# **REVIEW ARTICLE**

# Check for updates

# The role of sex and gender in hypertension

Zahra Azizi<sup>1,8</sup>, Pouria Alipour<sup>1,2,8</sup>, Valeria Raparelli <sup>□</sup><sup>3,4,5</sup>, Colleen M. Norris<sup>5,6</sup> and Louise Pilote <sup>□</sup><sup>1,7 ⋈</sup>

© The Author(s), under exclusive licence to Springer Nature Limited 2022

Hypertension (HTN) is a critical primary modifiable risk factor for the development of cardiovascular diseases, with recognized sex-based differences. While sex refers to one's biological genetic makeup and attributes, gender encompasses the individual's psychosocio-cultural characteristics, including their environment and living conditions. The impact of each gendered variable may differ amongst men and women with respect to HTN. Applying a sex and gender-based lenses to inform our understanding of HTN has the potential to unveil important contributors of HTN-related cardiovascular outcomes. For instance, increased life stressors, work related anxiety and depression, typically have more pronounced effect on women than men with HTN. The impact of social surrounding including marital status and social support on HTN also differs amongst men and women. While married men are less likely to have higher blood pressure, single women, and those who never married are less likely to have HTN. Additionally, the beneficial role of social support is more pronounced in more historically marginalized cultural groups compared to majority. Finally, socioeconomic status, including education level and income have a linear and inverse relationship in blood pressure control in more resource-rich countries. The aim of this review is to summarize how sex and gender interact in shaping the clinical course of HTN demonstrating the importance of both sex and gender in HTN risk and its treatment. Hence, when investigating the role of gendered factors in HTN it is imperative to consider cultural, and social settings. In this narrative we found that employment and education play a significant role in manifestation and control of HTN particularly in women.

Journal of Human Hypertension; https://doi.org/10.1038/s41371-022-00789-4

#### INTRODUCTION

The increase in the incidence and prevalence of HTN (HTN) worldwide is an alarming public health consideration, given the challenging nature of its control and multisystem impact. The World Health Organization (WHO) estimates that nearly 1.28 billion people are currently living with HTN, of which two-thirds reside in middle to low-income countries [1]. HTN is reported as being one of the leading causes of death and disability-adjusted life years worldwide [2, 3]. Additionally, it is responsible for more deaths secondary to cardiovascular disease than any other modifiable risk factors including smoking and diabetes [4]. Reporting on the 2001-2016 data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative survey, Peters et al. reported that the prevalence of HTN in the United States is 49% in males and 42% in females [5]. Furthermore, it has been noted that the prevalence of HTN is directly proportional to age noting that after the age of 65 years, there is a higher prevalence of HTN in females compared to males [6, 7]. More importantly, it has been reported that amongst those with HTN, 20% of males and 15% of females are unaware that they are hypertensive, and 29% (males) and 19% (females) are untreated HTN [8] albeit these findings vary by regions of the world.

The etiology and pathophysiology of many cardiovascular, cerebrovascular, and renal diseases stem from inadequate blood pressure control [9]. There is a substantial literature concerning

the manifestation and etiology of this disease specifically focusing on modifiable risk factors including lifestyle behaviors related to diet, inactivity, tobacco and alcohol consumption, and obesity, as well as non-modifiable risk factors such as age, sex, and family history of HTN [10, 11]. As a result, lifestyle modifications in addition to pharmacotherapy are mainstay strategies for the management of HTN [12].

While there has been substantial advancement in medical therapy aimed at controlling blood pressure, and reducing the disease burden and it subsequent sequalae, only one in five of those with known increased blood pressure are treated adequately worldwide. There are many possible explanations for these findings, including barriers to the access of healthcare services associated with social and financial limitations which have become even more pressing given that globally the majority of individuals with HTN reside in middle to lower income settings [13]. Grotto et al. report that factors including biological sex, level of formal education, and income level have important implications for being able to provide adequate medical therapy that results in successful blood pressure control [14]. Hence, over and above the physiological components associated with HTN, sociocultural factors are important consideration in the treatment and control of HTN.

Sex and gender are often mistakenly used interchangeably in medical literature. Sex refers to the genetic and biological characteristics of an individual, while gender encompasses the

<sup>1</sup>Centre for Outcomes Research and Evaluation, McGill University Health Centre Research Institute, Montreal, QC, Canada. <sup>2</sup>Faculty of Medicine, McGill University, Montreal, QC, Canada. <sup>3</sup>Department of Translational Medicine, University of Ferrara, Ferrara, Italy. <sup>4</sup>University Center for Studies on Gender Medicine, University of Ferrara, Ferrara, Italy. <sup>5</sup>Faculty of Nursing, Medicine, and School of Public Health Sciences University of Alberta, Edmonton, AB, Canada. <sup>6</sup>Heart and Stroke Strategic Clinical Networks-Alberta Health Services, Edmonton, AB, Canada. <sup>7</sup>Divisions of Clinical Epidemiology and General Internal Medicine, McGill University Health Centre Research Institute, Montreal, QC, Canada. <sup>8</sup>These authors contributed equally: Zahra Azizi, Pouria Alipour. <sup>™</sup>email: louise.pilote@mcgill.ca

