**Sex differences in pressure and flow waveform physiology across the life course**

**Invited Review**

Picone DS1, Kodithuwakku V1, Mayer CC2, Chapman N1, Rehman S1, Climie RE1

1Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

2Medical Signal Analysis, Center for Health & Bioresources, AIT Austrian Institute of Technology, Vienna, Austria

**Corresponding author:**

Dr Rachel E Climie, PhD

Menzies Institute for Medical Research, University of Tasmania,

17 Liverpool St, Hobart, 7001, Australia

Email: Rachel.Climie@utas.edu.au

**Introduction**

Cardiovascular disease (CVD) has long been deemed a disease of old men. However, in 2019 CVD accounted for 35% of all deaths in women and, therefore, remains the leading cause of death in *both* men and women. Globally, age-standardised CVD mortality rates have decreased for several decades, but concerning recent data shows increased mortality rates among women, as well as men in multiple countries [1,2]. There is increasing evidence to show that risk factors, pathophysiology and health outcomes related to CVD differ in women compared with men, yet CVD in women remains understudied, underdiagnosed and undertreated [3].

We have recently described how the underlying pathophysiological differences in CVD in women compared to men represent a series of known unknowns [4]. Differences exist between the sexes in relation to the structure of the heart and vasculature, which translate into differences in blood pressure (BP) and flow waveform physiology. These physiological differences between men and women may represent an important explanatory factor contributing to the sex disparity in CVD presentation and outcomes but remain understudied [3]. As an example, there are major differences in the presenting symptoms and signs of coronary heart disease in women compared with men that are postulated to be due to coronary heart disease being a macrovascular disease in men and microvascular disease in women [5].

The aims of this narrative review were to describe sex differences in arterial pressure and flow waveform physiology and explore how they may contribute to differences in CVD in women compared to men. Given that unfavourable alterations in the cardiovascular structure and function can start in newborns or, even earlier in the presence of adverse conditions in utero, we report sex differences in waveform physiology across the entire life course. For the purpose of this review, the focus is on biological sex defined according to sex chromosomes, gonads, sex hormones, external genitalia, internal reproductive organs presenting phenotypically as male or female. We acknowledge that this definition does not encompass gender and the associated social, environmental, behavioural and cultural aspects that may contribute to differences in health between women and men [6].

**Sex differences in cardiovascular disease incidence and mortality**

Data on incidence and mortality caused by ischemic heart disease, stroke and atrial fibrillation are detailed in Table 1 and were extracted from the Global Burden of Disease study online database [7]. Age-standardised rates per 100,000 people show that the incidence of ischemic heart disease and atrial fibrillation are lower in women compared to men, whereas incidence of stroke is similar between sexes. Age standardised mortality rates for ischemic heart disease and stroke are lower in women, but similar between sexes for atrial fibrillation. Heart failure was not reported specifically in the Global Burden of Disease study. The estimated incidence of heart failure in people aged 55 years or older in the United States was very similar between women and men (505,000 vs. 495,000) [8]. Women are more likely than men to present with heart failure with preserved ejection fraction [9].

**Sex differences in outcomes after a cardiovascular event**

Sex differences in outcomes after a CVD event have been reported widely. A systematic review and meta-analysis of >1 million patients that received percutaneous coronary intervention showed that in-hospital mortality, one year mortality and mortality at least two years of follow-up were higher in women compared with men [10]. Women under 60 years of age with ST-segment elevation myocardial infarction have higher 30-day mortality rates than men, even after adjustment for medication, percutaneous coronary intervention and co-morbidities [11]. Separate work in 10 963 patients (35% women) who underwent percutaneous coronary intervention found that women less than 50 years of age have a greater risk of repeated revascularisation procedures than younger men at five years post intervention [12], but sex differences in outcomes were not observed in people older than 50 years of age. Women have higher case-fatality, worse functional outcomes and poorer quality of life than men after stroke [13,14]. Women with atrial fibrillation are at greater risk of all-cause and cardiovascular mortality, and subsequent CVD events, stroke and heart failure compared to men [15]. Outcomes after a CVD event between women and men that are often reduced after accounting for confounding factors such as age and co-morbidities. In an analysis of United Kingdom primary health care patients over 45 years of age the risk of mortality caused by heart failure was not different between women and men after adjustment for age [16]. Overall, men usually present with typical or common cardiovascular disease symptoms compared to women [17-19]. This may be one of the reasons that they receive better hospital care and management compared to women [3,20-22], which subsequently may explain the differences between women and men in outcomes after CVD.

Sex differences have also been observed in numerous chronic diseases that contribute to pathophysiological arterial adaptions and may contribute to sex differences in CVD incidence, mortality and outcomes after a cardiovascular event. Chronic diseases that have sex differences in relation to prevalence include chronic kidney disease [23], vascular dementia [24], autoimmune disorders and obesity [25-27]. There are also sex differences observed in CVD risk factors including high BP [28]. A life course trajectory analysis from four US cohort studies (combined total of 32 833 participants, 54% women) revealed women have a much steeper systolic BP elevation compared with men from baseline systolic BP levels. Diastolic BP is higher in men throughout life; however, women experience a greater diastolic BP elevation from baseline levels. Of note is that the association between BP levels and incident stroke and myocardial infarction is different in women compared to men, with women at risk at lower levels of BP than men [29].

**Pressure and flow waveform physiology**

The development of the heart, macro- and micro-vasculature are directly linked to arterial pressure and flow waveform physiology. The physiological and pathophysiological remodelling of this system occurs across the life course. Pressure and flow waveforms originate from the heart every time blood the left ventricle expels blood into the circulatory system. Pressure and flow waveforms change across the arterial tree and with age [30]. Pulse wave analysis for the quantification of pressure and flow waveform physiology has a long history but has not yet made it to routine clinical practice [31-33]. There are various approaches that use aortic or upper-limb pressure waveforms alone or in combination with flow waveforms (Figure 1). Well-known approaches for the quantification of pressure and flow waveforms include [31]: (i) wave separation analysis, which separates the pressure curve into its forward and backward components in the frequency domain [34]; (ii) reservoir theory, calculating excess and reservoir pressure mimicking the reservoir behaviour of the arterial system in combination with characteristics of travelling waves (Figure 2); or (iii) wave intensity analysis, a powerful method that identifies forward and backward waves but using the intensity calculated by the product of differences of pressure and flow [35,36]. In recent years, pressure-only approaches for reservoir-excess pressure and wave intensity analysis have been developed [37].

Pressure waveforms can be measured non-invasively from palpable arteries via methods including applanation tonometry, pulse volume plethysmography [38], and invasive catheter. Specialist non-invasive devices can use these techniques to measure pulse wave velocity (pressure wave transit time between two arterial sites) and estimate central (aortic) pressure waveforms based on mathematical relationships between peripheral and central arteries [39]. Non-invasive devices are also used to estimate systolic or pulse pressure amplification, with and without the use of the mathematical algorithms for estimation of central BP [38]. Invasive BP measurement occurs via catheterization or cannulation of an artery. This is restricted to invasive hospital procedures, some of which are in acute care (e.g. intensive care units where invasive monitoring of BP is required) or non-acute care (e.g. planned coronary angiography).

