Prediction of cardiovascular risk: validation of a non-laboratory and a laboratory-based score in a Brazilian community-based cohort of the PURE study

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Summary

Background Risk scores are essential tools for implementing cardiovascular disease (CVD) prevention. Validating risk scores considering regional diversities and disparities is critical for reducing the burden of CVD on global morbidity and mortality. We aimed to validate two cardiovascular risk scores (laboratory and non-laboratory-based) to predict major adverse cardiovascular events in the Brazilian cohort of the PURE study.

Methods We validated two risk scores derived from the INTERHEART study, the non-laboratory INTERHEART risk score (NL-IHRS) and the laboratory fasting cholesterol INTERHEART risk score (FC-IHRS) using data from 4623 (urban areas) and 1415 (rural areas) participants without CVD in the Brazilian cohort of the PURE study enrolled in 2004 and 2005 and followed up to September 2021. The endpoint was major cardiovascular events (MACE), defined as the composite of myocardial infarction, stroke, heart failure, or death from cardiovascular causes. We evaluated the model performance of IHRS through c-statistic and calibration methods.

Findings After a mean follow-up of 8.8 years (range, 0.28–15.1 years), there were 312 cardiovascular events, corresponding to an incidence rate of 0.58% per year (0.56% per year in urban versus 0.64% per year in rural areas). For the NL-IHRS, the c-statistic was 0.69 (95% confidence interval, CI, 0.66–0.72) in the overall cohort, 0.68 (95% CI, 0.64–0.72) in the urban cohort, and 0.72 (95% CI, 0.66–0.78) in the rural cohort. C-statistic values for the recalibrated FC-IHRS were 0.71 (95% CI, 0.67–0.74), 0.71 (95% CI, 0.67–0.75), and 0.70 (95% CI, 0.64–0.76) in the overall, urban, and rural cohorts, respectively.

Interpretation In this Brazilian community-based prospective cohort, both NL-IHRS and FC-IHRS-based models performed with reasonable discriminative accuracy on the risk estimation of long-term risk of major CVD. A non-laboratory-based CVD risk score may be instrumental in Brazilian communities with limited access to medical resources.

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Keywords: Cardiovascular disease; Risk score; Risk factors; Brazil; Validation study

Introduction

In the past decades, progressive urbanization across South America has resulted in lifestyle changes and an increase in the prevalence of cardiometabolic risk factors in the population, consequently enhancing the contribution of non-communicable diseases to populational morbidity and mortality.[1,2] Cardiovascular disease (CVD) is the leading cause of death in Brazil. Nonetheless, additional data are required to estimate the impact of CVD and death rates according to different

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Research in context

Evidence before this study

Risk scores are essential tools for implementing cardiovascular disease (CVD) prevention. Validating risk scores considering regional diversities and disparities is critical for reducing the burden of CVD on global morbidity and mortality. Despite that, few studies have evaluated the performance of cardiovascular risk scores in Latin American populations. The non-laboratory INTERHEART risk score (NL-IHRS) and the fasting-cholesterol INTERHEART risk score (FC-IHRS) had been externally validated in other regions worldwide and showed a reasonable discriminatory capacity. In PubMed or Google Scholar, we searched for longitudinal studies in the adult population validating cardiovascular risk scores in the Latin American or Brazilian population. Four studies, including Latin American cohorts ranging from 918 to 376,177 participants, were of interest that validated different cardiovascular risk scores (ACC/AHA ASCV score, Globo-risk-LAC, and WHO CVD score). One Brazilian study has externally validated five cardiovascular risk scores (Framingham General Risk, Pooled Cohort Equations, WHO CVD score, Globorisk-LAC, and the Systematic Coronary Risk Evaluation 2 score) in 12,155 participants from the Brazilian Longitudinal Study of Adult Health-ELSA Brasil.

Added value of this study

We externally validated the office-based tool NL-IHRS and a laboratory-based tool FC-IHRS in the urban and rural Brazilian cohorts of the PURE study. Both risk scores showed moderate to good discrimination capacity in the Brazilian population.

Implications of all the available evidence

The NL-IHRS and FC-IHRS were suitable for the Brazilian population and can be used as potential new tools for CVD risk stratification in this population. A non-laboratory-based CVD risk score may be particularly useful in Brazilian communities with limited access to medical resources.

regions and their contributing risk factors.[3] The assessment of risk factors associated with CVD and their impact on mortality at a regional level can help develop prevention strategies, considering specific particularities of each region or country, such as income, social, and cultural factors.[4,5]

In low and middle-income countries, the World Health Organization (WHO) recommends implementing cardiovascular risk assessment to guide the initiation of primary prevention treatments based on available resources. In most regions of the world, a significant barrier to this approach is the scarcity of locally validated risk prediction tools and the requirement of laboratory tests (e.g., lipid parameters) for risk estimation, limiting their use in communities where laboratory facilities are not widely available.[6]

The Prospective Urban and Rural Epidemiological (PURE) study[7–9] offers a unique opportunity to provide information on cardiovascular risk, presenting contemporary and standardized data and conducting ongoing follow-up with validation of clinical events. In this study, we aimed to validate two cardiovascular risk scores (laboratory-based and non-laboratory-based) to predict major adverse cardiovascular events in the Brazilian cohort of the PURE study.

Methods

Study design

The methodology of the PURE study has been published elsewhere.[7] Briefly, PURE is a large, community-based cohort study that collected data on CVD risk factors and outcomes across various resource settings. The global study has enrolled 225,000 community-dwelling participants between 35 and 70 years of age from over 1000 urban and rural communities in 27 high, middle, and low-income countries. PURE was established to investigate associations between social, behavioral, genetic, and environmental factors and cardiovascular diseases. Information of non-fatal and fatal events have been obtained from participants or their family members during long-term follow-up and reviewed centrally within each country with available supporting documentation (including death certificate, verbal autopsy, and medical records) using standardized definitions. The demographics of the study population are broadly consistent with national data. Within each community, families and individuals were selected using sampling strategies that minimize the selection of individuals that could influence any association between risk factors and outcomes. We previously defined urban community as located in urbanized areas or not, corresponding to cities (municipal headquarters), villages (district headquarters), or isolated urban areas, and rural community as located outside the limits of the urban group, including rural-urban extension clusters, towns, and even smaller communities, and owning at least 70% of the household income from agricultural activity.

