

Preventing Heart Disease in the 21st Century Implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study

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We could prevent 90% of heart attacks. Such a claim would have seemed outrageous in the 1960s, as the coronary heart disease (CHD) epidemic reached new heights and accounted for one third of all deaths in the United States and most other developed countries.¹ The identification of conditions that predicted the probability of CHD (known as “risk factors”) stimulated hope that modification of these risk factors would reduce the frequency of CHD. Long before this idea was validated in clinical trials, individual physicians^{2,3} and voluntary health agencies⁴ began in the 1960s to promote the concept to the public. Many individuals accepted the idea, and many physicians adopted the recommendations in their practices.

The US CHD mortality rate declined to approximately half its former level by 1990.⁵ The associated favorable changes in risk factors accounted for about half of this decline, whereas improved treatment of CHD accounted for the other half.⁶ The extent and severity of atherosclerosis also declined during this period.^{7,8} CHD mortality continued to decline after 1990 but at a slower rate, and CHD remained the leading cause of death in the United States.⁹

A convergence of evidence from diverse sources in the last 2 decades now indicates that the claim that we can prevent 90% of CHD should no longer be thought of as outrageous but as achievable. For example, the absence of the major established CHD risk factors at 50 years of age has been shown to indicate a 90% lower lifetime risk (to age 95 years) for men and a 79% lower risk for women.^{10*} Subjects in several large cohorts without any of the major risk factors who were followed up for 16 to 22 years had 77% to 92% lower (men) or 79% lower (women) CHD mortality.^{11†} A mutation in PCSK9, a gene that

regulates low-density lipoprotein (LDL) cholesterol, has been shown to result in a 28% reduction in LDL cholesterol and an 88% lower risk of CHD.¹²

The present report reviews the benefits and limitations of CHD prevention efforts in adults and attempts to expand prevention efforts to young people. We summarize evidence showing that CHD risk factors are associated with both the early and advanced stages of atherosclerosis. This evidence supports the need to maintain a low lifetime risk by preventing development of risk factors in youth or controlling risk factors if they do develop, measures that will prevent atherosclerosis and thereby prevent CHD.

Risk Factor Control in Adults Reduces but Does Not Eliminate CHD

A number of controlled clinical trials of fat-modified diets¹³ and drugs¹⁴ yielded mixed results, but ultimately, modification of individual risk factors in adults was shown to reduce CHD risk. Cholestyramine was proven to lower LDL cholesterol levels and reduce CHD incidence¹⁵; a decade later, a statin was shown to lower LDL cholesterol and CHD incidence more effectively.¹⁶ Smoking cessation has also been shown to reduce the incidence of CHD.¹⁷ Pharmacological treatment of hypertension lowers both the incidence of CHD and the incidence of ischemic and hemorrhagic stroke.¹⁸

However, CHD was not eliminated. Control of blood glucose levels in individuals with type 2 diabetes mellitus resulted in a reduction in risk of microvascular renal disease but not of atherosclerotic disease.¹⁹ Obesity was associated with the incidence of CHD after long observation periods.^{20,21} No studies have demonstrated reduction in CHD after weight loss due to lifestyle changes, but bariatric surgery improved

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The online-only Data Supplement, consisting of a list of the PDAY research group, can be found with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.107.717033/DC1>.

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*Framingham Heart Study subjects with optimum risk factor levels at age 50 years had a lifetime risk of atherosclerotic cardiovascular disease of 5.2% for men and 8.2% for women. These lifetime risks were compared with 51.7% for men and 39.2% for women in the entire cohort studied (3564 men and 4362 women) and represent a reduction in risk of 90% for men and 79% for women.

†Multiple Risk Factor Intervention Trial subjects without risk factors at baseline and followed up for 16 years had age-adjusted relative risks of CHD mortality of 0.14 for men 35 to 39 years of age and 0.22 for men 40 to 57 years of age compared with all others; these represent 86% and 78% reductions, respectively. Chicago Heart Association Detection Project in Industry subjects without risk factors at baseline and followed up for 22 years had age-adjusted relative risks of CHD mortality of 0.08 for men 18 to 39 years old, 0.23 for men 40 to 59 years old, and 0.21 for women 40 to 59 years of age compared with all others; these represent 92% and 77% reductions for men, respectively, and a 79% reduction for women.

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risk factors and lowered cardiovascular mortality slightly.²² Interventions to control blood cholesterol, blood pressure, and smoking for 7 years led to a 11.4% reduction in CHD mortality after 16 years.²³ Even the best result obtained in a single study with statins in adults reduced CHD by only 40%, and the average reduction achieved in 14 trials was 23%.²⁴ Statins administered to high-risk persons without clinically manifest CHD lowered major cardiovascular event rates but not CHD mortality or overall mortality.²⁵ A Cochrane review concluded that multiple risk factor intervention in adults had no effect on mortality.²⁶

The partial protection conferred by risk factor modification in adults has contributed to the idea that the major established risk factors “explain” only half of all CHD events. Additional proposed risk factors added little, if anything, to the predictive ability of the established risk factors.^{27,28} One or more of the major risk factors (dyslipidemia, hypertension, smoking, and diabetes mellitus) were present in more than 85% to 90% of subjects experiencing CHD.^{29–31} These results indicate that the “only 50% myth” should be abandoned^{32,33} and support focusing on the major risk factors to reduce CHD.

