Title

Use of coronary artery calcium testing to improve coronary heart disease risk assessment in a lung cancer screening population: The Multi-Ethnic Study of Atherosclerosis (MESA).

Journal

Journal of cardiovascular computed tomography, 12(6)

ISSN

1934-5925

Authors

Garg, Parveen K
Jorgensen, Neal W
McClelland, Robyn L
et al.

Publication Date

2018-11-01

DOI

10.1016/j.jcct.2018.10.001

Peer reviewed

Published in final edited form as:

J Cardiovasc Comput Tomogr. 2018 ; 12(6): 493–499. doi:10.1016/j.jcct.2018.10.001.

Use of Coronary Artery Calcium Testing to Improve Coronary Heart Disease Risk Assessment in a Lung Cancer Screening Population: The Multi-Ethnic Study of Atherosclerosis (MESA)

Parveen K Garg, MD, MPH[a], **Neal W Jorgensen, MS**[b], **Robyn L McClelland, PhD**[b], **J Adam Leigh, MD**[c], **Philip Greenland, MD**[d], **Michael J Blaha, MD, MPH**[e], **Andrew J Yoon, MD**[a], **Nathan D Wong, PhD**[f], **Joseph Yeboah, MD, MS**[c], and **Matthew J Budoff, MD**[g]

[a]Division of Cardiology, University of Southern California Keck School of Medicine, Los Angeles, CA; parveeng@med.usc.edu, Andrew.Yoon@med.usc.edu [b]Department of Biostatistics, University of Washington, Seattle, WA; njorgens@u.washington.edu; rmcclell@u.washington.edu [c]Division of Cardiology, Wake Forest School of Medicine, Winston-Salem, NC; aleigh@wakehealth.edu; jyeboah@wakehealth.edu [d]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL; p-greenland@northwestern.edu [e]Divisions of Cardiology and Epidemiology, Johns Hopkins School of Medicine, Baltimore, MD; mblaha1@jhmi.edu [f]Heart Disease Prevention Program, Division of Cardiology, University of California at Irvine, Irvine, CA; ndwong@uci.edu [g]Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, CA; mbudoff@labiomed.org

Abstract

Background: Assessment of coronary artery calcium (CAC) during lung cancer screening chest computed tomography (CT) represents an opportunity to identify asymptomatic individuals at increased coronary heart disease (CHD) risk. We determined the improvement in CHD risk prediction associated with the addition of CAC testing in a population recommended for lung cancer screening.

Methods: We included 484 out of 6814 Multi-Ethnic Study of Atherosclerosis (MESA) participants without baseline cardiovascular disease who met U.S. Preventive Service Task Force CT lung cancer screening criteria and underwent gated CAC testing. 10 year-predicted CHD risks with and without CAC were calculated using a validated MESA-based risk model and categorized into low (<5%), intermediate (5%-10%), and high (≥10%). The net reclassification improvement (NRI) and change in Harrell's *C*-statistic by adding CAC to the risk model were subsequently determined.

Corresponding Author Parveen K Garg, MD, MPH, 1510 San Pablo St. Suite 322, Los Angeles, CA 90033, Telephone-323-442-6135, Fax- 323-442-6133, parveeng@med.usc.edu.

Disclosures: The authors declare that they have no conflicts of interest.

Results: Of 484 included participants (mean age=65; 39% women; 32% black), 72 (15%) experienced CHD events over the course of follow-up (median=12.5 years). Adding CAC to the MESA CHD risk model resulted in 17% more participants classified into the highest or lowest risk categories and a NRI of 0.26 (p=0.001). The *C*-statistic improved from 0.538 to 0.611 (p=0.01).

Conclusions: CHD event rates were high in this lung cancer screening eligible population. These individuals represent a high-risk population who merit consideration for CHD prevention measures regardless of CAC score. Although overall discrimination remained poor with inclusion of CAC scores, determining whether those reclassified to an even higher risk would benefit from more aggressive preventive measures may be important.

Keywords

Coronary artery calcium; Coronary heart disease; Risk prediction; Lung cancer screening

Introduction

Low dose non-contrast enhanced chest computed tomography (LDCT) to screen for lung cancer in current and former smokers reduces lung cancer-specific mortality by over 20%[1] and is recommended in appropriately selected individuals.[2,3]. More than 7 million individuals nationally are thought to be eligible for such screening.[4]

These individuals are at increased risk for cardiovascular disease as well and the rates of cardiovascular mortality and lung cancer-related mortality are similar in this population.[1] The presence and severity of coronary artery calcium (CAC) detected at the time of screening is independently associated with an increased risk of cardiovascular events similar to that seen with ECG-gating.[5-7] The concomitant assessment of CAC during lung cancer screening with LDCT, therefore, represents an opportunity to also identify asymptomatic individuals at increased coronary heart disease (CHD) risk who may potentially benefit from preventive measures such as high-intensity statin therapy or low-dose aspirin.

A recently published joint statement from the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology recommending the incorporation of CAC into chest CT examinations specifically highlighted the potential benefit it can have on CAD assessment in lung cancer screening populations.[8] While CAC testing improves CHD risk prediction independent of traditional risk factors in general asymptomatic populations[9-13], whether the addition of CAC can similarly improve CHD risk prediction and potentially identify those who may benefit from even more aggressive preventive measures in a population already at high baseline cardiovascular risk is unclear.[14] We determined the change in risk reclassification and improvement in risk prediction associated with adding gated CAC testing to a traditional risk factor based assessment of CHD risk in a population of individuals who would have been eligible for lung cancer screening with LDCT.

