ANNUAL CORONARY ARTERY CALCIUM PROGRESSION AND LIFESTYLE MODIFICATION: A PILOT STUDY

By

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CERTIFICATE OF APPROVAL

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Abbreviations Used

CAD	Coronary artery disease
CAC	Coronary artery calcium
MI	Myocardial infarction
MDCT	Multidetector computed tomography
BMI	Body mass index
LDL	Low density lipoprotein cholesterol
FC	Functional capacity
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SPC	Symmetric percent change
RPC	Robust percent change
hsCRP	High sensitivity C-reactive protein

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Abstract

Background: Coronary Artery Disease (CAD) is highly prevalent in the the United States and involves the progression of calcified atherosclerotic plaque in patients' coronary arteries.[1] Although many people adopt lifestyle changes to reduce CAD risk factors, the ability to alter calcified plaque burden is not well understood. Recent studies find Multidetector Computed Tomography (MDCT) to be an accurate and non-invasive method for CAD imaging and quantification of calcified atheroslcerotic plaque, measured as a Coronary Atery Caclium (CAC) score. ***Objectives:*** this study aims 1) to determine the magnitude and direction of CAC score change using 64-MDCT cardiac scans at baseline and 1-year post lifestyle modification, 2) to determine whether CAC progression is associated with the lowering of known CAD risk factors, including LDL cholesterol, systolic blood pressure, diastolic blood pressure, BMI, and functional capacity and 3) to determine which CAD risk factors are most predictive of CAC score changes through multivariable analysis. ***Methods:*** Baseline and 1-year MDCT cardiac scans measured participant CAC progression and CAD risk factors were assessed at baseline and 12-weeks. The relationship between change in CAD risk factors and change in CAC were evaluated through multivariable regression analyses. ***Results:*** Among participants with complete follow-up (n=22), 2 (9.1%) participants experienced reductions of CAC, and nearly 60% experienced greater than 20% CAC progression. None of the variables of interest was found to be significantly predictive of CAC progression in either multivariable linear or logistic regresison. Age was found to significantly predict CAC progression and a significant interaction between age and gender was observed. When assessing predictors of 1-year CAC score, baseline CAC score was statisitcally significant ($p<0.001$). ***Conclusion:*** Age, gender and baseline CAC score are most significantly predictive of CAC progression and future CAC scores. Future studies involving *Wellspring Heart* may find significant associations between improvements in other CAD risk factors and CAC progression when larger datasets are available and participants are followed for a longer periods of time.

Introduction

Coronary Artery Disease

Nearly 81 million adults in the United States suffer from cardiovascular diseases, which include coronary artery disease (CAD), heart failure, stroke, myocardial infarction, angina pectoris, and high blood pressure.[1] CAD is the No. 1 cause of death in the United States and occurs as coronary arteries narrow, blocking the delivery of oxygen-rich blood to the heart.[1] The most common cause of CAD is atherosclerosis, which has an insidious onset and commences with the formation of fatty streaks that develop into atheromas.[2-4] As CAD develops, fibrous tissue surrounds and hardens atheromas, creating calcified atherosclerotic plaque, referred to as hard plaque.[2]

The progression of hard plaque is complex. Studies that have analyzed whether a genetic predisposition to atherosclerosis exists, found that through improved nutrition and physical activity, individuals may alter gene expression, which in turn modifies the rate at which atherosclerotic plaque develops.[5] Also, the progression of atherosclerosis may be partially modified by drugs that have the potential to alter the biological processes involved in the calcification process.[6] As a surrogate marker of atherosclerosis, CAC scoring provides an estimate of total hard plaque burden and has been found in several studies to be an independent predictor of future coronary events.[7-11.]

Greenland describes the use of CAC scoring in clinical practice through The American College of Cardiology Foundation and American Heart Association's release, titled, *Clinical Expert Consensus Document on Coronary Artery Calcium Scoring by Computed Tomography in Global Cardiovascular Risk Assessment and in Evaluation of Patients with Chest Pain.*[6] This document, which was updated in 2007, describes the importance of CAC scoring in CAD assessment as it provides an accurate risk estimate

over and above traditional cardiac risk factors, including the Framingham Risk Score (FRS). The FRS is a frequently used risk assessment algorithm for hard coronary events (MI or sudden cardiac death) and it projects a 10-year absolute risk of event occurrence by accounting for: gender, total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure (or treatment for hypertension), cigarette smoking and age.[6] It has only been since 2000 that studies have provided data on the incremental prognostic capability of CAC scoring in the prediction of CAD events among populations with intermediate risk, for whom the FRS does not provide an adequate assessment, or for whom clinical decision-making is difficult.[6,11]

CAC is quantified using Agatstons scoring method, which is commonly used in clinical and research settings and is based on the area, density and peak Hounsfield units present within a detected calcified lesion.[12] An 'Agatstons score' is generated from cardiac scans, which report scores for every major coronary artery and a combined total score for the patient.[13] Meta-analysis of recently published reports indicates the relationship between increased total CAC score and CAD event rate and relative risk,[6,14] where, relative to the lowest risk patients (CAC score=0), the relative risk of hard coronary event increases as total CAC scores increases. Among those with CAC scores between 1-112 Agatstons, the relative risk estimate was 1.9; among those with CAC scores 112-400 Agatstons, the relative risk was 4.3; among those with CAC scores 400-999 Agatstons, the relative risk was 7.2; and those with a CAC score greater than 1,000 Agatstons were found to have a relative risk of 10.8. These estimates were derived from studies done over the past six years, involving 27,622 symptomatic and asymptomatic patients.[6] CAC quantification has outperformed the use of conventional CAD risk factors

(including hypertension, cigarette smoking, hyperlipidemia, diabetes mellitus and carotid intima media thickness) as an independent predictor of cardiovascular events, such as myocardial infarction (MI) or sudden cardiac arrest.[10,15-17]

Although present research indicates that individuals with a 2-fold or greater annual increase in CAC score are more likely to have an MI than those with less than a two-fold increase,[9] the association between CAC progression and clinical CAD risk factors is not well understood.[6] Budoff and others found that CAC progression was most strongly related to baseline CAC score, while others found age to be the greatest predictor of CAC progression.[18,19] Recent studies that tracked annual CAC progression among patients with CAD risk factors found CAC scores increase at least 20% when patients are followed for short timeframes, about one to two years.[15,19,20] In the presence of definite CAC progression (greater than 15% over a year), the risk of MI was significantly greater than those with stable scores, even when baseline scores were high.[6] Serial monitoring of calcified atherosclerotic plaque and assessment of CAC score progression remain important foci for cardiovascular research and ongoing investigation is needed to determine factors most closely associated with CAC progression.

It is well understood that lifestyle modification programs that aim to 1) reduce dietary fat intake, 2) improve exercise capacity, 3) improve stress management skills and 4) provide group support, help lower CAD risk factors and reduce the risk of future coronary events.[21,22] Promising research found patients who enrolled in a lifestyle modification program were able to reduce atherosclerotic risk factors and prevent the need for cardiac revascularization surgeries;[23] however assessments of CAC score change were not included in analyses. The impact of lifestyle modification on hard plaque

development has not been well documented in the literature, and both clinicians and patients would benefit from studies that analyze the relationship between these two indicators of cardiac health. In order to understand the ability for individuals to slow the progression of CAC, baseline and post-intervention measurements must be taken. Currently, an accurate and non-invasive technique for measuring CAC burden is through 64-multidetector computed tomography, which can be used to provide continued assessments of atherosclerosis.[24,25]

64 Multidetector Computed Tomography

Recent studies indicate that 64-multidetector computer tomography (MDCT) scans have the ability to detect and quantify the extent of coronary artery lesions with higher accuracy than previous generations of cardiac computed tomography.[32,45] Also, MDCT is a practical alternative to coronary angiography as it provides electrocardiogram-gated acquisition with improved temporal resolution and sub-millimeter spatial resolution needed to visualize the lumen of coronary arteries, and should be considered for routine diagnostic evaluations among people with suspected CAD.[24,26] By capturing multiple images of the heart within the time of a single beat, clinicians can carefully assess details of the heart structure and educate patients about the extent of CAD present. When used among symptomatic populations, MDCT provides a highly accurate and reliable measure of coronary artery calcification.[10,25,27,28]

Leber and others[29] support the use of MDCT, as their study found that MDCT outperformed invasive angiography in the detection of calcified coronary lesions in vessels with low stenosis. This is critical because areas of high stenosis (>50% blockage)

are most often *not* the area of cardiovascular events.[30] Greenland and others[26] indicate that inter-test variability must be determined prior to serial CAC monitoring with MDCT, however refinements in imaging technology have yielded great improvements in the prognostic capabilities of CAC monitoring. Studies involving over 76,000 symptomatic patients have demonstrated high negative predictive values (96%-100%), allowing for a high level of confidence that a person with no CAC (Agatstons score =0) has no obstructive angiographic disease.[17,24,25,31,32] Also, 64-MDCT has been shown to have a sensitivity of 99% and a specificity of 95%, values which are similar to conventional invasive coronary angiography.[24,25,33]

Lifestyle Modification: The Wellspring Heart Program

The design of *Wellspring Heart* was inspired through research conducted by Dr. Dean Ornish, who demonstrated that coronary heart disease could be reversed through lifestyle change alone.[22] *Wellspring Heart* differs from previous Ornish studies in that 64-MDCT cardiac scans are used to measure hard plaque at baseline and at a one-year follow-up exam. Upon enrollment into *Wellspring Heart*, participants enter an intensive 12-week program consisting of two group meetings per week at the Wellspring Medical Center in Woodburn, OR, where they partake in four specific modalities, each lasting approximately one hour. These modalities include 1) aerobic exercise and restorative training with an exercise physiologist 2) deep relaxation and yoga practice with a trained yoga instructor 3) group support with a counselor and 4) a heart healthy meal and nutrition education prepared by a dietitian. The goal of each component is to teach participants of varying lifestyle modalities that will help participants improve

cardiovascular fitness, lower stress levels, improve psychosocial health and improve nutrition habits when incorporated into a daily routine. After 12 weeks, participants meet with the nurse case manager to create goals and an action plan to ensure that these lifestyle modifications are sustained. One year from entrance into the study, MDCT scans were performed a second time to examine changes in coronary health.

Significance

Literature describing the ability for individuals to reduce coronary artery calcification is sparse—especially among individuals with either clinical CAD or multiple CAD risk factors who are also involved in lifestyle modification programs such as *Wellspring Heart*. The use of MDCT to describe CAC changes within this population is an innovative method of disease evaluation. This study provides information not only on CAC progression but also on CAC progression as it relates to changes in CAD risk factors within a population of individuals involved in a lifestyle modification program. This study also provides insight into the question of whether preventive lifestyle changes effectively slow the progression of CAC, or even reverse it, which may reduce the need for surgically implanted stents and other costly medical procedures that occur among persons with advanced CAD. Heart-healthy lifestyles have been shown to provide multitudes of benefits such as improved energy, lower stress levels and improved confidence—none of which have been shown to accompany surgical procedures.[22] Lastly, conclusions from this pilot study have vast implications for the field of cardiology as it may drive the development lifestyle modification programs and support continued use of MDCT technology to assess CAD and CAC changes.

Research Questions and Hypotheses

1. After one year of lifestyle modification, to what degree do CAC scores change among participants of *Wellspring Heart*?

Hypothesis: After one year of the *Wellspring Heart* program, participants will experience less than a 20% increase in CAC score. According to the American College of Cardiologists and the American Heart Association, it is expected that individuals symptomatic of CAD will have an annual CAC score increase of at least 20%.[6] Since individuals involved in *Wellspring Heart* are lowering their risk factors of heart disease, it is hypothesized that CAC progression will be less than expected.

2. Among *Wellspring Heart* participants, how will changes in CAD risk factors relate to CAC change?

Hypothesis: When comparing baseline and 1-year CAC scores, the smallest progression of CAC will be associated with the greatest improvement of CAD risk factors during the first 12 weeks of *Wellspring Heart*.

Specific Aims

The specific aims of this study are 1) to determine the magnitude and direction of CAC score change using 64-MDCT cardiac scans at baseline and 1-year post lifestyle modification, 2) to determine whether CAC progression is associated with the lowering of known CAD risk factors, including LDL cholesterol, systolic blood pressure, diastolic blood pressure, body mass index (BMI), and functional capacity and 3) to determine which CAD risk factors are most predictive of CAC progression through multivariable analysis.