**Sex differences in cardiovascular structure and pressure and flow waveform physiology across the life course**

***Heart***

In this section the primary focus is the left ventricle due to its importance to pressure and flow waveforms in the macro- and micro- vasculature. The coronary arteries will briefly be discussed due to the differences in the presentation of coronary heart disease between women and men. A study conducted in a cohort 0–36 months old observed no sex differences in ventricular, valvular, and arterial dimensions [40]. Indeed, prior to puberty, there is no significant difference in the growth of the left ventricle between girls and boys [41]. During puberty, the growth of the left ventricle occurs significantly more rapidly in men than women [41,42]. From the 2nd decade of life onwards, men have a greater left ventricular mass than women [41,43]. However, sex differences in left ventricular mass are attenuated by indexing the measurements to body size [41]. Relative wall thickness is not different between women and men [41,44]. The left ventricle outflow tract diameter is smaller in women compared with men. With respect the coronary arteries, women’s arteries have smaller diameters compared with men, even after adjustment for left ventricular mass and body size parameters [45,46]. Women compared with men also have more tortuous coronary arteries, however, data from one study suggests that women without severe tortuosity (defined as at least three bends ≥45° in the main trunk of ≥one artery) may have a lower degree of coronary disease compared to those with severe tortuosity [47]. The opposite phenomenon was observed in men. Overall, the heart has clear structural differences between women and men that may give rise to differences in pressure and flow physiology. For a more detailed review of sex differences in heart structure readers are referred to recent publications [48-51].

*Pressure and flow waveform physiology*

Left ventricular ejection fraction [52-54] and E/e′ ratios are higher in women compared with men [44,55]. Many other left ventricular functional parameters are also different between women and men [44,53]. Flow velocity measured from the left ventricular outflow tract is similar between the sexes [55]. Coronary artery haemodynamics can be measured in several ways including blood flow, coronary flow reserve, index of myocardial resistance and fractional flow reserve [56,57]. Coronary artery blood flow is greatest during diastole, and wave intensity analysis has shown this is primarily driven by a backward travelling ‘suction’ wave generated distally [58]. Coronary artery flow reserve is defined as the ratio between hyperaemic and resting coronary flow and represents the entire coronary system, including the microvasculature. Coronary artery flow reserve is significantly lower in women compared with men leading to notion that coronary artery disease is a microvascular disease in women and macrovascular disease in men [5]. However, recent work has challenged this hypothesis in physiology studies employing the index of microcirculatory resistance, which is described as a direct measure of coronary microvasculature [57]. In a study of 157 people (75% women) with angina but no obstructive coronary artery disease the index of microcirculatory resistance and coronary flow reserve was measured. There was no sex difference in the index of microcirculatory resistance, despite lower coronary flow reserve in women [59]. This led the authors to suggest there may be no sex difference in microvascular dysfunction [59], and these results have been reproduced in separate studies [60,61]. One study also demonstrated that low coronary flow reserve (<2.0) predicts major adverse CVD events equally between the sexes [62].

***Macrovasculature***

Most of the data on pressure and flow waveform physiology has been measured in the large elastic and mid-sized muscular arteries including the aorta, carotid, and brachial arteries. Greater aortic root size due to remodelling with advancing age is associated with adverse cardiovascular outcomes [63]. A study of 748 children (42% girls, aged 0-18 years) with normal heart structure found that girls had smaller aortic root dimensions even after adjustment for body size [64]. In a study of 1207 apparently healthy people 15 years and older (54% women), the aortic root was smaller in women compared with men (mean values of 2.98 cm vs. 3.34 cm) after adjusting for body surface area [65]. These values are consistent with work from the Framingham Heart Study [66], which also used longitudinal data to show that greater increases in aortic root diameter was associated with male sex, as well as, hypertension, obesity and advancing age. Women also have a smaller carotid artery diameter compared with men [54], even after adjustment for body size and neck size [67]. Carotid artery intima-media thickness, a well-accepted marker of sub-clinical atherosclerosis, is higher in men compared with women, although in children aged 4-5 years there are no appreciable sex differences [68].

The stiffness of the aorta is critical to BP, as well as pressure and flow waveform morphology. Aortic stiffness can be reliably measured using carotid-to-femoral pulse wave velocity (PWV). The Reference Values for Arterial Stiffness Collaboration showed that there was a slightly lower carotid-to-femoral PWV in women compared to men after adjustment for quadratic age and BP differences [69]. Other studies have also found slightly lower values in women compared to men [70]. In older age, women compared with men have a faster longitudinal increase (rate of change) in carotid-to-femoral PWV [71]. Muscular arteries such as the brachial, radial, and femoral arteries undergo less remodelling than elastic arteries throughout the life course [72,73]. Nevertheless, sex differences may still persist. For example, local brachial distensibility is higher and compliance lower in women [74]. Conversely, local femoral artery stiffness is higher in apparently healthy men compared with women and there are no large changes in stiffness from the 2nd to the 6th decade of life [75]. Cardio-ankle vascular index increases with age and is lower in women than in men [76]. Altogether, the structural differences in the large arteries likely contribute to sex differences in arterial haemodynamics. Sex differences in aortic stiffness and other measures of vascular aging were also recently reviewed in detail elsewhere [51,77].

*Pressure and flow waveform physiology*

Autonomic control of the large arteries and microvasculature modulates pressure and flow. Sympathetic nervous activity influences peripheral vascular resistance and BP upstream from the arterioles and blood flow and hydrostatic pressure downstream. Interestingly, female sex hormones result in less autonomic nervous support of BP pre-menopause but post-menopause these hormones result in greater control of BP. As previously mentioned, there are differences between women and men in standard upper-arm cuff measured BP, but there is emerging data that cuff BP measurements may be more inaccurate in women compared with men [78]. Two recent studies have found that for the same cuff systolic BP, invasive aortic systolic BP was significantly higher in women, but not men [78,79]. A key area for future research is to determine whether greater inaccuracy of BP measurement in women leads to poorer cardiovascular risk prediction.

Sex differences in pressure waveform features have primarily been identified using data from radial artery applanation tonometry. From 8 years of age until the 8th decade of life, central aortic augmented pressure and augmentation index, parameters associated with cardiovascular risk, are higher in women [80,81]. A study of 603 women and 549 men (68±12 years) selected from the electoral roll in Canberra, Australia, found that women and men taller than the median height had lower values of augmentation index and BP than the participants shorter than median height [82]. A separate Australian study examined 104 women (71±5 years) and 104 men (72±4 years) of the same height, age and mean arterial pressure [83]. Women had a higher augmentation index, lower aortic root diameter and lower arterial compliance. Sex-specific variation in the amplitude and peak width of the forward wave, and the slope of the backward upslope partly explains sex differences in augmentation index [84]. Another study in 530 men and women demonstrated sex differences across age quartiles (≤40 to ≥55 years) in properties of the arterial tree [54]. Despite lower mean BP and comparable arterial distensibility, women developed a higher degree of pulsatility with age, likely due to smaller body size compared to men. This appears to be independent of the effects of menopause [54]. Both stiffening and elevated augmentation index contribute to increased left ventricular load, thus these data suggest that women are predisposed to greater afterload compared to men. This hypothesis is supported by data from studies of sex differences in reservoir-excess pressure parameters that will be discussed in a following section [85].

Other conventional pulse wave analysis variables that exhibit sex differences include sub-endocardial viability ratio and aortic diastolic decay index [86]. Sub-endocardial viability ratio provides an estimate of the ratio between myocardial oxygen supply and demand [87] and, when derived from carotid or estimated aortic pressure waveforms, is lower in women compared with men across different ages [88,89]. It is unknown whether lower sub-endocardial viability ratio in women compared with men leaves women more predisposed to myocardial ischemia and adverse myocardial outcomes. Efforts to determine associations between sub-endocardial viability ratio and coronary flow reserve revealed a moderate correlation in a small sample of patients with hypertension and normal coronary arteries [90]. There was no data about whether the strength of the associations may differ between women and men.