Furthermore, few adults have adopted a healthy lifestyle that reduces CHD risk³⁴; the risk of CHD did not decrease during the decade ending in 2002³⁵; and the prevalence of individuals with no known major risk factors declined during the same period.³⁶ Primarily because of the epidemic of obesity, life expectancy may decline instead of continuing the increase of the last century.³⁷

The achievements in prevention and treatment of CHD are impressive. Some would argue that we are on the right track to prevention and that we only need to do better in getting adults to control their risk factors; however, as the foregoing review shows, risk factor control in adults, no matter how aggressively pursued as recommended by current guidelines and no matter how successfully implemented, does not seem likely to approach the 90% goal. Achieving this goal requires a more effective strategy for the 21st century.

The Childhood Origin of Atherosclerosis

The foundation for a more effective strategy for preventing CHD was laid early in the 20th century by reports of a high prevalence of fatty streaks in the large arteries of children.^{38,39} Seventy-seven percent of young men (average age 22 years) killed in the Korean war had advanced atherosclerosis⁴⁰; 18 years later, Vietnam casualties had a similar prevalence.⁴¹ The progression of atherosclerosis from childhood fatty streaks to clinically significant fibrous plaques during young adulthood was established in the 1950s⁴² and 1960s.^{43,44} A comparison of coronary artery lesions among racial and ethnic groups around the world indicated that among groups with high rates of CHD, the fatty streaks of childhood were converted into fibrous plaques and complicated lesions during the third and fourth decades of life, 20 years or more before clinically manifest CHD appeared.⁴⁵ Light and electron microscopy and chemical analyses of lesions have shown a seamless progression of atherosclerosis from the earliest fatty streaks to fibrous plaques.^{46–48} Fibrous plaques then undergo a variety of changes (hemorrhage, rupture, thrombosis) that lead to obstruction and clinically manifest CHD.

Atherosclerosis as a Pediatric Problem

Russell Holman in 1961 described atherosclerosis as a “pediatric problem.”⁴⁹ Seven similar editorials appeared during the following 20 years but received little attention because the beneficial effects of controlling CHD risk factors had not been firmly established in adults. However, as the natural history of atherosclerosis was appreciated and the effects of the risk factors in adult cardiovascular disease were demonstrated, investigators began in the 1970s to examine the prevalence of risk factors for adult CHD in children and adolescents in widely separated communities: Bogalusa, La⁵⁰; Muscatine, Iowa⁵¹; and multiple sites in Finland.⁵² The levels of the physiological characteristics identified as risk factors in adults were lower in children than in adults, but they were quite variable. Dyslipidemia, high blood pressure, smoking, and obesity were present.^{50,51,53} High serum cholesterol concentrations were associated with high saturated fat intake in the Finnish cohort.⁵⁴ Blood pressure was positively associated with ponderosity.^{55,56} Serum cholesterol and lipoprotein levels were associated with the prevalence of CHD and with CHD mortality in adult relatives.⁵⁷ Furthermore, serum lipids, blood pressure, and adiposity tracked through childhood and into young adulthood.^{58–60}

The Bogalusa Heart Study found that both coronary and aortic fatty streaks in 35 autopsied subjects were positively associated with LDL cholesterol and inversely with high-density lipoprotein (HDL) cholesterol measured during life.⁶¹ These associations suggested that risk factor control in young people might retard the progression of atherosclerosis.

The Pathobiological Determinants of Atherosclerosis in Youth Study

To examine more thoroughly the relation of CHD risk factors to atherosclerosis in young persons, in the early 1980s Robert Wissler of the University of Chicago recruited pathologists and scientists (principal investigators and grants are listed at <http://circ.ahajournals.org>) to participate in a multicenter project known as the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study.⁶² At the start of the PDAY study, assessment of atherosclerotic lesions was feasible only in autopsied individuals.

Design and Methods

The PDAY Research Group collected arteries, blood, tissue, and data from persons 15 through 34 years of age who died of external causes (accidents, homicides, and suicides) within 72 hours after injury and who were autopsied within 48 hours after death in 8 cooperating forensic laboratories. Between 1987 and 1994, PDAY investigators collected 2876 cases, ≈1500 of which had adequate material to measure all the risk factors. Approximately 25% of the subjects were women, and ≈54% were black.

Central laboratories stained the right coronary artery and the left half of the aorta with Sudan IV, and 3 pathologists estimated the percentage of intimal surface involved by fatty streaks and raised atherosclerotic lesions (fibrous plaques and complicated lesions). Four other pathologists estimated the fraction of fatty streaks that were raised (interpreted as advanced fatty streaks in transition to fibrous plaques).⁶³ Two

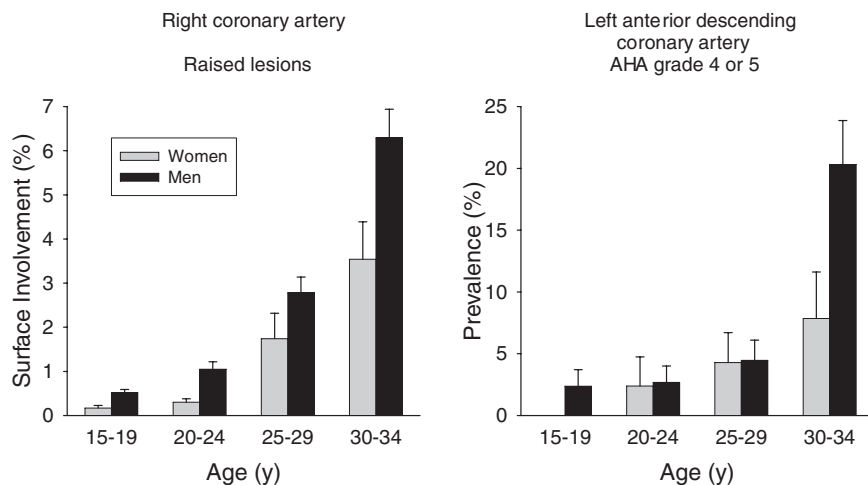


Figure 1. Extent of raised lesions in the right coronary artery (left; drawn from Strong et al,⁷⁰ copyright © 1999, American Medical Association; all rights reserved) and prevalence of AHA grade 4 or 5 lesions in the LAD (right; from McGill et al⁷²) in men and women. Bars represent SE.

