Masters Athlete Screening Study (MASS): incidence of cardiovascular disease and major adverse cardiac events and efficacy of screening over five years

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ABSTRACT

Background: The efficacy of cardiovascular screening in Masters athletes (MAs) (≥ 35y), and whether screening decreases their risk of major adverse cardiac events (MACE) is unknown.

Purpose: To evaluate the effectiveness of yearly cardiovascular screening, and the incidence of cardiovascular disease (CVD) and MACE over five years.

Methods: MAs (≥35 y) without previous history of CVD underwent yearly cardiovascular screening. Participants with an abnormal screen underwent further evaluations.

Results: In the initial year, 799 MAs (62.7% male, 55±10y) were screened; 11.4% (n=91) were diagnosed with CVD. Coronary artery disease (CAD) was the most common diagnosis (n=64; 53%). During follow-up, there were an additional 89 CVD diagnoses with an incidence rate of 3.58/100, 4.14/100, 3.74/100, 1.19/100, for years one to four, respectively. The most common diagnoses during follow-up were arrhythmias (n=33; 37%). Increasing age (OR=1.047, 95% confidence interval (CI): 1.003-1.094; p=0.0379), Framingham Risk Score (FRS) (OR=1.092, 95%CI: 1.031-1.158; p=0.003), and LDL cholesterol (OR=1.709, 95%CI: 1.223–2.401; p=0.002) were predictive of CAD, whereas moderate intensity activity (min/wk) (OR=0.997, 95%CI: 0.996-0.999; p=0.002) was protective. Ten MACE (2.8/1,000 athlete-years) occurred. All of these MAs were male, and 90% had ≥10% FRS. All underwent further evaluations with only two identified to have obstructive CAD.

Conclusion: MACE occurred despite yearly screening. All MAs who had an event had an abnormal screen; however, cardiac functional tests failed to detect underlying CAD in most cases.

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Keywords: Masters athletes, cardiovascular risk, cardiovascular screening, major adverse cardiac events, coronary artery disease, atrial fibrillation

INTRODUCTION

Masters athletes (MAs) (≥ 35y) are a rapidly growing population that participate in a variety of sports at a competitive level or for leisure activity. Regular physical activity has tremendous health benefits, including primary and secondary prevention in several medical conditions (e.g., coronary artery disease (CAD), diabetes, hypertension, obesity, and premature death).[1] Although regular physical activity reduces ones risk of developing such medical conditions, studies have shown that those with a lifelong exercise history have increased coronary artery calcium (CAC) and atrial fibrillation compared to the general population.[2-7] In a controlled study, male athletes had a higher prevalence of coronary plaques and higher prevalence of a high atherosclerotic burden (≥50% luminal stenosis) compared to sedentary males (44% vs 22% and 7.5% vs. 0%, respectively).[4] There was no difference in prevalence of CAD between female athletes and sedentary females.[4] Additionally, the odds of having atrial fibrillation is doubled in endurance athletes compared to the general population (OR=2.34, 95% CI:1.04-5.28).[3]

The incidence rates of sports-related sudden cardiac death (SCD) is low (4.6 cases per million per year), with recreational MAs comprising the majority (>90%) of these deaths.[8] This incidence rate does not include non-fatal events such non-fatal myocardial infarctions (MI) and stroke. Cardiovascular screening aims to identify cardiovascular risk factors and underlying cardiovascular disease (CVD) that may precipitate a major adverse cardiac event (MACE) (sudden cardiac arrest (SCA), SCD, fatal or non-fatal MI, stroke). The American Heart Association and European Society of Cardiology, agree that screening is justifiable and compelling on ethical, legal and medical grounds to identify underlying CVD. However, the

optimal screening protocol and frequency of screening remains in question, and has not been systematically evaluated.[9-13]

Current guidelines for CVD screening in MAs recommend consideration of an electrocardiogram (ECG) (rest and exercise), cardiovascular physical examination (i.e., cardiac auscultation, blood pressure), personal symptom assessment, family history, sport history, and comprehensive cardiovascular risk assessment including risk scoring (i.e., Framingham Risk Score (FRS).[10, 11, 13, 14] The FRS estimates a patient's 10-y risk of experiencing a MACE based on age, sex, total cholesterol, high-density lipoprotein (HDL) cholesterol, blood pressure, smoking history, presence of diabetes and family history of premature CVD.[14] Routine use of more advanced imaging investigations such as computed coronary tomography angiography (CCTA) in asymptomatic MAs with a normal exercise stress test (EST) is not recommended. However, in asymptomatic MAs with a high cardiovascular risk, a functional imaging test or CCTA may be considered.[13] The higher prevalence of CAD in the MA population raises the question on whether non-invasive cardiovascular imaging techniques, such as CCTA and/or coronary artery calcium score (CACS) should be included in the screening process to add diagnostic and prognostic value in those with no known CVD by improving long-term risk stratification.[12, 15-18]

The current study aimed to evaluate the efficacy of yearly cardiovascular evaluations and report the incidence of CVD and MACE over a 5-year period.

METHODS

Study Population and Design

This observational longitudinal study builds on an initial dataset *('initial year')* obtained from the cross-sectional study, with the addition of four years of follow-up *('follow-up years').*[19] The study occurred between April 2015 – November 2019 throughout British Columbia, Canada. From the initial population (n=799), 726 MAs participated in the present follow-up study with yearly attrition as outlined in Figure 1. The study design and population has been previously described.[19] Briefly, eligible participants, had to engage in moderate to vigorous intensity physical activity at least three days per week during the preceding three months. Those with known CVD at baseline were excluded.

Participants underwent cardiovascular screening on a yearly basis and followed three stages (Figure 2) **Stage 1**) baseline assessments (questionnaire to ascertain cardiac-related symptoms and family history, new CVD (diagnosed "outside of the study") and MACE, medications, and physical activity (type of activities, frequency, intensity and duration); resting 12-lead electrocardiogram (ECG); resting blood pressure; anthropometrics (height, weight, waist circumference); FRS (initial year, follow-up years one and two only); **Stage 2**) EST; **Stage 3**) consultation with a sports cardiologist and further evaluations if required. Masters athletes with an abnormal baseline assessment (Supplementary Material) progressed to Stage 2 and and/or Stage 3. Those with an abnormal EST also progressed to Stage 3. Sports cardiologists determined if subsequent evaluations were necessary based on their clinical discretion in a shared decision-making approach with the participant-athlete. The final decision to undergo further examination (i.e., CCTA, CACS, echocardiography, stress echocardiography, myocardial perfusion imaging (MIBI), cardiac magnetic resonance imaging (CMR), cardiac catheterization, Holter monitor, ambulatory blood pressure (ABP)) was based on the shared decision between the cardiologist and participant. Masters athletes diagnosed

with CVD at any timepoint continued in the study with yearly assessments and were followed clinically (additional evaluations performed at the discretion of the cardiologist). All ECGs (Mortara Instrument, Milwaukee, WI) were interpreted using the 'International Recommendations for Electrocardiographic Interpretation in Athletes'.[20] In the fourth year, due to COVID-19, all MAs completed the questionnaire; however, only a portion completed the ECG (n=131), blood pressure (n=444), weight (n=637) and waist circumference (n=613) measurements. Masters athletes that withdrew at any time point during the study received the lost to follow-up questionnaire to determine MACE and vital status. There was a total of 136 MAs that received the lost to follow-up questionnaire. Of those, 74.3% completed it resulting in 4.4% patients in whom we do not know cardiac events or vital status (Figure 1).