Received: 7 July 2022 Revised: 18 November 2022 Accepted: 30 November 2022

Published online: 12 December 2022

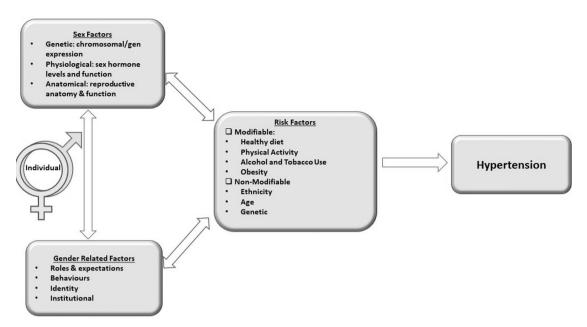


Fig. 1 Role of sex and gender in hypertension. The complex interaction of sex along with gendered factors in hypertension. Aside from traditional risk factors, the interplay of biological sex and gendered variables contribute to further risk and overall outcome.

psycho-socio-cultural aspects of one's identity [15–20]. Gender roles, relationships, identity, and institutions are associated with the manifestation and management of HTN, and more importantly, this relationship may vary between males and females, depending on the culture/country where they live [15–20].

Hence, in this narrative review, we sought to examine the role of sociocultural gender in explaining how blood pressure diagnosis, control, and outcome might vary between males and females (Fig. 1), while exploring whether the intersectionality between sex, gender, and other factors on HTN diagnosis and treatment have previously been explored. We, therefore, summarized the available evidence on the effect of gender on blood pressure, and its response to treatment in four main domains that embrace the multidimensionality that gender encompasses: gender identity, roles, relations, and institutionalized gender. The terms male and females are often confused with men and women, but it is important to note that while the former refer to one's biological sex and attributes, the latter refers to their gender and its social construct.

#### **SEX DIFFERENCES IN HTN**

The prevalence, etiology, and outcome of HTN differs amongst the sexes. Based on recent data, the overall prevalence of HTN is higher in males compared to females, though blood pressure control is poorer in females [21–23]. It is also important to note that while overall prevalence of hypertensive disorders is higher in males, females have a higher lifetime HTN development gradient and lower threshold for cardiovascular disease development [24]. More importantly, the majority of national and international guidelines on the treatment and prevention of HTN focus mostly on males, given that most of the participants in the studies utilized to form such recommendations are indeed males [25]. However, recently, in the 2018 guidelines of the European Society of hypertension and the European Society of Cardiology, a section has been dedicated to sex differences in factors affecting women [26].

The consequence of such biases in recommendations are disease undertreatment and a more resulting complications in females [25]. For instance, in the NHANES (1999–2004) study, of males and females diagnosed with hypertension, 49.2% and 44.1%

had controlled blood pressure, respectively [22]. This difference is minimized and reversed as individuals age beyond 65 years [27–29].

#### The effect of sex hormones

Though the exact etiology of the difference in hypertension prevalence amongst sexes is still unclear, previous studies hypothesized that estrogens play a significant cardioprotective role, and the decrease in endogenous estrogen results in reduced endothelial thickening and elasticity in females as compared to males [30]. Notably, at menopause and the discontinuation of the effect of such hormones, the risk increases significantly, in some cases surpassing males [31]. The role of menopause in increased prevalence of hypertension remains controversial as other cardiovascular comorbidities, increased body weight, and age may contribute to the observed manifestation [30, 32, 33]. In addition, females with history of gestational hypertension, and pre-eclampsia are 3.7 and 2 times more likely to have HTN and coronary heart disease later in life, respectively [34]. Furthermore, chronic use of oral contraceptives has been shown to increase the likelihood of HTN two to three times [33], especially, in females with more advanced age who are living with obesity [35]. In another investigation focusing on the effect of infertility and its treatment on hypertension manifestation, the authors found no significant differences amongst in HTN amongst those who underwent fertility treatment compared to the rest of the Nurse's study cohort [36, 37]. On the other hand, there has been extensive work studying the role of anabolic testosterone in HTN and cardiovascular disease. The result of these analyses suggests that use of testosterone replacement in males increases their likelihood of HTN, cardiac remodeling and sudden cardiac death [38]. Likewise, in the transitioning trans-gender men, gender affirming hormonal therapy was correlated with increased likelihood of hypertension, whereas opposite effect was observed in transgender women, whereby hormonal therapy yielded lower likelihood of hypertension in this population [39].

There are clear sex differences in various other cardiovascular diseases which are further exacerbated by HTN including valvular heart disease [40]. Females are at an increased risk of aortic insufficiency and aortic stenosis which is highly associated with

HTN and can portend worse prognosis for patients [40]. In addition to valvular heart diseases, prolonged, untreated HTN can result in hypertrophic cardiomyopathy, and eventual systolic heart failure. In a review by Khan et al, the prevalence and risk factors of heart failure in each of the sexes, along with its correlation with blood pressure was examined. The authors found that females with hypertension are at higher risk of heart failure compared to males. Such observations are multifactorial involving sex and gendered differences including reproductive periods, and variation in hormonal, epigenetics, cardiovascular physiology in addition to health behaviors and targeted treatment adequacies [41].

