

Comparison of Nonblood-Based and Blood-Based Total CV Risk Scores in Global Populations



Thomas A. Gaziano^{*,†}, Shafika Abrahams-Gessel[†], Sartaj Alam[†], Dewan Alam[†], Mohammed Ali[§], Gerald Bloomfield^{||}, Rodrigo M. Carrillo-Larco[¶], Prabhakaran Dorairaj^{§,##}, Laura Gutierrez^{**}, Vilma Irazola^{**}, Naomi S. Levitt^{††,‡‡}, J. Jaime Miranda^{¶,§§}, Antonio Bernabe-Ortiz[¶], Ankur Pandya[†], Adolfo Rubinstein^{**}, Krisela Steyn^{††}, Denis Xavier^{|||}, Lijing L. Yan^{¶¶,###}

Boston, MA, USA; Toronto, Ontario, Canada; Gurgaon, India; Durham, NC, USA; Lima, Peru; Buenos Aires, Argentina; Cape Town, South Africa; Bangalore, India; Beijing, China; and Kunshan, China

ABSTRACT

Background: Cost-effective primary prevention of cardiovascular disease (CVD) in low- and middle-income countries requires accurate risk assessment. Laboratory-based risk tools currently used in high-income countries are relatively expensive and impractical in many settings due to lack of facilities.

Objectives: This study sought to assess the correlation between a non-laboratory-based risk tool and 4 commonly used, laboratory-based risk scores in 7 countries representing nearly one-half of the world's population.

Methods: We calculated 10-year CVD risk scores for 47,466 persons with cross-sectional data collected from 16 different cohorts in 9 countries. The performance of the non-laboratory-based risk score was compared with 4 laboratory-based risk scores: Pooled Cohort Risk Equations (ASCVD [Atherosclerotic Cardiovascular Disease]), Framingham, and SCORE (Systematic Coronary Risk Evaluation) for high- and low-risk countries. Rankings of each score were compared using Spearman rank correlations. Based on these correlations, we measured concordance between individual absolute CVD risk as measured by the Harvard NHANES (National Health and Nutrition Examination Survey) risk score, and the 4 laboratory-based risk scores, using both the conventional Framingham risk thresholds of >20% and the recent ASCVD guideline threshold of >7.5%.

Results: The aggregate Spearman rank correlations between the non-laboratory-based risk score and the laboratory-based scores ranged from 0.915 to 0.979 for women and from 0.923 to 0.970 for men. When applying the conventional Framingham risk threshold of >20% over 10 years, 92.7% to 96.0% of women and 88.3% to 92.8% of men were equivalently characterized as “high” or “low” risk. Applying the recent ASCVD guidelines risk threshold of >7.5% resulted in risk characterization agreement for women ranging from 88.1% to 94.4% and from 89.0% to 93.7% for men.

Conclusions: The correlation between non-laboratory-based and laboratory-based risk scores is very high for both men and women. Potentially large numbers of high-risk individuals could be detected with relatively simple tools.

Cardiovascular disease (CVD) remains a leading cause of death. However, many countries have seen reductions in age-adjusted death rates over the last 4 decades. Although public health measures such as smoking cessation campaigns and advances in acute care are likely responsible for a large portion of the decline, much of this improvement has been accomplished by identifying individuals at high probability of developing CVD through many identifiable risk factors and implementing targeted interventions to lower risk [1]. Initially, separate guidelines were developed for each individual risk factor and treatment was recommended when the risk factor reached a threshold above a specified level, such as blood pressure >140/90 mm Hg

[2]. One limitation, however, is that for any given level of a risk factor, there is a broad range of overall risk for CVD depending on the level of other known risk factors.

In contrast, absolute risk scores using multiple risk factors have better precision and have been adapted into easily used score calculators that are more readily available [3]. Identifying those at highest risk with multiple risk factors will lead to the greatest benefit in terms of delaying onset of disease [4]. In addition, efforts to using a multiple risk factor approach are more cost-effective than basing interventions on single risk factors [5]. The calculation of the absolute CVD risk is usually based on age, sex, tobacco use status, blood pressure levels, and blood cholesterol

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From the *Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, USA; †Center for Health Decision Science, Harvard T.H. Chan School of Public Health, Boston, MA, USA; ‡Centre for Global Health Research, St. Michael's Hospital, Toronto, Ontario, Canada; §Centre for Chronic Disease Control, Gurgaon, India; ||Duke Clinical Research Institute, Durham, NC, USA;

¶CRONICAS Center of Excellence for Chronic Diseases, Universidad Peruana Cayetano Heredia, Lima, Peru; #Public Health Foundation of India, Gurgaon, India; **Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina; ††Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; ‡‡Division of Diabetic Medicine and Endocrinology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town,

South Africa;
 §§Department of Medicine,
 School of Medicine, Uni-
 versidad Peruana Cayetano
 Heredia, Lima, Peru; |||St.
 John's Medical College and
 Research Institute, St.
 John's National Academy of
 Health Sciences, Bangalore,
 India; ¶¶The George Insti-
 tute for Global Health at
 Peking University Health
 Science Center, Beijing,
 China; and the ##Duke
 Global Health Institute,
 Global Health Research
 Center, Duke Kunshan Uni-
 versity, Kunshan, China.
 Correspondence: T. Gaz-
 iano (tgaziano@partners.org).