Ethics

Ethics approval for the PURE study was obtained through local and national committees, and all participants provided informed consent. The Ethics Committee of Hospital Alemão Oswaldo Cruz (National Coordinating Center) gave ethical approval in Brazil.

Study population

The current study involves data analysis from the Brazilian cohort recruited into the PURE study between

2004 and 2005 and followed up to September 2021 (mean follow-up of 8.8 years). This cohort included 6038 participants without a history of cardiovascular disease at enrollment.

Data acquisition

This dataset was captured on unified questionnaires (electronic case report forms) based on standardized interviews to collect detailed information from the community, family, and individual, such as demography, psychosocial factors, medical history, access to healthcare services, and lifestyles. Physical measurements were also obtained to provide essential information on anthropometry, skinfolds, waist circumference, hip circumference (waist-hip ratio), non-invasive blood pressure, weight, and height (body mass index).

To ensure standardization and high-quality data, we used a comprehensive operations manual, periodic training workshops, training DVDs, and regular communication with study personnel. We entered all data in a customized database programmed with range and consistency checks. We transmitted electronically to the Project Office at the Population Health Research Institute in Hamilton (ON, Canada), where further quality control measures were implemented. We collected national, community, household, and individual data with standardized questionnaires. Questions about age, sex, education, smoking status, hypertension, diabetes, and obesity were identical to those in the INTERHEART and INTERSTROKE studies.[10,11] We assessed histories of cardiovascular and other diseases from every participant with standardized questionnaires. Coronary heart disease was ascribed based on self-reported myocardial infarction (MI), coronary artery bypass graft surgery, percutaneous coronary intervention with coronary stent implantation, or angina (categories were not identified separately). Stroke and heart failure (HF) were ascribed based on self-reports. Cardiovascular outcomes during follow-up were assessed, adjudicated, and validated using prespecified study definitions, guidelines, and the international classification of diseases' coding system.[12–14] We followed the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statements. The TRIPOD checklist is shown in Supplementary Table S3.

Long-term follow-up, cardiovascular outcomes, and adjudication

Annual follow-up has been performed to capture clinical outcomes through validated questionnaires. The adjudication of events has been assessed in each country, and periodically, a central adjudication committee is responsible for clinical event validation with quality control and cross-validation metrics. The cut-off for the time points of complete adjudication and validation of cardiovascular outcomes for this analysis was set as of September 2021. Therefore, this analysis aims to provide information on the accuracy of the risk model (non-laboratory versus laboratory-based) that could predict the first occurrence of fatal or non-fatal cardiovascular events in the PURE Brazil cohort.

Cardiovascular risk estimation tools

This current report represents the analysis of the performances of two risk prediction models derived from the INTERHEART study in the Brazilian cohort of the PURE study: the laboratory-based fasting cholesterol INTERHEART risk score (FC-IHRS) model, which required blood testing, and the non-laboratory-based model (NL-IHRS), which required only medical history and physical examination measurements.[15] The NL-IHRS and the FC-IHRS models were previously developed using the INTERHEART case-control study, which examined risk factors for incident MI in 27,043 participants (14,605 cases and 12,438 controls) across 52 countries.[10] The two scores, FC-IHRS and NL-IHRS, had already been validated for the MACE outcomes in prospective cohorts of the PURE study and showed moderate/good discrimination.[16,17]

The FC-IHRS model included the following variables collected from the Brazilian cohort of the PURE study at baseline: sex, age, history of hypertension and/or diabetes, smoking status (former smoker, active smoker of 1–5 cigarettes/day or 6–10 cigarettes/day or 11–15 cigarettes/day or 16–20 cigarettes/day or >20 cigarettes/day), passive smoking, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol.

The NL-IHRS model included the following variables collected from the Brazilian cohort of the PURE study at baseline: sex, age, smoking status (former smoker, active smoker of 1–5 cigarettes/day or 6–10 cigarettes/day or 11–15 cigarettes/day or 16–20 cigarettes/day or >20 cigarettes/day), passive smoking, history of hypertension and/or diabetes mellitus, familiar history of cardiovascular disease, stress and depression experience in the last 12 months, degree of physical activity in leisure time, diet (fruit consumption, vegetable consumption, fried food or trans/saturated fat consumption, salty food and read meat/poultry consumption) and body-mass index or waist-hip ratio. As per standardized data collection in the PURE study, all participants who reported current smoking status were not asked about passive smoking and, therefore, were classified as not having second-hand smoking exposure.

Variables related to socioeconomic factors, such as education level, employment, and socioeconomic status, were also collected.

Endpoint

The endpoint was the composite of major adverse cardiovascular events (MACE), defined as MI, stroke, HF, or death from cardiovascular causes. Using the

multinational INTERHEART case-control study, four risk prediction tools have been developed and validated to predict the risk of MI and coronary artery disease (CAD) development. The NL-IHRS was shown to predict CAD risk based solely on clinical history and simple physical measurements, making it well-suited for use across various geographic regions and resource settings. However, since the score was developed in a case-control study of MI, we aimed to evaluate its performance across a broad range of significant CVD endpoints (i.e., stroke, HF, fatal CVD) in a prospective cohort study.

Statistical analysis

We described the frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. All analyses were conducted with complete data, and the frequency of valid numbers was reported. Baseline characteristics and prevalence of cardiovascular risk factors are shown through descriptive analyses. To determine the impact of missing data, sensitivity analyses were performed following the imputation of missing variables using the multiple imputations by chained equation (MICE) method, as described by Vergouwe et al.[18] All analyses were performed using the R statistics (Rstudio 2023.12.0), and p-values < 0.05 were considered significant results.