The reservoir-excess pressure model is a method of wave separation that is both physiologically plausible [91,92], and clinically relevant [93]. There are numerous parameters derived from this wave separation approach and sex differences are apparent. Adult women have higher reservoir and excess pressure integral compared with men [85]. The findings for excess pressure remained after stratification according to age (<51 years and ≥51 years) and adjustment for either body mass index or body height. In the group ≥51 years, reservoir and excess pressure remained significantly higher in women after adjustment [85].

Sex differences in wave intensity analysis parameters have also been observed [94]. A study of 206 apparently healthy people (53% women) found that women have a lower aortic forward compression wave (pressure and flow velocity increase, related to left ventricular contraction) and a lower forward decompression (pressure and flow velocity decrease) wave compared with women. No sex differences were found in the backward compression wave. The authors suggested that these findings indicate poorer ventricular-arterial coupling in women compared to men. Macrovascular blood flow patterns also show some differences between women and men. Carotid blood flow waveform variables were found to generally be lower in women compared with men in a study of 50 healthy people aged 20-29 years (40% women) [95]. However, in that study a moderate relationship between the carotid flow waveform variables and body height was identified in the entire sample and this might explain the sex differences observed [95]. Differences between women and men in femoral flow waveform patterns have also been reported [96]. Altogether, there are major differences between women and men in macrovascular pressure and flow physiology. On the balance, women have a poorer haemodynamic profile than men, particularly in older age, which could lead to adverse cardiovascular outcomes.

***Microvasculature***

The microvasculature remains incompletely developed until late adolescence [97]. Its function and structure declines with ageing. The large, conduit vessels branch off to feed arteries and arterioles. Most studies examining microvascular arteriolar function have been conducted in a single sex. There are some studies where sex differences have been noted in relation to arteriolar structure and reactivity changes in response to sustained hypertension. Capillaries branch off terminal arterioles and are characterised by lack of vascular smooth muscle and presence of pericytes that are in contact with the endothelial cell lining [98]. It remains unclear whether sex differences in pericyte function or dysfunction exist. From the capillary network, flow converges to venular capillaries and into venules – a large majority of vascular volume occurs in the venous component of the microvasculature. Interestingly, coronary heart disease may more commonly be a microvascular disease in women and characterised by increased arteriolar constriction and vasospasm which are not typically observed in men [5]. On the contrary, coronary heart disease is more commonly a macrovascular disease in men, who adapt to coronary occlusion and plaque deposition by growing coronary collateral vessels, which is less common in women [99].

The entire network of microvessels is covered by a single layer of endothelial cells. The endothelium provides a physical barrier between the vessel wall and lumen that actively secretes several mediators that regulate platelet aggregation, coagulation, fibrinolysis, and vascular tone. A small number of studies have demonstrated sex differences in the primary function of capillary endothelial cells which are likely due to differences in endothelial cell morphology, cell signalling and endothelial cell response to various mediators [100-105]. Sex differences exist in plasma levels of endothelin 1 [106-108] (a potent vasodilator secreted by the endothelium) as does distribution, expression and activation of endothelin receptors and mediators of the endothelin system (such nitric oxide (NO)) [107,109]. In women, estrogen receptors promote NO release whereas androgen (testosterone) receptors impair endothelial NO release. Estrogen has long been thought to be cardioprotective in women, whereas androgen may contribute to elevated BP in men due to increased reactive oxygen species and decreased NO availability. However, the role of these hormones in cardioprotection is oversimplified and is very much dependent on the environment surrounding them. This is discussed in more detail elsewhere [110]. The decline in endothelial function with age occurs around the fourth decade of life in men and the fifth in women (coinciding with menopause). The rate of decline is much more rapid In women [111].

*Pressure and flow waveform physiology*

There is a paucity of studies on humans comparing sex differences in microvascular pressure and flow waveform physiology and for this reason we have also included data from animal studies in this section. In one study in rats placed on a high-salt diet, differences in skeletal muscle microvessel loss were observed in males but not females. After 4 weeks of the high-salt diet, microvascular remodelling was absent and females remained normotensive, whereas mean arterial pressure had risen significantly in males [112]. Males have higher oncotic pressure than females between the ages of 6 to 74 years of age [113]. In response to microgravity, sex differences in volume regulation become apparent. Female astronauts experience a greater shift of fluid out of the plasma space compared to men and on return to earth experience greater orthostatic intolerance [114,115]. Men respond to orthostatic stress by changing vascular resistance in the microvascular, while women alter heart rate. Endothelial function can be measured in humans by assessing the vasodilatory response to a period of arterial occlusion. Endothelial function is higher in younger (4-12 years) children than in older children/adolescents (12-18 years), but sex differences are only observed in older children [116]. Another study found no significant sex-differences in the reactive hyperaemic index in children and adolescents aged 10-16 years [97].

**Sex differences in the relationship between pressure and flow waveform physiology and cardiovascular disease outcomes**

An individual participant data meta-analysis of 17,635 people examined whether aortic (carotid-to-femoral) PWV predicts future CVD events, defined as coronary heart disease and stroke events with a minimum of one year follow up [117]. There were no sex differences observed in the prediction of CVD events at follow up (women HR=1.35 95%CI 1.18 to 1.53 compared with men HR=1.46, 95%CI 1.29 to 1.65). In a meta-analysis to determine if a relationship exists between brachial-ankle PWV and CVD events (6.4 years follow up), sex differences were not reported [118]. However, a recent single site analysis of 11 767 patients (42% women) found that increased brachial-ankle PWV was more strongly associated with a higher risk of CVD events and death in women compared with men, after 3.6 years median follow up [119].

Sex differences in BP and associations with incident CVD were recently examined using data from four cohort studies (n=27 542, 54% women) [29]. The primary finding was that CVD risk began increasing at lower levels of systolic BP in women (100-109 mmHg) compared to men (130-139 mmHg). The authors made an interesting observation that the ideal physiological BP could be lower for women than it is for men. Prospective data are required to determine whether guiding treatment of high BP in women differently from men would lead to improved outcomes. Reassuringly, there is no evidence that the efficacy of anti-hypertensive medications differs in women compared with men [120], and women appear to be treated more often than men [121,122]. However, the type of treatment prescribed may differ between sexes [123].

Most studies that have examined associations between estimated central BP and incident CVD events have used multivariable models that adjust for sex, and it is unclear whether interactions with sex were examined [124,125]. As stated above, women have a higher augmentation index than men at all ages from the second decade of life [88,126]. Importantly, a meta-analysis from 2010 found that augmentation index was associated with cardiovascular events independent of standard risk factors, but whether interactions with sex were examined is unknown [127]. In terms of subclinical data, one study of 808 Black African participants found a stronger cross-sectional relationship between augmentation index and left ventricular mass index in men, compared with women [128]. To our knowledge, there has not been a sex-disaggregated analysis assessing the association between augmentation index and future CVD events.