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TABLE 1. Study populations, inputs, and outcomes used to construct the risk scores

Score	Population*	Inputs	Outcome
Pooled Cohort Equations (ASCVD) [21]	U.S. population ages 40 to 79 drawn from ARIC [22], Cardiovascular Heart Study [23], CARDIA [24], Framingham (1968 to 1987) [25], Framingham Offspring Study Cohorts [26]	Age, sex, smoking, diabetes, systolic blood pressure, treatment for hypertension, race, total cholesterol, HDL cholesterol	Non-fatal MI or CHD death, or fatal or non-fatal stroke
Framingham CVD 2008 (D'Agostino et al., 2008) [20]	Framingham, MA, USA (1968 to 1987)	Age, sex, smoking, diabetes, systolic blood pressure, treatment for hypertension, total cholesterol, HDL cholesterol	MI, angina, coronary insufficiency, CHD death, stroke, TIA, CHF, PVD, CVD death
SCORE, high risk (Conroy et al., 2003) [7]	High-risk European countries [†]	Age, sex, smoking, systolic blood pressure, total cholesterol	Death from hypertensive disease, IHD, cerebrovascular disease
SCORE, low risk (Conroy et al., 2003) [7]	Low-risk European countries [†]	Age, sex, smoking, systolic blood pressure, total cholesterol	Death from hypertensive disease, IHD, cerebrovascular disease
Non-laboratory-based (Gaziano et al., 2008) [11]	NHANES I (USA, 1971 to 1975)	Age, sex, smoking, diabetes, systolic blood pressure, treatment for hypertension, BMI	CVD death, MI, stroke, CHF, coronary bypass, PTCA

ARIC, Atherosclerosis Risk in Communities; ASCVD, Atherosclerotic Cardiovascular Disease; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; HDL, high-density lipoprotein; IHD, ischemic heart disease; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PTCA, percutaneous transluminal coronary angioplasty; PVD, peripheral vascular disease; SCORE, Systematic Coronary Risk Evaluation; TIA, transient ischemic attack.

*Years indicate when baseline values were collected.

[†]Applicable for all non-low-risk European countries.

[‡]Applicable for Belgium, France, Greece, Italy, Luxembourg, Portugal, Spain, and Switzerland.

Adapted from Gaziano et al. [12].

levels as was done with data from the Framingham study and other cohorts [6–10].

Whereas the absolute risk determination approach holds particular promise for resource scarce settings, blood lipid determinations for screening purposes are far too costly in most developing country settings with limited resources and consequently are unlikely to be adopted as policy in these settings. Therefore, an investigation into the possibility of using other known CVD risk factors that are easier and less costly to measure instead of CVD risk factors that require costly laboratory tests when calculating absolute CVD risk scores has been proposed. This previous work compared the ability to predict first-time fatal and nonfatal CVD events in the NHANES (National Health and Nutrition Examination Survey) I follow-up study cohort by 2 risk prediction models: the laboratory-based Framingham risk score and the Harvard NHANES non-laboratory-based model [11], which requires only history and physical examination measures and no measure of cholesterol. The exchangeability of the non-laboratory-based score with commonly used laboratory-based approaches has been validated in a U.S. population and assessed for agreement in South Africa [12,13], but not in other populations.

Many countries are unlikely in the short term to have their own validated risk score because of the time involved and/or expense of following a cohort with confirmed outcomes for a minimum of 5 to 10 years. As a result, countries have turned to other risk scores such as the laboratory-based risk scores or the non-laboratory-based risk scores such as the Harvard NHANES score [11] or the World Health Organization risk charts [14] based on individual risk factors. In the meantime, countries need to understand whether these risk scores rank individuals comparably even if the absolute risk scores may be over-estimated or underestimated. We compare a non-laboratory-based risk score (Harvard NHANES) with 4 other commonly used laboratory-based risk scores to assess the level of correlations between them in 7 cohorts from 8 different countries representing nearly one-half the world's population.

METHODS

For the primary analysis, we needed to evaluate cohorts that had cross-sectional information to calculate both the non-laboratory-based risk score as well as the laboratory-based

TABLE 2. Summary of CVD risk factors by CoE study populations (35 to 74 years)

Center	n	Female (%)	Age ± SD (yrs)	BMI ± SD (kg/m ²)	Diabetes (%)	Current Smokers* (%)	Blood Pressure Treatment (%)	Mean SBP ± SD (mm Hg)	Mean HDL Cholesterol ± SD (mg/dl)	Mean Total Cholesterol ± SD (mg/dl)
Southern Cone, Latin America [†]	7,436	57.8	54.2 ± 10.6	29.2 ± 5.7	11.1	26.8	30.1	130.2 ± 20.6	46.6 ± 12.9	203.9 ± 42.9
Bangladesh	4,380	52.1	53.4 ± 9.2	22.6 ± 4.8	11.0	47.5	0.0	120.7 ± 21.3	NA [‡]	NA [‡]
China	4,938	51.5	60.8 ± 8.5	24.5 ± 3.6	11.5	30.2	31.2	145.0 ± 22.3	NA [‡]	NA [‡]
India—Bangalore	14,676	25.3	58.1 ± 9.4	23.6 ± 5.5	9.7	21.4	16.4	148.9 ± 32.0	43.1 ± 13.7	176.6 ± 44.9
India—New Delhi and Chennai	7,179	50.7	48.2 ± 9.7	25.9 ± 5.1	18.8	23.6	16.0	128.6 ± 20.5	44.1 ± 11.5	187.8 ± 39.4
Pakistan—Karachi	2,617	53.1	47.9 ± 10.0	26.2 ± 5.5	14.0	29.1	22.1	125.2 ± 21.7	42.2 ± 11.6	177.2 ± 39.2
Kenya	610	49.3	55.1 ± 10.3	26.1 ± 6.8	5.1	4.6	33.1	135.4 ± 30.1	35.3 ± 16.4	166.9 ± 56.1
Peru	3,286	51.3	53.4 ± 10.6	27.8 ± 4.6	7.4	14.7	13.9	117.5 ± 18.2	41.2 ± 11.3	200.2 ± 40.3
South Africa	742	63.5	49.9 ± 10.1	30.6 ± 8.7	12.9	25.7	28.8	131.6 ± 24.5	47.3 ± 18.7	179.6 ± 45.4
Aggregate	45,864	44.3	54.5 ± 10.6	25.8 ± 5.7	11.7	25.9	19.2	135.0 ± 27.0	44.2 ± 12.7	191.9 ± 43.2