Assessment of predicting variables in the NL-IHRS and FC-IHRS

Associations between single variables and incident CVD were calculated using simple logistic regression analysis of the NL-IHRS and FC-IHRS predicting variables. Results are presented as regression coefficients (β-coefficient) and odds ratios (OR) with 95% confidence intervals (CI), with a two-sided p-value of <0.05 considered statistically significant.

Discrimination and calibration of the NL-IHRS and FC-IHRS

From the 6038 participants included in the study, after excluding those with missing data, 4936 were included in the NL-IHRS analysis and 5201 in the FC-IHRS analysis. The performance of the INTERHEART risk scores was first evaluated using the original logistic regression model developed in the INTERHEART study. Discrimination reflects the ability of the logistic regression model to differentiate participants who had a cardiovascular event from those who did not and measured by applying the c-statistic.[18–20] Calibration measures how closely a model's estimate of predicted risk agrees with observed outcomes. Model calibrations were assessed by fitting a simple logistic regression model of the CVD outcome with the prognostic index (PI) as the only covariable. The PI was the weighted sum of the variables in each model, where weights are the original regression coefficients of the INTERHEART model (Supplementary data).[21] For each calibration measure, 95% CI was calculated, and deviations of the intercept (α) from 0 (a systematic overestimation or underestimation of risk) or the slope (β) from one indicated miscalibration.

Recalibration estimates of the CVD risk were calculated according to the following equation: $p\hat{} = 1/1 + \exp[-\{\alpha\hat{}+\beta\hat{} \times (\text{estimated PI})\}]$ where $\alpha\hat{}$ and $\beta\hat{}$ are the respective point estimates of the intercept and slope for the original NL-IHRS and FC-IHRS equation.[22] Non-parametric methods, as described by DeLong et al., were applied to compare areas under the ROC curve of the two recalibrated models.[23] INTERHEART score models were recalibrated after assessment of the overestimation bias of the original equation by using new intercepts and slopes precisely calculated for the entire population and by area of residence. The recalibrated model was then applied to categorize the participants into three levels of cardiovascular risk based on MACE incidence: low (annual risk <1%), intermediate (annual risk 1%–2%), and high (annual risk >2%). We opted to analyze the annual risk since the mean follow-up of our cohort was 8.8 years (lower than the usual 10-year risk estimated in other risk scores like the Framingham risk score).[24]

Incidence rates (observed occurrence) of cardiovascular events (MACE) per year were described for the overall cohort, residence area, and risk stratification (expected occurrence) up to September 2021 (mean follow-up 8.8 years). The annual incidence was calculated by dividing the number of new cases (numerator) and the person-year denominator, that is, the sum of the time free from CV events for each subject in the cohort divided by 365 days. The results were then multiplied by 100 to present the annual incidence per 100 person-years or % per year.

The Net Reclassification Index (NRI) between NL-IHRS and FC-IHRS was calculated using predicted CVD risk thresholds of 1%/year and 2%/year (to identify low-risk, intermediate-risk, and high-risk groups).[25,26]

Summary of the statistical approach

To clarify the statistical approach **to** evaluate the performance of the IHRS scores in the Brazilian cohort, we summarize in a step-by-step manner as follows:

1. Application of the IHRS scores (original equation) in the Brazilian population—PURE cohort.
2. The score obtained was analyzed in a simple logistic model. CV events were observed up to 9 years as the dependent variable, and the score (or PI Prognostic Index—see equations in the Supplementary material) as the only predictive (or independent) variable.
3. The logistic model's results revealed a miscalibration of the original equation when applied to the Brazilian population.

4 The recalibration process was conducted based on the following equations: estimated PI = −1.45 + 0.2875 × IHRS total points/2 and then, $p\hat{} = 1/1 + \exp[-\{\alpha\hat{}+\beta\hat{} \times (\text{estimated PI})\}]$, where $\alpha\hat{}$ and $\beta\hat{}$ are derived from a simple logistic model, with the cardiovascular events observed in the Brazilian population as the dependent variable and the PI from the original IHRS equation as the only predictor (or independent) variable. The measure ($p\hat{}$) represents the cardiovascular risk estimate over 9 years and was annualized by dividing by 9. Both estimates are presented as percentage risk.
5 A recalibrated PI was presented using the equation updated PI = estimated α + estimated β × PI, where estimated α and β were obtained through a simple logistic model, with CV events observed in the Brazilian population and the score ($p\hat{}$) (step 4) as the only predictor (independent) variable.
6 Steps 2, 3, 4, and 5 were applied to the general population and according to place of residence (rural or urban).

Role of the funding source

The Population Health Research Institute was responsible for the collection, analysis, and interpretation of the data, for writing the report, and for the decision to submit the article for publication.

Novartis Biociências S.A. was not involved in the collection, analysis, interpretation of the data, writing of the report, or the decision to submit the article for publication.

Results

The analysis included 4623 and 1415 participants from urban and rural areas, respectively. We excluded those without information on clinical outcomes during follow-up or those with follow-up shorter than 90 days. Mean age was 52.1 (SD, 9.4) years, and there was a slight predominance of women (3338; 55.2%). Low education levels and high unemployment rates were frequently observed, especially in those from rural areas. As shown in Table 1, most individuals (4619; 76.5%) were recruited from urban areas, and 4269 (70.7%) were categorized as having low socioeconomic status. The prevalence of both cardiometabolic and lifestyle risk factors was high, with high consumption of saturated fat in 5018 (84.6%) participants, salty foods in 3164 (52.4%) participants, and red meats in 2958 (49%) participants (Table 2).