Methods

Study Design

This was a pilot observational study that sought to describe change in CAC progression over time. The goal of this study was to determine whether *Wellspring Heart* participants slowed CAC progression over the course of one year and to determine whether participants improved CAD risk factors during the first 12-weeks of program involvement. Data for this study were collected from MDCT scans, medical records, lab results, and self-reported questionnaires and were compiled into a large database that was used for these analyses. No previous studies have used *Wellspring Heart* data and results from this study serve to provide preliminary information for the program clinicians, coordinators and participants, and will aid in the development and completion of future studies involving *Wellspring Heart.*

Selection Criteria, Recruitment and Informed Consent

Individuals were eligible for *Wellspring Heart* if they met any *one* of the following characteristics: diagnosis of CAD based on non-invasive testing including exercise tests, nuclear imaging, echocardiogram or other tests that clearly demonstrated ischemia; cardiac catheterization demonstrating CAD; eligibility for bypass surgery/Percutaneous Transluminal Coronary Angioplasty (PTCA); previous coronary bypass surgery; previous PTCA/Stent; previous MI; type I or II Diabetes Mellitus; male relative (father or brother) less than 55 years of age who has had a heart attack or died from a heart attack; or a female relative (mother or sister) less than 65 years of age who has had a heart attack or died from a heart attack.

Also eligible were individuals who met at least *two* of the following characteristics: male > 45 years of age or female > 55 years of age; 'never' or 'past' smoker (with at least 2 months smoking cessation); low-density lipoprotein (LDL) cholesterol >160 mg/dl or on lipid lowering medication; high-density lipoprotein (HDL) cholesterol < 40 mg/dl or on lipid medication; total cholesterol >240 mg/dl or on lipid medication; high sensitivity C-reactive protein between 3 mg/dl and 10 mg/dl; hypertension (blood pressure > 140/90 mmHg) or on blood pressure medication; elevated Apolipoprotein (a) > 30 mg/dl; or Body Mass Index (BMI) $\geq$ 30 (kg/m^2). Participants in this study were current or past employees of Silverton Hospital in Silverton, Oregon and were screened for risk factors prior to enrollment by the nurse case manager.

The purpose of the screening process was to determine potential participant's eligibility to collect baseline information. These meetings consisted of individual meetings with the nurse case manager, who reviewed the individual's health history and lipid panel lab records, and measured height, weight and blood pressure. After this meeting, those who met the eligibility criteria provided consent, and agreed to the program schedule and nutrition guidelines. It was only after eligibility was determined and after consent was given, that MDCT scans were scheduled. All MDCT scans were taken prior to the first week of *Wellspring Heart* classes.

To ensure confidentiality, all data were de-identified prior to entry and data were stored in password-protected computer file. Prior to data entry, the nurse case manager and lead physician reviewed results from MDCT scans, functional capacity tests and lipid panels. Research assistants and program staff entered data for this study from November 2007 to March 2009. To protect the identity and privacy of *Wellspring Heart*

participants, all clinicians, employees and volunteers working at Wellspring Medical Center completed HIPAA training, and all medical practices and associated risks were disclosed with participants prior to their enrollment into this program. The Oregon Health & Science University Institutional Review Board determined this study to be non-human subject research, IRB #:00004405.

Variables and Coding

Measurement of the Outcome Variable

The outcome variable of interest was change in CAC score, measured by Sensation 64 MDCT using Agatstons method to score CAC (Siemens Medical Solutions Forchheim, Germany). Both baseline and 1-year scans were performed at Silverton Hospital, Silverton, OR. One hour prior to the MDCT scans, Metoprolol was administered to participants so that heart rates were below 60 beats/minute (dosage varied by participant). Immediately prior to the scan, 90 ml Visipaque-320 was administered intravenously for color contrast and a 50 ml saline flush followed. Serial axial MDCT images of the heart were obtained through 0.5 mm thickness using gantry rotation of 400 meter-seconds, and following the scan, a single sublingual nitroglycerin spray (1/150 grain) was administered. A radiologist, who was neither affiliated with *Wellspring Heart* nor knowledgeable of participant's progress in the program, read MDCT scans.

Raw CAC score change and percent change were measured for each participant. Raw CAC score change was calculated by subtracting the baseline CAC score from the 1-year CAC score for each participant. Percent change was calculated using a Symmetrized Percent Change equation[34] (Equation 1.1) where B= baseline data, and F= follow-up data.

Equation 1.1 SPC = [(F-B)/(B+F)]*100

SPC is a folded percent change, which is robust to baseline zeros, has a bounded range (from -100% to 100%) and treats baseline and follow-up measures symmetrically.[34] To improve the interpretability of SPC, an inverse transformation knows as a Robust Percent Change (RPC) was calculated, which allows SPC to be analyzed as the traditional percent change scale (Berry and Ayers, 2006).

Equation 1.2 RPC= (200*SPC)/ (100-SPC)

RPCs were calculated for each participant with follow-up data. As a continuous outcome, RCP was used in multivariable linear regression. To perform multivariable logistic regression, it was determined whether participants experienced less than a 20 point increase in RPC; this was expressed as a binary outcome of 'Yes' (coded 1) or 'No' (coded 0).

Measurement of Explanatory Variables

The explanatory variables of interest in this study included: LDL cholesterol, systolic blood pressure, diastolic blood pressure, BMI and functional capacity. These variables are described in Table 1, and plans for analysis are provided in the *Statistical Analysis Plan*. These variables were of greatest interest because they are known risk factors for CAD and are highly associated with disease progression.[6]

LDL cholesterol was measured from twelve-hour fasting blood draws taken from each participant at the screening visit, 12-weeks and 1-year. Specimens were collected at a central lab located at the Silverton Hospital and reviewed by the nurse case manager prior to data entry. Since not all participants received 1-year LDL measures, changes that

occurred during the first 12-weeks of the program were used in regression analyses. Change in LDL was measured as a raw, continuous variable by subtracting baseline LDL levels from 12-week LDL levels, and also as a RPC (Equation 1.2)

The hospitalist at Silverton Hospital administered functional capacity tests with *Mortara X-Scribe* equipment (Milwaukee, WI). This type of stress test is an approved test by the American College of Cardiology and the American Heart Association and provides a comprehensive, objective test of each participant's ability to perform work-related tasks, measured in METs. METs are a unit of measurement that corresponds to the heat produced by the body during activity, 1 MET = 50 kcal/hour/m^2 of body surface area. Functional Capacity (FC) tests were given at baseline, 12-weeks and 1-year. Changes in FC that occurred during the first 12-weeks of the program were examined in regression analyses. Raw change in FC was measured by subtracting baseline FC levels from 12-week FC levels and also as a RPC (Equation 1.2)

The nurse case manager measured BMI, systolic and diastolic blood pressure during patients' screening visits, 12-week and 1-year follow-up visits. Changes that occurred during the first 12-weeks of the program were examined in regression analyses. Raw changes in anthropometric measures were calculated by subtracting baseline values from 12 week values, and BMI and blood pressure changes were also measured as RPC (Equation 1.2).

Table 1. Explanatory and outcome variables of interest.

Characteristic	*Variable type*	*Coding for analysis*
1-Year Raw CAC Score Change	Outcome	Continuous
1-Year Robust Percent Change in CAC Score	Outcome	Continuous
Less than 20% RPC	Outcome	1=Yes 0= No
12-week BMI Change (raw and RPC)	Explanatory	Continuous
12-Week LDL Change (raw and RPC)	Explanatory	Continuous
12-Week FC Change (raw and RPC)	Explanatory	Continuous
12-Week SBP Change (raw and RPC)	Explanatory	Continuous
12-Week DBP Change (raw and RPC)	Explanatory	Continuous

Confounders and Covariates

Aside from the primary explanatory variables of interest, other data were available for analyses, including personal characteristic data and medication data. Medication use among participants was identified as a potential confounder *a priori*, as certain medications are related to the exposure variables of interest and CAC progression. Medication assessment occurred through baseline and 1-year chart reviews. At both time points, participants were categorized as either taking the medication ('Yes') or not taking the medication ('No'); an exact form of McNemar's test assessed whether there were significant changes in medication use over follow-up (Table 2). No specific dosages were analyzed. Lipid lowering and hypertensive medications were of particular interest in this study.

The following population characteristics were also assessed: age, alcohol intake (units/week), annual household income, cohabitation status, education, ethnicity, baseline ejection fraction, family history of CAD, gender, hypertension status, hyperlipidemia status, obesity status, previous CAD diagnosis, and smoking history. These variables were used to describe the population of *Wellspring Heart* participants and are shown below (Table 3). Also, these variables were assessed as confounders in regression

analyses and were considered as such if, when added to the model, beta-coefficients of explanatory variables changed by 10%.

Table 2. Medications analyzed at baseline and 1-Year follow-up.

Variable	*Possible Responses*	*Coding for Analysis*	*Times Measured*
Aspirin	No or Yes	0= No 1= Yes	Baseline and 1- Year
Beta Blockers	No or Yes	0= No 1= Yes	Baseline and 1- Year
Calcium Channel Blockers	No or Yes	0= No 1= Yes	Baseline and 1- Year
Ace Inhibitors	No or Yes	0= No 1= Yes	Baseline and 1- Year
Lipid Lowering Medication	No or Yes	0= No 1= Yes	Baseline and 1- Year
Oral Antiglycemics	No or Yes	0= No 1= Yes	Baseline and 1- Year
Arthritis Medication	No or Yes	0= No 1= Yes	Baseline and 1- Year
GI Medication	No or Yes	0= No 1= Yes	Baseline and 1- Year
Menopause Medication	No or Yes	0= No 1= Yes	Baseline and 1- Year

Table 3. Static participant characteristics, measured at baseline.

Variable	*Variable Source*	*Possible Responses [coding]*
Age	Medical Record	Captured as age in years among participants between 40 and 89 years. Participants older than 89 years were captured in a range of '90 or above' [continuous]
Alcohol Use	Self-Reported	Unites/Week [continuous]
Annual Household Income	Self-Reported	<$100,000 [0] > $100,000 [1]
Education Level	Self-Reported	High school graduate [1] Partial college or specialty training [2] College graduate [3] Graduate degree [4]
Ejection Fraction	MDCT scan	The % of blood pumped out of the left ventricle with each heart beat [continuous]
Smoking History	Self-Reported	Never Smoker [0] Former Smoker with at least 2 months cessation [1]

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Table 3. *Continued*

Variable	*Variable Source*	*Possible Responses [coding]*
Gender	Medical Record	Male [0] Female [1]
Cohabitation Status	Self-Reported	Lives with other [0] Lives alone [1]
Ethnic Origin	Self-Reported	White [1] Hispanic [2] Asian [3] American Indian/Alaska Native [4] Black [5] Indian Subcontinent [6] Filipino [7] Middle Eastern [8] Other [9]
Diabetes Status	Medical Record	No [0] Yes [1]
Diabetes Type	Medical Record	Type 1 [1] Type 2 [2]
Hypertension	Medical Record	Blood pressure > 140/90 mmHg or on hypertension medication? [Yes=1; No=0]
Hyperlipidemia	Medical Record	LDL> 160 mg/dl or on lipid lowering medication? [Yes=1; No=0]
Family History of Coronary Heart Disease	Medical Record	Male relative < less than 55 years of age that has had a heart attack or died from a heart attack; or a female relative (mother or sister) less than 65 years of age that has had a heart attack or died from a heart attack? [Yes=1; No=0]
Obesity	Medical Record	BMI>25? [Yes=1; No=0]

Statistical Analysis Plan

Data Management

The database contained information regarding baseline, 12-week and 1-year measures of explanatory variables, as well as baseline and 1-year CAC scores. These data were joined with baseline characteristics and medication data, based on participant ID number. After data were joined, new variables were generated. An indicator variable was generated to designate whether participants received a follow-up MDCT scan, and

among those with baseline and follow-up MDCT scans, a variable for raw change and RPC was generated. An indicator variable was generated to designate whether participants experienced less than 20% CAC progression (RPC). Other generated variables included raw and robust percent change in BMI, LDL, FC, SBP and DBP that occurred between baseline and 12-weeks. All data were imported into Stata 10.1 (StataCorp LP, College Station, TX) for statistical analyses.

Descriptive Statistics

First, it was determined whether follow-up data among participants who received both MDCT scans differed significantly from those who did not receive both MDCT scans. To assess whether these groups were significantly different from one another, differences in baseline characteristics were assessed using t-tests on continuous variables and Pearson's Chi-square tests on categorical variables; Fisher's Exact Test was used if more than 20% of expected cell counts were less than 5 or if a cell had an expected value less than 1. These tests were performed at $\alpha=0.05$ significance level. Differences in explanatory variables were also assessed using t-tests at each time point with mean, median, standard error, and minimum and maximum reported to summarize the distribution of data.

Data among those with both MDCT scans were of greatest interest since these data were used for regression analyses. Paired t-tests compared baseline and 12-week measures for the continuous variables of interest, and mean, median, standard error and minimum and maximum values were examined. The distributions of RPC values of CAC, BMI, LDL, FC, SBP and DBP were also assessed through histograms and

summary statistics. Positively skewed data were also reassessed after log transformation.

To determine whether baseline and 1-year CAC scores changed significantly, a paired t-test was used. After grouping participants into those with less than and greater than 20% CAC progression, mean BMI, LDL, FC, SPB and DBP RPCs were assessed for their ability to discriminate between the two outcomes using likelihood ratio χ^2 test. A significance level of $\alpha=0.05$ was also used for these analyses.