CoE, Center of Excellence; NA, not available; SBP, systolic blood pressure; other abbreviations as in Table 1.
 *Current smokers are people who responded positively to the question “Which best describes your history of tobacco use? (current, former, never),” except for Peru where current smokers are people who reported a daily smoking in response to the question “Do you currently smoke tobacco on a daily basis, or less than daily?”
[†]Representing Argentina, Chile, and Uruguay.
[‡]No data available for this COE.

risk scores. In a secondary aim, assuming there was a high level of correlation between the non-laboratory-based risk and laboratory-based risk scores, we used the non-laboratory-based risk score to calculate the absolute CVD risk predicted for a larger set of cohorts where just the non-laboratory-based risk assessment data was available to estimate the overall risk in these populations representing 10 different countries.

Study population

Data for this study was obtained from 8 institutes that were part of the National, Heart, Lung and Blood Institute (NHLBI)/United Health Group Centers of Excellence (CoE) for chronic disease global network [15]. Each CoE focused on enhancing the monitoring, prevention, and control of chronic diseases by developing their infrastructures for research and training. The studies contributed by the CoE were conducted in both rural and urban populations, and the complete, combined dataset contained records for 64,177 individuals. Each CoE had a primary coordinating site in 1 city but collected data from either multiple locations within 1 country or across multiple countries. In all, a combination of 16 cross-sectional studies, longitudinal cohort studies, randomized trials, and survey studies were conducted in 9 countries and administered by the CoE. For the primary analysis, we evaluated 7 cohorts from 8 countries. The 7 populations include the following: the “Southern Cone” with individuals from Argentina, Chile, and Uruguay; the “Bangalore” group represents a rural

Indian population; the “New Delhi and Chennai” group is an urban Indian population; the “Karachi” is an urban Pakistani population coordinated from the New Delhi-based CoE; the “Kenya” population is both rural and urban; the “Peru” group is mixed urban and rural; and the “South Africa” population is from an urban township. More detailed descriptions of some of the populations have been published elsewhere [15–19]. Not all CoE study protocols included the collection of lipid information. Specifically, the “China” population from 120 villages and the “Bangladesh” population did not measure cholesterol values and were not included in the primary analysis. All study protocols were reviewed by the NHLBI and approved by the respective local institutional or ethics review boards. All adults aged 35 to 74 (n = 45,864) with complete risk factor information were eligible for inclusion in these analyses and a dataset containing sociodemographic and anthropometry variables, blood pressure measurements, self-reported medical history, smoking status, and lipid levels was created. All of the risk factor data were obtained using similar standardized methods for collecting self-reported data, anthropometry, and lab assays for lipid level values. Current smokers are defined as people who responded positively to the question, “Which best describes your history of tobacco use? (current, former, never)” except for Peru where current smokers are people who reported daily smoking in response to the question “Do you currently smoke tobacco on a daily basis, or less than daily?” The contents of the original dataset and the

TABLE 3. Spearman rank correlations (ρ) results comparing Harvard NHANES non-laboratory-based risk score to 4 laboratory-based risk scores, by sex

CoE	n	Pooled Risk Equations (ASCVD) [21]	Framingham 2008 [20]	SCORE High [7]	SCORE Low [7]
Women					
Southern Cone, Latin America*	4,197	0.93	0.92	0.97	0.97
India—Bangalore	553	0.94	0.81	0.94	0.94
India—New Delhi and Chennai	2,659	0.89	0.91	0.98	0.98
Pakistan—Karachi	950	0.87	0.91	0.97	0.97
Kenya	130	0.79	0.85	0.96	0.96
Peru	1,458	0.93	0.91	0.98	0.98
South Africa	454	0.91	0.91	0.97	0.97
Aggregate	10,401	0.92	0.92	0.98	0.98
Men					
Southern Cone, Latin America*	3,054	0.95	0.94	0.96	0.97
India—Bangalore	1,297	0.93	0.87	0.94	0.94
India—New Delhi and Chennai	2,317	0.92	0.93	0.96	0.96
Pakistan—Karachi	836	0.93	0.93	0.97	0.97
Kenya	112	0.94	0.82	0.95	0.96
Peru	1,369	0.95	0.93	0.98	0.98
South Africa	261	0.94	0.94	0.97	0.98
Aggregate	9,246	0.94	0.93	0.97	0.97

All missing CVD risk scores were excluded from analysis ($n = 19,647$), as well as data from China and Bangladesh because these sites did not have lipid information available.
Abbreviations as in Tables 1 and 2.
*Representing Argentina, Chile, and Uruguay.

data used for the analyses in this paper are described in the Online Appendix (Online Table 1).

Risk scores

The primary analyses compared individual-level absolute 10-year CVD risk prediction scores calculated with the non-laboratory-based Harvard NHANES risk score [11] to 4 laboratory-based risk scores: Framingham 2008 [20]; Pooled Cohort Equations (ASCVD [Atherosclerotic Cardiovascular Disease]) [21]; SCORE (Systematic Coronary Risk Evaluation)-High [7]; and SCORE-Low [7]. Following Gaziano et al. [12], descriptions of the 5 risk scores, their underlying populations, inputs, and outputs are described in Table 1 [22–26]. Additional score calculation details, including the beta-coefficients, for each score are provided in the Online Appendix (Online Table 2). CVD risk scores predict CVD events, which are defined as either fatal or non-fatal myocardial infarction (MI), angina, or ischemic heart disease; peripheral artery disease; coronary artery bypass surgery; percutaneous transluminal coronary angioplasty; transient ischemic attack; congestive heart failure; and fatal or non-fatal cerebrovascular disease.