After a mean follow-up of 8.8 years (range 0.28–15.1 years), there were 312 cardiovascular events (composite endpoint of MACE), corresponding to an incidence rate of 0.58% per year (0.56% per year in urban versus 0.64% per year in rural areas). The incidence rates of the MACE components were the following: acute MI (149; 0.28% per year), stroke (111; 0.21% per year), heart failure (54; 0.10% per year), and cardiovascular death (167; 0.31% per year). Out of 11 risk factors of the non-laboratory (NL-IHRS) model, five were significantly associated with the primary composite endpoint. Diet, passive smoking, depression, stress, and family history of CVD did not show a significant association with the endpoint. Smoking, diabetes, and hypertension had significant associations with cardiovascular events (Table 3). Among the seven risk factors in the laboratory-based risk score (FC-IHRS), we found no significant associations between passive smoking and LDL-cholesterol levels with the primary endpoint (Table 4).

The original performances before recalibration of the NL-IHRS and FC-IHRS are shown in Table 5. The c-statistic for the NL-IHRS was 0.69 (0.66–0.72) in the overall cohort, being 0.68 (95% CI 0.64–0.72) in the urban cohort and 0.72 (95% CI 0.66–0.78) in the rural cohort, and the c-statistic for the FC-IHRS was 0.71 (95% CI 0.67–0.74), 0.71 (95% CI 0.67–0.75) and 0.70 (95% CI 0.64–0.76) for the overall, urban, and rural cohorts, respectively. After applying the multiple imputation method, sensitivity analyses including 6038 participants did not reveal any significant increase in the discriminative accuracy of the risk model (data not shown). Calibration measures suggested a systematic overestimation of cardiovascular risk according to the NL-IHRS. This overestimation bias was also seen in both rural and urban cohorts. After this recalibration process, we found no significant change in the NL-IHRS performance. Nevertheless, both risk scores (NL-IHRS

	Urban (4623)	Rural (1415)	Total (6038)
Age			
Mean (SD)	52.6 (9.3)	50.6 (9.7)	52.1 (9.4)
Sex			
Male	2014 (43.6)	694 (49.0)	2708 (44.8)
Female	2609 (56.4)	721 (51.0)	3330 (55.2)
Education			
None	421 (9.1)	321 (22.7)	742 (12.3)
Primary	1142 (24.7)	963 (68.1)	2105 (34.9)
Secondary/High School/Higher	1144 (24.7)	106 (7.5)	1250 (20.7)
Trade School	277 (6.0)	13 (0.9)	290 (4.8)
College/University	1639 (35.5)	12 (0.8)	1651 (27.3)
Employed			
No	1409 (38.4)	622 (71.0)	2031 (44.7)
Yes	2258 (61.6)	254 (29.0)	2512 (55.3)
Missing data (n = 1495)			
Community socioeconomic status			
Low	2853 (61.7)	1415 (100.0)	4268 (70.7)
Middle	1511 (32.7)	0	1511 (25.0)
High	259 (5.6)	0	259 (4.3)

SD, standard deviation.

Table 1: **Baseline demographic and sociocultural characteristics of the study participants.**

	Urban (n = 4623)	Rural (n = 1415)	Total (n = 6038)
Age, n (%)			
Male ≥ 55 years or female ≥ 65 years of age	1043 (22.6)	294 (20.8)	1337 (22.1)
Smoking, n (%)			
Never smoked	2446 (52.9)	757 (53.5)	3203 (53.1)
Former smoker	1323 (28.6)	329 (23.3)	1652 (27.4)
1–5 cigarettes/day	162 (3.5)	103 (7.3)	265 (4.4)
6–10 cigarettes/day	180 (3.9)	84 (5.9)	264 (4.4)
11–15 cigarettes/day	102 (2.2)	34 (2.4)	136 (2.3)
16–20 cigarettes/day	279 (6.0)	85 (6.0)	364 (6.0)
>20 cigarettes/day	130 (2.8)	23 (1.6)	153 (2.5)
Passive smoking, n (%)			
Yes	1584 (34.6)	592 (42.3)	2176 (36.4)
Diabetes, n (%)			
Yes	480 (10.4)	99 (7.0)	579 (9.6)
Hypertension, n (%)			
Yes	2260 (53.2)	664 (51.0)	2924 (52.7)
Non-premature CVD family history, n (%)			
Yes	2331 (50.5)	702 (49.8)	3033 (50.3)
Waist-hip ratio (WHR), n (%)			
WHR first quartile (<0.873 cm)	1260 (29.7)	282 (21.7)	1542 (27.8)
WHR second quartile (0.873–0.917 cm)	783 (18.4)	310 (23.8)	1093 (19.7)
WHR third quartile (0.918–0.963 cm)	926 (21.8)	325 (25.0)	1251 (22.6)
WHR upper quartile (>0.963 cm)	1275 (30.0)	384 (29.5)	1659 (29.9)
Missing data (n = 493)			
Stress, n (%)			
Never or some periods	2823 (63.0)	883 (68.7)	3706 (64.3)
Several periods or permanent stress	1660 (37.0)	402 (31.3)	2062 (35.7)
Depression, n (%)			
Yes	1424 (30.8)	350 (24.8)	1774 (29.4)
Dietary factors, n (%)			
High salty food consumption (≥ 1 time/day)	2489 (54.1)	663 (47.0)	3152 (52.4)
High fried food/trans saturated fat consumption (≥ 3 times/week)	3917 (85.1)	1175 (83.2)	5092 (84.6)
Low fruit consumption (<1 time/day)	696 (15.1)	349 (24.7)	1045 (17.4)
Low vegetable consumption (<1 time/day)	45 (1.0)	10 (0.7)	55 (0.9)
Red meat/poultry consumption ≥ 2 times/day	2511 (54.5)	434 (30.7)	2945 (49.0)
Physical activity, n (%)			
Low physical activity (MET score <600)	508 (11.5)	117 (9.0)	625 (10.9)
LDL-Cholesterol, n (%)			
Quartile 1 (<46 mg/dL)	980 (24.4)	328 (26.5)	1308 (24.9)
Quartile 2 (46–57 mg/dL)	1093 (27.2)	365 (29.5)	1458 (27.8)
Quartile 3 (58–70 mg/dL)	1210 (30.2)	327 (26.4)	1537 (29.3)
Quartile 4 (>70 mg/dL)	730 (18.2)	217 (17.5)	947 (18.0)
HDL-Cholesterol, n (%)			
≥18 mg/dL	3257 (78.6)	879 (67.9)	4136 (76.1)
<18 mg/dL	886 (21.4)	416 (32.1)	1302 (23.9)

