

# Sex-based differences in hypertension: Understanding the trends

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## 1 | INTRODUCTION

Hypertension is a common complex clinical entity representing the leading risk factor for cardiovascular morbidity and mortality globally.<sup>1</sup> Despite its uniform phenotype, expressed as an abnormally elevated blood pressure (usually defined as a systolic blood pressure equal to or greater than 140 mm Hg and/or a diastolic blood pressure equal to or greater than 90 mm Hg), there are a number of intricately interwoven biological, behavioral, and pathophysiologic processes, which result in hypertension. Unraveling the complex tapestry of risk factors and processes that result in hypertension rightfully continues to be the source of much attention.

Through epidemiological studies, several patterns have emerged that have been key in enhancing our understanding of the factors driving the widespread clinical consequences of hypertension and cardiovascular disease. Variations in hypertension prevalence, treatment, and outcomes based on identifiable factors such as age, sex, race, and ethnicity have been demonstrated in large population-based surveys.<sup>2</sup> Employing this epidemiologic knowledge as the basis for optimizing hypertension management requires a deep exploration of how factors such as biological sex contribute to differences in clinical outcomes from the hypertensive process.

In this issue of the Journal, Aal and colleagues explore the difference in aspects of hypertension control and management using biological sex as the distinguishing variable. Their manuscript "Registry of the Egyptian Specialized Hypertension Clinics: Sex-related difference in clinical characteristics and hypertension management among low socioeconomic hypertensive patients" sheds further light on the need for specific risk factor identification to improve hypertension outcomes.

## 2 | BIOLOGICAL SEX AND HYPERTENSION

Several factors drive the prevalence of hypertension and influence outcomes such as the likelihood of disease awareness, successful blood pressure control, and the rate of subsequent complications. One such factor is biological sex (the genotypic state of woman and man) and gender (the socially and culturally constructed roles of each sex),<sup>3</sup> which has a complex pathophysiologic and sociologic basis on which observed differences in hypertension prevalence and hypertension outcomes are produced. For the purpose of this discussion, we will use the term sex to cover both the traditional terms of sex and gender as defined above.

Compounding the complexity of this further is the non-universal societal roles of the sexes in different geographic and cultural settings, which are difficult to distill, thus making contextual applications of these findings necessary.

## 3 | DIFFERENCES IN HYPERTENSION PREVALENCE BY SEX: THE BIOSOCIAL BASIS

Hypertension is a disease defined by blood pressure thresholds. While some variation exists based on the guideline used, the most recent definition of hypertension by the American College of Cardiology and American Heart Association and a consortium of medical societies published in 2017 is a blood pressure (BP) > 130/80 mm Hg, compared with the > 140/90 mm Hg used by older

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guidelines.<sup>4</sup> Therefore, examining the links between sex and hypertension requires examination of how sex-related factors might affect blood pressure levels.

Examination of blood pressure trends using 24-hour ambulatory blood pressure monitoring demonstrated that blood pressure is higher in men than in women until menopause, at which point the reverse is true.<sup>5</sup> This finding of higher blood pressures based on differences in sex (attributable to differences in sex hormone levels) has been studied in animal models with inconsistent findings.<sup>6</sup>

In the manuscript presented by Aal and colleagues, women were found to have lower systolic blood pressures (SBPs) and diastolic blood pressures (DBPs) as compared to the male participants (SBP  $144.2 \pm 22.6$  and DBP  $88.1 \pm 13.0$  mm Hg in women vs. SBP  $146.5 \pm 22.0$ ,  $P < .01$  and DBP  $89.9 \pm 12.6$  mm Hg,  $P < .01$  in men). While limitations exist to infer a true physiologic basis for the difference in blood pressure by sex noted in the study, it is reasonable to assume this demonstrates real-world representation of the interplay of biosocial factors in this population.

Epidemiological studies have demonstrated a higher prevalence of hypertension in men when compared to age-matched, premenopausal women.<sup>6</sup> Applied on a global scale, according to one large systematic analysis the prevalence of hypertension is higher in men when compared to women (31.9% vs. 30.1%).<sup>7</sup> While present in both high-income and low-income settings, this prevalence appears more pronounced in high-income settings where a 6.3% difference in prevalence is noted across sex lines (31.6% vs. 25.3%). In low- to middle-income countries, the sex disparity prevalence is much less pronounced (31.7% vs. 31.2%) suggesting the possible heightened presence of concomitant social risk factors in these settings leading to higher rates of hypertension in women.

However, this disparity in prevalence is not universal across all age groups. A higher prevalence is noted in women after the ages of 60–69 years and is more pronounced in women > 70 years in low- to middle-income countries where the prevalence is as high as 74.7% (compared to 65.6% in men).

The reason for the difference in hypertension prevalence by sex with the increase in age has been hypothesized to be multifactorial. For instance, in women, biological factors contributing to the relatively lower prevalence of hypertension prior to menopause than men include the blood pressure-lowering effect of estrogen, which decreases as women age. Estrogen influences mediators of blood pressure such as vascular tone, increasing nitric oxide bioavailability, inhibiting vascular remodeling, and mediating components of the renin-angiotensin-aldosterone system.<sup>8,9</sup>

After menopause, concomitant with the decline in estrogen levels and its presumed protective properties, the lower prevalence of hypertension in women compared with men is lost.<sup>9</sup> From the population of the participants in the study presented by Aal and colleagues, with a mean age of 51 years for women, only a proportion of the differences in blood pressure based on sex can be attributed to those associated with the blood pressure-lowering properties of estrogen typically seen in pre-menopausal women.

