Sex differences in cardiovascular ageing

Allison A Merz[1] and **Susan Cheng**[1,2]

[1]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Framingham Heart Study, Framingham, Massachusetts, USA

Abstract

Despite recent progress in identifying and narrowing the gaps in cardiovascular outcomes between men and women, general understanding of how and why cardiovascular disease presentations differ between the sexes remains limited. Sex-specific patterns of cardiac and vascular ageing play an important role and, in fact, begin very early in life. Differences between the sexes in patterns of age-related cardiac remodelling are associated with the relatively greater prevalence in women than in men of heart failure with preserved ejection fraction. Similarly, sex variation in how vascular structure and function change with ageing contributes to differences between men and women in how coronary artery disease manifests typically or atypically over the adult life course. Both hormonal and non-hormonal factors underlie sex differences in cardiovascular ageing and the development of age-related disease. The midlife withdrawal of endogenous oestrogen appears to augment the age-related increase in cardiovascular risk seen in postmenopausal compared with premenopausal women. However, when compared with intrinsic biological differences between men and women that are present throughout life, this menopausal transition may not be as substantial an actor in determining cardiovascular outcomes.

INTRODUCTION

In the decades to come, our society will face greater social, economic and medical challenges due to increasing longevity of the average individual and, in turn, the growing number of older adults in the population at large. The number of persons above age 60 will surpass two billion by the year 2015 worldwide.[1] While rapid growth of the older demographic is a well-recognised phenomenon, the health-related heterogeneity of older adults is often under appreciated. Despite the fact that many adults experience increasing morbidity with ageing, many others are able to reach even their 90s in excellent health.[2] While almost 10% of adults aged 80 years or older will die within the next 2 years, over half will live on for another decade or more.[3] Sex differences are a major contributor to the

clinical heterogeneity of older age, especially with respect to cardiovascular disease which is still the leading cause of illness and death in the Western world.

Cardiovascular disease remains essentially an age-related condition in both men and women. Progressive age-related changes in cardiac and vascular anatomy and physiology—collectively referred to as 'cardiovascular ageing'—interact with cumulative exposure to traditional risk factors to impact an individual's increasing likelihood of developing cardiovascular disease over the life course.[4] Much work has been done to understand how these changes predispose to eventual disease at an accelerated rate in some individuals and with more delayed timing in others. Herein, we review the current literature describing sex-specific patterns of cardiac and vascular ageing, and discuss how these patterns likely impact the variations in disease presentations and outcomes that are persistently seen between men and women.

CARDIAC AGEING

Over the life course, the heart progressively remodels and patterns of cardiac remodeling differ between the sexes (table 1 and figure 1). Typical age-related cardiac remodeling involves increasing left ventricular (LV) wall thickness, decreasing LV dimensions and increasing concentricity, all of which are associated with traditional risk factors and incidence of adverse cardiovascular events.[56] At all ages, men compared with women have greater absolute values of LV mass, wall thickness and cavity dimensions.[6] However, with advancing age and adjusting for body size, women experience a more accelerated increase in LV wall thickness than men, especially in the setting of risk factors such as hypertension and diabetes.[7] Furthermore, women experience more age-related concentric remodeling than men,[8] which may be accompanied by more pronounced diastolic dysfunction.[9] With respect to cardiac systolic function, LV ejection fraction (EF) increases with age in both sexes, and this increase is more pronounced in women.[10] Women have also been shown to exhibit greater age-related systolic torsion and circumferential shortening of the LV.[11] Together, these findings could be due to an augmented pulsatile load in older women[12] and differential gene expression of extracellular matrix components in pressure overload states.[13] Given that functional oestrogen receptors reside in the myocardium, withdrawal of oestrogens at the time of menopause could also contribute to age-related LV remodeling in women.[14]

Sex differences in cardiac ageing patterns likely contribute to differences in cardiac outcomes (figure 2). Although most data on heart failure (HF) prognosis are derived from randomised trials, wherein women are historically underrepresented, the majority of available evidence suggests that women compared to men with HF have an overall better long-term prognosis.[15–17] In particular, the more pronounced concentric remodelling seen in older women than men, along with potentially greater diastolic dysfunction,[918] could contribute to the higher incidence of HF with preserved EF (HFPEF) than reduced EF (HFREF) that is consistently seen more in women than in men.[19] In turn, greater rates of HFPEF could account for better HF outcomes seen in women than in men, given that HFPEF is just as likely as HFREF to lead to HF hospitalisations but less likely to lead to HF deaths. Indeed, considerable evidence suggests that the greater prevalence of HFPEF in women contributes to the female survival benefit. Some studies indicate that the female

survival benefit for women with HF persists even after adjusting for LVEF and HF aetiology,[16] suggesting that sex differences in age-related biology may also contribute to differences in HF outcomes. Accordingly, biomarkers of inflammation (GDF-15, TNF-αR1a), oxidative stress (MPO), remodelling (syndecan, galectin 3), cariomyocyte stretch (NTpro-BNP) and arteriosclerosis (ESAM) have all been shown to have sex-specific prognostic value in HF[20]; however, the extent to which these findings reflect the greater prevalence of HFPEF in women as opposed to distinct differences between the sexes in HF pathophysiology remains unclear and warrants further investigation.