There are clear differences in risk factors associated with manifestation of HTN amongst the sexes. While increased waist circumference, diabetes mellitus, and insulin resistance were more significant risk factors for developing HTN among males, in females, obesity, physical inactivity, and history of pre-eclampsia were more important in predicting future diagnosis of HTN [42, 43]. There remains a number of other factors including age, physical inactivity, increased sodium, and alcohol intake in addition to unhealthy diet, which play a major role in hypertension manifestation for males and females [42]. It is important to note, however, that there exists difference in association of blood pressure values amongst males and females as it pertains to sodium and potassium intake [44]. This means that female sex increases blood pressure sensitivity to dietary intake, hence leading to more adverse outcomes. Long-standing untreated HTN can result in several other complications including damage to end organs with more vulnerable, and sensitive microvasculature, including cardiovascular hypertrophy and remodeling, the renal tubules, and retinal arteries. Such clinical implications and its consequences have been discussed in detailed in previous studies, and hence will need to be taken into consideration when discussing complications and segualae of hypertensive disorder [24].

#### Medication adherence

Response to treatment and disease outcome also differs between males and females. While major randomized trials have demonstrated comparable benefits of hypertensive medication, additional analyses have shown sex differences in both treatment benefits and adverse outcomes. For instance, the VALUE trial revealed that females assigned to Valsartan treatment had increased relative risk for the primary outcome of mortality compared with those who received amlodipine [45]. On the other hand the LIFE trial demonstrated a significant reduction in primary and some of the secondary end points for women who were treated with losartan compared to atenolol [46]. Nonpharmacological treatments including weight loss, increased physical activity, consumption of more fruits and vegetables were found to be beneficial for males and females, though the magnitude of effect was slightly higher for females [35, 47]. However, very few studies have provided sex-disaggregated data to ascertain sex specific response to treatment.

## **GENDER AND HTN**

There are various aspects of gender that can affect blood pressure level, and response to treatment. Gender is subdivided into four domains [15–20]; gender identity, roles, relations, and institutionalized gender [15–20]. Hence in this review, we aim to explore the effect of such factors on HTN.

#### **GENDER IDENTITY AND HTN**

Gender identity is the personal sense of one's own gender and may correlate or differ with the sex assigned at birth. Such identity describes how an individual sees oneself, as woman, man or as a

"third gender" or "two-spirited" (masculinity, femininity, or gender nonconformity), and influences feelings and behaviors (i.e., depression, anxiety, and stress) [15-20]. Recently the American Heart Association (AHA) called for actions to understand the impact of gender identity specifically transgender and gender diverse (TGD) individuals on cardiovascular health [48] hypothesizing that gender related psychosocial stressors across the lifespan in individuals identifying as TGD may drive the increased CVD morbidity and mortality in this population. Indeed, there exists biological differences in manifestation of depression and anxiety. For instance, Current evidence on the impact of gender identity on the prevalence and clinical manifestations of HTN are limited to the reported association between gender identity in TGD individuals, and the mediating effects of psychosocial sequelae such as depression, anxiety, and level of stress. The limited data available to date come from studies which have been conducted to elucidate the effect of hormonal and conversion therapy on blood pressure control and symptoms. Yet there is no definitive evidence as to, whether the risk of HTN development and complications in transgender men, or women is based on their sex assigned at birth or whether the risk of HTN is related to their gender identity. The latest statement published by the AHA concludes that multiple systematic reviews, and studies conducted were unable to answer this question, though smaller cohort and retrospective studies examining data obtained from electronic medical records found that transgender men, are less likely to have HTN and experience complications related to HTN compared to cisgender men [48]. Hence, such aspect of gender identity requires further investigation and study.

As mentioned earlier there exists clear sex differences in risk of HTN development as it pertains to lifestyle choices and its respective modifications. There are gender differences that may explain such findings. Men typically have higher risk-taking characteristics which increases their likelihood to engage in more health adverse activities including smoking, increased alcohol and in some cases reduced adherence with medical therapy [49]. Overall, adherence to medical therapy differs amongst the sexes. Study performed by Holt et. Al demonstrated that depression and poorer communication with healthcare provider results in lower adherence in antihypertensives in women, whereas sexual dysfunction and obesity were important with non compliance in males [50]. On the other hand, women are more likely to lead a sedentary lifestyle, and consume poorer diet compared to men [51]. This can be explained by the roles defined for men and women in society. Women tend to take on more responsibility at home which results in less time dedicated to exercise or healthy diet intake. As such, it is imperative to appreciate gendered related factors in manifestation of such sex differences in HTN.

#### **PSYCHOSOCIAL VARIABLES AND HTN**

Beyond the self-perception of identity, psycho-social traits may partially capture the domain of gender identity. In this context, one of the factors reported to contribute to the manifestations and persistence of HTN is depression [52-54]. Various studies have demonstrated the correlation between those diagnosed with depression and the incidence of HTN [54]. Observed differences is most likely multifactorial as beyond gender differences there are clear biological component which contributes to female's higher likelihood of anxiety and depression. Some of such differences are abnormalities noted in the regulation of the hypothalamic-pituitary adrenal axis and the sympathoadrenomedullary system in females which is more sensitive to external stressors [55]. A systematic review by Scalo et al. revealed the increased prevalence of depression with HTN and the association between depressive symptomology and increased blood pressure [56]. Furthermore, while meta-regression analyses were not performed to assess whether sex differences exist in such finding,

the author found that the association between blood pressure, depressive symptoms, and stroke were higher in women compared to men. There are many possible physiological mechanisms, which may explain this finding. There is developing evidence demonstrating the over-activation of the sympathetic nervous system in individuals diagnosed with depression with increased blood pressure and HTN [57–59], suggesting that the exacerbation of depression and blood pressure share common pathways, and that the manifestation of one may increase the risk of the other [60].

