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FRAMINGHAM RISK SCORE AND PREDICTION OF CORONARY HEART DISEASE DEATH IN YOUNG MEN

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Abstract

Background—We tested the ability of the Framingham Risk Score (FRS) and the online ATP III risk estimator to estimate risk and to predict 10-year and longer term coronary heart disease (CHD) death in younger adults (age 18–39 years). Although prediction with individual risk factors has been tested in individuals less than 30 years, current multivariate risk prediction strategies have not been applied to prediction of clinical CHD in this age range.

Methods—We included 10,551 male participants of the Chicago Heart Association Detection Project in Industry (CHA) who were ages 18 to 39 years and free of baseline CHD and diabetes at enrollment in 1967–1973. CHD risk was estimated using both FRS and ATP-III online risk estimator for each individual. Men were stratified into deciles according to the magnitude of predicted risk calculated from measured baseline risk factors (CHA-predicted risk). Observed CHD mortality rates for 10-, 20-, and 30-years of follow-up were compared with estimated risks. CHD death rates were low across 30-years of follow-up.

Results—The Framingham Risk Score remained below 10% for all deciles of CHA-predicted risk in the 18 to 29 year old cohort. Framingham-predicted risk reached 12% only in the 30 to 39 year old cohort in the highest decile of CHA-predicted risk, despite substantial risk factor burden.

Conclusions—Neither method classified individuals under 30 years of age as high risk despite substantial risk factor burden. Future clinical guidelines should consider alternative strategies to estimate and communicate risk in populations below age 30.

INTRODUCTION

Approximately 90% of individuals with coronary heart disease (CHD) have at least one antecedent, traditional risk factor such as smoking, diabetes, hypertension and/or hypercholesterolemia[1]. Throughout the lifespan, exposure to high levels of these risk factors increases atherosclerotic burden[2, 3], resulting in an increased risk for future clinical CVD events[4, 5]. In middle-aged adults, measurement of traditional risk factors thus serves as a proxy for atherosclerotic burden and hence, increased risk of clinical CVD. The close association between traditional risk factors, atherosclerotic burden, and risk for clinical CVD in middle-aged adults allows for a single strategy of absolute risk assessment using the Framingham Risk

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Score or the Adult Treatment Panel III online risk estimator in order (1) to identify candidates for medical therapy and (2) to encourage therapeutic lifestyle changes[6].

The situation is different in *younger adults* less than 30 years. Even though the atherosclerotic process begins at a young age in accordance with the level of traditional risk factors such as smoking, high blood pressure, and high cholesterol[7], clinical cardiovascular disease (CVD) events do not occur until later in life[8, 9]. This apparent discrepancy between atherosclerotic burden and event rates in younger adults highlights an important question: can currently available risk estimation tools such as the FRS discriminate risk effectively when applied to individuals younger than 30 years? Available studies have not addressed this question to date.

Since the publication of ATP III, the continued publication of large-scale clinical trials of statin therapy[10, 11] have transformed the field of risk estimation to emphasize hard clinical outcomes. Thus, although one could argue that the limitations of risk estimates in different populations is of little clinical interest, we believe that the performance of risk estimates in younger individuals with high risk factor burden has importance for both clinical practice and public health recommendations. For clinicians, risk estimation provides the opportunity for an interactive dialogue through which patients incorporate knowledge of their disease into the decision to initiate medical therapy and/or lifestyle changes to improve their risk factor profile[12]. If currently available risk assessment tools cannot differentiate those young adults who are at eventual high risk from young adults who are truly low risk, this critical physician-patient communication will be compromised. For public health, raising awareness and changing behavior patterns successfully requires effective risk communication to the larger population [13,14].

Although prior studies have successfully created risk prediction tools for *subclinical* disease in young adults[15, 16], the ability of the Framingham risk score and/or the ATP III online risk estimator to discriminate risk for clinical CHD has not been examined in younger populations (age < 30 years). We therefore sought to examine the ability of the FRS and the online ATP III risk estimator to estimate 10-year and longer term risk for CHD death in these young men.

METHODS

Baseline Examination

From November 1967 to January 1973, the CHA study screened 39,522 men and women ages 18 years and older of varied socioeconomic backgrounds and ethnicities employed at 84 Chicago-area businesses. As previously reported in detail, standardized examination methods were used [17, 18]. Trained staff measured height, weight, supine blood pressure using a standard mercury sphygmomanometer, and serum total cholesterol from a non-fasting blood sample[19]. Participants completed a questionnaire about their demographic characteristics, smoking history (never, former, or current smoking, and number of cigarettes/day for current smokers), medical diagnoses and treatments (including hypertension and diabetes). Resting electrocardiograms (ECGs) were classified as showing major, minor, or no abnormalities [20]. The study has been periodically approved by the Northwestern University Institutional Review Board.