Reservoir-excess pressure parameters have been associated with increased risk of CVD events in some, but not all, studies [93]. One study using data from the Australian National Blood Pressure Study found that the systolic time constant was associated with future cardiovascular events [129]. However, in a sex-disaggregated sub-analysis, the association with cardiovascular events was only significant for men. One of the first outcomes studies was from the Conduit Artery Functional Evaluation Substudy of Anglo-Scandinavian Cardiac Outcomes Trial, which included 2069 participants with hypertension (mean age 63 years, only 18% women). The authors found that excess pressure integral predicted incident CVD events in the cohort, even after adjustment for age, sex, classical risk factors and, separately, Framingham Score. In a younger cohort of 1231 children aged 11-12 years old (50% women) from the Longitudinal Study of Australian Children there was a cross-sectional relationship between higher excess pressure and greater carotid intima-media thickness, but there were no differences between the sexes [130]. A detailed review on reservoir-excess pressure and clinical outcomes was recently published elsewhere [93]. There is limited data available with respect to associations between wave intensity analysis parameters measured from the large arteries and cardiovascular outcomes [131], and no data to our knowledge, that is sex disaggregated.

**Knowledge gaps and future research**

Knowledge gaps remain in relation to sex differences in waveform physiology. Below we address areas requiring future research, summarised according to three key focus points, mechanisms, outcomes, and populations.

*Mechanisms*

In this review, we have described differences in arterial pressure and flow waveform physiology between women and men (Table 2). The mechanisms of sex differences in augmentation index and some reservoir-excess pressure parameters are not exclusively related to body size [83,85]. More work is required to determine other mechanisms. While there are sex differences in multiple components of the macrovasculature, conclusions are contradictory, and the complete picture remains unclear. This is likely due to limited research in this area and in particular, a lack of studies that examine these multifactorial systems in women and men.

*Outcomes*

There is a lack of sex-disaggregated data in waveform physiology and relation to incident CVD events and outcomes after CVD events, making any conclusions difficult. Based on the current literature, sex differences in arterial pressure and flow waveform physiology likely play a role, but further research is required to determine how significant this role is. As stated by The Lancet Women and CVD Commission, sex-disaggregated analyses in research and clinical trials should be mandatory [3]. An immediate outstanding research question for the field is whether sex differences in pressure and flow waveform variables are associated with sex differences in incident CVD events, CVD mortality and outcomes after CVD events. Other noteworthy questions are whether patterns from pressure or flow waveforms, or waveforms measured from different arterial sites, have separate effects or relationships with coronary artery disease, stroke, heart failure in women compared with men. This will help to clarify the contribution of waveform physiology parameters to outcomes in women.

*Populations*

Most studies on sex differences in pressure and flow waveform physiology have been performed in the general adult population. However, comorbidities such as diabetes that display sex differences in terms of onset, frequency, morbidity, and mortality also impact cardiac, macro- and microvascular structure and function and likely pressure and flow waveform physiology [132-136]. Moreover, women compared to men with diabetes mellitus are at greater risk of stroke [137,138]. On the other hand, a study in those with type 2 diabetes found no sex differences in microvascular complications such as nephropathy, neuropathy and retinal measures compared to individuals with normal glucose metabolism [139]. Women with end-stage renal disease may have higher rates of mortality compared to men and sex differences in vascular function may explain this disparity [140,141]. Sex differences in pressure and flow waveform physiology in different race/ethnic groups is another important area for future work, given the higher rates of CVD in black African, African American, African Caribbean and Hispanic populations especially compared to Asian and white populations [142,143]. Furthermore, there is limited data and gaps in understanding in sex differences in pressure and flow waveform physiology in youth. More work is required in young people to determine what is due to growth or, physiological, and what is pathological.

In conclusion, there are marked differences between women and men in the structure of the heart, macrovasculature and microvasculature. Significant sex differences also exist in arterial pressure and flow waveform physiology, but more work specifically designed to examine sex differences is needed to determine whether these differences are clinically relevant for prediction of CVD events and mortality. Future research should aim to address knowledge gaps centred around mechanisms of sex differences in arterial waveforms, whether sex contribute to differences in CVD outcomes and whether differences persist or are exacerbated in various populations. Achieving this program of work may improve knowledge related to cardiovascular health and disease in women, who have long been understudied, underdiagnosed, and undertreated.

**References**

1. Lopez AD, Adair T. Is the long-term decline in cardiovascular-disease mortality in high-income countries over? Evidence from national vital statistics. Int J Epidemiol2019; 48 (6):1815-1823.

2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol2020; 76 (25):2982-3021.

3. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet2021; 397 (10292):2385-2438.

4. Picone DS, Mayer CC, Climie RE. Known unknowns of sex differences in cardiovascular physiology: can arterial waveforms provide answers? J Hypertens2022; 40 (6):1085-1087.

5. Huxley VH, Kemp SS. Sex-Specific Characteristics of the Microcirculation. Adv Exp Med Biol2018; 1065:307-328.

6. Clayton JA, Tannenbaum C. Reporting Sex, Gender, or Both in Clinical Research? JAMA2016; 316 (18):1863-1864.

7. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019. Institute for Health Metrics and Evaluation, Seattle, United States <http://ghdx.healthdata.org/gbd-results-tool> accessed 28 July 2022.

8. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation2019; 139 (10):e56-e528.

9. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. Eur Heart J2019; 40 (47):3859-3868c.

10. Guo Y, Yin F, Fan C, Wang Z. Gender difference in clinical outcomes of the patients with coronary artery disease after percutaneous coronary intervention: A systematic review and meta-analysis. Medicine (Baltimore)2018; 97 (30):e11644.

11. Cenko E, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Krljanac G, et al. Sex Differences in Outcomes After STEMI: Effect Modification by Treatment Strategy and Age. JAMA Intern Med2018; 178 (5):632-639.

12. Epps KC, Holper EM, Selzer F, Vlachos HA, Gualano SK, Abbott JD, et al. Sex Differences in Outcomes Following Percutaneous Coronary Intervention According to Age. Circ Cardiovasc Qual Outcomes2016; 9 (2 Suppl 1):S16-25.

13. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac D, Sturm J, et al. Sex Differences in Long-Term Mortality After Stroke in the INSTRUCT (INternational STRoke oUtComes sTudy): A Meta-Analysis of Individual Participant Data. Circ Cardiovasc Qual Outcomes2017; 10 (2).

14. Phan HT, Blizzard CL, Reeves MJ, Thrift AG, Cadilhac DA, Sturm J, et al. Factors contributing to sex differences in functional outcomes and participation after stroke. Neurology2018; 90 (22):e1945-e1953.

15. Emdin CA, Wong CX, Hsiao AJ, Altman DG, Peters SA, Woodward M, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. BMJ2016; 532:h7013.

16. Taylor CJ, Ordonez-Mena JM, Jones NR, Roalfe AK, Lay-Flurrie S, Marshall T, et al. National trends in heart failure mortality in men and women, United Kingdom, 2000-2017. Eur J Heart Fail2021; 23 (1):3-12.

17. Ali M, van Os HJA, van der Weerd N, Schoones JW, Heymans MW, Kruyt ND, et al. Sex Differences in Presentation of Stroke: A Systematic Review and Meta-Analysis. Stroke2022; 53 (2):345-354.

18. Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, et al. Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation2018; 137 (8):781-790.

19. Araujo C, Laszczynska O, Viana M, Melao F, Henriques A, Borges A, et al. Sex differences in presenting symptoms of acute coronary syndrome: the EPIHeart cohort study. BMJ Open2018; 8 (2):e018798.

20. Zhao M, Woodward M, Vaartjes I, Millett ERC, Klipstein-Grobusch K, Hyun K, et al. Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis. J Am Heart Assoc2020; 9 (11):e014742.

