Cardiovascular risk charts for 182 countries: application of laboratory-based and office-based risk scores to global populations

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Background: Treatment of cardiovascular risk factors based on risk is an effective strategy for prevention of cardiovascular diseases (CVD). Worldwide implementation of risk-based CVD prevention requires risk prediction tools that are contemporarily recalibrated for the target country, and can be used where laboratory measurements are unavailable. We present two cardiovascular risk scores, with and without laboratory-based measurements; and the corresponding risk charts for 182 countries to predict 10-year risk of fatal and non-fatal cardiovascular disease.

Methods: We used data from eight prospective studies to estimate coefficients of the risk equations using proportional hazard regressions. The laboratory-based risk score included smoking, blood pressure, diabetes and total cholesterol. In the non-laboratory (office-based) risk score, we replaced diabetes and total cholesterol with body mass index. We recalibrated risk scores for each sex and age-group in each country using average risk factor levels and CVD rates. We used recalibrated risk scores and data from national surveys to estimate proportion of the population at different levels of CVD risk in an illustrative subset of 10 countries. We estimated proportion of men and women who were similarly categorized as high-risk or low-risk by the two risk scores.

Findings: Predicted risks for the same risk factor profile were lower in high-income countries than in low- and middle-income countries (LMICs), with the highest risks in countries in Central and Southeast Asia, and Eastern Europe. In the national health surveys, the proportion of people aged 40-64 years at high-risk of CVD ranged from 1% for South Korean women to 41% for Czech men in high-income countries using ≥10% risk to define high-risk, and from 2% in Uganda to 13% in Iranian men in LMICs using a ≥20% risk threshold. More than 80% of adults were similarly classified as low- or high-risk by the laboratory-based and office-based risk scores. However, the office-based model substantially underestimated the risk among diabetes patients.

Interpretation: Our risk charts address a major technical bottleneck for worldwide implementation of risk-based CVD prevention by providing risk assessment tools that are recalibrated for each country, and by making the estimation of CVD risk possible without using laboratory-based measurements.

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Introduction

Cardiovascular diseases (CVDs) are the leading cause of death and disability worldwide, and over three quarters of CVD deaths occur in low- and middle-income countries (LMICs).[1] An effective strategy for CVD prevention is to provide lifestyle counselling to people at high risk of an event, and/or prescribing treatment to lower blood pressure and serum cholesterol. As part of the global response to non-communicable diseases (NCDs), countries have agreed to a target of 50% coverage of counselling and treatment for people who are at high risk of CVDs, including ischemic heart disease (IHD) and stroke.[1,2]

The risk-based approach to CVD prevention requires identifying high-risk people, for example those with a 30% or more risk of having a cardiovascular event in 10 years,[2,3] which is done using risk prediction equations (often presented as risk charts). A risk prediction equation estimates a person's risk of CVD during a specific period using their levels of CVD risk factors and a set of weights, usually log hazard ratios, that quantify the proportional effect of each risk factor on CVD risk. Risk equations developed in one population cannot be applied to other populations, or even used in the same population years after they were developed, because average CVD risk and CVD risk factor levels vary across populations and over time.[4,5] This challenge can be dealt with by recalibrating

the risk prediction equation, i.e. resetting the average risk factor levels and disease risks to current levels for the target population.[6–8] Such recalibration is, however, rarely done because most countries do not have the information, and current risk equations are difficult to recalibrate.[9] A previous set of risk charts published by the World Health Organization (WHO) only provided predicted CVD risk for regions and not countries.[3] This lack of reliable contemporary risk charts for all countries presents a major obstacle for worldwide implementation of risk-based prevention. A second obstacle to worldwide implementation is that most risk prediction equations require measurements of blood glucose and lipids which makes the assessment too costly or impractical in resource-poor settings.

We previously presented a novel approach for risk prediction in global populations (GLOBORISK) and applied the methods to predict 10-year risk of fatal CVD.[9] In this paper, we use the same methods to estimate the risk of fatal-and-nonfatal CVD and recalibrate the models using updated data for 182 countries. We also estimate an alternative model and corresponding risk charts using only risk factors that do not require blood tests. We then evaluate a two-stage strategy using a combination of the two risk scores to identify high-risk individuals while limiting the number of patients who need

laboratory tests.