Outcome Measures

The primary outcomes were incidence of MACE (SCA/SCD, MI, stroke) and new diagnoses of CVD divided into four sub-groups (CAD, arrhythmias (high PVC burden, atrial fibrillation/flutter, supraventricular tachycardia), aortic dilatation, valvular heart disease and other CVD (hypertrophic cardiomyopathy, dilated cardiomyopathy, coronary artery anomalies, myocarditis, and inherited electrical abnormalities (e.g. long QT syndrome)) (Supplementary Material S2). Masters athletes were included in the four-year incidence for CVD if they were diagnosed with CVD through the screening process and subsequent tests ordered by study physicians. Masters athletes that were diagnosed outside of the screening protocol (i.e., their family physician ordered the test and a CVD diagnosis resulted or CVD was discovered incidentally when diagnostic tests were ordered for other reasons were not included in the four-year incidence, but reported separately as "false-negatives".

Statistical Analysis

All parameters were checked for normality visually and tested using Shapiro-Wilk test. Continuous variables were expressed as means and standard deviations when normally distributed or as median (interquartile range) when not normally distributed. Frequency tables were generated for all categorical data and reported as number of participants (n) and percentage (%). Chi-square test were used to compare differences between categorical variables. Group differences were tested with an independent sample t-test or Mann-Witney U test for normally and non-normally distributed continuous variables, respectively. Analysis of variance (ANOVA) and the Kruskal-Wallis tests were used to compare means between more than one group for normally and non-normally distributed variables, respectively. Bonferroni was performed as a post-hoc to evaluate differences between more than two groups. A binary logistic regression analysis was performed to calculate odds ratios (OR) of risk factors associated with the presence CAD and arrhythmias. The variables of interest that were included in the modelling are included in Supplementary Material S3. The dataset was aggregated over the entire time period (including the initial year) depending on whether they were diagnosed with CAD or arrhythmias (including those detected outside of the study ("false-negatives") and those that had a MACE), or not. These aggregations involve aggregating all variables of interest across all timepoints pre-diagnosis up to the first diagnosis for those that were diagnosed (or had a MACE).

Statistical analysis was performed using SPSS software Version 27.0.1.0 (IBM Corp. Armonk, NY) or Excel Version 16.49 (Microsoft Corp. Redmond, WA). R statistical software[21] was used for regression analysis. Those with missing data were not included in the sample size for the associated variable and the mean, median or percentage was adjusted accordingly.

Ethics approval was granted by the University of British Columbia's Clinical Research Ethics Board (H15-00009) in accordance with the declaration of Helsinki. All participants provided written informed consent prior to enrolment.

RESULTS

Study Population

Over the mean follow-up time of 4.82±0.76y there were a total of 3594 athlete-years (Figure 1). Participant characteristics over the entire study are displayed in Table 1. Systolic and diastolic blood pressure decreased after the initial year. HDL, low-density lipoprotein (LDL), and HDL:total cholesterol ratio significantly improved between the initial year and year two of follow-up. Concomitantly, the number of participants taking lipid-lowering and anti-hypertensives increased each year, however, some participants who met the criteria for medication declined to initiate treatment. There were eight non-cardiac adverse events and three non-cardiac related deaths; two from cancer and one from a brain aneurysm (Supplementary Material S4).

Major Adverse Cardiac Events

Ten MACE occurred over the study period with an incidence of 2.8 MACE per 1,000 athlete years (Table 2). Five MIs with subsequent percutaneous coronary intervention, three strokes (one athlete had two strokes), one exertional SCD, and one presumed non-exertional SCD. The mean age of those that experienced a MACE was 63.6±12.5y; 100% male and the mean maximal METs achieved on EST was 13.4±3.4 (high fitness). Seven MAs had an intermediate FRS, one had a high FRS, and one had a low FRS (40y, father had coronary artery bypass

grafting at 55y). Out of the five MAs who had an MI, two were on lipid-lowering therapy due to positive secondary tests (one had a positive MIBI and the other underwent CCTA secondary to a positive EST to assist in the decision-making process and discovered obstructive CAD). The three MAs who did not initiate lipid-lowering therapy, two had a negative EST and one had a positive EST but negative MIBI. In the two MAs who died, both had a negative EST, with one of the MAs also having a negative stress echocardiogram. Neither of these MAs had initiated lipid-lowering therapy. In the two MAs who had a stroke, one had initiated lipid-lowering therapy after obstructive CAD was discovered on CCTA, and one did not undergo further testing after a negative EST.

Detection of Cardiovascular Disease

Over the entire study period, there were a total of 207 (61.2±8.2y; 79% male) CVD diagnoses occurring in 165 MAs (35 MAs diagnosed with >1 form of CVD) (Figure 3). Fifty-eight percent (n=120) of diagnoses occurred in the initial screening year with CAD as the predominant diagnosis (53%). There were 87 CVD diagnoses (63.3±8.0y, 69% male) made on subsequent screening during the four years of follow-up (26, 28, 25, and 5 in years one to four, respectively). The overall incidence of CVD diagnoses was 3.58, 4.00, 3.59 and 1.19 per 100-athete years, for years one to four, respectively. Arrhythmias were the most common diagnoses during the follow-up years (n=32; 37%).

Male MAs were approximately four-times more likely to be diagnosed with CVD compared to female MAs. Specifically, males were more likely to be diagnosed with CAD (85.2% vs. 14.8%), arrhythmias (83.0% vs. 17.0%), aortic dilatation (74.3% vs 25.7%), valvular heart disease (76.7% vs 23.3%) and other CVD (53.8% vs 46.2%) compared to females. When females were

examined for the influence of menopause on the presence of CAD, there was no statistical differences in the presence of CAD based on menopause status (p=0.361). However, there were only 13 females diagnosed with CAD during the study. Out of these 13 female MAs that were diagnosed with CAD, 6 (46.2%) had started menopause less than 10 years ago, 5 (38.5%) had started menopause more than 10 years ago and 2 (7.7%) had a hysterectomy. Coronary artery disease in females was predominately non-obstructive (n=11; 84.6%).