VASCULAR AGEING

As seen with patterns of cardiac ageing, patterns of vascular ageing also differ between the sexes across the life course and these differences have implications for overt disease risk (table 1 and figure 3). Age-related changes in vascular function generally include increasing endothelial dysfunction and arterial stiffness, accompanied by increasing systolic blood pressure and pulse pressure.[4] Men have greater endothelial dysfunction and arterial stiffness than women across the age spectrum until the sixth decade, when age-related arterial dysfunction progresses at a faster rate in women. Whereas premenopausal women have lower autonomic tone and baroreceptor response as well as better overall vascular function than men of similar age,[21][22] postmenopausal women have stiffer arteries than their male counterparts[23] even after accounting for body size and aortic diameter.[24] These vascular differences are clinically reflected in patterns of hypertension prevalence over the life course: prior to age 45, more men than women have hypertension; between 45 and 64, hypertension rates are similar between the sexes; and at age 65 and above, more women than men are hypertensive (figure 4C).[25]

Subclinical changes in arterial structure also differ between men and women. Carotid intima-media thickening (CIMT), coronary artery calcification (CAC) and carotid and femoral atherosclerotic plaques all increase in prevalence with advancing age.[26–28] Although more common in men than in women through midlife, sex differences in the prevalence of subclinical atherosclerosis and coronary calcium are diminished in later life.[29][30] Nonetheless, men are overall more likely than women to have severe plaques with associated flow disturbance[30] as well as high-risk morphologic plaque characteristics[31] such as a thin fibrous cap and lipid-rich or necrotic core even after controlling for potential confounders. Interestingly, progression of CIMT is more consistently associated with traditional risk factors in men.[32] Because they are highly correlated with traditional risk factors, neither CIMT nor CAC add much prognostic value on top of risk factors in men[33]; by contrast, the presence of CAC in women improves risk prediction of CVD in traditionally defined low-risk women[34] and in older women but not older men.[33] These findings offer pathophysiological insight into why men are more likely than women to develop typical rather than atypical forms of both subclinical as well as clinical atherosclerotic disease across the lifespan.

Sex differences in vascular ageing patterns appear to underlie the extent to which men versus women tend to present with typical versus atypical atherosclerotic disease (figure 2). Classic coronary artery disease (CAD) symptoms and diagnostic findings are relatively consistent

across the lifespan in men but vary with age in women. In women, the prevalence of typical obstructive coronary disease is low prior to menopause and then increases dramatically after age 50, affecting only 14% of women below age 45 and up to 79% of women age 75 or older.[35] By contrast, non-obstructive CAD is substantially more common in women than in men throughout life and especially in younger age. In the presence of non-obstructive CAD, women are more likely to have microvascular and/or endothelial dysfunction, in addition to conditions such as epicardial and microvascular spasm, myocardial bridging and conduit vessel stiffening, all of which can lead to myocardial ischaemia.[36] Women have also been found to have thicker arteriolar walls than men in the presence of CAD.[37] Accordingly, women are more likely than men to experience angina, ischaemia and acute coronary syndrome in the presence of non-obstructive CAD.[36] It has been proposed that both microvascular disease and epicardial atherosclerosis originate from arterial intimal injury but develop preferentially in women versus men based on sex differences in vascular remodeling and reactivity related to hormonal exposures and risk factor clustering.[38] The relatively greater prevalence of non-obstructive CAD in women, which is less easily diagnosed and treated than obstructive CAD,[36 39] may well contribute to the consistently reported worse outcomes related to acute coronary syndromes in women than in men[40]. Although men are more frequently diagnosed with acute coronary syndromes each year,[41] women have an almost double mortality rate at 30 days[42] and a 25% greater odds of having an adverse cardiac event at 6 months.[43] Notably, women up to 55 years old represent a major demographic in whom CAD mortality has not markedly declined in recent decades.[44]

