Evaluating the Framingham Hypertension Risk Prediction Model in Young Adults

The Coronary Artery Risk Development in Young Adults (CARDIA) Study

April P. Carson, Cora E. Lewis, David R. Jacobs Jr, Carmen A. Peralta, Lyn M. Steffen, Julie K. Bower, Sharina D. Person, Paul Muntner

Abstract—A prediction model was developed in the Framingham Heart Study (FHS) to evaluate the short-term risk of hypertension. Our goal was to determine the predictive ability of the FHS hypertension model in a cohort of young adults advancing into middle age and compare it with the predictive ability of prehypertension and individual components of the FHS model. We studied 4388 participants, aged 18 to 30 years without hypertension at baseline, enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, who participated in 2 consecutive examinations occurring 5 years apart between the baseline (1985–1986) and year 25 examination (2010–2011). Weibull regression was used to assess the association of the FHS model overall, individual components of the FHS model, and prehypertension with incident hypertension. During the 25-year follow-up period, 1179 participants developed incident hypertension. The FHS hypertension model (c-index=0.84; 95% confidence interval, 0.83–0.85) performed well in discriminating those who did and did not develop hypertension and was better than prehypertension alone (c-index=0.71; 95% confidence interval, 0.70–0.73). The predicted risk from the FHS hypertension model was systematically lower than the observed hypertension incidence initially (χ²=249.4; P<0.001) but demonstrated a good fit after recalibration (χ²=14.6; P=0.067). In summary, the FHS model performed better than prehypertension and may be a useful tool for identifying young adults with a high risk for developing hypertension. (Hypertension. 2013;62:1015-1020.) ● Online Data Supplement

Key Words: epidemiology ■ hypertension ■ prehypertension ■ risk

Hypertension affects ≈1 in 3 adults in the United States,1 with the lifetime risk of hypertension approaching 90% for middle-aged, normotensive adults.2,3 Because the sequelae of hypertension include cardiovascular morbidity and mortality, effective prevention strategies are essential for reducing the public health burden of hypertension. Lifestyle modification and pharmacological therapy have been shown to lower blood pressure and reduce the risk of developing hypertension4–6 and may be important components of early interventions among high-risk individuals. The precursors of cardiovascular risk factors manifest early in life, and so identifying young adults at high risk for hypertension has important implications for the development and implementation of prevention strategies.

To better identify high-risk individuals who should be targeted for early interventions, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)7 added prehypertension, defined as systolic blood pressure (SBP) between 120 and 139 mm Hg or diastolic blood pressure (DBP) between 80 and 89 mm Hg among individuals not meeting hypertension criteria, as an official blood pressure classification in 2003. Several studies have reported that individuals with prehypertension are more likely to progress to hypertension compared with individuals with normal SBP and DBP.8–10 However, with 28% of adults in the United States having prehypertension,1 additional approaches may be needed to better identify individuals at high risk for hypertension.

Framingham Heart Study (FHS) investigators developed a hypertension risk prediction model that included age, sex, SBP, DBP, body mass index (BMI), cigarette smoking, and parental history of hypertension.11 The prognostic value of this FHS model has been validated in external cohorts.12,13 However, it has also been reported that SBP alone predicted incident hypertension just as well as the FHS model in a multiethnic cohort of middle-aged and older adults in the United States.14 The performance of the FHS model among young adults has not been evaluated. The incidence of hypertension increases with age,1 so young adults are a key demographic for identifying those at high risk for hypertension. The purpose of this study was to evaluate the predictive ability of the FHS model for the incidence of hypertension and compare its performance with prehypertension alone and individual components of the...
FHS model among black and white adults from the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Methods

Study Design and Population
CARDIA is a prospective, community-based cohort study of young adults designed to investigate trends and determinants of cardiovascular disease in the United States. A detailed overview of the study design, recruitment, and objectives has been previously published.14 Briefly, the baseline examination (1985–1986) included 5115 black and white men and women aged 18 to 30 years from 4 urban areas: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. In-person follow-up examinations were conducted at 2 (1987–1988), 5 (1990–1991), 7 (1992–1993), 10 (1995–1996), 15 (2000–2001), 20 (2005–2006), and 25 (2010–2011) years after the baseline examination. Participant retention rates for each of the follow-up examinations were high, with 72% (n=3499) of surviving participants completing the year 25 examination. Each in-person examination included interviewer-administered questionnaires, physical examination, and specimen collection. Centralized training and certification, standardized methods, and quality control measures were implemented to ensure high data quality for all examinations. The Institutional Review Board at each participating site approved each study examination, and participants provided written informed consent.

