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Original Article

Estimating the Calibrating Coefficient of the Framingham Score to Predict Risk of Coronary Heart Disease in the Taiwanese Population

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SUMMARY

Background: The Framingham score, which was developed in the United States, is often calibrated and used in various countries to predict 10-year risk of coronary events, based on the measurements of age, sex, total cholesterol, high-density lipoprotein cholesterol (HDL-C), smoking status, and systolic blood pressure. However, no calibration coefficient is currently available for Taiwan.
Methods: Data from the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) were used to calibrate the Framingham equation for Taiwanese usage and compared with coefficients of the Chinese Multi-provincial Cohort Study (CMCS). Coronary events were identified through the link to National Health Insurance claim data and the national death registry for 2011. The risk factors were total cholesterol (mg/dL), systolic blood pressure (mmHg), cigarette smoking (yes/no), and diabetes (yes/no). The mean of these risk factors and the baseline survival probability were derived from TwSHHH. They were applied to the Framingham score function. Finally, the ratio of observed/predicted was applied to calibrate the predicted probabilities.
Results: When applying the Framingham function, agreement between the predicted and observed risk matched reasonably well in Taiwanese males, but not in females. The CMCS coefficients did not fit the Taiwanese population well. We recommend using 0.7958 and 1 as calibration coefficients for males and females, respectively.
Conclusion: We generated Framingham calibration coefficient for the Taiwanese population. We recommend that the mean of predictors and the baseline survivorship derived from TwSHHH should be used in the model. Nonetheless, it is crucial to develop a risk function specific for this population.

1. Introduction

Risk prediction equations for chronic diseases are often used to raise patient awareness of disease risk factors. Since the development of the Framingham score[1] to assess the risk of cardiovascular disease, many risk prediction models have been developed. The Framingham score predicts 10-year risk of coronary events based on age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking status, and systolic blood pressure. D'Angostino and colleagues found that the risk prediction function performed well in males, but overestimated the risk in females. Thus, they developed sex-specific Framingham scores and applied them to cohorts with various ethnic backgrounds.[2]

In a systematic review, Eichler and colleagues validated the Framingham score in 25 cohorts from different populations.[3] They found heterogeneity in the prediction of first-time coronary events. Overall, the Framingham score overestimated the risk for the majority of Western populations, except for people in the United Kingdom, New Zealand, and some groups in the United States.

The Asia Pacific Cohort Studies Collaboration evaluated the accuracy of several tools in predicting coronary events in Asia.[4] Similar to Western populations, there was heterogeneity in the risk, with the predicted risk for the Taiwanese population being higher than those observed in Chinese and other Asian populations. Age and smoking were found to have similar effects on the risk of cardiovascular events across different populations, whereas heterogeneity existed in the association between total cholesterol and cardiovascular events.[4] The Chinese Multi-provincial Cohort Study (CMCS) assessed the validity of the Framingham function in the Chinese population.[5] Liu et al reported that the original Framingham function consistently overestimated the absolute risk of coronary heart disease (CHD) in the Chinese population.[5] Therefore, they modified the coefficients of the Framingham score based on measurements of adults from 11 provinces in China, and concluded that the recalibrated function performed well in the Chinese population. Based on studies from other countries, the position paper of the International Atherosclerosis Society provided a list of recalibration coefficients for predicting the risk of CHD.[6] However,

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there are no data from Taiwan. Thus, the purpose of this study was to generate the calibration coefficient of the Framingham score for the Taiwanese population.

2. Materials and methods

Data from the Taiwanese Survey on Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) were used. The 2002 TwSHHH was a follow-up of the 2001 National Health Interview Survey conducted by the Bureau of Health Promotion, Department of Health of Taiwan. Half of the primary sampling units of the 2001 survey were selected; all household members aged 15 years were interviewed and waist circumference and hip circumference were measured. Participants' fasting blood samples were also drawn. Details are described elsewhere.[7] The same procedures were repeated in 2007 on subjects who were willing to come back for another measurement.

Questions on demographics, disease history, behaviors, and utilization of health care systems etc. were asked in the 2001 NHIS. In terms of cigarette smoking, participants were asked have they ever smoked. Those answered 'never' or 'only few times' were considered non-smokers. Otherwise, questions like whether they have smoked more than 100 cigarettes, followed by the age of initiation, duration, and current status were asked. Since we were following the healthy individuals till they developed the disease, those answered with heart diseases diagnosed by physician or taking medication for heart disease were excluded from the baseline.