pathologists graded histological sections of the left anterior descending coronary artery (LAD) according to the American Heart Association (AHA) grading system.⁶⁴

Central laboratories analyzed serum for total and lipoprotein cholesterol and thiocyanate (≥ 90 $\mu\text{mol/L}$ indicated smoking); analyzed red blood cells for glycohemoglobin ($\geq 8\%$ indicated hyperglycemia); measured the wall thickness of small renal arteries to estimate mean arterial blood pressure (increased renal artery thickness indicated hypertension); and computed the body mass index from body weight and length at autopsy (> 30 kg/m^2 indicated obesity). The results were published in a series of reports beginning in 1990.^{65–78}

Major Findings

Age, Sex, and Race: The Immutable Risk Factors

The extent of fatty streaks and raised lesions (Figure 1) in the right coronary artery increased with age.⁷⁰ The prevalence of AHA grades 4 and 5 in the LAD (Figure 1) increased slowly from 15 to 29 years of age and increased 2-fold in 30- to 34-year-old women and 3-fold in 30- to 34-year-old men.⁷² Because the characteristics of AHA grade 4 and 5 lesions indicate that they are vulnerable to rupture, a substantial proportion of young people had coronary artery lesions with the potential to precipitate CHD. The extent of fatty streaks in the abdominal aorta (not shown) increased between 15 to 19 and 25 to 29 years of age and decreased slightly in the 30- to 34-year-old age group as fatty streaks were replaced by a 2-fold increase in raised lesions. The extent of abdominal aortic raised lesions increased steadily with age.⁶⁸ Women consistently had about the same extent of fatty streaks in both the abdominal aorta and right coronary artery as men and about the same extent of raised lesions in the abdominal aorta as men; however, women had approximately half as extensive raised lesions in the right coronary artery by age 30 to 34 years, regardless of risk factors.⁶⁸ A similar sex difference appeared in the prevalence of advanced microscopic lesions in the LAD.⁷² Minor differences were present between whites and blacks in extent and qualities of atherosclerotic lesions, and blacks were more likely to be hypertensive, but the associations of lesions with risk factors were similar for both racial groups.

Lipids and Lipoproteins

The extent of fatty streaks and raised lesions in both the right coronary artery and the abdominal aorta was positively associated with non-HDL cholesterol concentration and inversely associated with HDL cholesterol concentration.^{65,68} Similar associations were seen with the AHA grade of histological sections of the LAD.⁷²

Hypertension

Hypertension was strongly associated with raised lesions in the right coronary artery.^{67,69} Hypertension also was associated with larger diameters of the right coronary artery and LAD and with the prevalence of AHA grades 4 to 5 in the LAD.^{69,72}

Hyperglycemia

Hyperglycemia was strongly associated with extent of fatty streaks and raised lesions in both the right coronary artery and the abdominal aorta⁶⁶ and with advanced microscopic lesions in the LAD.⁷²

Obesity

In men, obesity was strongly associated with more extensive fatty streaks and raised lesions in the right coronary artery⁷⁵ and with advanced microscopic lesions in the LAD.⁷² The associations were not explained by other risk factors. The effect of obesity on right coronary artery raised lesions was stronger among young men with a thick panniculus adiposus. No associations of obesity with atherosclerotic lesions existed in women; however, a trend was present for extent of right coronary artery fatty streaks to increase with increasing body mass index in women with a thick panniculus adiposus.

Smoking

Smoking had little effect on gross lesions of the right coronary artery,⁶⁸ but smokers had a higher microscopic grade of atherosclerosis in the LAD.⁷⁶ Smoking was associated with a much greater extent of fatty streaks and raised lesions in the dorsolateral aspect of the abdominal aorta,⁷¹ the site prone to atherosclerotic aortic aneurysms in older adults.

Nonlipid Risk Factors Without Dyslipidemia

Nonlipid risk factors were associated with atherosclerosis even in the presence of a favorable lipoprotein profile

(non-HDL cholesterol <160 mg/dL, HDL cholesterol ≥ 35 mg/dL),⁷⁴ a relationship that indicated that a poor lipoprotein profile is not a necessary condition for atherosclerosis. Because of limitations in a number of subjects, it was not practical to study the possibility that a lipoprotein profile exists in which the other major risk factors have no effect. A threshold for CHD risk associated with LDL cholesterol may not exist; relative risk of CHD has a log-linear relation with LDL cholesterol even at low levels, and the target level of LDL cholesterol should be lower when other risk factors are present.⁷⁹ Nonlipid risk factors may augment atherosclerosis at any level of LDL cholesterol.

PDAY Risk Scores

Individuals often have >1 risk factor, and their effects on atherosclerotic lesions are cumulative. PDAY risk scores for the coronary arteries (Table) and the abdominal aorta (not shown) were developed by use of logistic regression to provide a weighted summary of the effects of CHD risk factors on advanced atherosclerotic lesions.^{77,78} Although similar in concept to the Framingham risk score,⁸⁰ the PDAY risk scores predicted advanced atherosclerosis rather than clinical CHD events.