Statistical procedures

We calculated descriptive statistics of the cohorts within the 8 CoE for age, sex, systolic blood pressure, body mass index, smoking prevalence, diabetes mellitus status, history

of hypertension medication use, and total and high-density lipoprotein cholesterol levels. We recognize that many of the populations were not nationally representative by design, but we report the values as illustrative of the range of risk factor prevalences that existed between countries as well as to show what may have driven different predicted CVD risks in the countries. We then compared the correlation between the Harvard NHANES [11] absolute CVD risk scores to individual-level, score-specific rankings of absolute CVD risk for the other 4 laboratory-based scores. Individual-level risk predictions for each of the 5 scores were calculated and then subsequently assigned ranks for each risk score by sex. These ranks were used to assess Spearman rank correlation coefficients between the risk characterizations for the Harvard NHANES score compared with each of the 4 laboratory-based scores for each cohort. Pearson correlation coefficients were not reported because CVD risk prediction values were not normally distributed [27].

Next, individuals were divided into either “high” or “low” risk for each model based on their score-specific rank, and the threshold dividing the 2 risk categories was set to a risk >20% using the 10-year Framingham (2008) CVD risk score as this is a common level of risk used for treatment thresholds in many countries. Using this threshold, we then determined the risk level equivalent equal to the same proportion of individuals using each of the 4 other scores. In other words, if the CVD risk score

TABLE 4. Concordance between Harvard NHANES non-laboratory-based risk score and 4 laboratory-based risk scores using a Framingham (20%) CVD risk threshold

CoE	n	Pooled Risk Equations (ASCVD) [21]	Framingham 2008* [20]	SCORE High [†] [7]	SCORE Low [‡] [7]
Women					
Southern Cone, Latin America [‡]	4,197	95.3	90.8	93.5	93.8
India—Bangalore	553	92.4	83.7	86.6	86.8
India—New Delhi and Chennai	2,659	97.8	95.2	97.2	97.2
Pakistan—Karachi	950	97.2	94.6	97.3	97.2
Kenya	130	86.2	90.0	91.5	91.5
Peru	1,458	97.6	95.7	95.3	95.4
South Africa	454	96.0	93.4	95.6	95.4
Aggregate	10,401	96.2	92.7	94.8	94.9
Men					
Southern Cone, Latin America [‡]	3,054	91.2	88.6	92.6	93.3
India—Bangalore	1,297	89.2	84.7	89.1	90.7
India—New Delhi and Chennai	2,317	90.7	89.2	92.7	92.9
Pakistan—Karachi	836	92.0	89.4	93.1	93.3
Kenya	112	85.7	82.1	89.3	92.9
Peru	1,369	93.1	89.8	93.4	93.7
South Africa	261	87.7	88.9	93.1	93.1
Aggregate	9,246	91.0	88.4	92.3	92.9

All missing CVD risk scores were excluded from analysis (n = 19,647), as well as data from China and Bangladesh because these sites did not have lipid information available. Values are percentages. Abbreviations as in Tables 1 and 2.

*Agreement is based on dichotomous risk categorization corresponding to 10-year Framingham (2008) CVD risk >20%.

[†]Threshold of 10-year Framingham CHD risk >20%.

[‡]Representing Argentina, Chile, and Uruguay.

identified 15% of the population above this risk threshold, then we used the equivalent risk threshold of the Harvard NHANES score to identify 15% of the population. For example, when comparing the risk scores, a 20% Framingham CVD risk for fatal and nonfatal events is equivalent to a SCORE risk score of approximately 5% for fatal events only. Similar to analyses in a previous publication [12], the percentage agreement or concordance between Harvard NHANES score and each of the 4 laboratory-based scores was calculated by adding the proportions of individuals who were equivalently characterized as “high” or “low” risk by both scores. We then determined percentage agreement between Harvard NHANES score and the other 4 laboratory-based risk scores by comparing their Spearman rank correlation coefficients.

For our secondary aim, we calculated the mean 10-year CVD risk for each cohort using the Harvard NHANES non-laboratory-based score. In order to assess the generalizability of our findings, we standardized each cohort’s risk to country-specific age distributions for 2015, as well as to the global age distribution for 2015.

RESULTS

Overall 45,864 persons were included in the overall dataset for analyses of non-laboratory-based risk score calculation. Of these, 19,647 had data available to calculate

all 4 laboratory-based risk scores, whereas 35,450 had data available to calculate the Harvard NHANES risk score.

Descriptive statistics

The distribution of risk factors for CVD by CoE is provided in Table 2. Bangladesh had the lowest mean body mass index of 22.6 kg/m² whereas South Africa had the highest (30.6 kg/m²). Smoking prevalence varied from a low of 4.6% in Kenya to a high of 47.5% in Bangladesh. The aggregate mean systolic blood pressure (SBP) was 135.0 mm Hg with the lowest mean SBP in Peru (117.5 mm Hg), whereas China (145.0 mm Hg) and Bangalore (148.9 mm Hg) had the 2 highest means for SBP. China (60.8 years) and Bangalore (58.1 years) also had the highest mean ages. The mean high-density lipoprotein cholesterol level for Kenya fell well below the aggregate mean (35.3 vs. 44.2 mg/dl).

Correlation between ranks of Harvard NHANES risk score and 4 lab-based risk scores.