In the TwSHHH, two blood pressure measurements were made 10 min apart, and a third measurement was made if the two measurements differed by > 10 mmHg. Subjects were requested to fast 12 h prior to venous blood sample collection, with samples excluded from laboratory analysis if fasting time was less than 8 h. The blood samples were stored in a freezer at −20 °C and were sent back by express mail to the research center within 2 weeks. The methods used for analyzing each item were as follows: hexokinase for fasting plasma glucose, colorimetric for fasting serum uric acid, enzymatic for triglycerides, and oxidase, esterase, and peroxidase for cholesterol. Coronary events were identified through the link to the National Health Insurance (NHI) claim data and the national death registry for 2011. The repeated measurements in 2007 were also used to ascertain end-points. CHD is defined as having ICD-9 codes 410–414 in any of the outpatient and/or inpatient records or self-reported events in 2007. Event time was estimated based on the first record time. We used subjects free of CHD at baseline. The risk factors listed in the International Atherosclerosis Society report are total cholesterol (mg/dL), systolic blood pressure (mmHg), cigarette smoking (yes/no), and diabetes (yes/no). Since WHO defines a smoker as individuals have smoked over 100 cigarettes in lifetime, we used this definition for smokers. In addition, we used the cumulated number of cigarettes over 100 in lifetime plus whether individual was still smoking at the time of interview. This study was approved by the institutional review board of the National Health Research Institutes.

There are two major ways to recalibrate the Framingham function. One is by multiplying the risk estimated by the Framingham function by some factor, which is the inverse of the predicted over observed absolute risk.[6] The other is replacing the mean of risk factors, such as cholesterol levels, blood pressures, and smoking status, with values from the population of interest. The disease-free probability (survivorship) $S_0(t)$ is also replaced by that of the population of interest.[2] Both methods were attempted in the current study.

To analyze the agreement between predicted and observed events, chi-square statistics were used. In this approach, the predicted values 1-(S_t) are first rank ordered and divided into N groups. The upper group contains subjects who are least likely to experience the event, whereas the lower contains those who are most likely to experience the event. Here, o_l denotes the observed survival in group l calculated by:

Table 1
Frequency distributions of blood pressure, total cholesterol, HDL-C, diabetes, and smoking status in the sample.

Variable	Men (N = 1580)	Women (N = 1780)
Blood pressure	N (%)	N (%)
Optimal	596 (40.7)	885 (56.0)
Normal	316 (21.6)	300 (19.0)
High normal	197 (13.5)	164 (10.4)
Hypertension		
Stage I	256 (17.5)	181 (11.5)
Stages II–IV	100 (6.8)	51 (3.2)
Cholesterol (mg/dL)		
<160	62 (18.0)	296 (18.7)
160–199	679 (46.4)	680 (43.0)
200–239	406 (27.7)	434 (27.5)
240–279	86 (5.9)	137 (8.7)
≥280	32 (2.2)	34 (2.2)
HDL-C (mg/dL)		
<35	214 (14.6)	55 (3.5)
35–44	281 (19.2)	168 (10.6)
45–49	194 (13.2)	143 (9.0)
50–59	316 (21.6)	420 (26.6)
≥60	460 (31.4)	795 (50.3)
Diabetes (yes)	66 (4.5)	65 (4.1)
Smoking		
>100 cigarettes/lifetime	794 (54.2)	57 (3.6)
Current smoker and >100 cigarettes/lifetime	680 (46.5)	54 (3.4)
Coronary heart disease	224 (0.142)	272 (0.153)
Probability of free from the disease in 10 years, S0	0.8556	0.8506

Blood pressure: Optimal (SBP <120, DBP <80), Normal (120 ≤ SBP < 130, 80 ≤ DBP < 85), High normal (130 ≤ SBP < 140, 85 ≤ DBP < 90); Stage I hypertension (140 ≤ SBP < 160, 90 ≤ DBP < 100), Stage II–IV hypertension (SBP ≥ 160, DBP ≥ 100).

$$o_l = 1 - \frac{Number\ of\ events\ in\ group\ l}{Number\ of\ samples\ in\ group\ l}$$

Let e_l denote the average predicted risk value for group l, and a goodness-of-fit measure can be obtained by comparing o_l and e_l graphically for l = 1, ….,N. To quantify this analysis, a chi-square statistic is derived by:

$\chi^2 = \sum_{i=1}^{n} \frac{(o_l - e_l)^2}{e_l}$, with N-(p+1) degree of freedom, where p is the number of risk factors.