Mortality Follow-up

Vital status was ascertained through 2002, with an average follow-up of 32 years. Prior to 1979, follow-up was completed by direct mail, telephone, contact with employer, and matching of records with Social Security Administration files; from 1979–94 the National Death Index (NDI) was used to identify deaths[21 2000]. Death certificates were obtained and coded for multiple causes by trained research staff according to the Eighth Revision of the International

Classification of Diseases (ICD-8)[22]. Later, the NDI-*plus* service was used to obtain ICD Ninth Revision (ICD-9) cause of death coding for 1995–98 and ICD Tenth Revision (ICD-10) coding from 1999–02[23, 24]. For this report, the underlying cause of death was used. CHD mortality was defined as ICD-8 and ICD-9 codes 410.0–414.9 and ICD-10 codes, I20.x–I25.x.

Exclusions

Of 19,095 participants ages 18 to 39 years at baseline (1967–73), 1,368 were excluded for one or more of the following reasons: lost to follow-up (n=56); prevalent CHD (n=29), major ECG abnormality (n=753), or diabetes (n=461) at baseline, or missing baseline data on smoking, blood pressure, serum cholesterol, body mass index (BMI), or education (n=69). After these exclusions, 10,551 men and 7,176 women ages 18 to 39 years were eligible for the study sample.

Statistical Analyses

Because women experienced very low CHD mortality in these age ranges, they were excluded from these analyses. The male participants were stratified into two groups by age at baseline, 18–29 years and 30–39 years. Mortality rates per 10,000 person-years for 10-, 20-, and 30-years of follow-up were computed.

We calculated the 10-year FRS for each individual using the beta coefficients and mean values for risk factors from the Framingham cohort given by Wilson, et al [25]. This method has been used before in applying the FRS to other cohorts[26]. Because we excluded diabetics from our analyses, this variable was excluded from the calculated risk score. The 10-year risk for CHD death was also calculated using the ATP III online risk estimator[27]. Because the minimum age that can be incorporated is 30, all individuals age 18–29 years were given the risk estimate of a 30 year old. CHA did not measure HDL cholesterol values so the mean value for men in the Framingham cohort (44 mg/dL) was used for the online risk estimator.

In addition to the FRS and ATP III online risk estimator, we created a risk score from our dataset (CHA risk score) in which we incorporated age, body mass index (BMI), total cholesterol (TC), systolic blood pressure (SBP), and smoking status into multivariate regression models to predict CHD death. Within each age group, men were then stratified into deciles according to the magnitude of their predicted risk using the CHA risk score. Levels of estimated risk were then compared between the FRS and the ATP-III risk estimator, within deciles of risk as predicted by the CHA risk score. Finally, risk estimates from the FRS and ATP-III risk estimator were compared with observed event rates over 30 years of follow up. All analyses were conducted using SAS statistical software (v9.1, SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

Table I shows baseline characteristics of the two different age cohorts in the study sample. The younger cohort had a slightly lower BMI and a lower percentage of overweight or obesity and a substantially lower total cholesterol compared with the older men.

Prediction of CHD Risk

The participants were stratified into deciles of predicted risk for CHD death based on the CHA risk score, with decile 1 being the lowest and decile 10 the highest predicted risk (Table II). Each individual was also assigned a risk estimate using the ATP III online risk estimator and using the multivariate risk equation from the FRS. Both the ATP III online risk estimator and the FRS were able to order accurately the CHA risk estimate (Table II). Among both younger

and older men, the online risk estimator resulted in lower estimates of predicted risk compared with the FRS. Table III shows the mean levels of risk factors in representative deciles of predicted CHA risk. In both the older and younger male cohorts, higher decile of predicted risk was associated with higher levels of individual risk factors, with a substantial risk factor burden evident in the highest decile, despite low predicted event rates.

Even though the FRS estimated higher 10-year risks in both the younger and older cohorts, the average 10-year predicted risk only exceeded 10%--a current threshold for possible initiation of drug therapy--in the highest decile of the 30–39 year old group. The highest decile of the CHA risk score in the younger cohort (age 18 to 29) only reached a 10-year estimate of 7% by FRS. Thus, the FRS was unable to classify the young adults in this cohort as anything other than low risk even in the face of a substantial risk factor burden.

