

Clinical Implications of Revised Pooled Cohort Equations for Estimating Atherosclerotic Cardiovascular Disease Risk

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Background: The 2013 pooled cohort equations (PCEs) are central in prevention guidelines for cardiovascular disease (CVD) but can misestimate CVD risk.

Objective: To improve the clinical accuracy of CVD risk prediction by revising the 2013 PCEs using newer data and statistical methods.

Design: Derivation and validation of risk equations.

Setting: Population-based.

Participants: 26 689 adults aged 40 to 79 years without prior CVD from 6 U.S. cohorts.

Measurements: Nonfatal myocardial infarction, death from coronary heart disease, or fatal or nonfatal stroke.

Results: The 2013 PCEs overestimated 10-year risk for atherosclerotic CVD by an average of 20% across risk groups. Misestimation of risk was particularly prominent among black adults, of whom 3.9 million (33% of eligible black persons) had extreme risk estimates (<70% or >250% those of white adults with

otherwise-identical risk factor values). Updating these equations improved accuracy among all race and sex subgroups. Approximately 11.8 million U.S. adults previously labeled high-risk (10-year risk $\geq 7.5\%$) by the 2013 PCEs would be relabeled lower-risk by the updated equations.

Limitations: Updating the 2013 PCEs with data from modern cohorts reduced the number of persons considered to be at high risk. Clinicians and patients should consider the potential benefits and harms of reducing the number of persons recommended aspirin, blood pressure, or statin therapy. Our findings also indicate that risk equations will generally become outdated over time and require routine updating.

Conclusion: Revised PCEs can improve the accuracy of CVD risk estimates.

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Risk estimates for cardiovascular disease (CVD) have become particularly important for clinical practice after recent updates to CVD prevention guidelines (1–3). Major guidelines now recommend that decisions about aspirin, blood pressure, and statin treatments be informed by 10-year CVD risk estimates from the pooled cohort equations (PCEs, sometimes called the atherosclerotic CVD risk tool), which were derived in 2013 using data from 5 cohort studies. The 2013 PCEs have been controversial because of reports that they substantially misestimate risk (4–10). Because of the central role of PCEs in CVD prevention, improving accuracy could save lives by better targeting treatment to those who need it most and avoiding treatment-related adverse events among those who do not need therapy.

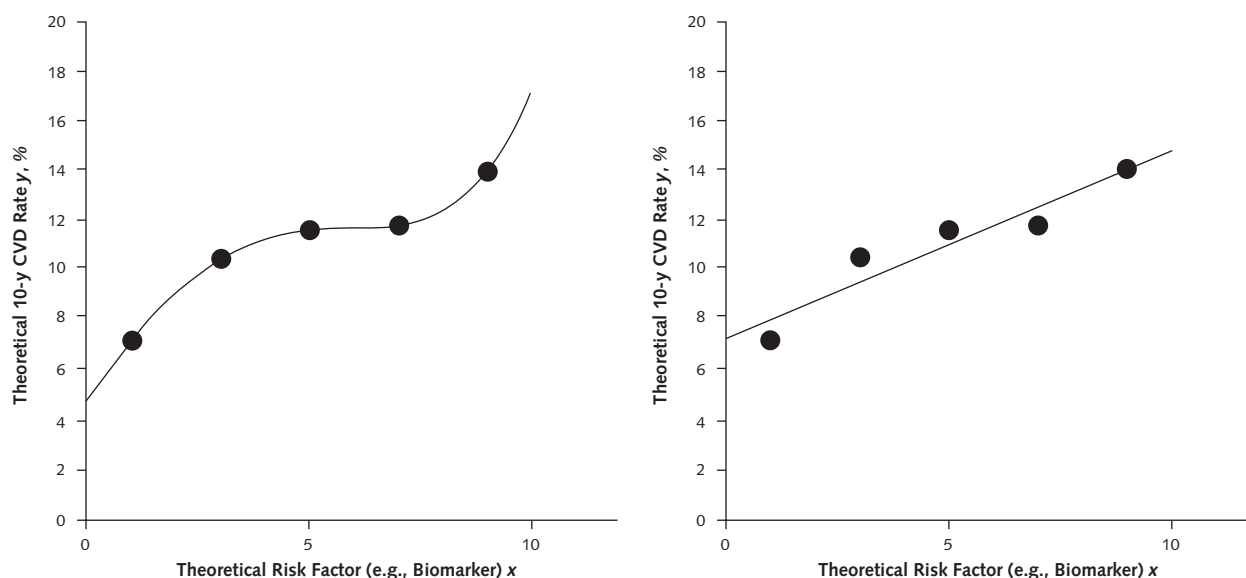
Two basic strategies to revise the PCEs could improve their accuracy: updating the data from which they are derived and changing the statistical methods used to derive them. The PCEs were developed using high-quality cohort data, but some of those data are now dated. For example, the FHS (Framingham Heart Study) original cohort, which was included in the PCE derivation, was aged 30 to 62 years in 1948 (11). Hence, updating the PCEs using newer cohort data may help account for therapeutic and societal changes between prior eras and the modern day (4, 6–10).