3. Results

We included subjects aged 35–70 years old and excluded those reported to have had CHD events at baseline. The final sample size was 3360, with 1580 (47%) males. A total of 496 CHD events occurred in 10 years, and the 10-year incidence rate was 0.1418 in males and 0.1528 in females. The frequency distribution of each predictor is listed in Table 1. Over 75% of males and 85% of females had optimal to high normal blood pressure. There were 64% of males and 62% of females who had a cholesterol level under 200 mg/dL. Females showed a better cholesterol profile (HDL-C > 45 mg/dL; 86% females vs. 66% males). The proportion of diabetes was around 4% in both males and females. Many more males smoked (54.2% males vs. 3.6% females).

The predicted risks were divided into 10 groups and arranged from the lowest to the highest centiles in figures (blank). Then, the actual disease status in each group were plotted next to the predicted (shaded). χ^2 was calculated as the square of the differences between observed and predicted, then divided by the number of predicted. Different conditions were applied in the figures. When χ^2 was less than 5.991 with 2 degree of freedom, the agreement was good at p = 0.05 level. Fig. 1a illustrates the agreement between the predicted and observed risk using Framingham coefficients, means of predictors, and baseline survivorship for 10 years. Then, the ratio

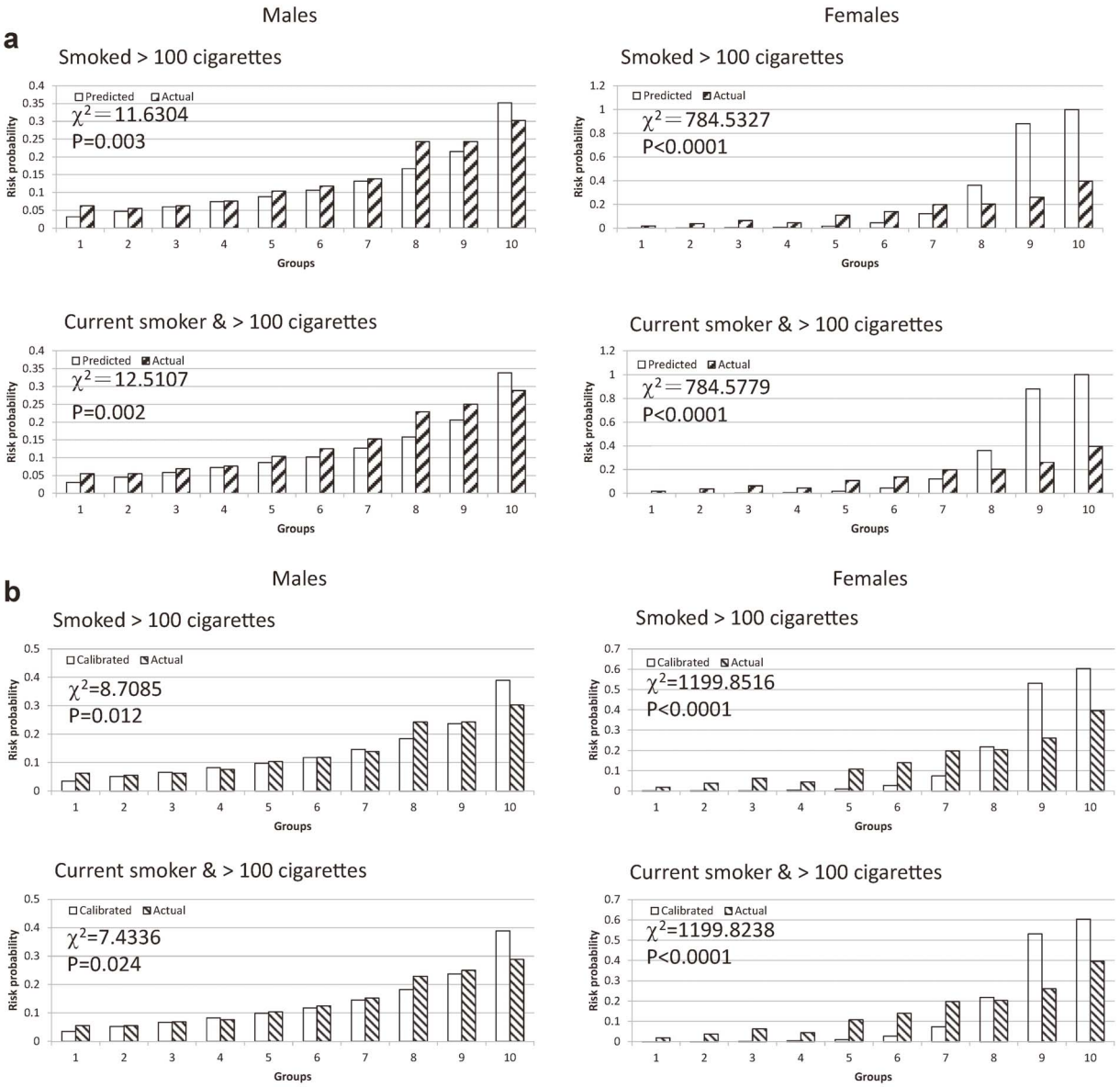

Fig. 1. (a) Comparison between predicted and observed probabilities. The Framingham coefficients, means, and baseline survivorship were used. The vertical axis was the probability of risk. The horizontal axis was the risk groups based on predicted risk divided into centiles evenly from the lowest (10%, group 1) to the highest (90%, group 10). (b). Comparison between predicted and observed probabilities. The Framingham coefficients, means, and baseline survivorship were used, and the calibration factor (observed/predicted) was applied. The vertical axis was the probability of risk. The horizontal axis was the risk groups based on predicted risk divided into centiles evenly from the lowest (10%, group 1) to the highest (90%, group 10).

