EDITORIAL

Journal of Human Hypertension special issue on sex and gender differences in hypertension

Journal of Human Hypertension (2023) 37:587–588; https://doi.org/10.1038/s41371-023-00847-5

Hypertension remains one of the most important modifiable risk factors for cardiovascular disease and mortality worldwide [1]. Considerable differences exist between men and women relating to the pathophysiology, epidemiology and outcomes relating to this condition [2]. Understanding the means by which sex related biology and gender mediated psycho-socio-cultural characteristics influence blood pressure regulation and the development of hypertension is imperative to ensuring equitable evidence based management of this condition, and broadening our understanding of the mechanisms responsible [3].

In this special issue we provide a diverse collection of reviews and original articles aiming to enhance our knowledge of the role of sex and gender in hypertension. This aimed to capture the latest research relating to the mechanisms by which sex (i.e. sex hormones, chromosomal complement and sex-specific factors) and gender (sociocultural factors) interact to modulate the development of this condition, and the impact this has upon those with hypertension [3–5]. We are therefore pleased to incorporate a variety of topics into this special issue pertinent to hypertension pathophysiology such as sex-hormone mediated mechanisms [6], the impact of psychosocial gender [3], the effect of menopause [7], preclinical models [8] and hypertensive multi-organ damage [9–12]. Importantly, this special issue provides the scope to discuss underrepresented and underserved populations who may experience hypertension, including women [13, 14], gender-diverse individuals [15], those with chromosomal aneuploidies [16], the young [17], and those living in low and middle income countries [18]. To translate findings into clinical practice we look at hypertension guidelines [13] and data from primary care [19].

A major strength of this special issue is that the articles included provide valuable insight into sex-dependent mechanisms evident in the development of hypertension. Kringeland et al. demonstrate in a cohort of 48 year old individuals from the Hordaland Health study that elevated inflammatory biomarkers, high-sensitive C-reactive protein and a measure of T cell activation, neopterin, were associated with elevated blood pressure and incident hypertension in women. These findings suggest sex-specific influences differentially regulate the innate and adaptive immune responses, resulting in sex-dependent vascular inflammation and the development of hypertension [20].

The influences of dietary salt intake upon sex-dependent renal mechanisms is also explored. Ferreri et al. show that the cytokine tumour necrosis factor-α (TNF-α), a product of thick ascending limb of Henle's loop (TAL) and regulator of the NaK2Cl-cotransporter type 2 (NKCC2), to be secreted in a sex-specific fashion in response to a dietary salt intervention [21]. NKCC2 mediates TAL salt handling, and dysregulation has been shown to elevate blood pressure in human and animal models [22]. Within this analysis, elevated levels of TNF-α were demonstrated in females in response to salt intake, potentially limiting NKCC2 activity and mitigating salt-dependent increases in blood pressure. Such mechanisms may represent an interplay between inherited sex-specific immune responses, and psychosocial dietary behaviours relevant to gender. Another protein that interacts with salt handling in the TAL is uromodulin [23]. Algharably et al. provide data on genetic variants of uromodulin and a range of physiological parameters in older women and men [24].

Moreover, sex-specific factors such as pregnancy undoubtedly influence cardiovascular risk in the female populations. Brown et al. show that women a history of pre-eclampsia have higher risk of cardiovascular events later in life in the Scottish Family Health Study [25]. This legacy effect of pre-eclampsia has significant implications with respect to the future cardiovascular risk in women, but also raises many questions regarding the underlying physiology responsible for such a pervasive influence upon cardiovascular disease development in later life [26].

Our special issue focusses on systemic hypertension but we couldn't resist and included a paper on pulmonary arterial hypertension [27]. This condition is not normally in the focus of "hypertensiologists" but being so much more prevalent in women than in men it not only fits nicely into this special issue but may also give us food for thought to better understand sex and gender differences in systemic hypertension. Indeed, in their paper Sless et al. provide insight into systemic vascular function in those with pulmonary arterial hypertension [27].

Taken together, the studies highlight the potential mechanisms by which sex-specific mediators may act across a variety of systems to regulate blood pressure and the development of hypertension. The editorial team and authors that contributed to this special issue urge those engaging in hypertension research to consider the influences of the sex and gender continuum in their work to ensure that it is not limited by traditional conformities.

Paul J. Connelly[1] ✉ and Christian Delles[1] ✉
[1]*School of Cardiovascular and Metabolic Health, University of Glasgow, BHF Glasgow Cardiovascular Research Centre, 126 University Place, Glasgow G12 8TA, UK.*
✉*email: Paul.Connelly@glasgow.ac.uk; Christian.Delles@glasgow.ac.uk*

REFERENCES

1. Yusuf S, Joseph P, Rangarajan S, Islam S, Mente A, Hystad P, et al. Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. Lancet. 2020;395:795–808.
2. Connelly PJ, Currie G, Delles C. Sex differences in the prevalence, outcomes and management of hypertension. Curr Hypertens Rep. 2022;24:185–92.