Similar trends have been observed concerning the relationships between HTN and anxiety and/or stress levels. Individuals diagnosed with generalized anxiety disorder and/or increased life stress have been reported to be at a higher risk of developing HTN. A study by Mushtaq et al. demonstrated that there is a significant positive correlation between HTN, and anxiety, stress, and depression [61]. Furthermore, other forms of life stressors including occupational stress, post-traumatic stress, have been reported to have a significant impact on the risk of HTN and consequent cardiovascular disease [62]. There is a dearth of evidence addressing the sex-specific association of depression/ anxiety/and stress and HTN. One study by Jackson et al. found that in a cohort of 9182 middle-aged women, anxiety (24% increase) and depression (30% increase) were positively, and significantly associated with increased odds of HTN, however, these relationships were no longer significant when included in fully adjusted models. The observed association can potentially be explained by the mediation effect of anxiety and depression (and vice versa) on diagnosis of HTN [63].

Previous studies have demonstrated higher incidence of depression, anxiety, and stress amongst women. In a study investigating the role of anxiety and depression on hypertension, Jackson et al. concluded that depression and anxiety were associated with a 30% and 12% increased odds of HTN respectively [63]. Considering the effect that such gendered factors have on the risk of HTN, the hypothesis that these factors may affect women more significantly than men is reasonable. However, no study was found that compared the role of such factors in HTN by sex. Hence, further investigations are needed to better understand the magnitude of effect of depression, anxiety, and stress on HTN in men and women separately.

# **GENDER ROLE**

Gender roles refer to social roles that result in a range of behaviors/attitudes ascribed to persons based on their sex. Gender roles influence our behaviors including the choices made regarding profession/employment, personal relationships and even the clothes one wears and affect everyday experiences and expectations [15-20]. There are a number of gender roles that have been reported to impact the manifestation and management of HTN. Recognized gender role factors include employment status, paid/unpaid working hours, the number of children, and whether an individual is the household primary earner. There have been several studies that have investigated the role of working hours on blood pressure in pregnant women, however, the results are contradictory. While one study of over 24,000 pregnant working women in China, concluded that shift work and extended work hours did not influence the overall risk of HTN and preeclampsia [64], a study by Lands Bergis et al. [65] reported that work related stressors including longer shifts may explain pregnancy-induced HTN [65].

Being the primary earner of a household brings with it financial, and psychological stressors that may result in poor blood pressure control. The Atherosclerosis Risk in Communities (ARIC) study conducted a sub-analysis to determine whether employment status was associated with the diagnosis of HTN amongst women. This study found that women who reported being employed at

baseline were less likely to be hypertensive compared to women not employed outside the home including "homemakers" and "stay-at-home" women. Hence, they concluded that there is an inverse relationship between employment status and HTN amongst middle-aged African American women participants [66]. Another study conducted across 13 European countries reported a similar association. The authors sought to determine whether gaps in employment were associated with an increased risk of high blood pressure. The findings of the study reported that no clear association was found between not working (unemployment) and HTN [67]. These contradictory results suggest that the relationship between HTN and employment is more complex. It does not discriminate between the type of employment, and more importantly the willingness/unwillingness to be employed and/or the role of work based on the level of employment (e.g., the service industry, professional), childcare responsibilities and other gender-role responsibilities.

There is little to no literature that investigates the role of employment, working hours, housework, number of children, as well as other gender roles in association with HTN development. However, the few studies available suggest that women are significantly more impacted by gender-role factors compared to their men counterparts. For instance, Clougherty et al. reported on 14,618 blue- and white-collar manufacturing employees to determine gender and sex differences in job status and HTN. The study found that after adjustment for sociodemographic factors, the effect of hourly (blue collar) status, and being a part time employee on HTN, was significant only amongst women. The authors concluded that the significant risk of HTN associated with hourly status for women may have been exacerbated by gender relations (women in the study were more likely to be single parents) and lower formal education levels [68]. This suggests that over and above biological sex, gender role may influence the development of HTN and should be included in the assessment of risk.

#### **GENDER RELATIONS**

Another important domain in the construct of gender is the effects of social relations with other individuals. Gender relations refers to the social relationships and power distributions between men and women both in private and public including interpersonal interactions, and dynamics [15–20] that influence health behaviors and outcomes. Concept such as marital status, caregiver responsibilities, and having adequate social support are gender relation factors that have been found to contribute the development of cardiovascular diseases including HTN. A study investigating the role of family support in association to HTN by Bahari et al. [69] reported that a lack of self-efficacy along with inadequate family and social support were factors that were significantly associated with HTN [69].

Marital status has also been shown to play an important role in blood pressure control. However, the relationship between HTN and marital status is reported to vary by sex. Men who reported never being married were nearly 50% more likely to have HTN compared to men who were married. There was however no significant difference for men who reported being divorced or widowed. On the other hand, in women, being widowed increased the risk of HTN by 92% while not ever being married and being single had a slightly protective effect [70]. To better understand the implications of marital status on health outcomes including blood pressure, it is imperative to appreciate the intersectionality between sex, gender, and cultures/traditions. For instance, a larger study performed in Ghana investigated the impact of marital status on HTN amongst men and women. In this study, the authors explored the role of family dynamics including marriage on the health of the population. The authors performed an overall sample analysis but included a sex-disaggregated

analysis to determine the impact by sex. After controlling for lifestyle and sociodemographic covariates, the authors found that being married (OR = 2.14, 95% CI = 1.30–3.53), cohabiting (OR = 1.94, 95% CI = 1.16–3.23) and previously married (OR = 2.23, 95% CI = 1.29–3.84) were independent predictors for HTN only in the women cohort [71]. Similar trends were noted within same-sex partnerships. Studies have found that being married is also a risk factors for HTN in same sex couples [72, 73]. These studies also found that being in same-sex relationship was correlated with higher likelihood of CVD when compared to opposite sex relationships (HR1.61, 95% CI: 1.27-2.04) [73].