Methods

Coefficients of risk prediction equations

As described in detail elsewhere,[9] we generated the risk prediction equation using data from eight cohort studies in the Unites States and a sex-and-cohort-stratified Cox proportional hazards model that used age as the time scale.[10] We allowed the coefficients of risk factors to vary with age because CVD hazard ratios often decrease by age.[11] We also included interaction terms between sex and diabetes and sex and smoking, based on prior evidence.[12,13]

In the office-based model, we replaced total cholesterol and diabetes with body mass index (BMI) as there is a strong correlation between BMI and diabetes/cholesterol both due to the direct effect of excess weight on these mediating physiological traits[14] and because common factors such as poor diet and physical inactivity increase body weight, blood glucose and serum cholesterol. As supported by previous research,[15] an interaction term between sex and BMI did not improve risk prediction, and was therefore not included.

We validated the models by assessing the ability of the risk score to assign a higher risk to individuals with shorter time to event (discrimination) using Harrell's C statistics and by comparing the predicted and observed 10-year risk by deciles of risk (calibration) (Appendix p 2 and Appendix Figure 1). We compared proportion of participants who went on to develop CVD during that was categorized as high-risk by the two risk scores (sensitivity) as well as proportion of the participants who were free of CVD at end of the follow-up who were categorized as low-risk (specificity) using 10, 20 and 30% 10-year CVD risk as thresholds for high-risk. Finally, we validated the model in three cohorts that had not been used to estimate the risk prediction equation.

Recalibration of the risk scores

The recalibration procedure is described in detail elsewhere.[9] Briefly, we replaced average risk factor levels and CVD event rates in each 5-year age-group and by gender with the best current estimates of these quantities for the target country. Age-and-sex-specific estimates of mean risk factor levels were taken from global analyses of health examination surveys.[16–20] We estimated fatal-and-nonfatal IHD and stroke rates for each country and age-sex-group by dividing the IHD and stroke death rates, from WHO,[21] by

case fatality rates.

We used two properties of case fatality to obtain its estimates. First, case fatality varies by region and is higher in LMICs than high-income countries.[22,23] We used previously published estimates of 28-day case fatality rates for IHD[22] and stroke.[23] We converted these to one-year case fatality rates using methods explained in the Appendix (Appendix pp 3-6 and Appendix Table 2). The second property of case-fatality is that they increase with age. To convert all-age case fatality rates from above to age-specific ones, we used the relative age pattern of one-year case fatality rates observed in nationwide Swedish registries (Appendix pp 3-6, Appendix Figures 3 and 4).

The total (fatal-and-nonfatal) CVD rate in each age-sex-country group was calculated as: $CVD = fatal\ \ IHD + fatal\ \ Stroke + [1 - (1 - nonfatal\ \ IHD) * (1 - nonfatal\ \ Stroke)$. This formula allows for the potential overlap between nonfatal IHD and stroke (e.g. a stroke event in the same person following a nonfatal IHD), which tends to happen where non-fatal IHD and stroke rates are higher (e.g. in older ages), therefore reducing the potential bias when simply adding non-fatal IHD and stroke rates. In the 8 US cohorts, adding non-fatal IHD and stroke rates would overestimate the observed CVD

rates by 3 to 31 per 1000 person-years, whereas the above method reduces the bias by up to 63%. Once fatal-and-nonfatal CVD rates were estimated, they were projected for 9 years (i.e. 2016-2024) using trends from 2000 to 2015 and a log-linear model.

We used the recalibrated risk scores to generate risk charts for 182 (of the 193) WHO member states for which we had data on CVD death rates. We limited prediction to those aged 40 to 74 years because this range is commonly considered for primary prevention of CVD, and CVD death rates in ages 85 and older are less reliable.