21. Eriksson M, Asberg S, Sunnerhagen KS, von Euler M. Sex Differences in Stroke Care and Outcome 2005-2018: Observations From the Swedish Stroke Register. Stroke2021; 52 (10):3233-3242.

22. Strong B, Lisabeth LD, Reeves M. Sex differences in IV thrombolysis treatment for acute ischemic stroke: A systematic review and meta-analysis. Neurology2020; 95 (1):e11-e22.

23. Hockham C, Bao L, Tiku A, Badve SV, Bello AK, Jardine MJ, et al. Sex differences in chronic kidney disease prevalence in Asia: a systematic review and meta-analysis. Clinical Kidney Journal2022:sfac030.

24. Gannon OJ, Robison LS, Custozzo AJ, Zuloaga KL. Sex differences in risk factors for vascular contributions to cognitive impairment & dementia. Neurochem Int2019; 127:38-55.

25. DuPont JJ, Kenney RM, Patel AR, Jaffe IZ. Sex differences in mechanisms of arterial stiffness. Br J Pharmacol2019; 176 (21):4208-4225.

26. Kanter R, Caballero B. Global gender disparities in obesity: a review. Adv Nutr2012; 3 (4):491-498.

27. Garawi F, Devries K, Thorogood N, Uauy R. Global differences between women and men in the prevalence of obesity: is there an association with gender inequality? Eur J Clin Nutr2014; 68 (10):1101-1106.

28. Collaboration NCDRF. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet2021; 398 (10304):957-980.

29. Ji H, Niiranen TJ, Rader F, Henglin M, Kim A, Ebinger JE, et al. Sex Differences in Blood Pressure Associations With Cardiovascular Outcomes. Circulation2021; 143 (7):761-763.

30. Nichols WW, O'Rourke M, Vlachopoulos C. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles.London2011.

31. Hametner B, Wassertheurer S. Pulse Waveform Analysis: Is It Ready for Prime Time? Curr Hypertens Rep2017; 19 (9):73.

32. Mitchell GF. Central pressure should not be used in clinical practice. Artery Res2015; 9:8-13.

33. Sharman JE. Central pressure should be used in clinical practice. Artery Research2014; 9 (C):1-7.

34. Westerhof N, Sipkema P, van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. Cardiovasc Res1972; 6 (6):648-656.

35. Parker KH, Jones CJ. Forward and backward running waves in the arteries: analysis using the method of characteristics. J Biomech Eng1990; 112 (3):322-326.

36. Parker KH. An introduction to wave intensity analysis. Med Biol Eng Comput2009; 47 (2):175-188.

37. Hughes AD, Park C, Ramakrishnan A, Mayet J, Chaturvedi N, Parker KH. Feasibility of Estimation of Aortic Wave Intensity Using Non-invasive Pressure Recordings in the Absence of Flow Velocity in Man. Front Physiol2020; 11:550.

38. Millasseau S, Agnoletti D. Non-invasive estimation of aortic blood pressures: a close look at current devices and methods. Curr Pharm Des2015; 21 (6):709-718.

39. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. Eur Heart J1993; 14 (2):160-167.

40. Cantinotti M, Scalese M, Murzi B, Assanta N, Spadoni I, Festa P, et al. Echocardiographic nomograms for ventricular, valvular and arterial dimensions in caucasian children with a special focus on neonates, infants and toddlers. J Am Soc Echocardiogr2014; 27 (2):179-191 e172.

41. de Simone G, Devereux RB, Daniels SR, Meyer RA. Gender differences in left ventricular growth. Hypertension1995; 26 (6 Pt 1):979-983.

42. Prabhavathi K, Selvi KT, Poornima KN, Sarvanan A. Role of biological sex in normal cardiac function and in its disease outcome - a review. J Clin Diagn Res2014; 8 (8):BE01-04.

43. Vasan RS, Larson MG, Levy D, Evans JC, Benjamin EJ. Distribution and categorization of echocardiographic measurements in relation to reference limits: the Framingham Heart Study: formulation of a height- and sex-specific classification and its prospective validation. Circulation1997; 96 (6):1863-1873.

44. Coutinho T, Borlaug BA, Pellikka PA, Turner ST, Kullo IJ. Sex differences in arterial stiffness and ventricular-arterial interactions. J Am Coll Cardiol2013; 61 (1):96-103.

45. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, et al. Gender differences in coronary artery diameter are not related to body habitus or left ventricular mass. Clin Cardiol2014; 37 (10):605-609.

46. Kucher N, Lipp E, Schwerzmann M, Zimmerli M, Allemann Y, Seiler C. Gender differences in coronary artery size per 100 g of left ventricular mass in a population without cardiac disease. Swiss Med Wkly2001; 131 (41-42):610-615.

47. Chiha J, Mitchell P, Gopinath B, Burlutsky G, Kovoor P, Thiagalingam A. Gender differences in the prevalence of coronary artery tortuosity and its association with coronary artery disease. Int J Cardiol Heart Vasc2017; 14:23-27.

48. St Pierre SR, Peirlinck M, Kuhl E. Sex Matters: A Comprehensive Comparison of Female and Male Hearts. Front Physiol2022; 13:831179.

49. Merz AA, Cheng S. Sex differences in cardiovascular ageing. Heart2016; 102 (11):825-831.

50. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction. Circulation2018; 138 (2):198-205.

51. Seeland U, Nemcsik J, Lønnebakken MT, Kublickiene K, Schluchter H, Park C, et al. Sex and Gender Aspects in Vascular Ageing – Focus on Epidemiology, Pathophysiology, and Outcomes. Heart, Lung and Circulation2021; 30 (11):1637-1646.

52. Chung AK, Das SR, Leonard D, Peshock RM, Kazi F, Abdullah SM, et al. Women have higher left ventricular ejection fractions than men independent of differences in left ventricular volume: the Dallas Heart Study. Circulation2006; 113 (12):1597-1604.

53. Petersen SE, Aung N, Sanghvi MM, Zemrak F, Fung K, Paiva JM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson2017; 19 (1):18.

54. Smulyan H, Asmar RG, Rudnicki A, London GM, Safar ME. Comparative effects of aging in men and women on the properties of the arterial tree. J Am Coll Cardiol2001; 37 (5):1374-1380.

55. Dalen H, Thorstensen A, Vatten LJ, Aase SA, Stoylen A. Reference values and distribution of conventional echocardiographic Doppler measures and longitudinal tissue Doppler velocities in a population free from cardiovascular disease. Circ Cardiovasc Imaging2010; 3 (5):614-622.

56. Morris PD, Al-Lamee RK, Berry C, Research B, Development C. Coronary physiological assessment in the catheter laboratory: haemodynamics, clinical assessment and future perspectives. Heart2022.

57. Fearon WF, Kobayashi Y. Invasive Assessment of the Coronary Microvasculature: The Index of Microcirculatory Resistance. Circ Cardiovasc Interv2017; 10 (12).

58. Davies JE, Whinnett ZI, Francis DP, Manisty CH, Aguado-Sierra J, Willson K, et al. Evidence of a dominant backward-propagating "suction" wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertrophy. Circulation2006; 113 (14):1768-1778.

59. Kobayashi Y, Fearon WF, Honda Y, Tanaka S, Pargaonkar V, Fitzgerald PJ, et al. Effect of Sex Differences on Invasive Measures of Coronary Microvascular Dysfunction in Patients With Angina in the Absence of Obstructive Coronary Artery Disease. JACC Cardiovasc Interv2015; 8 (11):1433-1441.