While the definition of "family" has changed over the years, the social definition of family as a group of two or more who live together, form an emotional connection, and function as an economic unit, falls into the realm of gender relations which have been reported to impact health and disease outcomes. Factors including caregiving responsibilities or having familial social support have been demonstrated to influence the trajectory of diseases including HTN. Using a cross-sectional cohort of white collar working women in Quebec, Canada, Brisson et al. investigated the impact of caregiving responsibilities on mean systolic and diastolic blood pressure, as measured by the number of children, family support at home, and work stress, assessed using the Job Content Questionnaire. The study concluded that for women with university degrees who were employed in a whitecollar occupation, that family responsibilities were correlated with significantly higher systolic and diastolic blood pressure [74]. Furthermore, the impact was potentiated in situations where job strain and stress were also increased. This was also shown by a study by Brown et al. who reported that job strain and physiological stress were predictors of daily blood pressure variability [75]. The effect of psychological stress on blood pressure and its effective control has been investigated thoroughly, identifying that caretaking responsibilities, are recognized stressors, that can result in poorer HTN related outcomes [76]. Of note, such stressors, including caretaking responsibility, can be effectively addressed through strategies that favor social support.

#### **INSTITUTIONALIZED GENDER**

Institutionalized gender reflects the distribution of power between individuals in political, educational, and social institutions [15–20]. This domain is recognizing the impact of socioeconomic status (SES) and societal gender inequality on the manifestation and progression of diseases including HTN. It is important to note that, education, income, and gender inequality can influence life decisions and resource allocation for those of lower SES. For instance, individuals with more limited resources may not be able to afford healthcare provider visits, have funds for medical therapy, or time dedicated to self-care regimens including exercise, and other wellness initiatives. Hence, the importance of SES and institutionalized gender in blood pressure control cannot be overstated [14].

Several studies worldwide have reported on the impact of institutionalize gender on blood pressure control. Retrospective data obtained from the World Health Organization's STEPwise approach to surveillance of chronic disease risk factors, demonstrated that risk of HTN in men and women differ significantly based on factors related to institutionalized gender. The authors found that in a cohort in rural Vietnam, SES (including lower income, and less formal education) was associated with a lower likelihood of HTN in men, however, this relationship was completely reversed in women [77]. Another Canadian study by Kaplan et al. investigated the relationship between household income and self-reported HTN prevalence among persons aged 65 and older in the United States (U.S.) and Canada. The authors found that there was a linear but inverse relationship between blood pressure control and income. It is interesting to note that

this relationship was only observed in the U.S, but not Canada. The authors attributed the findings to the lower financial burden of healthcare and medical therapy in Canada (publicly funded health care) compared to the U.S (privately funded), demonstrating the importance of income, and equal access to health care on health outcomes [78]. Institutional-level educational policies that reflect gender biases may also impede health outcomes. Pandit et al. conducted interviews and literacy assessments of numerous patients with HTN. They found that those who had higher formal education and literacy levels were more aware of their overall health, more compliant with medical therapy, which ultimately resulted in better blood pressure control [79].

Finally, in 2015 Leng et al. conducted a comprehensive systematic review and meta-analysis reporting on studies investigating the correlations and relationships between income, education, and SES with HTN The authors reported a 19% higher prevalence of HTN amongst those in the lowest income strata (OR 1.19, 95% CI: 0.96-1.48). Those with the lowest SES were two times more likely to have high blood pressure (OR 2.02, 95% CI: 1.55-2.63). Of note, this relationship between SES and HTN was especially noteworthy in higher income and developed (HIC) countries including Canada, U.S., and some European countries. In contrast, the relationship was reversed for lower income African countries (LIC) [80]. The exact cause of these relationships is still unclear, but it may be secondary to lifestyle and cultural differences amongst individuals living in different countries. It has been postulated that those who live in LICs may not have enough resources to purchase food, whereas in HICs that have more resource rich areas, calorie heavy foods are typically inexpensive and rapid to prepare and consume. Hence, while those with lower income in a resource rich country tend to eat unhealthier fast food and processed sugars, those who live in more developing countries may not have access to sufficient food, resulting in lower caloric intake and blood pressure. Importantly, the results of this meta-analysis demonstrates the importance of assessing gender factors at both individual and population (country level) in health and disease outcomes analyses.

#### INTERSECTIONALITY BETWEEN SEX, GENDER, AND RACE

While factors discussed above have been shown to contribute considerably to the manifestation, and consequent treatment and outcomes of HTN, it is important to consider the intersectionality that exists between such factors. The inequities in various societies, particularly regarding identified gaps in care and timely access to healthcare results in more adverse outcome and poorer prognosis for those in more socially disadvantaged positions. Richardson et al. used an intersectional framework to investigate health disparities and found that race (ethnicity), gender, and sex had multiplicative impacts on hypertension. This study found that not only non-Caucasians, but women of lower social standing had a disproportionally higher likelihood of hypertensive disorder over their lifetime. Furthermore, these factors demonstrated strong intercorrelations and predicted poorer outcomes [81].