The first stage of the screening process was abnormal in 513 (63.4%), 190 (26.2%), 173 (24.7%), 153 (21.2%) and 103 (15.3%) MAs in the initial year to follow-up year four, respectively (Figure 1). These MAs progressed to stage two of the screening process where an EST was performed in 498 (62.3%), 84 (11.6%), 100 (14.3%), 76 (10.9%), and 37 (5.5%) MAs in the initial year to follow-up year four, respectively. A total of 347 (43.4%), 166 (22.9%), 146 (20.9%), 134 (19.3%) and 100 (14.9%) MAs progressed to stage three of the screening process (cardiologist follow-up) in the initial year to follow-up year four, respectively. Overall, there were 1,132 abnormal screens resulting in 207 CVD diagnoses over the entire study period, an abnormal screen resulted in a diagnosis 18.3% of the time.

The most common screening indicators that warranted a follow-up were a high cardiovascular risk (27%), symptoms (angina, dyspnea, syncope, or exertional fatigue) (17%), and an abnormal ECG (13%) (Figure 4a). The screening indicators that were the most prevalent in those diagnosed with CAD was a high cardiovascular risk (37%), an abnormal ECG (14%), and age (> 65y) (13%) (Figure 4c). The screening indicator that was the most prevalent in those diagnosed with an arrhythmia was high cardiovascular risk (24%), an abnormal ECG (20%) and palpitations (13%) (Figure 4d), and those diagnosed with valvular heart disease, high

cardiovascular risk (24%), palpitations (15%) and a heart murmur (14%) were the most prevalent (Figure 4e). In those in which aortic dilation was detected incidentally, the most prevalent abnormal screening indicators were high cardiovascular risk (26%) and age (> 65y) (Figure 4f).

Twenty-one MAs (86% male) were diagnosed outside of the screening protocol with CVD (four with obstructive CAD, four with non-obstructive CAD, three with unknown CAD severity, one with cerebrovascular disease, five with atrial fibrillation, three with atrial flutter, one genotype positive/phenotype negative hypertrophic cardiomyopathy) (Supplementary Material S5). Most (75%) of these MAs with CAD (obstructive and non-obstructive) had an intermediate FRS and a negative EST.

Exercise Stress Test

The mean maximal METs achieved for all ESTs performed was 14.1±2.8. A summary of the diagnostic utility of the EST in those diagnosed with CAD, coronary artery anomalies and myocardial bridging is presented in Supplementary Material S6. Three (23%) MAs with significant CAD and eight (57%) MAs with moderate CAD had a negative EST. A CCTA was ordered in these MAs due to a high FRS or a strong family history as it was believed that shared decision-making would result in behaviour modification if CAD was discovered (Supplementary Material S7). After identification of CAD in these MAs, all except one MA initiated lipid-lowering therapy. There were 13 MAs that had a positive EST, who were not diagnosed with CAD. Of these, five (27.8%) did not undergo further testing (i.e., initiated medication or declined testing), six (33.3%) underwent MIBI (all negative), one (5.6%) had a stress echocardiogram (negative), and one (5.6%) had a CCTA (negative).

Determinants of CAD and Arrhythmias

Risk factors for CAD were increasing age (y) (OR=1.047, 95% CI:1.003-1.094; p=0.0379)), FRS (%) (OR=1.092, 95% CI:1.031-1.158; p=0.003), and LDL cholesterol (mmol/L) (OR=1.709, 95% CI:1.223-2.401; p=0.002), whereas moderate intensity activity (minutes/week) (OR=0.997, 95% CI:0.996-0.999; p=0.002) was protective (Supplementary Table S8). None of the traditional risk factors were predictive of arrhythmias; however, light and vigorous intensity physical activity (1.003, 95% CI:1.001-1.004; p=0.002 and 1.003, 95% CI:1.001-1.005; p=0.007, respectively) were predictive for arrhythmias in binary regression analysis (Supplementary Table S9). Additionally, in a bivariate comparison, those with arrhythmias had greater lifetime training hours (p=0.038) and had spent more time being physically active (p<0.001) compared to those not diagnosed with an arrhythmia.

Cost of the Program

The cost of the program reflects the cost of screening up to a MAs' first CVD diagnosis to the third year of follow-up) (Supplementary Material S10). For each participant, the calculated cost included their yearly screening cost and all further examinations performed to their first CVD or hypertension diagnosis, and removed from the analysis thereafter. Participants that had a MACE were also removed from the cost analysis in subsequent years. The cost of the evaluations were calculated according to the current British Columbia Medical Service Plan payment schedule.[22] A total of 799 MAs were included in the initial year, and a total of total of 636, 591 and 566 MAs were included in years one, two, and three of the follow-up study, respectively. There were 181 (22.6%) MAs who did not undergo any additional testing and therefore no further cost implications. The cost of the remaining MAs who had additional

testing varied depending on additional investigations performed. The highest cost was attributed to the eight MAs that underwent a cardiac catheterization.

The first year of screening was the most expensive, compared to years one to three follow-up study years ($334.702 vs. $101,923 vs. $90,826 vs. $70,677) due to the higher cost of the baseline examination, the greatest number of additional investigations performed and the greatest number of participants that underwent the baseline screen. However, the first year had the highest number of diagnoses detected (120 vs. 21 vs. 28 vs. 17), thereby had the lowest cost per diagnosis ($2,789 vs. $4,853 vs. $3,244 vs. $4,157). The cost of the overall screening program was $605,205 or $3,072 per diagnosis.

DISCUSSION

To our knowledge, this is the first study to report the incidence of MACE and CVD over five years in a cohort of MAs participating in a yearly screening programme. The main findings were 1) 10 MACE (seven cardiac events and three CVAs) (2.8 MACE per 1,000 athlete-years) occurred in exclusively male athletes, 2) 207 MAs were identified with CVD, 3) the identification of CVD was associated with a high number of secondary tests and associated increased cost implications that did not result in identification of CVD most of the time; 4) increasing age, FRS, LDL cholesterol is predictive of CAD identification, whereas increasing amounts of moderate intensity activity was protective. The male predominance for MACE is consistent with previous literature.[8] One previous study reported four MACE in 108 male marathon runners; however, the follow-up duration was only 21.3±2.8 months.[5] In the Canadian general population, the prevalence of a MI in 40-54y is 0.3% and 1.3%, and increases to 1.2% and 4.3% in 55-64y in women and men, respectively.[23] While a direct comparison

cannot be made with the present population, there were five MIs over the five-year study period, providing an annual incidence of (1.4 per 1,000 athlete-years). Potential reasons for this lower rate include: yearly screening resulting in risk factor modification, and higher cardiorespiratory fitness than the general population.