BEYOND THE MENOPAUSAL TRANSITION

The more pronounced age-related cardiovascular risk seen in postmenopausal compared with premenopausal women is commonly attributed to the midlife withdrawal of endogenous sex steroids, often referred to as the 'menopausal transition'. However, recent experimental and population data suggest that hormonal changes alone are unlikely to completely explain observed sex differences in cardiovascular presentations and outcomes. On the one hand, the potential relationship between endogenous oestrogen and cardiovascular disease is supported by several lines of evidence[45]: the existence of oestrogen receptors in the myocardium, vascular endothelium, smooth muscle and adventitial cells[46]; genomic and non-genomic effects of oestrogen on endothelial and vascular smooth muscle cells[47] and an inverse association between brachial artery flow-mediated dilation and years since menopause[48] coupled with a positive association between serum E_2 levels and brachial artery flow-mediated dilation in postmenopausal women.[49] On the other hand, only a limited number of longitudinal studies have investigated associations between circulating sex steroids, sex hormone binding globulin levels and incident CAD with variable results.[44 50] In addition, a meta-analysis of observational studies found no convincing associations between postmenopausal status or average age of menopause and outcomes.[51]

The extent to which menopause versus biological ageing processes contribute to age-related cardiovascular risk in women remains a subject of ongoing debate. The question is methodologically challenging to investigate given the concurrent timing and interrelatedness of these two processes.[52] Data from several large-scale transition and cohort studies offer some insights. In the Study of Women Across the Nation, only select lipid measures

including LDL cholesterol and apolipo-protein B changed within a year of a woman's last menstrual period; common cardiovascular risk factors changed in association with age, but not with menopause.[53] Similarly, data from the Framingham Heart Study have suggested that cardiovascular risk status, represented by weight, blood pressure and total cholesterol level, influences age at menopause and not vice versa.[54] Nonetheless, it should be recognised that risk factor levels in women can indeed change around the time of menopause, and in some cases dramatically,[55] likely related to the combination of chronologic ageing and the menopausal transition. Thus, irrespective of the ultimate cause, women should be made aware that their cardiovascular risk is likely to increase around the time of menopause and women should be counselled regarding the importance of risk factor modification and therapeutic lifestyle changes. Risk factor monitoring should be prioritised to identify women who may benefit from pharmacologic risk factor management.

With respect to the possible role of menopause in conferring cardiovascular risk, additional insights can be gained from examining age-based trends in the incidence of breast cancer, a condition that is biologically more clearly related to endogenous oestrogen levels. The Women's Health Initiative (WHI) demonstrated that breast cancer incidence and related mortality were lower for postmenopausal women who took oestrogen alone as compared with placebo,[56][57] regardless of when hormone therapy was initiated. By contrast, major trials of hormone therapy in menopause including the WHI have demonstrated no obvious reduction in either subclinical CVD[58] or overt CVD outcomes,[56][59][60] although with some evidence suggesting that hormone therapy initiated at an earlier versus later age could confer more protective than harmful cardiovascular effects.[61] In fact, a fair amount of data support the hypothesis that the cardioprotective effects of hormone therapy are time dependent and more beneficial than harmful if started in the perimenopausal or early postmenopausal period rather than late after menopause. Accordingly, experimental and physiology data also suggest differential effects of oestrogen on vascular reactivity depending on when therapy is initiated with respect to age and menopausal status.[62]

Population studies also offer additional insights regarding the contrasting patterns of age-related cardiovascular versus breast cancer risk. Two decades ago, Elizabeth Barrett-Connor analysed mortality statistics and suggested that menopause itself has no discernible effect on the exponential increase in coronary death with age, given that coronary death rates in women do not markedly accelerate after menopause, in contrast to the relatively abrupt drop in deaths attributable to breast cancer.[63] Updated national mortality data from the US Centers for Disease Control continue to support this observation (figure 4),[64] where the apparent perimenopausal increase in CAD mortality in women may actually be more reflective of a relative decrease in CAD mortality in men, beginning around age 45. Thus, it has been suggested that the observed gender gap is not primarily due to oestrogen deficiency but instead due to CAD mortality rates that tend to decrease in men while continuing to steadily rise in women with advancing age.[65] Importantly, observational studies have noted that the sexual dimorphism in both subclinical and clinical cardiovascular phenotypes exists in prepuberty,[66–68] suggesting that intrinsic non-hormonal factors acting throughout the life course may play a more important role than midlife hormonal shifts, with respect to sex differences in cardiovascular risk.

