INTRODUCTION

In Singapore, cardiovascular disease (CVD) was the top cause of all deaths by broad cause and top cause of early death and disability, accounting for 30.2% of all deaths in 2018, with 17 deaths daily due to CVD. Primary prevention of CVD and coronary artery disease (CAD) requires identification of at-risk individuals, allowing for swift implementation of effective preventive or corrective measures, including lifestyle changes. This has traditionally been done using risk scores such as the Framingham Risk Score (FRS), which is calculated using a combination of cardiovascular risk markers and clinical characteristics such as age and gender.\(^\text{[1,2]}\)
Traditional risk scoring systems such as FRS predict risk by assessing a variety of parameters routinely obtained from simple clinical assessment and blood tests. However, the traditional FRS has some disadvantages. The original Framingham risk function was developed based on the Framingham Heart Study of white middle-class individuals; hence, additional recalibration of the risk function to improve predictive accuracy in other populations is required. FRS does not take into account well-known CVD risk factors such as diet and physical activity level, which provide important discriminatory value, especially in healthy cohorts. It predicts only 60%–65% of myocardial infarctions (MIs) or sudden cardiac deaths; however, in most individuals, the first presentation of disease is a major adverse cardiovascular events (MACE), such as MI, or even death.\(^4\)

While there is a recalibrated Framingham risk function that provides a more accurate estimate of CVD risk for the Singaporean population (SG FRS), the study was done more than a decade ago and coefficients are likely to be outdated today. However, it remains the most precise estimate of absolute CVD risk for the Singaporean population that is currently available and is still widely used in clinical practice. There is, therefore, a pressing need to recalibrate and improve the prediction capability of SG FRS to identify asymptomatic individuals who are at high risk of CVD and MACE to implement preventive strategies in our Singaporean population.

In healthy Singaporeans enrolled in the SingHEART study and using baseline data, we proposed to investigate potential improvements in the performance of the Singapore-adapted FRS for 10-year risk of hard coronary heart disease (SG FRS) as a clinical tool to predict the risk of MI based on the high/low calcification classifications of the Agatston coronary artery calcium score (CACS) as a surrogate outcome in the absence of any clinical outcomes.

While it would be ideal to develop an improved risk model for MI in our Singaporean cohort using incident MACE in our SingHEART cohort, the SingHEART study is the first population-based study conducted in Asia combining conventional clinical information with the latest technology in genomics, imaging, wearable data and analytics, and was only recently established in 2015. Given our study population of 663 volunteers, an extensive time horizon would be required to accrue enough events in the form of MI or other MACE, and this is beyond the scope of our study.

Agatston CACS is a highly specific feature of coronary atherosclerosis and reflects coronary age. Several large long-term observational studies produced evidence of a strong association between CACS and MACE in asymptomatic individuals and showed that CACS improves statistical risk re stratification.\(^5,6\) Relative risk of MI also increases with higher CACS, and CACS has been widely used to guide lipid therapy for primary prevention of CVD.\(^7\) As an excellent predictor of MI, the Agatston high/low CACS classification was, therefore, chosen as a surrogate outcome for MI in our study.

**METHODS**

The SingHEART/Biobank study was established at National Heart Centre Singapore (NHCS) to characterise normal reference values for various cardiovascular and metabolic disease (CVMD)-related markers in Singaporeans. The study aimed to combine conventional clinical information with the latest technology in genomics, imaging, wearable data and analytics to assess pre-existing risk markers and identify new risk markers in CVD, especially in our local context, and to characterise cardiovascular health in Asians.\(^8\)

Volunteer recruitment was carried out as described previously.\(^8\) Normal volunteers were enrolled in this study using a protocol and a written informed consent form approved by the SingHealth Centralised Institutional Review Board (ref: 2015/2601). A secondary written informed consent for this sub-study was required, and only those completing the secondary informed consent were enrolled in the study. The volunteers underwent comprehensive profiling in the following areas: (a) activity tracking using the Fitbit Charge HR wearable sensor, (b) lifestyle questionnaire, (c) cardiac imaging consisting of coronary magnetic resonance imaging (MRI) and coronary non-contrast computed tomography (CT), (d) fasting lipid and glucose panel and (e) assessment of clinical parameters (e.g., heart rate [HR], blood pressure, waist circumference, body mass index [BMI]). A total of 663 volunteers were included in this study after evaluation for completeness of activity tracking data (details below). Inclusion criteria were as follows: (a) age between 30 and 69 years; (b) no personal medical history of MI, CAD, peripheral arterial disease, diabetes mellitus (DM), psychiatric illness, asthma, or chronic lung disease and chronic infective disease and (c) no personal medical history of cardiomyopathies.