Different statistical methods may also improve the accuracy of CVD risk estimation. We have noted during clinical use of the 2013 PCEs that the CVD risk estimate for a black patient is often substantially lower than that

for a white patient with otherwise-identical, nonextreme values for risk factors. For example, a 46-year-old white man in NHANES (National Health and Nutrition Examination Survey, 2013 to 2014) with untreated systolic blood pressure of 108 mm Hg, total cholesterol level of 6.79 mmol/L (262 mg/dL), and high-density lipoprotein cholesterol level of 0.85 mmol/L (33 mg/dL) who smokes tobacco but does not have diabetes has an estimated 10-year risk for atherosclerotic CVD of 10.9% according to the 2013 PCEs. A black man with otherwise-identical risk factors has an estimated risk of 6.7% (an approximately 40% reduction in risk attributed to being black). Yet, prior literature suggests that black adults generally have somewhat higher risk than whites (12). Extreme estimates for black adults may indicate overfitting, a problem that can produce particularly erroneous estimates for subpopulations with fewer data (such as black adults). Equations that are overfitted capture not only true variations in risk between persons with different risk factor values but also random noise in the data sets, producing the appearance of high accuracy while actually generating very unlikely risk estimates. Some newer methods avoid overfitting

See also:

Editorial comment 1
 Web-Only
 Supplement

Figure 1. Conceptual illustration of overfitting.

Suppose we have data correlating a theoretical risk factor (e.g., a biomarker), x , to 10-y CVD rate, y . The equation (*fitted curve*) on the left may appear to be “better fit” to the data than that on the right, but we would not expect the curve on the left to reliably predict CVD rate y given some new values of risk factor x from another cohort, because the curve has fitted random error in the data set. In addition, the equation will extremely under- or overestimate CVD rates when applied to new cohorts that may have lower or higher values of x than the derivation data set. By contrast, the simpler equation (*line*) on the right may have poorer fit to the derivation data but better captures a more generalizable relationship between risk factor x and actual CVD rate y . CVD = cardiovascular disease.

(13), which can be particularly important when estimating risk for black adults and other subpopulations with smaller sample sizes (14). Further, the PCE derivation process used Cox proportional hazards modeling, a strategy that requires a strong statistical assumption about CVD risks among different groups of persons. The proportional hazards assumption requires that the hazard of a CVD event will be proportional over time between persons with and without a particular characteristic (for example, between smokers and nonsmokers). Violations of this assumption can affect the accuracy of risk estimates among subgroups (15–18). Whether the proportional hazards assumption was met by the 2013 PCE models was previously unknown. Fortunately, newer statistical methods can address these concerns (13).

The objective of this article was to identify the clinical implications of revising the 2013 PCEs with more recent data and newer statistical methods.

METHODS

We compared the original 2013 PCEs with 2 new alternatives: a revision that used the same derivation method as in 2013 but was applied to updated cohort data and a revision that also changed the derivation method to address statistical concerns with the 2013 method. This study was approved by the Stanford University Institutional Review Board.

Data

To update the PCEs, we included individual participant data from the following 6 longitudinal cohorts: ARIC (Atherosclerosis Risk in Communities Study, 1987

to 2011), CHS (Cardiovascular Health Study, 1989 to 1999), CARDIA (Coronary Artery Risk Development in Young Adults Study, 1983 to 2006), FHS offspring cohort (1971 to 2014), JHS (Jackson Heart Study, 2000 to 2012), and MESA (Multi-Ethnic Study of Atherosclerosis, 2000 to 2012). These samples corresponded to those used to derive the original 2013 PCEs (11), excluding the most dated cohort (FHS original cohort, 1948 to 2014) and including 2 more modern cohorts (JHS and MESA). The samples were also chosen to ensure reproducibility by including data readily accessible to researchers through data sharing policies. Which cohorts to pool is inherently a matter of judgment—we decided to keep some older cohorts because they include age groups (older adults) still seen in clinical practice.

Participants

Eligibility criteria matched those used to derive the original PCEs in 2013 (11): age 40 to 79 years; white or black race; and no history of myocardial infarction, stroke, congestive heart failure, percutaneous coronary intervention, coronary artery bypass grafting, or atrial fibrillation ($N = 26\,689$) (Supplement Tables 1 and 2, available at Annals.org). The sample included only participants with complete data on predictor variables, matching 2013 derivation procedures (11); 4.9% of cohort participants were excluded because they were missing at least 1 predictor.

Outcome

For consistency and comparability, we used the same outcome as the 2013 PCEs (11): nonfatal myocar-

dial infarction, death from coronary heart disease, or fatal or nonfatal stroke over a 10-year period among persons without CVD at the beginning of the period.

Predictors

The following predictors used in the 2013 PCEs were assessed for inclusion: age, sex, black race, current tobacco smoking, total and high-density lipoprotein cholesterol, treated or untreated systolic blood pressure, and diabetes. We considered other predictors (Supplement Table 1), such as statin therapy, but excluded them because of inconsistent definitions or measurement across cohorts (as did the original PCE derivation [11]). Age interactions and squared terms were considered, as with the original PCEs.

Analysis

Model Set 1

We first compared the 2013 PCEs with a new set of equations produced by applying the original derivation process to the updated cohort data. As with the 2013 PCEs, 4 Cox proportional hazards models were derived, 1 each for black women, white women, black men, and white men. The 2013 PCEs included the above predictor terms, along with interaction terms between each predictor and age if—per the 2013 derivation committee—the *p* value for the interaction term was less than .01, or the *p* value was .01 to .05 and the continuous net reclassification improvement for non-events was 15 percent or greater, or the integrated dis-

crimination improvement index . . . was statistically significant” (11). We replicated the derivation approach used by the 2013 PCE committee to test the hypothesis that updating the data without updating the derivation method would improve estimation by the PCEs. The resulting equations were labeled model set 1.