Participants with hypertension at baseline (n=146), with missing covariates (n=50), and who did not attend 2 consecutive examinations occurring 5 years apart during the study period (n=504) were excluded. Additionally, participants with diabetes mellitus at baseline (n=27) were excluded to correspond with the FHS exclusion criteria, resulting in a sample size of 4388 participants eligible for these analyses.

Blood Pressure Measurement
SBP and DBP were measured at each CARDIA examination following standardized protocols.15 After resting for 5 minutes in the seated position, blood pressure was measured 3× at 1-minute intervals using an appropriate sized cuff, with the average of the second and third measurements used to determine SBP and DBP. SBP and DBP were measured using a random zero sphygmomanometer at baseline and years 5, 10, and 15 and a standard automated BP measurement monitor (Omron model HEM907XL) at years 20 and 25. The BP measurements at years 20 and 25 were calibrated to random zero sphygmomanometer values based on dual readings on a subset of CARDIA participants to ensure comparability (please see the online-only Data Supplement).15 Data on use of antihypertensive medication were collected at each examination via self-report and data abstraction of medication bottles brought to the examination. Incident hypertension was defined as the first study examination in which participants developed hypertension, unknown, uniform resampling of event times was used for calculating the c-index and its 95% confidence interval (CI) based on 200 resamples. Bayes information criterion (BIC) was used to compare the performance of the models, with a lower BIC indicating better model fit. Using the FHS model, the predicted risk for hypertension was calculated for each participant for each time period at risk. Participants were grouped into deciles on the basis of their predicted risk for hypertension, and calibration was evaluated using the modified Hosmer–Lemeshow goodness of fit χ² statistic to compare predicted risk with observed risk for hypertension across deciles.16 Additionally, a recalibrated model was generated by replacing the FHS hypertension incidence with the observed CARDIA hypertension incidence,17 and a best-fit model was generated using the variables from the FHS model applied in the CARDIA study. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Participant characteristics at baseline are presented overall in Table 1. The mean age of participants was 24.9 years; 55.5% of the participants were women and 49.3% were black. Most participants had SBP <120 mmHg and DBP <80 mmHg although 22.1% had prehypertension at baseline.

Between the baseline and year 25 examinations, 1179 incident hypertension events occurred, with a higher incidence noted among those who were obese, who had higher SBP and DBP levels, and who had prehypertension (Table 2). In a multivariable adjusted model, each of the individual components of the FHS model was associated with incident hypertension during follow-up (please see the online-only Data Supplement). Additionally, prehypertension was associated...
with incident hypertension in an unadjusted model (hazard ratio=6.81, 95% CI, 6.06–7.66).

The FHS model performed well in discriminating between those who did and did not develop hypertension (c-index=0.84; 95% CI, 0.83–0.85). This model demonstrated better performance than a model that included prehypertension only (c-index=0.71; 95% CI, 0.70–0.73). The FHS model also demonstrated better performance when compared with the individual components of the FHS model (Table 3). Overall, current smoking and sex discriminated poorly, whereas the
interaction of age and DBP had the highest discrimination (c-index=0.81; 95% CI, 0.79–0.82) among the individual FHS model components. The FHS model had a lower BIC (BIC=6322.49), indicating good model fit, than prehypertension (BIC=7291.02) and each of the individual components of the FHS model. When analyses were stratified by race, the discrimination performance for each of the models was similar for black and white participants, and the FHS model had the lowest BIC for black and white participants.

Within each decile of predicted hypertension risk, the FHS model underestimated the mean observed hypertension risk ($\chi^2=249.4; P<0.001$). Using the hypertension incidence from CARDIA to recalibrate the model, a good model fit was obtained ($\chi^2=14.6; P=0.067$), which was comparable with the best-fit model ($\chi^2=12.9; P=0.116$; Figure).

**Discussion**

In this cohort study of young adults, the FHS model provided good discrimination for identifying those who did and did not develop incident hypertension during 5-year follow-up periods and performed better than prehypertension. The prehypertension classification is meant to be used to identify individuals at high risk for hypertension, but the current results suggest that the use of additional demographic and clinical parameters in the FHS model may better identify high-risk individuals. The FHS model systematically underestimated hypertension risk initially, but this was corrected by recalibrating the model using the hypertension incidence rates from our population.

