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INTRODUCTION

As observed in many countries in the world, cardiovascular disease (CVD) remains the main cause of mortality and morbidity in Brazil. According to Brazilian Ministry of Health, from all recorded deaths and hospitalisations, 29.6% and 12.1%, respectively, were related to CVD in 2013¹. Besides the impact on mortality and morbidity, its budget commitment is highly substantial. The Brazilian Public Health System spends no less than 8% of its budget to manage major cases of CVD².

Newer interventions for CVD are being developed and a platform to assess them in terms of efficiency does not exist within the Brazilian setting. Estimating efficiency of alternative interventions has also become relevant³ as its findings help taking decisions under uncertainty conditions. The aim is to determine which strategy is associated with the most benefit to each monetary unit invested. As a result, this ensures that scarce monetary resources are invested in a more rational manner³.

CVD is a complex disease where a number of personal risk factors play a role to define the chance of experiencing CVD events and hence resource use. Thereafter, decision analyses using mean values from a population to populate pharmacoeconomic models are capable to predict costs and consequences for a narrow range of subjects, leading to limited use in decision-making^{4,5}. An individual-based approach seems to be the most appropriate methodology for predicting costs and consequences of interventions aiming to prevent primary CVD events⁶. However, such studies demand an extensive dataset of patient-level data, what may not be available in several countries and for populations of interest.

One alternative is to adapt existing and well validated models for the desired population and perspective^{7,8}. From potential sources to be used⁹⁻¹¹ the Scottish CVD Policy Model¹² was chosen for presenting a number of important aspects, as capability to predict risks for the most important CVD events annually; taking into account secondary events to predict morbidity and mortality; estimating risks through a competing risk framework and, finally incorporating the most relevant risk factors for CVD in the Brazilian population^{20,36}.

We sought to adapt the Scottish CVD Policy Model¹² to predict life expectancy, incidence of coronary heart disease (CHD), cerebrovascular disease (CBVD), fatal CVD and fatal non-CVD events in the Brazilian population.

METHODOLOGY

This model adaptation followed the best practices currently available in literature ^{7,13} and was performed separately for men and women. The diagram below describes the strategy created to adapt the Scottish Cardiovascular Disease Policy Model ¹² to the Brazilian setting.

Original Scottish CVD Policy Model

The Scottish CVD Policy Model was developed to assess interventions capable to prevent primary CVD events in Scotland ¹². It consists of a state transition model based on patient-level data added to a time-to-event individual history approach, being described as a hybrid model. It is composed by four primary events CHD (ICD9 410-414; ICD10 I20-I25), CBVD (ICD9 430-438; ICD10 G45, I60-I69), fatal CVD (ICD9 390-459, ICD10 I00-I99) and fatal non-CVD. A final transition to 'death due to all cause' following primary non-fatal event is also represented. An illustration of the state-transition model is available in Appendix.

From the Scottish Heart Health Extended Cohort (SHHEC) ^{14,15} data, a survival analysis (Gompertz regression) was used to model the cause specific hazards of the first events. In addition, life expectancy after CHD and CBVD was also estimated by means of Gompertz regression. The choice for the risks factors was based on ASSIGN score, currently the risk calculator recommended by The Scottish Intercollegiate Guidelines Network to be used in Scotland ¹². For predicting risks of the aforementioned primary CVD events, were considered: age (years), systolic blood pressure (SBP), total cholesterol (TC), HDL cholesterol (HDL), cigarettes per day (CPD), diagnosis of diabetes, family history of heart disease (FHHD) and SIMD score, a measure of socioeconomic deprivation. For secondary events, the non-modifiable risk factors age at first event, FHHD and SIMD score, were taken into account. Additional information is available elsewhere ¹².

SIMD score 2004 is a specific tool for Scotland composed by six domains ²¹, current income, employment deprivation, health deprivation, education skills and training deprivation and geographic access and telecommunications deprivation. Its purpose is to serve as a tool for measuring level of deprivation in different areas across the country. In order to make possible running the model, it was estimated an artificial correspondent

SIMD score for Brazil. Limitations and opportunities about this subject were discussed.

Defining target data

Target data is an empirical data the model needs to reproduce ¹³. For life-expectancy, Brazilian Life-Table ¹⁷ was chosen as it is a real-world data representative of entire country. Target data for incidence of the events CHD, CBVD, fatal CVD and fatal non-CVD corresponded to a Brazilian Cohort study entitled *Brazilian Population-based Cohort Study* ²⁰. It consisted of a population-based research, in which 1,091 participants from the city of Porto Alegre were enrolled. Limitations of selected dataset were further discussed.

Assessing need of calibration

For the sake of clarity, risk factors data for a given subject are now referred as *profile*.