Methods

Cohort

The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based study of 6814 adults aged 45-84 years free from cardiovascular disease who were recruited from 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; NewYork, NewYork; and St Paul, Minnesota) and underwent baseline examination between July 2000 and September 2002.[15] The study participants were 53% female and consisted of 4 ethnic groups: non-Hispanic White (38%), African (28%), Hispanic (22%), and Chinese-Americans (12%). MESA conducted 4 subsequent examinations of the cohort between 2002 and 2012. Institutional review boards at each site approved the study, and all participants gave written informed consent.

MESA participants meeting United States Preventive Services Task Force (USPSTF) criteria[3] for lung cancer screening (55-80 years old, ≥30 pack-year smoking history, and either actively smoking or quit smoking within the last 15 years) with coronary artery calcium scores and complete covariate information at baseline were included in the main analysis (n=484).

Measurement of CAC

CT scanning and interpretation methods in MESA have been previously reported.[16] Scanning centers assessed CAC with either a electrocardiogram-gated electron-beam CT scanner (Chicago, Los Angeles County, and New York City field centers) or a multidetector CT system (Baltimore, Forsyth County, and St Paul field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. Images were analyzed independently at a central reading center (Los Angeles Biomedical Research Institute), and the amount of CAC was quantified using the Agatston scoring method.[17] Rescan agreement was high using both electron-beam and multidetector computed tomography scanners.[18] The mean Agatston score for the 2 scans was used in all analyses. Intraobserver and interobserver agreements were very high (Kappa = 0.93 and 0.90, respectively).

Measurement of covariates

Standardized questionnaires were used at baseline to obtain demographic information, smoking history, medication usage, and family history of CHD. Fasting blood samples were drawn to determine total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), triglycerides, and glucose. Low-density lipoprotein cholesterol (LDL-c) was calculated by the Friedewald equation in those with triglycerides <400 mg/dl. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Three separate systolic and diastolic resting blood pressure measurements were taken in seated participants, with the last 2 measurements being averaged for analysis.[19]

Cigarette smoking for current and former smokers was calculated in pack-years based on responses to the following questions: “How old were you when you first started smoking cigarettes?”, “On average, about how many cigarettes a day do/did you smoke?”, and, for

former smokers only, “How old were you when quit smoking cigarettes?”. Current smoking was defined as answering yes to the question “Have you smoked cigarettes during the last 30 days?”

Aspirin use was defined as a self-reported use of at least 3 days per week. Lipid-lowering therapy and anti-hypertensive medication use were based on positive responses to “Are you taking medicines for high blood pressure or hypertension?” and “Are you taking medications for high cholesterol?” Additionally, participants were asked to bring containers for all medications used during the 2 weeks before the clinic visit.

Positive family history referred to a heart attack at any age in a parent, sibling, or child. The age at which the relative experienced the heart attack was not collected at baseline in MESA, precluding consideration of premature family history. Hypertension was defined as self-report of physician diagnosis and use of an antihypertensive medication, or systolic blood pressure (SBP) ≥140, or diastolic blood pressure (DBP) ≥90 mm Hg. Diabetes mellitus (DM) was defined as fasting glucose >125 mg/dl or use of anti-diabetic medications.

Coronary heart disease ascertainment

At 9-12 month intervals, participants or family members were contacted regarding interim hospital admissions, outpatient diagnoses of CVD, and deaths. Follow-up for this analysis extended through 2014. To verify self-reported diagnoses, trained personnel abstracted data from hospital records. Next of kin and physicians were contacted for participants with out-of-hospital cardiovascular deaths. Two physician members of the MESA mortality and morbidity review committee independently classified events. The full committee made final classifications if there were disagreements. Hospital records were obtained for an estimated 98% of hospitalized cardiovascular events and some medical record-based information was available for 95% of outpatient encounters.

CHD events included myocardial infarction (MI), resuscitated cardiac arrest, fatal CHD, and revascularization only if the participant also had prior or concurrent adjudicated angina. The diagnosis of MI was based on symptoms, electrocardiographic findings, and levels of circulating cardiac biomarkers. Reviewers classified resuscitated cardiac arrest when a patient successfully recovered from full cardiac arrest through cardiopulmonary resuscitation (including cardioversion). A death was considered related to CHD if it occurred within 28 days after a myocardial infarction, if the participant had chest pain within 72h before death, or if the participant had a history of CHD and there was no known non-atherosclerotic, non-cardiac cause of death. Adjudicators graded angina using their clinical judgment. A classification of definite or probable angina required clear and definite documentation of symptoms distinct from the diagnosis of MI. Classification of definite angina also required objective evidence of reversible myocardial ischemia or obstructive coronary artery disease.

Statistical methods

Comparison of baseline characteristics was performed between those who developed incident CHD and those who did not in participants meeting USPSTF lung cancer screening

criteria. Adjusting for age and sex, we used a *t*-test for continuous variable and a χ^2 test for dichotomous variables to test differences between these two groups.