Observed Mortality Rates

Both CHD and total mortality were low among the younger cohort of men with a progressive increase in incident CHD deaths with longer follow-up (Table IV). The FRS and ATP-III risk estimator were able to rank appropriately the order of observed CHD mortality rates (Table II, Right Columns). In the younger cohort (age 18–29 years) the observed mortality rate in the first 10 years of follow-up did not exceed zero until the 10th decile of the CHA risk score (Table II). CHD death rates did not rise above zero at 20 years of follow-up until the 6th decile of the CHA risk score. Even with follow-up to 30 years, the observed CHD mortality rate in the highest decile of the CHA risk score was only 6 %. In the older cohort, the observed mortality rate followed similar trends, with the highest decile of the CHA risk score reaching 1.72 % at 10 years and 11.3% at 30-years.

DISCUSSION

There were several important findings in this study. First, as expected, CHD death rates were low across 10-, 20-, and 30-years of follow-up for young men, particularly among the 18 to 29 year old cohort. The predicted risk using either the online or the FRS calculated version remained below 10% for all participants in the 18 to 29 year old cohort and only reached 12% in the 30 to 39 year old cohort in the highest decile of the CHA risk score. Despite these low risk estimates by both the FRS and the online risk estimator, the risk factor burden was remarkably high in young individuals with the highest deciles of the CHA risk score.

Clinical and Public Health Implications

Prior authors have made a compelling case for a *public health* approach aimed at lowering the overall burden of CVD risk factors in the population[28]. Indeed, successful public health efforts can have a substantial effect on the knowledge and behavior of a population. For example, the successful communication of lifetime breast cancer risk in women had a substantial influence on the knowledge and behavior of women in the 1990s [13, 14]. Could a parallel argument be made for CVD risk reduction in the population? If so, what are the available means through which risk for CVD can be communicated?

In older adults, the Adult Treatment Panel III (ATP III) Panel recommended the incorporation of individual CHD risk factors into a single, global risk assessment strategy[6] in an effort to identify and target those individuals at the highest overall risk. Currently, the Framingham Risk Score (FRS) and the online ATP III risk estimator provide such a strategy for individuals over 30 years through the calculation of 10-year absolute risk estimates for CHD events.

In younger adults, no such strategy currently exists. We believe that a parallel approach aimed at identifying young individuals at the highest risk could provide the necessary means of risk

estimation and communication in this population. Such an approach could support both clinicians and public health officials in their efforts to reduce the risk factor burden among young adults. Prior to now, the ability of the currently available methods for risk estimation in this age range was unknown. Our results are among the first to examine systematically the performance of these methods in estimating risk in young adults.

Alternative Strategies to Risk Communication

The inability of these methods to classify young individuals as "high risk" reflects some important limitations to these models[25] and their current application in clinical practice. The Framingham risk equations appropriately place significant weight on age in predicting *absolute risk.*[25] The effect of this weighting of age is that typically only older patients exceed thresholds for treatment in guidelines such as ATP-III. *Although risk assessment provides a successful framework for clinical decision-making regarding treatment thresholds, it is also a critical tool for effective risk communication. Without effective risk communication about the relationship between lifestyle choices and risk, behavior change is unlikely*[12].

Recently, some authors have argued for a return to relative risk estimates in place of age-dependent absolute risk estimates for individuals with low short term risk[29]. Others have argued for estimation of absolute lifetime risks [30, 31]. In contrast to short term risk, lifetime risk estimates may provide an estimate of absolute risk during the remaining lifespan, thereby avoiding the problem of the age-dependency of the current global risk assessment strategies. Such an approach may allow identification of younger individuals with low short-term but high lifetime risks, who would benefit from intensive lifestyle modification or in whom early initiation of drug therapy is likely to be more cost effective. A final strategy might include using similar 10-year risk estimates for this patient population with lower, or age-specific, cut-points for "high-risk". For example, a calculated FRS of > 4% for men under 30 years and >7% for men 30–39 years would identify individuals in the highest quartile of risk for their age group. Nevertheless, those individuals in the highest quartile of risk by FRS may not be the same individuals at highest lifetime risk: prior research has shown that the FRS is poor at stratifying lifetime risk in younger men [30].