Regression Analyses

Prior to model building, scatter plots of data and pairwise Spearman correlations were assessed between 1-year CAC score change (measured as RPC) and 12-week changes in the explanatory variables (measured as RPC). The first step in the model building process was univariate analysis of each explanatory variable using a significance level of $\alpha=0.25$. Variables that were significant at $\alpha=0.25$ level were added to a larger model and the covariates age, sex, ethnicity and smoking status were added to the model individually to determined whether they had an effect on the β-coefficients corresponding to each explanatory variable. Other variables available for analyses were also assessed as possible predictors of CAC progression, and the final model used a significance level of $\alpha=0.05$. To assess the linear regression models, residuals versus fitted value plots, linear prediction plots, and P-P and Q-Q plots were generated. Also, graphs of leverage and Cook's distance were generated, and adjusted R^2 values were examined to assess models.

Multivariable logistic regression analysis illustrated the predictive ability of 12-week changes in the explanatory variables (measured as RPC) on whether participants had a less than 20% CAC progression over 1-year. Change in exposure variables were

first analyzed through univariate analyses and were considered significant at $\alpha = 0.25$ significance level. Significant variables were then examined in larger logistic regression models, and covariates were assessed by individually being added to the final models. The Hosmer-Lemeshow Goodness of Fit Test was used to determine whether the model accurately described the data and a Receiver Operating Characteristic curve was used to characterize the predictive ability of the model. Also, BIC and AIC values were examined when multiple models provided similar fits of the data.

Multivariable linear and logistic regression models that included the primary predictors of interest were built to achieve the third specific aim of this study (Table 4.). With a small number of observations, it was expected that not all variables would be included in final models.

Table 4. Primary multivariable linear and logistic regression models of interest in this study.

Explanatory Variable	***Outcome Variable***	***Model***
Δ BMI, Δ LDL, Δ FC, Δ SBP, Δ DBP	Δ CAC SCORE (1-Year)	Linear Regression
Same	Δ CAC RPC< 20% (1-Year)	Logistic Regression

Δ BMI, LDL, FC, SBP, DBP= 12-week Robust percent change

Results

Wellspring Heart Population Characteristics

A total of 55 participants completed the first year of the *Wellspring Heart* program, however, only 22 participants (40%) received a second MDCT scan. Reasons that participants did not receive a second scan were that they had an initial CAC score of zero, no longer presented multiple risk factors for CAD after one year, or the participant did not wish to undergo a second scan. A summary of baseline characteristics of the entire study population is provided below (Table 5 a & b), as is a comparison of those who did and did not receive a second MDCT scan after one year of the program (Table 6 a & b).

These results indicate that the sample of participants receiving follow-up MDCT scans were not statistically different than those without MDCT scans with regards to: income, education, ethnicity, cohabitation status, smoking history, hypertension status, family history of CAD, prior CAD diagnosis, obesity status, alcohol intake and ejection fraction. However, participants with follow-up MDCT scans were significantly different (α=0.05) from those without follow-up scans with regards to gender and age distribution. The mean age of those receiving a second scan was 4.7 years greater than those not receiving a second scan (95% CI: 0.93 to 8.4 years greater, two sample t-test, p=0.0154). And, there was a statistically significant association between gender and MDCT follow-up, where males accounted for 64% of follow-up scans (χ_1^2= 4.9, p=0.027). Further analyses indicated that among men, the odds of receiving a second MDCT scan is 3.5 times those for women (95% CI: 1.13- 10.84, p= 0.03) and for a 1-year increase in age,

the odds of receiving a second scan increases by 12%. (OR= 1.12, 95% CI: 1.02-1.2, p=0.021).

Table 5a. Baseline categorical demographic and clinical characteristics of *Wellspring Heart* participants.

Characteristic	*Categories*	*n*	*Percent*
Annual Household Income (n=44)	< $100,000	21	47.7%
	> $100,000	23	52.3%
Cohabitation Status (n=53)	Lives with other(s)	48	90.6%
	Lives alone	5	9.4%
Education (n=50)	High school graduate	4	8%
	Partial college or specialty training	19	38%
	College graduate	18	36%
	Graduate degree	9	18%
Ethnicity (n=51)	White	45	88.2%
	Hispanic	3	5.9%
	Native America	2	3.9%
	Asian	1	2%
Family History of CAD (n=24)	No	13	54.2%
	Yes	11	45.8%
Gender (n=55)	Male	25	45.5%
	Female	30	54.6%
Hyperlipidemia (n= 24)	No	7	29.2%
	Yes	17	70.8%
Hypertension (n= 28)	No	9	32.1%
	Yes	17	60.7%
Obesity (n=35)	No	13	37.1%
	Yes	22	62.9%
Previous CAD Diagnosis (n=34)	No	14	41.2%
	Yes	20	58.8%
Smoking History (n= 50)	Never Smoker	31	62%
	Former Smoker	11	38%
MI History (n=15)	No	12	80%
	Yes	3	20%
Revascularization History (n= 28)	No	21	75%
	Yes	3	10.7%
	Unknown	4	14.3%
CABGS (n= 28)	No	27	96.4%
	Yes	1	3.6%
Stent Procedure (n= 28)	No	26	92.9%
	Yes	2	7.1%
Diabetes Status (n= 28)	No	25	89.3%
	Yes	3	10.7%
Diabetes Type (n= 3)	Type 1	0	0.0%
	Type 2	3	100%

Table 5b. Baseline continuous demographic and clinical characteristics of *Wellspring Heart* participants at baseline.

Characteristic	*n*	*Mean (SD)*	*Median*	*Min*	*Max*
Age	55	57.6 (7.1)	58.1	42.8	72
Alcohol Intake (units/week)	50	4.5 (5.1)	2	0	16
Ejection Fraction	51	62 % (12.1)	62	5	79

Table 6a. Comparison of categorical baseline demographic and clinical characteristics of *Wellspring Heart* participants with and without both baseline and follow-up MDCT scans.

Characteristic	*Categories*	*Received 2 MDCT Scans*	*Did not receive 2 MDCT scans*	*p-value*
		n (%)	**n (%)**	
Annual Household Income (n=44)	< $100,000	8 (47.1%)	13 (48.1%)	0.944
	> $100,000	9 (52.9%)	14 (51.9%)	
Cohabitation Status (n=53)	Lives with other(s)	19 (90.5%)	29 (90.6%)	0.986
	Lives alone	2 (9.5%)	3 (9.4%)	
Education (n=50)	High school graduate	2 (10%)	2 (6.67%)	0.923
	Partial college or specialty training	7 (35%)	12 (40%)	
	College graduate	8 (40%)	10 (33.3%)	
	Graduate degree	3 (15%)	6 (20%)	
Ethnicity (n=51)	White	18 (90%)	27 (87.1%)	0.408
	Hispanic	1 (5%)	2 (6.5%)	
	Native America	1 (5%)	0	
	Asian	0	27 (87.1%)	
Family History of CAD (n=24)	No	6 (37.5%)	7 (36.8%)	0.557
	Yes	10 (62.5%)	12 (63.2%)	
Gender (n=55)	Male	14 (63.6%)	11 (33.3%)	0.027*
	Female	8 (36.4%)	22 (66.7%)	
Hyperlipidemia (n= 24)	No	3 (18.75%)	4 (21.1%)	1.000
	Yes	13 (81.25%)	15 (79.0%)	
Hypertension (n= 28)	No	6 (37.5%)	7 (36.8%)	0.405
	Yes	10 (62.5%)	12 (63.2%)	
Obesity (n=35)	No	4 (25%)	9 (47.4%)	0.172
	Yes	12 (75%)	10 (52.6%)	
Previous CAD Diagnosis (n=34)	No	8 (53.3%)	9 (47.4%)	0.201
	Yes	7 (46.7%)	10 (52.6%)	
Smoking History (n= 50)	Never Smoker	11 (55%)	20 (66.67%)	0.405
	Former Smoker	9 (45%)	10 (33.33%)	

***= significant at 0.05 level**

Table 6b. Comparison of continuous baseline demographic and clinical characteristics of *Wellspring Heart* participants with and without both baseline and follow-up MDCT scans.

	Received 2 MDCT scans				***Did not receive 2 MDCT scans***				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline Age	22	60.4 (6.5)	48.6	72	33	55.7 (6.9)	42.8	70.2	0.0154*
Alcohol Intake	20	4.3 (5.5)	0	14	30	4.6 (4.9)	0	16	0.806
Ejection Fraction	20	62.7 (7.3)	52	75	31	61.5 (14.6)	5	79	0.746

Variables of Interest

Differences in baseline, 12-week and 1-year measures were examined among all participants for the following characteristics: BMI, low-density lipoprotein, functional capacity, systolic blood pressure, and diastolic blood pressure (Table 7). It was then determined whether these measures differed among those with and without complete follow-up. These data indicate that there were no statistically significant differences between participants who received 1-year MDCT scans and those who did not at each time point for each variable of interest.

Table 7. Comparison of explanatory variables of interest between participants with and without follow-up MDCT scans measured by t-tests at each time point.

A. Body Mass Index

	Received 2 MDCT scans				*Did not receive 2 MDCT scans*				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline	22	33 (8.7)	18.7	55.4	32	30.9 (6.6)	21.3	46.7	0.328
12-weeks	22	29.5 (6.6)	17.8	47.5	32	29.03 (5.6)	20.4	43	0.769
1-year	12	29.7 (5.7)	22.8	43	10	27.8 (5.1)	21.1	37.9	0.422

B. Low Density Lipoprotein

	Received 2 MDCT scans				*Did not receive 2 MDCT scans*				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline	22	122.8 (39.0)	44	199	33	116.5 (33.7)	57	209	0.525
12-weeks	22	93.2 (29.1)	39	158	30	100.1 (26.5)	59	169	0.379
1-year	13	101.3 (23.4)	58	134	11	108.7 (29.1)	69	162	0.50

C. Functional Capacity

	Received 2 MDCT scans				*Did not receive 2 MDCT scans*				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline	22	9.0 (3.3)	2.1	15.1	33	8.9 (2.5)	5.5	17.1	0.931
12-weeks	22	12.7(3.7)	7.05	21.4	28	12.1(2.5)	7.05	17	0.5065
1-year	12	11.2 (3.3)	6.4	19.3	10	10.2 (2.2)	7.2	14.4	0.4283

D. Systolic Blood pressure

	Received 2 MDCT scans				*Did not receive 2 MDCT scans*				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline	22	137.6 (22.3)	100	186	33	133.3 (19.9)	100	176	0.4583
12-weeks	22	118.8 (9.5)	106	144	32	120.6 (14.7)	94	170	0.6167
1-year	12	129.5 (15.3)	104	152	10	126.8 (18.3)	100	150	0.7103

E. Diastolic Blood Pressure

	Received 2 MDCT scans				*Did not receive 2 MDCT scans*				
	n	***Mean (SD)***	***Min***	***Max***	***n***	***Mean (SD)***	***Min***	***Max***	***P- value***
Baseline	22	83.4 (12.3)	60	102	33	80.1 (11.1)	60	106	0.3065
12-weeks	22	71.2 (8.7)	50	84	32	70.2 (7.3)	58	84	0.6527
1-year	12	72.8 (9.62)	60	90	10	69.6 (6.5)	62	80	0.3778

Participants Receiving both MDCT scans

For the purpose of answering the research questions and achieving the specific aims, results concerning participants with both baseline and follow-up MDCT scans were of greatest interest. CAD risk factor changes were assessed for these 22 participants and changes in CAD risk factors were assessed during the first 12-weeks of *Wellspring Heart* because there was complete follow-up at this time point for all participants, and it was during the most 'intensive' part of the *Wellspring Heart* program with regards to lifestyle modification.

Outcome and Explanatory Variables

We used a paired t-test to determine whether participants who experienced CAC progression also experienced significant changes in BMI, LDL, FC, SBP and DBP over the first 12-weeks of the *Wellspring Heart* program. One-sided p-values were reported because it was expected that participants would reduce BMI, LDL, SBP and DBP measures overtime, but increase FC levels and CAC score. One sample t-tests were also performed on RPC variables, and one-sided p-values were reported, since it was expected that RPC would be greater than zero. At $\alpha=0.05$ level, all explanatory and outcome variables changed significantly (Table 8).

Table 8. Twelve-week raw change and RPC in explanatory and outcome variables of interest (n=20).