10 year-predicted CHD risk with and without CACS was calculated using a previously derived and validated MESA-based risk model.[20,21] Variables to determine initial CHD risk were age, race/ethnicity, sex, family history of heart attack, SBP, DM, TC, HDL-c, smoking status, use of anti-hypertensive therapy, and use of lipid lowering therapy. Since CAC scores are previously known to not be normally distributed across the study population, CHD risk was recalculated with inclusion of CAC score entered as log (CAC+1).[20] Cross-tabulations of risk categories based on the models with and without CACS were then performed to describe the number and percentage of participants who are reclassified according to the following classifications: <5% (low), 5%-10% (intermediate), & >10% (high). The improvement in predictive accuracy of the CHD risk model was evaluated by calculating the net reclassification improvement with addition of CACS into the CHD risk model.[22] The improvement in discrimination associated with addition of CACS was evaluated using ROC curves, Harrell's c-statistics, and discrimination slope.

The analyses were repeated excluding individuals with diabetes and those already on lipid-lowering therapy at baseline. We also repeated the above-mentioned analysis with CAC as an ordinal variable. CAC scores were categorized as follows: 0, 1-99, 100-400, and >400, and values falling with each of these categories were given the same CAC score. Cox proportional hazards models were also used to investigate the association of baseline CAC category with incident CHD (referent group: CAC=0), adjusting for all variables used to determine risk in the MESA CHD model.

Finally, we repeated the main analysis to include a broader population of current and former smokers in MESA. The population was first expanded to include all current or former smokers with ≥30 pack-year smoking history regardless of age or quit date (n=918), and then further expanded to include all current smokers regardless of pack-year history (n=1487). All analyses were performed using StataCorp. 2017 (College Station, TX)

Results

Figure 1 shows the flow of participants that were eligible for the analyses. Over a median follow-up of 12.7 years, 72 (14.8%) incident CHD cases were observed among 484 participants. Of these 72 participants, 11 had revascularization with underlying angina, 36 had an MI, 3 had resuscitated cardiac arrest, and 22 died from CHD. Comparison of baseline characteristics in participants who developed CHD versus those who did not is shown in Table 1. Participants who developed CHD were older with a higher SBP and CAC score and a lower HDL-c.

Continuous CAC score and estimation of CHD risk

Cross-tabulations of the 10-year estimated risk using the models with and without CAC score are shown in Table 2. Adding CAC to the MESA CHD risk model resulted in 17% more participants classified into the highest or lowest risk categories. Event rates across the low, intermediate, and high-risk categories were 13.4%, 16.1%, and 14.4%, respectively,

before addition of CAC score into the risk model. Event rates across the low, intermediate, and high-risk categories changed to 10.1%, 10.0%, and 20.8%, respectively, after including CAC score in the risk model.

Overall, 225 individuals in the entire cohort were reclassified, with an event rate of 21.8% among the 119 reclassified to a higher risk category and an event of rate of 7.5% among the 106 reclassified to a lower risk category. The NRI for events was 0.25 and the NRI for nonevents was 0.01, achieving an NRI for the entire study cohort of 0.26 (95% confidence interval (CI), 0.09-0.43; p=0.001). The NRIs for events and nonevents were similar after excluding participants with diabetes or receiving lipid-lowering therapy at baseline (Supplemental Table 1).

The area under the receiver-operating characteristic curves for the prediction of CHD events with and without the addition of CAC values are shown in Figure 2. The c-statistic increased from 0.538 (95% CI, 0.469-0.607) to 0.611 (95% CI, 0.548-0.675) with the addition of CAC, representing an improvement of 0.0738 (p=0.01). The discrimination slope improved from 0.005 to 0.024. Although measures of discrimination significantly improved, they still remained poor even with the inclusion of CAC score to the prediction model. None of the cardiovascular risk factors included in the prediction model aside from CAC score were associated with incident CHD for this population (Table 3).

Categorical CAC score and estimation of CHD risk

A graded association between higher CAC strata and risk of incident CHD was observed (Supplemental Table 2). CHD event rates were 10%, 12%, 18%, and 21% for CAC scores of 0 (n=135), 1-99 (n=146), 100-400 (n=104), and >400 (n=99) respectively. Cross-tabulations of the 10-year estimated risk using the models with and without CAC score, defined as a categorical variable instead of continuous variable, are shown in Table 4. Improvements in the NRI (0.19, p=0.013) and c-statistic (0.517 to 0.602, p=0.001) were similar to those seen with a continuous CAC score.

CAC score and estimation of CHD risk in an expanded population of current and former smokers

Baseline characteristics for MESA participants for the following 3 groups are shown in Supplemental Table 3: (1) lung cancer screening eligible participants, (2) all current or former smokers with ≥30 pack-years, and (3) all current smokers and only those former smokers with ≥30 pack-years.