Application in national surveys

We used the recalibrated laboratory-based risk score and individual-level data from nationally representative surveys to estimate the proportion of population at different CVD risk levels in 10 countries with recent (2007 or later) surveys (Appendix Table 3). For each country, we compared the average 10-year risk of fatal CVD from the previously published Globorisk model that we revised to update the average risk factor and cardiovascular event rates with 10-year fatal-and-nonfatal CVD risk predicted by the office-based and the laboratory-based risk scores. We also used scatter plots to compare predicted risks for each individual and estimated the proportion of men and women who

were similarly categorized as low- or high-risk by the two risk scores. We considered three different thresholds to define high-risk: 10% for high-income countries, and 20% in LMICs based on recent guidelines;[3,24–26] and 30% as the threshold used in the global NCD target.[2]

We also evaluated a two-stage strategy to identify high-risk individuals, which could be useful in resource-poor settings. In this strategy, patients would be first assessed using the office-based risk score and those with a borderline predicted risk which is just below the threshold for high-risk (i.e. potential false negatives) would be referred for further laboratory-testing. We estimated proportion of those at high-risk who were identified by the office-based risk score and determined the range of office-based risk levels that needed further laboratory tests to identify 95% of those at high laboratory-based risk.

Analyses were done with Stata 12.0. The study protocol was approved by the institutional review board at the Harvard T.H. Chan School of Public Health (Boston, MA, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data

interpretation, or writing of the paper. PU, KH, and GD had full access to all the data in the study and GD had final responsibility for the decision to submit for publication.

Results

The coefficients for the risk scores are shown in Table 1. Both scores performed well (Appendix p 2 and Appendix Figure 1). In internal validation, the C statistic was 0.71 (95% confidence interval = 0.70-0.72) for the laboratory-based model, and 0.69 (0.68-0.70) for the office-based model. In external validation (using Tehran Lipid and Glucose Study, Scottish Heart Health Extended Cohort, and The Australian Diabetes, Obesity and Lifestyle Study), the C-statistic ranged from 0.73 to 0.78 for the laboratory-based model and from 0.70 to 0.77 for the office-based model. (Appendix Figure 2) Both models predicted risks that were close to those observed ones in internal and external validation. (Appendix Figure 1 and Appendix Figure 2)

The average 10-year risk of fatal-and-nonfatal CVD was similar in the two risk scores and were expectedly higher than risk of fatal CVD (Table 2). In the pooled cohorts and using 10% as the risk threshold, the laboratory-based risk score categorized 1,956 (65.1% [95% Confidence Interval 64.2 - 65.9%], and the office-based risk score categorized

1,881 (62.6% [61.7 - 63.5] of the 3,005 participants who later had a CVD event as high-risk (Appendix Table 4).

At any age and risk factor level, 10-year risk of CVD varied considerably across countries for both models. Overall, predicted risks in the country risk charts were lower in high-income countries than in LMICs, with the highest risks estimated for the same risk profile in Southeast and Central Asia, and Eastern Europe (Appendix Figures 8 and 9). For example, for some of the most populous countries presented in Figure 1, the predicted 10-year CVD risk for a non-smoking 65-year-old man with diabetes, SBP of 160 mmHg, and a total cholesterol of 6 mmol/L spanned from 21% in Japan and United States to 53% in China, and the predicted risks for the same profile for a smoker ranged from 26% in Japan to 62% in China. The complete set of risk charts and a risk calculator is available online at www.globorisk.org.

Distribution of 10-year risk of CVD, using laboratory-based model varied substantially across countries (Figure 2). The share of population with a ≥10% CVD risk in four high-income countries ranged from 7% for men and 1% for women in South Korea to 41% for men and 15% for women in Czech Republic. In four middle-income countries, the

percentage of population at ≥20% CVD risk ranged from 3% for men and 2% for women in Jamaica to 13% for men and 11% for women in Iran. In the two low-income countries, percentage who were at ≥20% risk in both men and women was <2% in Uganda and 9% in Cambodia.

When using a 10% risk threshold for high-risk in high income countries, the two risk scores assigned the same risk status to between 85 and 93% of men, and 89 and 95% of women in each country. The corresponding percentages using a 20% threshold for middle-income countries were 90% to 96% in men and 89 to 95% in women; and for low-income countries 94-95% to 99% for both men and women (Table 3 and Appendix Figure 10). The largest differences between the risks estimated using the two models were seen among people with diabetes (Figure 3 and Appendix Figure 10) where the office-based model underestimated risk by 23% to 75% in various ages across the 10 countries. Accordingly, the proportion of the population correctly categorized as low- or high-risk using the office-based model was lower in countries with a high diabetes prevalence (Table 3).

