



Review

Sex differences in mechanisms, presentation and management of ischaemic heart disease

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ABSTRACT

Ischaemic heart disease (IHD) is the leading cause of death in women as in men, although presentation in women is on average 7–10 years later. Recent temporal trends show declining IHD incidence and mortality among men but not among women. Other gender differences concern the prevalence of underlying mechanisms. Women more frequently than men have nonobstructive epicardial artery disease, nonatherosclerotic spontaneous coronary artery dissection, stress cardiomyopathy, plaque erosion, microvascular dysfunction, and a heavier risk factor burden, even after adjustment for age. Atypical symptoms of IHD are more common in women. The crude outcomes of both chronic and acute coronary syndromes are worse in women than in men, in relation to older age and comorbidities. After adjustments, in-hospital mortality after acute myocardial infarction is reported to remain higher among younger women compared to male peers. Such female vulnerability, in apparent contrast with the delayed average onset and lesser extent of epicardial atherosclerosis, likely reflects gender differences in early presentation, as well as in mechanisms, prevention, diagnosis, comorbidities, management, and response to treatment. Recognition and quality of care of IHD are still not the same for women and men.

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The myth that angina and heart attacks are “male diseases” is vanishing: cardio-cerebrovascular diseases are the major cause of death in both genders [1,2], accounting in Europe for 56% of deaths in women and 43% in men (Fig. 1A) [3,4]. Clinically manifest ischaemic heart disease (IHD) however develops 7–10 years later in women than in men [4–6]. Other gender-differences concern the mechanisms, presentations, and management of disease. The present review focuses on gender-specific aspects and possible reasons for disparities.

1. General considerations

1.1. Prevalence, incidence and temporal trends

The prevalence and incidence of IHD are reported to be lower in women than in men, increasing with age in both genders (Fig. 1B) [4,6]. However, at advanced ages women outnumber men, so the absolute number of female patients is actually greater [5]. Moreover, while the incidence and mortality of IHD are declining in men, this

is not the case for women [7]. The risk of heart disease in women is still underestimated owing to the misperception that females are not affected [8], while in fact it is estimated that 1 of 2 American women will die of heart disease or stroke, compared to 1 in 25 of breast cancer [9,10]. Gender-differences in the contribution of various pathophysiological processes, combined with suboptimal recognition of female specificities - such as smaller body size and weight, slower drug metabolism, and lower renal function - may explain sex-differences in presentation and outcomes of IHD. Of note, the gender-related presentations of stable and acute coronary syndromes (ACS) are evolving [11,12]: in the early Framingham Heart Study, begun in 1948, angina was the initial diagnosis of IHD in 61% of women and 38% of men, while men exhibited more often myocardial infarction (MI) or sudden death as first manifestation [13]; more recent data from the National Health and Nutrition Examination Surveys show that the prevalence of MI has increased in women aged 35–54 years and declined in similarly aged men [7]. These temporal trends may reflect multiple factors, including increasing awareness of female disease, unhealthy lifestyle changes among women, and management disparities favouring men. These issues have led the American Heart Association to develop women-specific recommendations for the prevention of cardiovascular disease (CVD) [14], with similar initiatives from the European

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Society of Cardiology [2,3].

1.2. Cardiovascular risk factors

For any given risk factor or combination, the likelihood of future adverse events is generally lower among apparently healthy women than among age-matched men, as illustrated by the European and American charts for estimating individual cardiovascular risk [5]. Hypertension however is more prevalent in older women than men and may explain the higher female prevalence of strokes, left ventricular (LV) hypertrophy, and heart failure with preserved ejection fraction [15,16]. Interestingly, the risk of fatal IHD in women with type 2 diabetes compared to non diabetic women has been reported to be 50% higher than in male counterparts [17]; this has been attributed to a greater prevalence of risk factors, inflammation, diffuse coronary atherosclerosis and small vessel disease in diabetic women than diabetic men, combined with treatment disparities favouring men [17–20]. According to the “higher risk factor burden hypothesis”, women, who *per se* are relatively protected against IHD, seem to require a heavier load of risk factors compared to men before developing IHD [5]. Accordingly, once IHD has developed, the prevalence of all risk factors except smoking is typically greater

among female than among age-matched male patients, given that IHD ‘selects’ women with a cluster of risk factors [5]. The Study Of Risk Factors For First Myocardial Infarction in 52 Countries And Over 27,000 Subjects (INTERHEART) supports this view, showing worse odds ratios for MI and numerically higher population attributable risks among female than male MI patients in relation to hypertension, diabetes, low physical activity, low alcohol consumption, abdominal obesity, adverse psychosocial factors, and low fruit and vegetable diet: statistically significant gender-differences were found for hypertension, diabetes, exercise, and alcohol [21].