#### CONCLUSION

Psycho-socio-cultural characteristics are gendered and may differ amongst men and women in different environments /living conditions and countries. Overall, we have found that the most important gendered factors in HTN are education and employment. Though both sexes are affected by these elements, their effect on women is more pronounced than in their men counterparts. Results of this comprehensive review have reenforced the importance of understanding the role of sex and gender-related factors in the development and prevalence of HTN. Further studies on the impact of psychosocial gendered factors on

the management and treatment of HTN are warranted to better inform our clinical management of the disease.

#### **Summary**

What is already known about this topic

- Hypertension is a critical modifiable risk factor of cardiovascular diseases for which sex-specific differences exist.
- Sex and gender are different concepts whilst the former refers to one's biological attributes, the latter encompasses the individual's psycho-socio-cultural characteristics.
- Gendered factors may have a different magnitude of effects in females compared to males with regards to hypertension, and hence the exact nature of such factors is poorly understood.

#### What this study adds

- Life stressors, anxiety, and depression can have a more severe effect on women with hypertension compared to men.
- While married men are less likely to have higher blood pressure, single women and those who never married are less likely to have HTN.
- Social support plays an important role in blood pressure, control particularly in women.
- Socioeconomic status, including education level and income have a linear and inverse relationship in blood pressure control in more resource-rich countries.

#### **REFERENCES**

- WHO. Hypertension. Fact Sheets. WHO; 2021 2021 [updated 25/08/2021. Available from: https://www.who.int/news-room/fact-sheets/detail/hypertension.
- Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.
- Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. Jama. 2017:317:165–82.
- Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med. 2009;6:e1000058.
- Peters SAE, Muntner P, Woodward M. Sex differences in the prevalence of, and trends in, cardiovascular risk factors, treatment, and control in the United States, 2001 to 2016. Circulation. 2019;139:1025–35.
- Whelton PK. The elusiveness of population-wide high blood pressure control. Annu Rev Public Health. 2015;36:109–30.
- Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, et al. Prevalence of hypertension in the US adult population: results from the Third National Health and Nutrition Examination Survey, 1988-1991. Hypertension. 1995;25:305–13.
- Statistics NCfH. Health, United States, 2013: With special feature on prescription drugs. 2014.
- Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127–e248.
- Savica V, Bellinghieri G, Kopple JD. The effect of nutrition on blood pressure. Annu Rev Nutr. 2010;30:365–401.
- Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. Circulation Res. 2015;116:937–59.
- Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165:1410–9.
- Ibrahim MM, Damasceno A. Hypertension in developing countries. Lancet (Lond, Engl). 2012;380:611–9.

- Grotto I, Huerta M, Sharabi Y. Hypertension and socioeconomic status. Curr Opin Cardiol. 2008:23:335–9.
- CIHR. Online Training Modules: Integrating Sex & Gender in Health Research 2022 [Available from: https://cihr-irsc.gc.ca/e/49347.html.
- Connelly PJ, Azizi Z, Alipour P, Delles C, Pilote L, Raparelli V. The importance of gender to understand sex differences in cardiovascular disease. Can J Cardiol. 2021;37:699–710.
- Raparelli V, Norris CM, Bender U, Herrero MT, Kautzky-Willer A, Kublickiene K, et al. Identification and inclusion of gender factors in retrospective cohort studies: the GOING-FWD framework. BMJ Glob Health. 2021;6:e005413.
- Tadiri CP, Raparelli V, Abrahamowicz M, Kautzy-Willer A, Kublickiene K, Herrero M-T, et al. Methods for prospectively incorporating gender into health sciences research. J Clin Epidemiol. 2021;129:191–7.
- Johnson JL, Greaves L, Repta R. Better science with sex and gender: A primer for health research: Women's Health Research Network Vancouver; 2007.
- Johnson JL, Greaves L, Repta R. Better science with sex and gender: Facilitating the use of a sex and gender-based analysis in health research. Int J Equity Health. 2009;8:14.
- 21. Wassertheil-Smoller S, Anderson G, Psaty BM, Black HR, Manson J, Wong N, et al. Hypertension and its treatment in postmenopausal women: baseline data from the Women's Health Initiative. Hypertension. 2000;36:780–9.
- Ong KL, Tso AW, Lam KS, Cheung BM. Gender difference in blood pressure control and cardiovascular risk factors in Americans with diagnosed hypertension. Hypertension. 2008;51:1142–8.
- 23. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Merz CNB, et al. Sex differences in blood pressure trajectories over the life course. JAMA Cardiol. 2020;5:255–62.
- Connelly PJ, Currie G, Delles C. Sex differences in the prevalence, outcomes and management of hypertension. Curr Hypertens Rep. 2022;24:185–92.
- Regensteiner JG, Reusch JEB. Sex differences in cardiovascular consequences of hypertension, obesity, and diabetes: JACC focus seminar 4/7. J Am Coll Cardiol. 2022;79:1492–505.
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018;39:3021–104.
- 27. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM. et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011;123:e18–e209.
- Wassertheil-Smoller S, Hendrix SL, Limacher M, Heiss G, Kooperberg C, Baird A, et al. Effect of estrogen plus progestin on stroke in postmenopausal women: the Women's Health Initiative: a randomized trial. Jama. 2003;289:2673–84.
- Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrumcurrent outcomes and control in the community. JAMA. 2005;294:466–72.
- Dubey RK, Oparil S, Imthurn B, Jackson EK. Sex hormones and hypertension. Cardiovascular Res. 2002;53:688–708.
- 31. Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. J Hum Hypertens. 1989;3:427–33.
- Staessen JA, Ginocchio G, Thijs L, Fagard R. Conventional and ambulatory blood pressure and menopause in a prospective population study. J Hum Hypertens. 1997;11:507–14
- Curtis KM, Mohllajee AP, Martins SL, Peterson HB. Combined oral contraceptive use among women with hypertension: a systematic review. Contraception. 2006;73:179–88.
- Pimenta E. Hypertension in women. Hypertension research: official journal of the Japanese Society of Hypertension. 2012;35:148-52.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–52.
- Barekat M, Ahmadi S. Hypertensive disorders in pregnant women receiving fertility treatments. Int J Fertil Steril. 2018;12:92–8.
- Farland LV, Grodstein F, Srouji SS, Forman JP, Rich-Edwards J, Chavarro JE, et al. Infertility, fertility treatment, and risk of hypertension. Fertil Steril. 2015;104:391–7.
- Dalmasso C, Patil CN, Cardozo LLY, Romero DG, Maranon RO. Cardiovascular and Metabolic Consequences of Testosterone Supplements in Young and Old Male Spontaneously Hypertensive Rats: Implications for Testosterone Supplements in Men. J Am Heart Assoc. 2017;6:e007074.
- Banks K, Kyinn M, Leemaqz SY, Sarkodie E, Goldstein D, Irwig MS. Blood pressure effects of gender-affirming hormone therapy in transgender and gender-diverse adults. Hypertension. 2021;77:2066–74.
- Hahn RT, Clavel M-A, Mascherbauer J, Mick SL, Asgar AW, Douglas PS. Sex-related factors in valvular heart disease: JACC focus seminar 5/7. J Am Coll Cardiol. 2022;79:1506–18.