of observed/predicted was applied to calibrate the predicted probabilities when comparing the changes of χ^2 statistics, improvement was noted in males. On the other hand, χ^2 value increased a lot for females (Fig. 1b). Fig. 2 shows the estimates using means and baseline survivorship derived from TwSHHH. The agreement between the predicted and observed risk improved a lot in females (χ^2 decreased from 1199.85 to 340.4), but worsened a bit in males (χ^2 increased from 8.7 or 7.4 to 16.3 or 14.7) (Fig. 2a). After applying the calibration coefficients, the agreement improved in males, but worsened slightly in females (Fig. 2b).

4. Discussion

This study compared the accuracy of the Framingham function in predicting CHD in a nationally representative sample of the Taiwanese population. The level of agreement between the predicted and observed risk was reasonable for males, but not for females. In terms of calibration coefficients, we suggest using 0.7958 and 1 for males and females, respectively. The reason for using 0.7958 for males was that the prediction using our data and Framingham coefficients improved the prediction slightly. On the other hand, when applied our population means of risk factors and the disease free probability to females reduced the χ^2 value sharply, even though it was not ideal. After applying the calibration factor, the χ^2 value became slightly worse in females. These calibration factors resulted in the best agreement in males, even though the predictability in females is far from ideal. In addition, the mean of predictors and the baseline survivorship derived from TwSHHH should be used in the model. From the viewpoint of preventing CHD, considering whether an individual has smoked more than 100 cigarettes in his/her lifetime is suggested, regardless of whether this person is a current smoker.

When the coefficients of the CMCS were applied, the agreement between the predicted and observed risk was worse than that