Future research is needed to clarify which of these strategies, if any, is effective in the identification of "high-risk" individuals under 30 years. Once identified, these strategies will need to be tested further in clinical and public health applications to determine their efficacy in communicating risk, encouraging therapeutic lifestyle change, improving adherence with therapy, and reducing risk factor burden.

Individual Risk Factors in Young Adults

Although the absolute event rates in individuals under 30 years are low, individual risk factors measured in this age range are significant and strong predictors of future clinical events. Among 1017 male medical students, serum total cholesterol was a strong and independent predictor of future CHD events over the course of 27 to 42 years of follow-up [9]. Forty years of follow-up from 595 young adults (age 30–39) in the Framingham Heart Study found similar associations between total cholesterol and both cardiovascular and all-cause mortality[32]. In a prior analysis of the CHA cohort, major coronary disease risk factors such as age, serum total cholesterol, blood pressure, and cigarette smoking were observed to be strong and independent risk factors for CHD death in younger adults (age 18–39) in long-term follow-up[8].

These risk factors are associated with future clinical events in part because of their ability to promote subclinical atherosclerosis at very young ages. Autopsy studies from the Korean[33] and Vietnam[34] wars were the first to document the presence of significant subclinical coronary atherosclerosis among young individuals who died of non-CVD related causes. Premature

atherosclerosis does not affect all young adults equally and varies according to the presence of major cardiovascular risk factors[35]. More recently, the Bogalusa Heart Study has shown that smoking, blood pressure, blood cholesterol, and age are significantly associated with the accumulation of aortic and coronary atherosclerosis among a younger population (age 2 to 39)[7].

Cost-Effectiveness of Global Risk Assessment in Young Adults

In older adults, identifying individuals at the highest risk using global risk assessment provides a cost-effective approach to decisions regarding cholesterol-lowering drug therapy. Prior studies have shown that from a societal standpoint, the greatest benefit is achieved when the highest risk individuals are treated with statin drugs[36]. Although it would not be cost-effective to treat large percentages of young adults with intermediate risk factor burden, it likely would be cost-effective to treat only the very *highest* risk young adults. Finally, cost-effective primary prevention with statins is markedly different from cost-effective primary prevention with therapeutic lifestyle changes. Prior estimates suggest that in men with a variety of risk factor levels, primary prevention with diet can be a very cost-effective strategy[36]. Thus, development of more accurate risk estimates and more effective means of risk communication could be a very cost effective approach to risk factor reduction in individuals under 30 years.

Limitations

Our study has some limitations. Whereas the Framingham Risk Score provides estimates for both fatal and non-fatal CHD events, the present study reports only fatal CHD events. Based on prior studies, we estimate that CHD death represents approximately 1/3 of all incident CHD events in this age range[37, 38]. Thus, we undoubtedly underestimated the overall CHD event rate in the CHA cohort since we did not ascertain non-fatal events. When the FRS overestimates absolute risk, recalibration of the FRS using the risk factor means and the event rate in the study population can produce an accurate estimate of absolute risk for CHD[26, 39]. Nevertheless, even in these circumstances the FRS is capable of providing an accurate rank order of CHD risk without recalibration. We confirmed this in the present study, demonstrating that the FRS can accurately order risk in a cohort with lower event rates than the original Framingham cohort. Thus, over-estimation of 10-year risk by the FRS was an anticipated finding in the present study, and the ability to rank-order CHD risk is consistent with prior literature. There may have been bias in our findings due to a “healthy worker effect,” although numerous prior publications from this dataset have produced results that are consistent with other large cohort studies. In addition, the event rates observed in the present study in other age ranges are quite similar to other published findings. Finally, although classification of deaths using death certificates can be inaccurate, prior literature has shown this to be less of a concern in younger individuals[40].

Conclusions

In conclusion, both the FRS and the ATP III online risk estimator were able to order risk estimates accurately among young adult men. However, neither strategy was able to identify high risk individuals (i.e. >20% absolute risk in 10 years) younger than 30 years despite substantial risk factor burden. Future clinical guidelines should consider alternative strategies to estimate and communicate CVD risk to the young adult population.