Model Set 2

We created another set of equations using revised derivation methods to address 2 potential statistical problems with the 2013 PCEs. First, choosing equation terms on the basis of *P* values and model fit can cause overfitting, particularly for subpopulations with fewer participants, such as black adults (Figure 1) (13). Second, the 2013 derivation method used a Cox proportional hazards model, a traditional survival model that requires the proportional hazards assumption. We tested this assumption (because it was not previously tested to our knowledge) and found that the Cox proportional hazards assumption was violated by the cohort data used to derive the original 2013 PCEs (Supplement Table 3, available at Annals.org).

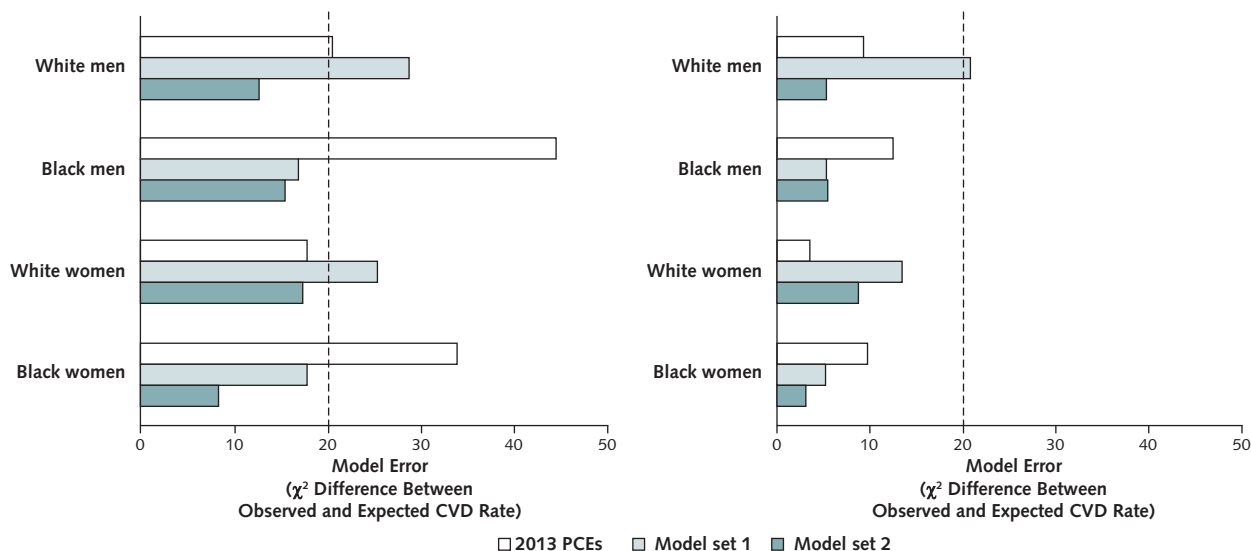
We addressed these 2 statistical problems in revised equations labeled model set 2. The revised equations avoided overfitting using a method known as elastic net regularization, which uses repeated cross-validation rather than *P* values to select predictors and coefficients (19, 20). We also avoided overfitting by de-

Table 1. Model Performance Metrics*

Variable	Derivation: Internal Cross-Validation Sample (N = 21 356)			Validation: Prospective Holdout Sample (N = 5333)		
	Original 2013 PCEs	Model Set 1: Updated Cohort Data	Model Set 2: Updated Data and Newer Derivation Method	Original 2013 PCEs	Model Set 1: Updated Cohort Data	Model Set 2: Updated Data and Newer Derivation Method
Black women (N_{derivation} = 3765; N_{validation} = 944)						
GND <i>P</i> value	<0.001 (failure)	0.037 (failure)	0.51	0.020 (failure)	0.153	0.68
Calibration slope	0.78	1.23	0.92	0.73	1.24	0.92
c-statistic	0.77	0.80	0.81	0.74	0.78	0.77
White women (N_{derivation} = 8224; N_{validation} = 2051)						
GND <i>P</i> value	0.120	0.014 (failure)	0.140	0.74	0.035 (failure)	0.184
Calibration slope	0.95	1.16	0.91	1.07	1.34	1.08
c-statistic	0.76	0.80	0.80	0.79	0.83	0.83
Black men (N_{derivation} = 2503; N_{validation} = 623)						
GND <i>P</i> value	<0.001 (failure)	0.155	0.167	0.006 (failure)	0.25	0.139
Calibration slope	0.78	1.01	0.89	0.72	1.05	0.87
c-statistic	0.71	0.73	0.73	0.74	0.73	0.74
White men (N_{derivation} = 6864; N_{validation} = 1715)						
GND <i>P</i> value	0.084	0.011 (failure)	0.56	0.50	0.022 (failure)	0.91
Calibration slope	0.88	1.19	0.94	0.94	1.31	1.10
c-statistic	0.70	0.74	0.74	0.74	0.77	0.78

GND = Greenwood-Nam-D'Agostino; PCE = pooled cohort equation.

* The GND calibration test assesses the significance of differences between expected and observed cardiovascular disease event rates such that higher *P* values are desirable (indicative of less-significant differences between expected and observed event rates). The calibration slope corresponds to the regression line between expected and observed Kaplan-Meier event rates (see Supplement Figure 1 [available at Annals.org] for calibration plots) such that a value near 1 is desirable and values <1 indicate overestimation of risk. The c-statistic assesses model discrimination (ability to distinguish a higher- from lower-risk person) such that values closer to 1 are desirable and was calculated using the Harrell bootstrap adjustment for optimism (28).