Data were stored behind a hospital firewall at NHCS in accordance with the Personal Data Protection Act and other applicable laws. Data was anonymised and processed before being received by the author, who then performed data processing and statistical analysis. Socioeconomic status, diet, smoking, alcohol consumption, traditional Chinese medicine use and activity history were obtained as described previously.\(^8\)

Volunteers were issued a Fitbit Charge HR wearable activity tracker to be worn over 5 days. However, as the first and last days of the study tended to be partial days, the average yield for each study was 3.24 and 3.16 days of complete tracking in males and females, respectively. Complete tracking was defined as ≥ 20 h with steps and HR data. Data for each subject were obtained as described previously.\(^8\)
To determine data completeness, presence of HR data was used as an indicator that the subject was wearing the device. Heart rate values were merged with the steps table by the timepoints. Days with ≥20 valid hours were considered to be complete. Days with no step data were excluded. To determine Resting HR, the average HR value for timepoints that met the following criteria was calculated: (a) had ≤100 steps taken place within a 15-min interval and (b) had a valid HR value. To determine DailySteps, the average sum of steps that took place in data-complete days was calculated for each subject. DailySteps was used as a measure of wearable-derived physical activity for this study. Clinical and laboratory parameters were collected as described previously.\[^9\]

The SG FRS was used in this study, as several studies have shown that the US Framingham function overpredicts cardiovascular risk when applied to Asian populations, especially Chinese.\[^9,10\]\ The SG FRS was calculated according to the Ministry of Health (MOH) Clinical Practice Guidelines on Screening of Cardiovascular Disease and Risk Factors. The recalibrated SG FRS is used in the MOH Clinical Practice Guidelines on Lipids 2006. The risk scores in the Singapore MOH guidelines were derived from the Framingham-based National Cholesterol Education Program Adult Treatment Panel-III 10-Year Risk Score Tables, which were then modified to take into account the Singapore cardiovascular epidemiological data.

The following clinical markers were considered for calculation of SG FRS in this study: systolic blood pressure (SBP), total cholesterol and high-density lipoprotein (HDL). Other parameters considered were BMI, waist circumference, diastolic blood pressure (DBP), low-density lipoprotein (LDL), triglyceride, fasting blood glucose (FBG), urea, alkaline phosphatase and gamma-glutamyl transferase.

Moderately or severely elevated CACS was defined as an Agatston score ≥75\(^{th}\) percentile for each individual according to age- and gender-adjusted thresholds.\[^11\]\ For both SG FRS and US FRS, a score of ≤10 is considered ‘low’ risk, a score between 10 and 20 as ‘intermediate’ risk and a score >20 as ‘high’ risk. In this study, the cohort consisted of healthy individuals, which resulted in a very small percentage of ‘high-risk’ individuals. The ‘intermediate-’ and ‘high-risk’ groups were, therefore, merged to form an ‘InterHigh-’ risk group to be compared to the ‘low-’ risk group in the subsequent analysis. Coronary MRI and coronary non-contrast CT were performed as described previously.\[^9\]

For the primary analysis, 663 out of 800 volunteers were included, as only those of aged ≥30 years underwent coronary CT scan for calcium scoring. For the analysis including wearable metric data, 443 of 800 volunteers were included based on availability of data downloaded from the Fitbit API and after excluding missing and invalid data according to the criteria stated in the ‘Activity Tracking’ section.

All statistical analyses were performed using Statistical Analysis System (SAS) University Edition (SAS Institute Inc, Cary, NC, USA). Intermediate data processing and data cleaning were done in Python language. Variables with >20% missing values were excluded from analysis. Logistic regression analysis was used to assess multiple potential risk factors and identify a subset of ‘best’ independent predictors. Variables investigated included clinical parameters and lifestyle factors such as physical activity not accounted for in SG FRS. These predictors were used to improve SG FRS to predict the risk of MI based on the Agatston CACS high/low classification. Analyses were performed using both continuous and categorical forms of SG FRS. Continuous SG FRS scores (Risk) were reflected by an integer percentage risk FRS, while categorical SG FRS groups (RiskClass) were reflected as low-risk (≤10% continuous SG FRS) and intermediate-/ high-risk (>10% continuous SG FRS) groups.

Receiver operator characteristic (ROC) analysis was conducted to investigate predictive capabilities of the risk models for MI. The ROC curves based on SG FRS were compared to SG FRS+ and SG FRS++ alone [Figures S1 and S2, Supplemental Digital Appendix]. The SG FRS, SG FRS+ and SG FRS++ were compared to check for significant differences between ROC curves. Recalibration of SG FRS was done using multivariable logistic regression to predict a binary outcome of high/low Agatston. We also evaluated whether the SG FRS++ new risk model provided meaningful improvements in accuracy of risk classification. The net reclassification index (NRI) and two-sided 95% confidence interval were calculated.\[^12\]\ To determine NRI, we used cut-off points of 10% for 10-year risk of congenital heart disease (CHD) when using SG FRS and defined a threshold for high or low MI risk with the new SG FRS++ model determined from ROC analysis. All reported \(P\) values were two sided and statistically significant at \(P < 0.05\).

