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Prediction of Coronary Heart Disease Events Part 2: The Contribution of Lifestyle Factors and New Issues

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Part 1 of this topic, in the last issue of *Cardiology Rounds*, presented traditional risk factors such as age, gender, cholesterol, blood pressure, smoking, and diabetes and the part they play in predicting coronary heart disease (CHD). In Part 2, the focus is on lifestyle factors (eg, nutrition, physical activity, and obesity) and their contribution to the development of CHD. Other issues that can influence multivariate CHD risk assessment are also discussed such as lifetime risk, inflammatory markers, newer lipid biomarkers, the metabolic syndrome and insulin resistance, genetics, subclinical cardiovascular disease, and kidney disease.

Lifestyle aspects that underlie risk factors

Nutrition, physical activity, and obesity are key lifestyle and environmental features that generally underlie the development of risk factors. Prevention programs often emphasize the importance of these features. For example, greater dietary intake of cholesterol and saturated fat has been related to higher cholesterol levels in several populations.[1,2] Finland, the region with the highest mean levels of cholesterol in the 1970s, enacted countrywide programs to improve the diet. As a result, the proportion of adults in that country with blood cholesterol levels >250 mg/dL declined from 16% to 3% of the population by the 1990s.[3] On the other hand, cholesterol levels have diminished modestly in the U.S. population over the past 2 decades and the average cholesterol in adults is approximately 204 mg/dL.[4]

There is great interest in popular diets, but long-term vascular disease outcome data are generally not available and observational data continue to be the mainstay of nutritional guidelines for the overall consumption of calories, fat, and carbohydrates. Dietary cholesterol guidelines promulgated by expert committees[48] now recommend consumption of a variety of foods, including fruits, vegetables, grains, and that a healthy body weight, desirable cholesterol level in the blood, and desirable blood pressure (BP) levels are all important.[5]

Increased oxidation has been proposed as an important contributor to atherosclerosis and led to an interest in nutrients that have anti-oxidant properties.[6] Vitamins B, C, and E have been studied the most, with several observational studies suggesting that greater intake of these vitamins in regular food or as supplements has favorable effects on cardiovascular risk.[7,8] However,

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recent controlled clinical trials of supplemental vitamins have generally not demonstrated reductions in risk of cardiovascular disease (CVD).[9-11]

Alcohol intake in the range of >2 drinks/day in men and >1 drink/day in women has consistently been related to a reduced risk of CHD.[12] Favorable effects on high-density lipoprotein (HDL) cholesterol levels are thought to be important in exerting this effect, as well as anti-inflammatory and anti-platelet effects. Greater alcohol intake is not without hazards, however, and a greater risk of gastrointestinal bleeding, hemorrhagic stroke, accidents, suicide, and cirrhosis may be associated with increased intake.[13]

A more active lifestyle generally leads to lower risk for CHD. Early studies investigated occupations and risk for CVD, but more recent research has concentrated on leisure-time physical activity. Data from the Harvard Alumni Study showed that greater exercise was inversely related to risk of fatal and nonfatal myocardial infarction (MI) over an 8-year interval.[14] This result and others showed that physical activity in middle-aged adults was important in reducing CVD risk.[15] There is, however, an increased risk for sudden cardiac death during or following exercise in persons who generally perform little exercise, but adverse events are uncommon.[16,17]

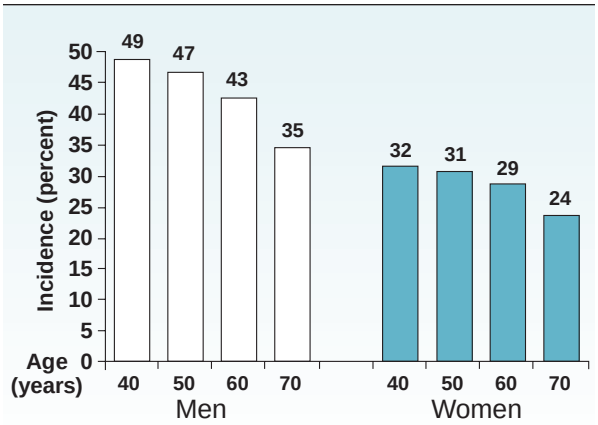
Greater fitness that has been documented by longer exercise treadmill times has been related to reduced risk for CHD in men and women.[18] Persons in the lowest quintile of fitness experienced the highest CHD event rates and even modest degrees of fitness were related to lower risk of CHD in studies of middle-aged men and women.

Obesity

Excess adiposity has been defined by the World Health Organization and 2 general measures are used: body mass index (BMI, which is calculated using body weight in kilograms divided by height in meters squared); and abdominal girth (greatest circumference of the abdomen when a subject is standing).[19] A person is considered overweight when the BMI is 25-29.9 kg/m^2 and obese when the BMI is >30 kg/m^2. Increased abdominal adiposity is defined as >90 cm for women and >100 cm for men.