Screening Tools and Risk Factors in the Prediction of Coronary Artery Disease and Arrhythmias

Over the course of five years, 207 CVD diagnoses were identified. The majority of diagnoses were made during the first year of the study (n=120), and 87 diagnoses were made over the four follow-up years. Coronary artery disease was the most prevalent diagnosis in the initial year (64;53%). Arrhythmias (32;37%) were the most common diagnosis during follow-up. However, despite the detection of CVD in some cases, yearly screening produced a high number of secondary testing without the identification of underlying CVD diagnoses in 82% of cases. Increasing age and presence of risk factors are known to increase the likelihood of developing CAD, which is supported by the present findings. The risk of CAD increased with increasing age, LDL cholesterol, FRS, and decreased with increasing amounts of moderate intensity activity. Aengevaeren et al. similarly reported that in a group of competitive and recreational male athletes, those with CAC were older, and more likely to have traditional risk factors compared to those without CAD.[2] Additionally, high lifetime exercise volumes (>2000 min/wk) and increased time spent doing very vigorous intensity exercise (>9 METs) was associated with increased CAC presence.[2] Conversely, in a study of 152 MAs (70% male), all with a low FRS, the male athletes had a higher prevalence of atherosclerotic plaques (44.3% vs. 22.3%) compared to controls, and only male athletes had a CAC > 300 and luminal stenosis

>50%. These findings suggest that those with a lifelong exercise may be more susceptible to the development of CAC, despite the absence of traditional risk factors.[4] Age and years of training were the only risk factors that predicted significant CAD in these men.[4] Increasing levels of physical activity volume, vigorous intensity exercise, nor lifetime training hours were predictive of CAD in the present study cohort. Potential reasons for this include: 1) the prevalence of CAD was underestimated due to a limited proportion of participants undergoing Gold Standard evaluations to diagnose CAD (i.e. CCTA), particularly in those with a low FRS as few MAs with low FRS underwent CCTA; and 2) cardioprotective benefits of moderate intensity exercise may outweigh the potential deleterious effects associated with vigorous intensity exercise. Cardiovascular risk scores have been shown to underestimate the presence of CAC in athletes.[4, 5, 7, 12, 24] However, most of these studies used the ESC score, which is used to predict CVD mortality.[12, 15, 24] The FRS was designed to predict the 10-year risk of CAD events, potentially making it a better tool to measure the presence of significant CAD at risk of MACE.[25] Studies that found an increased CAC in MAs with a low cardiovascular risk score compared to healthy controls did not follow the athletes longitudinally, therefore, it is possible that even though MAs with a low cardiovascular risk score may have a higher CACS than healthy controls, it may not translate to an increase risk of mortality, due to the predominately calcific stable nature of the plaques found in these athletes.[2, 4] In the Cooper Centre Longitudinal Study of 21,758 men it was demonstrated that although the adjusted risk of CACS of $\geq$100 AU was 11% greater among individuals with high physical activity compared to those with lower levels, there was not a concomitant increase in all-cause or cardiovascular mortality after a decade of follow-up.[26] Additionally, elite athletes have been shown to live longer (5-6y) than the general population and have a lower risk of cardiovascular and all-cause mortality.[27, 28]

The EST had modest diagnostic accuracy to detect CAD at risk of a MI. While it would be expected that the EST would detect those with obstructive CAD, it would not be expected that the EST would detect non-obstructive/non flow-limiting CAD. Non-obstructive CAD lesions are the source of significant amount of MIs.[29] In the seven MAs who had a cardiac event, three (43%) had a positive EST. Of those, two initiated a lipid-lowering medication after either a positive MIBI or CCTA. The third did not initiate cholesterol-lowering medication after a negative MIBI. Ten MAs who had a negative EST, but underwent a CCTA due to a high FRS and/or a strong family history of CAD that were identified with obstructive CAD. After identification of CAD on CCTA, all of these MAs, except one, initiated lipid-lowering medication. There were four MAs that were identified with obstructive CAD outside of the study, all of whom had an intermediate FRS and/or strong family history, and a negative EST conducted through the study. Therefore, it may be reasonable to include a CCTA to confirm or refute the presence of CAD in those with a $\geq$10% FRS to assist in positive behaviour change and intensification of risk factor reduction.

An increased prevalence of atrial fibrillation has been seen in endurance MAs who train at high-intensity, and have a large volume of endurance exercise even in the absence of structured heart disease.[3, 30] Arrhythmias, particularly atrial fibrillation was common in the present cohort and time spent performing high-intensity exercise was predictive in the development of arrhythmias. Additionally, increasing time spent in light intensity physical activity was predictive for arrhythmias. These findings suggest a curvilinear response similar to that seen in the Cardiovascular Health Study where those exercising at the highest intensity had a risk of atrial fibrillation similar to exercising at low intensity, whereas moderate intensity

physical activity had the greatest reduction in atrial fibrillation.[31] In contrast to previous research, lifetime training hours was not predictive of arrhythmias in the logistic regression models; however, in a bivariate comparison those with arrhythmias had significantly greater lifetime training hours and years spent being physically active compared to those that were not diagnosed with an arrhythmia.

Feasibility and Cost of the Programme

The initial year of screening was the most expensive due to the higher cost of the baseline examination that included cardiac auscultation, a greater number of MAs that underwent the baseline screen, and the greatest number of additional investigations performed. The cardiac auscultation was removed from subsequent years as a cost-effective strategy as serial cardiac auscultations (which requires a qualified physician to perform) had limited utility in detecting clinically relevant valvular heart disease at the expense of a high cost.[19] Concomitantly, the initial year had the highest number of diagnoses detected (120 vs. 21 vs. 28 vs. 17), thereby had the lowest cost per diagnosis ($2,779 vs. $4,853 vs. $3,244 vs. $4,157). Only one previous study of MAs, reported the cost of their programme. The cost after one year of screening was US$ 5,052 (~$6,290 CAD) per new CVD finding which is double than the cost of the initial screen in the present study (CAN $3,072).[32] While the cost of some examinations are more expensive in the United States, the higher cost is also attributed to fewer diagnoses (3% vs. 15%). Studies that included a CCTA in all athletes found a prevalence of 34-71% of athletes with CAD.[2, 4, 5] The prevalence of CAD is therefore expected to be higher due to all athletes undergoing CCTA or coronary angiography. While the cost of performing a CCTA in MAs with a $\geq$10% FRS would be high, the early identification of CAD and earlier initiation of prevention therapies and positive behaviour change could lead to less MACE in the long-term.

Additionally, there were significant cost implications associated with yearly screenings and high numbers of secondary testing which did not result in identification of CVD most of the time. This high cost could likely be reduced if a more sensitive test such as a CCTA was performed in those with ≥10% FRS in the initial year without subsequent yearly screenings. The overall higher cost may also be justifiable if the cost of hospitalizations, invasive interventions, emergency transportation and on the individual (i.e., years of life lost, lost wages, decreased productivity, decreased quality of life, psychological impact, burden on the family) is reduced. However, the potential benefits alongside all costs (i.e. initial of medications) requires further study. Additional risk and logistical factors (i.e., radiation exposure, risk of adverse reactions, accessibility, availability of skilled personnel and insurance implications in the event of a diagnosis) of performing a CCTA in those with FRS ≥10% also needs to be taken into consideration and may vary between cities and countries.

