



# A Life Course Approach to Cardiovascular Disease Prevention

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During the past 2 decades, life-course social-ecological frameworks have emerged across health, developmental, social, behavioral, and public health disciplines as useful models for explaining how health trajectories develop over an individual's lifetime and how this knowledge can guide and inform new approaches to clinical and public health practice, multilevel policies, and research. Viewed from this perspective, and with emphasis on global cardiovascular health promotion and prevention of cardiovascular disease (CVD), this article summarizes evidence on the early origins and progression of CVD processes across the life course of individuals and diverse populations. Current evidence-based guidelines for CVD prevention are summarized, and recommendations for future research are suggested.

**KEY WORDS:** CVD, life course, prevention

## Cardiovascular Disease Processes and Prevention in Early Life

Considerable evidence has accumulated over the past 5 decades indicating that atherosclerotic and hypertensive processes begin early in life and are influenced over time by the interaction of potentially modifiable behaviors and environmental exposures. Important to note, however, is that multidecade, population-based longitudinal data linking absolute levels of risk factors in childhood to incident cardiovascular disease (CVD) in adult life are not existent. Similarly, no randomized clinical trial data exist indicating that reduction of risk factors in childhood prevents cardiovascular events in adult life. The collective evidence, however, reviewed briefly in this article, supports a life course social-ecological approach to CVD prevention<sup>1,2</sup> and has

prompted and informed the development of guidelines focused on prevention and management of risk factors for CVD in children and adolescents.<sup>3–5</sup>

## Evidence from Pathology, Autopsy, and Noninvasive In Vivo Studies

The Bogalusa Heart Study,<sup>6</sup> a long-term epidemiologic study of cardiovascular risk factors, included cross-sectional and longitudinal surveys of healthy, community-dwelling children ( $n = 3500$ ; 65% white; 35% black) and a pathology/autopsy component designed to examine the associations of established risk factors for CVD measured prior to accidental death and the extent of postmortem aortic and coronary artery atherosclerosis. Autopsy data from 93 individuals (35% black; 31% female) who were 15 to 28 years of age at time of death indicated that the extent of fatty streaks and fibrous plaques in the aorta and coronary arteries increased with age and was stronger in the coronary arteries ( $r = 0.60$ ;  $P < .001$ ) than in the aorta ( $r = 0.23$ ;  $P = .03$ ). As a group, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure, and serum concentrations of total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were strongly associated with the extent of lesions in the aorta and coronary arteries (canonical correlation,  $r = 0.70$ ;  $P < .001$ ). Of note, cigarette smoking increased the percentage of intimal surface involved with fibrous plaques in the aorta (1.22% in smokers vs 0.12% in nonsmokers,  $P = .02$ ). Important and oft-cited results

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from this Bogalusa pathology study, subjects with multiple risk factor clustering had more extensive atherosclerosis; the extent of fatty streak lesions in the coronary arteries was 8.5 times as great in persons with 3 or 4 risk factors compared with those with none ( $P = .03$ ), and the extent of fibrous-plaque lesions in the coronary arteries was 12 times as great ( $P = .006$ ).

These findings concur with those observed in the multicenter Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study of 1443 persons (25% female, 53% black) 15 to 34 years of age who died of noncardiovascular causes and were autopsied within 48 hours after death in forensic laboratories. Specifically, in this PDAY analysis, atherosclerosis of the aorta and right coronary arteries was quantitated as the extent of intimal surface involved with both fatty streaks and raised lesions and analyzed postmortem serum for lipoprotein cholesterol (very-low-density lipoprotein cholesterol, LDL-C, HDL-C) and thiocyanate (indicator of smoking) were included and viewed as risk factors for CVD. Similar to Bogalusa results, atherosclerosis increased with age in all arterial segments of all sex and race groups. Although some sex and race differences in fatty streaks and raised lesions were observed, 3 potentially modifiable risk factors measured (very-low-density lipoprotein cholesterol + LDL-C, smoking) adversely affected atherosclerotic processes to the same extent in black and white males and females. Combined with the pathology results from Bogalusa,<sup>6</sup> PDAY findings<sup>7,8</sup> added to the developing database regarding the associations of established risk factors for CVD and atherosclerotic processes in childhood and young adulthood, provided support for primary prevention beginning early in life, and prompted the need for additional research.

More recently, noninvasive imaging has been used to examine the association of potentially modifiable risk factors for CVD with vascular structure and function in childhood and adolescence and atherosclerosis in young adult life (Table 1). Data from the Muscatine Study, a longitudinal study of CVD risk factors in children and youth, demonstrated positive associations between carotid intima-media thickness (CIMT) measured in adults 33 to 42 years of age and levels of serum TC and BMI measured in childhood.<sup>9</sup> In the Bogalusa Heart Study, similar results were observed: childhood LDL-C and BMI predicted increased CIMT in adulthood.<sup>10</sup> Results from the Young Finns Study, a population-based prospective cohort study of young adults 24 to 39 years of age, reaffirm the link between risk factors present in adolescence and preclinical atherosclerosis in adulthood.<sup>11</sup> The potentially modifiable risk factors and behaviors that predicted preclinical atherosclerosis included LDL-C, BMI, cigarette smoking, and SBP. More recently, in a cross-sectional comparative study of lean and obese children and children

and youth with type 2 diabetes mellitus (T2DM), Urbina and colleagues<sup>12</sup> showed that adolescents and young adults with T2DM have significantly greater CIMT than lean controls for all carotid artery segments examined. Of note, obese and T2DM children and youth had stiffer carotid arteries with higher Young elastic modulus and  $\beta$  stiffness index than their lean counterparts. Collective results indicated that youth with T2DM demonstrate significant abnormalities in carotid function and structure. In obese youth, changes were observed before progression to overt T2DM. Importantly, given the global increase in obesity and T2DM in children and youth, the presence of either of these conditions contributed independently to adverse changes in carotid structure and function.<sup>12</sup>

