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

**Invited Review**

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**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.

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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) |

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| **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  |