Improvements in NRI for the expanded populations with the addition of CAC score were similar to that seen in the lung cancer screening eligible participants (Supplemental Table 4). Although improvements in the c-statistic and discrimination slope were similarly significant as compared to the lung cancer screening eligible population, overall discrimination for the risk model was significantly better in this expanded population. Among current or former smokers with ≥30 pack-years, the c-statistic increased from 0.622 (95% CI, 0.575-0.669) to 0.670 (95% CI, 0.625-0.715) with the addition of CAC, representing an improvement of 0.0481 (p=0.006). The discrimination slope improved from 0.023 to 0.046. Among all current smokers and only those former smokers with ≥30 pack-years, the c-statistic

increased from 0.665 (95% CI, 0.627-0.704) to 0.705 (95% CI, 0.667-0.743) with the addition of CAC, representing an improvement of 0.0397 (p=0.006). The discrimination slope improved from 0.033 to 0.057.

Discussion

Actual CHD risk was found to be high across all categories of estimated risk in a cohort of individuals without baseline cardiovascular disease who were eligible for lung cancer screening. Although adding CAC to a validated MESA-based CHD risk model significantly improved risk classification in this population, overall discrimination remained poor.

CAC scores on non-gated LDCT have already been reported to predict cardiovascular events in lung cancer screening trials.[5-7, 23, 24] Qualitative visual assessment of coronary artery calcification, categorized as mild, moderate, or heavy, was also each associated with an increased CHD death risk compared to no calcification in these same participants.[7] Similarly, amongst nearly 3600 male participants followed for approximately 3 years as part of the Dutch-Belgian Randomized Lung Cancer Screening Trial trial, CAC scores between 1-10, 11-100, 101-400, and greater than 400 were all independently associated with an increased cardiovascular event risk compared to those with a CAC score of 0.[23] In a subsequent analysis of these same participants, application of a derived cardiovascular event risk prediction model that included coronary artery calcium volume performed very well in the validation cohort (c-statistic=0.71).[24]

Study participants from lung cancer screening trials, however, were poorly characterized for baseline cardiac risk factors. In approximately 600 asymptomatic well-characterized Framingham Heart Study participants eligible for lung cancer screening, the Pooled Cohort Equation (PCE) 10-year atherosclerotic cardiovascular disease risk calculator performed remarkably well (predicted 11.4% versus observed 11.7%).[25] CAC scores were performed only in a subset of these participants and performance of CAC testing with respect to further enhancing cardiovascular risk prediction was not determined. A recent analysis in this same lung cancer screening eligible MESA cohort using the PCE found no significant improvement in the c-statistic with the addition of CAC scores.[14] The PCE, however, overestimates risk by from 25% to 115% in MESA.[21] Considering the improved performance of MESA-based CHD prediction model in this population and incorporation of CAC scores into the model[20], it was important to determine whether this model might perform better in this lung cancer screening eligible population.

Consistent with the reported performance of the PCE in this lung cancer screening eligible population, the MESA-based CHD risk prediction model also performed poorly even with inclusion of CAC. While the improvement in the c-statistic and the NRI with addition of CAC was significant for this risk prediction model as opposed to the PCE, overall performance was similar and different thresholds were for classifying risk categories. Lung cancer screening eligible individuals, therefore, are characterized by a high rate of incident CHD but whose risk is not appropriately reflected by traditional risk parameters. A higher CAC score was the only variable associated with an increased risk of CHD. Increased presence of non-calcified, unstable coronary plaque or a higher risk of fatal arrhythmias may

potentially explain the increased risk; however, formal investigation into underlying etiology is needed.

The study population experienced an overall CHD event rate of 15% that was evenly distributed across all risk categories before incorporation of CAC score. “Low” and “intermediate” risk individuals still experienced a 10% CHD event rate even after incorporation of CAC score. Many of these individuals would likely not have been recommended to be on statin or aspirin therapy according to predicted event rates.[26-30] The observed event rates indicate, however, that nearly all of these participants should have been considered for these therapies based on current clinical practice guidelines and that increased efforts aimed at primary cardiovascular disease prevention should be made for lung cancer screening eligible individuals, especially those younger than the age of 75 [26-29, 31] Despite the similarities in performance between the PCE and MESA risk score, individuals considered “high” risk after reclassification with CAC testing with this model experienced a 10-year event rate that was twice that of “low” and “intermediate” risk individuals (20%). Our results suggest use of the MESA risk score may identify individuals in whom even more aggressive measures, such as those recommended for secondary cardiovascular disease prevention, may be considered.

Our study has limitations. The study population, although derived from a well-characterized cohort that was prospectively followed for the development of cardiovascular events, was small and limits the interpretation of results. Application of a traditional risk-factor based prediction model for cardiovascular events performed much better in a similar sized cohort of Framingham Study participants eligible for lung cancer screening than that observed in this study.[25] Additional studies with larger cohorts of lung-cancer screening eligible individuals are clearly needed to better understand our findings. CAC was scored with ECG-gating and results cannot be directly applied be to the non-gated setting without formal validation. Prior studies, however, have demonstrated strong agreement between low-dose non-gated and ECG-gated CAC scoring methods.[32-34] Qualitative CAC values were not available in MESA and we could not determine the utility of this method of CAC assessment on CHD risk prediction.

Conclusion

Gated CAC assessment performed in a population of lung cancer screening eligible individuals improved CHD risk prediction; however, overall discrimination remained poor and observed risk was high across all categories. Primary cardiovascular disease prevention efforts are an important consideration for all of these individuals. Determining whether those reclassified to even higher risk categories based on CAC scores would benefit from even more aggressive preventive measures to reduce CHD risk may be important. Further study with non-gated CAC in similar, well-characterized populations can ultimately determine any potential utility of CAC scoring to improve CHD risk prediction in the setting of LDCT for lung cancer screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Funding sources: This research was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute, and by grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from NCATS.