The Spearman rank correlation coefficients for the comparison of the non-laboratory-based (Harvard NHANES) CVD risk score to the 4 laboratory-based scores are presented in Table 3. The aggregate Spearman correlation for women was >0.91 for all laboratory-based scores when compared to the non-laboratory-based score, and the aggregate Spearman correlation for men was >0.92. The correlation between both

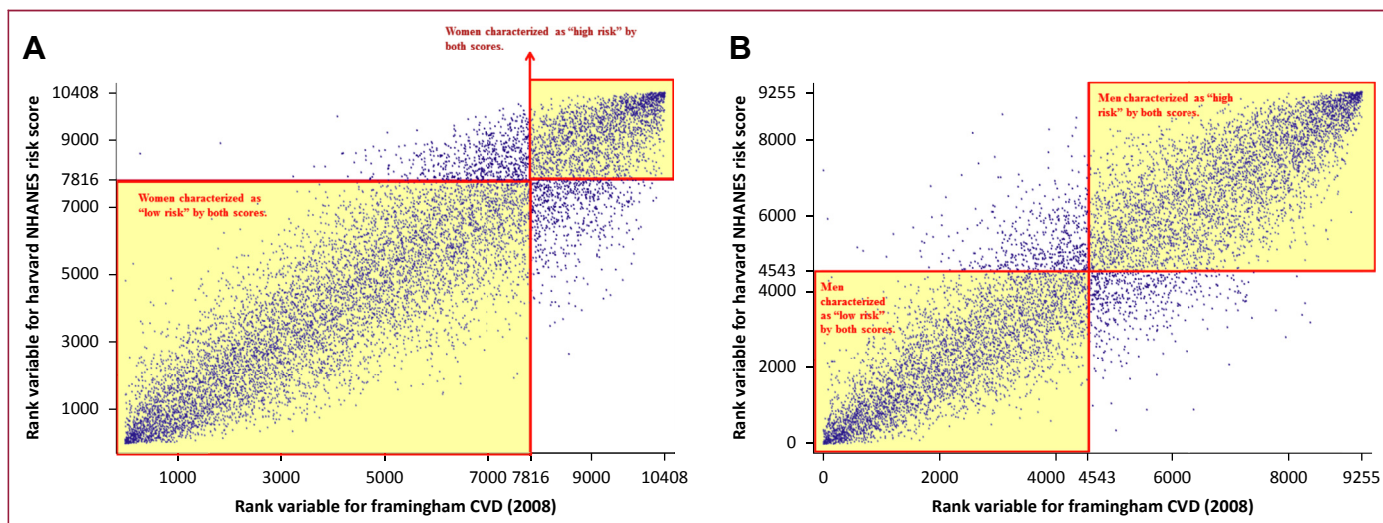


FIGURE 1. Rank variables for Harvard NHANES non-laboratory-based score plotted against rank variables for the Framingham risk score for participants ages 35 to 74 years with complete data in the aggregate study population. (A) Women; (B) men. CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

the high- and low-SCORE risk scores, respectively, and the Harvard NHANES scores were consistently higher than both the ASCVD and Framingham risk scores. The high- (aggregate $\rho = 0.98$ for women; aggregate $\rho = 0.97$ for men) and low-SCORE scores (aggregate $\rho = 0.98$ for women; aggregate $\rho = 0.97$ for men) were almost identical for all populations.

Using the 20% Framingham risk threshold, we find there is for women and men over 93% agreement and 88% concordance, respectively, in aggregate across the centers between the non-laboratory-based risk score and the 4 laboratory-based risk scores (Table 4). The percentage agreement was lowest for the Framingham risk score for men and women. However, all percentage agreement levels were above 80% for all populations. Figures 1A and 1B compare the rank variables for the Harvard NHANES risk score (y-axis), set at a 20% risk score threshold, to the Framingham risk score (x-axis), also using a threshold of 20%. Throughout the figures, we depict the subjects in agreement as either high or low risk based on the threshold in the shaded portions for each risk score. Those in disagreement are unshaded and represent on average of <10% of the population. Given the new risk guidelines used in the United States [21,28], we characterized the agreement across the centers between the non-laboratory-based risk score and the 4 laboratory-based risk scores when the ASCVD risk threshold is set at 7.5% (Table 5). At this threshold, the aggregate level of concordance is 88% for both women and men. We also reproduced additional scatter plots (Figures 2A and 2B), which compare the rank variables for the Harvard NHANES risk score (y-axis) to the ASCVD risk score (x-axis), for the 7.5% ASCVD risk threshold. In all these graphs, larger ranks indicate higher CVD risk and each risk categorizes individuals as either

“high” or “low” risk using the individual risk thresholds as described. These figures show a larger proportion of the population that would be eligible for treatment if this lower threshold is used. However, the percentage agreements were similar for different levels of risk.

The Harvard NHANES risk score was calculated for 35,450 persons for whom the required data were available (Table 6). Average non-laboratory-based (Harvard NHANES) 10-year risk was 18.58%, ranging from 12.24% in Bangladesh to 29.32% in China. The China population’s risk is higher largely due to the older mean age of the population and its higher mean blood pressure. Figure 3 displays the individual groups’ CVD risk scores by age using the Harvard NHANES risk score. As expected, risk scores increased by age in all the cohorts. Risk of CVD was <5% for those under 45-years-old and ranged from 35% to 60% for those ages 74 or older.

DISCUSSION

In this study, we showed that a non-laboratory-based CVD risk score compared with 4 risk scores commonly used throughout the world similarly ranked individuals in all the cohorts studied, which represent 8 different countries. Furthermore, we observed strong agreement in the risk characterization between the laboratory-based risk scores and the non-laboratory-based risk scores. Spearman correlation was >0.9 for the aggregate of all the cohorts as well as for most of the cohorts for all the risk scores compared. The level of CVD risk characterized in each of the cohorts and between cohorts was quite wide, suggesting the non-laboratory-based risk score performed well across a broad range of at-risk populations. The greatest correlation with Harvard NHANES risk prediction tool was

TABLE 5. Concordance between Harvard NHANES non-laboratory-based risk score and 4 laboratory-based risk scores using an ASCVD (7.5%) CVD risk threshold