## Evidence From Epidemiologic Studies

Evidence from epidemiologic studies conducted in the United States and globally indicates that risk factors and adverse health behaviors associated with CVD in adulthood, such as cigarette smoking, dyslipidemias (high levels of LDL-C and low levels of HDL-C), high blood pressure, physical inactivity, obesity, and diabetes, have their origins in childhood and adolescence. Population-based studies including those conducted in Muscatine,<sup>13</sup> Bogalusa,<sup>14</sup> Europe (European Youth Heart),<sup>15</sup> Finland (Young Finns),<sup>16</sup> and Canada<sup>17,18</sup> describe the distribution and determinants of CVD risk factors in their countries' youth (Table 2). Tracking of risk factors, maintenance of percentile rank over time, from childhood to young adulthood has been documented in males and females from diverse racial/ethnic groups and is particularly evident in the upper and lower extremes of the distribution.<sup>13,14,16</sup> Tracking is relevant to primary prevention because of the potential for identifying children at risk for CVD early in life. Intraindividual clustering of risk factors (obesity, elevated blood pressure, dyslipidemia) and adverse health behaviors has also been observed in children and adolescents in studies conducted in the United States and globally.<sup>19–24</sup>

Obesity, a recognized major risk factor for CVD, has increased in prevalence in children and adolescents in the United States and globally throughout the past 3 decades (Table 2). Although precise global estimates of the prevalence of childhood obesity are difficult to ascertain because of the use of nonrepresentative samples in many countries and between country differences in measurement of obesity, an international study (Health Behaviour in School-aged Children Study), conducted in collaboration with the World Health Organization, provides relevant global data.<sup>19</sup> This 2001–2002 cross-sectional survey of 137 593 children and adolescents (10–16 years of age) from 34 countries, primarily European, documented the highest prevalence

**TABLE 1** Noninvasive Imaging Studies: Cardiovascular Disease (CVD) Risk Factors and Vascular Structure and Function in Childhood, Adolescence, and Young Adulthood

Study	Purpose	Method and Sample	Results	Conclusions
Davis et al <sup>9</sup> (2001)	Examine the association of CVD risk factors measured in childhood, young, and middle adulthood and load from childhood to adulthood and CIMT in young and middle adulthood	Carotid ultrasound studies were performed in n = 346 men and n = 379 women aged 33–42 y who were representative of a cohort followed since childhood (8–18 y of age at baseline) as part of Muscatine study	The significant current/adulthood predictors of CIMT were age and LDL-C in both males and females and DBP in females. TC was a significant childhood predictor in both males and females; BMI was also significant in females. For males, in risk factor load model, LDL-C, HDL-C, and DBP were predictive of CIMT; in females, LDL-C, BMI, and triglycerides were predictive. Significant predictors for being in top vs lower 3 quartiles of CIMT in young adults were childhood measures of LDL-C, BMI, and adulthood measures of LDL-C, HDL-C, and SBP. An increasing trend in CIMT across quartiles of childhood measures of LDL-C was observed with a mean value of 0.761 mm (95% CI, 0.743–0.780 mm) for those at top quartile vs 0.724 mm (95% CI, 0.715–0.734 mm) for those in lower 3 quartiles ( $P < .001$ ).	In this primarily white population, higher CIMT in young and middle-aged adults was associated with childhood and current CVD risk factors as well as risk factor load.
Li et al <sup>10</sup> (2003)	Examine the association of CIMT in young adults and traditional CVD risk factors measured since childhood	This cohort study of n = 486 adults aged 25–37 y (71% white; 39% men) was conducted in a semirural biracial community in Bogalusa, Louisiana. Participants had $\geq 3$ measurements of traditional risk factors since childhood.	In multivariable models adjusted for age and sex, CIMT in adulthood was associated with childhood LDL-C levels ( $P = .001$ ), SBP ( $P = .02$ ) and with adult SBP ( $P < .001$ ), BMI ( $P < .001$ ), and smoking ( $P = .004$ ). Number of CVD risk factors measured in 12- to 18-y-olds (LDL-C, SBP, BMI, and cigarette smoking) was directly related to CIMT in young adults (at ages 33–39 y) and remained significant ( $P < .001$ ) after adjustment for adult measures.	Potentially modifiable childhood measures of LDL-C and BMI predict CIMT in black and white male and female young adults.
Raitakari et al <sup>11</sup> (2003)	Examine the relationship between CVD risk factors in childhood and adolescence and CIMT as marker of clinical atherosclerosis measured in adulthood	Population-based prospective cohort study conducted at 5 centers in Finland and included n = 2229 white adults 24–39 y old who were examined during childhood and adolescence and then 21 y later	In this Young Finns study, risk factor profiles assessed in adolescence predict adult CIMT independently of adult risk factor levels suggesting that exposure to CVD risk factors early in life may induce adverse changes in arteries that contribute to development of atherosclerosis.	
Urbina et al <sup>12</sup> (2009)	Examine and compare CIMT and carotid stiffness in youth who are lean, obese, and those with T2DM	Cross-sectional, comparative study of n = 446 youth (10–24 y of age; 65% nonwhite; 39% male)	Adolescents and young adults with T2DM had significantly greater CIMT than lean controls for all carotid artery segments. Obese and T2DM participants had stiffer carotid arteries with higher Young elastic modulus and $\beta$ stiffness index than lean counterparts.	Adolescents and young adults with obesity and/or T2DM are at risk for adverse changes in carotid function and structure. Although additional research is warranted, these results suggest the need for prevention of obesity and T2DM early in life.