CONCLUSIONS

Over the past two decades, tremendous progress has been made in identifying and narrowing the gaps in cardiovascular outcomes observed between men and women. Despite this progress, general understanding of how and why manifestations of cardiovascular disease differ between the sexes remains limited. Evidence to date indicates that the development and progression of cardiovascular disease varies between women and men due to both intrinsic biological sex differences as well as sex differences in how age-related changes in cardiac and vascular anatomy and physiology progress over the life course. Although men are more susceptible to typical subclinical and clinical vascular changes beginning earlier in life, women are more at risk for atypical vascular disease in general in addition to more accelerated age-related vascular changes at midlife—predisposing them to both typical and atypical manifestations in older age. Given the acceleration in arterial stiffness and subclinical atherosclerosis that can be seen in perimenopausal women, in particular, coupled with changes in cardiac remodeling and diastolic function, a key target for risk factor modification is hypertension. Ideally, hypertension or even prehypertension should be targeted for treatment well prior to the onset of menopause, if present. Targeting premature chronic elevations in arterial pressure and afterload may, in turn, prove to be the most efficacious strategy for preventing HFPEF in older women as well as in older men. It is well recognised that hormone therapy should not be used for long-term chronic disease prevention, as it may increase cardiovascular risk in some older women and especially women farther out from menopause. As it turns out, avoidance of hormone therapy in ageing women is not likely to represent a substantially missed opportunity. While considerable evidence has pointed to the influence of the menopausal withdrawal of endogenous oestrogen on the increase in age-related cardiovascular risk in postmenopausal compared with premenopausal women, chronologic ageing processes acting on top of inherent biological differences between men and women likely play a more important role.

Acknowledgments

References

1. United Nations DoEaSA. Population Division World Population Ageing 2013. 2013 ST/ESA/SER.A/348.

2. Lowsky DJ, Olshansky SJ, Bhattacharya J, et al. Heterogeneity in healthy aging. J Gerontol A Biol Sci Med Sci. 2014; 69:640–9. [PubMed: 24249734]

3. Arias E. United States life tables, 2010. Natl Vital Stat Rep. 2014; 63:1–63.

4. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. Circulation. 2003; 107:139–46. [PubMed: 12515756]

5. Lieb W, Xanthakis V, Sullivan LM, et al. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham offspring study. Circulation. 2009; 119:3085–92. [PubMed: 19506113]
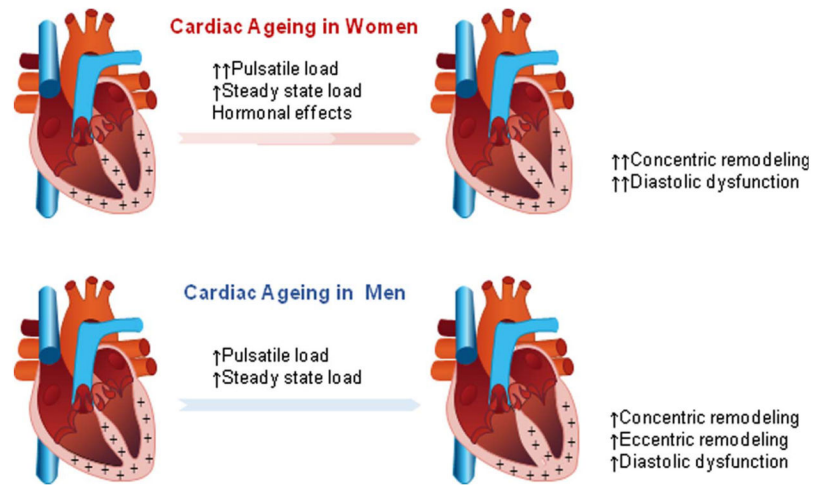
6. Cheng S, Fernandes VR, Bluemke DA, et al. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. Circ Cardiovasc Imaging. 2009; 2:191–8. [PubMed: 19808592]

7. Cheng S, Xanthakis V, Sullivan LM, et al. Correlates of echocardiographic indices of cardiac remodeling over the adult life course: longitudinal observations from the Framingham Heart Study. Circulation. 2010; 122:570–8. [PubMed: 20660804]

8. Krumholz HM, Larson M, Levy D. Sex differences in cardiac adaptation to isolated systolic hypertension. Am J Cardiol. 1993; 72:310–3. [PubMed: 8342510]

9. Gori M, Lam CS, Gupta DK, et al. Sex-specific cardiovascular structure and function in heart failure with preserved ejection fraction. Eur J Heart Fail. 2014; 16:535–42. [PubMed: 24574260]

10. Gebhard C, Stähli BE, Gebhard CE, et al. Age- and gender-dependent left ventricular remodeling. Echocardiography. 2013; 30:1143–50. [PubMed: 23742210]

11. Yoneyama K, Gjesdal O, Choi EY, et al. Age, sex, and hypertension-related remodeling influences left ventricular torsion assessed by tagged cardiac magnetic resonance in asymptomatic individuals: the multi-ethnic study of atherosclerosis. Circulation. 2012; 126:2481–90. [PubMed: 23147172]