References

1. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409 [PubMed: 21714641]
2. Smith RA, Manassaram-Baptiste D, Brooks D, Doroshenk M, Fedewa S, Saslow D, Brawley OW, Wender R. Cancer screening in the United States, 2015: a review of current American cancer society guidelines and current issues in cancer screening. CA Cancer J Clin 2015;65:30–54. [PubMed: 25581023]
3. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2014;160:330–338. [PubMed: 24378917]
4. Humphrey L, Deffebach M, Pappas M, Baumann C, Artis K, Mitchell JP, Zakher B, Fu R, Slatore C. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Ann Intern Med 2013;159:411–420. [PubMed: 23897166]
5. Sverzellati N, Cademartiri F, Bravi F, Martini C, Gira FA, Maffei E, Marchiano A, La Vecchia C, De Filippo M, Kuhnigk JM, Rossi C, Pastorino U. Relationship and prognostic value of modified coronary artery calcium score, FEV 1 and emphysema in lung cancer screening population: the MILD trial. Radiology 2012;262:460–467. [PubMed: 22114241]
6. Jacobs PC, Gondrie MJ, van der Graaf Y, de Koning HJ, Isgum I, van Ginneken B, Mali WP. Coronary artery calcium can predict all-cause mortality and cardiovascular events on low-dose CT screening for lung cancer. Am J Roentgenol 2012;198:505–511. [PubMed: 22357989]
7. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS, DeMello S, Desjardins SS, Munden RF. Association of coronary artery calcification and mortality in the national lung screening trial: A comparison of three scoring methods. Radiology 2015;276:82–90. [PubMed: 25759972]
8. Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, Yankelevitz D, Abbara S. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. J Cardiovasc Comput Tomogr 2017; 11: 74–84. [PubMed: 27916431]
9. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–1345. [PubMed: 18367736]
10. Erbel R, Möhlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, Dragano N, Gronemeyer D, Seibel R, Kalsch H, Brocker-Preuss M, Mann K, Siegrist J, Jockel KH. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: The Heinz Nixdorf Recall Study. J Am Coll Cardiol 2010;56:1397–1406. [PubMed: 20946997]
11. Paixao ARM, Berry JD, Neeland IJ, Ayers CR, Rohatgi A, de Lemos JA, Khera A. Coronary artery calcification and family history of myocardial infarction in the Dallas Heart Study. J Am Coll Cardiol Img 2014;7:679–686.

12. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610–1616. [PubMed: 20424251]
13. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, Carr JJ, Goff DC, Greenland P, Herrington DM. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate risk individuals: the Multi-Ethnic Study of Atherosclerosis. JAMA 2012;308:788–795. [PubMed: 22910756]
14. Leigh A, McEvoy J, Garg P, Carr JJ, Sandfort V, Oelsner EC, Budoff M, Herrington D, Yeboah J. Coronary artery calcium scores and atherosclerotic cardiovascular disease risk stratification in smokers. JACC Cardiovasc Imaging 2018; Epub ahead of print.
15. Bild DE, Bluemke, DA, Burke GL, Detrano R, Diez-Roux AV, Folsom AR, Greenland P, Jacobs DR Jr, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–881. [PubMed: 12397006]
16. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr, Sidney S, Bild DE, Williams OD, Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) Study. Radiology 2005;234:35–43. [PubMed: 15618373]
17. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827–32. [PubMed: 2407762]
18. Detrano RC, Anderson M, Nelson J, Wong ND, Carr JJ, McNitt-Gray M, Bild DE. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility —MESA Study. Radiology 2005;236:477–484. [PubMed: 15972340]
19. Ramsey M Blood pressure monitoring: automated oscillometric devices. J Clin Monit 1991;7:56–67. [PubMed: 1999699]
20. McClelland RL, Jorgenson NW, Budoff M, Blaha MJ, Post WS, Kronmal RA, Bild DE, Shea S, Liu K, Watson KE, Folsom AR, Khera A, Ayers C, Mahabadi AA, Lehmann N, Jockel KH, Moebus S, Carr JJ, Erbel R, Burke GL. 10-year coronary heart disease risk prediction using coronary artery calcium and traditional risk factors: Derivation in the MESA (Multi-Ethnic Study of Atherosclerosis) with validation in the HNR (Heinz Nixdorf Recall) Study and the DHS (Dallas Heart Study). J Am Coll Cardiol 2015;66:1643–1653. [PubMed: 26449133]
21. DeFilippis AP, Young R, Carruba CJ. An Analysis of Calibration and Discrimination Among Multiple Cardiovascular Risk Scores in a Modern Multiethnic Cohort. Ann Intern Med 2015;162:266–275. [PubMed: 25686167]
22. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–172. [PubMed: 17569110]
23. Takx RA, Isgum I, Willemink MJ, van der Graaf Y, de Koning HJ, Vliegenthart R, Oudkerk M, Leiner T, de Jong PA. Quantification of coronary artery calcium in nongated CT to predict cardiovascular events in male lung cancer screening participants: Results of the NELSON study. J Cardiovasc Comput Tomgr 2015;9:50–57.
24. Mets OM, Vliegenthart R, Gondrie MJ, Viergever MA, Oudkerk M, de Koning HJ, Mali WP, Prokop M, van Klaveren RJ, van der Graaf Y, Buckens CF, Zanen P, Lammers JJ, Groen HJ, Isgum I, de Jong PA. Lung cancer screening CT-Based prediction of cardiovascular events. JACC Cardiovasc Imaging 2013;6:899–907. [PubMed: 23769488]
25. Lu MT, Onuma OK, Massaro JM, D'Agostino RB, O'Donnell CJ, Hoffmann U. Lung cancer screening eligibility in the community: Cardiovascular risk factors, coronary artery calcification, and cardiovascular events. Circulation 2016;134:897–899. [PubMed: 27647299]
26. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Golberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/