CoE	n	Pooled Risk Equations (ASCVD) [21]	Framingham 2008 [20]	SCORE High* [7]	SCORE Low* [7]
Women					
Southern Cone, Latin America [†]	4,197	91.7	86.5	92.6	92.8
India—Bangalore	553	91.9	78.1	89.9	90.1
India—New Delhi and Chennai	2,659	96.1	91.8	96.5	96.6
Pakistan—Karachi	950	94.2	90.8	96.6	96.4
Kenya	130	85.4	89.2	94.6	94.6
Peru	1,458	95.1	90.2	94.1	94.1
South Africa	454	92.7	87.7	94.7	94.7
Aggregate	10,401	93.5	88.4	94.2	94.2
Men					
Southern Cone, Latin America [†]	3,054	91.4	90.4	94.0	94.4
India—Bangalore	1,297	88.0	86.6	92.7	93.6
India—New Delhi and Chennai	2,317	89.1	89.2	92.1	92.4
Pakistan—Karachi	836	90.4	89.4	94.9	95.2
Kenya	112	85.7	83.9	93.8	92.9
Peru	1,369	90.9	88.7	94.0	94.3
South Africa	261	93.5	92.7	94.3	95.0
Aggregate	9,246	90.2	89.2	93.4	93.8

All missing CVD risk scores were excluded from analysis ($n = 19,647$), as well as data from China and Bangladesh because these sites did not have lipid information available. Values are percentages. Abbreviations as in Tables 1 and 2.

*Agreement is based on dichotomous risk categorization corresponding to 10-year Pooled Cohort Equations (ASCVD) risk $>7.5\%$.

[†]Representing Argentina, Chile, and Uruguay.

with the European SCORE [7] prediction tool with levels of agreement of approximately 95% or higher in most of the cohorts. For any particular country, the percentage correlation was higher for women than for men when comparing the non-laboratory-based score to the SCORE tools, and the correlation was higher for men than for women when comparing the U.S. laboratory-based scores in comparison to the non-laboratory-based risk score.

Assessing CVD risk in the general population without the additional costs and inconvenience of measuring cholesterol could be valuable in many low- and middle-income settings. The non-laboratory-based risk score allows health providers to correctly classify those at high versus low risk, which can guide treatment or other intervention decisions that may limit scarce resources to those at highest risk. Furthermore, the ability to make decisions on treatment during a single clinic visit could improve compliance and reduce inefficiencies associated with a required follow-up visit. Many patients have to give up a full day of work to queue in clinic lines, and return visits can discourage further follow-up and engagement and thus could reduce the number of individuals lost to follow-up. In some of the countries, cholesterol testing and the follow-up visit can cost more than \$10 per visit [29]. Individuals can now be treated with a year's supply of

simvastatin for less than one-half that price [30]. Furthermore, the risk tool can be used by community health workers to assess risk in the community, which can offset demands of busy primary health centers [31].

Although not all the cohorts evaluated were representative samples, evaluation of all the cohort participants showed that there is significant risk of CVD that exists in many of the populations in the countries evaluated in the analysis. After adjustment to either the country's population structure or the world population, the mean 10-year-CVD risk was about 15%, which is commonly considered as being at "intermediate" risk. Furthermore, after adjustment for age over one-quarter of the population had a risk $>20\%$, which is used by many countries for a threshold for initiating treatment with medications such as statins. If countries begin to adopt lower treatment thresholds such as the United Kingdom ($>10\%$) or the United States ($>7.5\%$) have [28], then up to 50% of these populations could be considered at high enough risk to warrant intervention. Risks were particularly high in the Chinese group that had higher mean blood pressure and mean age as well as relatively high smoking rates. Even after adjustment to a standard age-distribution, more than 50% of the Chinese had $>20\%$ risk using the Framingham equation or the non-laboratory-based risk score. It has been shown that the

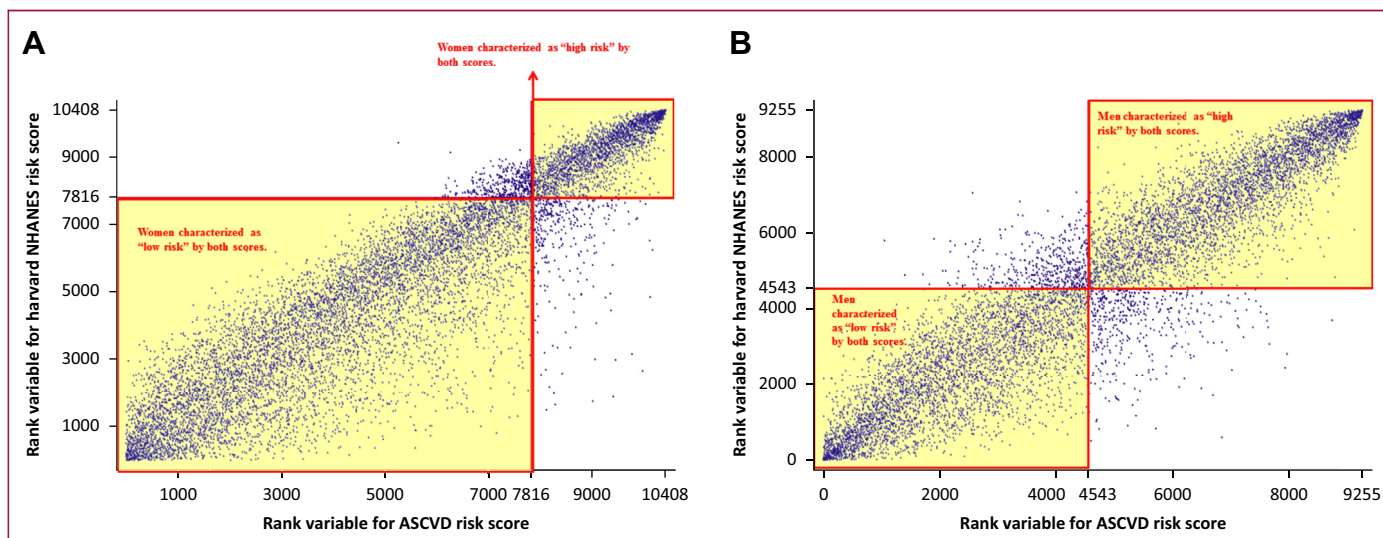


FIGURE 2. Rank variables for Harvard NHANES non-laboratory-based score plotted against rank variables for the ASCVD risk score for participants ages 35 to 74 years with complete data in the aggregate study population. (A) Women; (B) men. ASCVD, atherosclerotic cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

Framingham risk score overestimates risk in China by as much as 97% [32], so it is important to acknowledge that the actual risks reported here may be an overestimation. However, our results show that many countries have a significant proportion of their population at risk especially among the elderly. An additional value of the non-laboratory-based risk score was that in this study ~44,000 individuals were able to have their risk score calculated compared with just then ~20,000 using the laboratory-based scores. Thus for many countries, in practice as in this research, the potential for access to risk assessment is increased by the non-laboratory-based risk scores.