60. Hoshino M, Hamaya R, Kanaji Y, Kanno Y, Hada M, Yamaguchi M, et al. Sex Differences in Long-Term Outcomes in Patients With Deferred Revascularization Following Fractional Flow Reserve Assessment: International Collaboration Registry of Comprehensive Physiologic Evaluation. J Am Heart Assoc2020; 9 (4):e014458.

61. Chung JH, Lee KE, Lee JM, Her AY, Kim CH, Choi KH, et al. Effect of Sex Difference of Coronary Microvascular Dysfunction on Long-Term Outcomes in Deferred Lesions. JACC Cardiovasc Interv2020; 13 (14):1669-1679.

62. Murthy VL, Naya M, Taqueti VR, Foster CR, Gaber M, Hainer J, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation2014; 129 (24):2518-2527.

63. Gardin JM, Arnold AM, Polak J, Jackson S, Smith V, Gottdiener J. Usefulness of aortic root dimension in persons > or = 65 years of age in predicting heart failure, stroke, cardiovascular mortality, all-cause mortality and acute myocardial infarction (from the Cardiovascular Health Study). Am J Cardiol2006; 97 (2):270-275.

64. Zilberman MV, Khoury PR, Kimball RT. Two-dimensional echocardiographic valve measurements in healthy children: gender-specific differences. Pediatr Cardiol2005; 26 (4):356-360.

65. Devereux RB, de Simone G, Arnett DK, Best LG, Boerwinkle E, Howard BV, et al. Normal limits in relation to age, body size and gender of two-dimensional echocardiographic aortic root dimensions in persons >/=15 years of age. Am J Cardiol2012; 110 (8):1189-1194.

66. Lam CS, Xanthakis V, Sullivan LM, Lieb W, Aragam J, Redfield MM, et al. Aortic root remodeling over the adult life course: longitudinal data from the Framingham Heart Study. Circulation2010; 122 (9):884-890.

67. Krejza J, Arkuszewski M, Kasner SE, Weigele J, Ustymowicz A, Hurst RW, et al. Carotid artery diameter in men and women and the relation to body and neck size. Stroke2006; 37 (4):1103-1105.

68. Madhloum N, Luyten LJ, Provost EB, De Boever P, Dockx Y, Sleurs H, et al. Establishing reference values for macro- and microvascular measurements in 4-to-5 year-old children of the ENVIRONAGE prospective birth cohort. Sci Rep2020; 10 (1):5107.

69. Reference Values for Arterial Stiffness Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J2010; 31 (19):2338-2350.

70. Kim JY, Park JB, Kim DS, Kim KS, Jeong JW, Park JC, et al. Gender Difference in Arterial Stiffness in a Multicenter Cross-Sectional Study: The Korean Arterial Aging Study (KAAS). Pulse (Basel)2014; 2 (1-4):11-17.

71. Scuteri A, Morrell CH, Orru M, Strait JB, Tarasov KV, Ferreli LA, et al. Longitudinal perspective on the conundrum of central arterial stiffness, blood pressure, and aging. Hypertension2014; 64 (6):1219-1227.

72. Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, et al. Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. Circulation1985; 71 (2):202-210.

73. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension2004; 43 (6):1239-1245.

74. van der Heijden-Spek JJ, Staessen JA, Fagard RH, Hoeks AP, Boudier HA, van Bortel LM. Effect of age on brachial artery wall properties differs from the aorta and is gender dependent: a population study. Hypertension2000; 35 (2):637-642.

75. Bossuyt J, Engelen L, Ferreira I, Stehouwer CD, Boutouyrie P, Laurent S, et al. Reference values for local arterial stiffness. Part B: femoral artery. J Hypertens2015; 33 (10):1997-2009.

76. Nishiwaki M, Kurobe K, Kiuchi A, Nakamura T, Matsumoto N. Sex differences in flexibility-arterial stiffness relationship and its application for diagnosis of arterial stiffening: a cross-sectional observational study. PLoS One2014; 9 (11):e113646.

77. Ogola BO, Zimmerman MA, Clark GL, Abshire CM, Gentry KM, Miller KS, et al. New insights into arterial stiffening: does sex matter? Am J Physiol Heart Circ Physiol2018; 315 (5):H1073-H1087.

78. Abbaoui Y, Fortier C, Desbiens LC, Kowalski C, Lamarche F, Nadeau-Fredette AC, et al. Accuracy Difference of Noninvasive Blood Pressure Measurements by Sex and Height. JAMA Netw Open2022; 5 (6):e2215513.

79. Picone DS, Stoneman E, Cremer A, Schultz MG, Otahal P, Hughes AD, et al. Sex-differences in blood pressure and potential implications for cardiovascular risk management. Hypertension (accepted for publication)2022.

80. McEniery CM, Yasmin, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). J Am Coll Cardiol2005; 46 (9):1753-1760.

81. Barraclough JY, Garden FL, Toelle B, O'Meagher S, Marks GB, Cowell CT, et al. Sex differences in aortic augmentation index in adolescents. J Hypertens2017; 35 (10):2016-2024.

82. Reeve JC, Abhayaratna WP, Davies JE, Sharman JE. Central hemodynamics could explain the inverse association between height and cardiovascular mortality. Am J Hypertens2014; 27 (3):392-400.

83. Gatzka CD, Kingwell BA, Cameron JD, Berry KL, Liang YL, Dewar EM, et al. Gender differences in the timing of arterial wave reflection beyond differences in body height. J Hypertens2001; 19 (12):2197-2203.

84. Torjesen AA, Wang N, Larson MG, Hamburg NM, Vita JA, Levy D, et al. Forward and backward wave morphology and central pressure augmentation in men and women in the Framingham Heart Study. Hypertension2014; 64 (2):259-265.

85. Guzik P, Schneider A, Piskorski J, Klimas K, Krauze T, Marciniak R, et al. Sex differences in excess and reservoir arterial blood pressures as markers of phenotype. J Hypertens2019; 37 (11):2159-2167.

86. Tagawa K, Tsuru Y, Yokoi K, Aonuma T, Hashimoto J. Aortic diastolic pressure decay explains sex-related differences in the subendocardial viability ratio: the Wakuya study. J Hypertens2022; 40 (6):1099-1106.

87. Buckberg GD, Fixler DE, Archie JP, Hoffman JI. Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res1972; 30 (1):67-81.

88. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. J Am Coll Cardiol1997; 30 (7):1863-1871.

89. Namasivayam M, McEniery CM, Wilkinson IB, Yasmin, Cockroft JR, McDonnell BJ, et al. Different Effects of Vascular Aging on Ischemic Predisposition in Healthy Men and Women. Hypertension2018; 72 (6):1294-1300.

90. Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, et al. Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. J Hum Hypertens2012; 26 (1):64-70.

91. Schultz MG, Davies JE, Hardikar A, Pitt S, Moraldo M, Dhutia N, et al. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. Arterioscler Thromb Vasc Biol2014; 34 (7):1597-1603.

92. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol2003; 284 (4):H1358-1368.

93. Armstrong MK, Schultz MG, Hughes AD, Picone DS, Sharman JE. Physiological and clinical insights from reservoir-excess pressure analysis. J Hum Hypertens2021; 35 (9):758-768.