RESULTS

Summary statistics of the cohort containing 663 volunteers grouped by gender and Agatston CACS category, respectively, are shown in Table 1. Cohort median ages were 48.9 and 50.2 years in females and males, respectively (range 30–69 years), with a preponderance of females (366/663, 55.2%). Of note, there were no females in the intermediate-/high-risk FRS category.

Table 1 compares the baseline characteristics between males and females. Males had significantly higher BMI, waist circumference, blood pressure, lipids, FBG, Agatston and FRS scores compared to females. Wearable-derived activity levels did not differ significantly between males and females. Table 1 also compares the baseline characteristics between the high Agatston CACS group and the low Agatston CACS group. Volunteers with high Agatston CACS had significantly higher FRS, blood pressure, total cholesterol, FBG, ambulatory blood
| Characteristic | Mean ± SD (n (%)) | P* |
|---------------|------------------|----|
| Age (yr)      | 49.4 ± 9.15      |    |
| Weight (kg)   | 65.0 ± 13.8      |    |
| Height (cm)   | 1.64 ± 0.08      |    |
| Body mass index (kg/m²) | 23.6 ± 3.7 |    |
| Systolic blood pressure (mmHg) | 131.9 ± 11.0 |    |
| Diastolic blood pressure (mmHg) | 79.2 ± 13.9 |    |
| Total cholesterol (mmol/L) | 5.02 ± 0.82 |    |
| Low-density lipoprotein cholesterol (mmol/L) | 3.12 ± 0.34 |    |
| High-density lipoprotein cholesterol (mmol/L) | 0.94 ± 0.03 |    |
| Triglycerides (mmol/L) | 1.92 ± 0.56 |    |
| Fasting blood glucose (mmol/L) | 5.2 ± 0.93 |    |
| Alkaline phosphatase (mmol/L) | 4.44 ± 0.18 |    |
| ECG_HR (bpm) | 71.4 ± 11.0 |    |
| Resting_HR: wearable-derived resting heart rate | 71.1 ± 11.0 |    |
| Fitbit-derived DailySteps | 11,185 ± 4,520 |    |
| ABPM_HR: ambulatory blood pressure monitor-derived heart rate | 77.5 ± 12.8 |    |
| Morning_ABP: ambulatory blood pressure monitor-derived morning blood pressure | 77.5 ± 12.8 |    |
| Framingham Risk Score | 2.50 ± 0.39 |    |
| Agatston coronary artery calcium score | 47.7 ± 5.24 |    |

For continuous variables, Student's t-test was used whereas categorical values were evaluated using the chi-square test. Non-parametric test (Wilcoxon rank-sum test) and normalising transformation of variables were applied to the data. Significant for P < 0.05. ABPM_HR: ambulatory blood pressure monitor-derived heart rate, DailySteps: wearable-derived average daily steps, ECG_HR: electrocardiogram heart rate, SD: standard deviation, Valid_days: average valid days of data tracking using wearable-derived data.
pressure monitor-derived pulse rate and wearable-derived Resting_HR. Higher HRs potentially reflect poorer HR control. We also note that volunteers with high Agatston CACS showed higher activity levels (daily step counts).

Table 2 shows the results of the univariate logistic regression analysis performed, including SG FRS to identify potential predictors of high Agatston as a surrogate outcome of MI. In the multivariable analysis, DBP (odds ratio [OR] 1.026, 95% confidence interval [CI] 1.002–1.050), LDL (OR 1.458, 95% CI 1.016–2.092), FBG (OR 1.805, 95% CI 1.098–2.966), wearable-derived lnDailySteps (OR 2.561, 95% CI 1.168–5.612) and Resting_HR (OR 1.051, 95% CI 1.002–1.102) were identified as independent predictors for high Agatston, with statistical significance ($P < 0.05$).

In Figure S1 [see Supplemental Digital Appendix], we compared the area under the ROC curve (AUC) for the improved SG FRS+ which included selected variables (FBG, DBP, lnDailySteps, Resting_HR) with the basal AUC for SG FRS. Our results showed that additional variables such as FBG, DBP, LDL and wearable-derived metrics such as lnDailySteps and Resting_HR improved SG FRS for both categorical and continuous risk scores and increased the predictive value of both models (SG FRS+) in our healthy cohort.