Variable	*Mean (SE)*	*95% CI*	*Median*	*Min*	*Max*	t_{21}	P^0
BMI							
Raw Change	-3.6[a] (0.69)	(-5.1, -2.2)	-2.5	-14.2	-0.8	-5.2	<0.001*
RPC	-9.71[b] (1.3)	(-12.5, -7.0)	-8.5	-29.5	-3.2	-7.4	<0.001*
LDL							
Raw Change	-28.6 (5.8)	(-40.7, -16.4)	-28.6	-83.0	35.0	-4.9	<0.001*
RPC	-21.1 (4.9)	(-31.4, -10.8)	-22.7	-61.0	36.8	-4.3	<0.001*
Functional Capacity							
Raw Change	3.5 (0.6)	(2.3, 4.7)	3.5	0	9.9	6.0	<0.001*
RPC	55.9 (13.2)	(28.2, 83.5)	42.1	0	235.7	4.2	0.002*
Systolic Blood Pressure							
Raw Change	-20.95 (5.2)	(-31.8, -10.1)	-16.0	-76.0	20.0	-4.0	0.004*
RPC	-13.1 (3.3)	(-20.0, -6.1)	-11.8	-40.9	17.9	-3.9	0.005*
Diastolic Blood Pressure							
Raw Change	-12.95 (2.7)	(-18.7, -7.2)	-12.3	-40.0	10.0	-4.7	<0.001*
RPC	-14.1 (3.1)	(-20.5, -7.6)	-15.3	-44.4	16.1	-4.6	<0.001*
CAC Score (1-Year)							
						t_{19}	
Raw Change	48.5 (26.1)	(-6.14, 103.0)	14.5	-28	534	1.9	0.0394*
RPC	151.5 (60.9)	(24.1, 279.0)	42.9	0	1066.7	2.5	0.011*
Outlier removed							
						t_{18}	
Raw Change	22.9 (5.5)	(11.3, 34.5)	17	0	79	4.2	0.0003*
RPC	153.0 (64.2)	(18.2, 287.8)	39.1	0	1066.7	2.4	0.014*

[0] All p-values reflect one-sided tests, * significant at 0.05 level

a. Value -3.6 is interpreted as a 3.6 unit reduction in mean 12-week BMI compared to mean baseline BMI

b. Value -9.71 is interpreted as a 9.71% reduction in mean 12-week BMI compared to baseline BMI.

These results indicate that over the course of 12 weeks, on average, participants reduced BMI by nearly 10%, LDL cholesterol by 21%, SBP by 13%, and DBP by 14%. On average, the group improved functional capacity by over 50%. Wilcoxon signed-ranked tests were also performed on each variable above, and all conclusions were consistent with those shown above.

With regards to CAC score progression, the mean CAC score increased by 48.5 (± 26) Agatstons—a 151% increase from baseline (Table 8). The magnitude of the mean raw change was influenced by an outlying observation—a participant with a CAC score increase of 534 points. After removing this observation, the mean CAC change lowered to 22.9 (± 5.5) units. Mean RPC did not change much after removing this observation because the RPC that corresponded to this outlier was not an outlying RPC value. The max RPC value was generated from an individual with a baseline CAC score of 3, and a follow-up score of 35. Although the raw change between these two scores was not very high, the percent increase on the RPC scale was much greater than other participants; for this individual, a raw change of 32 Agatstons corresponded to a 1,066.7% increase. This participant exemplifies one of the limitations of interpreting CAC score change on the traditional percent scale.

Two participants experienced CAC reductions, and were examined independently of participants with CAC progression. One participant had a 31-point CAC regression, which corresponds to a 90% reduction, and another participant had a 2-point CAC regression, which corresponds to a 1.34% reduction.

Assessment of Medication Change

Medication use did not change significantly when comparing the proportion of participants taking each medication at baseline and 1-year. McNemar's test (exact form) was used to compare baseline and 1-year medication use, and because there were low cell counts (often 0 or 1) in discordant cells, all p-values associated with medication use change equaled 1.0. Although some participants did benefit from CAD improvements

insofar that some medications were no longer necessary, changes were not of statistical significance. No participant started taking a new medication over the course of follow-up, and no participants in this study took nitrates, insulin or psychiatric medications. Medication changes were not evaluated in linear regression models.

Multivariable Linear Regression

Multivariable linear regression was carried out using the outcome variable of CAC change, expressed as RPC, and explanatory variables: BMI, LDL, FC, SPB, DPB, expressed as RPC and raw CAC change. As indicated in Table 8, both raw change and RPCs were statistically significant for explanatory and outcome variables of interest. For this reason, RPC measures were included in regression analyses since it is a more standardized form than raw change. Age, gender, and smoking history were assessed as confounders and covariates.

The variable CAC RPC was positively skewed, and a $\log_2$ transformation was examined. Since there were three CAC RPC values that equaled zero, 0.5 was added to each observation prior to log transformations. With regards to the other predictor variables of interest, BMI RPC and DBP RPC were negatively skewed; LDL RPC and SBP RPC were approximately symmetric and FC RPC was positively skewed, however, the generation of a $\log_2$FC RPC did not improve the fit of tested models. Univariate analyses illustrate the relationship between explanatory variables and the $\log_2$ of CAC RPC (Table 9). Neither of the two participants with CAC regression was included in these analyses.

Table 9. Univariate Linear Regression Analyses, outcome variable = log_2CACRPC.

Variable	*B Coefficient (95% CI)*	*P-value*
BMI (RPC)	-0.034 (-0318, 0.25)	0.804
LDL (RPC)	-0.06 (-0.130, 0.009)	0.085*
FC (RPC)	-0.0002 (-0.028, 0.28)	0.986
SBP (RPC)	0.055 (-0.054, 0.163)	0.303
DBP (RPC)	0.070(-0.046, 0.187)	0.222*
Baseline CAC	0.000178 (-0.015, 0.0157)	0.981
Age	-0.248 (-0.485, -0.010)	0.042*
Gender	1.31 (-1.94, 4.57)	0.407
Smoking History	-1.68(-5.02, 1.66)	0.303
Family History	-0.959 (-5.07, 3.16)	0.623
Baseline Medication	0.057 (-1.303, 1.42)	0.931
Baseline Alcohol	-0.319 (-0.59, -0.049)	0.024*
Baseline Ejection Fraction	0.02 (-0.021, 0.423)	0.073*

* significant at 0.25 level

Pairwise correlations indicated that DBP RPC and SBP RPC were the only two significantly correlated predictor variables (r_s= 0.534, $p<0.05$). To reduce collinearity, these two variables were analyzed separately in models. Incorporating at least one or a combination of the explanatory variables of interest into a linear regression model to describe CAC change was a specific aim of this study, and although many of these variables were non-significant when added to the model, a moderately good fit was achieved with a linear regression model where Log_2CAC RPC was used as an outcome variable and LDL RPC and age, centered at age 55, were explanatory variables (Table 10). This model had an adjusted R^2 of 0.303, and p-value of 0.047. The two participants who experienced CAC regression were excluded from this model. Results from this model indicate that when controlling for change in LDL cholesterol, baseline age was nearly statistically significant (p=0.076); and after controlling for change in LDL cholesterol, a 10 year increase in a participant's age corresponds a reduction in median CAC RPC by 77 %. Therefore, as a person ages, the percent CAC progression decreases.

Table 10. CAC progression predicted by change in low-density lipoprotein cholesterol and age centered at 55 years (Model 1).

Explanatory Variable	*B-Coefficient*	*P-value*	*95% CI*
Δ LDL	-0.0476	0.151	(-0.114, 0.1923)
Age (Centered at 55)	-0.212	0.076	(-0.448, 0.0245)
Intercept	4.98	0.001	(2.43, 7.53)

R^2= 0.303, Adj. R^2= 0.2205 $F_{(2,17)}$ = 3.69, p<0.0468

When other variables were assessed in predicting $\log_2$CAC RPC, both baseline alcohol intake and baseline ejection fractions were found to be significantly associated with the outcome. Neither of these two explanatory variables was hypothesized to be significantly associated with CAC progression, and when included in a model with age and gender, alcohol use remained significant. However, after analyzing the same model with an age*gender interaction term, neither baseline alcohol intake nor baseline ejection fraction were significant (Table 11). The interaction between age and gender was nearly statistically significant at the 0.05 level, and indicates differences in CAC progression among men and women as they age. Results from this model show that when controlling for ejection fraction and alcohol intake, CAC progression among 55-year-old women will be less than that of 55-year old men. However, at about the age of 68, CAC progression among men is less than that of women (Figure 1). This model underlines the importance of examining CAC progression among men and women separately. A 55-year-old woman with an ejection fraction of 62% who consumes 2 drinks per week would experience a 0.62% reduction in median CAC RPC annually, whereas a 55-year-old man with an ejection fraction of 62% who consumes 2 drinks per week would experience a 30.4% reduction in median CAC RPC. Three participants were excluded from this model; two were not included in this model because they experienced CAC regression, and one other participant was not included due to missing baseline alcohol intake data.

Table 11. CAC progression predicted by baseline alcohol intake, ejection fraction, age, and an age-gender interaction (Model 2).

Explanatory Variable	*B-Coefficient*	*P-value*	*95% CI*
Baseline Alcohol Intake (centered at 2drinks/week)	-0.133	0.346	(-0.427, 0.161)
Ejection Fraction (centered at 62%)	0.069	0.517	(-0.155, 0.292)
Age (centered at 55)	-0.522	0.035	(-1.001, -0.043)
Gender	-1.95	0.056	(-5.42, 1.52)
Age (centered at 55)*Gender	0.513	0.054	(-0.010, 1.04)
Intercept	7.523	0.016	(4.82, 10.23)

Outcome Variable: $\log_2$CAC
R^2= 0.605, Adj. R^2= 0.454,$F_{(3,15)}$ = 3.99, p<0.0206

The following figure illustrates the interaction between age and gender that occurs when predicting CAC progression among women and men while controlling for ejection fraction centered at 62% and baseline alcohol intake centered at 2 drinks per week (Figure 1). In addition, a corresponding 95% confidence interval was generated for these estimates using a common mean-square error, which was created in the full model and adjusts for both centered baseline alcohol and centered baseline ejection fraction. From this illustration it is apparent that CAC progression among women (colored blue) remains stable over time relative to CAC progression among men (colored red), which reduces over time.

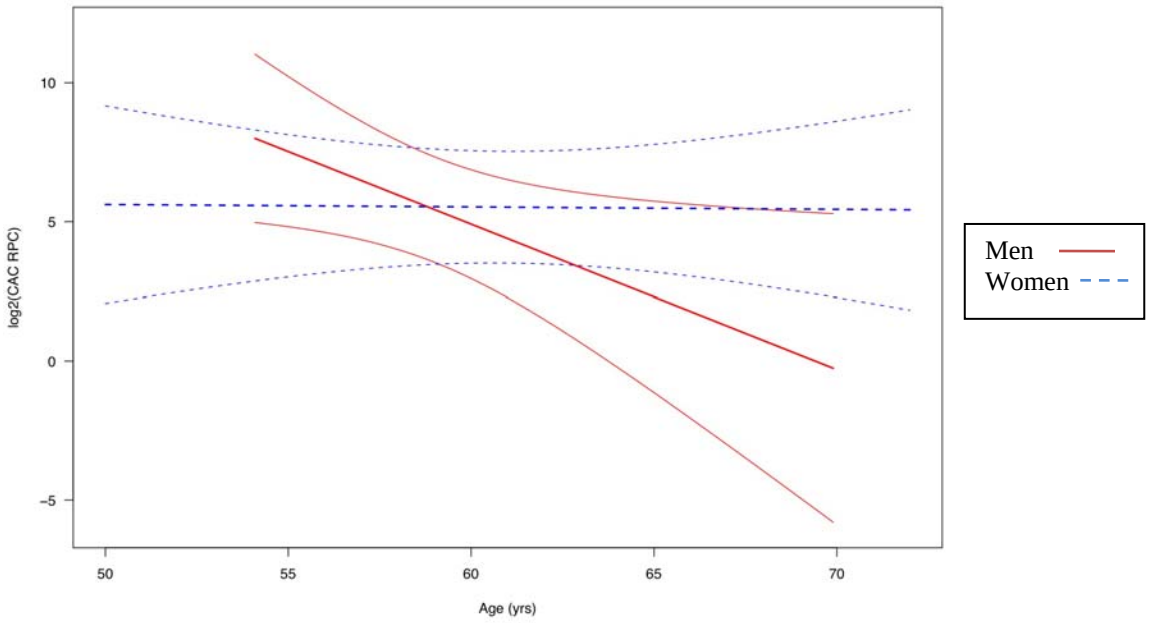

Figure 1. CAC progression among men and women over time and corresponding 95% confidence interval.

The third model examined the outcome variable of 1-year CAC score. This was done to determine whether any of the explanatory variables of interest and baseline CAC scores were significant predictors of follow-up CAC. These results show that when accounting for age, gender and smoking history, the most significant predictor for follow-up CAC score is baseline CAC score (Table 12). These results also show that among individuals of similar age, sex and smoking history, those who differ by 10 units in CAC score at baseline are expected to differ by 11.7 units at 1-year (95% CI: 9.6-13.8 units at 1-year). This model was generated from 19 observations. Two participants were not included because they experienced CAC regression, and one outlying observation was removed.

Table 12. 1-year CAC scores predicted by baseline CAC score, age, gender and smoking history (Model 3).

Explanatory Variable	*B-Coefficient*	*P-value*	*95% CI*
Baseline CAC score (centered at 50)	1.87	<0.001	(1.51, 2.2)
Age (centered at 55)	-2.84	0.316	(-8.7, 3.0)
Gender	-4.07	0.908	(-78.42, 70.3)
Smoking history	-20.3	0.651	(-93.1, 52.5)
Intercept	102.3	0.008	(31.6, 173.1)

Outcome Variable: 1-year CAC score
R^2= 0.92, Adj. R^2= 0.89,$F_{(4,14)}$ = 37.69, p<0.001

Multivariable Logistic Regression

Robust percent change in CAC scores were calculated for each participant, and over half (59.1%) of the participants experienced a greater than 20% increase in CAC over the course of one year (Table 13).