Notes: Missing data: Smoking (n = 1); Passive smoking (n = 55); Hypertension (n = 489); Waist-hip ratio (n = 493); Stress (n = 270); Depression (n = 13); Dietary factors (n = 22); Physical activity (n = 308); LDL-Cholesterol (n = 788); HDL-Cholesterol (n = 600). CVD, cardiovascular disease; WHR, waist-hip ratio; MET, metabolic equivalent; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2: **Baseline prevalence of risk factors in the study population according to INTERHEART risk score.**

and FC-IHRS) performed reasonably well, with NL-IHRS c statistics of 0.69 (95% CI 0.66–0.72), 0.68 (95% CI 0.64–0.72) and 0.72 (95% CI 0.66–0.78) for the overall, urban, and rural cohorts, respectively. C-statistic values for the recalibrated FC-IHRS were very close to those observed for the NL-IHRS, with 0.71 (95% CI 0.67–0.74), 0.71 (95% CI 0.67–0.75) and 0.70 (95% CI 0.64–0.76) for the overall, urban, and rural cohorts, respectively. Comparison of areas under receiver operating characteristic (ROC) curves of C-statistic values revealed non-significant differences between the discriminative models, with p-values for overall, urban, and rural locations of 0.456, 0.323, and 0.664, respectively (Fig. 1 and Table 6).

Table 7 shows the annual observed incidence of the composite outcome based on predicted risk from non-laboratory INTERHEART risk score. There was a gradual increase in the incidence rate according to the cardiovascular risk score, which emphasizes the predictive accuracy and the adequate adjustment of the risk model after recalibration. The distribution of the predicted risk according to the total score observed in each estimation tool is shown in Supplementary Tables S1 and S2 (Supplementary Material). Comparison of areas under receiver operating characteristic (ROC) curves revealed non-significant differences between the discriminative models, with p-values for overall, urban, and rural locations of 0.113, 0.103, and 0.895, respectively (Fig. 1). Reclassification with the NL-IHRS was relatively small when compared with the FC-IHRS: Net Reclassification Index (NRI) = 0.158 (0.08–0.23) and Integrated Discrimination Improvement (IDI) 0.004 (0.003–0.005).

Discussion

In this study, we aimed to validate laboratory- and non-laboratory cardiovascular risk stratification scores using data from the Brazilian cohort of the PURE study. We tested how well each risk model predicted the first occurrence of cardiovascular events in the Brazilian cohort of the international prospective community-based cohort PURE study. The c-statistic discrimination values varied from 0·68 (NL-IHRS) to 0·73 (FC-IHRS) for the overall cohort, thus yielding close results between the non-laboratory-based and laboratory-based models, respectively. The discrimination capacity of the NL-IHRS and FC-IHRS in our population was similar to the other two studies, which evaluated these scores in other regions worldwide.[16,17]

The principal CVD risk scores used worldwide to predict cardiovascular events are based on North American and European cohorts with a predominantly Caucasian population, such as the Framingham Risk Score, Score, and Pooled Cohorts Equation

Calculator.[27–30] Few studies have validated cardiovascular risk scores focused on the Latin American population, which is characterized by diversity in ethnic, cultural, and socio-economic aspects. Rodríguez-Ariza et al. analyzed the performance of the ACC/AHA ASCVD score to predict the 10-year risk of major cardiovascular events in a primary prevention cohort of 918 patients followed in a Colombian hospital, showing an area under the ROC curve of 0.782 (95% CI 0.71–0.85).[31] However, unlike our analysis, this study design was based on a retrospective cohort, and cardiovascular death was not included in the primary composite endpoint. The Globorisk LAC study encompassed data from cohorts participating in the Cohort Consortium of Latin America and the Caribbean (CC-LAC) with 21,378 participants and 1202 events (coronary events and stroke) and developed a CVD risk score.[32] Similar to our analysis, the Globorisk LAC study validated two models, one laboratory-based (systolic blood pressure, total cholesterol, diabetes, and smoking) and one office-based (body mass index replaced total cholesterol and diabetes), and showed good performance in both models with a c-statistics of 0.72 (95% CI 0.70–0.74) for the laboratory-based model and 0.71 (95% CI 0.69–0.72) for the office-based model. In a critical initiative led by the WHO, cardiovascular disease risk prediction charts were developed using data from 85 cohorts from 21 different regions of the world, using 10-year risk prediction models. The risk model derivation involved 376,177 individuals and 19,333 incident cardiovascular events recorded; however, only data from Uruguay were incorporated in the South American region.[33] A recently published study examined the performance of five widely used cardiovascular risk scores (Framingham General Risk, Pooled Cohort Equations, WHO CVD score, Globorisk-LAC, and the Systematic Coronary Risk Evaluation 2 score) in 12,155 public servants from higher education and research institutes from the Brazilian Longitudinal Study of Adult Health. They found that Framingham General Risk and Pooled Cohort Equations demonstrated the highest overestimation and that the WHO CVD score showed the best calibration, but the risk discrimination was poor in women.[34]

When choosing and broadly applying a simpler scoring model to provide risk stratification, some essential requirements are validating and calibrating clinical tools in different countries, mainly those with wide diversity and less favourable socioeconomic status. The PURE study offers a unique opportunity to test the performance of either risk model based on the large sample size, long-term follow-up, standardized data collection, and adjudication of outcomes with excellent quality control metrics. In addition to the overall predictive discrimination between adding lab tests versus not requesting blood samples for lipid measurements, in large developing countries such as Brazil, relevant issues include individual costs, availability, and affordability of standard diagnostic tests to be widely used as cardiovascular screening and preventive strategies. Adopting a cheaper, easy-to-obtain, and widely available clinical tool for risk stratification, the NL-IHRS may be as helpful as the FC-IHRS laboratory-based model, thus being cost-effective and economically attractive, especially in lower-income countries.