Figure 2 shows that the PDAY coronary artery risk score computed from the modifiable risk factors was associated with all microscopic grades of atherosclerotic lesions in the LAD.⁷⁸ Because grades 2 to 5 lesions were grade 1 lesions at an earlier age, these associations are interpreted as including accelerated transition from grade 0 (normal tissue) to a grade 1 lesion. Although the prevalence of intermediate (grade 3) and advanced (grades 4 and 5) lesions was low for risk scores 6 to 10 and ≥ 11 in persons 15 to 24 years of age, the prevalence of earlier lesions (grades 1 and 2) was substantial. These results further confirm that atherosclerosis is under way in a substantial number of young people by the late teenage years.

Figure 3 shows that the risk score computed from the modifiable risk factors was associated with the extent of gross lesions of all degrees of severity in the right coronary artery; these associations included accelerated transition from normal tissue to fatty streaks.⁷⁸ These effects on early lesions were observed at younger ages than ages at which effects on raised lesions occur.⁷³

The PDAY abdominal aorta risk score computed from the modifiable risk factors was associated with the extent of lesions of all degrees of severity in the abdominal aorta; these associations included accelerated transition from normal tissue to fatty streaks.⁷⁸ Advanced coronary atherosclerosis was strongly associated with advanced abdominal aortic atherosclerosis.⁷⁷

High relative risk at young ages likely will be transformed into high absolute risk of advanced coronary artery lesions later in life. When age is included along with the risk score computed from the modifiable risk factors, high relative risk due to the modifiable risk factors results in the probability of an advanced coronary artery lesion increasing dramatically with age (Figure 4).

When tested in subjects from another study of risk factors in older (35 to 54 years) autopsied persons, the PDAY risk score also was associated with advanced lesions.⁸¹

Table. PDAY Risk Score for Predicting Advanced Atherosclerotic Lesions in the Coronary Arteries

Risk Factor/Category	PDAY Coronary Artery Risk Score
Immutable risk factors	
Age, y	
15–19*	0
20–24	5
25–29	10
30–34	15
Sex	
Male*	0
Female	–1
Modifiable risk factors	
Non-HDL cholesterol, mg/dL†	
$<130^*$	0
130–159	2
160–189	4
190–219	6
≥ 220	8
HDL cholesterol, mg/dL†	
<40	1
40–59*	0
≥ 60	–1
Smoking	
Nonsmoker*	0
Smoker	1
Blood pressure	
Normotensive*	0
Hypertensive	4
Obesity	
Men	
BMI ≤ 30 kg/m ² *	0
BMI >30 kg/m ²	6
Women	
BMI ≤ 30 kg/m ²	0
BMI >30 kg/m ²	0
Hyperglycemia	
glycohemoglobin $<8^*$	0
glycohemoglobin $\geq 8\%$	5

BMI indicates body mass index.

*Reference category.

†To convert mg/dL to mmol/L, multiply values for non-HDL and HDL cholesterol by 0.0259.

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Risk Factor Effects on Atherosclerosis Are Underestimated

Atherosclerotic lesions are focal and occur in distinct patterns.⁷¹ Risk factor effects on sites where lesions are likely to develop are $\approx 25\%$ greater than effects estimated for an entire artery. Because only a small part of an artery needs