Table 13. CAC progression status.

Characteristic	*Coding*	*n*	*Percent*
CAC regression	Not included in analysis	2	9.1%
Less than 20% increase	1	7	31.8%
Greater than 20% increase	0	13	59.1%

Robust percent change for each explanatory variable of interest was compared between participants who experienced less than 20% CAC progression and participants who experienced greater than 20% CAC progression; those who experienced CAC regression were excluded from analyses (Table 14). There were no significant changes in the BMI, LDL, FC, SBP or DBP between those who did and did not experience 20% annual CAC progression. Differences in the age and gender distributions across these two groups were also examined and found to be statistically non-significant through t-tests and chi-square tests, respectively. Univariate logistic regression was performed with each

of the variables listed below. No single predictor variable was significantly associated with whether or not a participant experienced less than 20% annual CAC progression (Table 15).

Table 14. Explanatory variables of interest stratified by 20% CAC RPC (n=20).

	Annual CAC Change < 20% (n=9)	*Annual CAC Change >20% (n=13)*		
Characteristic RPC	***Mean (SE)***	***Mean(SE)***	χ_1^{2}*	***p-value****
BMI	-9.04 (1.5)	-10.1 (1.9)	0.16	0.69
Low Density Lipoprotein	-17.7 (8.2)	-22.9 (6.3)	0.27	0.61
Functional Capacity	43.9 (11.8)	62.3 (19.4)	0..50	0.48
Systolic Blood Pressure	-10.4 (5.8)	-14.5 (4.2)	0.37	0.54
Diastolic Blood Pressure	-15.7 (6.6)	-13.2 (3.3)	0.15	0.70

* measured from likelihood ratio test

Table 15. Univariate Logistic Regression (n=20).

Variable	***OR (95% CI)***
BMI (RPC)	1.03 (0.87-1.23)
LDL (RPC)	1.01 (0.97-1.06)
FC (RPC)	0.994 (0.98-1.01)
SBP (RPC)	1.02 (0.96-1.1)
DBP (RPC)	0.99 (0.92-1.06)
Baseline CAC	1.0 (0.99-1.01)
Age	1.07 (0.92-1.26)
Gender	0.47 (0.065-3.34)
Smoking History	1.17 (0.17-8.09)
Family History	2.5 (0.19-32.19)
Baseline Medication	0.99 (0.46, 2.14)

Several logistic regression models were made to fit these data, however, the best-fitting model involved baseline CAC score, FC RPC and controlled for age. Among the models compared, the model presented here had the lowest BIC value and greatest area under the ROC curve. Although none of the variables listed in Table 15 was statistically significant at α=0.05, these variables provided insight into some of the variables which

were more closely associated with whether or not participants experienced less than 20% CAC progression (Table 16).

Table 16. Association between experiencing less than 20% CAC progression and both change in functional capacity and age (Model 4).

Explanatory Variable	*Odds Ratio*	*P-value*	*95% CI*
Δ FC	0.993	0.5	(0.97, 1.01)
Age (centered at 55)	1.08	0.326	(0.92, 1.28)
Gender	0.44	0.443	(0.056, 3.53)

Outcome Variable: Less than 20% CAC progression
Likelihood ratio test, $\chi_3^2 = 2.11$, p= 0.551

An ROC curve was generated to illustrate this model (Figure 2). The area under the curve is 0.6923, indicating that the model does not have excellent discriminative ability. However, results from the Hosmer-Lemeshow Goodness of Fit test indicate that this model provides a good fit to these data (χ_{16}^2= 19.16, p=0.2604). It was also determined that this model correctly classifies 65% of participants as having less than 20% annual CAC progression. Results from this model do not provide clear answers to the question of whether participants with greater CAC progression differed from participants with more modest CAC progression. In establishing a clearer understanding of CAC progression over time, assessment of CAC as a continuous variable may be the best method of assessing CAC progression under and above a certain set point.

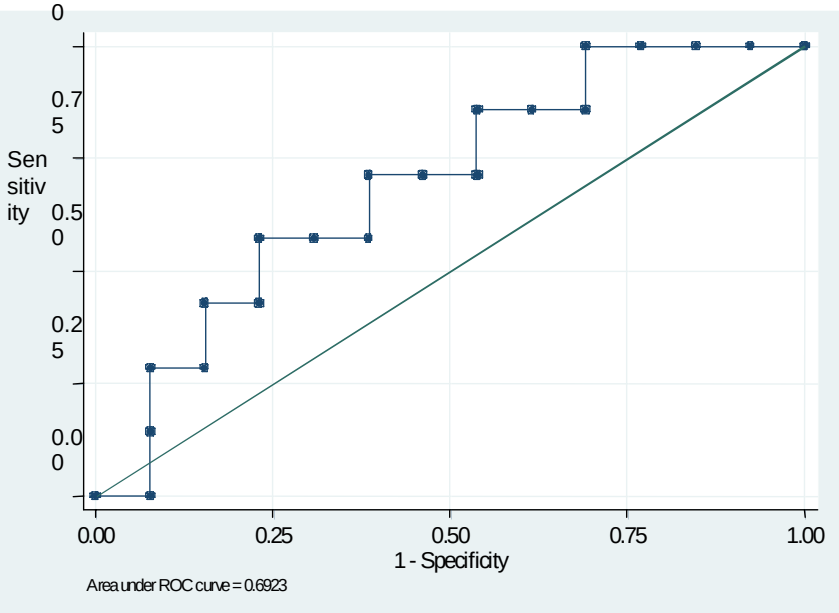

Figure 2. ROC curve for logistic regression model, predicting less than 20% CAC progression when accounting for change in functional capacity, age and gender (Model #4).

Discussion

This study found that the most significant predictor of follow-up CAC scores was baseline CAC scores and that age is the most significant predictor of CAC progression. Another interesting finding from this study, which has not been widely documented in previous research, is the interaction that occurred between age and gender when predicting CAC progression. This interaction is beneficial for clinicians, patients and other researchers because it indicates that CAC progression differs between men and women overtime—specifically showing that men have greater reductions in CAC progression than women. Although Maher and others found that CAC progression decreases with age, these researchers did not observe differences in CAC progression between men and women.[20]

Although no longer significant after controlling for the covariates of age and gender, the finding that baseline alcohol intake was a significant predictor of CAC progression was interesting because multiple reports have examined the risks and benefits of alcohol consumption associated atherosclerosis progression[35,36] and the results from some of these studies remain debated. Although not statistically significant, this model predicts that CAC progression will decrease as alcohol intake (units/week) increases—results that could have interesting implications for *Wellspring Heart* participants and should be carefully assessed in future studies before conclusions are drawn from this small dataset.

Changes in LDL cholesterol were not found to significantly predict CAC progression; however, after controlling for change in LDL, age was nearly statistically significant. This finding may be more pronounced when a greater number of participants

are followed for longer periods of time. Examining change in LDL remains important for future studies as dramatic changes in LDL cholesterol that occurred during the first 12-weeks of *Wellspring Heart* may not have elicited significant physiologic effects on CAC progression over one year. The relationship between change in LDL cholesterol and CAC scores may be better captured when assessing both CAC and LDL over a longer period of time and assessing changes in both hard and soft plaque. And, as suggested by Greenland and others,[6] the exact roles that low-density and high-density lipoprotein cholesterols play in the progression of CAC remains unclear, and future studies will provide greater insight into the relationship between CAC progression and cholesterol.

The results showing that baseline CAC scores significantly predict follow-up CAC scores support the findings by Schmermund and Yoon.[18,19] An interaction between age and gender was examined in this model (Model 3), but was found to be statistically non-significant, and compared to other models that contained the primary explanatory variables of interest, this model provided the best fit to the data in terms of adjusted R^2 values and plots of the residual values, and included the covariates of interest: age, gender, and smoking history. An outlying observation was examined, and model diagnostics were done with and without the observation (comparison in Appendix). Whether the outlier was included or not included in the model, baseline CAC score remained a significant explanatory variable in predicting 1-year CAC score, and the variables age, gender, and smoking history were not significant in either model. A different approach to evaluating these data is to examine CAC change on the SPC scale rather than the more easily interpretable RPC scale; this would reduce the influence of outlying RPC values.

In assessing whether participants had a less than 20% CAC increase, no significant associations existed with any of the explanatory variables of interest. Functional capacity is a strong predictor of heart disease,[37] and when this variable was included in the logistic regression model it provided a good fit to the data, however, remained statistically non-significant. Possibly with more data, a significant association between functional capacity and CAC change will be determined, which will correspond to previously published literature.

Covariates

Besides the variable age, none of the covariates determined *a priori* was significantly associated with CAC progression—whether or not CAC progression was measured as a continuous RPC variable or dichotomized into less than or greater than 20% progression. Much of the literature regarding CAC progression indicates that the greatest predictors of CAC progression are older age, male sex, Caucasian ethnicity, family history and history of smoking,[38-44] each of which are individually discussed below.

Age

Age is used as an estimator of atherosclerotic burden; however there exists substantial heterogeneity among adults of the same age. In future studies, vascular age could be used as a substitute for chronological age to improve risk assessment; then it could be examined whether chronological or vascular age provides a better prediction of CAC progression.[45] Age was found to be a statistically significant predictor of whether participants completed follow-up with a second MDCT scan. Older men were the most likely to receive both baseline and 1-year MDCT scans, and therefore, both gender and

age are important factors in assessing whether participants receive both MDCT scans within this population. An interaction term was generated and examined in analyses; however, it was only found to be significant in one linear regression model (Model 2).

Gender

Differences in CAC progression between genders are typically most substantial in middle-aged populations, [6] and compared to men, women have slower CAD onset until about the age of 60.[46] Also, as these data indicate, CAC progression among women is steadier over time compared to men, and future studies that involve more participants should examine gender-differences in CAC progression among those aged less than 60 years and those older than 60 years to verify the findings of this study and to determine whether CAC progression in men steadies over time.

It is important to account for age and gender differences when analyzing cardiac health and assessing CAD risk factors and this study underlines the need for gender-specific and age-specific reference points when CAC scores are assessed over time. In this study, it was important to determine whether gender differences existed, especially since this sample was composed of middle-aged participants. Among those with complete follow up, age differences across genders did not differ significantly, however when examining all participants, women were less likely to have complete follow-up.

Ethnicity and Family History

Neither ethnicity nor family history was found to significantly predict CAC progression when analyzed through univariate analyses and multivariable linear and logistic regression. Regarding ethnicity, the majority of participants were Caucasian.

Due to this small, non-representative sample, any associations would be subject to selection bias. Family history was also found to be statistically non-significant. These results may have been affected by under reporting if participants either did not know their family's history of CAD, or program eligibility was based on other CAD risk factors causing family history to be a less apparent risk factor. Future studies that involve a much larger sample may provide more data regarding associations between CAC progression and differences in ethnicity and family history.

Smoking History

Any current smoker required at least 2 months of smoking cessation before they would be eligible for *Wellspring Heart.* Therefore, no participants were current smokers, and some previous smokers indicated on their health history surveys that they had abstained from smoking at least 20 years prior to this intervention. Pack years were not assessed in this study, and therefore, it is difficult to make any inference about the relationship between prior tobacco exposure and CAC progression. Future studies would benefit from studying pack-year data to determine whether a closer association exists between CAC progression and smoking history.

Medication Change

Budoff and Lane[11] found that age, gender and number of risk factors failed to predict regression of CAC, and that the only independent predictor of lower follow-up CAC scores was statin use. Despite the results from this observational study, two large statin clinical trials failed to find an association between CAC score and statin use.[47,48] Whether statins promote or slow CAC progression remains unknown, and these

contradictory studies indicate that statin use should continue to be examined in future studies.

Medication use was identified as a potential confounder, and since the proportion of participants taking each medication at baseline and follow-up did not differ significantly, only baseline medication use was assessed in analyses. Baseline lipid lowering medication use was most closely examined in model building but was not significantly associated with CAC progression. Among individuals who changed medications over the course of 1-year, lipid-lowering medications were most often changed. This indicates that participants' cholesterol levels were significantly lower after one year of *Wellspring Heart* and that participants could lower their cholesterol levels through exercise, proper nutrition, stress management, and group support.

Calcium Score Regression

Two participants lowered CAC scores from baseline to follow-up—one individual experienced CAC regression of 28 points and another by 2 points. Although the latter may have been due to inter-scan variability, it is unlikely that a difference of 28 Agatstsons would be due to the same variability. A possible mechanism for CAC regression involves a consolidation of CAC in artery lesions over time or vascular remodeling of hard and soft plaque.[49] These findings were exemplified in an animal model using the rhesus monkey, where calcified lesions decreased in area when monkeys were fed a low cholesterol diet.[49] Regarding *Wellspring Heart* participants, it remains unresolved whether participants who had lower follow-up CAC scores experienced a decrease in calcium or rather a remodeling of calcified plaque. If soft plaque had been

assessed at baseline and follow-up, it may be clearer as to whether changes in soft plaque change accompanied CAC change.