Published online: 20 July 2023

3. Azizi Z, Alipour P, Raparelli V, Norris CM, Pilote L. The role of sex and gender in hypertension. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00789-4.
4. Reckelhoff JF. Mechanisms of sex and gender differences in hypertension. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00810-4.
5. de Ruiter SC, Schmidt AF, Grobbee DE, den Ruijter HM, Peters SAE. Sex-specific Mendelian randomisation to assess the causality of sex differences in the effects of risk factors and treatment: spotlight on hypertension. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00821-1.
6. Visniauskas B, Kilanowski-Doroh I, Ogola BO, Mcnally AB, Horton AC, Imulinde Sugi A, et al. Estrogen-mediated mechanisms in hypertension and other cardiovascular diseases. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00771-0.
7. Rethy L, Polsinelli VB, Muntner P, Bello NA, Cohen JB. Association of blood pressure variability with Endothelin-1 by menopause status among Black women: findings from the Jackson Heart Study. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00824-y.
8. Olivera S, Graham D. Sex differences in preclinical models of hypertension. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00770-1.
9. Cuspidi C, Gherbesi E, Sala C, Tadic M. Sex, gender, and subclinical hypertensiveorgan damage-heart. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00750-5.
10. Bruno RM, Varbiro S, Pucci G, Nemcsik J, Lønnebakken MT, Kublickiene K, Sex and Gender VascAgeNet Expert Group, et al. Vascular function in hypertension: does gender dimension matter? J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00826-w.
11. Dawson J, MacDonald A. Sex and hypertensive organ damage: stroke. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00830-0.
12. Mayne KJ, Sullivan MK, Lees JS. Sex and gender differences in the management of chronic kidney disease and hypertension. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00843-9.
13. Meinert F, Thomopoulos C, Kreutz R. Sex and gender in hypertension guidelines. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-022-00793-8.
14. Brewster LM, Perrotta ID, van Montfrans GA. Should women have lower thresholds for hypertension diagnosis and treatment? J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00838-6.
15. Irwig MS. Hypertension in transgender individuals. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00721-w.
16. McCarrison S, Carr A, Wong SC, Mason A. The prevalence of hypertension in paediatric Turner syndrome: a systematic review and meta-analysis. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00777-8.
17. Edwards S, Foster M, Ahmed SF, Lucas-Herald AK. Preventative interventions that target cardiovascular dysfunction in children and young people: a systematic review of their effectiveness and an investigation of sexual dimorphism. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00780-z.
18. Ezeala-Adikaibe BA, Mbadiwe CN, Okafor UH, Nwobodo UM, Okwara CC, Okoli CP, et al. Prevalence of hypertension in a rural community in southeastern Nigeria; an opportunity for early intervention. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00833-x.
19. Bager JE, Manhem K, Andersson T, Hjerpe P, Bengtsson-Boström K, Ljungman C, et al. Hypertension: sex-related differences in drug treatment, prevalence and blood pressure control in primary care. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00801-5.
20. Kringeland E, Gerdts E, Ulvik A, Tell GS, Igland J, Haugsgjerd TR, et al. Inflammation, sex, blood pressure changes and hypertension in midlife: the Hordaland Health Study. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00772-z.
21. Drugge ED, Farhan K, Zhao H, Abramov R, Graham LA, Stambler N, et al. Sex and race differences in urinary Tumor Necrosis Factor-α (TNF-α) levels: Secondary analysis of the DASH-sodium trial. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00748-z.
22. Gonzalez-Vicente A, Saez F, Monzon CM, Asirwatham J, Garvin JL. Thick ascending limb sodium transport in the pathogenesis of hypertension. Physiol Rev. 2019;99:235–309.
23. Mary S, Boder P, Padmanabhan S, McBride MW, Graham D, Delles C, et al. Role of uromodulin in salt-sensitive hypertension. Hypertension. 2022;79:2419–29.
24. Algharably EAH, Villagomez Fuentes LE, Toepfer S, Konig M, Regitz-Zagrosek V, Bertram L, et al. Longitudinal effects of a common UMOD variant on kidney function, blood pressure, cognitive and physical function in older women and men. J Hum Hypertens. 2022. https://doi.org/10.1038/s41371-022-00781-y.
25. Brown CE, Casey H, Dominiczak AF, Kerr S, Campbell A, Delles C. Impact of preeclampsia on cardiovascular events: An analysis of the Generation Scotland: Scottish family health study. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00812-2.
26. Fraser A, Catov JM. Placental syndromes and long-term risk of hypertension. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00802-4.
27. Sless RT, Wright SP, Bentley RF, Valle FH, Mak S. Sex differences in pulmonary and systemic vascular function at rest and during exercise in healthy middle-aged adults. J Hum Hypertens. 2023. https://doi.org/10.1038/s41371-023-00822-0.

ACKNOWLEDGEMENTS

We are grateful to the British Heart Foundation (BHF Centre of Research Excellence Award, RE/18/6/34217) and Wellcome (221774/Z/20/Z) for supporting our research.

AUTHOR CONTRIBUTIONS

PC wrote the first draft of the manuscript. CD reviewed and provided critical revision for the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Paul J. Connelly or Christian Delles.