American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–2934. [PubMed: 24239923]

27. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National lipid association recommendations for patient-centered management of dyslipidemia: Part 1—full report. J Clin Lipidol 2015;9:129–169. [PubMed: 25911072]
28. US Preventive Services Task Force. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force Recommendation Statement. JAMA 2016;316:1997–2007 [PubMed: 27838723]
29. Bibbins-Domingo K on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: US Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:836–845. [PubMed: 27064677]
30. Pencina MJ, Navar-Boggan AM, D'Agostino RB, Williams K, Neely B, Sniderman AD, Peterson ED. Application of New Cholesterol Guidelines to a Population-Based Sample. N Engl J Med 2014;370:1422–1431. [PubMed: 24645848]
31. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DS, Mechanick JI, Pessah-Pollock R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract 2017;23S:1–87.
32. Budoff MJ, Nasir K, Kinney GL, Hokanson JE, Graham Barr R, Steiner R, Nath H, Lopez-Garcia C, Black-Shinn J, Casaburi R. Coronary artery and thoracic calcium on noncontrast thoracic CT scans: Comparison of ungated and gated examinations in patients from the COPD Gene cohort. J Cardiovasc Comput Tomogr 2011;5:113–118. [PubMed: 21167806]
33. Wu MT, Yang P, Huang YL, Chen JS, Chuo CC, Yeh C, Chang RS. Coronary arterial calcification on low-dose ungated MDCT for lung cancer screening: concordance study with dedicated cardiac CT. Am J Roentgenol 2008;190:923–928. [PubMed: 18356438]
34. Kim SM, Chung MJ, Lee KS, Choe YH, Yi CA, Choe BK. Coronary calcium screening using low-dose lung cancer screening: effectiveness of MDCT with retrospective reconstruction. Am J Roentgenol 2008;190:917–922. [PubMed: 18356437]