Although 64-MDCT cardiac scans have the capacity to measure both hard and soft plaque, only hard plaque scores were available for this study, and the extent to which coronary artery remodeling occurred could not be ascertained. Soft plaque is an important factor in CAD progression as it represents areas of the artery rich in lipids and macrophages, provides an estimate of coronary stenosis, and it is a precursor to calcified hard plaque.[29,50] Changes in hard plaque are marked by fibrous tissue growth and calcium deposition within the coronary artery.[51] Although high CAC scores correspond to increased risk for future cardiovascular events,[7] recent studies indicate that some degree of CAC progression provides healthful benefits in stabilizing the fibrous cap.[51] With less elasticity and lower metabolic activity than either soft plaque or plaque that is undergoing remodeling, calcified plaque is also less prone to rupture.[50] Contrast-enhanced MDCT is an important tool that would help clinicians and researchers assess changes in both soft and hard plaque over time and determine the extent to which artery remodeling is occurring.

Calcium Score Progression

Nearly 60% of participants in this study had a greater than 20% annual CAC score increase. These data are consistent with previous studies, which found that most individuals experience a greater than 20% increase in annual CAC score.[15,18,20] Since participants in this study were taking on dramatic lifestyle changes within the first 12-weeks of *Wellspring Heart,* it was hypothesized that CAC progression would be less than

that shown in other studies. From this small sample of participants who were followed for a short period of time, CAC progression was much greater than 20% despite anthropometric changes and reductions of CAD risk factors.

Limitations & Strengths

Limitations

The primary limitation of this study is the small sample size and low statistical power. Although there were approximately 55 *Wellspring Heart* participants who received baseline MDCT scans, less than half opted to receive a second MDCT scan at 1-year follow-up. With only 22 participants with both MDCT scans, it is difficult to draw conclusive evidence on the effect of CAD risk factor change on CAC progression.

To determine the power that this study had to detect a significant increase in CAC scores, the mean baseline CAC score and the mean 1-year CAC score were calculated for the 20 participants who experienced CAC progression. A one-sided test was done with $\alpha=0.05$, and the mean baseline and 1-year CAC scores were approximately 80 ($\pm$105) and 127 ($\pm$211) respectively. These data yielded 22.6% power, which is far below the ideal 80% power; this can be attributed to the small sample size and large standard deviations. However, the fact that statistically significant increases in CAC scores were detected despite the low power and sample size, there is confidence that a true difference exists between baseline and 1-year CAC scores, and differences would accentuate as more participants are involved in analyses. On the other hand, if future studies are interested in examining a stabilization of CAC scores and it is hypothesized that CAC scores will not vary over time, a power of 22.6% would be problematic because the probability of

committing a Type II error (concluding that there was no significant change in CAC score, when in reality there was) would be 77.4%.

For a pilot study, these data do offer important information regarding the benefits of annual MDCT scans, the ability to modify CAC progression with lifestyle change, and these data offer further understanding of CAD progression. Therefore, despite the small number of participants included in this study, the results bear weight when assessing CAC progression among individuals who adopt lifestyle changes to reducing CAD risk factors. These results are generalizable to small populations of people, such as those in cardiac rehabilitation programs and future cohorts of *Wellspring Heart.*

Results from this study are subject to selection bias. *Wellspring Heart* had capacity for approximately 30 participants per session, and although there were many eligible Silverton Hospital employees, it was not disclosed as to whether participants were randomly selected. It is possible that selection was based on whether a participant would follow the program guidelines closely since analyses from the first graduating group were used for advertisement purposes to gain support and entice enrollment. If this was the case, future cohorts in *Wellspring Heart* may not experience the same degree of CAD improvement as seen in this study and results would be less generalizable.

Differential loss to follow-up also introduces selection bias due to the fact that those who did receive a second MDCT scan differed from other participants with respect to age and gender. To determine eligibility for a follow-up MDCT scan, participants spoke with the nurse case manager, physician and/or cardiologist to determine whether a second MDCT scan was appropriate. As previously stated, younger individuals and women were less likely to have second CT scans. Interestingly, since MDCT technology

is used to provide patients with an assessment of CAD changes, younger persons would benefit most from these scans because they would have more years ahead of them to practice lifestyle changes and reverse CAD. Decisions to undergo repeated scans, however, should be made only after an individual determines that the benefits of the scan outweigh the risks of radiation exposure associated with the scan; this is discussed further in a later section (page 49).

To reduce the influence of diagnostic bias, outcome and predictor variables were measured using standardized procedures. Observer bias was limited as clinicians not associated with *Wellspring Heart* performed lipid panels, functional capacity tests, and MDCT scans. Standardized instructions and demonstrations were also given to participants in each cohort, and complete 12-week follow-up by the nurse case manager was performed. *Wellspring Heart* participants entered the program with the primary purpose of lowering current CAD and associated risk factors, and adopting healthy lifestyle changes. For this reason it may not be appropriate to generalize results from this study to asymptomatic populations. This research does, however, provide great insight to the benefits that lifestyle modification programs have on reducing CAC scores and CAD risk factors.

Further limitations in this study evolve from potential non-compliance to the program guidelines during the follow-up year. Changes in BMI, LDL, SBP, DBP and FC were evaluated after 12-weeks of the program, and follow-up MDCT scans were performed at 1-year. It is expected that the greatest changes in the explanatory variables would occur during the first 12-weeks of the program since participants met twice a week and were followed more closely with the nurse case manager and modality leaders. After

the 12-weeks, participants were responsible to practice the lifestyle modification techniques independently. It was anticipated participant's compliance to the program guidelines would wane over time, and so *Wellspring Heart* developed exercise classes and nutrition classes for participants. Loss to follow-up over 1-year was evident as some participants failed to schedule exit evaluations. To reduce loss to follow-up, participants were advised to meet with their support groups over the course of the year to continue practicing group support and stress management techniques. This study indicates that if a larger longitudinal study is to be done, improvements in participant follow-up after 12-weeks is necessary.

Strengths

As a pilot study for *Wellspring Heart*, this study demonstrates associations between early changes in CAD risk factors and 1-year progression of CAC. Participants experienced dramatic changes over the course of this program and improved their overall heart health greatly by reducing risk factors, yet it may not be for another two years that changes in hard plaque are more evident. These results also provide information for the *Wellspring Heart* program as further studies are undertaken. If longitudinal studies are to be done in the future, it is vital that individuals without complete follow-up are assessed in analyses. These results also offer information on the use of MDCT scans to monitor CAC progression and provide information to both clinicians and patients.

Future Studies

Following this cohort forward in time, further changes in CAC scores and CAD can be measured and more data will be available for this longitudinal study. In addition to the variables examined in this study, future studies involving *Wellspring Heart* would benefit from including baseline and follow-up soft plaque scores in analyses, other indicators of atherosclerosis progression, such as high-sensitivity C-reactive protein measures, data regarding nutritional compliance, and lastly, an assessment of individuals' Stages of Change.

The importance of including soft plaque assessment in the context of CAC progression in future studies has been discussed previously (page 42). Another important marker of atherosclerosis progression, which was not available for analysis in this study, is high sensitivity C-reactive protein (hsCRP). Large prospective studies have found hsCRP, a biomarker of inflammation, to be an independent predictor of future cardiovascular events.[52] Not only has hsCRP correctly reclassified individuals into more accurate risk categories, but hsCRP has also been found to be as clinically relevant of a CAD event predictor as low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, blood pressure or smoking history.[52]

Nutritional changes that occurred among *Wellspring Heart* participants were not available for this study. Participants of other *Wellspring Heart* cohorts will have these data available in the form of food diaries, which serve as a 'snapshot' of the foods consumed at baseline, 12-weeks and 1-year. These diaries will provide data on the nutritional component of lifestyle modification, and changes that occurred during follow-up will be assessed.

Lastly, future studies would benefit from including participant's self-reported Stage of Change score derived from the Transtheoretical Model in health psychology. These scores provide predictive information about whether a participant is likely to succeed in achieving the proposed lifestyle change, and participants report themselves as being in a *pre-contemplative stage*, not seriously considering change; *contemplative stage*, considering change; *preparation stage*, getting ready to make a change; *action stage*, making the change; or *maintenance stage*, maintaining the change.[53] These scores represent the dominant model used to describe health behavior change[54] and would provide insight into participants' progress during the first 12-weeks of the program and over the year of follow-up. Future studies may determine that participants in the *action* or *maintenance* stage differ from other participants in their likelihood to have follow-up MDCT scans.

Clinical Recommendations

Although MDCT cardiac scans were administered after 1-year of lifestyle modification, going forward, it may be more appropriate to administer cardiac scans every two or three years for these participants. Similar to recommendations released by the AHA and ACC, screening for CAC should be reserved for individuals of intermediate risk (men older than 45 and women older than 55), symptomatic individuals or asymptomatic individuals with a high pretest probability of disease.[6] Also CAC assessment should not be used to predict the presence of coronary luminal stenoses, but rather as a tool to improve risk assessment in the individual patient when the patients' medical histories and CAD risk factors have been closely assessed.[55,56]

Also, there should not be indiscriminant screening for CAC in asymptomatic persons, particularly for those without multiple risk factors. MDCT scans are highly sensitive to CAC [27]and provide an accurate estimate of CAD while preventing the use of invasive and costly angiography.[10] Referral by physician should always be required prior to MDCT scans and it is crucial that each participant weigh the risks of radiation exposure with their risks for CAD progression and the potential benefits that would evolve from scan results.

The major drawback to MDCT is the amount of ionizing radiation to which patients are exposed in comparison to conventional, invasive coronary angiography. The amount of absorbed ionizing radiation varies greatly from person to person when 64-MDCT is used, and recent studies found that obese individuals absorb greater amounts of radiation in comparison to over-weight and normal-weight individuals.[57] Also scan length and absence of stable sinus rhythm are associated with increased dose. However, Takakuwa and others found that emitted radiation can be lowered by tube current modulation.[57]

The amount of ionizing radiation absorbed by patients from 64-MDCT scans ranges from 13 to 21 mSv (milli-Sieverts) when tube current modulation is not practiced; with tube current modulation, doses are typically 7 to 16 mSv. [27,57] Although 64-MDCTs are non-invasive, Hoffman and others found that the radiation dose from these scans was approximately 2-3 times that of diagnostic invasive angiography (4.5 to 10 mSv).[27] For comparison, the occupational exposure limit for an individual who works around radiation in the United States is 50 mSv per year,[13] and therefore, it is highly recommended that individuals do not receive more than one MDCT scan annually.

More accurate estimates of radiation exposure are currently being evaluated, as are ways in which radiation exposure can be reduced. The field of cardiac imaging is growing rapidly, and both clinicians and researchers are hoping to amend that trade-off that occurs with lower radiation doses and poorer quality of images.[58] Discussions about radiation exposure from repeated MDCT scans and the potential benefits of continued CAD and CAC assessment must take place on a patient-by-patient basis with cardiologists. MDCT should be reserved as a test secondary to vague or unclear stress test results, and these scans should not be used in younger, low-risk populations.[26] However, despite these recommendations, there has been growing interest in determining whether MDCT scans act as a motivational tool for improved performance during lifestyle modification programs.[28] Individuals for whom the benefits of MSCT results greatly outweighs the risks associated with radiation exposure, may be inclined to follow lifestyle modification programs more closely and for longer periods of time in comparison to individuals who do not garner the same benefit from repeated scans.

Public Health Impacts

Using MDCT to detect the presence and progression of CAC, combined with lifestyle modification interventions like *Wellspring Heart*, aids in the shift of care from an inpatient setting to the outpatient sector with substantial cost saving. The prognostic validity of CAC as a major CAD risk factor continues to accumulate and has been embraced more widely for preventive programs.[55] Screening appropriate patient populations for CAC may provide early CAD detection and allow patients to make healthy lifestyle modifications or enroll in programs like *Wellspring Heart*. An example

of this was recently shown by Akosah and others [59] where MDCT was successfully used to assess CAC and CAD among individuals admitted to Emergency Departments, and results from these scans provided a more accurate risk assessment than the Framingham Risk Score. These data are especially valuable for developed countries in which technologies continue to advance and the burden of CAD continues to increase. MDCT will not replace the prognostic value of lipid analyses, electrocardiography, nuclear perfusion testing, or stress electrocardiography, but MDCT may guide preventive and therapeutic strategies.[26]

A major public health impact of this research is the potential for MDCT to be assimilated into standard clinical practice. However, prior to routine use, there must be a larger collection of evidence-based studies in peer-reviewed literature. From this pilot research, it is apparent that participants were able to make significant changes in CAD risk factors over time, illustrating the vast benefits of lifestyle modification programs like *Wellspring Heart.* Similar lifestyle modification programs could be implemented for populations at risk around the world which combine improvements in diet, exercise, stress management and group support to significantly reduce CAD burden. Regarding the use of MDCT technology, there are still more studies to be completed prior to assimilation into public health practice.

