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The burden of cardiovascular risk factors and coronary heart disease in Europe and worldwide

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Cardiovascular disease (CVD) is estimated to be the leading cause of death and disability-adjusted life years lost worldwide being coronary heart disease the most prevalent form of heart disease. The underlying cause of most CVD is atherosclerosis, a process mainly governed by lifestyle factors. Several epidemiological studies have enabled the recognition of the major risk factors for CVD development, 'the so-called conventional risk factors'. Identification of such global risk factors have led, in turn, to the development of risk-prediction algorithms and cardiovascular risk models for men and women. Indeed, during the last years, there has been increasing credit of the importance of CVD in women accompanied by growing awareness of gender differences in natural history, preventive strategies, treatment, and prognosis of CVD. Classical risk factors, however, cannot fully explain the excess cardiovascular risk, and at least 25% of all future events occur in individuals with only one of the classical risk factors. This scenario has prompted the interest for discovering new risk factors. Time-trend analysis of surveys by the European Society of Cardiology (EUROASPIRE surveys) has reflected, however, that large proportions of European coronary patients are failing to achieve lifestyle, risk factor, and therapeutic targets for the prevention of CVD leaving room from improvement. Moreover, although overt CVD takes place during adulthood, lifestyle and dietary changes that have occurred over the last two decades support the need to instigate primary prevention measures during childhood as the best strategy to retard atherogenic processes.

Worldwide, cardiovascular disease (CVD) is estimated to be the leading cause of death and disability-adjusted life years (DALY) lost. According to the World Health Organization (WHO) global estimates of mortality and burden of disease, around 17.3 million people died from CVD in 2008 representing 30% of all global deaths.[1,2] Of these deaths, an estimated 7.3 million were due to coronary heart disease (CHD) and 6.2 million were due to stroke.[2] In fact, CHD is the second cause of death in people aged under 59 years after HIV/AIDS, reaching the first position in those aged 60 years and above (http://www.who.int/cardiovascular_diseases). Moreover, it is estimated that by 2030, more than 23.3 million people will die annually from CVDs.[3] Despite this epidemic has receded in many developed countries in the past decades, low- and middle-income countries have experienced an increase in the prevalence of CVD and 80% of the global burden of CVD occurs there. The higher exposition to cardiovascular risk factors, the lack of prevention programmes, and the fact that they have far less access to effective and equitable healthcare services (including early detection

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services) seem to have largely contributed to increase the prevalence of the disease.[4]

CVD also causes mass disability. DALY represents the 'healthy years of life lost' and combines years of potential life lost due to premature death with years of productive life lost due to disability, thereby, indicating the total burden of a disease as opposed to simply the resulting death. Within the coming decades, DALYs estimate for CVD is expected to rise from a loss of 85 million DALYs in 1990 to a loss of 150 million DALYs globally in 2020, thereby remaining the leading somatic cause of loss of productivity. As for CHD global burden, this is projected to rise from around 47 million DALYs globally in 1990 to 82 million DALYs in 2020. Currently, CHD disease burden occupies the third position in DALY lost in women (5.3%) after unipolar depressive disorders (8.4%) and HIV/AIDS (7.2%), whereas among men, it is found to be the second major cause of disease burden (6.8%) after HIV/AIDS (7.4%) (http://www.who.int/cardiovascular_diseases).

The cause of most CVD is a build-up of atheroma inside the arteries, a process mainly governed by lifestyle factors.[5] Two major studies conducted during the second half of the 20th century, the *Framingham Heart Study*[6] and the *Seven Countries Study*,[7] made a significant contribution in identifying the major risk factors for CVD development, 'the so-called conventional risk factors' (*Table 1*). These classical risk factors met the following criteria: (i) presented a high prevalence in different populations, (ii) had a significant independent impact on the risk of CHD and stroke, and (iii) reduced cardiovascular risk with treatment and control. In this context, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, insufficient consumption of fruits and vegetables, excess consumption of alcohol, and lack of regular physical activity account for most of the modifiable risk factors of CHD worldwide.[8] Yet, contemporary women have shown increased burden of some of these risk factors as depicted in *Table 1*. Actually, the past decade has witnessed a long overdue recognition of the importance of CVD in women accompanied by an increasing awareness of gender differences in natural history, preventive strategies, treatment, and prognosis of CVD.[9–11] The identification of the global risk factors for CHD in the early large epidemiological studies led to the development of risk-prediction algorithms and cardiovascular risk models for men and women (Framingham, Reynolds, PROCAM, and SCORE) in order to estimate the risk profile for developing CHD and, hence, optimize and individualize preventive/treatment strategies.[12]

The large international INTERHEART study,[8] conducted from 1990 to 2010, concluded that conventional risk factors account for over 75% of CVD being dyslipidaemia and smoking the two most important risk factors for CHD around the globe, with abdominal obesity, diabetes, and hypertension following closely behind. However, the absence of cardiovascular risk factor exposure should not necessarily be viewed as a guarantee of a favourable prognostic sign.[13] In fact, classical risk factors cannot fully explain the excess cardiovascular risk and at least 25% of all future events occur in individuals with only one of the classical risk factors.[14] Moreover, the prevalence of traditional risk factors is almost as high in individuals without the disease as in patients affected by it.[15] These observations have strengthened the need to discover new risk factors. In this regard, within the last years, diverse emerging risk factors have been directly associated with increased risk of CVD (*Table 1*).[16] These novel risk factors are measurable, improve cardiovascular risk prediction, and also assist clinicians in making decisions concerning patients at increased risk for specific diseases.[17,18] Among them, the highly sensitive C-reactive protein and genetic markers borne out of genome-wide linkage sibs-pair analyses for single nucleotide polymorphisms have emerged as potential candidates for CVD risk prediction.[19,20] However, causative, quantitative, and independent contributions of these new risk factors to CVD have not yet been fully elucidated. In fact, the ESC and AHA guidelines do not support routine genetic testing as part of the CVD risk-prediction process.