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Table I

Baseline characteristics for men in Chicago Heart Association Study by age in 1967–1973

Characteristics	Men Age	
	18–29 Years	**30–39 Years**
N	5154	5221
Age, years	25.0 ± 3.0	34.5 ± 2.9
BMI, Kg/m^2	25.5 ± 3.8	26.5 ± 3.4
Overweight (% BMI > 25 Kg/m^2)	51.4	65.2
Obese (% BMI > 30 Kg/m^2)	10.4	13.4
Serum Cholesterol, mg/dl	180.0 ± 33.3	199.4 ± 36.2
SBP, mmHg	133.9 ± 14.8	134.8 ± 15.7
DBP, mmHg	76.3 ± 10.0	79.8 ± 10.5
Current smoker (%)		
1–19 cigarettes/day	15.2	11.5
20 + cigarettes/day	34.2	33.2

Numbers are mean ± SD or percent

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table II

Deciles of Chicago Heart Association risk score[†] and Framingham risk score for Chicago Heart Association men by age in 1967–1973

Decile of Risk by CHA Cox Model	CHD Deaths	Framingham 10-yr Risk Estimate (%)		Predicted Risk (CHA Model) (%)		Observed CHD Mortality Rate[*] (%)		
	N	Calculated[¶]	Online[#]	10-yr	30-yr	10-yr	20-yr	30-yr
Ages 18–29 years								
1	1	1.39	< 1	0.004	0.288	0.00	0.00	0.19
2	4	1.96	< 1	0.009	0.462	0.00	0.19	0.78
3	3	2.36	< 1	0.013	0.604	0.00	0.00	0.58
4	3	2.84	< 1	0.019	0.768	0.00	0.00	0.58
5	2	3.12	< 1	0.024	0.963	0.00	0.00	0.39
6	6	3.46	2	0.033	1.192	0.00	0.39	1.16
7	5	3.97	2	0.047	1.502	0.00	0.00	0.97
8	8	4.60	2	0.067	1.977	0.00	0.58	1.55
9	17	5.34	3	0.105	2.753	0.00	1.75	3.30
10	31	7.18	4	0.247	5.491	0.58	2.72	6.02
Ages 30–39 years								
1	1	2.64	< 1	0.029	0.708	0.00	0.00	0.19
2	6	3.60	2	0.051	1.103	0.00	0.19	1.15
3	5	4.25	3	0.076	1.424	0.00	0.38	0.96
4	8	4.87	4	0.109	1.839	0.19	0.19	1.53
5	18	5.62	4	0.156	2.369	0.19	0.77	3.45
6	18	6.37	5	0.220	2.975	0.38	1.53	3.45
7	21	7.14	6	0.312	3.743	0.00	1.72	4.02
8	25	8.03	6	0.446	4.918	0.96	2.49	4.79
9	30	9.39	7	0.712	6.783	0.57	3.45	5.75
10	59	12.37	12	2.102	13.497	1.72	6.51	11.30

[†] CHA Score calculated using beta coefficients from Cox proportional hazards models using continuous measures for age, body mass index (BMI), total cholesterol (TC) and systolic blood pressure (SBP), and categorical measures for moderate smoking and heavy smoking.

CHD: coronary heart disease

[*] Cumulative risk.

[¶] Risk was calculated for each person within decile using equation derived from Framingham cohort data (Peter W.F published paper, *Circulation, 1998*), then averaged.

[#] Calculated using the ATP III online risk estimator. Because the minimum age that can be incorporated is 30, all individuals age 18–29 years were given the risk estimate of a 30 year old.

Table III

Risk Factor Means by Representative Deciles of Predicted Risk

	18–29 Years			30–39 Years		
	Decile			Decile		
Characteristics	**1**	**5**	**10**	**1**	**5**	**10**
Age, years	22.1	25.2	26.6	32.2	34.3	36.0
BMI, Kg/m^2	22.5	25.4	28.8	24.2	26.7	28.8
Serum Cholesterol, mg/dl	142.1	178.4	226.0	157.2	196.1	248.2
SBP, mmHg	124.7	132.5	146.0	124.7	134.3	147.4
% Smoking	10.0	41.2	93.4	3.2	34.9	93.2

BMI: body mass index; SBP: systolic blood pressure

Table IV

CHD mortality in Chicago Heart Association Study Men during 10, 20, 30 years of follow-up by age in 1967–1973.

Age Group	N		Number of Deaths		Person-years	Mortality Rate*	
			CHD	Total		CHD	Total
18–29 years	**5154**	**10 years**	3	51	51,278	0.6	9.9
		20 years	29	147	101,866	2.8	14.4
		30 years	80	416	150,989	5.3	27.6
30–39 years	**5221**	**10 years**	21	86	51,889	4.0	16.6
		20 years	90	303	102,322	8.8	29.6
		30 years	191	910	149,415	12.8	60.9