Conclusion

Regarding the first specific aim of this study, baseline and 1-year CAC score assessment revealed that the majority of participants experienced progressions in CAC over time; however, about 30% of participants had less than 20% progression, and 2 (9%) participants had reductions in CAC over time. In addressing the second specific aim, there were no significant associations between CAC progression and changes in the explanatory variables of interest, including BMI, LDL cholesterol, functional capacity and systolic blood pressure and diastolic blood pressure. Lastly, CAC score change was described through multivariable logistic and linear regression models. Through linear regression, it was determined that age was nearly a significant predictor of annual CAC percent change when controlling change in LDL cholesterol. Also, in assessing CAC progression, an interaction between gender and age was nearly statistically significant when controlling for baseline alcohol intake and baseline ejection fraction. Through the final multivariable linear regression model, it was determined that baseline CAC score was the only significant predictor of 1-year CAC score. Multivariable logistic regression indicated that there were no statistically significant associations between changes in the CAD risk factors of interest and whether participants had a less than 20% annual CAC progression. This report provides beneficial preliminary information about the impact of lifestyle change on CAC progression among *Wellspring Heart* participants, and this study leads the way for larger studies involving *Wellspring Heart* that may reveal closer associations between lifestyle change and CAC progression.

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Appendix. Model Diagnostics for Multivariable Linear Regression Models

A. Table 10. CAC progression predicted by change in low-density lipoprotein cholesterol and age centered at 55 years (Model 1).

Explanatory Variable	*B-Coefficient*	*P-value*	*95% CI*
Δ LDL	-0.0476	0.151	(-0.114, 0.1923)
Age (Centered at 55)	-0.212	0.076	(-0.448, 0.0245)
Intercept	4.98	0.001	(2.43, 7.53)

R^2= 0.303, Adj. R^2= 0.2205 $F_{(2,17)}$ = 3.69, p<0.0468

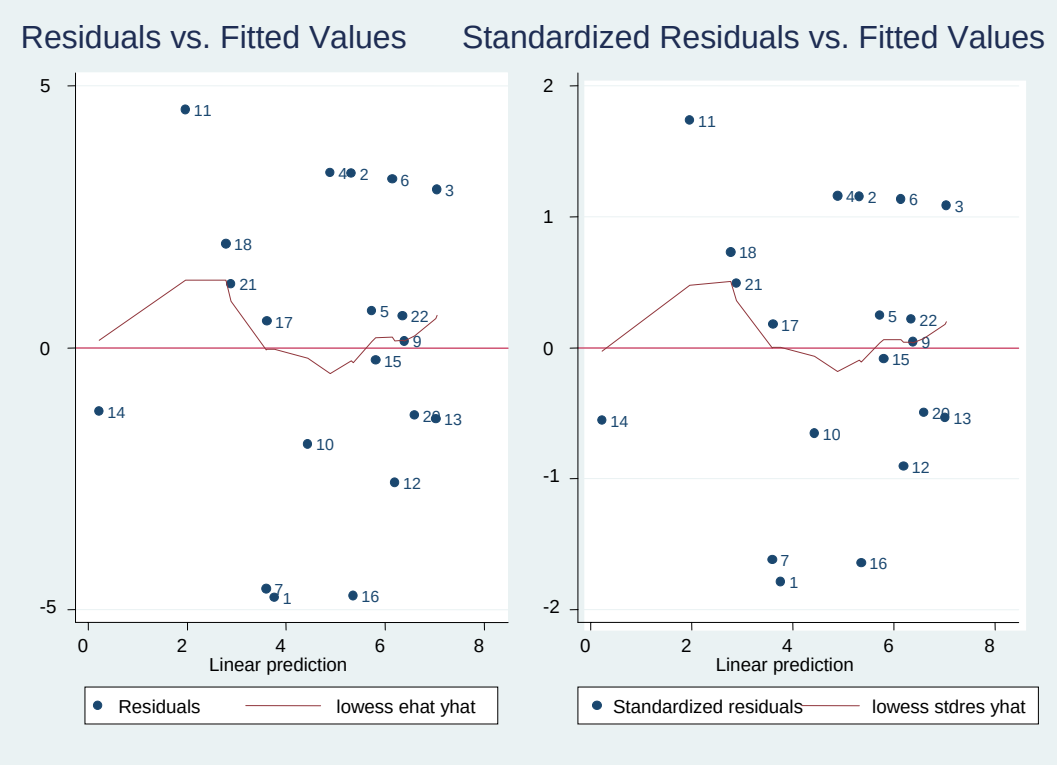

Figure 1.1. Non-standardized and standardized residuals and fitted values for Model 1.

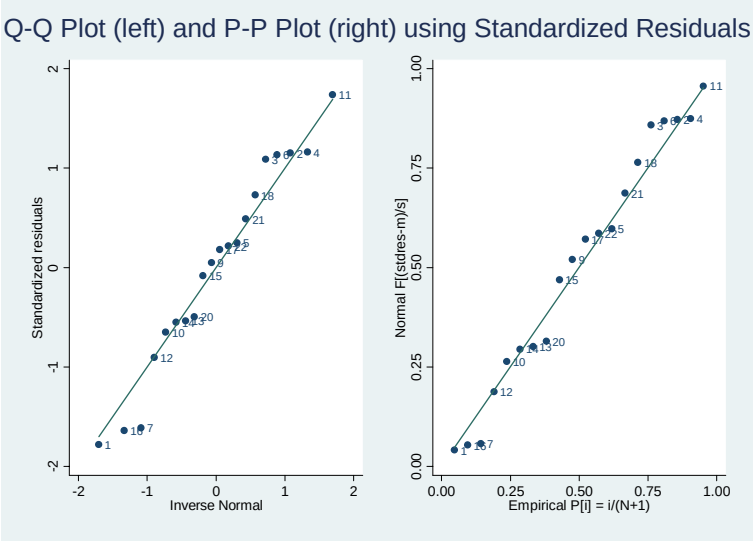

Figure 1.2. P-P and Q-Q plots of standardized residuals from Model 1.

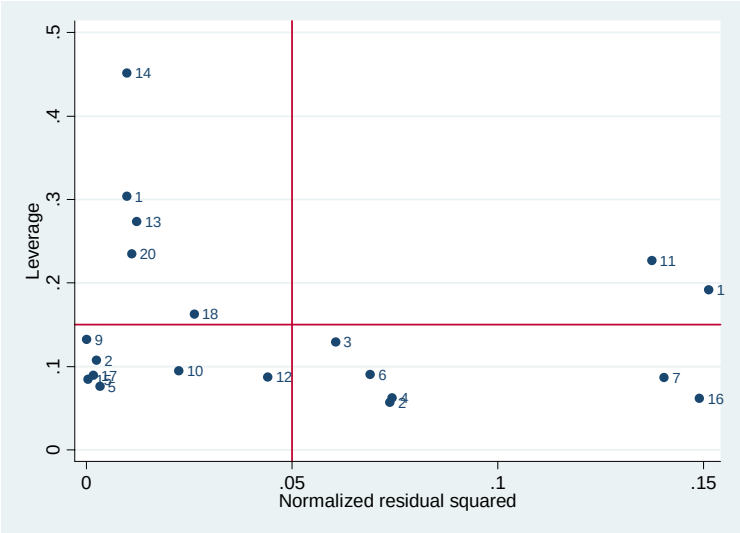

Figure 1.3. Squared normalized residuals versus leverage for Model 1.

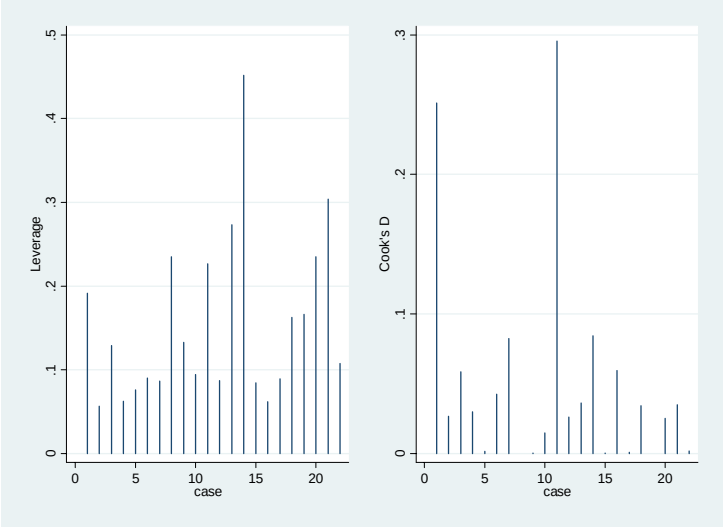

Figure 1.4. Leverage and Cooks Distance of each observation in Model 1.

B. Table 11. CAC progression predicted by baseline alcohol intake, ejection fraction, age, and an age-gender interaction (Model 2).

Explanatory Variable	***B-Coefficient***	***P-value***	***95% CI***
Baseline Alcohol Intake (centered at 2drinks/week)	-0.133	0.346	(-0.427, 0.161)
Ejection Fraction (centered at 62%)	0.069	0.517	(-0.155, 0.292)
Age (centered at 55)	-0.522	0.035	(-1.001, -0.043)
Gender	-1.95	0.056	(-5.42, 1.52)
Age (centered at 55)*Gender	0.513	0.054	(-0.010, 1.04)
Intercept	7.523	0.016	(4.82, 10.23)

Outcome Variable: $\log_2$CAC
R^2= 0.615, Adj. R^2= 0.454,$F_{(3,15)}$ = 3.99, p<0.0206

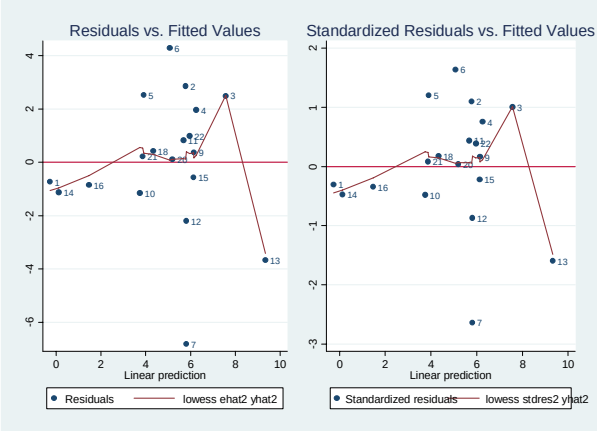

Figure 2.1. Non-standardized and standardized residuals and fitted values for Model 2.

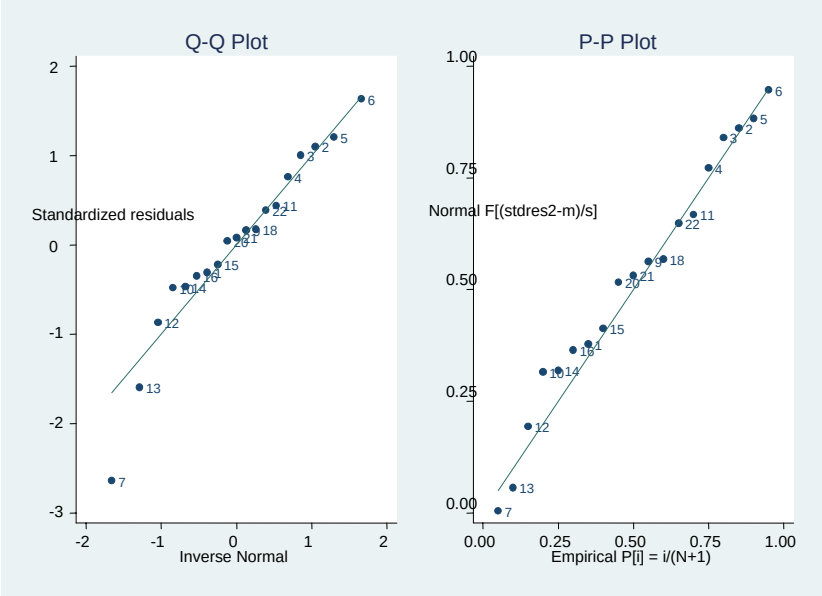

Figure 2.2. P-P and Q-Q plots of standardized residuals from Model 2.