Although SG FRS+ showed improved predictive capability for high Agatston, it remains that the original SG FRS may not be reflective of the present Singaporean population. This is in view that the SG FRS model was developed from an old study on a different cohort and coefficients for the original variables, such as age, gender, SBP, total cholesterol and HDL cholesterol, and thus may be outdated.

To recalibrate the coefficients of the original SG FRS while still incorporating additional variables with predictive capability to generate the final risk model (SG FRS++), we repeated the above logistic regression and ROC analyses using the variables in SG FRS as basal variables rather than the computed SG FRS score as the basal AUC [Figure S2, Supplemental Digital Appendix]. This allowed investigation of potential interactions between the newly incorporated variables such as DBP and FBG and the original variables such as age, gender, SBP, total cholesterol and HDL cholesterol, recalibrating the coefficients of the original variables in SG FRS. Although the statistically optimal cut-off was defined as $P = 0.15$ with a Youden index of 0.40 [blue dashed line in Figure S2], we lowered the predictive probability threshold from $P = 0.1$ with a Youden index of 0.40 [blue dashed line in Figure S2], increasing NPV from 91.1% to 93.1% for the 10-fold cross-validated, recalibrated and improved SG FRS++ model.

Recalibration for volunteers with and without events is summarised in Table 3, with interim data shown in Table S1 [see Supplemental Digital Appendix]. For 50 volunteers experiencing events (high Agatston as a surrogate outcome), classification improved using the SG FRS++ model, which was recalibrated to incorporate additional variables, and for two volunteers it became worse, resulting in a significant net reclassification gain of 0.219. The calculated NRI was 0.219 (95% CI 0.109, 0.329) ($P = 0.00254$).

### DISCUSSION

The primary aim of this study was to identify variables that are good predictors of high Agatston CACS—and hence MI risk—to augment SG FRS. Fasting blood glucose, DBP, wearable-derived Resting_HR and wearable-derived average daily steps (lnDailySteps) were found to be independent predictors of CHD risk. The improved model (SG FRS+) using basal SG FRS and incorporating the above variables resulted in a predictive model with a significantly improved predictive value ($AUC = 0.708$) for high Agatston and MI risk compared to the original SG FRS [Figure S1, Supplemental Digital Appendix]. Ultimately, the final model (SG FRS++) involved recalibration of the existing SG FRS variables and incorporation of the above variables, resulting in further improvement of predictive capability ($AUC = 0.774$) of high Agatston (hence the MI risk) compared to SG FRS+ [Figure S2, Supplemental Digital Appendix].

In our analysis, we made the decision to lower the predictive probability threshold to attain a higher NPV in our SG FRS++ model. This decision was made considering the clinical implications of erroneously classifying a high-risk individual to the low-risk group. The benefit of this decision is a lowered risk of adverse outcomes due to additional follow-up consultations and implementation of primary prevention strategies.

We report a further improvement in the predictive capability of SG FRS after incorporation of variables shortlisted from the SingHEART database. Even though DBP and LDL are known to correlate with existing FRS variables such as SBP,
Table 2. Univariate and multivariable logistic regression analyses to identify potential predictors for high Agatston score.