94. Bhuva AN, D'Silva A, Torlasco C, Nadarajan N, Jones S, Boubertakh R, et al. Non-invasive assessment of ventriculo-arterial coupling using aortic wave intensity analysis combining central blood pressure and phase-contrast cardiovascular magnetic resonance. Eur Heart J Cardiovasc Imaging2020; 21 (7):805-813.

95. Azhim A, Akioka K, Akutagawa M, Hirao Y, Yoshizaki K, Obara S, et al. Effect of gender on blood flow velocities and blood pressure: role of body weight and height. Annu Int Conf IEEE Eng Med Biol Soc2007; 2007:967-970.

96. Hashimoto J, Ito S. Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. Hypertension2010; 56 (5):926-933.

97. Radtke T, Khattab K, Eser P, Kriemler S, Saner H, Wilhelm M. Puberty and microvascular function in healthy children and adolescents. J Pediatr2012; 161 (5):887-891.

98. Scallan J, Huxley VH, Korthuis RJ. Capillary Fluid Exchange: Regulation, Functions, and Pathology. San Rafael (CA)2010.

99. Johansson S, Bergstrand R, Schlossman D, Selin K, Vedin A, Wilhelmsson C. Sex differences in cardioangiographic findings after myocardial infarction. Eur Heart J1984; 5 (5):374-381.

100. Huxley VH, Wang J, Whitt SP. Sexual dimorphism in the permeability response of coronary microvessels to adenosine. Am J Physiol Heart Circ Physiol2005; 288 (4):H2006-2013.

101. Huxley VH, Wang JJ, Sarelius IH. Adaptation of coronary microvascular exchange in arterioles and venules to exercise training and a role for sex in determining permeability responses. Am J Physiol Heart Circ Physiol2007; 293 (2):H1196-1205.

102. Maggioli E, McArthur S, Mauro C, Kieswich J, Kusters DHM, Reutelingsperger CPM, et al. Estrogen protects the blood-brain barrier from inflammation-induced disruption and increased lymphocyte trafficking. Brain Behav Immun2016; 51:212-222.

103. Panazzolo DG, Silva LH, Cyrino FZ, Sicuro FL, Kraemer-Aguiar LG, Bouskela E. Gender differences in microcirculation: observation using the hamster cheek pouch. Clinics (Sao Paulo)2013; 68 (12):1537-1542.

104. Siamwala JH, Macias BR, Lee PC, Hargens AR. Gender differences in tibial microvascular flow responses to head down tilt and lower body negative pressure. Physiol Rep2017; 5 (4).

105. Szabo A, Vollmar B, Boros M, Menger MD. Gender differences in ischemia-reperfusion-induced microcirculatory and epithelial dysfunctions in the small intestine. Life Sci2006; 78 (26):3058-3065.

106. Gohar EY, Giachini FR, Pollock DM, Tostes RC. Role of the endothelin system in sexual dimorphism in cardiovascular and renal diseases. Life Sci2016; 159:20-29.

107. Gohar EY, Yusuf C, Pollock DM. Ovarian hormones modulate endothelin A and B receptor expression. Life Sci2016; 159:148-152.

108. Ak G, Buyukberber S, Sevinc A, Turk HM, Ates M, Sari R, et al. The relation between plasma endothelin-1 levels and metabolic control, risk factors, treatment modalities, and diabetic microangiopathy in patients with Type 2 diabetes mellitus. J Diabetes Complications2001; 15 (3):150-157.

109. Leblanc AJ, Chen B, Dougherty PJ, Reyes RA, Shipley RD, Korzick DH, et al. Divergent effects of aging and sex on vasoconstriction to endothelin in coronary arterioles. Microcirculation2013; 20 (5):365-376.

110. Stanhewicz AE, Wenner MM, Stachenfeld NS. Sex differences in endothelial function important to vascular health and overall cardiovascular disease risk across the lifespan. Am J Physiol Heart Circ Physiol2018; 315 (6):H1569-H1588.

111. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. J Am Coll Cardiol1994; 24 (2):471-476.

112. Papanek PE, Rieder MJ, Lombard JH, Greene AS. Gender-specific protection from microvessel rarefaction in female hypertensive rats. Am J Hypertens1998; 11 (8 Pt 1):998-1005.

113. Huxley VH, Wang J. Cardiovascular sex differences influencing microvascular exchange. Cardiovasc Res2010; 87 (2):230-242.

114. Mark S, Scott GB, Donoviel DB, Leveton LB, Mahoney E, Charles JB, et al. The impact of sex and gender on adaptation to space: executive summary. J Womens Health (Larchmt)2014; 23 (11):941-947.

115. Harm DL, Jennings RT, Meck JV, Powell MR, Putcha L, Sams CP, et al. Invited review: gender issues related to spaceflight: a NASA perspective. J Appl Physiol (1985)2001; 91 (5):2374-2383.

116. Schlager O, Giurgea A, Hammer A, Charwat-Resl S, Margeta C, Mueller M, et al. Impact of age and gender on microvascular function. Eur J Clin Invest2014; 44 (8):766-774.

117. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, et al. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol2014; 63 (7):636-646.

118. Ohkuma T, Ninomiya T, Tomiyama H, Kario K, Hoshide S, Kita Y, et al. Brachial-Ankle Pulse Wave Velocity and the Risk Prediction of Cardiovascular Disease: An Individual Participant Data Meta-Analysis. Hypertension2017; 69 (6):1045-1052.

119. Kwak S, Kim HL, Lim WH, Seo JB, Kim SH, Zo JH, et al. Sex-specific associations of brachial-ankle pulse wave velocity with adverse cardiac remodeling and long-term cardiovascular outcome. J Hypertens2022; 40 (2):364-373.

120. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart J2008; 29 (21):2669-2680.

121. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Sex differences in the pharmacological treatment of hypertension: a review of population-based studies. J Hypertens1997; 15 (6):591-600.

122. Gasse C, Hense HW, Stieber J, Doring A, Liese AD, Heller G, et al. Factors associated with differences in antihypertensive drug treatment: results from the MONICA Augsburg Population Surveys 1989/90 and 1994/95. Soz Praventivmed2002; 47 (2):128-142.

123. Muiesan ML, Salvetti M, Rosei CA, Paini A. Gender Differences in Antihypertensive Treatment: Myths or Legends? High Blood Press Cardiovasc Prev2016; 23 (2):105-113.

124. Mitchell GF, Hwang SJ, Larson MG, Hamburg NM, Benjamin EJ, Vasan RS, et al. Transfer function-derived central pressure and cardiovascular disease events: the Framingham Heart Study. J Hypertens2016; 34 (8):1528-1534.

125. Lamarche F, Agharazii M, Madore F, Goupil R. Prediction of Cardiovascular Events by Type I Central Systolic Blood Pressure: A Prospective Study. Hypertension2021; 77 (2):319-327.

126. Janner JH, Godtfredsen NS, Ladelund S, Vestbo J, Prescott E. The association between aortic augmentation index and cardiovascular risk factors in a large unselected population. J Hum Hypertens2012; 26 (8):476-484.

127. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. Eur Heart J2010; 31 (15):1865-1871.

128. Sibiya MJ, Norton GR, Hodson B, Redelinghuys M, Maseko MJ, Majane OH, et al. Gender-specific contribution of aortic augmentation index to variations in left ventricular mass index in a community sample of African ancestry. Hypertens Res2014; 37 (11):1021-1027.

129. Narayan O, Davies JE, Hughes AD, Dart AM, Parker KH, Reid C, et al. Central aortic reservoir-wave analysis improves prediction of cardiovascular events in elderly hypertensives. Hypertension2015; 65 (3):629-635.