Life expectancy

Since it was not expected to find profiles for Brazilian adults without history of CVD events, it was retrieved from official reports ^{16–19} average data of Brazilians aging 35 years or more. The assumption of both populations having similar profiles is reasonable, as most part of individuals have not experienced CVD events. When data was not present in official reports, a systematic review was carried out to identify studies capable to estimate them. From these data, it was generated a simulated cohort of 1,000 profiles to be used in the calibration process by considering variance of identified data. Normal distribution was applied to age, SBP, TC and HDL. Beta distribution was set to prevalence of diabetes and FHHD whereas Gamma distribution for CPD.

Prevalence of diabetes in Brazil was retrieved for different ages and sex, from *Telephone-based Surveillance of Risk and Protective Factors for Chronic Diseases* report (2014) ¹⁶. FHHD was estimated regardless sex or age considering the number of families ¹ and diagnosis of CVD in 2013 ¹⁸. The average SBP was calculated taking into account the prevalence of hypertension ²², the estimated proportion of controlled hypertensive patients ²³ and the average SBP for normotensives, controlled and uncontrolled hypertensive patients ^{24,25}. Estimates for CPD considered the percentage of individuals who smoke more and less than 20 cigarettes per day ¹⁶. Mean and variances for both groups were estimated taking into account sex and age ²⁶. A systematic search in databases Medline, EMBASE and SciELO (Scientific Electronic Library Online) was carried out to identify studies reporting results for lipid profile of Brazilian population. It was identified nine studies which

complied with inclusion criteria comprising 4,781 individuals from seven different national states ²⁷⁻³⁵. Data from TC and HDL of patients who have never experienced CVD events were collected and an overall estimate according to sex and age was calculated. A summary of those profiles is available in Appendix. For each random profile was assigned a corresponding life expectancy ¹⁷ according to baseline age.

Incidence of CHD, CBVD, fatal CVD and non-CVD

To assess the necessity of calibrating incidence for the primary CVD events, mean values of risk factors were retrieved from the Brazilian Cohort study ²⁰. Average prevalence of diabetes, FHHD, SBP, TC, HDL and CPD, separated by genre, were obtained for six ranges of age (30-39; 40-49; 50-59; 60-69; 70-79; 80-more) during a follow-up of seven years. It was randomly generated 1,000 profiles by considering variance of each risk factor. Normal distribution was applied to age, SBP, TC and HDL. Beta distribution was set to prevalence of diabetes and FHHD whereas Gamma distribution to CPD.

For each range of age, separated by sex, yearly incidences of primary CVD events were obtained. Cumulative incidence was calculated by means of the equation:

$$CI_k(t) = \sum p_k t_j.$$

The cumulative incidence at time t , $CI_k(t)$, is the sum of the unconditional probabilities, p , of experiencing event k at time t_j . The four primary events are competing among each other. Hence, care was taken to avoid overestimations.

Acceptance criteria, algorithm search and stopping rule

Assessing the necessity of calibration consisted of comparing predicted life expectancy and risk of each of the four assessed primary CVD events for a given profile, with observed data (target data). When acceptance criteria were not complied, a calibration was undertaken. For life expectancy, acceptance criteria consisted of observing absolute differences equal or lesser than one year between predicted and observed data. For the risk of each CVD event, acceptance criteria were defined as an absolute difference equal or lesser than 1% between predicted and observed data.

A pragmatic approach was performed when calibration was required, by adjusting linear prediction of the first four events. For the Gompertz

regression, cause specific hazard for event k at time t_j is obtained by the equation:

$$h_k(t_j) = \exp(xb) \exp(\gamma t).$$

Linear predictor is represented by xb and γ corresponds to the ancillary parameter. Therefore, calibration was statistically expressed as:

$$h_k(t_j) = \exp[(xb)(CF)] \exp(\gamma t).$$

Where CF is the calibration factor. It was assumed CF of 1.00 in the original model. An algorithm running through different values of CF was undertaken for life expectancy and the cumulative incidences of the first four events. Differences between predictions and observed data were explored by root mean square error (RMSE). Therefore, calibration had the goal of decreasing RMSE up to a point when acceptance criteria are met. Stopping rule consisted of running the model with all identified CFs and meet acceptance criteria for all target data simultaneously.

Population eligible to be assessed in the adapted model

From all random profiles tested during adaptation, it was summarized characteristics of those that met acceptance criteria after calibration. Potentially, the adapted model is capable to predict correctly life expectancy and cumulative incidence of CHD, CBVD, fatal CVD and fatal non-CVD events for individuals with such a profile.