- Khan SS, Beach LB, Yancy CW. Sex-based differences in heart failure: JACC focus seminar 7/7. J Am Coll Cardiol. 2022;79:1530–41.
- 42. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020;16:223–37.
- Carlsson AC, Wändell PE, De Faire U, Hellénius M-L. Risk factors associated with newly diagnosed high blood pressure in men and women. Am J Hypertens. 2008;21:771–7.
- He J, Gu D, Chen J, Jaquish CE, Rao DC, Hixson JE, et al. Gender difference in blood pressure responses to dietary sodium intervention in the GenSalt study. J Hypertens. 2009;27:48–54.
- 45. Zanchetti A, Julius S, Kjeldsen S, McInnes GT, Hua T, Weber M, et al. Outcomes in subgroups of hypertensive patients treated with regimens based on valsartan and amlodipine: an analysis of findings from the VALUE trial. J Hypertens. 2006;24:2163–8.
- Os I, Franco V, Kjeldsen SE, Manhem K, Devereux RB, Gerdts E, et al. Effects of losartan in women with hypertension and left ventricular hypertrophy: results from the Losartan Intervention for Endpoint Reduction in Hypertension Study. Hypertension 2008;51:1103–8.
- Mosca L, Banka CL, Benjamin EJ, Berra K, Bushnell C, Dolor RJ, et al. Evidencebased guidelines for cardiovascular disease prevention in women: 2007 update. Circulation. 2007;115:1481–501.
- 48. Streed CG, Beach LB, Caceres BA, Dowshen NL, Moreau KL, Mukherjee M, et al. Assessing and addressing cardiovascular health in people who are transgender and gender diverse: a scientific statement from the american heart association. Circulation. 2021;144:e136–e48.
- Humphries KH, Izadnegahdar M, Sedlak T, Saw J, Johnston N, Schenck-Gustafsson K, et al. Sex differences in cardiovascular disease—Impact on care and outcomes. Front Neuroendocrinol. 2017:46:46–70.
- Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatrics Soc. 2013;61:558–64.
- 51. Barnes AS. Obesity and sedentary lifestyles: risk for cardiovascular disease in women. Tex Heart Inst J. 2012;39:224–7.
- Carroll D, Phillips AC, Gale CR, Batty GD. Generalized anxiety and major depressive disorders, their comorbidity and hypertension in middle-aged men. Psychosom Med. 2010;72:16–9.
- Patten SB, Beck CA, Kassam A, Williams JV, Barbui C, Metz LM. Long-term medical conditions and major depression: strength of association for specific conditions in the general population. Can J Psychiatry. 2005;50:195–202.
- Patten SB, Williams JV, Lavorato DH, Campbell NR, Eliasziw M, Campbell TS. Major depression as a risk factor for high blood pressure: epidemiologic evidence from a national longitudinal study. Psychosom Med. 2009;71:273–9.
- Altemus M. Sex differences in depression and anxiety disorders: Potential biological determinants. Hormones Behav. 2006;50:534–8.
- 56. Scalco AZ, Scalco MZ, Azul JB, Lotufo Neto F. Hypertension and depression. Clin (Sao Paulo, Braz). 2005;60:241–50.
- Jones-Webb R, Jacobs DR Jr, Flack JM, Liu K. Relationships between depressive symptoms, anxiety, alcohol consumption, and blood pressure: results from the CARDIA Study. Coronary Artery Risk Development in Young Adults Study. Alcohol, Clin Exp Res. 1996;20:420–7.
- Townsend MH, Bologna NB, Barbee JG. Heart rate and blood pressure in panic disorder, major depression, and comorbid panic disorder with major depression. Psychiatry Res. 1998:79:187–90.
- Rahn KH, Barenbrock M, Hausberg M. The sympathetic nervous system in the pathogenesis of hypertension. J Hypertension Suppl: Off J Int Soc Hypertension. 1999:17:S11–4.
- Rubio-Guerra AF, Rodriguez-Lopez L, Vargas-Ayala G, Huerta-Ramirez S, Serna DC, Lozano-Nuevo JJ. Depression increases the risk for uncontrolled hypertension. Exp Clin Cardiol. 2013;18:10–2.
- 61. Mushtaq M, Najam N. Depression, anxiety, stress and demographic determinants of hypertension disease. Pak J Med Sci. 2014;30:1293–8.
- Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. Int J Psychiatry Med. 2011;41:365–77.
- Jackson CA, Pathirana T, Gardiner PA. Depression, anxiety and risk of hypertension in mid-aged women: a prospective longitudinal study. J Hypertension. 2016;34:1959–66.
- 64. Chang P-J, Chu L-C, Hsieh W-S, Chuang Y-L, Lin S-J, Chen P-C. Working hours and risk of gestational hypertension and pre-eclampsia. Occup Med. 2009;60:66–71.
- Landsbergis PA, Hatch MC. Psychosocial work stress and pregnancy-induced hypertension. Epidemiol (Camb, Mass). 1996;7:346–51.
- Rose KM, Newman B, Tyroler HA, Szklo M, Arnett D, Srivastava N. Women, employment status, and hypertension: cross-sectional and prospective findings from the Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol. 1999;9:374–82.