130. Peng X, Picone DS, Schultz MG, Cai G, Wake M, Burgner DP, et al. Brachial-cuff excess pressure is associated with carotid intima-media thickness among Australian children: a cross-sectional population study. Hypertens Res2021; 44 (5):541-549.

131. Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NR, et al. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: an ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. J Am Coll Cardiol2010; 56 (1):24-30.

132. Schuetz P, Yano K, Sorasaki M, Ngo L, St Hilaire M, Lucas JM, et al. Influence of diabetes on endothelial cell response during sepsis. Diabetologia2011; 54 (5):996-1003.

133. Nussbaum C, Cavalcanti Fernandes Heringa A, Mormanova Z, Puchwein-Schwepcke AF, Bechtold-Dalla Pozza S, Genzel-Boroviczeny O. Early microvascular changes with loss of the glycocalyx in children with type 1 diabetes. J Pediatr2014; 164 (3):584-589 e581.

134. Dantas AP, Franco Mdo C, Silva-Antonialli MM, Tostes RC, Fortes ZB, Nigro D, et al. Gender differences in superoxide generation in microvessels of hypertensive rats: role of NAD(P)H-oxidase. Cardiovasc Res2004; 61 (1):22-29.

135. Chen Q, Williams R, Healy CL, Wright CD, Wu SC, O'Connell TD. An association between gene expression and better survival in female mice following myocardial infarction. J Mol Cell Cardiol2010; 49 (5):801-811.

136. Arnetz L, Ekberg NR, Alvarsson M. Sex differences in type 2 diabetes: focus on disease course and outcomes. Diabetes Metab Syndr Obes2014; 7:409-420.

137. Read SH, McAllister DA, Colhoun HM, Farran B, Fischbacher C, Kerssens JJ, et al. Incident ischaemic stroke and Type 2 diabetes: trends in incidence and case fatality in Scotland 2004-2013. Diabet Med2018; 35 (1):99-106.

138. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet2014; 383 (9933):1973-1980.

139. de Ritter R, Sep SJS, van der Kallen CJH, van Greevenbroek MMJ, de Jong M, Vos RC, et al. Sex differences in the association of prediabetes and type 2 diabetes with microvascular complications and function: The Maastricht Study. Cardiovasc Diabetol2021; 20 (1):102.

140. Guajardo I, Ayer A, Johnson AD, Ganz P, Mills C, Donovan C, et al. Sex differences in vascular dysfunction and cardiovascular outcomes: The cardiac, endothelial function, and arterial stiffness in ESRD (CERES) study. Hemodial Int2018; 22 (1):93-102.

141. Earle KA, Ng L, White S, Zitouni K. Sex differences in vascular stiffness and relationship to the risk of renal functional decline in patients with type 2 diabetes. Diab Vasc Dis Res2017; 14 (4):304-309.

142. Carnethon MR, Pu J, Howard G, Albert MA, Anderson CAM, Bertoni AG, et al. Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association. Circulation2017; 136 (21):e393-e423.

143. Graham G. Disparities in cardiovascular disease risk in the United States. Curr Cardiol Rev2015; 11 (3):238-245.

144. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, et al. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement--a survey of 12517 subjects. Atherosclerosis2003; 166 (2):303-309.

145. Bohm B, Hartmann K, Buck M, Oberhoffer R. Sex differences of carotid intima-media thickness in healthy children and adolescents. Atherosclerosis2009; 206 (2):458-463.

146. Karikkineth AC, AlGhatrif M, Oberdier MT, Morrell C, Palchamy E, Strait JB, et al. Sex Differences in Longitudinal Determinants of Carotid Intima Medial Thickening With Aging in a Community-Dwelling Population: The Baltimore Longitudinal Study on Aging. J Am Heart Assoc2020; 9 (22):e015396.

147. Stensland-Bugge E, Bonaa KH, Joakimsen O, Njolstad I. Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later : the Tromso study. Stroke2000; 31 (3):574-581.

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| **Table 1.** Global incidence and mortality of ischemic heart disease, stroke and atrial fibrillation for women and men. Data are age-standardized incidence and mortality rates per 100,000 people for 2019 [7]. | | |
|  | **Women** | **Men** |
| **Ischemic heart disease** | | |
| Incidence | 198.5 (176.4 to 221.2) | 333.5 (297 to 371.9) |
| Mortality | 95.1 (83.9 to 103.1) | 144.6 (132.9 to 155) |
| **Stroke** | | |
| Incidence | 149.7 (135.6 to 166.6) | 151.1 (136.9 to 167.5) |
| Mortality | 73.5 (65.2 to 80.7) | 96.4 (87.6 to 104.2) |
| **Atrial fibrillation** | | |
| Incidence | 53.5 (41.1 to 67.7) | 60.8 (47.1 to 76.3) |
| Mortality | 4.4 (3.7 to 5.1) | 4.3 (3.5 to 5.3) |

|  |  |
| --- | --- |
| **Table 2.** Sex differences in structural, pressure and flow waveform variables relevant to the heart, macrovasculature and microvasculature. | |
| **Variable** | **Women, compared with men** |
| **Heart** | |
| Left ventricular mass | ↓ from the 2nd decade of life, ↔ after indexing to body size [41,43] |
| Left ventricular wall thickness | ↓ [44] |
| Left ventricular outflow tract | ↓ |
| Left ventricular ejection fraction | ↑ [52,53] |
| E/e′ ratio | ↑ [44,55]. |
| Left ventricular outflow tract flow velocity | ↔ [55] |
| Coronary artery diameter | ↓ including after adjustment for left ventricular mass and body size [45,46] |
| Coronary flow reserve | ↓ [59] |
| Index of microcirculatory resistance | ↔ [57] |
|  |  |
| **Macrovasculature** | |
| Aortic root size | ↔ in children, differences explained by body size [64]  ↓ in people 15 years of age and older, including after adjustment for body surface area [65]. |
| Carotid-to-femoral PWV | ↓ but a near negligible difference after adjustment for quadratic age and blood pressure differences [69,70]  ↑ longitudinal rate of change [71] |
| Brachial-to-ankle PWV | ↓ [144] |
| Cardio-ankle vascular index | ↓ [76] |
| Carotid diameter | ↓ including after adjustment for body and neck size |
| Carotid intima media thickness | ↔ in children aged 4-5 years then ↓ [68,145-147] |
| Invasive aortic systolic BP | ↑ select sample of patients undergoing coronary angiography aged 40 – 89 years [79] |
| Augmentation index | ↑ from 8 years of age to the 8th decade of life [80,81,89] |
| Subendocardial viability ratio | ↓ from 11 years to 90 years of age [89] |
| Reservoir pressure integral | ↑ unadjusted, ↔ after adjustment for height [85] |
| Excess pressure integral | ↑ unadjusted, ↔ after adjustment for height [85] |
| Excess pressure integral / total pressure integral | ↑ in women > 51 years of age including after adjustment for height [85] |
| Reservoir pressure integral / total pressure integral | ↑ in women > 51 years of age including after adjustment for height [85] |
| Forward compression wave | ↓ [94] |
| Backward compression wave | ↔ [94] |
| Forward decompression wave | ↓ [94] |
| **Microvasculature** | |
| Endothelial function | ↔ [97] |
| PWV, pulse wave velocity, BP, blood pressure  ↑, higher in women compared to men; ↓, lower in women compared to men; ↔, no sex difference | |