12. Hayward CS, Kelly RP. Gender-related differences in the central arterial pressure waveform. J Am Coll Cardiol. 1997; 30:1863–71. [PubMed: 9385920]

13. Gerdts E, Okin PM, de Simone G, et al. Gender differences in left ventricular structure and function during antihypertensive treatment: the Losartan Intervention for Endpoint Reduction in Hypertension Study. Hypertension. 2008; 51:1109–14. [PubMed: 18259011]

14. Mahmoodzadeh S, Eder S, Nordmeyer J, et al. Estrogen receptor alpha up-regulation and redistribution in human heart failure. FASEB J. 2006; 20:926–34. [PubMed: 16675850]

15. Martinez-Sellés M, Doughty RN, Poppe K, et al. Gender and survival in patients with heart failure: interactions with diabetes and aetiology. Results from the MAGGIC individual patient meta-analysis. Eur J Heart Fail. 2012; 14:473–9. [PubMed: 22402958]

16. O'Meara E, Clayton T, McEntegart MB, et al. Sex differences in clinical characteristics and prognosis in a broad spectrum of patients with heart failure: results of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. Circulation. 2007; 115:3111–20. [PubMed: 17562950]

17. Parashar S, Katz R, Smith NL, et al. Race, gender, and mortality in adults > or =65 years of age with incident heart failure (from the Cardiovascular Health Study). Am J Cardiol. 2009; 103:1120–7. [PubMed: 19361600]

18. Kane GC, Karon BL, Mahoney DW, et al. Progression of left ventricular diastolic dysfunction and risk of heart failure. JAMA. 2011; 306:856–63. [PubMed: 21862747]

19. Lam CS, Donal E, Kraigher-Krainer E, et al. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail. 2011; 13:18–28. [PubMed: 20685685]

20. Meyer S, van der Meer P, van Deursen VM, et al. Neurohormonal and clinical sex differences in heart failure. Eur Heart J. 2013; 34:2538–47. [PubMed: 23666250]

21. Barnett SR, Morin RJ, Kiely DK, et al. Effects of age and gender on autonomic control of blood pressure dynamics. Hypertension. 1999; 33:1195–200. [PubMed: 10334811]

22. Christou DD, Jones PP, Jordan J, et al. Women have lower tonic autonomic support of arterial blood pressure and less effective baroreflex buffering than men. Circulation. 2005; 111:494–8. [PubMed: 15687139]

23. Mitchell GF, Gudnason V, Launer LJ, et al. Hemodynamics of increased pulse pressure in older women in the community-based Age, Gene/Environment Susceptibility-Reykjavik Study. Hypertension. 2008; 51:1123–8. [PubMed: 18259005]

24. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension. 2004; 43:1239–45. [PubMed: 15123572]

25. National Center for Health Statistics. [accessed 27 November 2015] Health, United States, 2014: with Special Feature on Adults Aged 55–64. 2015. http://www.cdc.gov/nchs/data/hus/hus14.pdf

26. Howard G, Sharrett AR, Heiss G, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke. 1993; 24:1297–304. [PubMed: 8362421]

27. McClelland RL, Chung H, Detrano R, et al. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006; 113:30–7. [PubMed: 16365194]

28. Kelley RE, Dasmahapatra P, Wang J, et al. Prevalence of atherosclerotic plaque in young and middle-aged asymptomatic individuals: the Bogalusa heart study. South Med J. 2011; 104:803–8. [PubMed: 22089358]

29. Janowitz WR, Agatston AS, Kaplan G, et al. Differences in prevalence and extent of coronary artery calcium detected by ultrafast computed tomography in asymptomatic men and women. Am J Cardiol. 1993; 72:247–54. [PubMed: 8342500]

30. Prati P, Vanuzzo D, Casaroli M, et al. Prevalence and determinants of carotid atherosclerosis in a general population. Stroke. 1992; 23:1705–11. [PubMed: 1448818]

31. Ota H, Reeves MJ, Zhu DC, et al. Sex differences in patients with asymptomatic carotid atherosclerotic plaque: in vivo 3. 0-T magnetic resonance study. Stroke. 2010; 41:1630–5. [PubMed: 20616325]

32. Stensland-Bugge E, Bønaa KH, Joakimsen O, et al. Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later: the Tromso study. Stroke. 2000; 31:574–81. [PubMed: 10700488]

33. Elias-Smale SE, Kavousi M, Verwoert GC, et al. Common carotid intima-media thickness in cardiovascular risk stratification of older people: the Rotterdam Study. Eur J Prev Cardiol. 2012; 19:698–705. [PubMed: 21697209]

