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**Authors**

Pearson, Thomas A
LaCroix, Andrea Z
Mead, Lucy A
et al.

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# The Prediction of Midlife Coronary Heart Disease and Hypertension in Young Adults: The Johns Hopkins Multiple Risk Equations

Thomas A. Pearson, MD, PhD, Andrea Z. LaCroix, PhD, Lucy A. Mead, ScM, and Kung-Yee Liang, PhD

Educating medical students about the identification of risk factors for coronary disease and hypertension should be enhanced by exercises in which medical students identify their own risk factors and visualize the impact of current risk status on future risk of disease. A cohort of 1,130 former Johns Hopkins medical students were examined in medical school and followed annually from 1948 to 1964 to identify youthful factors associated with the development of coronary heart disease and hypertension in midlife. In the ensuing years through 1984, 51 cases of coronary heart disease and 114 cases of hypertension developed. Multiple risk equations using Cox proportional hazards regression were developed to predict these endpoints. Incidence of coronary heart disease was predicted best by an equation containing age, serum cholesterol at baseline, cigarette smoking at baseline, and paternal history of coronary disease. Hypertension was predicted best by an equation containing age, systolic blood pressure at baseline, paternal history of hypertension, and Quetelet index. These equations were applied to a class of present-day medical students to demonstrate the considerable variability in 30-year risk of coronary disease or hypertension. Thus, coronary heart disease and hypertension in midlife can be predicted by factors identified in youth. The Johns Hopkins multiple risk equations may be valuable as tools in preventive cardiology education to illustrate risk assessment and the importance of risk factor interventions. [Am J Prev Med 1990;6 (suppl 1):23–8]

Educating medical students about epidemiology and preventive medicine is often hampered by a lack of teaching material that emphasizes the tenets of these disciplines to the individual. As a consequence, these important areas of study often seem theoretical rather than applied and boring rather than immediately rewarding. One approach to this problem has been the screening of medical students for risk factors that cause disease to foster interest in the epidemiology of these diseases. This educational technique has been shown to be well received by medical students and to stimulate enthusiasm for preventive concepts.[1,2]

Data from the Framingham Heart Study have been used to illustrate the effect of cardiovascular risk factors on the development of coronary disease. The regression coefficients used generally have been those for the risk of developing coronary disease in eight years.[3] However, the youngest person in the Framingham cohort was 35 years of age at the inception of the study. To develop risk estimates for the majority of medical students, who are typically much younger (usually 25 years of age or less), risk estimates based on these regression coefficients must be extrapolated beyond the age range of the Framingham cohort. Furthermore, the risk of heart disease developing within eight years is very small for persons in their 20s; consequently, the effect of even the poorest cardiovascular risk-factor profile is not impressive. Finally, the Framingham cohort consists of persons of all occupations and educations, whereas medical students and physicians generally have enjoyed lower rates of various chronic diseases. Therefore, any estimates using the Framingham data

may not be generalizable to medical students. The lack of age-appropriate data for use in teaching programs has been lamented.[1]

The opportunity to develop equations predicting cardiovascular disease has arisen recently in the Johns Hopkins Precursors Study. This long-term, prospective study of Johns Hopkins medical students was begun by Dr. Caroline Bedell Thomas in 1946 as a study of precursors of hypertension and coronary heart disease (CHD). It entailed the collection of considerable data from medical students in the classes of 1948 through 1964. This cohort has been followed annually for the development of CHD and hypertension. Based on the experience of this cohort, multivariate risk equations were developed to identify youthful predictors of hypertension and coronary disease that are more relevant for predicting these diseases when present-day medical students are in midlife. These equations were applied to the risk profiles of Johns Hopkins medical students in 1984 who participated in the Preventive Cardiology Academic Award (PCAA) Collaborative Data Project.