| Variable | Univariate OR (95% CI) | P       | Multivariable adj. OR (95% CI) | P       |
|----------|------------------------|---------|--------------------------------|---------|
| Singapore-adapted FRS (Risk) | 1.076 (1.020, 1.135) | 0.0069  |                                |         |
| Singapore-adapted Framingham Risk Class (RiskClass) |  |  |                                |         |
| Low risk | 1.00 | 0.7054 | 1.00 | -  |
| Intermediate and high risk | 1.192 (0.480, 2.962) |         | 0.642 (0.161, 2.555) | 0.5297  |
| Gender |  |  |                                |         |
| Female | 1.00 | 0.0339 |                                |         |
| Male | 1.573 (1.035, 2.392) |         |                                |         |
| Age | 1.064 (1.038, 1.091) | <0.001  |                                |         |
| SBP | 1.033 (1.021, 1.046) | <0.001  |                                |         |
| DBP | 1.046 (1.029, 1.065) | <0.001  |                                |         |
| Total cholesterol | 1.477 (1.192, 1.831) | <0.001  |                                |         |
| HDL cholesterol | 1.678 (0.914, 3.078) | 0.0948  |                                |         |
| LDL cholesterol | 1.477 (1.154, 1.892) | 0.0020  | 1.458 (1.016, 2.092) | 0.0407* |
| Triglycerides | 1.190 (0.899, 1.575) | 0.2235  |                                |         |
| Fasting blood glucose | 1.657 (1.229, 2.233) | 0.0009  | 1.805 (1.098, 2.966) | 0.0198* |
| Urea | 1.213 (1.013, 1.453) | 0.0359  |                                |         |
| ECG_HR | 1.023 (1.002, 1.045) | 0.0338  |                                |         |
| LVMass | 1.020 (1.010, 1.030) | <0.001  |                                |         |
| Fitbit-derived DailySteps | 1.000 (1.000, 1.000) | 0.0352  |                                |         |
| Fitbit-derived ln(DailySteps) | 2.412 (1.190, 4.890) | 0.0146  | 2.561 (1.168, 5.612) | 0.0188* |
| Fitbit-derived Resting_HR | 1.058 (1.015, 1.103) | 0.0076  | 1.051 (1.002, 1.102) | 0.0414* |
| Marital status |  |  |                                |         |
| Married | 1.00 | 0.1288 |                                |         |
| Separated/divorced | 2.052 (0.774, 5.439) |         |                                |         |
| Single | 0.603 (0.318, 1.146) |         |                                |         |
| Widowed | 2.052 (0.392, 10.750) |         |                                |         |
| Coffee consumption |  |  |                                |         |
| Never/rarely | 1.00 | 0.2208 |                                |         |
| <1 cup a week | 1.664 (0.685, 4.042) |         |                                |         |
| ≥1 cup a week but≤1 cup a day | 1.808 (1.031, 3.172) |         |                                |         |
| Others | 1.571 (0.873, 2.829) |         |                                |         |
| Tea consumption in cups per day |  |  |                                |         |
| Chinese tea | 1.293 (0.998, 1.675) | 0.0515  |                                |         |
| Green tea | 1.234 (0.966, 1.577) | 0.0930  |                                |         |
| Tea consumption |  |  |                                |         |
| English tea weekly |  |  |                                |         |
| Never/rarely | 1.00 | 0.2324 |                                |         |
| <1 cup a week | 0.368 (0.090, 1.500) |         |                                |         |
| ≥1 cup a week but≤1 cup a day | 0.278 (0.060, 1.290) |         |                                |         |
| Others | 0.588 (0.124, 2.785) |         |                                |         |
| Chinese tea weekly |  |  |                                |         |
| Never/rarely | 1.00 | 0.1618 |                                |         |
| <1 cup a week | 0.657 (0.341, 1.265) |         |                                |         |
| ≥1 cup a week but≤1 cup a day | 1.126 (0.656, 1.933) |         |                                |         |
| Others | 2.186 (0.872, 5.480) |         |                                |         |
| Green tea weekly |  |  |                                |         |
| Never/rarely | 1.00 | 0.1442 |                                |         |
| <1 cup a week | 0.879 (0.482, 1.603) |         |                                |         |
| ≥1 cup a week but≤1 cup a day | 0.920 (0.538, 1.572) |         |                                |         |
| Others | 2.175 (1.049, 4.506) |         |                                |         |
| Smoking in pack-years | 1.027 (0.997, 1.058) | 0.0801  |                                |         |

Contd...
Table 2. Univariate and multivariable logistic regression analyses to identify potential predictors for high Agatston score.

| Variable                                      | Univariable Analysis | Multivariable Analysis |
|-----------------------------------------------|----------------------|------------------------|
| Age                                           | Yes                  | Yes                    |
| Sex                                           | Yes                  | Yes                    |
| Smoking status                                | Yes                  | Yes                    |
| Diabetes status                               | Yes                  | Yes                    |
| Hypertension                                 | Yes                  | Yes                    |
| Hypercholesterolemia                          | Yes                  | Yes                    |
| Diabetes status                               | Yes                  | Yes                    |
| Hypertension                                 | Yes                  | Yes                    |
| Hypercholesterolemia                          | Yes                  | Yes                    |
| Diabetes status                               | Yes                  | Yes                    |
| Hypertension                                 | Yes                  | Yes                    |
| Hypercholesterolemia                          | Yes                  | Yes                    |

The traditional Framingham risk function only accounts for the presence or absence of a formal diagnosis of DM but fails to take into account prediabetic individuals with impaired glucose tolerance or impaired fasting glucose. These early metabolic abnormalities in glucose regulation, such as insulin resistance and impaired insulin secretion, are associated with CVMD and higher risk of development of DM. Impaired fasting glucose has predictive value for all-cause mortality and CVD risk independent of other CVD risk factors which are traditionally used to calculate SG FRS. Non-diabetic individuals have different risk levels for CHD, which are not accounted for in SG FRS. Studies have shown that the relationship between glucose levels and CVD risk extends below the diabetic threshold. Using a risk prediction method which includes glucose as a risk factor has also been shown to improve the risk prediction for cardiovascular mortality. Similarly, in our cohort, we identified FBG as a predictor for high Agatston, which improves the predictive capability of existing SG FRS for CHD and MI risk.