Proposed screening algorithm

A predictive model for MACE was unable to be developed due to limited events. The descriptive analysis of MACE and the screening indicators, alongside the logistic regression model allowed for a theoretical model to be suggested (Figure 5). A CCTA may be reasonable in MAs with FRS ≥10% and/or a strong family history of premature CAD to assist in behaviour modification (i.e., initiation of cholesterol-lowering treatment if CAD is identified on CCTA). In the presence of an abnormal ECG, a CCTA and/or echocardiogram, and/or Holter may be recommended depending on the abnormality identified. If the CCTA has uncertain functional significance or is undiagnostic, a stress echocardiogram or MIBI may be suggested. Findings from our previous work provides additional management guidance in the event a CVD diagnosis is made.[33]

Limitations

The incidence of CVD is likely underestimated as not all MAs underwent the complete battery of gold standard tests (e.g., CCTA, echocardiogram) to accurately delineate coronary anatomy, plaque presence and morphology nor cardiac structure and function. Previous studies that performed a CCTA in all MAs have demonstrated that 34-71% of MAs have CAD with 19%-36% possessing a high atherosclerotic burden [4, 5, 7, 12, 24] which is higher than that reported in the present study. Conducting all of these tests in all of the MAs was not clinically justified at the time of study conception. Additionally, in the shared decision-making model, concern regarding the identification of CAD and the resulting impact on insurance, one's self-identity, sport eligibility were reasons for not wanting to pursue definitive diagnosis with CCTA. Furthermore, there was no control population to determine whether screening decreased the incidence of MACE. While we did not find a difference in the presence of CAD based on menopause status in our female MA, further research in female MAs is needed to confirm the present findings.

There are some limitations related to the logistic regression models. Firstly, they were conducted to predict the presence of CVD by CVD sub-group, however, since the modelling used a diagnosis-based aggregation, the results can only infer (and not strongly conclude) that certain variables may be important to use in diagnosis prediction models and in more focused research. Secondly, they may have underestimated the odds of having CVD, as they only included MAs that were flagged as high risk or had symptoms and underwent subsequent testing. Previous research has indicated that MAs with low cardiovascular risk may have CAD, particularly those with high physical activity volumes and intensity, therefore, the group that

was deemed low risk in the current study may indeed have CVD and thereby, limited the odds of predicting CVD in this group.

Lastly, 4.4% MAs that withdrew at some point in the study, did not respond to our correspondence (emails, phone calls, and/or contact by family physician) in the last year of the study despite numerous attempts, therefore, we do not know cardiac events or vital status in these MAs.

Conclusion

Major adverse coronary events occurred in MAs despite yearly screening. All MAs who had a MACE had an abnormal screen; however, a negative functional stress test (i.e., EST, stress echocardiogram, MIBI) did not ensure event-free survival over five years of the study period. The inclusion of CCTA may be reasonable in MAs with an intermediate FRS or greater to assist with positive behaviour change to prevent MACE. Coronary artery disease and atrial fibrillation were the most common diagnoses with moderate physical activity being protective against their development. The inclusion of the FRS to predict the presence of CAD is supported. Further study is warranted to refine the screening strategy to reduce false-positive screens, decrease costs, and improve accuracy.

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Conflict of Interest: None.

Data Availability: The data underlying this article will be shared on reasonable request to the corresponding author.

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Figure legends

Figure 1 - Study overview

CAD: coronary artery disease; CVD: cardiovascular disease; MACE: major adverse cardiac event; SCA: sudden cardiac arrest

Figure 2- Yearly screening procedures

BP: blood pressure; CACS: coronary artery calcium score; CCTA: coronary computer tomography angiography; MIBI; myocardial perfusion imaging; ECG: electrocardiogram; Echo: echocardiogram; FRS: Framingham Risk Score; abnormal exercise stress test included: equivocal ST-changes (upsloping ST-depression >1mm), positive ST-changes (horizontal or down sloping ST depression >1mm), complex ventricular arrhythmias (i.e., ventricular run > 3 beats, non-sustained ventricular tachycardia, polymorphic premature ventricular contractions (PVCs), accelerated idioventricular rhythm (with left bundle branch morphology)), >7 PVCs/min at peak or during recovery, angina or marked shortness of breath. The Bruce protocol performed on a treadmill was utilized in the majority of the cases. A bike was used if an injury prohibited the participant from using the treadmill or if the MAs strongly preferred using the bike as it was their primary sport and therefore was better suited to elicit their reported symptoms.

Figure 3 - Incidence of cardiovascular disease

Valvular heart disease: mitral valve prolapse (n = 18), bicuspid aortic valve (n = 4); aortic insufficiency (n = 5), aortic stenosis (n = 3); Arrhythmias: atrial fibrillation/flutter (n = 19), high PVC burden (n = 17), supraventricular tachycardia (n = 7), conduction system disease (n = 4); Other: myocarditis (n = 2), myocardial bridging (n = 3), cerebrovascular disease (n = 1), dilated cardiomyopathy (n = 1), probable Long QT syndrome (n = 1), papillary fibroelastoma (n= 1)

Figure 4 – a) Screening indicators that elicited follow-up, b) Screening indicators present in those not diagnosed with CVD, c) Screening indicators present in those with CAD, d) Screening indicators present in those with arrhythmias, e) Screening indicators present in those with valvular heart disease, f) Screening indicators present in those with aortic dilation

*high CV risk: includes those with an intermediate or high Framingham Risk Score, diabetes, high cholesterol (≥8mmol/L), high blood pressure (>180/110mmHg);
CVD: cardiovascular disease; ECG: electrocardiogram; Fhx: Family history; HR: Heart rate; SCD: sudden cardiac death

Figure 5 - Theoretical screening algorithm for Masters athletes to detect cardiovascular disease

*inclusion based on clinical likelihood of CVD, availability of tests and local expertise
**Equivocal or positive ST-depression; complex ventricular arrhythmias; > 7 PVCs/min at peak or during recovery; angina or marked shortness of breath; HRE
- perform ambulatory blood pressure and proceed to CCTA if hypertensive and required to guide treatment
CCTA: coronary computed tomography angiography; CV: cardiovascular; Echo: echocardiogram; ECG:electrocardiogram; EST: exercise stress test; LAD: left axis deviation; LAE: left atrial enlargement MIBI: myocardial perfusion imaging; PVC: premature ventricular contractions; RAE: right atrial enlargement; RBBB: right bundle branch block