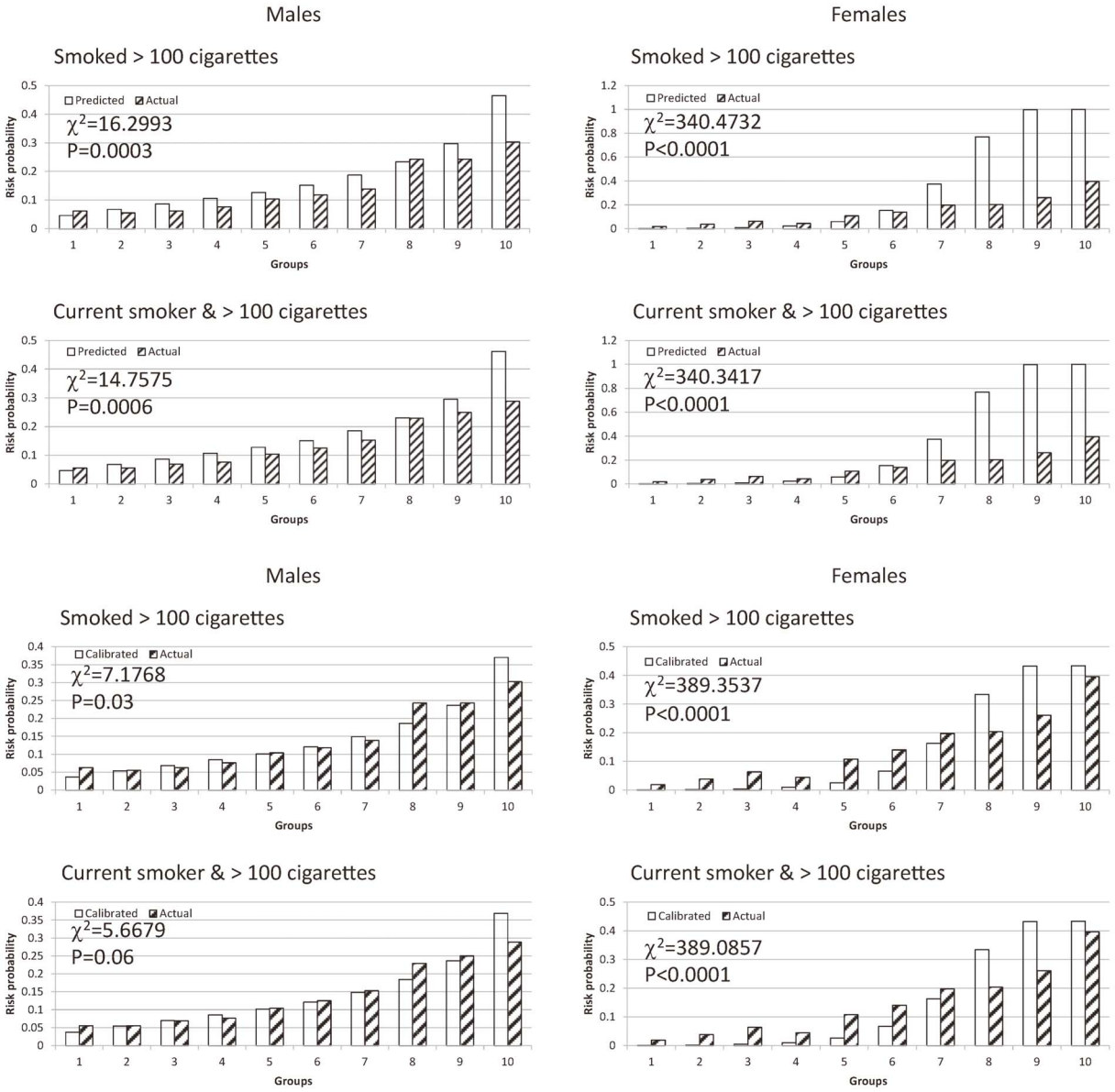

Fig. 2. (a) Comparison between predicted and observed probabilities. The Framingham coefficients, TwSHHH means and baseline survivorship were used. The vertical axis was the probability of risk. The horizontal axis was the risk groups based on predicted risk divided into centiles evenly from the lowest (10%, group 1) to the highest (90%, group 10). (b) Comparison between predicted and observed probabilities. The Framingham coefficients, TwSHHH means, and baseline survivorship were used, and the calibration factor (observed/predicted) was applied. The vertical axis was the probability of risk. The horizontal axis was the risk groups based on predicted risk divided into centiles evenly from the lowest (10%, group 1) to the highest (90%, group 10).

of the Framingham function for males, but better for females. The predicted risk of CHD for both males and females in Taiwan is not ideal. Thus, because members of the population share the same ethnic background, living environment likely plays a role in CHD risk. Some researchers used data of individuals of different ethnicities in the same region (e.g., the United States) to calibrate the Framingham function,[2] and their findings suggested the need for a gender-specific function with the mean and baseline survival of the ethnicity of interest. Based on our experience, the same ethnicity showed different levels of CHD risk across different regions. Thus, each population should have its own prediction function.