1.3. Pathophysiology

The relative contribution of various processes leading to ischaemia differs markedly between genders: women with IHD less frequently than men have obstructive and extensive epicardial artery disease (Table 1) [22]; this implies that other mechanisms in women – such as abnormal coronary vasomotion, nonatherosclerotic coronary artery dissection, impaired coronary microcirculation, thrombophilia, or as yet unknown processes [5,23–25] – contribute to ischaemic syndromes more frequently than in men [5]. In one series of symptomatic women, abnormal

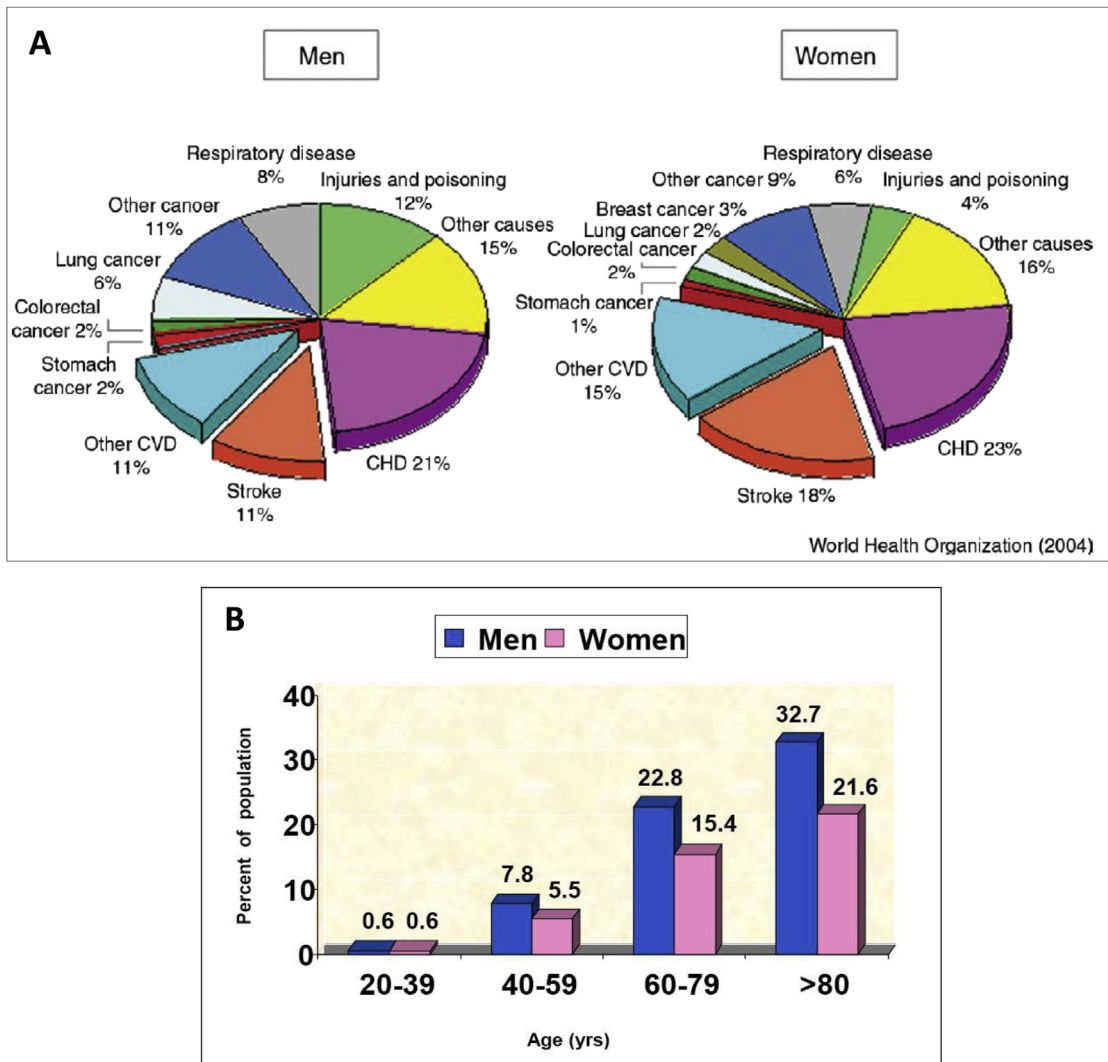


Fig. 1. A) Causes of death by gender in Europe. Global cardiovascular mortality (including coronary heart disease – CHD, stroke and other cardiovascular diseases – CVD) is higher in women than in men (56% vs 43%). Reproduced with permission from reference [3]. B) Prevalence of ischaemic heart disease in the USA by sex and age. Reproduced with permission from reference [4].

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