SUPPLEMENTARY MATERIAL

Table S1 - Criteria for abnormal assessment / screening indicators

Personal History

- Cardiac-related syncope and/or pre-syncope during and after exertion for no apparent reason
- Angina during exertion
- Dyspnea during exertion
- Unusual fatigue/decrease in performance
- Palpitations during exercise
- Exercise-related cardiovascular event (i.e., MI/revascularization/atrial fibrillation/flutter, hospitalization, stroke)
- Any other potentially concerning conditions

Family History

- Family history of SCD or any unexpected or unexplained sudden death before 50
- Family history (first or second degree relative) of inheritable heart conditions (hypertrophic cardiomyopathy, arrhythmogenic ventricular cardiomyopathy, Marfan's syndrome, long QT

syndrome, short QT syndrome, Brugada syndrome, Wolf-Parkinson-White Syndrome, catecholaminergic polymorphic ventricular tachycardia, dilated cardiomyopathy, thoracic aorta aneurysm, bicuspid aortic valve, or other potentially disabling CV disease)

- Family history of premature CAD (first degree relative) < 50 years
- *A family history of autosomal dominant disorders requires follow-up in first and second degree relatives.

Physical Examination

- >180/110 mmHg on more than one reading (all years)
- Mid or end-systolic clicks (Initial year)
- Abnormal second heart sound (single or widely split and fixed with respiration) (Initial year)
- Any diastolic murmur (Initial year)
- Systolic murmur grade ≥ 2 (Initial year)
- Abnormal femoral pulses indicative of aortic coarctation (Initial year)
- Morphological features of Marfan's syndrome (Initial year)
- Irregular heart rate (all years)

Cardiovascular Risk (initial year, follow-up years 1 and 2)

- Intermediate (10-19%) to high (≥ 20%) Framingham Risk Score
- Diabetes (≥ 7.0 mmol/L)
- High cholesterol (≥ 8 mmol/L blood cholesterol)
- Age ≥ 65 years

Abnormal resting 12-lead ECG

- Seattle Criteria (Initial Year) International Recommendations for ECG Interpretation in Athletes (Years 2-5)

Previous CVD (diagnosed through study or outside)**

Follow-up and associated cardiac examinations as per clinical discretion, CVD guidelines and when clinically indicated (new symptoms)
**not included as a 'screening indicator'

Table S2 – Cardiovascular diagnoses definitions by sub-group

Coronary artery disease[34]
Mild CAD/non-obstructive
Mild coronary calcium burden (10-100 AU) Minimal stenosis or plaque with no stenosis (1-24%); CAD-RADs 1 Mild stenosis (25-49%); CAD-RADs 2
Moderate CAD/obstructive
Moderate coronary calcium burden (>100-400 AU) Moderate CAD (50-69%); CAD-RADs 3
Significant CAD/obstructive
Extensive coronary calcium burden (≥400 AU) Stenosis (70-99%) or LM (>50%) or 3 vessel obstructive disease CAD-RADs 4
Arrhythmias
Atrial fibrillation or flutter (paroxysmal, persistent, permanent) High PVC Burden (> 720 PVCs/24 hours (measured on a Holter))[35] Supraventricular tachycardia Conduction system disease (i.e., 2nd, or 3rd degree AV block requiring pacemaker insertion)
Aortic dilatation

*Used dilated proximal ascending aorta indexed to height if measurement was available (newest guidelines suggest index to height not BSA). If either measurement was greater than the cut-off, labelled as 'true': Proximal ascending aorta[36]: > 19.8 mm/m Aortic root[37]: calculated z score: > 2
Valvular heart disease
Bicuspid aortic valve Mitral valve prolapse and myxomatous mitral valve disease Aortic stenosis (any grade) Aortic insufficiency (any grade)
Other CVD
Coronary artery anomalies Myocarditis Myocardial bridge Cardiomyopathies Rheumatic heart disease valve

Table S3 – Aggregation method and variables used in logistic regression models

Variable of interest	Base or variable selection	Aggregation method
Age (y)	Base	Age at initial screen
Sex	Base	n/a
FRS (%)	Base	Mean score pre-diagnosis
Family history of premature CVD	Base	Presence of family history pre-diagnosis
BMI (kg/m^2)	Base	Mean BMI pre-diagnosis
History of hypertension	Base	Presence of hypertension pre-diagnosis
LDL cholesterol (mmol/L)	Base	Mean value pre-diagnosis
HDL cholesterol (mmol/L)	Base	Mean value pre-diagnosis
Menopause status	Variable selection	Status in year diagnosed
Alcohol (drinks per week)	Variable selection	Status reported most frequently pre-diagnosis
Light intensity exercise (minutes/week)	Variable selection	Mean value pre-diagnosis
Moderate intensity exercise (minutes/week)	Variable selection	Mean value pre-diagnosis
Vigorous intensity exercise (minutes/week)	Variable selection	Mean value pre-diagnosis
Physical activity volume (MET-hr/wk)	Base	Mean value pre-diagnosis
Lifetime training (hours)	Base	Sum of all years pre-diagnosis
Stressed at work	Variable selection	Highest level pre-diagnosis
Stressed at home	Variable selection	Highest level pre-diagnosis
Number of life events	Variable selection	Highest level pre-diagnosis
Depression	Variable selection	Presence in any year pre-diagnosis

In individuals that were diagnosed with CVD, variables were aggregated up to the diagnosis timepoint rather than over the entire time period as it was believed that the MAs may change behaviors and/or take medication after their diagnoses which could significantly alter variable results.

For those that weren't diagnosed, the aggregations involved aggregating across all timepoints.

Variables were included based on previous literature (potential co-founders) or because they were critical variables of interest (i.e., physical activity). This base model was then used to conduct variable selection using the Akaike Information Criterion (AIC). If the variables did not contribute to the goodness-of-fit model substantially, then they were not included to avoid "overfitting" the model.

Table S4 - Other adverse events

Master athlete #	Year	Age, sex	FRS (%)	Primary sport	Volume Physical Activity	Event	Previous diagnosis	Medication

					(MET-hrs/week)			
1	2	66, M	13.3	Marathon	55	Pulmonary embolism	None	None
2	2	56, M	15.6	Cycling	49	Pulmonary embolism	None	None
3	2	54, F	2.0	Running	35	Pulmonary embolism	None	None
4	2	64, M	7.9	Cycling	42	Pulmonary embolism	None	None
5	3	62, M	7.3	Hockey	88	Deep vein thrombosis	Mild to moderate MR	None
6	5	66, M	28.2	Orienteering	97	Mild chronic small vessel ischemic disease; Proneal vein blood clot	SVT (year 5); Hypertension	Anti-hypertensive
7	5	53, M	6.7	Basketball	43	Deep vein thrombosis, pulmonary embolism	None	None
8	5	64, M	9.4	Triathlon	113	Deep vein thrombosis, pulmonary embolism	MVP (year 3)	None
9	5	78, F	9.5	Hiking	32	Died of cancer	None	Anti-hypertensive
10	5	70, M	17.6	Triathlon	73	Died of cancer	None	Anti-hypertensive
11	5	54, F	2	Cycling	88	Died of brain aneurysm	None	None