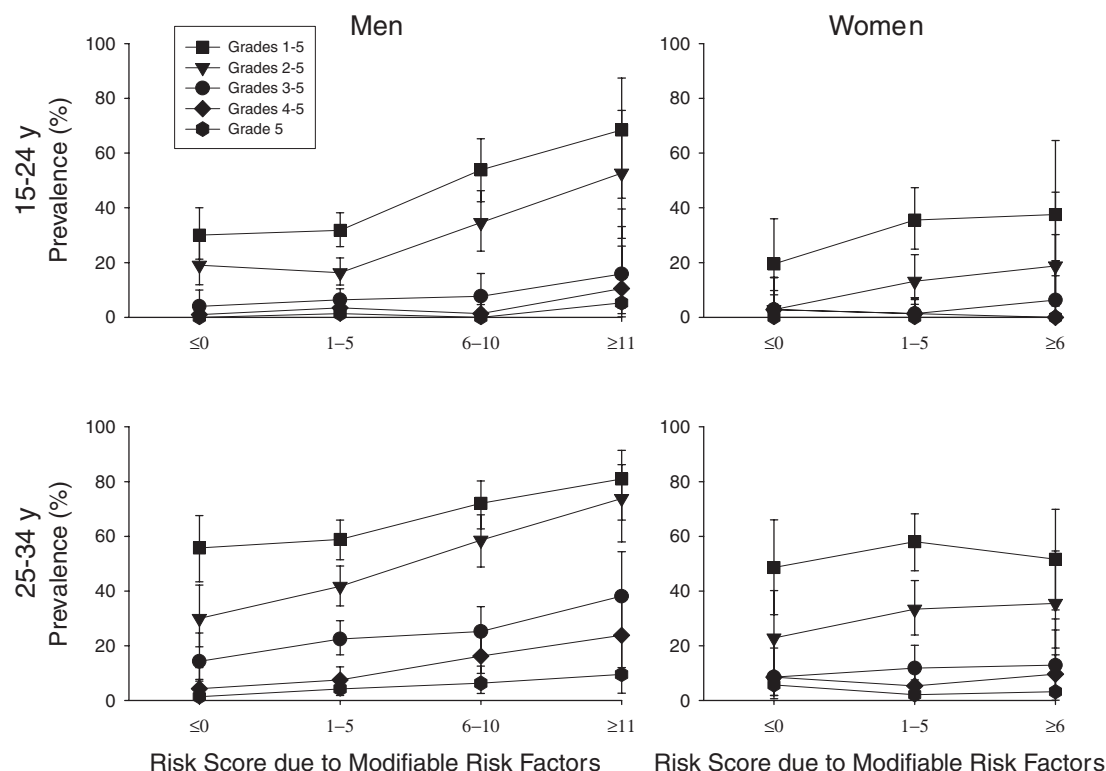


Figure 2. Prevalence of atherosclerosis in the LAD at varying levels of microscopic severity by PDAY coronary artery risk score computed from modifiable risk factors, sex, and 10-year age group. Severity was defined by a series of incremental cut points with increasing AHA grade, which dichotomized PDAY cases into lesion-positive and lesion-negative classifications. ■ indicates any lesion (ie, initial fatty streaks and more severe lesions, AHA grades 1 to 5); ▼, advanced fatty streaks and more severe lesions (AHA grades 2 to 5); ●, intermediate (transitional) lesions and more severe lesions (AHA grades 3 to 5); ◆, initial fibrous plaques and more severe lesions (AHA grades 4 to 5); and ●, advanced fibrous plaques (AHA grade 5). Bars represent 95% confidence intervals. Regardless of the cutpoint used to dichotomize the AHA grades, the odds of being in the worst category increased with increasing risk score (ie, the risk score was associated with prevalence of all degrees of severity of lesions). These associations include accelerated transition from normal tissue to the earliest detectable anatomic lesion. Reproduced with permission from McMahan et al,⁷⁸ copyright © 2006 by the American Academy of Pediatrics.

to be involved to cause clinical disease, some young adults may have been closer to a clinical disease event than indicated by the percent of intimal surface involved for an entire artery.

Variation in postmortem measurements of risk factors in serum (non-HDL and HDL cholesterol concentrations), which are subject to day-to-day variability as well as agonal and postmortem effects, are expected to attenuate associations of these risk factors and lesions. The resulting associations are estimated to be approximately two thirds of the correct magnitude.⁸²

Comparison With Another Study of Autopsied Individuals

The Bogalusa Heart Study expanded the initial investigation of 35 autopsied subjects⁶¹ to 93 subjects 2 to 39 years of age.⁸³ Body mass index, systolic and diastolic blood pressure, smoking, and serum concentrations of cholesterol, LDL cholesterol, and HDL cholesterol (inversely) were associated with the extent of atherosclerotic lesions in the aorta and coronary arteries.

Risk Factor Effects on Markers of Atherosclerosis in Living Young Adults

While the PDAY study was being conducted, the children whose risk factors had been measured in cohort studies grew

into young adults, and noninvasive methods of measuring markers of atherosclerosis, thickness of the carotid artery intima and media, and coronary artery calcification were developed. Reports began to appear in 2000^{84–87} that the risk factors measured in childhood were associated with carotid intima-media thickness or coronary calcification measured up to 15 years later. Remarkably, risk factors measured at younger ages were better predictors than risk factors measured concurrently with atherosclerosis assessment.^{86,87}

The PDAY risk score based on risk factors measured at 18 to 30 years of age predicted coronary calcification in 33- to 45-year-olds in the CARDIA (Coronary Artery Risk Development In Young Adults) study, and the change in risk score during the 15-year interval also predicted coronary calcification (Figure 5).⁸⁸ The PDAY risk score computed from risk factors measured at 12 to 24 years of age predicted carotid intima-media thickness at ages 27 to 39 years in participants in the Cardiovascular Risk in Young Finns Study, and risk score change during the 15-year interval also predicted intima-media thickness.⁸⁹

What These Results Mean for Achieving the Goal of 90% Reduction of CHD

Consistency of Evidence

A convergence of evidence from the PDAY and cohort studies demonstrates that risk factors are associated with