Abbreviations: BMI, body mass index; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

**TABLE 2** Epidemiologic Studies of Cardiovascular Risk Factors and Cardiovascular Disease (CVD) Related Health Behaviors in Children and Adolescents

Study	Purpose	Method	Results	Conclusions
Lauer and Clarke <sup>13</sup> (1990)	Examine the validity and utility of cholesterol screening tests for school-aged children in relation to prediction of adult hypercholesterolemia	Six biennial cross-sectional surveys were conducted with n = 2367 children (51% female), 8–18 y of age at baseline) and followed to 20–30 y of age	For children with TC levels >75% tile on 2 occasions, 75% females and 56% males would not qualify for intervention as adults by the NCEP criteria (TC ≥200 mg/dL). For children with TC >90th percentile: 57% females and 30% males would not qualify as adults	In this white population of children from Muscatine, Iowa, childhood results suggest that screening for TC without measuring LDL-C in childhood may fail to identify those at risk and falsely label those not at risk.
Webber et al <sup>14</sup> (1991)	Assess tracking of serum lipids and lipoproteins over 12-y period from childhood to adulthood	Community-based population study including n = 1586 children (55% female; 36% black) examined at baseline in 1973–1974 and in 1984–1986	Approximately 50% of children with TC or LDL-C levels >75th percentile at baseline remained elevated 12 y later. Tracking, as measured by correlation coefficients and persistence at extreme quartiles, was evident for all lipids and lipoproteins. The best predictor of follow-up lipid or lipoprotein level was baseline level, and the next best predictor was increase in weight as defined by weight/height <sup>3</sup> , an index of obesity.	In this biracial community-based sample, childhood levels of serum lipids and lipoproteins are predictive of young adult levels. Lipids and lipoproteins track from childhood into young adulthood, suggesting the utility of baseline measures early in life and emphasis on development of healthy lifestyle behaviors early in life.
Riddoch et al <sup>15</sup> (2005)	Ultimate goal: establish nature, strength, and interactions between personal, environmental, and lifestyle influences on CVD risk factors in children and youth. Analyze tracking and predictiveness of serum lipoprotein measurements in Finnish youth	Cross-sectional survey of n = 4169 children (9–15 y of age) from 4 countries: Denmark, Estonia, Norway, Portugal. Protocol includes physiological, behavioral-lifestyle, personal, (biological and psychological), and environmental measures.	Results demonstrated the feasibility of field-based assessment, reliability and validity of measures/methods, and acceptability of the survey protocol.	Multilevel influences on CVD risk factors in children can be measured with advanced technology and quality control.
Porkka et al <sup>16</sup> (1994)	Examine temporal trends (1994–2005) in risk factors for CVD and impact of socioeconomic status (SES) on risk factors	Main cross-sectional study conducted in 1980 with follow-up studies in 1983, 1986, 1989, 1992. Sample consisted of n = 3596 children 3–18 y of age at baseline. Follow-ups were conducted 4 times over a 12-y period. Cohort for analysis: n = 883 (47% male)	Approximately 50% of subjects initially in extreme quintiles of TC, LDL-C, and HDL-C were in same quintiles after 12 y. Multiple regression results: childhood serum lipid levels are the most important predictor of adult lipid levels.	In this study of young Finns, serum lipids and lipoproteins track from childhood and adolescence to adulthood and suggest that screening in childhood—particularly in children with family history of premature CHD may assist in identifying children at risk early in life
Lee et al <sup>17</sup> (2009)	Examine temporal trends (1994–2005) in risk factors for CVD and impact of socioeconomic status (SES) on risk factors	Data from the National Population Health (NPH) Survey and Canadian Community Health Survey (CCHS) used to examine trends in CVD, hypertension, T2DM and, obesity (BMI) (1994–2005), adjusted for age and sex. Data were stratified by category of income adequacy, BMI and region of residence. Sample included individuals ≥12 y of age who participated in NPH in 1994 (n = 17 626); 1996 (n = 73 402) and CCHS: 2001 (n = 131 535); 2003 (n = 135 573); and 2005 (n = 132 947).	CVD increased by 19% for men and 2% for women (1994–2005); CVD increased significantly in lowest-income category (27%), in lower middle category (37%), and upper middle category (12%). In highest-income group, CVD increased by 6%. Diabetes increased in all but highest-income group (56% in lowest-income group). Hypertension and BMI increased in all groups; lowest (85% and 20%, respectively).	Trends over time (1994–2005) in CVD and risk factors indicate increasing prevalence particularly in lower SES groups and point to the need for population-based prevention and targeted efforts to reduce disparities in CVD and its major risk factors.

(continued)

**TABLE 2** Epidemiologic Studies of Cardiovascular Risk Factors and Cardiovascular Disease (CVD) Related Health Behaviors in Children and Adolescents, continued

Study	Purpose	Method	Results	Conclusions
Janssen et al <sup>19</sup> (2005)	Present and compare international estimates of prevalence of overweight and obesity in school-aged children and youth from 34 countries and examine relationship of diet and physical activity to weight status	Data consisted of a cross-sectional survey: (n = 137 593, 10–16 y of age; 47% female). Prevalence of overweight and obesity: based on self-reported height and weight and international child body mass index standards. Dietary intake was measured with food frequency questionnaires; physical activity and sedentary behaviors were measured by self-report.	Two countries with highest prevalence of overweight and obese children were Malta (25.4% and 7.9%) and US (25.1% and 6.8%), respectively. Within most countries, physical activity levels were lower, and TV viewing times were higher in overweight compared with normal-weight children. Overweight status was not associated with intake of fruits, vegetables, or soft drinks or computer time.	Increasing physical activity and decreasing TV viewing (sedentary behaviors) should be focal points of strategies for preventing and managing overweight and obesity in children and youth. Results viewed in context of limitations of self-reported weight status and health behaviors.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