Figure 2. Model error in the internal cross-validation sample (*left*) and prospective holdout validation sample (*right*).

Error was calculated as the χ^2 statistic for distance between expected (predicted) and observed event rates of atherosclerotic CVD in the derivation sample, using the Greenwood-Nam-D'Agostino method for time-to-event data (27). Values <20 (dashed line) are generally considered to indicate acceptably low error. Model set 1 was the 2013 PCEs updated with newer cohort data; model set 2 additionally used a newer derivation method to avoid overfitting and the proportional hazards assumption. See Table 1 for additional calibration statistics and Supplement Figure 1 (available at [Annals.org](#)) for calibration plots. CVD = cardiovascular disease; PCE = pooled cohort equation.

iving only 2 equations (1 for men and 1 for women, with potential black race coefficients and interaction terms with race) rather than 4 (1 for each combination of men or women and black or white race), because deriving 4 equations assumes that black race necessarily interacts with each other predictor in the model (thus predisposing to overfitting). The revised equations in model set 2 also followed recommendations that when the proportional hazards assumption is violated, a logistic regression model adjusted for censoring can produce more accurate coefficient estimates than a Cox proportional hazards model (13, 15, 21). Hence, 2 logistic equations were selected through elastic net regularization, 1 for men and 1 for women.

Validation

First, the equations were derived through internal cross-validation, following current recommendations (13), using stratified random sampling of 80% of each cohort (22). Second, the remaining 20% of data were reserved as a prospective holdout validation sample, which was used only to assess performance of the finalized equations, not for predictor selection, coefficient estimation, or recalibration. This approach incorporates as many diverse populations as possible in derivation and validation of risk scores intended for clinical application, rather than using the older method of omitting 1 or more entire cohort studies from derivation and using only omitted studies for validation. The older approach can increase design effects during derivation and fail to distinguish miscalibration from overfitting during validation (13, 23-26). However, we did additional derivation and validation experiments to test the idea that our methodological revisions would be insuff-

ficient on their own to improve performance and that updated data would also be required. In particular, we evaluated whether we received different validation results if we derived the models among cohorts enrolled before the year 2000 and validated them among those enrolled during or after 2000.

Performance Measures

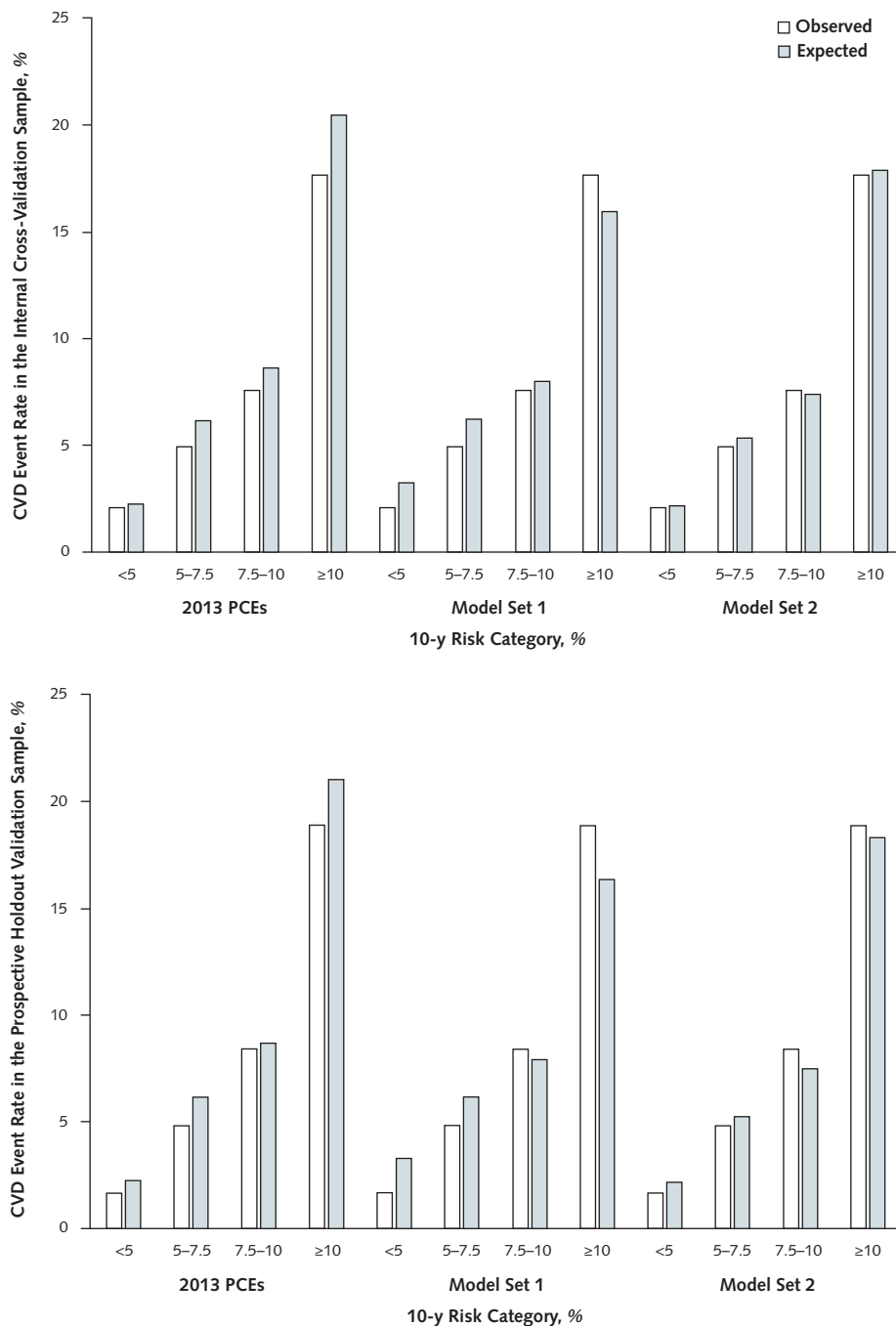
Calibration (how well estimated CVD event rates correspond to observed rates) was assessed by the Greenwood-Nam-D'Agostino (GND) test (27). This test assesses the significance of χ^2 differences between expected and observed event rates (ideally having a large *P* value), the calibration slope of the regression line between expected and observed Kaplan-Meier CVD event rates (ideally 1), and the observed versus expected CVD rate by expected risk group (10-year expected risk of $<5\%$, 5% to $<7.5\%$, 7.5% to $<10\%$, or $\geq 10\%$).