The prevalence of obesity has increased dramatically over the course of the past 30 years in the United States.[20] Data from U.S. surveys from 1960 to 2000 have shown that the prevalence of obesity more than doubled, from 10% to 27% in men and from 16% to 34% in women.

Figure 1: Lifetime risk of CHD – Framingham men and women[24]



Correspondingly, the prevalence of overweight has also increased and it is now estimated that >50% of American adults are either overweight or obese.[19,49] A similar worrisome pattern is occurring in adolescents.

Obesity contributes to the development of several CHD risk factors, especially hypertension, diabetes mellitus, low HDL cholesterol, elevated triglycerides, and elevated levels of inflammatory markers. Weight gain, even relatively modest increases, during the adult years is highly related to developing a greater risk factor burden.[21] Obesity augments the effects of traditional risk factors and accounts for approximately 23% of CHD in men and 15% in women in long-term analyses of Framingham data.[22] When obesity is considered as an additional risk factor for the development of CHD over and above the traditional risk factors, there is no added benefit in knowing the level of obesity. The absence of an effect potentially has many sources as adiposity is highly related to BP, low HDL cholesterol, diabetes mellitus, age, and inflammatory markers.

Newer issues for multivariable CHD risk assessment

Lifetime risk

The lifetime risk of CHD is highly related to gender and age. At age 40 years, the Framingham men experienced a 49% risk of developing CHD (angina pectoris, MI, or CHD death) prior to death. The lifetime incidence was lower in older persons who had never experienced CHD and, at age 70 years, the lifetime risk for CHD in men was 35% (Figure 1). The lifetime risks for CHD in women were lower at each age in comparisons to the men. Overall, the lifetime risk for CHD was approximately 40% in men and 30% in women.[23] In contrast, the lifetime

risk for developing breast cancer in women is approximately 10%, a rate that is much lower than a woman's lifetime risk for CHD. Lifetime risk estimates extend the traditional 5- to 10-year CHD risk estimates to a distant horizon, but this approach has not been incorporated into CHD risk estimating strategies that are in common usage in the United States and Europe.

Inflammation

A variety of factors related to hematologic, endothelial, or inflammatory processes have been studied regarding their relationship to CHD. Early studies investigated leukocyte count and these were followed by fibrinogen determinations. In a meta-analysis, patients with fibrinogen levels in the top third had a doubling of risk for initial and recurrent CVD events.[24] A European investigation assessed the relationships between recurrent CHD and levels of fibrinogen, von Willebrand factor antigen, t-PA antigen, and C-reactive protein (CRP) in persons with angina pectoris. Each of these markers was highly related to a greater risk of subsequent CHD in categorical analyses that used quintiles of each factor.[25] Subsequent research in a large number of studies has shown that inflammatory markers, especially CRP, are highly related to increased risk of atherosclerotic events,[26] including initial and recurrent CVD, as well as stroke.[70-73] Therefore, measurement of inflammatory markers, specifically high sensitivity C-reactive protein (hsCRP), is now considered a reasonable adjunct to the major risk factors to further assess absolute risk for coronary disease primary prevention.[31]

Blood levels of the amino acid homocysteine have been studied for their relationship to CVD risk. In the early 1990s, investigations demonstrated that a lower intake of B vitamins (folate, vitamin B_6, vitamin B_{12}) was related to greater concentrations of homocysteine.[32] Persons with higher homocysteine levels experienced greater risk for CVD; however, reports of this relationship were more frequent in earlier studies than in more recent investigations.[33,34] Folate fortification of cereals and grains was undertaken in the United States during the late 1990s to reduce the risk of neural tube defects during pregnancy and this appears to have reduced the frequency of elevated homocysteine levels in the free living population.[35] Additional folate intake from supplementary vitamins and multivitamins may be contributing to the reduced importance of homocysteine as a CVD risk factor. However, homocysteine may still be an important contributor to greater CHD risk in specific situations, such as in persons with impaired kidney function.[36,37]

Newer lipid biomarkers

A large variety of lipoprotein particles have been identified and several techniques are available for assessing their density, diameter, electrophoretic characteristics, and nuclear magnetic resonance properties. Initially, the low-density lipoprotein (LDL) particles received the most attention, as apolipoprotein B is present in the LDL fraction. Research interest has spread to investigating the role of all particle groups as newer methods have allowed rapid assessment of the numbers and concentrations of lipoprotein particles.[38-40] The smaller denser LDL particles may be associated with greater risk, but the added usefulness of these measurements for the assessment of CVD risk in prospective studies is not assured at this time.[41,42]