of overweight and obesity in Malta (25.4% and 7.9%, respectively) and the United States (25.1% and 6.8%, respectively). The 2 countries with the lowest prevalence were Lithuania (5.1% and 0.4%, respectively) and Latvia (5.9% and 0.5%, respectively). Overweight and obesity rates were higher in countries in North America, Great Britain, and southwestern Europe. Of note, reported levels of physical activity were lower and television viewing higher in countries with the highest prevalence of overweight and obesity.<sup>19</sup> Results from clinical and epidemiologic studies indicate that overweight and obese children and adolescents are at greater risk for early-onset comorbidities including insulin resistance,<sup>20</sup> type 2 diabetes,<sup>21</sup> dyslipidemia,<sup>22</sup> and hypertension,<sup>23</sup> all of which contribute to and accelerate risk for CVD in adulthood.<sup>24</sup>

As a result of these clinical and epidemiologic studies and the known obesity-CVD associations, a number of countries have established guidelines for the prevention and management of obesity in children and adolescents.<sup>25,26</sup>

### Emerging Evidence: Research in Progress

Morrison and colleagues<sup>27</sup> recently initiated the prospective longitudinal Canadian Family Atherosclerosis Monitoring In earLY life (FAMILY) study, which is designed to follow a cohort of 850 children and their families (mother, father, eldest sibling). The purpose of this study was to examine the fetal/maternal and early childhood family-based determinants for the development of obesity and CVD risk factors (dysglycemia, dyslipidemia, and hypertension) in the progression of atherosclerosis in childhood.<sup>27</sup> Other countries have also initiated prospective cohort studies to examine the distribution and determinants of risk factors for CVD in childhood.<sup>28,29</sup> These data are necessary to guide and inform country-specific CVD prevention practices and policies for children and adolescents.

### Prevention of CVD in Early Life: Current Guidelines

As noted above and based on available evidence, a series of guidelines for cardiovascular health promotion and risk reduction in childhood and adolescence has been issued by the American Heart Association (AHA) and US and Canadian child health agencies and pediatric expert panels.<sup>3–5,25,26</sup> Coordinated by the National Heart, Lung, and Blood Institute, National Institutes of Health, integrated guidelines for assessing and managing risk factors and health behaviors in children and youth have been developed and will be available in 2011.<sup>30</sup> In addition, initiatives are currently in progress in several countries that are designed to result in guidelines for cardiovascular health promotion/risk

reduction beginning early in life and extending across the life course. Major emphasis in current guidelines for cardiovascular health promotion and risk reduction in children and youth is focused on development and maintenance of healthy lifestyle behaviors and therapeutic behavioral-lifestyle change (TLC), respectively.<sup>3–5,25,26,30</sup> Smoke-free lifestyles and environments, 60 minutes of moderate-to-vigorous-physical activity per day, less than 2 hours per day of leisure-time sedentary activity, and a heart-healthy pattern of dietary intake are recommended in the majority of guidelines for children 2 years or older.<sup>3–5,25,26,30</sup> The AHA's most recent dietary recommendations for all children and youth ( $\geq 2$  years of age) emphasize balancing caloric intake with physical activity to maintain normal growth and developmental processes while minimizing the development of CVD risk factors, particularly dyslipidemia, elevated blood pressure and glucose levels, and excessive body weight.<sup>5</sup> Recommendations for essential and discretionary calories based on age, sex, and activity level as well as specific guidelines for daily intakes of macronutrients and micronutrients are suggested with emphasis on establishing and maintaining a healthful overall dietary pattern. The AHA recommends patterns of dietary intake that include a variety of fruits and vegetables, whole grains, low-fat and nonfat dairy products, legumes, fish (preferably oily fish high in omega-3 fatty acids), poultry, and lean meat.<sup>5</sup> For all children 2 years or older, moderate fat intake (25%–35% of daily energy intake), with primary sources of added fats from vegetable oils (soybean, canola, corn, olive, sunflower, and safflower), is recommended. Limiting saturated fat intake to less than 7%, *trans*-fat to less than 1% of daily energy intake, and cholesterol to less than 300 mg/d is also recommended along with minimizing intake of foods and beverages with added sugars and processed foods with added salt.

Whereas an extensive discussion of TLC recommendations for children with specific CVD risk factors is beyond the scope of this article, an adequate trial of TLC (normally 3 months) with emphasis on normalization of body weight is recommended in most guidelines for initial management of risk factors including dyslipidemias and elevated blood pressure in children and youth.<sup>3–5,25,26,30</sup> Many factors are recommended for consideration before progressing beyond TLC to pharmacotherapy or other treatment modalities, including family history of CVD, the child's age and maturational level, total risk profile, response to TLC, and patient and family preferences and resources.<sup>3–5,25,26,30</sup> Important from a social-ecological perspective is that recent guidelines also consider such contexts as the child's family, school, and community environments, which influence health behaviors and lifestyles central to cardiovascular

health.<sup>30</sup> The AHA and American Academy of Pediatrics guidelines, for example, encourage parent and family involvement in the development and implementation of strategies for health behavior change including patterns of dietary intake and physical activity, parent and consumer advocacy for healthy school environments with emphasis on healthy foods served in all venues, and advocacy for multilevel policies that affect access to and availability of healthy foods and outlets and built environments conducive to physically active and smoke-free lifestyles.<sup>3–5</sup>