Discrimination (how likely the equations are to correctly pick the higher-risk person in a pair) was measured by the c-statistic (ideally 1) (28). We used a reclassification table to assess discrimination improvement, tabulating persons who did and did not have a CVD event and were classified as high or low risk ($\geq 7.5\%$ or $<7.5\%$ expected 10-year risk, respectively [1]) by 1 model and correctly or incorrectly reclassified as high or low risk by an alternative model. We did sensitivity analyses using 10-year risk of 5% or 10% rather than 7.5% as the threshold for "high risk." We avoided the net reclassification index because of multiple reports that it is biased toward overfitted models even when independent test data sets are used (29, 30); hence, fully disaggregated reclassification tables were presented.

Finally, the *black-white expected risk ratio* was estimated, which is a black adult's estimated risk divided by that of a white adult with otherwise-identical risk factor values. We aimed to detect implausible risk estimates for black adults that may be due to overfitting by

comparing the black-white expected risk ratio with the empirical ratio range of 70% to 250% (12). We estimated the ratio among adults aged 40 to 79 years in NHANES who met the inclusion criteria above after excluding participants receiving statins and those with ex-

Figure 3. Observed versus expected CVD event risk, by risk group, in the internal cross-validation sample (*top*) and prospective holdout validation sample (*bottom*).



Sample sizes were $n = 8329$ for <5%, $n = 2510$ for 5% to <7.5%, $n = 1899$ for 7.5% to <10%, and $n = 7145$ for $\geq 10\%$ 10-year expected risk by the 2013 PCEs in the derivation sample. The risk groups defined by the 2013 PCEs were used consistently across model comparisons to keep the same number of participants in each group, for fair comparison. Model set 1 was the 2013 PCEs updated with newer cohort data; model set 2 additionally used a newer derivation method to avoid overfitting and the proportional hazards assumption. See also Supplement Figure 3 (available at Annals.org). CVD = cardiovascular disease; PCE = pooled cohort equation.

Table 2. Examples of Highly Variable Risk Ratios for Black Versus White Adults From the 2013 PCEs Versus Our Proposed Alternative, Model Set 2*

Example	Predictor Variables									
	Age, y	Sex	Systolic BP, mm Hg	BP Treatment	Total Cholesterol Level		HDL Cholesterol Level		Smokes Tobacco	Diabetes
					mmol/L	mg/dL	mmol/L	mg/dL		
Black-white estimated risk ratios <0.7 per 2013 PCEs										
1	46	Male	108	No	6.79	262	0.85	33	Yes	No
2	68	Male	115	No	5.08	196	1.04	40	No	No
3	43	Female	111	No	7.28	281	2.07	80	Yes	No
4	76	Female	132	Yes	3.63	140	1.73	67	No	No
5	70	Male	138	No	3.96	153	0.96	37	No	No
Black-white estimated risk ratios ≥2.5 per 2013 PCEs										
1	41	Male	123	Yes	4.82	186	1.27	49	No	Yes
2	41	Female	186	Yes	4.09	158	1.17	45	Yes	No
3	41	Male	133	Yes	4.82	186	1.66	64	No	Yes
4	53	Female	147	No	4.64	179	1.45	56	No	Yes
5	47	Female	163	Yes	3.65	141	1.09	42	No	No

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; HDL = high-density lipoprotein; PCE = pooled cohort equation.

* Examples are from NHANES (National Health and Nutrition Examination Survey) 2013-2014 participants aged 40-79 y, excluding those who had a history of cardiovascular disease, received statins, or had missing or extreme values for input parameters (HDL cholesterol level <0.52 or >2.59 mmol/L [<20 or >100 mg/dL], total cholesterol level <3.37 or >8.29 mmol/L [<130 or >320 mg/dL], or systolic BP <90 or >200 mm Hg).

treme biomarker values (as defined by the 2013 PCE derivation committee [11]: systolic blood pressure <90 or >200 mm Hg, total cholesterol level <3.37 or >8.29 mmol/L [<130 or >320 mg/dL], or high-density lipoprotein cholesterol level <0.52 or >2.59 mmol/L [<20 or >100 mg/dL]). The 10-year CVD risk for each person in NHANES was calculated using the equations for blacks and then reestimated using the equations for whites to calculate the expected risk ratio.

Role of the Funding Source

The National Institutes of Health had no role in the study's design, conduct, or reporting.