Beyond biological factors, hypertension is heavily influenced by behavioral factors. Some of these factors include alcohol consumption, tobacco use, high levels of stress, and increased body mass index, which appear to be more common in men. These factors may augment concomitant biological factors in producing the higher prevalence of hypertension in men when compared to women of similar ages.

#### 4 | HYPERTENSION AWARENESS, TREATMENT RATES, AND CONTROL: DOES SEX PLAY A ROLE?

The awareness rate of hypertension (the number of persons who have elevated blood pressure and know that they have hypertension) is linked to the overall control of hypertension. Generally, awareness of hypertension is associated with how robust the health care system is and how well it is utilized.

Studies have shown the rate of awareness of hypertension is lower in men than in women. In one study of young adults in the United States, the awareness rate of hypertension was 32% in women.<sup>10</sup> This is significantly higher than the 25% awareness rate in men. This difference is even more startling given the higher prevalence of hypertension in young men when compared to young women (30% vs. 12%). Along similar lines, globally, women are more likely to be treated for hypertension compared with men. They are also more likely to have their hypertension controlled, and this trend has been noted in both high- and low-income countries.<sup>7</sup>

Some worthwhile observations along this line can be made from the published study under discussion. While no inference can be made to the prevalence of hypertension in the Egyptian population, some glimpse into differences in hypertension awareness and clinic utilization can be made along the basis of sex. Specifically, the registry contained more women than men (58.5% women vs. 41.5%) in spite of prior studies showing an only slightly higher prevalence of hypertension in women compared with men.<sup>11</sup> As the registry was based on persons presenting to a specialized hypertension clinic, it is evident that these clinics are utilized more by women as compared to men, which at minimum represents a difference in health care utilization between the sexes. In this study, the authors attributed this difference in utilization to be due to the operating hours of the clinic, which may be more accessible to women as compared to men by virtue of differences in work-related time obligations.

The effects of these findings are propagated downstream. For instance, the social factors surrounding poor health care utilization result in delays in hypertension diagnosis and relatively lower treatment rates at the population level. This cascade often manifests as poorly controlled hypertension and high complication rates including heart attacks, heart failure, and strokes as has been described in large studies.<sup>7</sup>

The control of hypertension is the culmination of several key interventions and hinges on a number of patient, provider, and health

system factors. The findings noted in the study by Aal, Youssef et al are not unique, in which women had higher levels of hypertension control compared with their male counterparts. In the span of the study, however, it was demonstrable that control of hypertension could be achieved with follow-up visits. One key factor to this trend likely surrounds the slightly higher adherence to antihypertensive medications noted by women compared with men, a phenomenon that has been speculated to be commonly seen but has not been demonstrated in large meta-analyses.<sup>11</sup>

## 5 | TAILORING TREATMENT TO ADDRESS SEX-BASED DIFFERENCES IN HYPERTENSION OUTCOMES

The findings of manuscripts such as those presented by Aal, Youssef et al call to question how to use this information to improve outcomes in hypertension. Questions such as should hypertension diagnosis and management efforts be sex-specific are reasonable. To date, none of the major hypertension guidelines use sex as a factor to define how hypertension should be diagnosed or treated. At this time, there are limited data to support the need for a sex-specific definition of hypertension.

Another worthwhile question is: Should drug choices in hypertension management be sex-specific? There may be sex-based differences in the pharmacologic management of hypertension due to inherent sex-specific concerns with certain antihypertensive medications. As an example, due to the potential of fetal complications associated with renin-angiotensin system inhibitors may lead to them being prescribed less in women of child-bearing age than men. Similarly, the presence of sex-specific side effects, such as impotence that could be attributed to thiazide diuretics and beta-blockers, may make these medications used less in men. While sex-specific variations in the pharmacokinetic and pharmacodynamic properties of antihypertensive medications exist, further research is needed to determine whether this is significant enough to warrant sex-specific treatment algorithms. Despite the potential role that estrogen may play in providing protection from hypertension in pre-menopausal women, the introduction of exogenous estrogen therapy has not been shown to reduce blood pressure in post-menopausal women.<sup>8,12</sup>

Given the sex differences in hypertension and cardiovascular disease, additional effort must be put forth to address the inherent differences in risk factor profiles that contribute to the difference in hypertension detection and management along sex lines. The American Heart Association, World Heart Federation, and other notable associations have programs that spotlight the heightened need to increase the awareness of the impact of cardiovascular disease in women.<sup>13</sup> Beyond this, improving the overall setting in which hypertension is managed, paying close attention to where deficiencies exist, and correcting these deficiencies using a health system approach are likely to see dividends. In addition, the publication of the manuscript by Aal and colleagues in this issue of the journal provides

new specific population-based data, which contributes to our understanding of sex-based differences in hypertension and for the need of further research in this area.

Sex-based factors influencing outcomes in hypertension are multifaceted. Using the knowledge of these factors to shape the management of hypertension is needed. Therefore, continuing to tailor programs to address inherent differences in the biological and behavioral trends across the sexes is likely to realize dividends in producing improved outcomes in hypertension.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTIONS

Jamario Skeete, MD, was a lead author, formulated manuscript design, prepared its content, and edited the manuscript to ensure clarity and accuracy of its key points. Elizabet Ramsey, MD, was a co-author and assisted in manuscript design, preparation, and editing. Sean Battle, MD, assisted in manuscript design, preparation, and editing. Donald DiPette, MD, was a senior author, assisted in manuscript design and structure, preparation, and editing, and reviewed content for accuracy and clarity.

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