## **Cardiovascular Disease Processes and Prevention in Midlife**

Viewed from a life course perspective, CVD prevention in midlife, similar to childhood and adolescence, places emphasis on healthy lifestyle behaviors and the contexts and social influences that affect these behaviors.<sup>1,2,31–33</sup> The Framingham Heart Study (FHS) documented the associations of age, sex, hypertension, hyperlipidemia, and diabetes with absolute risk for developing coronary heart disease (CHD).<sup>32</sup> In most industrialized nations, CVD increases with age; however, in developing countries, the age at onset is much younger. Although CVD is the No. 1 cause of mortality in the United States, age-specific data in 2000 showed that malignancy surpassed heart disease as the leading cause of death from ages 35 to 74 years. In this age group, heart disease has declined by 26% since 1980, although it is now the major cause of death after age 75 years.<sup>31</sup> In industrialized nations, clinical and community-based initiatives that have focused on promotion of heart-healthy diets, smoking cessation, smoke-free environments, and physically active lifestyles, together with drug treatment for hypertension and hypercholesterolemia, and percutaneous and surgical interventions when needed, have combined to reduce overall deaths from CVD and to shift CVD as a cause of death from middle to old age. This is not the case in the developing world. In the Russian Federation, CVD mortality is 5 times the US rate for working-age people, 30 to 59 years.<sup>33</sup> In India, the prevalence of CHD has risen 4-fold over the last 40 years, and now CVD is the leading cause of death, responsible for 29% of all deaths in 2005. In the age group of 35 to 64 years, deaths due to CVD resulted in 9.2 million "potentially productive" years of lost life in 2000, almost 6-fold more than in the United States.<sup>34</sup>

The AHA estimates that approximately 44% of the decline in the CHD death rate between 1980 and 2000 was attributable to changes in risk factors, particularly lower TC (24%), lower SBP (20%), lower smoking prevalence (12%), and increased physical activity (5%).<sup>35</sup> In addition, clinical outcome trials conducted in the United States, Europe, and Asia have shown

significant reductions in CHD events, strokes, and CVD mortality when major risk factors including blood pressure and cholesterol are lowered with behavioral interventions (TLC) and pharmacotherapy.<sup>36–38</sup> The benefits of maintaining optimal cardiovascular risk profiles in midlife are detailed in the next section of this article.

## Cardiovascular Disease Prevention in Older Adults

Although there is wide geographic variability, currently, 10% of the world's population is 60 years or older. This is expected to increase to 22% by 2050, ranging from 10% of the population in Africa to 35% in Europe. Asia will see its elderly population almost doubled.<sup>39–41</sup> In addition, the percentage of the population 80 years or older is expected to increase rapidly. In 2005, this segment accounted for 1% of the population, whereas by 2050 it is expected to reach more than 4%; in Europe, those 80 years or older will comprise 10% of the population, and in North America, 8%.<sup>40,41</sup> Global population trends reveal several important factors in relation to CVD in older adults. The transformation from levels of high mortality and high fertility to one of low mortality and low fertility, known as the “demographic transition,” is responsible for rapid and accelerating population growth, along with slowing of that growth and for population aging.<sup>42</sup> Nearly all the population growth is occurring in less developed countries,<sup>39</sup> and life expectancy varies widely by region. In more developed countries, life expectancy averages 76 years, compared with only 49 years in Africa. Currently, infants born around the world can expect to live an average of 65 years, which represents an increase of 9 years since the late 1960s. Asia has experienced the largest increase in life expectancy, from 54 years to 67 years.<sup>39</sup> Although different areas of the world are at different stages of the demographic transition, with less developed countries having significantly younger populations than more developed countries, these countries will eventually experience a similar increase in their older adult population relative to their younger population. This shift presents important challenges to governments and policy makers, as well as to health care providers, as it is changing the old-age dependency ratio; that is, there will be fewer workers to support the growing number of older adults, and with a decrease in fertility, there will be fewer children to care for aging parents.<sup>43</sup> The burden of CVD in older adults over the next 50 years will be greatest in the Asian-Pacific region.<sup>44–46</sup> Finally, these trends have important implications given the prevalence of CVD in women, particularly in older women. Currently, women comprise about half the world's population. By the end of the next quarter century, women will account for more than half

(54%) of people 60 years or older, and 63% of very old people (aged  $\geq 80$  years).<sup>39</sup>

As noted above, the prevalence of risk factors for CVD increases with increasing age in both men and women. The metabolic syndrome, which includes elevated blood pressure, TGs, and blood glucose, low HDL-C, and central obesity, predicts CVD morbidity and mortality as well as the development of T2DM, rises sharply with increasing age, and is present in almost 44% of the population aged 60 to 69 years.<sup>47</sup> These same risk factors are important, not only for their contribution to chronic disease, but also for their impact on disability in the elderly. Therefore, efforts to reduce modifiable health risks may postpone the onset of initial disability as well as decrease lifetime disability.<sup>48</sup> This is important, as persons 65 years or older account for the largest percentage of the disability in the United States, and this percentage will increase as the older population increases.<sup>49</sup> Maintaining functional independence is an important goal of health care for older persons, yet at least 10% of nondisabled, community-living older adults develop dependence in 1 or more activities of daily living each year.<sup>49</sup> The onset of dependence frequently heralds a downward spiral, with increasing frailty, greater use of formal and informal home care services, and frequent hospitalization and nursing home placement, all of which translate into higher health care costs.<sup>49</sup>

A prevalent chronic condition that poses challenges for maintaining functional independence in older adults, T2DM has been associated with a 2- to 4-fold higher risk of CVD as well as increased risk of mortality by up to 3-fold.<sup>35</sup> A recent report from FHS designed to examine change in all-cause, CVD, and non-CVD mortality rates among FHS participants in 2 time periods (1950–1975 and 1976–2001) reaffirms the T2DM-mortality associations.<sup>50</sup> Specifically, although a decline in all-cause and CVD mortality rates was observed among both men and women with and without diabetes, both men and women remained at higher risk of all-cause and CVD mortality than those without diabetes. Among women, the hazard ratios (HRs) for all-cause mortality in the later (1976–2001) versus the earlier (1950–1975) time period were 0.59 (95% confidence interval [CI], 0.50–0.70;  $P < .0001$ ) for those without diabetes and 0.48 (95% CI, 0.32–0.71;  $P = .002$ ) for those with diabetes. Similar results were observed in men. In the earlier time period, comparing participants with diabetes to those without diabetes, the HRs for CVD mortality were 5.08 ( $P < .001$ ) for women and 2.95 ( $P < .001$ ) for men; in the later time period, the HRs for CVD mortality were 3.49 ( $P < .0001$ ) for women and 2.35 ( $P < .0001$ ) for men.