Table S5 - Participant characteristics with false-negative screen

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
Obstructive CAD									
1	1	53, M	13.4	Marathon running	74	Obstructive CAD (moderate (LAD), triple vessel	GP ordered due to new angina, palpitations and family FH (brother CAD at 48 years, mother CAD at 68 years)	Int FRS, FH	EST (15 METS, HRE, no ischemic changes)
2	4	60, M	9.1	Hockey	36	Obstructive CAD (moderate, quadruple vessel, mixed)	GP ordered due to FH (father CABG at 68; Brother CAD (angioplasty) at 56 years)	Int FRS	EST (16 METs, HRE, no ischemic changes)
3	4	69, M	21.8	Cycling	162	Moderate CCB, 4 vessel	GP ordered due to 'abnormal ECG'	Int FRS; ECG (PVCs, left	EST (17 METs, no ischemic changes),

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
								axis deviation)	point of care echo, Holter monitor Was suggested to take a statin, but declined
4 (WD)	4	50, M	4.6 (initial y)	Squash	62	PCI with stent	Angina	None (WD after initial screening)	None
Non-obstructive CAD									
5	1	60, M	10.6	Hockey	27	Non-obstructive CAD (mild, triple vessel, mixed plaque)	GP ordered due to new FH (brother stent at age 56)	Int FRS	EST (12 METs, HRE, no ischemic changes)

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
6	1	57, M	11.2	Rowing	74	Minimal CAD, single vessel, calcified	GP ordered due to palpitations and HRE on EST	Int FRS, palpitations	EST (18 METs, HRE, no ischemic changes)
7	2	69, M	17.6	Triathlon	76	Non-obstructive CAD, (mild, single vessel, calcified)	Incidentally when completed tests for myeloproliferative/ myelodysplatic disorder	> 65 years, Int FRS	EST (8 METs, no ischemic changes)
8	2	58, M	9.4	Cycling	99	Mild CCB	GP ordered due to dyspnea	None	None
Cerebrovascular disease									
9	2	72, M	15.6	Cycling	102	Cerebrovascular disease (<50% stenosis bilaterally)	Incidentally seen on dental x-rays	Int FRS, > 65 y	EST (11 METs, HRE, no ischemic changes)

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
CAD - unknown severity									
10	1	74, M	11.2	Rowing	132	Atherosclerosis, 'calcification within the coronary vessels'	Incidentally when underwent computed tomography for prostate cancer	Int FRS, > 65 y, palpitations	EST (9 METs, HRE, no ischemic changes)
11	3	62, F	6.2	Rowing	53	Atherosclerosis; LAD calcification 'greater than expected for patient age and sex'	Incidentally through lung exam	Physical examination (3/6 systolic murmur)	EST (15 METs, HRE, no ischemic changes), echo (aortic valve raphes)
12 (WD)	4	60, F	3.3 (initial y)	Squash	80	Atherosclerosis	Incidentally through abdominal ultrasound	None	None
Atrial fibrillation or flutter									

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
13	1	70, M	30	Cycling	84	Atrial fibrillation	Palpitations, high heart rate on monitor	High FRS, physical examination (IV/VI holosystolic murmur), >65 y	EST (11 METs, HRE, >7 PVCs/min), ECHO (moderate aortic insufficiency), CCTA (mild CAD),
14	3	72, M	23	Golf	65	Atrial fibrillation	Had 'symptoms', went to emergency room	High FRS, >65 y	EST (12 METs, ST depression), ABP (HTN), ECHO (mild-moderate AR, dilated aorta and enlarged thoracic aorta, PFO),

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
									CCTA (moderate CAD),
15	3	62, M	17	Cycling	97	Atrial fibrillation	Had 'symptoms', went to emergency room	High FRS, Irregular HR	EST (16 METs, HRE)
16	4	55, M	10	Hockey	53	Atrial flutter	Had 'symptoms', went to emergency room	Int FRS, fatigue	EST (15 METs, HRE)
17	4	69, M	12	Cycling	120	Atrial flutter	DYS, fatigue	Int FRS, ECG (LA dev'n, RBBB)	EST (19 METs, HRE)
18	4	79, M	20	Cycling	118	Atrial fibrillation	Had 'symptoms', captured while wearing a monitor	High FRS, >65 y	EST (17 METs, ST depression)

Participant	Year	Age, sex	FRS (mean)	Primary sport	Volume of Physical Activity (MET-hrs/week)	Diagnosis	Indication for test (outside of study)	Previous screening indicators	Further tests conducted through study (results)
19	4	49, M	9	Orienteering	72	Atrial flutter with cardioversion	Captured on holter monitor, ordered by GP	Int FRS, FH (CAD)	EST (18 METs), MACE (stent) in yr 3
20	4	52, M	4	Cycling	70	Atrial fibrillation with cardioversion	Captured on holter monitor, ordered by GP	None	None
21	4	41, F	1	Marathon	62	Genotype positive HCM	Mother diagnosed at 69 with HCM	FH of HCM, CP	EST (18 METs), Echo (normal)

ABP: ambulatory blood pressure; AR: aortic regurgitation; CABG: coronary artery bypass graft; CAD: coronary artery disease; CCB: coronary calcium burden; CCTA: computed coronary tomography angiography; DYS: dyspnea; ECHO: echocardiogram; EST: exercise stress test; F: Female; FH: family history; FRS: Framingham Risk Score; GP: general practitioner; HCM: hypertrophic cardiomyopathy; HR: heart rate; HRE: hypertensive response to exercise; Int: intermediate; LA dev'n: left axis deviation; M: male; METs: Metabolic Equivalent Tasks; PFO: patent foramen ovale; PVCs: premature ventricular complexes; RBBB: right bundle branch block; WD: withdrew after initial year of screening

Table S6- Presence of coronary artery disease in relation to exercise stress test findings

EST marker	Mild CAD (n = 53)	Moderate CAD (n = 14)	Obstructive CAD (n = 13)	Myocardial bridging (n = 3)	Coronary artery anomaly (n = 2)	Calcified (n = 22)	Mixed (n = 29)	Non-calcified (n = 4)
No ST depression	28 (52.8)	8 (57.1)	3 (23.1)	1 (33.3)	-	12 (54.5)	9 (31.0)	2 (50.0)
Equivocal ST depression	9 (17.6)	-	3 (23.1)	-	1 (50.0)	2 (9.1)	3 (10.3)	1 (25.0)
Positive ST depression	15 (29.4)	6 (42.9)	6 (46.2)	1 (33.3)	1 (50.0)	8 (36.4)	16 (55.2)	1 (25.0)
Non-diagnostic ST-changes	1 (2.0)	-	1 (7.7)	1 (33.3)	-	-	1 (3.4)	-
Other markers on EST								
Complex ventricular arrhythmias	7 (13.2)	-	1 (7.7)	1 (33.3)	1 (50.0)	6 (27.3)	2 (6.9)	-
HRE	25 (47.2)	4 (30.8)	7 (58.3)	1 (33.3)	1 (50.0)	12 (54.4)	11 (37.9)	3 (75.0)

All values reported as n (%).