Despite the absence of reliable and effective risk predicting biomarkers, the WHO has always claimed that most CVD can be prevented by addressing classical risk factors. In this sense, in the mid-90s, Joint European Societies' gathered under the auspices of the ESC to rise clinical standards in secondary prevention against CHD based on European surveys (the EUROASPIRE surveys). EUROASPIRE I, II, and III (1997–2009)[21–23] demonstrated a high prevalence of unhealthy lifestyles, modifiable risk factors, and inadequate use of drug therapies to achieve CVD prevention in CHD patients and people at high risk of developing CVD in Europe. There also detected wide variations in medical practice between countries in the treatment of these patients. In fact, the EUROASPIRE III time trends survey showed a compelling need for more effective lifestyle management of patients with CHD and concluded that, despite a substantial increase in antihypertensive and lipid-lowering drugs, blood pressure management remained unchanged, and almost half of all patients remain above the recommended lipid targets. Moreover, the recently presented EUROASPIRE IV (ESC Congress 2013) further highlighted the pressing need for modern preventive cardiology programmes with lifestyle changes at their core. Moreover, although there is extensive evidence showing that drug treatment of conventional risk factors is effective in reducing cardiovascular events, the REACH registry[24,25]—aimed at examining the impact of adherence to guidelines for the control of atherothrombotic risk factors—demonstrated that there is an important underutilization of established medical therapy and lifestyle interventions. For instance, the use of guideline-recommended angiotensin-converting enzyme inhibitors is only 50%, about 80% of patients use antiplatelet therapy, and 70% are receiving statins.

Overall, these studies indicate that further efforts need to be implemented in European medical practice to optimally prevent and treat the risk of recurrence and death among patients with CHD. In 2012, the ESC published an updated guideline on CVD prevention in which the key message conveyed was 'prevention works'. '[Greater than] 50% of the reductions seen in CVD mortality relate to changes in risk factors and 40% to improved treatments'.[26] The guidelines also stressed that prevention should remain a lifelong effort to combat the progressive

Table 1 Classical and emerging cardiovascular risk factors

Conventional risk factors	*Non-modifiable*		Advancing age
			Heredity or family history
			Gender
			Ethnicity or race
	Modifiable	*Major modifiable*	High blood pressure
			Abnormal blood lipids
			Tobacco use (chewing or smoking)
			Physical inactivity
			Diabetes mellitus[a]
			Nutrition
			Obesity[a]
		Other modifiable	Hormone replacement therapy (women only)[a]
			Polycystic ovary syndrome (women only)[a]
			Low socioeconomic status
			Depression[a]
			Psychosocial stress
			Alcohol use
			Use of certain medication
			Left ventricular hypertrophy
Novel/emerging risk factors	*Lipid-related factors*		ApoB/ApoA1
			Small dense low-density lipoprotein (LDL)
			Lipoprotein(a)
			Remnant lipoproteins
			High-density lipoprotein subtypes
			Oxidized LDL
			Lipoprotein-associated phospholipase A(2)
			Myeloperoxidase
	Inflammation		High-sensitivity C-reactive protein
			Interleukins (e.g. IL-6)
			Serum amyloid A
			Vascular and cellular adhesion molecules
			Soluble CD40 ligand
			Leucocyte count
			F2-Isoprostanes
	Haemostasis and thrombosis		Fibrinogen
			von Willebrand factor antigen
			Plasminogen activator inhibitor 1 (PAI-1)
			Tissue-plasminogen activator
			Factors V, VII, and VIII
			D-dimer
			Fibrinopeptide A
			Prothrombin fragment 1+2
			PAI-1 genotype
			Thrombin
			Platelet size and volume
	Imaging markers		Coronary artery calcium score (CAC)
			Carotid intima-media thickness (CIMT)
	Others		Homocysteine
			Insulin resistance
			Ankel-brachial index
			Cardiac troponins
			B-type natriuretic peptide
			Microalbuminuria
			Oxidative stress
			Periodontal disease
			Genetic markers (SNPs)

[a]Risk factors that present a higher prevalence in women than men.

nature of atherosclerosis in both men and women. Although overt CVD typically occur in middle age or later, risk factors are determined to a great extent by behaviours learned in childhood and youth and continued into adulthood, such as dietary habits and smoking. Throughout the world, cardiovascular risk factors are starting to appear earlier.

Moreover, physical activity has markedly decreased in adolescence; obesity rates have increased substantially, not only in Europe and North America, but also in Eastern traditionally slim populations (Chinese and Japanese); and, there has been a global spread of type 2 diabetes in children and adolescents.[4] Most importantly, markers of CVD can be seen in young children. Post-mortems of children who died in accidents have found fatty streaks and fibrous plaques in their coronary arteries and they were most frequently found in those children whose risk factors included smoking, elevated plasma lipids, high blood pressure, and obesity. These observations leave no doubt about when we need to start meaningful preventive measures. Instil healthy lifestyle habits early in life is certainly the best strategy to reduce the global burden of CVD.

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