Our results have several important implications. First, we showed that information on the prediabetic state — such as FBG levels — provides important discriminative value to the risk stratification of a healthy, non-diabetic cohort. Prediabetic individuals in healthy cohorts can then be offered more aggressive interventions, such as lifestyle interventions, to treat their hyperglycaemia and other risk factors. Early identification of the prediabetic state and implementation of intervention strategies are important steps in the progress on we have shown that they still serve as independent predictors of CHD risk, even after recalibration of the original SG FRS.

The ideal risk stratification model should have a good balance of complexity and utility, and adding variables to a risk stratification model increases the complexity of the clinical tool. It is necessary to examine the clinical and public health implications involved, and hence, further studies to investigate the additional burden of obtaining the extra variables are needed. If the cost is low, it might be worth including these additional variables in the risk prediction model. Therefore, we suggest that additional variables may be incorporated into CHD risk stratification for healthy cohorts, as they provide the additional discriminative value to group these individuals into low- or high-risk group.
the War on Diabetes, which was launched in MOH Singapore in 2016 in response to the significant health and societal burden posed by DM.

SG FRS has been used to identify Singaporeans at high cardiovascular risk for preventive care and disease management. When used in a healthy Singaporean cohort, as in this study, incorporating additional variables can provide important discriminative value to improve SG FRS as a clinical tool (AUC = 0.641). We found that the recalibrated and improved function (SG FRS++) showed greater predictive capability for the risk of MI compared to SG FRS+, raising AUC from 0.704 to 0.774. Even after the 10-fold cross-validation, SG FRS++ AUC still maintained useful predictive capability (AUC = 0.721).

We showed that the recalibrated and improved SG FRS++ significantly improved risk prediction accuracy and identified high-risk individuals who were previously classified as low risk (NRI = 0.219). Identifying such high-risk individuals at improved accuracy is an important strategy for primary prevention of CVD. Currently, SG FRS is used to calculate cardiovascular risk to guide important clinical management, such as the initiation of statin therapy for high-risk individuals. We suggest that individuals with high SG FRS++ risk scores can be advised to start empirical medical treatment, more aggressive treatment of their underlying risk factors or to undergo additional testing for CVD.

Sedentary lifestyle is associated with higher risk of CVMD, and obtaining patient history on their physical activity is important for risk stratification. Although self-reporting measures via questionnaires are useful, wearable technology measuring actual motion of the body rather than participant recollections and perceptions of activity, which are subject to bias, can provide more objective and accurate measures of activity levels.\textsuperscript{[15]}
Coupled with the recent advancements in wearable technology, personal fitness tracking is becoming increasingly affordable and used by the population.[16] Our results showed that wearable-derived activity level data improved the discriminatory ability of existing CVD risk stratification methods. However, this large pool of continuously logged objective wearable health data is not actively used for risk stratification purposes by clinicians or researchers. To increase the accuracy of risk stratification based on lifestyle and activity patterns, we suggest adopting the use of wearable metric data for monitoring activity levels and other health metrics of patients in the community setting.

Based on NRI and its components, we conclude that our new model SG FRS++, which includes recalibration and additional variables, improved classification for a net of 21.9% in our Singapore cohort. This improvement is comparable or even superior to the NRI found in other similar studies—albeit in Western cohorts — which investigated the incorporation of biomarkers to augment FRS, reporting NRI of 20.7[12] and 12.1.[17]

Our findings suggest that the existing guidelines by MOH Singapore, which utilise SG FRS for CHD risk prediction, need to be updated to improve our risk classification methods. There are several reasons for this. First, patient demographics and underlying risk factors have changed since the last risk function recalibration. In addition, new data types such as wearable-derived metrics are now available and have been shown to improve existing risk prediction models. Finally, we have identified the prediabetic state, which has not been considered in previous risk functions, as an important risk factor for CHD and MACE.

The present study has some limitations. First, high/low classification of Agatston CACS is only a surrogate outcome for MI. Ideally, actual MI outcome data should be used to build the predictive model. Using Agatston as a surrogate outcome is less ideal, but still necessary at this point to identify potential predictors of MI risk and to guide clinical practice before outcome data is available in the future. Second, there were no females allocated to the high-risk group according to SG FRS. Third, our study population consisted mostly of Chinese (93.8%), which is an overrepresentation of the proportion of Chinese in the Singaporean population (75%).[18] With underrepresentation of other ethnic groups such as Indians, Malays and other races in our study cohort, we were unable to accurately determine ethnic differences. Lastly, even though this study showed that short duration of tracking (3 days) was sufficient to observe associations, perhaps longer tracking periods would prove to be even more useful to improve the power of detecting associations between activity and calcium scores.