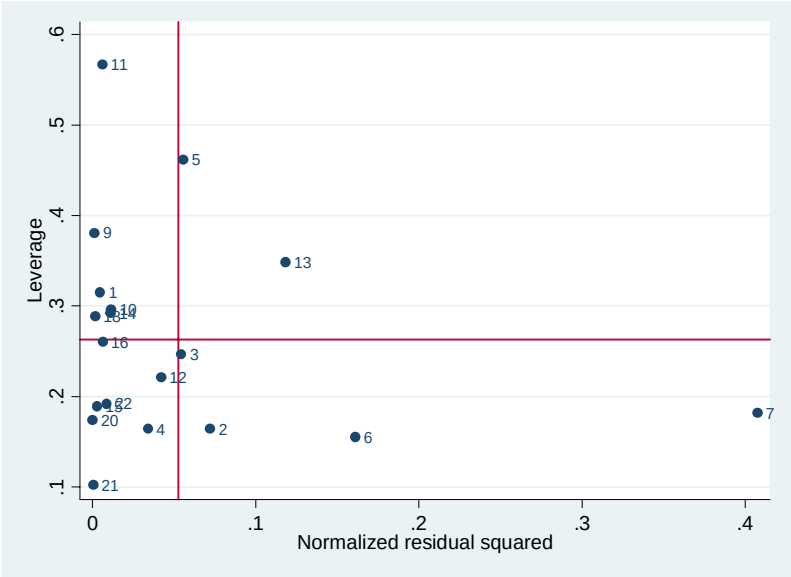

Figure 2.3. Squared normalized residuals versus leverage for Model 2.

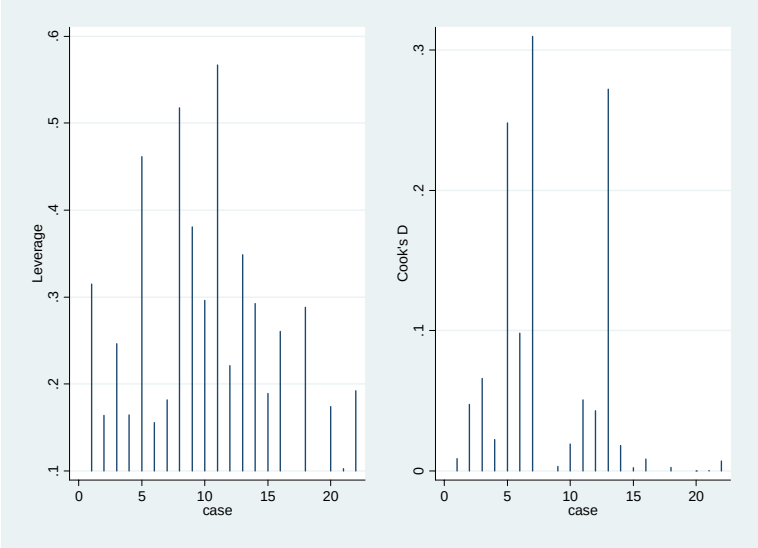

Figure 2.4. Leverage and Cooks Distance of each observation in Model 2.

C. **1-year CAC scores predicted by baseline CAC score, age, gender and smoking history (Model 3).**

Explanatory Variable	***B-Coefficient***	***P-value***	***95% CI***
Baseline CAC score (centered at 50)	1.87	<0.001	(1.51, 2.2)
Age (centered at 55)	-2.84	0.316	(-8.7, 3.0)
Gender	-4.07	0.908	(-78.42, 70.3)
Smoking history	-20.3	0.651	(-93.1, 52.5)
Intercept	102.3	0.008	(31.6, 173.1)

Outcome Variable: 1-year CAC score

R^2= 0.92, Adj. R^2= 0.89,$F_{(4,14)}$ = 37.69, p<0.001

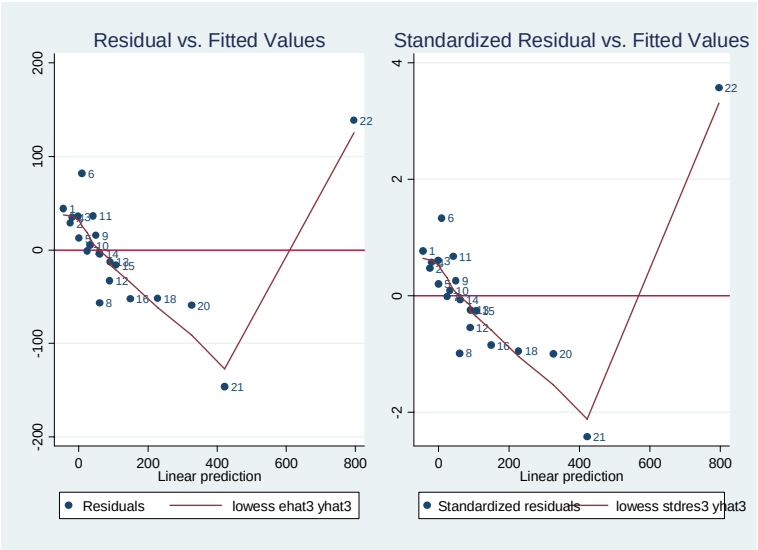

Figure 3.1 Non-standardized and standardized residuals and fitted values for Model 3.

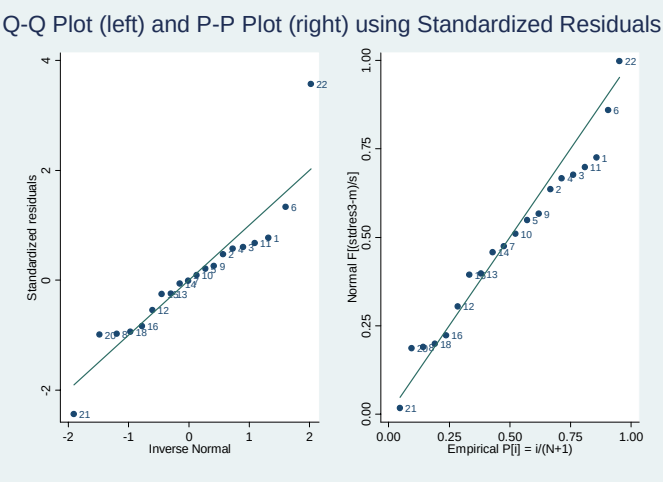

Figure 3.2. P-P and Q-Q plots of standardized residuals from Model 3.

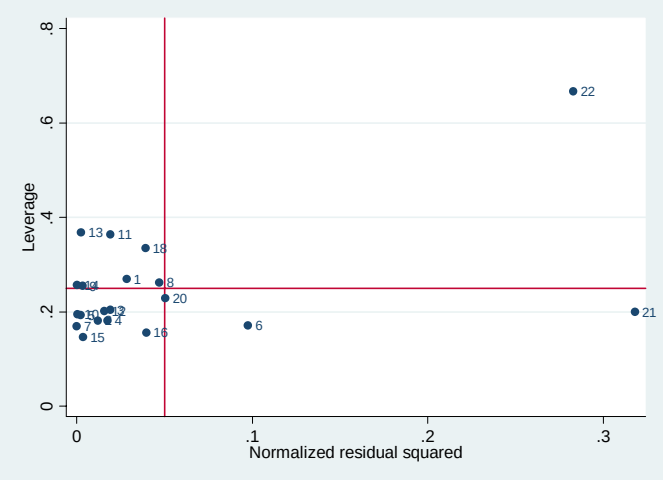

Figure 3.3. Squared normalized residuals versus leverage for Model 3.

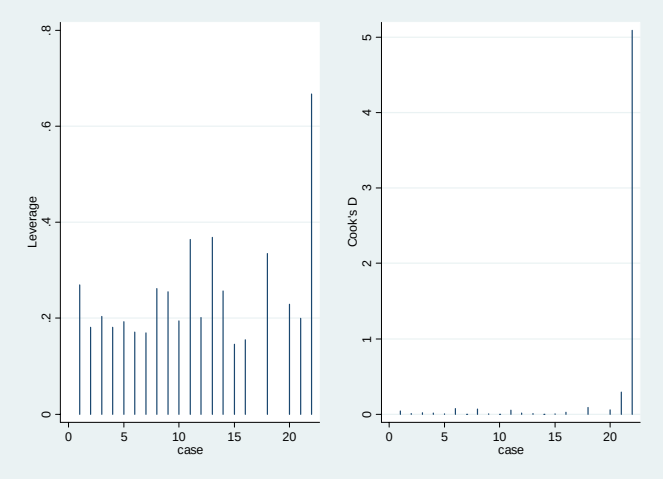

Figure 3.4. Leverage and Cooks Distance of each observation in Model 4.

Observation 22 was removed from the data set, and a model was generated using the same explanatory variables. From this output it is apparent that all p-values associated with each explanatory variable remain non-significant.

D. **Table 12. Mulitple Linear Regression, Model 3; the association between baseline CAC score, age, gender and smoking history with 1-year CAC score, after outlier was removed.**

Explanatory Variable	***B-Coefficient***	***P-value***	***95% CI***
Baseline CAC score (centered at 50)	1.15	<0.001	(0.96, 1.34)
Age (centered at 55)	-0.734	0.442	(-2.73, 1.26)
Gender	-5.16	0.660	(-35.78, 12.89)
Smoking history	-11.45	0.328	(-35.79, 12.89)
Intercept	26.70	0.052	(-0.31, 53.71)

Outcome Variable: 1-year CAC score

R^2= 0.934, Adj. R^2= 0.914, $F_{(4,13)}$ = 46.15, p<0.001

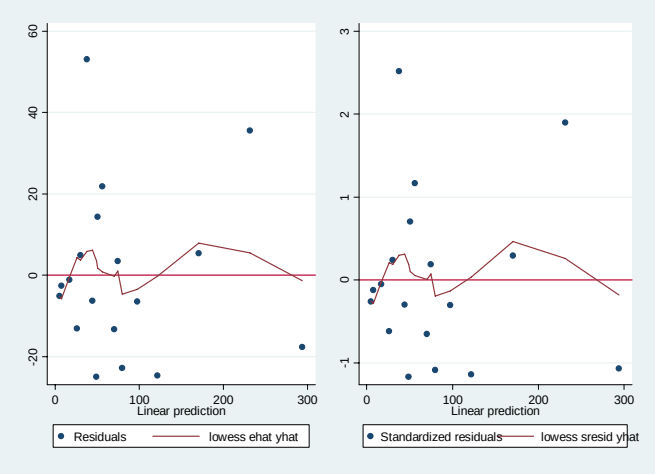

Figure 4.1 Non-standardized and standardized residuals and fitted values for Model 3.

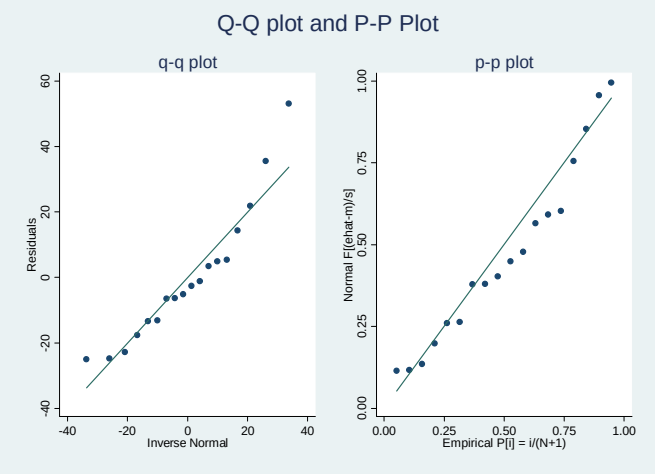

Figure 4.2. P-P and Q-Q plots of standardized residuals from Model 4.

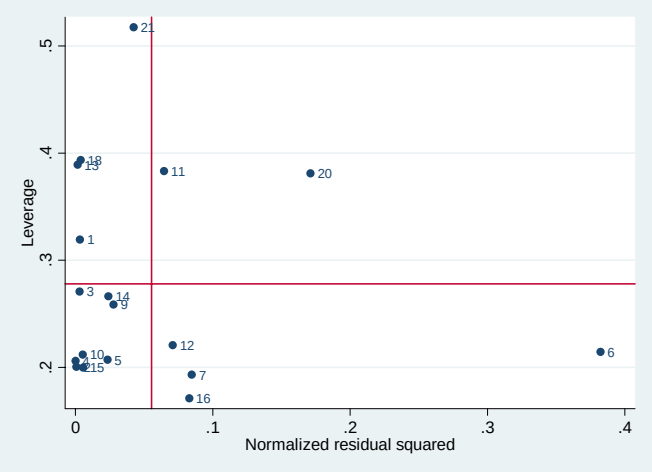

Figure 4.3 Squared normalized residuals versus leverage for Model 4

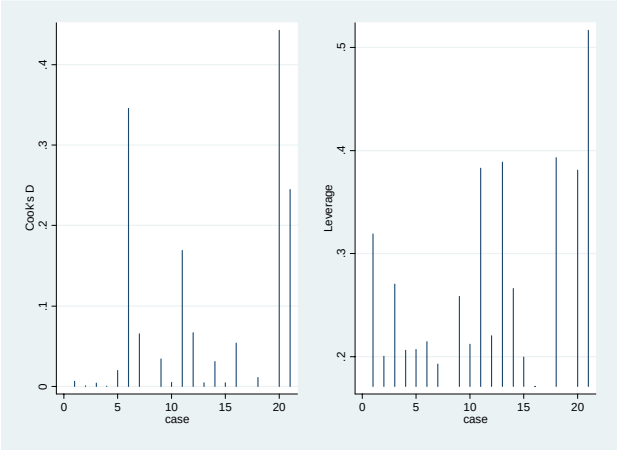

Figure 4.4 Leverage and Cooks Distance of each observation in Model 4.