Important to note is that FHS participants are primarily white; thus, observed mortality trend data may not be generalizable to men and women from other

racial/ethnic groups. Despite this limitation, data from clinical and epidemiologic studies underscore the adverse cardiovascular consequences of T2DM and support the need for prevention of this chronic condition beginning early in the life course and reduction and control of other established risk factors for CVD in individuals with T2DM.<sup>35,36</sup>

Results from population-based and clinical studies support the importance of risk reduction in older adults with and without CVD. The Scandinavian Simvastatin Survival Study (4S), conducted in patients with known CHD demonstrated that reduction in TC, LDL-C, and TGs, along with increases in HDL-C, was just as pronounced in patients 65 years or older as in younger patients and that patients on simvastatin had significantly lower rates for total mortality, coronary mortality, and the need for revascularization.<sup>51</sup> Furthermore, the reductions in major coronary events, CHD mortality, nonfatal myocardial infarction (MI), all-cause mortality, and the need for revascularization in patients 65 years or older were as great or greater than in younger subjects, with an overall relative risk reduction (RRR) in major coronary events of 32% in persons 65 years or older and 31% in persons younger than 65 years. This resulted in an absolute risk reduction in mortality that was twice as great in older patients (44 per 1000; 95% CI, 30–58 per 1000) compared with individuals younger than 65 years (32 per 1000; 95% CI, 24–40 per 1000).<sup>51</sup> These results are consistent with other lipid-lowering trials.<sup>52–54</sup> In addition, in the Diabetes Prevention Program, a greater reduction in development of diabetes was demonstrated in older subjects as compared with their younger counterparts.<sup>55</sup>

The INTERHEART study demonstrated that 9 modifiable risk factors—smoking, low fruit and vegetable consumption, lack of exercise, alcohol consumption, high apolipoprotein B–apolipoprotein A<sub>1</sub> ratio, self-reported hypertension and diabetes, abdominal obesity, and psychosocial factors—were consistently and strongly associated with MI across the globe and across different subgroups—geographic regions and ethnic groups, young and older adults, men and women, and different socioeconomic strata.<sup>56</sup> Daily consumption of fruits or vegetables, moderate or strenuous physical exercise, and consumption of alcohol 3 or more times per week were associated with a lower risk of MI.<sup>56</sup> As all MIs were included as cases, and controls were matched to within 5 years of cases, adults older than 60 years accounted for more than 25% of the subjects, with the highest end of the interquartile range varying from 59 (Middle East) to 72 years (western Europe). Thus, INTERHEART has provided important information not only on the global contribution of these risk factors, but also on their importance in older adults.<sup>56</sup>

Overall, the population attributable risk (PAR) for all 9 risk factors was 90.4% (99% CI, 88.1%–92.4%),

meaning that 90.4% of all MIs could be accounted for by these factors. Conversely, 90.4% of MIs could be eliminated if these 9 factors were eliminated. Although, at 93.8% (99% CI, 90.9%–95.8%), the PAR was significantly greater ( $P < .0001$ ) in younger individuals ( $\leq 55$  years in men and  $\leq 65$  years in women), the PAR was still high in older individuals at 87.9% (99% CI, 84.1%–90.9%). Although the strength of the risk factors, as assessed by odds ratios (ORs), was lower for smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, and high apolipoprotein B–apolipoprotein A<sub>1</sub> ratio, and less protective for fruit and vegetable consumption in older versus young individuals, alcohol consumption and exercise were more protective in older adults, although the difference was not significant. Lipid levels (OR, 2.50; 99% CI, 2.05–3.05), smoking (OR, 2.44; 99% CI, 2.10–2.84), and psychosocial factors (OR, 2.43; 99% CI, 1.86–3.18) were the factors most strongly associated with MI. Importantly, given the global epidemic of type 2 diabetes, the risk of MI associated with diabetes was greater in women at both younger (OR, 3.53; 99% CI, 2.49–5.01) and older ages (2.59; 99% CI, 1.78–3.78) than in younger (OR, 2.66; 99% CI, 2.04–3.46) and older men (OR, 1.93; 99% CI, 1.58–2.37). Similar to these observations of Western populations, in the Asia-Pacific Cohort Studies Collaboration, the risk of stroke and CHD jointly increased according to levels of SBP and serum cholesterol.<sup>57</sup>

Thus, the strength of these associations and the high PAR challenges the assumption that established CVD risk factors are not as informative in predicting risk or targeting interventions in older adults. The debate remains, however, as to the predictive validity of traditional risk factors in older adults, as most risk equations were developed in populations younger than 75 years of age (Table 3). In adults 85 years or older, available data suggest that major, classic risk factors may not be as useful in predicting CVD mortality as in younger male and female counterparts.<sup>58</sup> Nevertheless, despite the ongoing controversy about the predictive ability of classic CVD risk factors in older adults and the fact that few studies have included adults 75 years or older, the data regarding efficacy of treatment and prevention of adverse cardiac events in older adults in Western countries are overwhelmingly positive. Smoking cessation, hypertension and lipid management, and obesity, psychosocial, and physical activity interventions have all shown that these interventions reduced risk to a level comparable to younger adults.<sup>59–61</sup> Given that older adults are at higher risk for CVD than are younger individuals, this translates into significant reductions on a population level. Despite this evidence, however, primary and secondary prevention in the elderly is frequently compounded by age bias, the belief that older individuals should not be treated aggressively.