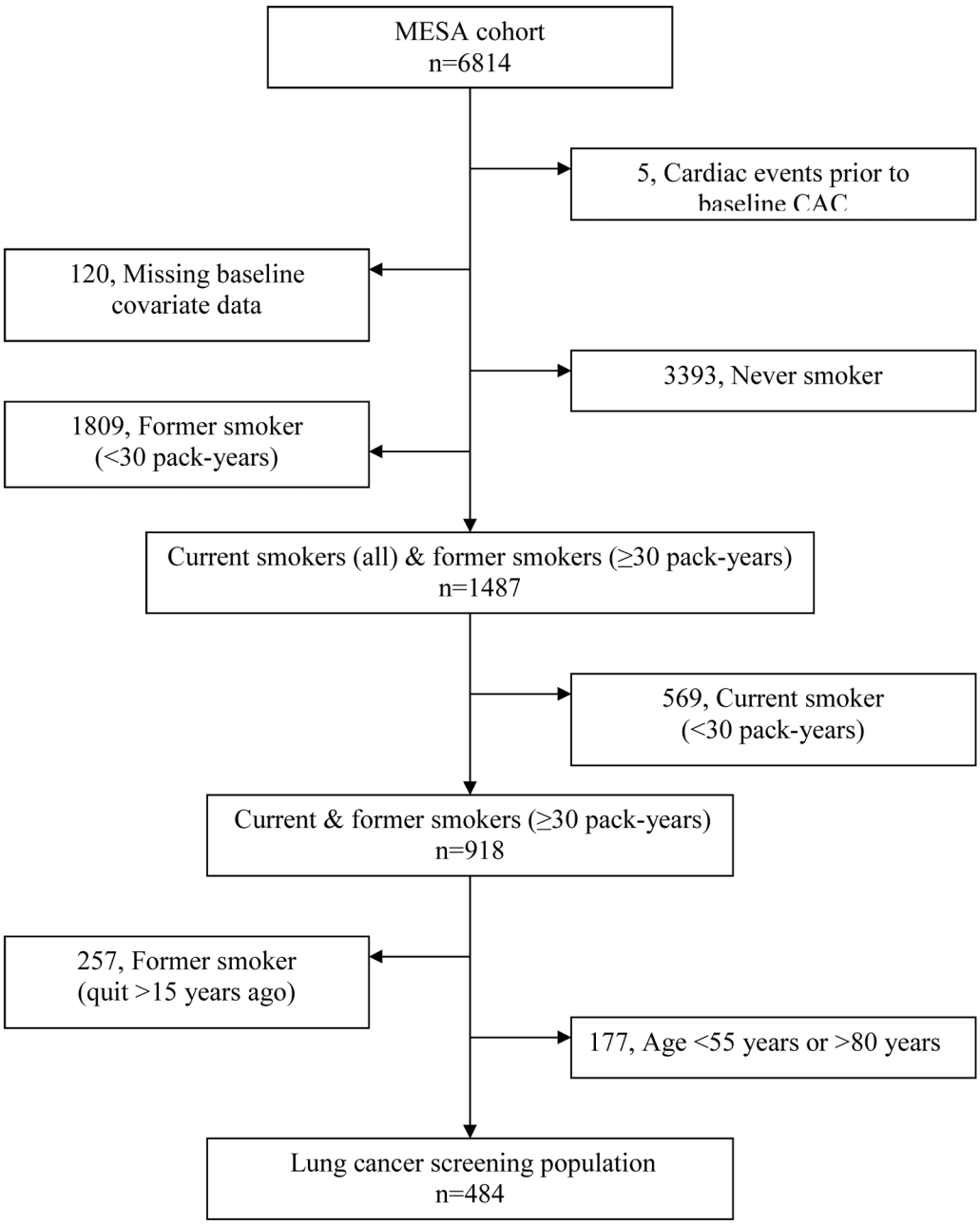

Figure 1.
Flowchart of participants included in the analysis

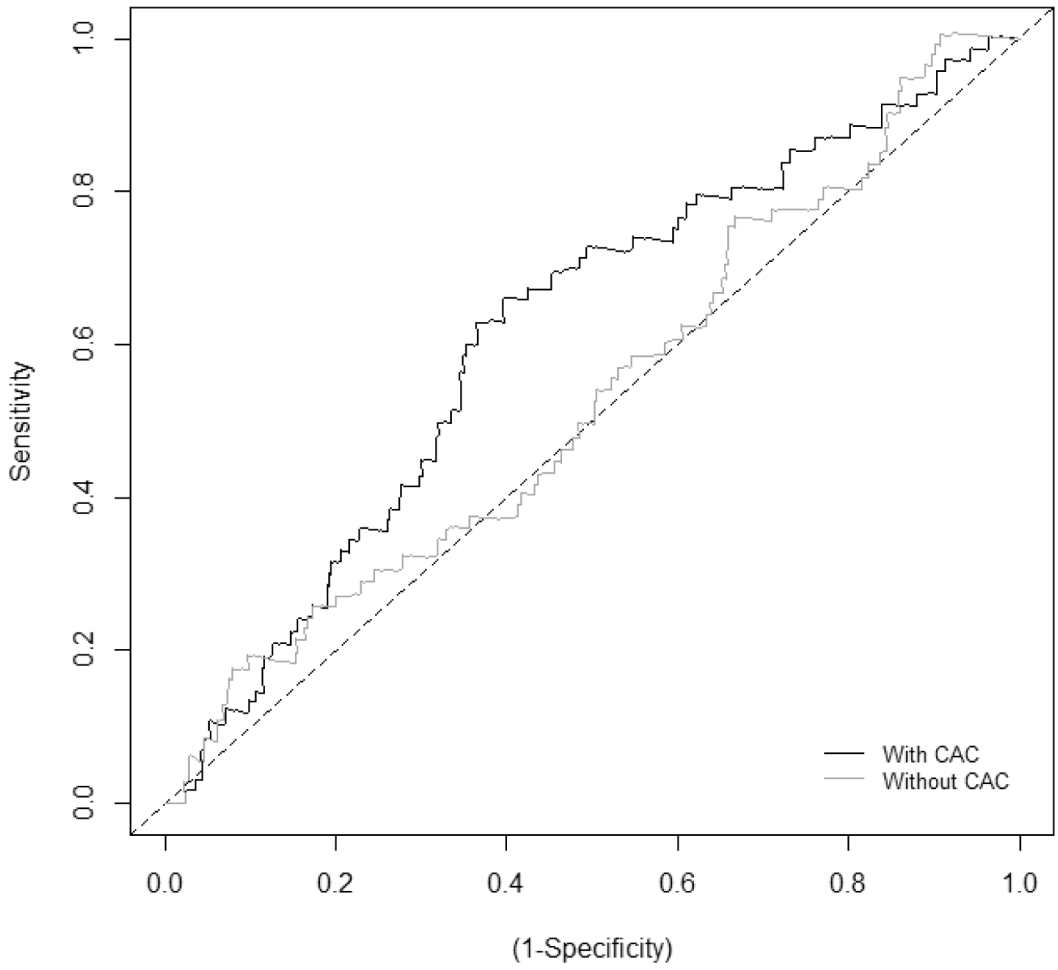

Figure 2.

Receiver operating characteristic curves showing area under the curve for ten-year risk of incident coronary heart disease predicted by models with and without continuous CAC score in a lung cancer screening population

Table 1.