RESULTS

All results come from validation analyses. We detail the prospective holdout validation results here, but internal cross-validation results were not substantially different (Table 1 and Figures 2 and 3).

Original 2013 PCEs

The 2013 PCEs overestimated risk by an average of 20% across risk groups, with 10-year estimated risk ranging from less than 5% to 10% or greater (Figures 2 and 3); they failed the GND calibration test among both black women and black men (Table 1). Model discrimination ranged from a c-statistic of 0.74 (for white and black men and black women) to 0.79 (for white women) (Table 1). Because some data in the holdout validation sample were used to fit the 2013 PCEs, estimates of calibration and discrimination may be more favorable to the 2013 PCEs than to model sets 1 and 2.

The 2013 PCEs produced highly variable risk ratios for black versus white adults. Table 2 and Figure 4 show how the 2013 PCEs produce risk estimates for black adults that can be more than 80% lower to more than 500% higher than those for white adults with

otherwise-identical risk factor values. We estimate that 3.9 million U.S. black adults meeting our eligibility criteria (33% of eligible black adults) would have extreme estimates using the 2013 PCEs (<70% or >250% those of white adults with otherwise-identical, nonextreme risk factor values). For 1 in 29 black adults (3.4%), the race variable would shift risk estimates above or below the common clinical decision-making threshold of a 10-year risk of 7.5%.

Updated Model Set 1: 2013 PCE Derivation Method With Newer Cohort Data

Model set 1 (Supplement Table 4, available at Annals.org) had slightly improved calibration statistics among black men (with more data on black men from MESA and JHS), but not among white adults or black women, failing the GND calibration test among whites (Table 1 and Figure 2). In fact, model set 1 overestimated risk among low-risk adults and underestimated risk among high-risk adults: Predicted CVD event rates were 87% of observed rates among the risk group with 10% or greater predicted 10-year risk, but they were 199% of observed rates among the group with less than 5% predicted risk (Figure 3).

Model set 1 also failed to resolve the widely variable risk ratios for black versus white adults. When model set 1 was used, 1 in 71 black adults (1.4%) who met our eligibility criteria had the 10-year risk estimate shifted above or below 7.5% by the race variable and had an extreme risk estimate (<70% or >250% that of an otherwise-identical white adult) (Figure 4).

Updated Model Set 2: Newer Cohort Data and an Updated Derivation Method

Model set 2 (Appendix Table, available at Annals.org) had substantially better calibration than the 2013 PCEs and model set 1; it was also the only model to

Table 2—Continued

Original 2013 PCEs			Model Set 2		
ASCVD 10-y Risk per 2013 PCEs, %		Black-White Risk Ratio per 2013 PCEs	ASCVD 10-y Risk per Model Set 2, %		Black-White Risk Ratio per Model Set 2
If White	If Black		If White	If Black	
Black-white estimated risk ratios <0.7 per 2013 PCEs					
10.9	6.7	0.61	6.4	4.3	0.67
14.6	9.7	0.66	7.6	5.7	0.75
1.9	0.5	0.26	0.8	1.3	1.63
24.4	13.2	0.54	8.4	7.9	0.94
20.4	13.5	0.66	12.7	9.5	0.75
Black-white estimated risk ratios ≥2.5 per 2013 PCEs					
2.4	9.3	3.88	4	8.4	2.10
6.3	26.7	4.24	5.7	11.8	2.07
1.9	9.9	5.21	3.8	9.3	2.45
3.5	8.9	2.54	4.2	6.7	1.60
1.8	8.9	4.94	1.8	3.6	2.00

pass the GND calibration test for all subgroups (Table 1 and Figure 2). Model set 2 predicted CVD event rates that were 89% to 132% of observed rates across risk groups (Figure 3).

Model set 2 also had better discrimination than the other models, with a c-statistic ranging from 0.74 (for black men) to 0.83 (for white women) (Table 1). When “high risk” was defined as an expected 10-year risk of 7.5% or greater, model set 2 correctly reclassified 13 persons as being low risk (who were incorrectly classified as high risk by the 2013 PCEs) for every 1 person it incorrectly reclassified as low risk (who was correctly classified as high risk by the 2013 PCEs) (Supplement Table 5, available at Annals.org). The ratio was 23:1 when “high risk” was defined using the threshold of at least 5% expected 10-year risk and 8:1 when using the threshold of at least 10% (Supplement Tables 6 and 7, available at Annals.org).

Model set 2 substantially narrowed the variable risk ratios for black versus white adults, such that fewer than 1% of eligible black adults had their risk estimate shifted above or below a 10-year risk of 7.5% by the race variable and had an extreme risk estimate (<70% or >250% that of an otherwise-identical white adult). Predicted risk for eligible black adults ranged from 41% lower to 277% higher than that of a white adult with otherwise-identical risk factor values (Table 2 and Figure 4).

Both white and black adults could have very different CVD risk estimates when model set 2 was used instead of the 2013 PCEs (Table 2). Based on the NHANES sample weights, 10-year risk estimates for about 11.8 million U.S. adults would be 7.5% or greater using the 2013 PCEs but would be less than 7.5% using model set 2. Conversely, there were no adults in NHANES whose risk estimates were less than 7.5% using the 2013 PCEs but 7.5% or greater using model set 2. If “high-risk” persons were defined with a 10% risk

threshold, 11.7 million U.S. adults would have 10-year risk estimates of 10% or greater using the 2013 PCEs but less than 10% using model set 2. Conversely, there no adults from the NHANES sample whose risk estimates were less than 10% using the 2013 PCEs but 10% or greater using model set 2.