**TABLE 3** Examples of Currently Available Cardiovascular Disease (CVD) Risk Assessment/Prediction Tools<sup>64,a</sup>

Name	Description/Comments
Framingham <sup>32</sup> (1998) ATP-III Risk Estimator (Framingham) <sup>65,66</sup> ETHRISK <sup>67</sup>	End point: all CHD; includes CHD death, MI unstable angina, and angina pectoris End point: hard CHD; includes CHD, death, and nonfatal MI  Framingham Risk Score recalibrated to estimate 10-y risk for CHD and CVD in 7 British black and minority ethnic groups; 3778 men and 3544 women, aged 35–54 y
Framingham <sup>68</sup> global CVD, 2008 PROCAM <sup>69</sup>	End point: global CVD; includes CVD death, all CHD, stroke, heart failure, and claudication End point: hard CHD; includes CHD death and nonfatal MI; <a href="http://www.assmann-stiftung.de/en/procam/procam-risk-scores/">http://www.assmann-stiftung.de/en/procam/procam-risk-scores/</a>
QRISK <sup>70</sup> Reynolds risk score (women) <sup>71</sup>	End point: CVD; includes CHD, stroke, and transient ischemic attack End point: global CVD; includes CVD death, MI, stroke, revascularization; <a href="http://www.reynoldsriskscore.org/">http://www.reynoldsriskscore.org/</a>
Reynolds risk score (men) <sup>72</sup> New Zealand cardiovascular risk assessment and management chart <sup>73</sup> Joint British Society <sup>63</sup>	End point: global CVD; includes CVD death, MI, stroke, revascularization <a href="http://www.sld.cu/galerias/pdf/servicios/hta/ebm_cardio_new_zeland.pdf">http://www.sld.cu/galerias/pdf/servicios/hta/ebm_cardio_new_zeland.pdf</a>  <a href="http://www.patient.co.uk/doctor/How-to-use-the-Coronary-Risk-Prediction-Charts-for-Primary-Prevention.htm">http://www.patient.co.uk/doctor/How-to-use-the-Coronary-Risk-Prediction-Charts-for-Primary-Prevention.htm</a>
SCORE <sup>74</sup>	End point: CVD death; includes CVD death only; does not include nonfatal events; multiple region-specific (northern European, southern European) and country-specific versions available

Abbreviations: CHD, coronary heart disease; MI, myocardial infarction.

<sup>a</sup>Adapted from Lloyd-Jones, *Circulation*. 2010;121:1769.<sup>64</sup>

Clearly, assessment of CVD risk and management of established and nontraditional risk factors for CVD in older adults in the United States and globally remains a fertile area for future research.

## Global Risk Assessment

The AHA and the Joint British Societies recommend that all adults 40 years or older or those with 2 or more risk factors should have a global risk assessment performed.<sup>62,63</sup> Several CVD risk assessment and prediction tools being used with ethnically diverse populations are available in the literature and/or via the Internet; these tools generally depict an individual's short-term risk for developing a CVD event (Table 3).<sup>32,63–74</sup> These tools involve the assignment of a point value to selected risk factors and the calculation of a global risk score. For example, the Framingham Risk Score (FRS),<sup>65</sup> which estimates the 10-year absolute risk for developing CHD, is particularly useful in patients with multiple risk factors and a high risk for CHD in the next 10 years ( $\geq 20\%$ ). A clinical limitation of the FRS and other short-term risk estimates is the underestimation of risk in women and younger individuals, as age is the most heavily weighted risk factor. Individuals with low or intermediate 10-year risk for CHD may actually be at high risk in the long term, because any single risk factor can lead to cumulative atherosclerotic burden and adverse outcomes if left untreated for many years.<sup>75</sup> Therefore, the determination of lifetime risk is useful for assessing the cumulative risk of developing a disease during the remainder of an individual's life.<sup>76</sup>

Lloyd-Jones and colleagues<sup>77</sup> used FHS cohorts of patients to estimate lifetime risk for CVD and to examine overall survival with regard to established risk factors. Framingham Heart Study participants were free of CVD (MI, coronary insufficiency, angina, stroke, claudication) at 50 years of age and were followed up to 95 years of age. Participants included 3564 men and 4362 women who were followed up for a total of 111 777 person-years. During follow-up, 1757 participants had an incident CVD event, and 1641 died of something other than overt CVD. Men who were free of CVD at 50 years of age had a lifetime risk (to 95 years of age) for developing CVD of 51.7% (95% CI, 49.3%–54.2%).<sup>77</sup> Median overall survival for men was 30 years. Women who were free of CVD at 50 years of age had a lifetime risk (to 95 years of age) for developing CVD of 39.2% (95% CI, 37.0%–41.4%). Median overall survival for women was 36 years. The effect of individual risk factors, such as elevated blood pressure and TC, was associated with increased lifetime risk for CVD and with shorter median survival in both men and women. The presence of diabetes at age 50 years yielded the highest lifetime risk for CVD of any single risk factor—67.1% for men and 57.3% for women through 75 years of age. Smokers had CVD events much earlier than nonsmokers. Although lifetime risk for CVD was similar for smokers and nonsmokers, the risk of death from other smoking-related causes shortened the median survival of smokers by 5 years. Compared with participants who had 2 or more major risk factors at age 50 years, participants with optimal risk factor levels had much lower lifetime risks (5.2% vs 68.9% in men; 8.2% vs 50.2% in women) and

significantly longer median survival (>11 years in men, >8 years in women). In addition, when low HDL-C (<40 mg/dL in men, <50 mg/dL in women) and obesity (BMI  $\geq$ 30 kg/m<sup>2</sup>) were evaluated, lifetime risks for CVD were similar to those associated with major risk factors (elevated TC and blood pressure).