Baseline characteristics of lung cancer screening eligible MESA participants according to presence or absence of incident coronary heart disease (CHD)*

Characteristic	Incident CHD (n=72)	No CHD (n=412)	*p*-value†
Age	64 (10)	61 (10)	0.001
Female, %	23 (32%)	165 (40%)	0.19
Race, %			
White	32 (44%)	207 (50%)	0.25
Chinese	6 (8%)	18 (4%)	
Black	21 (29%)	136 (33%)	
Hispanic	13 (18%)	51 (12%)	
Family history of heart attack, %	30 (47%)	181 (48%)	0.91
Body mass index, kg/m^2	28.0 (4.7)	28.5 (5.4)	0.35
Smoking status, %			
Former	37 (51%)	224 (54%)	0.64
Current	35 (49%)	188 (46%)	
Pack-years smoking	42.7 (28.6)	38.2 (29.4)	0.061
Diabetes, %	11 (15%)	65 (16%)	0.91
SBP, mm Hg	130 (22)	125 (21)	0.002
DBP, mm Hg	74 (11)	72 (10)	0.05
Total cholesterol, mg/dL	193 (38)	192 (38)	0.61
LDL cholesterol, mg/dL	118 (34)	115 (32)	0.22
HDL cholesterol, mg/dL	46 (14)	49 (15)	0.004
Lipid lowering therapy, %	17 (24%)	82 (20%)	0.47
Antihypertensive use, %	32 (44%)	163 (40%)	0.44
Aspirin use (≥3 times/week), %	17 (24%)	131 (32%)	0.15
CAC score	350 (576)	176 (468)	<0.001

*Continuous variables are expressed as mean (SD). Categorical variables are N (percent).

†Comparisons were made between incident CHD and no CHD groups using chi-square tests for categorical variables and t-tests for continuous.

Table 2:

Ten-year risk of coronary heart disease predicted by models with and without continuous CAC score in a lung cancer screening population (n=484)*

	Events					Nonevents			
	MESA CHD Model + CAC					MESA CHD Model + CAC			
	<5%	5%-10%	≥10%	Total		<5%	5%-10%	≥10%	Total
MESA CHD Model									
<5%	10	4	2	16		69	31	3	103
5%-10%	6	5	20	31		59	43	59	161
≥10%	0	2	23	25		14	25	109	148
Total	16	11	45	72		142	99	171	412
Net effect of CAC									
Increased risk			26					93	
Decreased risk			8					98	
Net correctly reclassified			25%					1%	
Net reclassification improvement			0.26 (95% CI: 0.09, 0.43)						

*Baseline model included age, gender, race, diabetes, current smoking status, family history of heart attack, total cholesterol, hdl cholesterol, systolic blood pressure, lipid-lowering medication, and hypertension medication.

Table 3:

Risk of Coronary Heart Disease Events Associated With Traditional Risk Factors as Predicted by Models With and Without CAC score in a lung cancer screening population (n=484)

	MESA CHD model	*p*-value	MESA CHD model + CAC	*p*-value
	HR (95% CI)		HR (95% CI)	
Age*	0.98 (0.81, 1.19)	0.85	0.91 (0.74, 1.11)	0.33
Male	1.24 (0.69, 2.23)	0.46	1.00 (0.55, 1.81)	1.00
Diabetes	0.96 (0.48, 1.90)	0.91	0.93 (0.47, 1.86)	0.84
Current smoker	1.23 (0.74, 2.02)	0.42	1.25 (0.76, 2.07)	0.38
Family history of heart attack	1.01 (0.61, 1.67)	0.96	0.88 (0.53, 1.46)	0.63
Total cholesterol†	1.01 (0.94, 1.08)	0.79	1.01 (0.94, 1.08)	0.88
HDL cholesterol†	0.90 (0.73, 1.12)	0.34	0.88 (0.71, 1.09)	0.25
Systolic blood pressure‡	1.00 (0.99, 1.01)	0.93	1.00 (0.99, 1.01)	0.76
Anti-hypertensive medication use	1.25 (0.74, 2.13)	0.41	1.13 (0.66, 1.94)	0.65
Lipid-lowering medication use	1.18 (0.64, 2.17)	0.59	1.12 (0.61, 2.06)	0.70
CAC score, Log CAC+1			1.18 (1.05, 1.31)	0.004

*Per 5 year increase

†Per 10 mg/dL increase

‡Per 10 mmHg increase

Table 4:

Ten-year risk of coronary heart disease predicted by models with and without categorical CAC score in a lung cancer screening population (n=484) [*,†]

	Events					Nonevents			
	MESA CHD Model + CAC					MESA CHD Model + CAC			
	<5%	**5%-10%**	**≥10%**	**Total**		**<5%**	**5%-10%**	**≥10%**	**Total**
MESA CHD Model									
<5%	9	4	3	16		59	40	4	103
5%-10%	5	7	19	31		51	42	68	161
≥10%	0	1	24	25		12	14	123	148
Total	14	12	46	72		122	95	195	412
Net effect of CAC									
Increased risk			26					112	
Decreased risk			6					76	
Net correctly reclassified			28%					−9%	
Net reclassification improvement			0.19 (95% CI: 0.02, 0.36)						

[*] Baseline model included age, gender, race, diabetes, current smoking status, family history of heart attack, total cholesterol, hdl cholesterol, systolic blood pressure, lipid-lowering medication, and hypertension medication.

[†] CAC scores were categorized as follows: 0, 1-99, 100-400, and >400, and values falling with each of these categories were given the same CAC score.