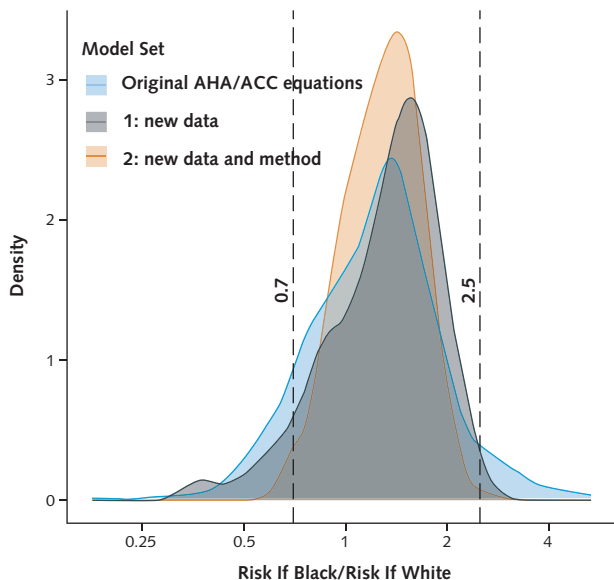
Alternative Derivations and Validations

Our revisions to the statistical methods by themselves would be insufficient to improve performance, and the updated data were also required to pass calibration tests. In particular, we found that model performance in terms of calibration would be markedly worse if we derived the models among cohorts enrolled before the year 2000 and validated them among those enrolled during or after 2000, even when applying the newer statistical methods (Supplement Table 8, available at Annals.org).

DISCUSSION

We found that by revising the PCEs with newer data and statistical methods, we could substantially improve the accuracy of CVD risk estimates. In particular, the equations labeled model set 2, which used newer data and statistical methods (hereafter, the “revised PCEs”), reduced overestimation among modern populations versus the 2013 PCEs. They also reduced the problem of extreme (and highly implausible) risk estimates for black adults compared with whites with otherwise-similar risk factors. Previous literature established that the 2013 PCEs generally overestimated risk among modern populations (4–10); in our analysis, we also found implausibly low or high risk estimates for black adults. Whereas prior studies suggested updating the derivation data to newer cohorts (6, 7, 9, 10, 25), our findings showed that this was not sufficient to

Figure 4. Effect of black race on 10-y estimated risk for atherosclerotic cardiovascular disease, per alternative models.



Risk ratios were calculated for all participants in NHANES (National Health and Nutrition Examination Survey, 2013–2014) aged 40–79 y with no history of cardiovascular disease. We calculated their 10-y event risk if they were black and divided by the same risk if they were white (i.e., all other risk factors being held constant). We omitted participants who were of neither white nor black race, had missing values, were receiving statins, or had extreme values for input variables (high-density lipoprotein cholesterol level <0.52 or >2.59 mmol/L [<20 or >100 mg/dL], total cholesterol level <3.37 or >8.29 mmol/L [<130 or >320 mg/dL], or systolic blood pressure <90 or >200 mm Hg). Note the log scale of the x-axis. ACC = American College of Cardiology; AHA = American Heart Association.

correct misestimation problems; the statistical methods also required revision to improve equation accuracy.

These findings have important clinical implications. Roughly 11.8 million U.S. adults would have 10-year risk estimates of 7.5% or greater using the 2013 PCEs but these estimates would be less than 7.5% using the revised PCEs derived here; this may substantially reduce the number of U.S. adults recommended for statin therapy (1). Similarly, using the threshold of 10% risk to define “high-risk” persons as recommended in other guidelines (2, 3), 11.7 million U.S. adults would have 10-year risk estimates of 10% or greater using the 2013 PCEs but less than 10% using the revised PCEs, potentially reducing the number of adults recommended for aspirin or blood pressure therapy. Clinically, our results suggest that the revised PCEs will reduce overestimation of risk in general and may prevent adverse events, health care costs, and inflated expectations of absolute risk and corresponding absolute therapeutic benefit. In addition, use of the updated equations will correct erroneous, implausible risk estimates for many black adults; at present, 1 in 29 of these persons would be expected to have an implausibly low or high risk estimate that crosses a critical threshold for clinical decision making of a 10-year risk of 7.5% because of the

black race coefficient in the 2013 PCEs. Even adults with risk estimates far from such thresholds may have erroneous risk estimates from the 2013 PCEs that could influence patient–physician conversations around the risks and benefits of lifestyle modifications and therapy.

Our results also have methodological implications for clinical risk estimation in general. First, our findings highlight that when researchers use *P* values and model fit to estimate risk equations without a penalty for producing equations with many terms, the resulting equations can be overfitted. Overfitting may cause miscalibration and extreme risk estimates, particularly for subpopulations with smaller sample sizes. Second, although use of a Cox proportional hazards model is common for medical risk estimation, the proportional hazards assumption may be violated and should be tested to avoid miscalibration before the Cox model formula is applied. Finally, in our alternative derivation and validation experiments, we found that simply updating our statistical methods was not sufficient to correct misestimation by the 2013 PCEs; both updated data and revised statistical methods were necessary.