The results of this study fully support the observation that CVD is a major cause of mortality in the United States. For individuals free of CVD at age 50 years, more than half of men and almost 40% of women will develop CVD during their remaining life span.<sup>77</sup> Therefore, the presence of risk factors in a young or middle-aged individual will make a substantial contribution to the development of atherosclerosis if they are not modified early in the life course.

Important to emphasize is that CVD risk prediction (in the United States and globally) has been a focal point for substantial controversy and research. Historically, the assessment of risk has been a key component in efforts to define risk factors for CVD, to identify and assess potential targets for therapy, and to enhance the cost-effective implementation of therapies for both primary and secondary prevention.<sup>64</sup> Recent emphasis has been placed on the need for additional research to understand the clinical utility and impact of both short- and long-term risk estimation and corresponding strategies for provider-patient risk communication.<sup>64</sup> A cornerstone of CVD risk assessment and management, as CVD risk prediction models and prevention algorithms for risk communication, patient motivation, and clinical decision making are modified to reflect results of ongoing research, guidelines for primary and secondary prevention (discussed in the following section) will also be modified.

### Primary and Secondary Prevention of Cardiovascular Disease: Overview of Recent Evidence-Based Guidelines

Based on available evidence, the AHA issued revised guidelines for primary prevention of CVD and stroke in 2002.<sup>62</sup> These guidelines present a comprehensive approach to the prevention of a first episode of CHD or stroke and focus in large part on the adoption of a healthy lifestyle, which is the cornerstone of primary prevention. Included in the guidelines are recommendations for the avoidance of tobacco, healthy dietary patterns, weight control, and regular exercise, as well as blood pressure and lipid targets, and aspirin therapy based on individual CVD risk status. The need for the management of diabetes and atrial fibrillation is also addressed. In 2006, the AHA and the American College of Cardiology published secondary prevention guidelines for patients with CHD and other atherosclerotic vascular disease.<sup>78</sup> These differ from the primary prevention guidelines by including recommen-

dations for aggressive risk-reducing therapies that have been shown to improve survival and quality of life and to prevent recurrent events and the need for coronary interventions. The secondary prevention guidelines added the optional lower LDL-C target of less than 70 mg/dL for very high-risk CHD patients. Complete smoking cessation, good blood pressure control, regular physical activity, weight management, a heart-healthy diet, and diabetes management are recommended, in addition to antiplatelet agents, renin-angiotensin-aldosterone system–blocking agents, and  $\beta$ -blockers in most patients, unless otherwise contraindicated. Finally, the guidelines state that patients with CVD should have an annual influenza vaccination.<sup>78</sup>

Evidence-based prevention guidelines specific to women were updated in 2011 by the AHA.<sup>79</sup> These guidelines were prompted by the recognition of CVD as a major cause of mortality among women worldwide. They address the limitations of the Framingham global risk score in women and appreciate that the average lifetime CVD risk in women is very high. Recommendations are based on a risk stratification scheme that classifies women into high risk, at risk, or at optimal risk. These guidelines provide recommendations for both primary and secondary prevention, including both lifestyle and drug therapies. Daily administration of omega-3 fatty acids and screening for depression were added as considerations for women with CHD. In addition, potential risks and benefits of hormone replacement therapy, antioxidant vitamins, folic acid supplementation, and aspirin to prevent MI in women younger than 65 years of age were identified and discussed. As noted above, these guidelines for women are likely to be revised as additional evidence becomes available.

The Joint British Societies (British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, and The Stroke Association) have published integrated prevention guidelines for patients with established CVD, those with diabetes, and healthy individuals at high risk ( $\geq$ 20% over 10 years).<sup>63</sup> These guidelines are similar to the AHA/American College of Cardiology secondary prevention guidelines; however, they are written in more comprehensive, narrative form with substantiating evidence and also include audit standards for CVD prevention. They represent the combined work and agreement of many medical societies and organizations committed to the important goal of CVD prevention.

### Summary

Global evidence indicates that CVD processes begin early in life and are influenced over the life course by both nonmodifiable and potentially modifiable behaviors, risk factors, and environmental exposures. Viewed from a life course social-ecological perspective,

### Clinical Pearls

- Global evidence indicates that CVD processes begin early in life and are influenced over time by both nonmodifiable and potentially modifiable behaviors, risk factors, and environmental exposures.
- Viewed from a life course social-ecological perspective, efforts to promote cardiovascular health and reduce the risk and burden of CVD globally must extend beyond the level of the individual and include such contexts as the family, school, community, and broader societal influences.
- Extensive evidence has emerged over the past several decades that prompted the development of CVD prevention guidelines for children, adolescents, and adults.
- Ongoing research is focused on determining optimal individual and population-based approaches to CVD prevention on a global level.

efforts designed to promote cardiovascular health and reduce the risk and burden of CVD globally must attend to individual modifiable factors and those that extend beyond the level of the individual including such contexts as the family, school/community, and broader societal influences. Extensive evidence has emerged over the past several decades that prompted the development and dissemination of CVD prevention guidelines for children, adolescents, and adults. As new evidence becomes available, guidelines for CVD prevention will be revised. Ongoing research is focused on determining and developing optimal individual and population-based approaches to CVD prevention on a global level.

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