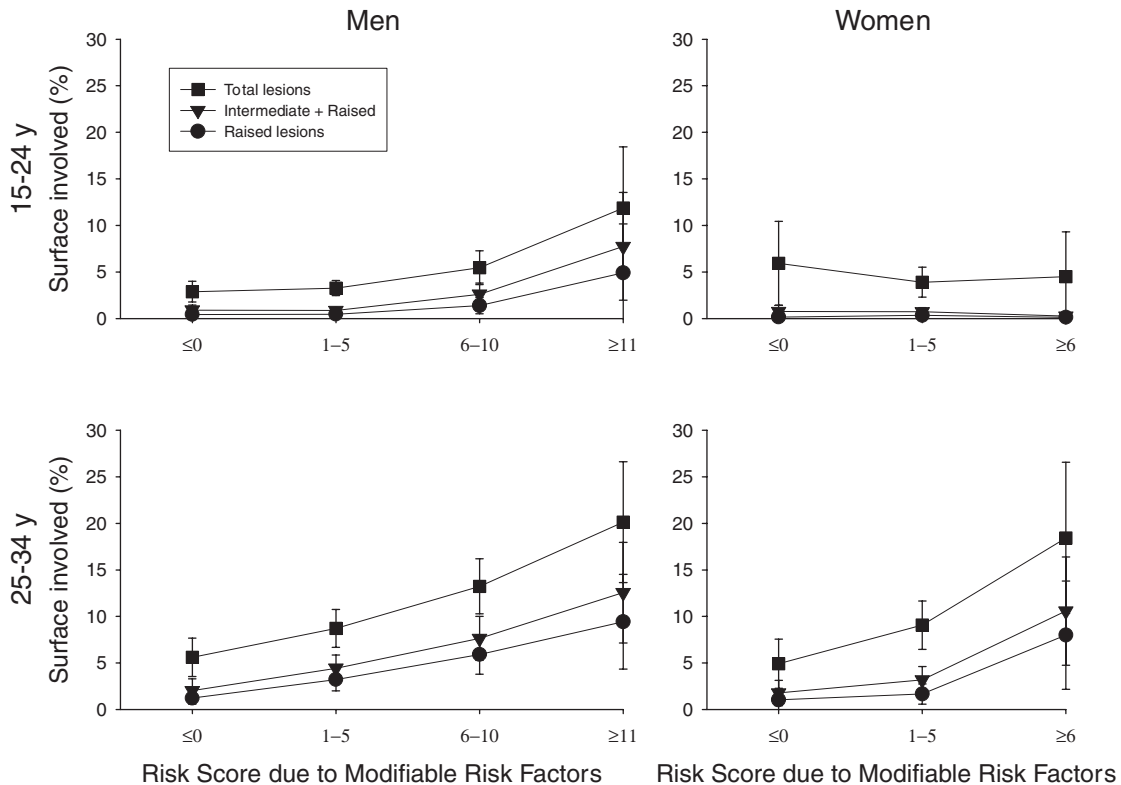


Figure 3. Extent of lesions in the right coronary artery by PDAY coronary artery risk score computed from the modifiable risk factors by sex and 10-year age group. ■ indicates any lesion (ie, fatty streaks, intermediate lesions, and raised lesions); ▼, intermediate lesions and raised lesions; and ●, raised lesions. Bars represent 95% confidence intervals. The risk score computed from the modifiable risk factors was associated with the extent of lesions of all degrees of severity in the right coronary artery. These associations include accelerated transition from normal tissue to fatty streaks. Reproduced with permission from McMahan et al,⁷⁸ copyright © 2006 by the American Academy of Pediatrics.

atherosclerosis from the teenage years through middle age and that the risk factors measured early in life predict advanced lesions later in life. Furthermore, changes in risk factors affect atherosclerosis later in life. Low risk during adolescence and young adulthood minimizes the severity of atherosclerosis that will exist when individuals enter the age during which clinical events occur. The differences between

men and women in extent and severity of atherosclerosis observed in young adulthood and the later occurrence of CHD in women than in men indicate that retarding the progression of lesions early in life would delay the subsequent onset of CHD. These results are consistent with the evidence that a lifetime low risk factor profile dramatically lowers CHD incidence.^{10–12}

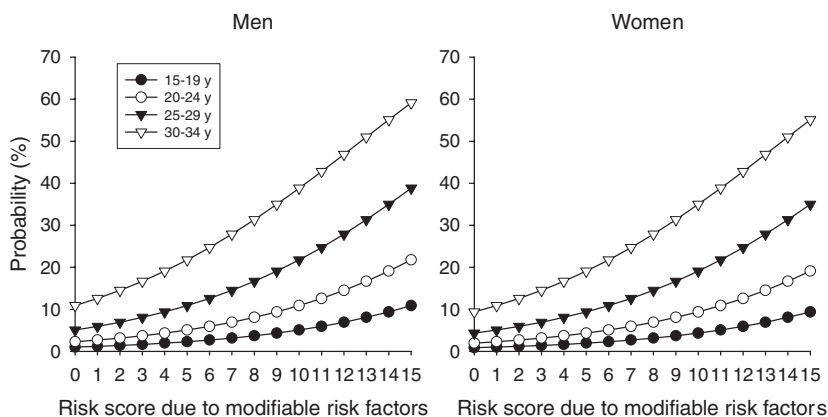


Figure 4. Estimated probability of advanced atherosclerotic lesions in the coronary arteries by PDAY risk score computed from modifiable risk factors and 5-year age group for men (left) and women (right). Example: A 16-year-old male with non-HDL cholesterol 160 to 189 mg/dL (4 points), smoker (1 point), obesity (6 points), and no other risk factors has 11 points in the coronary artery risk score due to modifiable risk factors. This figure shows that a male of age 15 to 19 years with these risk factors has only a 6% chance of having an advanced coronary artery lesion, but he has an ≈70% chance of having any (grades 1 to 5) lesion in the LAD (Figure 2) and has ≈12% surface area involvement with any lesion in the right coronary artery (Figure 3). These results indicate that atherogenesis

is well underway in this individual's late teenage years. When the age component is included in the risk score for this sample individual, high relative risk due to modifiable risk factors results in the chance of an advanced coronary artery lesion being ≈13% at age 20 to 24 years, ≈25% at age 25 to 29, and ≈43% at age 30 to 34. Redrawn from McMahan et al,⁷⁷ copyright © 2005, American Medical Association, all rights reserved; also from McMahan et al,⁷⁸ reproduced with permission from the American Academy of Pediatrics, copyright © 2006.