Moreover, our study showed that five main variables were independently associated with a higher risk of MACE in NL-IHRS after replacing cholesterol levels with anthropometric measurements such as BMI and

	CVD events[b]/N	OR (95% CI)	p-value
Age			
Male ≥ 55 years or female ≥ 65 years	118/1142	2.01 (1.51–2.68)	**<0.0001**
Smoking			
Former smoker	79/1355	1.36 (0.99–1.88)	0.060
1–5 cigarettes/day	16/211	2.90 (1.61–5.22)	**<0.0001**
6–10 cigarettes/day	13/211	2.41 (1.28–4.55)	**0.007**
11–15 cigarettes/day	8/110	2.72 (1.24–5.99)	0.013
16–20 cigarettes/day	31/293	3.99 (2.49–6.41)	**<0.0001**
>20 cigarettes/day	18/131	4.55 (2.51–8.26)	**<0.0001**
Passive smoking			
Yes	82/1789	1.15 (0.84–1.57)	0.390
Diabetes			
Yes	64/484	2.36 (1.71–3.25)	**<0.0001**
Hypertension			
Yes	205/2614	2.62 (1.88–3.63)	**<0.0001**
Family history of cardiovascular disease			
Yes	123/2505	0.90 (0.69–1.17)	0.442
Waist-hip ratio			
WHR second quartile (0.873–0.917 cm)	38/969	1.52 (0.92–2.52)	0.099
WHR third quartile (0.918–0.963 cm)	56/1102	1.61 (1.00–2.58)	**0.048**
WHR upper quartile (>0.963 cm)	135/1502	2.01 (1.29–3.14)	**0.002**
Stress			
Several periods or permanent stress	92/1747	1.16 (0.87–1.55)	0.320
Depression			
Yes	70/1478	0.89 (0.65–1.22)	0.474
Dietary factors			
High salty food (≥ 1 time/day)	139/2586	1.18 (0.89–1.56)	0.240
High fried food/trans and saturated fat (≥ 3 times/week)	213/4191	0.85 (0.59–1.22)	0.368
Low fruit consumption (<1 time/day)	53/858	1.18 (0.84–1.64)	0.343
Low vegetable consumption (<1 time/day)	2/43	0.60 (0.13–2.65)	0.497
Red meats or poultry meat consumption (≥ 2 times/day)	119/2460	0.82 (0.62–1.07)	0.143
Physical activity			
Low PA (MET score <600)	44/529	1.38 (0.96–1.97)	0.080

Notes: NL-IHRS, Non-laboratory INTERHEART risk score; CVD, Cardiovascular; CI, confidence interval; WHR, waist-hip ratio; OR, odds ratio, PA, physical activity; MET, metabolic equivalent. Simple logistic regression models were performed. Reference category: Age (Male <55 years or female <65 years); Smoking (Never smoked); Passive smoking (No)/Diabetes (No)/Hypertension (No)/Family history of CVD/Depression (No); Waist-hip ratio (WHR first quartile (<0.873 cm)); Stress (Never or some periods); High salty food (<1 time/day); High fried food/trans and saturated fat (<3 times/week); Fruit consumption (1 ≥ time/day); Vegetable consumption (≥1 time/day); Red meats or poultry meat consumption (<2 times/day); Physical activity (moderate or high PA, MET score ≥ 600). [a]Analysis sample (n = 4936). [b]CVD events (n = 258).

Table 3: **Associations of the composite outcome with each predictor included in the NL-IHRS.**[a]

	CV events[b]/N	OR (95% CI)	p-value
Age			
Male ≥ 55 years or female ≥ 65 years of age	116/1165	2.20 (1.68–2.88)	**<0.0001**
LDL-cholesterol			
Quartile 2 (46–57 mg/dL)	56/1437	0.87 (0.60–1.27)	0.483
Quartile 3 (58–70 mg/dL)	82/1528	1.24 (0.88–1.75)	0.221
Quartile 4 (>70 mg/dL)	56/940	1.21 (0.82–1.77)	0.339
HDL-cholesterol			
<18 mg/dL	83/1157	1.33 (1.00–1.77)	0.053
Smoking			
Former smoker	77/1412	1.36 (0.99–1.86)	0.058
1–5 cigarettes/day	18/230	3.13 (1.79–5.47)	**<0.0001**
6–10 cigarettes/day	15/224	2.66 (1.46–4.83)	**0.001**
11–15 cigarettes/day	8/117	2.55 (1.17–5.55)	**0.019**
16–20 cigarettes/day	33/303	4.40 (2.79–6.94)	**<0.0001**
>20 cigarettes/day	16/129	4.14 (2.26–7.60)	**<0.0001**
Diabetes			
Yes	67/496	2.71 (1.98–3.70)	**<0.0001**
Hypertension			
Yes	206/2696	2.82 (2.07–3.84)	**<0.0001**

Notes: FC-IHRS, fasting-cholesterol INTERHEART risk score; CV, cardiovascular; LDL, low-density lipoprotein; HDL; high-density lipoprotein; OR, odds ratio; CI, confidence interval. Multivariate logistic regression models were performed. Reference category: Age (Male < 55 years or female < 65 years); Smoking (Never smoked); Diabetes (No)/Hypertension (No); LDL-cholesterol (<46 mg/dL); HDL-cholesterol (>18 mg/dL). [a]Analysis sample (n = 5201). [b]CV events (n = 264).