Studies have examined the risk of CHD death due to elevated blood pressure in different populations. Van den Hoogen et al compared the risks in middle-aged men among the United States, northern Europe, Mediterranean southern Europe, inland southern Europe, Serbia, and Japan and found that the relative increases in 25-year CHD mortality was similar across populations, although the absolute CHD mortality differed.[8] CMCS generated lower coefficients in predicting CHD than the Framingham score,[5] which could be one reason that CMCS coefficients did not fit our population well.

The population attributable risk of total cholesterol to CHD was high.[9–12] Low-density lipoprotein (LDL) cholesterol had a fairly good ability to discriminate 1-year CHD risk.[10] A large study examined the population variation of total cholesterol level and the relationship with CHD.[13] The results showed that the total cholesterol levels were higher in Australia and New Zealand than in Asia as a whole, but the risk of CHD was similar in these cohorts. Despite consensus on the risk of high cholesterol level, many studies have teased out the importance of the components of total cholesterol.[14] Investigators used data from the Atherosclerosis Risk in Communities study to compare the predictability of LDL, triglycerides, lipoprotein(s), and HDL on CHD and found these factors provided substantial CHD predictability without additional apolipoproteins or lipid subfractions.[14] However, a prediction of CHD without total cholesterol was shown to be reasonable.[15] More than 30% of our population had total cholesterol greater than 200 mg/dL and more than 50% had HDL-C greater than 50 mg/dL. This finding suggests the need to re-evaluate the importance of HDL-C and total cholesterol in predicting CHD in the Taiwanese population.

One strength of this study is that we used nationally representative data and follow-up for 10 years. However, the CHD events were identified from NHI records, meaning we might have missed some events that were not registered in the NHI claims. Because over 99% of the Taiwanese population is covered by the national insurance, however, we believe that the data are a valid representation of CHD events in this population.

5. Conclusion

We estimated the Framingham calibration coefficient for the Taiwanese population. We recommend using 0.7958 and 1 as calibration coefficients for males and females, respectively. These values have been submitted to the International Society of Lipids and Atherosclerosis. The predicted risk can be implemented during the health check-up to raise awareness of one's CHD risk over the next 10 years. However, because the performance of this calibrated Framingham score is not yet satisfactory, it is necessary to develop a risk function for the Taiwanese population.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijge.2018.04.004.

References

1. Dawber TR, Meadors Jr GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health Nations Health*. 1951;41(3):279–281.
2. D'Agostino RB, Grundy Sr S, Sullivan LM, et al, CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2): 180–187.
3. Eichler K, Puhan MA, Steurer J, et al. Prediction of first coronary events with the Framingham score: a systematic review. *Am Heart J*. 2007; 153(5):722–731, 731 e1–8.
4. Asia Pacific Cohort Studies, Barzi CF, Patel A, Gu D, et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health*. 2007;61(2):115–121.
5. Liu J, Hong Y, D'Agostino RB, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004;291(21):2591–2599.
6. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel Members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia–full report. *J Clin Lipidol*. 2014;8(1):29–60.
7. Su TC, Bai CH, Chang HY, et al. Evidence for improved control of hypertension in Taiwan: 1993-2002. *J Hypertens*. 2008;26(3):600–606.
8. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, et al. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med*. 2000;342(1):1–8.
9. Emberson JR, Whincup PH, Morris RW, et al. Re-assessing the contribution of serum total cholesterol, blood pressure and cigarette smoking to the aetiology of coronary heart disease: impact of regression dilution bias. *Eur Heart J*. 2003;24(19):1719–1726.
10. Avins AL, Browner WS. Improving the prediction of coronary heart disease to aid in the management of high cholesterol levels: what a difference a decade makes. *JAMA*. 1998;279(6):445–449.
11. Page IH, Berrettoni JN, Butkus A, et al. Prediction of coronary heart disease based on clinical suspicion, age, total cholesterol, and triglyceride. *Circulation*. 1970;42(4):625–645.
12. Paynter NP, Crainiceanu CM, Sharrett AR, et al. Effect of correcting for long-term variation in major coronary heart disease risk factors: relative hazard estimation and risk prediction in the Atherosclerosis Risk in Communities Study. *Ann Epidemiol*. 2012;22(3):191–197.
13. Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol*. 2003;32(4):563–572.
14. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2001;104(10): 1108–1113.
15. Nordet P, Mendis S, Duenas A, et al. Total cardiovascular risk assessment and management using two prediction tools, with and without blood cholesterol. *MEDICC Rev.* 2013;15(4):36–40.