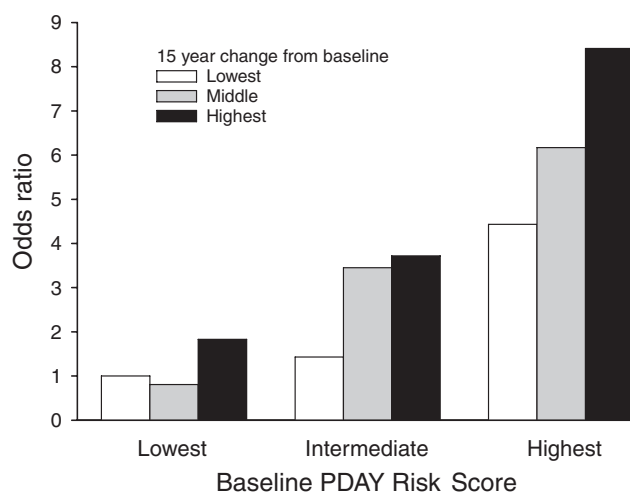


Figure 5. Odds ratios for coronary artery calcium at the year 15 Coronary Artery Risk Development in Young Adults (CARDIA) examination by PDAY risk score computed from modifiable risk factors at year 0 (lowest risk [scores of -1 or 0], intermediate risk [scores of 1 or 2], or highest risk [scores ≥ 3]) and by change in PDAY risk score from year 0 to year 15 within each of the risk groups. Reference category (odds ratio 1.00) is lowest year 0 risk, lowest change group. The PDAY coronary artery risk score predicts coronary artery calcium 15 years before its assessment, and change in risk score during the 15-year interval affects the likelihood of coronary artery calcium. From Gidding et al,⁸⁸ copyright © 2006, American Medical Association; all rights reserved.

Start Early

PDAY results confirm earlier observations that atherosclerosis begins in childhood and progresses seamlessly through adolescence and young adulthood into middle age. By their 30s, many young adults already have advanced coronary atherosclerosis, which includes not only calcified plaques detectable by radiography but also soft plaques more susceptible to rupture. Intervention in the fourth decade and later is actually secondary prevention, because advanced atherosclerosis likely is already present.

The PDAY risk score is associated with all stages of atherosclerosis, including the earliest detectable anatomic lesions (microscopic AHA grade 1 lesions and gross fatty streaks). Preventing the risk factors from developing is likely to yield maximum benefit. The finding that both a high baseline PDAY risk score and an increase in risk score over time were associated with the prevalence of markers of atherosclerosis further emphasizes the need for early control.

Figure 4 shows an increase in probability of advanced lesions with age for all PDAY risk scores. We interpret this relationship with age as due to an increased duration of exposure to the risk factors and not a result of the intrinsic aging process. A small increase in the probability of advanced coronary lesions occurs with age even for those with a PDAY risk score due to modifiable risk factors of zero. This result may be due to deficiencies in postmortem measurements of risk factors or to less than optimum definition of “no risk.”

Starting at Any Age Is Beneficial

It would be most effective to begin to control risk factors early in life, but the PDAY finding that risk factors are

associated with all stages of atherosclerosis indicates that risk factor control is likely to be beneficial regardless of the stage of disease when control is implemented. This PDAY finding is consistent with the positive benefits of intervention in adults.

All Risk Factors Are Important

All the major established risk factors accelerate the progression of atherosclerosis in the teenage and young adult years, and their effects are cumulative. Although risk factor effects vary in magnitude and in the arterial segments affected, no established risk factor can be safely ignored. These results reinforce the importance of controlling all the risk factors beginning in childhood and adolescence, as emphasized in AHA reports in 1992⁹⁰ and 2002.⁹¹

Prediction of Atherosclerosis in Youth Can Be Improved

The PDAY risk score identifies a young person at high likelihood of having advanced atherosclerosis. Noninvasive techniques applied to high-risk individuals can separate those with advanced lesions from those without, to guide individual interventions. Furthermore, longitudinal studies using noninvasive measurements of atherosclerosis will permit investigators to refine the PDAY risk score.⁸⁸

Are Clinical Trials Necessary Before Risk Factor Control Is Implemented in Youth?

The evidence supporting the usefulness of risk factor control in young people is based primarily on observational studies and inferences from studies of adults. Except for statin treatment of young individuals with familial hypercholesterolemia,^{92,93} no controlled clinical trial, the “gold standard” of proof of efficacy, has been conducted. Any trial that requires random assignment to lifestyle modification (healthy diet with caloric intake balanced with physical activity, avoidance of smoking) and evaluation for 15 or more years of follow-up does not appear to be feasible and perhaps is even unethical. The evidence demonstrating absence of harm and the benefits of preventing the development of CHD risk factors is sufficient to justify aggressive promotion of risk factor control in youth now. Evaluation of the benefits of risk factor control in young persons in shorter trials can use noninvasive methods, such as those used in assessing the effects of lowering blood lipids in children,⁹³ and measurement of functional markers associated with atherosclerosis.^{94,95}

Efforts to Control Risk Factors in Youth

Institutional and Expert Group Recommendations

The first formal institutional recommendation on risk factors in children came from the Committee on Nutrition of the American Academy of Pediatrics⁹⁶ in 1972 and focused on diet as a means of controlling plasma cholesterol levels in children with familial hypercholesterolemia. The AHA made a similar recommendation in 1978 and expanded the application to all types of hyperlipidemia.⁹⁷ The Cardiovascular Disease in the Young Council of the AHA recommended reduction of dietary fat and salt for all children to control serum lipids and blood pressure in 1983.⁹⁸ Similar but more

guarded recommendations were echoed by the American Academy of Pediatrics in 1983⁹⁹ and again in 1986.¹⁰⁰ In 1991, the National Cholesterol Education Program focused on serum cholesterol and lipoproteins in children but mentioned other risk factors only briefly.¹⁰¹ The AHA broadened its recommendations to include control of smoking, hypertension, and obesity in children in 1992⁹⁰ and repeated them in 2002,⁹¹ 2003,¹⁰² 2005,¹⁰³ and 2006,¹⁰⁴ with an increasing emphasis on all the major CHD risk factors. Other expert groups emphasized controlling blood pressure¹⁰⁵ and managing dyslipidemia in diabetic children.¹⁰⁶ Eleven editorial calls for CHD risk factor control in childhood and adolescence continued into 2006.