## METHODS

### Data Collection and Follow-up

All first-year medical students matriculating into the Johns Hopkins School of Medicine classes of 1948 through 1964 were asked to participate in the Precursors Study. Of 1,337 eligible students, 66 (5%) did not participate (18 refused, 36 were never asked because of entrance in advance standing, and 12 left medical school before they could be asked to participate). The remaining 1,271 students (1,160 men, 111 women; 35 nonwhites) make up the Precursors Study cohort. The present analysis is confined to the 1,130 white males in this cohort. The procedures for data collection in the Precursors Study are recorded in detail elsewhere.[4] Briefly, all participants completed an extensive questionnaire, which included a history of CHD or hypertension in father or mother. Smoking habits were recorded as the number of cigarettes smoked per day. A thorough physical examination was performed, including height and weight. Blood pressure was recorded in the supine position, in the right arm, after a short rest. Serum total cholesterol was measured on nonfasting blood samples, using the Bloor method.[5]

The study cohort has been contacted by mail questionnaire annually since leaving medical school. Response rates to annual endpoint questionnaires have remained high during the follow-up period, approximately 87%–94% for return of at least one questionnaire during a five-year span of annual contacts. The present study is based on annual surveillance through 1984. The number of years of follow-up is variable, ranging between 19 and 35 years.

Incident cases of CHD include myocardial infarction (21 cases), angina pectoris (21 cases), and sudden death (nine cases). Of the 51 cases, 74.5% were verified with medical records or death certificates. Hypertension (114 cases) was defined as a history of elevated blood pressure requiring pharmacologic therapy.

### Statistical Methods

The relationship between risk factors measured in medical school and incidence of CHD and hypertension during the 19- to 35-year follow-up period first was evaluated by examining Kaplan-Meier survival curves;[6] differences in survival curves were tested for statistical significance using the log rank test.[7] Multivariate Cox proportional hazards models were then developed using risk factors selected from univariate analyses.[8]

### Application to Present Medical Students

Variables selected for testing in the multiple risk equations were those available in the PCAA Collaborative Data Project. This program involves the collection of knowledge and attitudes pertaining to preventive cardiology from first-year medical students at eight U.S. medical schools. As part of this data collection effort, an inventory of cardiovascular risk factors was obtained. A brief physical examination included height, weight, and blood pressure in the right arm after a five minute rest in the sitting position. Quetelet index computed as weight (kilograms)/height (meters)$^2$ was included as a measure of obesity. A fasting sample of plasma was analyzed for serum total cholesterol using methods standardized by the Lipid Research Clinics program.[9]

Data from the Johns Hopkins Medical School class of 1984 were entered into the multiple risk equations. The probabilities (cumulative incidence) of developing CHD or hypertension in 30 years were calculated for each student in the class matriculating in September 1984. The frequency distributions of these probabilities were plotted in histogram form.

## RESULTS

Based on Kaplan-Meier survival curves considering one risk factor at a time, the development of coronary disease was predicted by age, total cholesterol, and cigarette smoking. Paternal history of CHD at

the time of medical school and Quetelet index were not predictive of CHD in the Precursors cohort. Treated hypertension was not prevalent in the students during medical school, and subsequently was not predictive of CHD. Therefore, age, total cholesterol, and the number of cigarettes smoked daily were entered into the multivariate Cox proportional hazards model (Table 1). Paternal history of CHD was added for educational purposes, although it was not significantly related to CHD. Age, cholesterol, and smoking remained significantly predictive in the multivariate model, with relative risks of 4.45 for a 10-year difference in age, 1.69 for a 40-mg/dL difference in serum cholesterol, and 2.14 for current smokers of at least one pack per day versus nonsmokers (Table 2).

The probability of developing CHD in 30 years was then calculated for each of the male preventive cardiology students in the class matriculating in 1984. The distribution of risk is approximately log-normal, with most students having low risk (0%–2%; Figure 1). However, the probabilities ranged considerably, from 0.5% to 4.9% for risk of CHD within 30 years, illustrating the extent to which even youthful risk profiles may vary.

The equations were further applied to demonstrate potential effects of risk-factor alteration. Age, cholesterol level, and family history were kept constant for a single student. Cumulative incidence curves were then calculated for various amounts of cigarette smoking to demonstrate graphically the probability of developing CHD over time at various risk factor levels (Figure 2). A heavy smoker of two packs of cigarettes a day in medical school had a risk probability for developing CHD of 8.6% in 30 years; in contrast, the risk probability for his nonsmoking counterpart was 2.0%.

Using the same analytic strategy, multiple risk equations were developed for the prediction of hypertension. Baseline systolic blood pressure, Quete-

let index, and paternal history of hypertension were associated with later development of hypertension in the Precursors cohort. They were entered into the Cox proportional hazards model, in which they remained significantly predictive (Table 3). Age was included in the model even though it was not significantly associated with later hypertension. The relative risk of developing hypertension was 2.13 for a 20 mm Hg difference in baseline systolic blood pressure; 1.3 for a 30-pound difference in weight assuming height of 70 inches; and 2.50 for a positive paternal history of hypertension (Table 4).