Previous studies have reported that prehypertension alone may not be the most useful metric for discriminating between those who will and will not develop hypertension. In the Multiethnic Study of Atherosclerosis, a model with SBP alone performed better than a model with prehypertension alone and just as well as the FHS model. Also, a predicted risk >20% from the FHS hypertension risk score was a better predictor of incident hypertension compared with prehypertension alone in the Whitehall II study. Both of the previous studies evaluated middle-aged and older adults, whereas the current study assessed a cohort of young adults just on entry into middle age and also found that the FHS model was a better predictor of incident hypertension than prehypertension. It is important to identify predictors of hypertension among young adults.
because 78.8% of young adults have ideal blood pressure levels,21 thus highlighting the importance of promoting and sustaining ideal blood pressure levels in this age demographic for the prevention of hypertension later in life.

Individuals with prehypertension are more likely to have elevated levels of cardiovascular risk factors,23 but the prehypertension classification alone does not take into account these risk factors. Prehypertension is a simple classification that has been advocated for use clinically, but it is infrequently conveyed to patients23 and may not be the best risk stratification tool with 28% of adults meeting prehypertension criteria.1 It has been reported that individuals in the upper range of prehypertension (ie, SBP of 130—139 mmHg or DBP of 85—89 mmHg) have an increased risk of hypertension compared with individuals in the lower range of prehypertension (ie, SBP of 120—129 mmHg or DBP of 80—84 mmHg).5–10 However, when the predictive ability of the upper range of the prehypertension classification was evaluated in this study, the discrimination for incident hypertension was poorer than the overall prehypertension classification and the FHS model. Given the unsettled issue on whether pharmacological therapy should be prescribed for individuals who meet prehypertension criteria,24,25 the findings from the current study suggest that better characterization of individuals at risk for hypertension based on the assessment of multiple factors is needed to develop appropriate prevention and treatment strategies.

DBP increases during young adulthood but decreases after middle age,26 and DBP is more strongly associated with an increased risk of coronary heart disease than SBP at younger ages.27 This suggests that DBP may play a key role in hypertension risk prediction among young adults. DBP and the age and DBP models demonstrated good discrimination in the current study compared with the other individual components and were comparable to the overall FHS model for predicting incident hypertension.

In our community-based study of young adults transitioning into middle age, the predicted hypertension risk estimates obtained from the FHS model overestimated the observed hypertension risk. Applying the FHS model to external populations is likely to result in a systematic overestimation or underestimation of predicted hypertension risk for a particular population when differences in incidence rates and mean levels of risk factors occur. The overestimation observed in our study was corrected after recalibrating the model for our population, but these observed differences highlight the importance of properly adjusting prediction models for use in external populations to prevent an overestimation or underestimation of risk.

This study has several potential limitations. The FHS model used parental medical records and clinical assessments to obtain a validated measure of parental history of hypertension, whereas only self-reported parental history of hypertension was available in the current study. A previous study indicated that children’s self-reported parental history of hypertension had a high positive predictive value but a low negative predictive value,28 suggesting that more participants may classify their parents as normotensive when their parents were actually hypertensive. However, self-reported measures of parental history of hypertension are the most feasible if the FHS model is used in clinical settings and self-reported parental history of medical conditions is routinely collected at clinic visits. Additionally, parental history of hypertension was assessed at baseline and years 5 and 10, so this variable could not be updated for each time interval evaluated. Although we used appropriate sized cuffs, calibrated instruments, and standardized protocols to assess blood pressure, these measures may not be universally implemented in clinical settings. This could affect the accuracy and validity of blood pressure readings obtained for use in hypertension risk prediction models. Finally, hypertension status was determined based on mean blood pressure at a single clinic visit. JNC 7 guidelines recommend using blood pressure from ≥2 clinic visits,7 but this was not available in the current study.

**Perspectives**

Although the prehypertension classification is simple to use for identifying young adults with an increased risk of hypertension, it did not discriminate as well in this study when compared with the FHS model that contains demographic and clinical predictors that are routinely collected in clinical practice. The FHS model was able to identify those who did and did not develop hypertension, but the prediction model had to be recalibrated to obtain better-fitting risk estimates for this population. Risk prediction models that go beyond the prehypertension classification may be used to better identify young adults with an increased risk of hypertension, who may benefit from the adoption of preventive measures early in life. The ability to identify young adults at high risk for hypertension will provide the opportunity to efficiently apply risk reduction interventions in addition to population-based approaches for the prevention of hypertension.