34. Lakoski SG, Greenland P, Wong ND, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: the multi-ethnic study of atherosclerosis (MESA). Arch Intern Med. 2007; 167:2437–42. [PubMed: 18071165]

35. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol. 2006; 47(3 Suppl):S21–9. [PubMed: 16458167]

36. Pepine CJ, Ferdinand KC, Shaw LJ, et al. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. J Am Coll Cardiol. 2015; 66:1918–33. [PubMed: 26493665]

37. Campbell DJ, Somaratne JB, Jenkins AJ, et al. Differences in myocardial structure and coronary microvasculature between men and women with coronary artery disease. Hypertension. 2011; 57:186–92. [PubMed: 21135353]

38. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. J Am Coll Cardiol. 2009; 54:1561–75. [PubMed: 19833255]

39. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012; 60:e44–e164. [PubMed: 23182125]

40. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016 Jan 25.

41. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation. 2014; 129:e28–e292. [PubMed: 24352519]

42. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. Jama. 2009; 302:874–82. [PubMed: 19706861]

43. Dey S, Flather MD, Devlin G, et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009; 95:20–6. [PubMed: 18463200]

44. Wilmot KA, O'Flaherty M, Capewell S, et al. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. Circulation. 2015; 132:997–1002. [PubMed: 26302759]

45. Crandall CJ, Barrett-Connor E. Endogenous sex steroid levels and cardiovascular disease in relation to the menopause: a systematic review. Endocrinol Metab Clin North Am. 2013; 42:227–53. [PubMed: 23702399]

46. Vitale C, Fini M, Speziale G, et al. Gender differences in the cardiovascular effects of sex hormones. Fundam Clin Pharmacol. 2010; 24:675–85. [PubMed: 20199585]

47. Qiao X, McConnell KR, Khalil RA. Sex steroids and vascular responses in hypertension and aging. Gend Med. 2008; 5(Suppl A):S46–64. [PubMed: 18395683]

48. Vitale C, Mercuro G, Cerquetani E, et al. Time since menopause influences the acute and chronic effect of estrogens on endothelial function. Arterioscler Thromb Vasc Biol. 2008; 28:348–52. [PubMed: 18063808]

49. Li X-P, Zhou Y, Zhao S-P, et al. Effect of endogenous estrogen on endothelial function in women with coronary heart disease and its mechanism. Clin Chim Acta. 2004; 339:183–8. [PubMed: 14687908]

50. Barrett-Connor E, Goodman-Gruen D. Prospective study of endogenous sex hormones and fatal cardiovascular disease in postmenopausal women. BMJ. 1995; 311:1193–6. [PubMed: 7488894]

51. Atsma F, Bartelink ML, Grobbee DE, et al. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. Menopause. 2006; 13:265–79. [PubMed: 16645540]

52. Bittner V. Menopause, age, and cardiovascular risk: a complex relationship. J Am Coll Cardiol. 2009; 54:2374–5. [PubMed: 20082926]

53. Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? J Am Coll Cardiol. 2009; 54:2366–73. [PubMed: 20082925]

54. Kok HS, van Asselt KM, van der Schouw YT, et al. Heart disease risk determines menopausal age rather than the reverse. J Am Coll Cardiol. 2006; 47:1976–83. [PubMed: 16697313]

55. Mikkola TS, Gissler M, Merikukka M, et al. Sex differences in age-related cardiovascular mortality. PLoS ONE. 2013; 8:e63347. [PubMed: 23700418]

56. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288:321–33. [PubMed: 12117397]

57. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol. 2012; 13:476–86. [PubMed: 22401913]

58. Harman, SM. Effects of Oral Conjugated Estrogen or Transdermal Estradiol Plus Oral Progesterone Treatment on Common Carotid Artery Intima Media Thickness (CIMT) & Coronary Artery Calcium (CAC) in Menopausal Women: Initial Results from the Kronos Early Estrogen Prevention Study (KEEPS). Orlando, FL: The North American Menopause Society; 2012.

59. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280:605–13. [PubMed: 9718051]

60. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6. 8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002; 288:49–57. [PubMed: 12090862]

61. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465–77. [PubMed: 17405972]

62. Giordano S, Hage FG, Xing D, et al. Estrogen and Cardiovascular Disease: Is Timing Everything? Am J Med Sci. 2015; 350:27–35. [PubMed: 26110752]

63. Barrett-Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. Circulation. 1997; 95:252–64. [PubMed: 8994444]

64. Centers for Disease Control and Prevention. [accessed 18 May 2015] Current Multiple Cause of Death Data. http://wonder.cdc.gov/mcd.html

65. Vaidya D, Becker DM, Bittner V, et al. Ageing, menopause, and ischaemic heart disease mortality in England, Wales, and the United States: modelling study of national mortality data. BMJ. 2011; 343:d5170. [PubMed: 21896608]

66. Guillaume M, Lapidus L, Lambert A. Differences in associations of familial and nutritional factors with serum lipids between boys and girls: the Luxembourg Child Study. Am J Clin Nutr. 2000; 72:384–8. [PubMed: 10919931]

67. Urbina EM, Williams RV, Alpert BS, et al. Noninvasive assessment of subclinical atherosclerosis in children and adolescents: recommendations for standard assessment for clinical research: a scientific statement from the American Heart Association. Hypertension. 2009; 54:919–50. [PubMed: 19729599]

68. Böhm B, Hartmann K, Buck M, et al. Sex differences of carotid intima-media thickness in healthy children and adolescents. Atherosclerosis. 2009; 206:458–63. [PubMed: 19389672]

69. Redfield MM, Jacobsen SJ, Borlaug BA, et al. Age- and gender-related ventricular-vascular stiffening: a community-based study. Circulation. 2005; 112:2254–62. [PubMed: 16203909]

Cardiac Ageing in Women

↑↑Pulsatile load
↑Steady state load
Hormonal effects

↑↑Concentric remodeling
↑↑Diastolic dysfunction

Cardiac Ageing in Men

↑Pulsatile load
↑Steady state load

↑Concentric remodeling
↑Eccentric remodeling
↑Diastolic dysfunction

Figure 1.
Patterns of cardiac ageing in men and women. '+' symbols represent the presence of oestrogen receptors in the myocardium (including cardiac myocytes and fibroblasts).
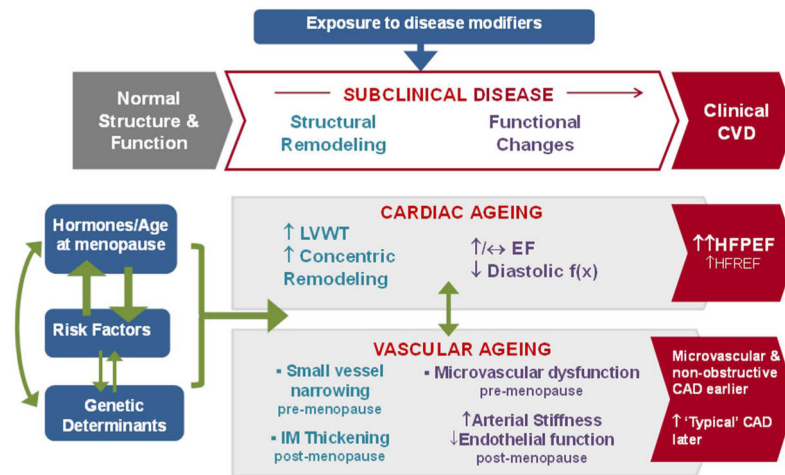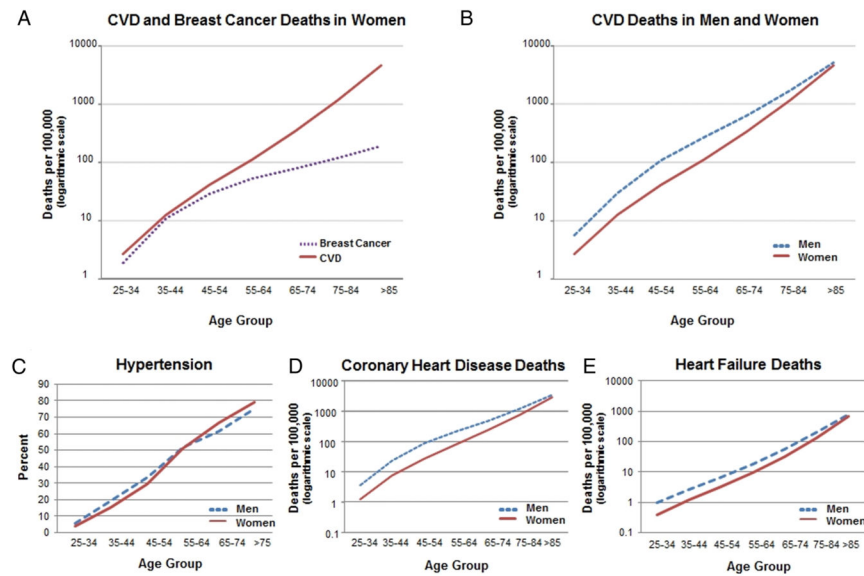
Figure 2.
Cardiac and vascular structural and functional ageing processes and the progression to disease in women. Throughout the life course, subclinical changes in cardiac and vascular structure and function interact with traditional pathophysiological disease mechanisms to impact an individuals increasing likelihood of developing disease across the life course. Female-specific disease modifiers and structural and functional changes predispose to different presentations and outcomes compared with men. CAD, coronary artery disease; EF, ejection fraction; HFPEF, heart failure with preserved EF; HFREF, heart failure with reduced EF.
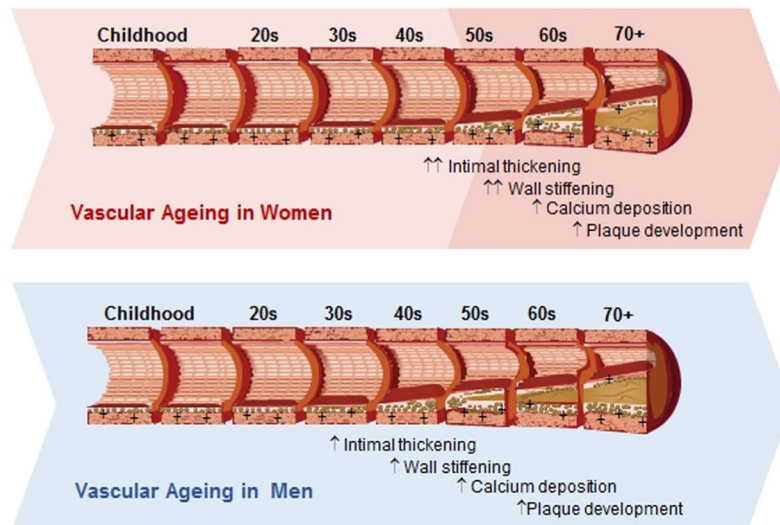
Figure 3.
Patterns of vascular ageing in men and women. '+' symbols represent the presence of oestrogen receptors in the arterial vasculature (including endothelium, smooth muscle cells and extracellular matrix).