When risk-factor data from preventive cardiology students were plotted based on this equation, the probabilities of developing hypertension within 30 years ranged from 3% to 49%, a much greater range in risk than that observed for CHD (Figure 3). Although most students clustered in the low-risk range

## Table 2. Final multiple risk-factor survivorship model for coronary artery disease

| Variable | Risk comparison | Relative risk | 95% CI |
|---|---|---|---|
| Age | 10-year difference | 4.45 | (2.61, 7.58) |
| Cholesterol | 40 mg/dL difference | 1.69 | (1.30, 2.20) |
| Smoking | Nonsmokers vs. 20 cigarettes/day smokers | 2.14 | (1.31, 3.48) |
| Paternal history | Present vs. absent | 1.16 | (0.54, 2.51) |

## Table 1. Johns Hopkins multiple risk equation for coronary artery disease

| Variable | Beta | Standard error | Chi square | $P$ value |
|---|---|---|---|---|
| Age (years) | .149 | .027 | 29.97 | .0000 |
| Cholesterol (mg/dL) | .013 | .003 | 15.36 | .0001 |
| Smoking | .380 | .125 | 9.28 | .002 |
| Paternal history | .152 | .392 | 0.15 | .70 |

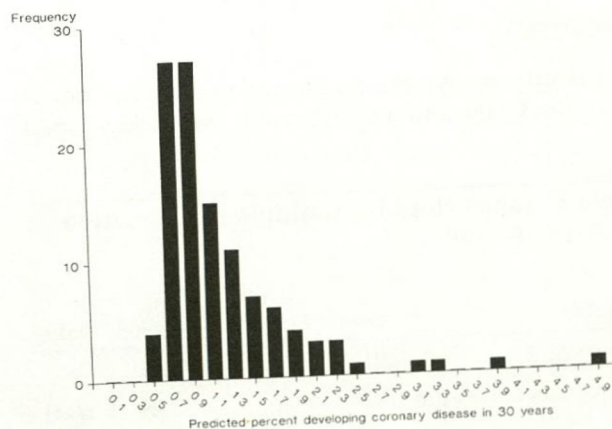Final Cox regression model relating baseline risk factors to incidence of CHD.



Figure 1. Frequency distribution of estimated probability of CHD at 30 years of follow-up in current Johns Hopkins medical students based on the Johns Hopkins multiple risk equation.
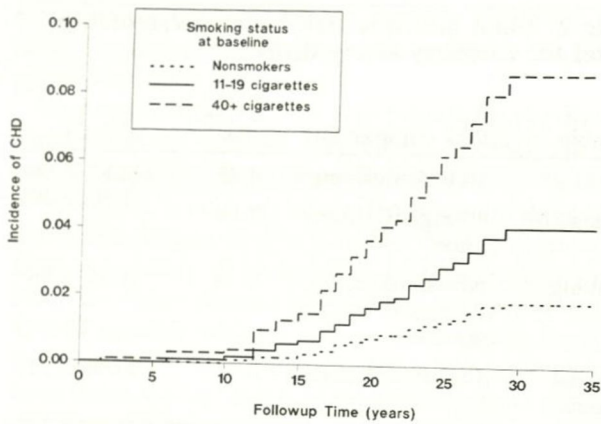
*Figure 2. Cumulative risk of developing CHD over 35 years of follow-up, according to three baseline levels of smoking, in a 22-year-old white male with a negative paternal history of CHD and cholesterol levels of 220 mg/dL.*

(0%–20%), Figure 3 shows the ability of this equation to identify high-risk subjects.

The effect of various levels of baseline variables was then illustrated by plotting cumulative incidence of hypertension, keeping values of all other risk factors constant. As an example, the effect of three levels of body weight on the development of hypertension is shown in Figure 4. A medical student with a height of 70 inches weighing 220 pounds (31.63 kg/m²) had a predicted risk of hypertension in 30 years of 42.2%; the predicted probability for a similar medical student weighing 160 pounds (23.01 kg/m²) was 27.2%. Similarly, systolic blood pressure during medical school can be presented visually as an important predictor of later hypertension requiring pharmacologic intervention (Figure 5).