In conclusion, updating SG FRS is necessary to account for the demographic changes and risk factors which contribute to higher CHD risk in the Singaporean population. This can be done via recalibration and incorporation of additional variables, which impart additional discriminative value but at the cost of increased complexity. By adopting the use of wearable health metric data in risk stratification, access can be obtained to a large pool of objective and continuously logged health data obtained from patients in the community setting. To strike a balance between complexity and utility of risk prediction tools, we suggest that additional variables such as FBG be considered for CHD risk stratification in healthy cohorts. Further studies on the utility of proactive screening in healthy cohorts and follow-up studies using data from the SingHEART database to re-evaluate the improved Framingham risk model using actual outcome data are warranted.

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Conflicts of interest
There are no conflicts of interest.

Supplemental digital content
Appendix at http://links.lww.com/SGMJ/A81

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APPENDIX

Table S1 — Cross tabulation tables of reclassification of volunteers using the old model SG FRS and new model SG FRS++, grouped by events and non-events using Agatston coronary artery calcium score as a surrogate outcome.

| Old Model (SG FRS) | Intermediate model (SG FRS+) |  |
|-------------------|-------------------------------|---|
|                    | Low          | High | Column total |
| Events (high Agatston) (n=105) |               |     |             |
| Low                | 45           | 54   | 99          |
| InterHigh          | 2            | 4    | 6           |
| Row Total          | 47           | 58   | 105         |

54 events correctly reclassified to high risk; 2 events incorrectly reclassified to low risk; 49 events not reclassified

Net of 49.52% (52/105) of events correctly reclassified by the intermediate model SG FRS+

| Non-events (Low Agatston) (n=558) |          |     |             |
|----------------------------------|----------|-----|-------------|
| Low                              | 341      | 190 | 531         |
| InterHigh                        | 15       | 12  | 27          |
| Row Total                        | 356      | 202 | 558         |

190 non-events incorrectly reclassified to high risk; 15 non-events correctly reclassified to low risk; 353 non-events not reclassified

Net of 31.36% (175/558) of non-events incorrectly reclassified by the intermediate model SG FRS+

\[
\text{NRI} = \left( \frac{54}{105} - \frac{2}{105} \right) + \left( \frac{15}{558} - \frac{190}{558} \right) = 18.16\%
\]

NRI was done to determine if the intermediate model SG FRS+ provides improvements in risk prediction. NRI (95% CI) was 0.182 (0.0703, 0.2929), indicating a statistically significant net improvement in accuracy of risk classification by the new model SG FRS+ ($P = 0.0165$). NRI: net reclassification index, SG FRS: Singapore-adapted Framingham Risk Score
Figure S1 – ROC curves based on the improved Framingham model (SG continuous FRS+) compared to the Singapore adapted continuous Framingham Risk Score (SG continuous FRS) alone. Both curves are based on logistic regression models using the SG continuous FRS with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR). AUC indicates area under curve.

Logistic regression myocardial infarction linear predictor:

\[ y = -19.3011 + 0.0257 \cdot \text{Risk} + 0.6147 \cdot \text{Glucose} + 0.0265 \cdot \text{DBP} + 1.0200 \cdot \ln(\text{DailySteps}) + 0.0400 \cdot \text{Resting_HR} \]

Predicted probability of myocardial infarction: \[ p = \frac{e^y}{1 + e^y} \]

| Predicted probability Agatston ≥ 75th percentile | Sensitivity | Specificity | PPV | NPV | Youden Index |
|-------------------------------------------------|-------------|-------------|-----|-----|--------------|
| 0.13                                            | 0.77976     | 0.49132     | 0.24725 | 0.91236 | 0.27108 |
| 0.14                                            | 0.74405     | 0.55391     | 0.26327 | 0.91001 | 0.29796 |
| 0.15                                            | 0.72768     | 0.59723     | 0.27887 | 0.91110 | 0.32491 |
| 0.16                                            | 0.69271     | 0.62653     | 0.28429 | 0.90501 | 0.31924 |

High Agatston calcium score (High MI risk)

Low Agatston calcium score (Low MI risk)

Youden index 'optimal' cut-point for 'low' vs 'high' risk of myocardial infarction (using Agatston calcium score as a surrogate outcome) Predicted Probability = 0.15
**Figure S2** – ROC curves based on the improved and recalibrated Framingham model (SG continuous FRS++) compared to the Singapore adapted continuous Framingham Risk Score (SG continuous FRS) alone. Both curves are based on logistic regression models using variables from the SG continuous FRS (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking) with and without the additional variables incorporated (Glucose, DBP, lnDailySteps, Resting_HR). AUC indicates area under curve.