Table 4: **Associations of the composite outcome with each predictor included in the FC-IHRS.[a]**

waist-hip ratio for assessing abdominal obesity. Indeed, our findings are consistent with the INTERHEART and INTERSTROKE studies, in which a stronger association between waist-hip ratio and risk of MI and stroke was observed, as compared with the odds ratio for MI observed when assessing global obesity with BMI. Diet, passive smoking, depression, stress, and family history of CVD did not show a significant association with the endpoint. This observation does not necessarily mean that these risk factors were not associated with a higher risk of developing cardiovascular events. All of them have been identified as independent risk factors in the

	C-statistic (95% CI)	Intercept (95% CI)	Slope (95% CI)
NL-IHRS			
Overall	0.69 (0.66–0.72)	−3.52 (−3.73 to −3.33)	0.83 (0.68–0.98)
Urban	0.68 (0.64–0.72)	−3.56 (−3.80 to −3.34)	0.80 (0.63–0.98)
Rural	0.72 (0.66–0.78)	−3.40 (−3.83 to −3.03)	0.94 (0.63–1.27)
FC-IHRS			
Overall	0.71 (0.67–0.74)	−3.35 (−3.52 to −3.18)	1.33 (1.11–1.56)
Urban	0.71 (0.67–0.75)	−3.43 (−3.64 to −3.24)	1.35 (1.09–1.62)
Rural	0.70 (0.64–0.76)	−3.11 (−3.44 to −2.81)	1.35 (1.09–1.62)

NL-IHRS, non-laboratory INTERHEART risk score; FC-IHRS, fasting cholesterol INTERHEART risk score; CI, confidence interval.

Table 5: **Performance (discrimination and calibration) of the original NL-IHRS and FC-IHRS for endpoint prediction.**

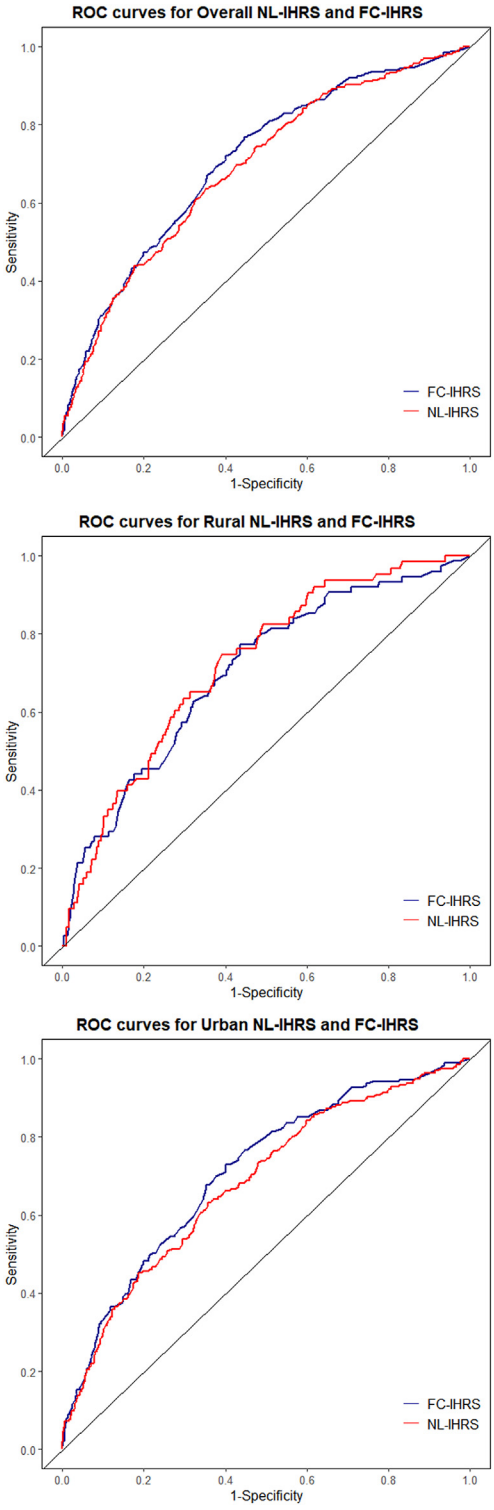

Fig. 1: ROC curves for the overall, urban, and rural population for non-laboratory INTERHEART risk score (NL-IHRS) and fasting-cholesterol INTERHEART risk score (FC-IHRS).

INTERHEART and INTERSTROKE studies, which involved several countries and many events. Therefore, our study may not have the statistical power to detect significance for these variables in the multiple logistic regression models. On the other hand, we found that age, smoking status, diabetes, hypertension, and waist-hip ratio assessing abdominal obesity were independently associated with a higher risk of cardiovascular outcomes. These variables had greater effect size and concordance with metabolic and behavior pathways in atherosclerotic diseases. Other studies with the same objective of comparing laboratory-versus non-laboratory risk estimation tools did not measure HDL cholesterol. They used body mass index to evaluate obesity, which contrasted with our study, as we included HDL in the laboratory-based prediction model and calculated the waist-hip ratio.[35,36]

In this cohort, we found that nearly one-fifth of participants were classified as having an intermediate/high cardiovascular risk at the time of enrollment into the PURE study. An interesting and somewhat unexpected observation was the relatively higher proportion of participants from rural areas at high risk (22%) than those from urban areas (19%). Our findings differ from other studies. The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)[37] enrolled 15,105 civil servants from universities or research institutes; therefore, only people from urban areas were recruited, which did not allow for an assessment of health determinants in the settings of the rural environment and of multiple communities and different socioeconomic profiles. Moreover, the proportions of some risk factors such as hypertension, obesity, and current smoking were higher in our study as compared with those from ELSA-Brasil. Regarding the derivation and recalibration of both models, there was a gradual increase in the cardiovascular risk and incidence rates of events according to scoring points, which emphasizes the predictive accuracy and the adequate adjustment of either FC-IHRS or NL-IHRS after recalibration.