One limitation of our analysis is that the risk discrimination and performance of the non-laboratory-based risk score has not been validated in these cohorts from these multiple countries. The lack of reliable death data and non-fatal event data in these cross-sectional datasets make it impossible to validate the risk scores. It is possible that any of the risk scores may overestimate or underestimate risk in any of the centers' cohorts. Unfortunately, few of the countries have the cohorts or the linked death and event data to validate risk scores. However, our results show that in the absence of such validations, use of the non-laboratory-based risk score will identify up to 95% of the same people without the millions of dollars required to achieve the laboratory testing. Furthermore, the ability to make treatment or referral decisions on the spot in the community by community health workers could dramatically improve the outcome of those at highest risk without issues of loss to follow-up or inordinate costs.

The risk scores we compared all had different outcomes for the prediction tool. The U.S.-based risk scores used both fatal and non-fatal CVD events as their outcome measures, whereas the European-based SCORE tool used only fatal CVD events. We cannot with certainty say how the different outcomes could affect the results but the highest correlations with the non-laboratory Harvard NHANES score were with the SCORE risk scores, which use only fatal outcomes. In general, the risk scores based on fatal events only generally produce lower absolute risk scores compared with those calculated using the U.S.-based risk scores. Therefore, a country using a risk score result for initiating therapy may wish to have a higher threshold for those risk scores based on a combination of fatal and non-fatal CVD events.

CONCLUSIONS

A non-laboratory-based risk assessment tool appears to correlate very highly with the most commonly used laboratory-based CVD risk assessment tools in multiple countries across multiple regions of the world. Furthermore, these populations appear to show large portions of the populations at risk for which there are cheap and generically available interventions such as statin and blood pressure treatment. Efforts should begin soon for low- and middle-income countries to increase their screening programs and should include pragmatic screening techniques such as non-laboratory-based multivariate risk tools.

TABLE 6. Unadjusted and adjusted non-laboratory-based (Harvard NHANES) predicted CVD risk by CoE

CoE	n	Overall 10-Year Risk of CVD (Harvard NHANES Non-Laboratory-Based Score)*			Proportion of People With CVD Risk >20% Over 10 Years*		
		Unadjusted Risk	Age-Adjusted Risk to Country Population (2015) [†]	Age-Adjusted Risk to World Population (2015) [‡]	Unadjusted Risk	Age-Adjusted Risk to Country (2015) [†]	Age-Adjusted Risk to World Population (2015) [‡]
Southern Cone, Latin America [§]	7,416	19.04 (18.59–19.49)	15.34 (14.94–15.74)	13.99 (13.61–14.36)	36.14	28.07	24.69
Bangladesh	3,569	12.24 (11.76–12.71)	8.54 (8.18–8.90)	9.33 (8.95–9.71)	19.78	10.87	12.69
China	4,936	29.32 (28.76–29.88)	24.68 (24.16–25.20)	24.62 (24.10–25.15)	60.90	51.07	50.66
India—Bangalore	8,156	24.27 (23.85–24.70)	18.43 (18.06–18.81)	19.39 (19.01–19.78)	47.82	34.00	36.44
India—New Delhi and Chennai	5,247	10.42 (10.03–10.80)	7.09 (6.80–7.38)	7.82 (7.51–8.13)	16.45	8.94	10.45
Pakistan—Karachi	1,965	9.87 (9.24–10.51)	6.53 (6.06–7.01)	7.24 (6.74–7.74)	15.57	8.25	9.67
Kenya	507	17.63 (16.11–19.16)	11.16 (9.97–12.35)	13.31 (12.01–14.61)	33.93	17.68	22.75
Peru	2,918	13.01 (12.45–13.57)	9.02 (8.58–9.47)	9.38 (8.93–9.83)	22.04	12.86	13.54
South Africa	736	13.85 (12.60–15.10)	10.69 (9.65–11.73)	10.37 (9.36–11.39)	22.69	15.81	15.04
Aggregate	35,450	18.58 (18.38–18.78)	13.51 (13.34–13.68)	13.81 (13.64–13.97)	35.10	23.54	24.10