## DISCUSSION

In this prospective study, multiple risk-factor equations for CHD and hypertension were developed

## Table 3. Johns Hopkins multiple risk equation for hypertension

| Variable | Beta | Standard error | Chi square | P value |
|---|---|---|---|---|
| Age (years) | .012 | .037 | 0.11 | .74 |
| Systolic blood pressure (mm Hg) | .038 | .006 | 35.89 | .0000 |
| Quetelet index | .063 | .033 | 3.77 | .05 |
| Paternal history | .918 | .239 | 14.80 | .0001 |

Final Cox regression model relating baseline risk factors to incidence of hypertension.

## Table 4. Final multiple risk-factor survivorship model for hypertension

| Variable | Risk comparison | Relative risk | 95% CI |
|---|---|---|---|
| Age | 10-year difference | 1.13 | (0.55, 2.34) |
| Systolic blood pressure | 20 mm Hg difference | 2.13 | (1.66, 2.73) |
| Quetelet index | 190 vs. 220 lb. | 1.31 | (1.00, 1.71) |
| Paternal history | Present vs. absent | 2.50 | (1.57, 3.99) |

based on the experience of Johns Hopkins medical students followed for up to 35 years. These equations were applied to the risk factor profiles of present-day medical students to estimate future risk of these diseases. These equations provide an excellent opportunity to develop educational tools for current medical students. The ability to predict disease 30 years later and the similarity of the Precursors Study participants to current students with respect to age, education, and occupation are strengths of the models developed. The equations are relatively simple, allowing the risk for hypertension and CHD to be calculated quickly. The long follow-up (35 years) results in a wide range of risk probabilities for developing CHD or hypertension, which in turn allows the students to visualize "high risk" well into the future. The degree to which a characteristic elevates risk was also illustrated by plotting cumulative incidence curves by various baseline levels of these risk factors.
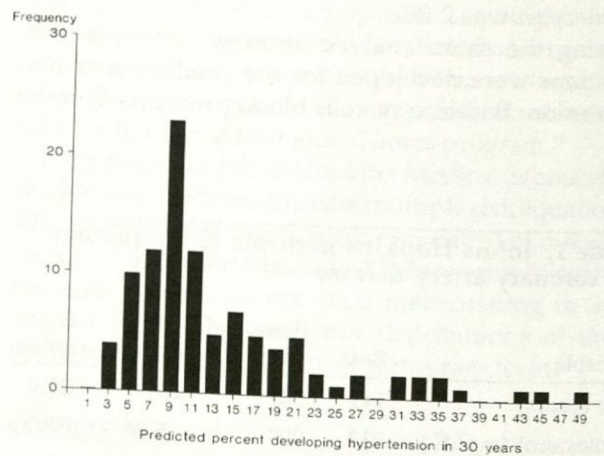


*Figure 3. Frequency distribution of estimated probability of hypertension at 30 years of follow-up in current Johns Hopkins medical students based on the Johns Hopkins multiple risk equation.*
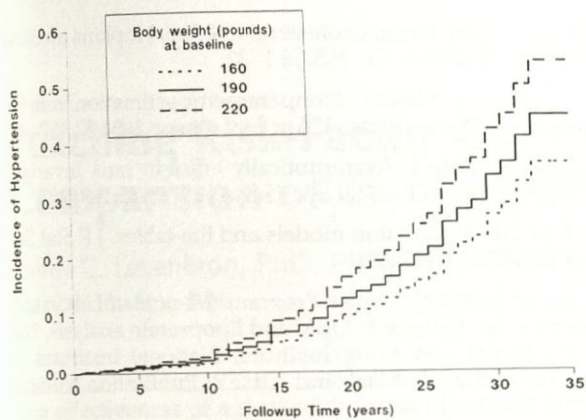
*Figure 4. Cumulative risk of developing hypertension over 35 years of follow-up, according to three baseline levels of body weight, in a 22-year-old white male with a positive paternal history of hypertension, baseline systolic blood pressure of 130 mm Hg, and a height of 5 feet 10 inches.*

This may be especially helpful in the illustration of the tracking of hypertension, in which high-risk blood pressure in youths may predict later requirement of treatment for hypertension.

In the Precursors Study, the factors predictive of later CHD (smoking, cholesterol, age) and hypertension (baseline blood pressure, Quetelet index, and paternal history) are well-established risk factors for these two chronic diseases. However, most studies documenting these associations were performed in middle-aged populations (e.g., Framingham Heart Study[3]), with only small numbers of subjects being in the third or even fourth decades of life. Our study

of a group of medical students predominantly 22–26 years of age demonstrated that CHD and hypertension may be predicted even in youths. Screening for these predictive factors may allow identification of high-risk young adults, before end-organ damage from hypertension or the development of extensive but clinically silent atherosclerotic disease.