Logistic regression myocardial infarction linear predictor:

\[
y = -23.9046 + 0.0527 \cdot \text{Age} + 0.2774 \cdot \text{Gender} + 0.00282 \cdot \text{SBP} + 0.1705 \cdot \text{Cholesterol_Total} + 1.1040 \cdot \text{Cholesterol_HDL} + 0.4671 \cdot \text{Smoking(Previously=1, Yes/No=0)} - 0.1120 \cdot \text{Smoking(Yes=1, Previously/No=0)} + 0.5548 \cdot \text{Glucose} + 0.0349 \cdot \text{DBP} + 0.0498 \cdot \ln \text{DailySteps} + 0.8632 \cdot \ln \text{DailySteps}
\]
Supplemental Digital Content: Yeo, et al. Improving the predictive capability of Framingham Risk Score for risk of myocardial infarction based on coronary artery calcium score in healthy Singaporeans. Singapore Med J

**Predicted probability of myocardial infarction:** $p = \frac{e^y}{1 + e^y}$

| Predicted probability Agatston ≥ 75th percentile | Sensitivity | Specificity | PPV    | NPV    | Youden Index |
|------------------------------------------------|------------|------------|--------|--------|--------------|
| 0.09                                           | 0.90625    | 0.40954    | 0.24426 | 0.95399 | 0.31579      |
| **0.10**                                       | **0.86393**| **0.45984**| **0.25196** | **0.94166** | **0.32377** |
| 0.11                                           | 0.83807    | 0.51196    | 0.26556 | 0.93759 | 0.35003      |
| 0.12                                           | 0.82813    | 0.54441    | 0.27682 | 0.93766 | 0.37253      |
| 0.13                                           | 0.82500    | 0.57664    | 0.29096 | 0.93995 | 0.40164      |
| 0.14                                           | 0.78613    | 0.61123    | 0.29875 | 0.93140 | 0.39736      |
| 0.15                                           | 0.75426    | 0.64892    | 0.31133 | 0.92627 | 0.40318      |
| 0.16                                           | 0.70313    | 0.66118    | 0.30406 | 0.91364 | 0.36431      |
Figure S3 – 10-fold cross validation analysis ROC curve based on the improved and recalibrated Framingham model (SG continuous FRS++). The curve is based on logistic regression models using variables from the SG continuous FRS (Age, Gender, SBP, Cholesterol_Total, Cholesterol_HDL, Smoking) with and without the additional variables incorporated (Glucose, DBP, InDailySteps, Resting_HR). AUC indicates area under curve.

| High Agatston calcium score (High MI risk) | Low Agatston calcium score (Low MI risk) |
|------------------------------------------|----------------------------------------|
| TN                                       | FP                                     |
| 15                                       | 15                                     |
| 10                                       | 10                                     |
| 5                                        | 5                                      |
| 1                                        | 1                                      |
| 0                                        | 0                                      |
| FN                                       | TP                                     |
| 0                                        | 0                                      |
| 1                                        | 1                                      |
| 5                                        | 5                                      |
| 10                                       | 10                                     |
| 15                                       | 15                                     |
| 20                                       | 20                                     |

Youden index 'optimal' cut-point for 'low' vs 'high' risk of myocardial infarction (using Agatston calcium score as a surrogate outcome)
Predicted Probability = 0.15
| Predicted probability Agatston ≥ 75<sup>th</sup> percentile | Sensitivity | Specificity | PPV  | NPV  | Youden Index |
|---------------------------------|------------|-------------|------|------|--------------|
| 0.06                            | 0.94370    | 0.26935     | 0.21384 | 0.95831 | 0.21305      |
| 0.07                            | 0.88739    | 0.32000     | 0.21553 | 0.93092 | 0.20739      |
| 0.08                            | 0.87144    | 0.36111     | 0.22312 | 0.93034 | 0.23256      |
| 0.09                            | 0.83417    | 0.39767     | 0.22578 | 0.91942 | 0.23183      |
| 0.10                            | 0.81300    | 0.45233     | 0.23812 | 0.91964 | 0.26533      |
| 0.11                            | 0.80500    | 0.50000     | 0.25311 | 0.92403 | 0.30500      |
| 0.12                            | 0.79033    | 0.53642     | 0.26419 | 0.92400 | 0.32675      |
| 0.13                            | 0.74467    | 0.56642     | 0.26557 | 0.91340 | 0.31108      |
| 0.14                            | 0.71688    | 0.60650     | 0.27732 | 0.91051 | 0.32338      |
| 0.15                            | 0.70300    | 0.63820     | 0.29035 | 0.91079 | 0.34120      |
| 0.16                            | 0.68314    | 0.65357     | 0.29337 | 0.90740 | 0.33671      |