgender, and non-binary individuals and rapidly advance our understanding of outcome differences for different gender groups.

Transgender people are a vulnerable population that are hidden from the majority of researchers, unless one knows someone personally to understand their stigma, ostracism, stresses, and fears. In 1952, Ralph Ellison’s *Invisible Man* provided a complex portrayal of black identity and individuality. In the prologue, Ellison wrote, “I am invisible, understand, simply because people refuse to see me.” Today, the contemporary invisible individual is the transgender person. As researchers, we can take the first step and recognize those who are invisible by acknowledging that gender is more than binary and conduct our research accordingly.

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