RESULTS

As previously described, real-world data was linked to each profile randomly generated. Profiles used for life expectancy assessment were estimated by means of national reports. For cumulative incidence of primary CVD events, profiles were estimated by taking into account mean characteristics of subjects enrolled in the Brazilian Cohort study ²⁰. Each created profile aimed to be representative of existing profiles within Brazilian population, given sex and age. Full description of these profiles is provided in Appendix.

Data from both official reports *Brazilian National Household Sample Survey 2012* ¹⁹ and *Health Informatics Department of the Brazilian Ministry of Health* ¹ were used for obtaining a SIMD score of 65.13 following the methodology reported elsewhere ²¹. Variations in SIMD score alter significantly the risks predicted from adapted model. Nevertheless, since the

calibration process was performed considering the value of 65.13, the importance of this parameter was nullified.

Life expectancy checking

Original model underestimated life expectancy when compared to findings reported in Brazilian life table in more than one year for men and women (RMSE=2.85 and 1.91, respectively). It was run the calibration algorithm and the multiplicative factor that complied with the stopping rule was the linear regression $CF = 0.0036 \times age + 0.877$ for men and $CF = 0.0023 \times age + 0.911$ for women. Thus, linear predictors for fatal-CVD and fatal non-CVD primary events were calibrated by those functions. Comparison of predicted and observed life expectancy after calibration resulted in RMSE=0.61 for men and 0.21 for women (Figure 2).

From all random profiles used to assess life expectancy predictions, 96% and 95% met the acceptance criteria after calibration for men and women, respectively. Disagreements were observed for profiles with age greater than 70 years old.

Checking cumulative incidence for primary events (CHD, CBVD, fatal CVD and non-CVD)

Profiles obtained from the cohort study ²⁰ for different sex and ages and which were used to assess predictions for primary events, are described in the appendix. For male, comparison between predictive and observed cumulative incidences of CBVD, fatal CVD and fatal non-CVD complied with the acceptance criteria. On the other hand, for predicted CHD event was identified an important difference between prediction and observed data, varying from 0.50-2.10% throughout the seven years of follow-up (RMSE=0.031). Therefore, calibration was conducted by means of the already described algorithm, which pointed the multiplicative factor **1.05** as capable to adjust the differences observed, resulting in RMSE=0.008. As an implication of it, the linear predictor for non-fatal CHD passed to be multiplied by 1.05 (figure 3).

For female model, predicted and observed cumulative incidences of fatal CVD and fatal non-CVD met the acceptance criteria. However, such fitting was not observed for CHD and CBVD events, where an absolute difference of 0.2-1.6% (RMSE=0.044) and 0.4-2.0% (RMSE=0.041), respectively, was observed across the seven years of follow-up. Calibration algorithm was run and pointed the multiplicative factor **0.98** (RMSE=0.016) and **0.93** (RMSE=0.017), respectively, as the most appropriate for each event (figure 3).

In men and women, respectively, 81% and 79% of profiles met acceptance criteria of all target data after calibration. Profiles involving older people (more than 70 years-old), having all risk factors under control, presenting extreme high values of SBP (SBP>190 mmHg), TC (TC>300 mg/dL), HDL (HDL>80 mg/dL) or CPD (more than 60 CPD) were responsible for disagreements between observed data and predictions.

DISCUSSION

This is the first study to introduce an individual-based decision analytic model for Brazilian individuals with the goal of assessing interventions to prevent primary cardiovascular events. That model has the potential to adjust for background morbidity impacts and subsequent consequences of experiencing first and following CVD events. Furthermore, prevention of primary CVD events is likely to extend life expectancy, what in turns lead to individuals accumulating comorbidities, impacting directly in costs, as hospitalisation episodes, and quality of life. All these conditions were taken into account for estimating costs and quality-adjusted life years.

Four main reasons justify choosing risk equations from Scottish CVD Policy Model over other existing options to build this first version of the Brazilian CVD Model. Firstly, it is capable to predict risks for all the main CVD events. This is of such importance as avoids resorting to several data sources to populate the model. Secondly, hazard functions to estimate further events after non-fatal CHD or CBVD were estimated and clearly reported¹². Thirdly, the most relevant risk factors for CVD in the Brazilian population^{20,36} were taken into account. Finally, a competing risk framework was carried out in order to avoid over predictions in yearly estimations.

Overall, after adaptation, both male and female models were capable to reproduce the observed cumulative incidences²⁰ with less than 1% of absolute difference. In addition, predicted life expectancies matched the observed life in less than 1 year of difference. It is noticeable in the calibration charts that observed incidences are slightly higher compared to predictions. That seems to be reasonable considering that the cohort studied²⁰ is representative for *Porto Alegre*, the capital city of *Rio Grande do Sul* (RS) state. Population in *Porto Alegre* corresponds to 18% of individuals in RS. Data from National Research of Health¹⁸ pointed out that 5.3% of adults living in RS in 2013 were diagnosed with heart disease whereas in Brazil 4.2%. Similarly, there were 2.2% of individuals who have experienced stroke at least once in RS and in Brazil 1.5% in the same year. It has also been observed a higher annual incidence of death due to circulatory diseases in RS since 1990 compared to the annual incidences of Brazil (in 2011 was 0.074% and 0.054%, respectively)¹.