Hyperlipidemia

In 1972, teenage boys in a New England boarding school lowered their mean serum cholesterol concentration by 15% after consuming a fat-modified diet.¹⁰⁷ A fat-modified diet produced a nearly identical result in Finnish children 8 to 18 years of age in 1986.¹⁰⁸ Intensive intervention in schools to change diet among 13- to 15-year-old adolescents reduced serum cholesterol levels by 0.5 mmol/L (19 mg/dL).¹⁰⁹ Repeated dietary counseling of parents of children from infancy to 14 years of age about a fat-modified diet reduced the usual age-related rise in serum cholesterol and did not adversely affect growth or development.¹¹⁰ A pediatric practice-based program of dietary counseling for 295 hypercholesterolemic children resulted in a decrease in total serum cholesterol by 11 mg/dL and in LDL cholesterol by 12 mg/dL.¹¹¹ More than 600 children 8 to 10 years of age who consumed a fat-modified diet for 5 years lowered their LDL cholesterol levels modestly and experienced no adverse effects on growth, development, or a number of biochemical variables.^{112,113} Statins are effective for the small fraction of children with genetically programmed hypercholesterolemia.¹¹⁴

Obesity, Hypertension, and Diabetes Mellitus

The prevalence and consequences of obesity among children, the need to prevent obesity, and recommendations for efforts to reduce its prevalence were thoroughly reviewed in a recent Institute of Medicine report.¹¹⁵ Overweight in adolescents resulted in a relative risk of CHD mortality of 2.3, independent of adult weight, after 55 years of follow-up.¹¹⁶ Despite a few high-profile indications of progress, little or no indication can be observed of an actual reduction in childhood obesity.¹¹⁷

Blood pressures among children and adolescents increased between 1975 and 1990,¹¹⁸ between 1971 and 1981,⁵⁵ and between 1990 and 2000.¹¹⁹ In all 3 studies, the change was attributed in part to the increase in prevalence of obesity.

Smoking

An enormous body of literature is concerned with preventing young persons from starting to smoke tobacco and with smoking cessation, but most results are discouraging: 23% of United States high school students smoked cigarettes in 2005, only slightly fewer than the 28% reported in 1991.¹²⁰ A Cochrane analysis of tobacco cessation programs for young people concluded that “complex approaches show promise”

but that controlled trials are needed to identify effective programs.¹²¹

Physical Activity and Fitness

The Institute of Medicine report¹¹⁵ summarized a substantial body of literature and concluded that physical activity is associated with reduced CHD risk factors in youth, including serum lipoproteins and blood pressure, and a reduced incidence of type 2 diabetes mellitus and obesity.

Community- and School-Based Trials of Risk Factor Control

A review of the mixed results from a number of community- and school-based intervention trials reported between 1980 and 2000 concluded that school-based programs must be supplemented with “broader environmental and community change” to achieve substantial improvements in healthy behaviors among youth.¹²²

Where Do We Go From Here?

Converging evidence from autopsy and cohort studies reviewed in the present report supports the idea that control of the currently defined major risk factors throughout youth and into adulthood will substantially reduce CHD in middle age and later. Controlled clinical trials to support this conclusion are not needed before we adopt this strategy. The editorials and expert group reports calling for intervention in youth have appeared only in the medical literature, and most recommendations that have reached the public in newspapers, magazines, and television focus on risk factor control beginning in early middle age. By early middle age, individuals who have been at high risk for several decades likely already have advanced lesions.

Many pioneering efforts, too many to review in detail here, have been undertaken since 1980 to control CHD risk factors in children and adolescents by school- and community-based programs, individual counseling, pediatric practices, and legislation. These efforts targeted behaviors that affect the major CHD risk factors: nutrition, physical fitness and activity, and smoking. They have met with limited success, and all have concluded that better interventions are needed.

Two major strategies are available to pursue the goal of 90% reduction in CHD. The first is the clinical medicine model, in which physicians are encouraged to identify individual young people with CHD risk factors and to vigorously advocate lifestyle changes and, if necessary, pharmacological treatment that will modify their risk profile. The PDAY risk score may be useful in selecting young persons at extremely high risk who should be examined by a noninvasive method and treated even more aggressively if they have detectable lesions. This model can, at best, be applied to only a few individuals, because physician effort is limited, preventive care is not reimbursed, and interventions directed toward individuals are often ineffective because they are not supported by the surrounding culture.

The second major strategy is the public health engineering model, in which the environment is changed. Ultimately, broad social and cultural changes that pervade the entire population will be necessary to change behaviors in youth,

prevent or control CHD risk factors, and thereby prevent atherosclerosis. The support of parents, physicians and other health professionals, educators, scientists, and legislators will be required. The evidence justifies igniting a social movement that eventually will be supported by government. The AHA, the National Heart, Lung, and Blood Institute, and professional societies whose CHD prevention programs now focus primarily on adults should modify their programs to incorporate prevention or control of CHD risk factors in youth into the mainstream of programs to prevent CHD in the 21st century.

The goal of eliminating 90% of CHD is feasible with control of the major established risk factors beginning in youth. We need to create a society in which youths enter adulthood at low risk of CHD and maintain that low risk throughout life. The cultural and societal changes necessary to achieve this goal won't be easy, and they won't happen soon, but it's time to start.

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