- Rumball-Smith J, Nandi A, Kaufman JS. Working and hypertension: gaps in employment not associated with increased risk in 13 European countries, a retrospective cohort study. BMC Public Health. 2014;14:1–6.
- Clougherty JE, Eisen EA, Slade MD, Kawachi I, Cullen MR. Gender and sex differences in job status and hypertension. Occup Environ Med. 2011;68:16–23.
- Bahari G, Scafide K, Krall J, Mallinson RK, Weinstein AA. Mediating role of selfefficacy in the relationship between family social support and hypertension selfcare behaviours: A cross-sectional study of Saudi men with hypertension. Int J Nurs Pract. 2019;25:e12785.
- Ramezankhani A, Azizi F, Hadaegh F. Associations of marital status with diabetes, hypertension, cardiovascular disease and all-cause mortality: A long term followup study. PloS One. 2019;14:e0215593.
- 71. Tuoyire DA, Ayetey H. Gender differences in the association between marital status and hypertension in Ghana. J Biosoc Sci. 2019;51:313–34.
- Sharma Y, Taylor JY, Hughes T, Caceres B. Abstract 9744: cardiovascular stroke nursing best abstract award: investigating sexual identity disparities in hypertension and hypertension treatment among adults. Circulation. 2021;144:A9744–A.
- 73. Xu Y, Rahman Q, Montgomery S. Same-sex partnership and cardiovascular disease in men: the role of risk factors in adolescence. LGBT Health. 2021;9:18–26.
- Brisson C, Laflamme N, Moisan J, Milot A, Mâsse B, Vézina M. Effect of family responsibilities and job strain on ambulatory blood pressure among white-collar women. Psychosom Med. 1999;61:205–13.
- Brown DE, James GD, Nordloh L, Jones AA. Job strain and physiological stress responses in nurses and nurse's aides: predictors of daily blood pressure variability. Blood Press Monit. 2003;8:237–42.
- Gasperin D, Netuveli G, Dias-da-Costa JS, Pattussi MP. Effect of psychological stress on blood pressure increase: a meta-analysis of cohort studies. Cad de Saude Publica. 2009;25:715–26.
- 77. Hoang Van Minh M, Byass P, Huong DL, Chuc NTK, Wall S. Risk factors for chronic disease among rural vietnamese adults and the association of these factors with sociodemographic variables: findings from the WHO STEPS survey in rural vietnam. Prev Chronic Dis. 2005;4:A22.
- Kaplan MS, Huguet N, Feeny DH, McFarland BH. Self-reported hypertension prevalence and income among older adults in Canada and the United States. Soc Sci Med (1982). 2010;70:844–9.
- Pandit AU, Tang JW, Bailey SC, Davis TC, Bocchini MV, Persell SD, et al. Education, literacy, and health: Mediating effects on hypertension knowledge and control. Patient Educ Counseling. 2009;75:381–5.
- 80. Leng B, Jin Y, Li G, Chen L, Jin N. Socioeconomic status and hypertension: a metaanalysis. J Hypertens. 2015;33:221–9.
- 81. Richardson LJ, Brown TH. (En)gendering racial disparities in health trajectories: a life course and intersectional analysis. SSM Popul Health. 2016;2:425–35.

# **AUTHOR CONTRIBUTIONS**

ZA, PA, VR, CN, LP: Have made a substantial contribution to the concept or design of the article; or the acquisition, analysis, or interpretation of data for the article, drafted the article or revised it critically for important intellectual content, approved the version to be published, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are questions related to the accuracy or integrity of any part of the work.

#### **COMPETING INTERESTS**

The authors declare no competing interests.

# ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Louise Pilote.

Reprints and permission information is available at http://www.nature.com/reprints

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.