By comparing male and female predictions, it can be seen that results are in concordance with Brazilian real life observations, where men are at higher risk of experiencing CHD events and for CBVD, risks are nearly the same ^{8,13}. In addition, fatal CVD events are more frequent among men ^{1,38} and women present higher life-expectancy ¹⁷.

Validation is an important step for any decision analytic model in health economics. It is conceptualized as the estimation of how well the model reproduces reality ¹³. External validation is the most important type of validation since it compares model results and real-world data ¹³. It can be split in dependent, partially dependent and independent external validation according to the way real world data was used. Dependent validation consists of using real-world data to fit model parameters and validate it. Partially dependent validation uses the same source to build or calibrate part of the model but that part does not play an important role on defining the outcome to be validated. Finally, independent validation takes into account real-world data not used in the model. Although the process of calibration we carried out in this study can be understood as a dependent external validation ¹³, we still recommend an independent external validation to be performed using a broader representative dataset.

Potential population eligible for this model

Covariance among risk factors was not considered. Thus, profiles unlikely to be seen within the population might be generated. In fact, lack of fitting between observed and predicted data was mainly related to profiles with extreme values of age, SBP, TC, HDL and CPD.

Overall, after calibration it was observed that men and women aging 30-70 years old and presenting at least one of the following risk factors: diabetes diagnosis, family history of heart disease, smoker, systolic blood pressure between 120-190 mmHg, total cholesterol between 200-300 mg/dL or HDL cholesterol under 40 mg/dL are more likely to promote predictions similar to observed data. An external validation should be able to corroborate what patients included in this wide population are eligible to bring about reliable costs and consequences outputs.

Future

There are several studies pointing the family income and level of deprivation as whole, as an important independent variable for myocardial infarction ³⁹ and as a risk factor to CVD events ^{40, 41}. It is important to highlight that observed risks for a given patient's profile will vary according to his level of deprivation. Since Brazil does not have a straightforward tool to comprise this independent variable in researches (as SIMD score in Scotland and England), the predicted risks from this model depict the average observed in

Brazilian population. The creation of a score to predict deprivation across Brazil is of such a value for the society. Ignoring socioeconomic gradients lead to increase of inequalities.

There is an important lack of broad longitudinal studies of Brazilian population assessing chronic diseases, what prevent the development of analytic decision models more accurate. *ELSA Brasil (Longitudinal Study of Adult's Health)* ⁴² is an ongoing and promising study to start changing this reality. Ideally, replacing hazard functions from this model to others derived from the Brazilian population would be the best approach to assure that hazards are accurate. However, it is also valuable to carry out an external validation as soon as newer data become available with the goal of assessing the reliability of this adapted model. Moreover, an appropriate external validation shall point out for what patients this model is representative.

This analytic decision model can be helpful to face the rising of chronic diseases, as obesity and diabetes by assessing interventions to prevent primary CVD events in those specific populations. After all, this model encompasses the most relevant consequences of such diseases.

Limitations

Nullifying the independent variable SIMD score is to waive the information about differences across the country in regard to level of deprivation. Trying to validate this tool in Brazil proved to be extremely time-consuming and technically questionable. By our understanding the most appropriate approach was undertaken in this adaptation. Future researches with the intention to create a similar tool in Brazil taking into account its singularities shall have a massive impact in public health.

The Scottish CVD Policy Model is capable to predict later CVD events after first non-fatal episode. We did not find enough data in literature to calibrate these predictions. Therefore, we are assuming that secondary events happen as observed in SHHEC ¹².

The importance of each risk factor might vary across different populations. Currently, we are able to assure that sex, diabetes, FHHD, SBP, TC and smoking are the major independent variables for predicting CVD events in Brazil ³⁷. Nevertheless, there are not published data to demonstrate, quantitatively, the importance of each of them. Rather than calibrating these coefficients, we opted to carry out a trustworthier but more limited approach by calibrating linear factors.

External validation must be carried out before using this model for decision-making.

CONCLUSION

The adapted model, named Brazilian Analytic Decision Model for CVD, has the purpose of serving as a tool for assessing efficiency of interventions to prevent primary CVD events. This model is calibrated in terms of life expectancy and incidence of the most common CVD events. It is imperative to perform a thorough external validation as data become available in order to identify eligible population and assure reliability.