In the four high-income countries, percentage of individuals at high-risk (≥10% laboratory-based CVD risk) who were correctly identified by the office-based risk score ranged from 66 to 82% among men and from 36 to 71% among women (Table 4). In these countries, between 14 and 61% of the population who had a borderline risk would need further laboratory tests to identify 95% of those at high-risk. In low- and middle-income countries, the proportion of high-risk (≥20% CVD risk) individuals who were correctly identified by the office-based risk score varied from 33 to 83%, and the percentage of the population that would need laboratory tests to correctly identify 95% of those at high-risk, ranged from 11 to 50%.

Discussion

We developed CVD risk charts for predicting fatal-and-nonfatal CVD, with and without laboratory-based measurements, for 182 countries. These risk charts support worldwide implementation of risk-based prevention by providing healthcare professionals with risk assessment tools that are recalibrated for each country and can be used in settings without access to laboratory-based measurements. The predicted risk for the same risk factor profile tended to be lower in high-income countries than in LMICs, a pattern that was also observed in the Prospective Urban and Rural Epidemiological study.[27] When risk

scores were applied to data from national health surveys, prevalence of high CVD risk varied substantially by country and sex and was generally lower in high-income countries compared with LMICs.

Our risk scores and risk charts will be particularly useful in LMICs because most of these countries lack locally-developed risk scores. In addition, the office-based risk score allows for risk prediction in environments where access to a laboratory is limited, such as during home care visits. Similar to previous research,[28] more than 80% of adults were similarly classified as low- or high-risk by laboratory-based and office-based risk scores. Nonetheless, we noted that the office-based risk score substantially underestimates the risk among diabetics.

In several LMICs (e.g. Uganda, China, and Jamaica), a two-stage strategy using the 20% risk threshold for high-risk seemed efficient because only a small proportion of individuals with borderline office-based risk would need further laboratory tests to detect 95% of high-risk individuals. In contrast, half of women in Cambodia and men in Mexico would need further laboratory tests. Further developments of strategies to use office-based risk scores should apply country-specific risk thresholds and balance the benefits

of reducing costs with the possibility of missing truly high-risk individuals. Where a difference was observed among the laboratory-based and office-based score, it was mostly among diabetes patients, highlighting the importance of including diagnosis of diabetes in the risk score if laboratory measurements are available. In addition, including diabetes in the laboratory-based risk score would further motivate screening for diabetes which remains largely undiagnosed in LMICs.[29] Therefore, integrating diabetes diagnosis into CVD risk stratification programs will improve early detection and management of diabetes and risk-based CVD prevention.

Most existing risk scores have been developed for specific populations.[30,31] WHO developed regional risk charts in 2007,[3] but coefficients of the risk score were not derived from the same regression model or even from a consistent set of epidemiological studies. Moreover, risk charts were only presented for regions and not for each country, although CVD risk differs between countries in the same region. The only other country-specific risk score, the Systematic Coronary Risk Evaluation (SCORE), provides risk charts for European countries. However, the charts only predict risk of fatal CVD[32], which disfavors younger individuals who have a proportionally

higher risk of non-fatal CVD. Moreover, SCORE risk charts do not include diabetes which is an important predictor of CVD.

In addition to providing a unified risk score and risk charts that can be used for all countries, our risk charts can be easily updated as new national data on average risk factor levels and CVD rates become available. Our risk scores also include interactions between age and risk factors. The age-interactions improve risk prediction, and, because they are negative, help highlight the need for intervention in younger individuals with increased risk factors levels whose lifetime risk of CVD is high.[33] In fact, as evident in the risk charts, the predicted risks for individuals with high levels of multiple risk factors do not substantially increase with age. Other strengths of the study are the use of multiple high-quality prospective cohorts to estimate risk score coefficients, and application of the risk score to individual-level, national data from countries in different world regions to estimate prevalence of high CVD risk, as opposed to summary statistics used in the 2007 WHO report[3] which ignore correlation between different CVD risk factors in each country.