HRE: hypertensive response to exercise (systolic blood pressure > 210 mmHg for males and > 180 mmHg for females)

Table S7 – Characterization of participants with obstructive CAD who had a false-negative exercise stress test

Participant	EST METs, % THR achieved	Rationale for additional testing	Initiated cholesterol-lowering medication
Significant CAD			
1	18, 96%	Father MI at 49 y (19% FRS)	Yes
2	15, 99%	Intermediate FRS, no additional testing	After MACE
3	13, 95%	High FRS	Declined
Moderate CAD			
4	14, 103%	High FRS	Yes
5	15, 106%	High FRS, family history of aortic stenosis	Yes
6	13, 101%	High FRS	Yes
7	15, 103%	Brother CAD at 48 years, intermediate FRS	Yes
8	17, 109%	Intermediate FRS and LDL-C >3.5, midsystolic click	Yes
9	17, 99%	High FRS	Yes
10	9, 94%	High FRS	Yes
11	14, 91%	Brother CAD at 50y (11% FRS)	Yes

Table S8 - Logistic regression model for coronary artery disease

Predictor	Odds ratio	95% CI	P-value
Age (per year)	1.047	1.003-1.094	0.0379*
Sex			
Female	Reference	Reference	Reference
Male	1.276	0.572 - 2.971	0.560
Framingham Risk Score (%)	1.092	1.031 - 1.158	0.003*

BMI (kg/m2)	0.964	0.893 - 1.031	0.316
LDL cholesterol (mmol/L)	1.709	1.223-2.401	0.002*
HDL cholesterol (mmol/L)	0.483	0.223 - 1.029	0.066
History of hypertension			
False	Reference	Reference	Reference
True	0.792	0.417 - 1.454	0.462
Family history of premature CVD			
False	Reference	Reference	Reference
True	1.331	0.487 - 3.349	0.558
Physical activity volume (MET-hr/wk)	1.0004	0.995 - 1.011	0.372
Lifetime training (hours)	0.9999	0.9999-1.0000	0.304132
Moderate intensity activity (min/wk)	0.997	0.996-0.999	0.002*

Table S9 - Logistic regression model for arrhythmias

Predictor	Odds ratio	95% CI	P-value
Age (years)	1.051	0.995 – 1.111	0.080
Sex			
Female	Reference	Reference	Reference
Male	2.513	0.937 – 7.452	0.078
Framingham Risk Score (%)	1.050	0.973 – 1.132	0.204
BMI (kg/m2)	1.005	0.919 – 1.090	0.910
LDL cholesterol (mmol/L)	0.952	0.609 – 1.478	0.827
HDL cholesterol (mmol/L)	1.249	0.529 - 2.840	0.602
History of hypertension			
False	Reference	Reference	Reference
True	1.791	0.851 – 3.680	0.117
Family history of premature CVD			
False	Reference	Reference	Reference
True	0.944	0.200 – 3.196	0.933
Lifetime training (hours)	0.99999	0.999 - 1.000	0.942
Physical activity volume	0.993	0.979 – 1.006	0.296
Light intensity activity (min/wk)	1.003	1.001 – 1.004	0.002*
Vigorous intensity activity (min/wk)	1.003	1.001 – 1.005	0.007*

Table S10 - Cost of the screening program

	Initial year		Year one follow-up		Year two follow-up		Year three follow-up	
Exam (cost per exam, $CAN)	**Number of participants (%)**	**Total cost per test ($CAN)**	**Number of participants (%)**	**Total cost per test ($CAN)**	**Number of participants (%)**	**Total cost per test ($CAN)**	**Number of participants (%)**	**Total cost per test ($CAN)**
Baseline cardiovascular screening*	799 (100)	108,664.00	636 (100)	54,060.00	591 (100)	50,235.00	566 (100)	39,054.00
EST ($155)	498 (62)	77,190.00	70 (11)	10,850.00	61 (10.3)	9,455.00	51 (9.0)	7,905.00
Cardiologist consult ($172)	347 (43)	59,684.00	108 (17)	18,576.00	90 (15.2)	15,480.00	66 (11.7)	11,352.00
Echo ($253)	105 (13)	26,565.00	27 (4.2)	6,831.00	26 (4.4)	6,578.00	25 (4.4)	6,325.00
CCTA ($400)	57 (7)	22,800.00	4 (0.6)	1,600.00	4 (0.7)	1600.00	4 (0.7)	1,600.00
CACS ($230)	24 (3)	5,520.00	1 (0.2)	230.00	0	-	3 (0.5)	690.00
Holter ($91)	47 (6)	4,277.00	16 (2.5)	1,456.00	27 (4.6)	2,457.00	20 (3.5)	1,820.00
MIBI ($274)	18 (2)	4,932.00	4 (0.6)	1,096.00	4 (0.7)	1,096.00	2 (0.4)	548.00
Stress echo ($235)	16 (2)	3,760.00	2 (0.3)	470.00	0	-	1 (0.2)	235.00
ABP ($100)	14 (2)	1,400.00	-	-	13 (2.2)	1,300.00	6 (1.1)	600.00

CMR ($875)	10 (1)	8,750.00	2 (0.3)	1,750.00	3 (0.5)	2,625.00	2 (0.4)	548.00
Cath ($2500)	5 (0.6)	11,000.00	2 (0.3)	5,000.00	-	-	-	-
Event monitor ($80)	2 (0.3)	160.00	-	-	-	-	-	-
Total cost of screen and subsequent tests		334,702.00		101,923.00		90,826.00		70,677.00
Diagnoses/cost per diagnoses**	120	2,789.18	21	4,853.48	28	3,243,79	17	4,157.47
Total cost	$598,128/197 = $3,036 per diagnosis							

*Initial year ($136): cardiovascular physical exam and history review ($86), electrocardiogram (ECG) ($34), lipid blood work ($16); year one and two ($85): ECG, blood work, blood pressure and history review ($35); year three ($69): ECG, blood pressure and history review;

**Included diagnoses of hypertension

ABP: ambulatory blood pressure; CAN: Canadian dollars; CACS: coronary artery calcium score; Cath: cardiac catherization; CCTA: computed coronary tomography angiography; CMR: cardiac magnetic resonance imaging; echo: echocardiogram; EST: exercise stress test; MIBI: myocardial perfusion imaging