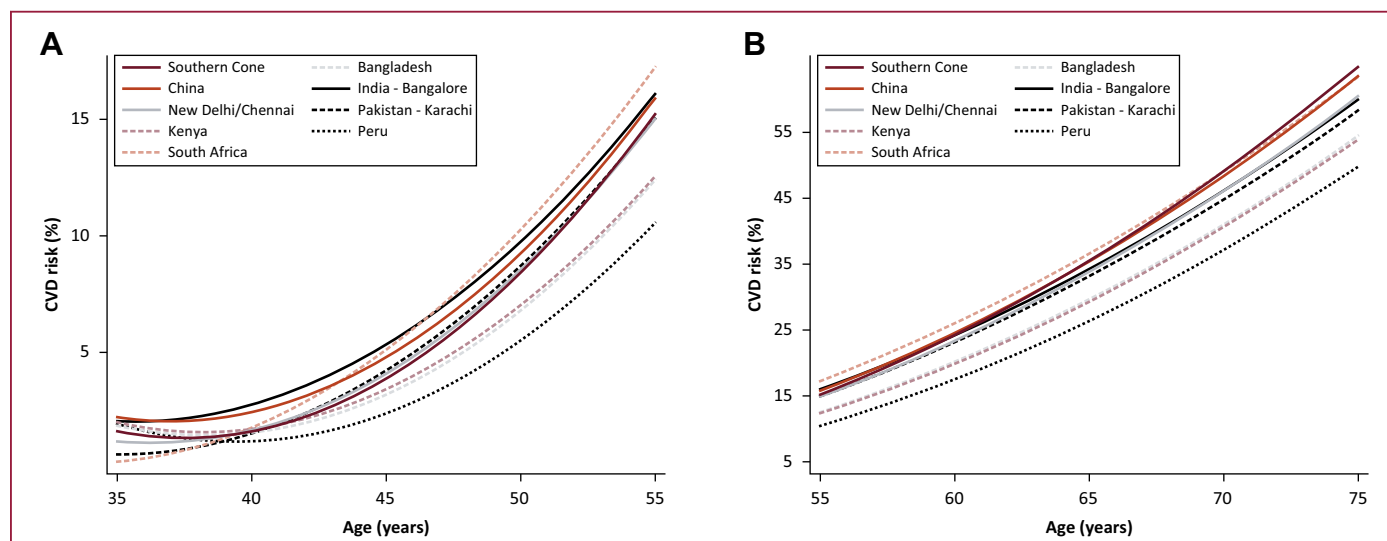
Values are mean % (95% CI) or %. All missing NHLBI CVD risk scores were excluded from this analysis (n = 35,450). CI, confidence interval(s); NHLBI, National Heart, Lung, and Blood Institute; other abbreviations as in Tables 1 and 2.

*CVD risk is the risk of experiencing CVD over the 10 years following risk assessment using the non-laboratory-based Harvard NHANES score.

[†]Risk standardized to individual country population (2015).

[‡]Age standardized to world population (2015).

[§]Representing Argentina, Chile, and Uruguay.

**FIGURE 3.** Distribution of unadjusted 10-year Harvard NHANES non-laboratory-based CVD risk score by CoE. (A) Ages 35 to 55 years; (B) 55 to 75 years. CoE, Center of Excellence; other abbreviations as in Figures 1 and 2.

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APPENDIX

ONLINE TABLE 1. Description of variables available in the original data set and the final data used in the analyses

Variable	Original Data Set (n = 64,177)	Analysis Data Set (n = 45,864)
	Number of Observations (n)	Number of Observations (n)
Age	59,711	43,332
Sex	60,179	43,258
Body mass index	49,869*	35,630
Weight	50,125	35,829
Height	51,421	36,680
Systolic blood pressure	57,070	40,841
History of diabetes	56,808	41,867
Current smokers	57,966	41,989
History of blood pressure treatment	34,244	45,864
High-density lipoprotein	27,339	21,706
Total cholesterol	27,545	21,874

*Body mass index was not computed in the original data set but was computed for use in the analyses.

ONLINE TABLE 2. Risk scores used for analyses of CVD risk for adults aged 35–74 years*

Variable (and Beta Coefficients) [†]	Pooled Cohort Equations (ASCVD) (Goff et al., 2013) (1)		Framingham CVD 2008 (D'Agostino et al., 2008) (2)	Harvard NHANES Non-Laboratory-Based (Gaziano et al., 2008) (3)	SCORE (Conroy et al., 2003) (4)
	Population (years for baseline values, age ranges)	US Population aged 40–79 drawn from ARIC (5), Cardiovascular Heart Study (6), CARDIA (7), Framingham (1968–1987) (8), Framingham Offspring Study Cohorts (9)		Framingham, MA, U.S. (1968–1987, 30–74 years)	NHANES I, representative U.S. (1971–75, 25–74 years)
Age	Included		3.061, 2.329	5.228, 6.035	Included
Sex	Included		sex-specific predictions	sex-specific predictions	Included
Smoking	Included		0.655, 0.529	0.658, 0.724	Included
History of diabetes	Included		0.574, 0.692	0.511, 0.488	Not included
SBP	Included		1.933, 2.762	2.588, 2.080	Included
Total cholesterol	Included		1.124, 1.209	Not included	Included
HDL cholesterol	Included		–0.933, –0.708	Not included	Not included
Treatment of hypertension	Included		changes coefficients for SBP to: 1.999, 2.823	0.190, 0.257	Not included
BMI	Not included		Not included	0.901, 0.872	Not included
Race	Included		Not included	Not included	Not included
Outcome	Non-fatal MI or CHD death, or fatal or non-fatal stroke.		MI, angina, coronary insufficiency, IHD death, stroke, TIA, CHF, PAD, CVD death	Death from: MI, CHF, cardiac arrest, other IHD, and cerebrovascular disease	Death from: hypertensive disease, IHD, cerebrovascular disease

ARIC, Atherosclerosis Risk In Communities; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CARDIA, Coronary Artery Development In Young Adults; CHF, congestive heart failure; CVD, cardiovascular disease; HDL, high-density lipoprotein; IHD, ischemic heart disease; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral vascular disease; PTCA, percutaneous transluminal coronary angioplasty; SBP, systolic blood pressure; TIA, transient ischemic attack.

*Adapted from Gaziano et al (2013) (10).

[†]Beta coefficient listed (for men, women), if included in risk score inputs, and refer to natural logs for continuous variables for Framingham CVD 2008, Framingham CHD 1991, and non-laboratory-based risk scores.

[‡]Applicable for all non-low risk European countries.

[§]Applicable for Belgium, France, Greece, Luxembourg, Portugal, Spain, and Switzerland.

^{||}Specific risk factor coefficients not displayed due to complex equation.

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