Our study has important limitations. We responded to numerous articles calling for rederivation of the PCEs after incorporation of updated cohorts and removal of a dated cohort from the data pool (6, 7, 9, 10, 25). Yet, because the 2013 PCEs generally overestimated risk, our derivation approach of updating them by including cohorts with lower CVD rates inherently reduced the number of persons considered “high-risk,” causing some persons to be incorrectly converted from high- to low-risk status. At a common definition of high risk (10-year risk $\geq 7.5\%$), 13 persons who did not have a CVD event were correctly reclassified as low risk for each 1 person who had a CVD event and was erroneously reclassified as low risk by the revised PCEs versus the 2013 PCEs. At a more liberal definition of “high risk” (10-year risk $\geq 5\%$), the ratio improved to 23:1, whereas at a more conservative definition ($\geq 10\%$), it was 8:1. These estimates may still overestimate the number of high-risk persons because they include data from older cohorts. Nevertheless, risks and benefits of rederiving models with newer cohorts must be discussed among practitioners, patients, and guideline committees. In addition, as with the 2013 PCEs, the definition of the CVD outcome did not include heart failure or coronary revascularization to avoid biases due to ascertainment, definition, and physician recommendations.

Factors that cannot be included in the PCEs because of inconsistent definitions or measurement in the included cohorts, such as renal biomarkers, should be considered in the future. Risk equations should also be updated as newer cohort data become available. The next appropriate step would be for independent authors to reproduce and validate the revised PCEs among additional independent cohorts to identify whether the equations derived here outperform existing alternatives among diverse populations.

On the basis of our current results, we find that the revised PCEs can improve the accuracy of CVD risk estimates. The revised equations should be further inves-

tigated to determine whether they can improve the targeting of CVD therapies by maximizing benefits and minimizing adverse events among patients.

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Appendix Table. Example Calculation for Model Set 2, the Proposed Revision of the PCEs for Estimating ASCVD Risk*

Variable	Coefficient	Example Value	Coefficient × Value
Women			
(Intercept)	-12.823110	-	-12.823110
Age	0.106501	55	5.857555
Black race (1/0 for black/white)	0.432440	1	0.432440
Systolic blood pressure (mm Hg) squared	0.000056	14 400	0.806400
Systolic blood pressure	0.017666	120	2.119920
Taking blood pressure medication (1/0 for yes/no)	0.731678	-	0.000000
Diabetes mellitus (1/0 for yes/no)	0.943970	-	0.000000
Current smoker (1/0 for yes/no)	1.009790	-	0.000000
Ratio of total cholesterol (mg/dL) to high-density lipoprotein cholesterol (mg/dL)	0.151318	4.26	0.644615
Age if black (0 if not)	-0.008580	55	-0.471900
Systolic blood pressure if taking blood pressure medication (0 if not)	-0.003647	-	0.000000
Systolic blood pressure if black (0 if not)	0.006208	120	0.744960
Black race and taking blood pressure medication (1/0 for yes/no)	0.152968	-	0.000000
Age × systolic blood pressure	-0.000153	6600	-1.009800
Black race and diabetes mellitus (1/0 for yes/no)	0.115232	-	0.000000
Black race and current smoker (1/0 for yes/no)	-0.092231	-	0.000000
Ratio of total cholesterol to high-density lipoprotein cholesterol if black	0.070498	4.26	0.300321
Systolic blood pressure if black and taking blood pressure medication (0 if not)	-0.000173	-	0.000000
Age × systolic blood pressure if black (0 if not)	-0.000094	6600	-0.620400
Sum of terms	-	-	-4.018999
10-y probability of ASCVD event = $\frac{1}{1 + \exp(-\text{sum of terms})}$	-	-	0.017654 (1.8%)
Men			
(Intercept)	-11.679980	-	-11.679980
Age	0.064200	55	3.531000
Black race (1/0 for black/white)	0.482835	1	0.482835
Systolic blood pressure (mm Hg) squared	-0.000061	14 400	-0.878400
Systolic blood pressure	0.038950	120	4.674000
Taking blood pressure medication (1/0 for yes/no)	2.055533	-	0.000000
Diabetes mellitus (1/0 for yes/no)	0.842209	-	0.000000
Current smoker (1/0 for yes/no)	0.895589	-	0.000000
Ratio of total cholesterol (mg/dL) to high-density lipoprotein cholesterol (mg/dL)	0.193307	4	0.773228
Systolic blood pressure if taking blood pressure medication (0 if not)	-0.014207	-	0.000000
Systolic blood pressure if black (0 if not)	0.011609	120	1.393080
Black race and taking blood pressure medication (1/0 for yes/no)	-0.119460	-	0.000000
Age × systolic blood pressure	0.000025	6600	0.165000
Black race and diabetes mellitus (1/0 for yes/no)	-0.077214	-	0.000000
Black race and current smoker (1/0 for yes/no)	-0.226771	-	0.000000
Ratio of total cholesterol to high-density lipoprotein cholesterol if black	-0.117749	4.26	-0.501611
Systolic blood pressure if black and taking blood pressure medication (0 if not)	0.004190	-	0.000000
Age × systolic blood pressure if black (0 if not)	-0.000199	6600	-1.313400
Sum of terms	-	-	-3.354248
10-y probability of ASCVD event = $\frac{1}{1 + \exp(-\text{sum of terms})}$	-	-	0.033756 (3.4%)

ASCVD = atherosclerotic cardiovascular disease; PCE = pooled cohort equation.

* Example is shown for a nonsmoking black adult aged 55 y without diabetes who has a total cholesterol level of 5.52 mmol/L (213 mg/dL), high-density lipoprotein cholesterol level of 1.29 mmol/L (50 mg/dL), and untreated systolic blood pressure of 120 mm Hg. An online calculator is available at <https://sanjaybasu.shinyapps.io/ascvd>.