Figure 4.

Age-specific death rates attributed to cardiovascular disease and breast cancer and prevalence of hypertension, compiled from US Centers for Disease Control and Prevention data collected from 1999 to 2013. In women, the age-specific death rate due to breast cancer decreases around the time of menopause whereas the age-specific cardiovascular death rate increases steadily across the lifespan (A). In men, cardiovascular death rates decline after midlife whereas continuing to steadily increase across the lifespan in women (B). Prevalence of hypertension is greater in men prior to age 45, similar between the sexes between 45 and 64, and greater in women above age 65 (C). Age-specific death rates for coronary heart disease (D) and heart failure (E).

Table 1

Patterns of cardiac and vascular ageing in men and women

Men	Women	Comments
Cardiac (LV) structure		
• Greater absolute values of LV mass, wall thickness and cavity dimensions at all ages[5]	• More accelerated increases in LV wall thickness, especially in the setting of risk factors such as hypertension and diabetes[7] • More age-related concentric remodelling[8]	Differences could be due to: • augmented pulsatile load in older women[12] • differential gene expression of extracellular matrix components in pressure overload states[13] • withdrawal of oestrogens at the time of menopause (given functional ERs in the myocardium)[14]
Cardiac (LV) function		
• Earlier onset of impaired systolic pump performance • Relatively less impairment in diastolic function[10]	• Greater age-related increases in EF • Greater age-related systolic torsion and circumferential shortening of the LV[11] • Later onset of impaired systolic pump performance[10] • Greater impairment in diastolic function	• Greater age-related concentric remodeling may be accompanied by more pronounced diastolic dysfunction in women[9]
Arterial structure		
• CIMT,[26] CAC,[27] and atherosclerotic plaques[28] are all more common in men than in women in young adulthood and middle age	• CIMT,[26] CAC,[27] and atherosclerotic plaques[28] prevalence increases later in life in women	• CIMT progression is more consistently associated with traditional risk factors in men[32] • Presence of CAC in women improves risk prediction of CVD in low-risk women and older women but not older men[33][34] • Men are more likely to have more severe plaque and plaques with more high-risk features[31]
Arterial function		
• Greater endothelial dysfunction and arterial stiffness until the sixth decade[21]	• Endothelial dysfunction and arterial stiffness increase postmenopause[24]	• Ventricular–vascular coupling is more pronounced in women; may also contribute to their higher incidence of HFPEF[69]

CAC, coronary artery calcification; CIMT, carotid intima-media thickening; EF, ejection fraction; HFPEF, heart failure with preserved EF; LV, left ventricular.