The current study is the first prospective community-based study conducted in Brazil with individuals from urban and rural areas. It represents one of the largest follow-up cohorts, still ongoing towards 2030. In addition, continuous structured data collection of all-cause hospitalizations and non-fatal or fatal events, along with standardized adjudication of major non-communicable diseases, specifically acute MI, stroke, heart failure, and death, provide clinically and scientifically relevant real-world evidence from individuals living in urban or rural areas. The analyses offer contemporary and reliable estimates of an individual's risk for developing major cardiovascular events.

We recognize several limitations. We may assume that longer study duration with regional variations in socioeconomic and political aspects might impact ascertainment bias and loss-to-follow-up numbers over time. The difference between the mean and maximum follow-up indicates that not all individuals have complete follow-up, which would be ideal for logistic regression. Furthermore, 1102 participants in the NL-IHRS and 831 participants in the FC-IHRS analyses were excluded due to at least one missing variable, a common challenge in risk score development and validation studies. However, in our sensitivity analysis using imputed data, the discrimination performance of both scores was similar in the overall study cohort. As the original equations for the FC-IHRS and NL-IHRS were based on data from the case-control study INTERHEART, one limitation could be their use to validate this score in a prospective cohort. Indeed, despite the analysis of time-dependent variables in the analysis and treating the MACE composite outcome as a time-to-event variable, we kept unconditional logistic regression analysis and considered only the baseline measures of the time-varying variables to adhere to the

	C-statistic (95% CI)	Intercept (95% CI)	Slope (95% CI)
NL-IHRS			
Overall	0.69 (0.65–0.72)	0.00 (−0.51 to 0.50)	1.00 (0.82–1.18)
Urban	0.68 (0.64–0.72)	0.00 (−0.61 to 0.59)	1.00 (0.79–1.21)
Rural	0.72 (0.66–0.78)	0.00 (−0.90 to 0.88)	1.00 (0.67–1.34)
FC-IHRS			
Overall	0.71 (0.67–0.74)	0.00 (−0.47 to 0.47)	1.00 (0.83–1.17)
Urban	0.71 (0.67–0.75)	0.00 (−0.56 to 0.55)	1.00 (0.81–1.20)
Rural	0.70 (0.64–0.76)	0.00 (−0.87 to 0.86)	1.00 (0.67–1.34)

NL-IHRS, non-laboratory INTERHEART risk score; FC-IHRS, fasting cholesterol INTERHEART risk score; CI confidence interval.

Table 6: **Performance of recalibrated INTERHEART risk score for endpoint prediction.**

	Risk Fraction (%)	Outcome/N	Annual observed incidence (100 person-year)
Population			
NL-IHRS risk[a]			
Overall			
Low	81.9	147/4044	0.40
Intermediate	14.3	81/706	1.34
High	3.8	30/186	1.98
Urban			
Low	80.9	109/3149	0.40
Intermediate	16.2	66/629	1.26
High	2.9	20/112	2.26
Rural			
Low	77.3	32/809	0.40
Intermediate	17.2	20/180	1.19
High	5.5	11/57	2.03

[a]NL-IHRS risk as low (probability of MACE < 1% per year), intermediate (probability of MACE between 1% and 2% per year), and high (probability of MACE >2% per year). MACE, major adverse cardiovascular event.

Table 7: **The annual observed incidence of the composite endpoint based on predicted risk from non-laboratory INTERHEART risk score (NL-IHRS).**

original statistical methods used to derive the NL- and FC-IHRS equations in the INTERHEART study.

However, the performance of these INTERHEART scores in two other studies was adequate for other populations of the PURE study.[16,17] The analysis did not include ethnicity, which might have influenced the prediction performance. In Brazil, the multiethnicity and the miscegenation patterns of the population make it difficult to assert the exact ethnic phenotype in many participants.

Conclusions

In this Brazilian community-based prospective cohort, both the NL-IHRS and FC-IHRS-based models can be clinically useful in estimating the long-term risk of non-fatal or fatal cardiovascular events in individuals without a previous history of atherosclerotic cardiovascular disease. These simple, validated, and broadly applicable risk scores can be easily integrated into CVD primary prevention strategies, aiming to reduce the burden of CVD in Brazil. A non-laboratory-based CVD risk score may be particularly useful in Brazilian communities with limited access to medical resources.

Contributors

Conceptualization, G.B.F.O. and A.A.; Study design, G.B.F.O. and A.A.; Data collection, G.B.F.O, R.A.B.N., P.D.M.M.N., A.H.K.T, M.L.D, J.P.L, F.L. and A.A.; Data verification and curation, G.B.F.O, R.A.B.N, P.D.M.M.N., V.A.H.S., H.A.O, A.H. K.T. and A.A.; Investigation G.B.F.O., R.A.B.N., P.D.M.M.N., V.A.H.S., A.A.; Formal analysis; G.B.F.O., R.A.B.N., L.B.O.A., P.J. and A.A. Funding acquisition, G.B.F.O. and A.A. Methodology, G.B.F.O, R.A.B.N, L.B.O.A. and A.A.; Project administration, V.A.H.S. and A.A.; Resources, G.B.F.O., P.R.R. and A.A.; Software, L.B.O. A.; Supervision, A.A.; Visualization, all authors; Validation, all authors; Writing original draft, G.B.F.O. and R.A.B.N; Writing review and editing, all authors.

Data sharing statement

Requests for access to information should be sent to the PURE Publications Committee and the PHRI study-project office (phri.contracts@phri.ca).

Declaration of interests

Dr. Priscila Raupp da Rosa is an employee of Novartis Biociências Brazil. Prof. Álvaro Avezum has a contract with PHRI for research funding at Hospital Alemão Oswaldo Cruz and is an advisory board member of OPTIMAL DIABETES, OPTIMAL STROKE, ACHIEVE-BP and IMPACT-BP studies. The other authors declare no competing interests related to this research.

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The authors had full access to all study data and were the final ones to decide whether to submit it for publication. They are responsible for the data integrity and accuracy of the current analysis.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2025.101009.

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