Our study has some limitations. First, because national CVD incidence rates are not available for most countries, we estimated fatal-and-nonfatal CVD rates using national IHD and stroke death rates from WHO, and estimates of case fatality rates by age, sex and region.[22,23] Our estimated CVD rates were close to those observed in nationwide studies and health registries in several high-income countries (Appendix Figures 4 to 6). This estimation, however, had a few limitations: (1) WHO death rates in countries with incomplete vital registration are estimated using partial information and demographic and epidemiological methods[34]; (2) we used the age-pattern of case fatality from Sweden, where high-quality data was available from more than one million events in registries because age-specific case fatality rates were not available from other countries. As Appendix Figures 5, 6 and 7 show for several countries, the estimated event rates are quite close to the observed ones; (3) the estimated CVD rates that we used for recalibration underestimate the overlap between non-fatal events and therefore overestimate the non-fatal CVD rate as there is a positive correlation between non-fatal IHD and stroke rates because they share risk factors. Empirical data to quantify this correlation for all countries is not available. The scarcity of data on CVD rates underscores the need for monitoring. Second, although the coefficients of the risk scores were derived from eight high-quality cohorts including diverse ethnic origins, all cohorts

were from US and Puerto Rico. Evidence from cohort pooling show that the proportional effects of risk factors are similar in Western and Asian populations, and over time in the same populations.[11,35] Future research should include pooling studies across different regions. Third, in our application of the risk score in country surveys, we did not account for patients with a previous CVD event who are at high risk of a future event and should receive treatment. Fourth, we used 10, 20 and 30% as thresholds to define high-risk based on national and international guidelines for CVD prevention.[3,24–26] However, the threshold above which a patient is considered high-risk and eligible for counseling and treatment depends on the priorities set for disease control in each country. The threshold also changes the sensitivity and specificity of the risk score which also varies across countries. Finally, we presented 10-year CVD risk as this is most commonly used in risk scores and risk charts. However, 10-year risks underestimates lifetime risk and may therefore lead to under-treatment especially in younger individuals.

Risk-based prevention of CVD is now a major strategy proposed by national and international guidelines.[3,24,25] The risk charts presented here can be used to predict 10-year risk of fatal-and-nonfatal CVD in 182 countries worldwide, removing a major obstacle in applying risk-based prevention strategies both for individuals and populations.

Further research is required to identify the most cost-effective interventions for high-risk individuals. There are ongoing trials to establish whether the efficacy of multi-drug therapy and lifestyle advice in LMICs is similar to those observed in high-income countries. There is also ongoing research on whether non-physician clinicians, aided by new information technologies such as risk charts, can identify and manage high-risk individuals, especially if regular contact leads to better adherence.

Research in context

Evidence before this study

We searched PubMed for articles related to cardiovascular disease risk prediction in global populations using the following key terms: cardiovascular disease, risk prediction, risk score, risk equation, developing countries, low-and-middle-income countries, global. We reviewed the 209 articles retrieved from this search to include risk prediction equations that could be applied to more than one country. Only three risk prediction equations qualified for our review and each had major limitations. WHO presented regional risk charts in 2007. However, the coefficients of the risk score were not derived from the same regression model or even from the same set of epidemiological studies, and cardiovascular risk patterns might differ between countries in the same sub-region.

The Systematic Coronary Risk Evaluation (SCORE) provided separate risk charts for European countries but the risk charts only predict risk of fatal cardiovascular disease and did not include diabetes which is an important predictor of cardiovascular disease. Finally, the INTERHEART Modifiable Risk score was developed from a multi-country case-control study, unlike other models that are based on prospective cohorts, and did not include stroke as an outcome.

Added value of this study

We provided risk scores, with and without laboratory-based measurements, for predicting 10-year risk of fatal and non-fatal cardiovascular disease and recalibrated the risk score to produce risk charts for 182 countries. The two risk scores are designed in a way that allows and necessitates updating as new data on average risk factor levels and cardiovascular disease rates become available.

Implications of all the available evidence

Our risk charts support worldwide implementation of risk-based prevention by providing healthcare professionals with risk assessment tools that are recalibrated for

each country and can be used in settings without access to laboratory-based measurements.

Contributions

GD, ME, and MW conceived the study. RAW, CAAS, AA, FA, JB, RC, MDC, LE, FF, TSF, NI, DK, YK, VL, LLM, DM, PM, KPM, GNM, KO, SO, FRA, RRM, GV, RW, JES, GAS, JT, and BZ collected and managed risk factor, survey or external cohort data. PU, KH and YL analysed cohort and survey data and prepared results. PU, GD, ME and MW wrote the manuscript with input from all other co-authors. GD and ME oversaw the research. GD is the study guarantor.

Declaration of interests

MW reports fees from Amgen for being a research project consultant. All other authors report no competing interests.

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