Lipoprotein (a) [Lp(a)] is an accepted determinant of CVD risk and this particle includes an LDL moiety that is linked to a protein chain that bears homology to plasminogen. The length of the apo (a) protein varies and is heritable. A variety of methods have been undertaken to assay Lp(a),[43] but standardization has been difficult because the particle varies in composition from person to person.[44] Levels of Lp(a) are higher in Africans and African Americans than in whites.[45] In African populations, the particle concentrations follow a normal statistical distribution, but Lp(a) levels are lower and the distribution is skewed in whites. Lp(a) has generally been shown to be a CVD risk factor, especially at the higher concentrations (>30 mg/dL) in whites.[46] Routine screening for Lp(a) levels has been recommended for persons with premature CVD that is not explained by conventional risk factor levels.[47,48]

Metabolic syndrome and insulin resistance

Several CVD risk factors occur at a greater frequency than expected and insulin resistance is thought to account for a clustering of traits, especially higher BP, impaired fasting glucose, increased triglycerides, decreased HDL cholesterol, and greater abdominal adiposity. The presence of ≥3 of these 5 abnormalities has been named the "metabolic syndrome," and some of the criteria are sex-specific.[50]

The metabolic syndrome is present in approximately 24% of American adults according to U.S. survey data from the early 1990s and the prevalence is highly related to age, ranging from 7% in persons aged 20-29 years to 43% in persons aged 60-69 years.[51] The presence of the metabolic syndrome in adults has been shown to confer an increased risk of diabetes mellitus, CHD, and CVD death.[52-54]

Genetics

Determining the contribution of genetic abnormalities and variants in common genes to the risk of atherosclerotic disease is an intensely active area of investigation.[55,56] Diseases such as familial hypercholesterolemia have been shown to have several potential causes and, taken together, they probably account for approximately 5% of the case burden of persons with MI.[57] The different alleles of apolipoprotein E have been related to cholesterol and triglyceride levels in young adults, the risk of CVD in middle age, and dementia in older age.[58-60] The apolipoprotein E4 allele is present in approximately 24% of the population and is associated with a relative risk for CHD of 1.5. This has led to the realization that this gene variant accounts for approximately 10% to 15% of CHD.[59,61] Variants of several other genes, including the angiotensin-converting enzyme, lipoprotein (a),[44] cholesterol ester transfer protein, hepatic lipase, and methylene tetrahydrofolate reductase [MTHFR] (related to folate and homocysteine metabolism), are some examples of candidate genes being studied for their relationship to metabolic factors and CHD risk and the list of candidates is growing rapidly. It is likely that genetic information will be used to assess the potential of developing risk factors in middle-age and to evaluate differential responses to environmental and pharmacologic interventions.

Subclinical cardiovascular disease

Modern techniques can provide an assessment of subclinical vascular disease in smaller arteries. The carotid arteries have been studied with B-mode ultrasound and, more recently, with magnetic resonance imaging. Greater carotid stenoses in older persons have been correlated with the burden of smoking, high BP, and higher cholesterol levels during the adult years,[62] and increased intima media thickening of the carotid arteries in the elderly has been shown to be predictive of the subsequent development of CVD.[63] The usefulness of these testing modalities is limited by the need for accurate measurements and trained sonographers.

Over the past few years, scanning the coronary arteries for the presence of calcification has been proposed as a useful strategy for identifying persons at high risk for the development of clinical CVD.[64,65] Data from less potentially biased groups without self-referral are limited at the present, but large investigations, such as the Multi-Ethnic Study of Atherosclerosis, should help provide a critical assessment of the added usefulness of these newer screening modalities in non-selected population cohorts.[66]

Kidney disease

In the 1980s, proteinuria was shown to be related to an increased risk of CHD[67] and more recent research has focused on microalbuminuria (> 30 mg/gm urinary creatinine) as a marker of renal impairment in persons with hypertension or diabetes mellitus. Modest decrements in estimated glomerular filtration rate and the presence of microalbuminuria have been shown to be important predictors of decline in renal function and the development of CVD.[68,69] Assessment of albumin excretion is now recommended at regular intervals for persons with diabetes mellitus or hypertension.

Long-term treatment of hypertension and type 2 diabetes mellitus has led to the extension of life, but chronic kidney failure may occur. These 2 diseases are now the most common diagnoses for persons who need to start chronic dialysis.[70] Once renal failure has developed, the prognosis is quite poor since atherosclerosis appears to enter an accelerated phase and death from CVD or from cardiac failure is quite common.

Summary

The summation of risk factors, using modern research methods, provides a quantitative estimate of an individual's odds of manifesting CHD in the future. Even more important, these factors provide a rationale and target for therapies and lifestyle modifications to substantially reduce, but probably not eliminate, the absolute risk for future atherosclerotic events in westernized societies.

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