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**Disclosures**

None.

**References**

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Methods
Blood pressure instrument calibration
Dual readings for the Omron oscillometer (HEM907XL) and random zero
sphygmomanometer were taken in 903 participants. These dual readings were used to
calibrate the measurements from the Omron oscillometer used at years 20 and 25 to
the random zero sphygmomanometer measurements at baseline and years 5, 10, and
15. The recalibrated systolic BP was $3.74 \pm 0.96$ times the observed Omron systolic
BP, while the recalibrated diastolic BP was $1.30 \pm 0.97$ times the observed Omron
diastolic BP for exams at years 20 and 25.

Sensitivity Analyses
The point scoring system of the FHS model assigns points to categories of the
component variables for ease of use in clinical settings. When the point scoring system
was evaluated in a sensitivity analysis, the discrimination of the model (c-index=0.83,
95% CI=0.82, 0.85) was similar to the FHS equation performance.

The FHS model was originally developed to predict incident hypertension over short
periods of time (i.e., 1, 2, or 4 years), so a sensitivity analysis was also done to evaluate
its predictive ability over 25 years of follow-up using only the predictor variables from the
CARDIA study baseline examination. In another sensitivity analysis evaluating the risk
of hypertension over the entire follow-up period, the FHS model did not perform as well
over predicting risk over 25 years (c-index=0.74, 95% CI=0.72, 0.75).

Lastly, individuals with blood pressure levels in the upper range of the prehypertension
classification have an increased risk of hypertension compared with those in the lower
range of prehypertension classification,\textsuperscript{1-3} so additional analyses investigated the
association of the upper range of prehypertension (i.e., SBP=130-139 mmHg and/or 85-
89 mmHg) with incident hypertension. In the analysis evaluating the upper range of
prehypertension as the only predictor of incident hypertension, discrimination was poor
(c-index=0.59, 95% CI=0.58, 0.61).

FHS Model Recalibration
When the absolute risk obtained from a prediction model underestimates or
overestimates the observed risk, the prediction model has to be recalibrated. In a
recalibrated model, the average incidence rate and mean values of risk factors used to
develop the original prediction model are replaced with the average incidence rate and
mean values of risk factors for the population that the prediction model is being applied
to.\textsuperscript{4} For this study, the FHS incidence rate and mean risk factor levels were replaced
with the CARDIA incidence rate and mean risk factor levels in the Weibull regression
model to improve the absolute risk estimates obtained from the model.
References
Table S1. Hazard ratios and 95% confidence intervals for incident hypertension associated with variables included in the Framingham Hypertension Model and prehypertension separately: the Coronary Artery Risk Development in Young Adults (CARDIA) Study

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Hazard Ratios (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham Model*</td>
<td>Age</td>
<td>1.19 (1.10, 1.29)</td>
<td>0.0418</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>1.29 (1.15, 1.46)</td>
<td>0.0434</td>
</tr>
<tr>
<td></td>
<td>Current smoking</td>
<td>1.35 (1.18, 1.54)</td>
<td>0.0404</td>
</tr>
<tr>
<td></td>
<td>Body mass index</td>
<td>1.04 (1.03, 1.05)</td>
<td>0.0260</td>
</tr>
<tr>
<td></td>
<td>Parental history of hypertension</td>
<td>1.27 (1.17, 1.38)</td>
<td>0.0332</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure</td>
<td>1.06 (1.05, 1.07)</td>
<td>0.0232</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure</td>
<td>1.15 (1.10, 1.19)</td>
<td>0.0305</td>
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<tr>
<td></td>
<td>Age by diastolic blood pressure interaction</td>
<td>0.998 (0.997, 1.000)</td>
<td>0.0674</td>
</tr>
<tr>
<td>Prehypertension Only Model†</td>
<td>Prehypertension</td>
<td>6.81 (6.06, 7.66)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

*Age (per 1 year increase), body mass index (per 1 kg/m² increase), systolic blood pressure (per 1 mm Hg increase), and diastolic blood pressure (per 1 mm Hg increase) were evaluated as continuous predictors. Sex (women vs. men), smoking (current vs. former or never smoker), and parental history of hypertension (per increment increase for both, one, or no parental history) were evaluated as categorical predictors. All predictors in the Framingham model were included in a single multivariable Weibull model.

†Prehypertension defined as systolic blood pressure 120-139 mm Hg or diastolic blood pressure 80-89 mm Hg. Prehypertension was the only predictor included in the Weibull model.