These equations have some limitations to their usefulness. First, all the students were white. It is possible that risk factors for hypertension or CHD differ between blacks and whites, although data from middle-aged populations of black and white men suggest that risk factors are similar.[10] This cohort included only 111 women, so it was not possible to develop accurate risk equations for them. This is unfortunate considering the increasing percentage of medical students who are female. Second, some of the methods by which risk factors were measured have changed over time. These include the measurement of serum cholesterol; the Bloor method is no longer in use and may be systematically different from current methods. However, the present equations demonstrate merely the change in CHD risk with change in risk factors. The general relationships with serum cholesterol levels should not depend on the measurement technique. The lack of relation of paternal history of CHD with development of CHD in the Precursors cohort may have resulted from the measurement of paternal history at a single point in early adulthood. Finally, the risk of CHD for students today may be different than it was for students of 1948–1964. Since 1965, CHD mortality rates have been falling in the United States, and, thus, the probability of developing CHD may be lower for students today. However, the CHD equation should still be able to identify the high-risk subjects relative to their lower-risk classmates.

Although these risk equations have not yet been applied to a class of medical students, their use in a medical curriculum should be amenable to evaluation of their ability to affect behavior change. Such an evaluation would be needed before their widespread application in medical education. It is hoped the application of these equations will allow medical students to take a more active role in educational programs on preventive cardiology. They should be encouraged to calculate their risk of these major chronic diseases and understand the importance of risk-factor modification in themselves and their future patients.
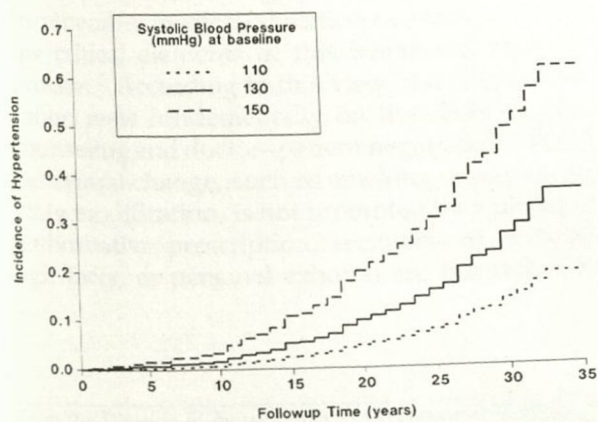


*Figure 5. Cumulative risk of developing hypertension over 35 years of follow-up, according to three baseline levels of systolic blood pressure, in a 22-year-old white male with a positive paternal history of hypertension, a height of 5 feet 10 inches, and a weight of 160 pounds.*

## REFERENCES

1. Blackburn H, Trapp E, Prineas R, Jacobs D. Coronary risk screening and evaluation: a learning exercise for medical students. Prev Med 1975;4:579–90.

2. Thompson PD, Conrad S, Siconolfi S, Cullinane E, Wincze J. The use of a cardiovascular risk factor self-change project to teach behavioral medicine to medical students. J Med Educ 1982;57:724–26.

3. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: The Framingham Study. Am J Cardiol 1976;38:46–51.

4. Thomas CB. Observations on some possible precursors of essential hypertension and coronary artery disease. Bull Johns Hopkins Hosp 1951;89:419–41.

5. Thomas CB, Eisenberg FF. Observations on the variability of total serum cholesterol in Johns Hopkins medical students. J Chron Dis 1957;6:1–32.

6. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.

7. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. J R Stat Soc (Ser A) 1972;135:185–207.

8. Cox DR. Regression models and life-tables. J R Stat Soc (Ser B) 1972;34:187–202.

9. Lipid Research Clinics Program. Manual of Laboratory Operations. Volume 1: Lipid and lipoprotein analysis. National Heart and Lung Institute, National Institutes of Health, Bethesda, Maryland. DHEW Publication Number (NIH) 75-628, 1974.

10. Tyroler HA, Knowles MG, Wing SB, et al. Ischemic heart disease risk factors and twenty-year mortality in middle-aged Evans County black males. Am Heart J 1984;108:738–46.