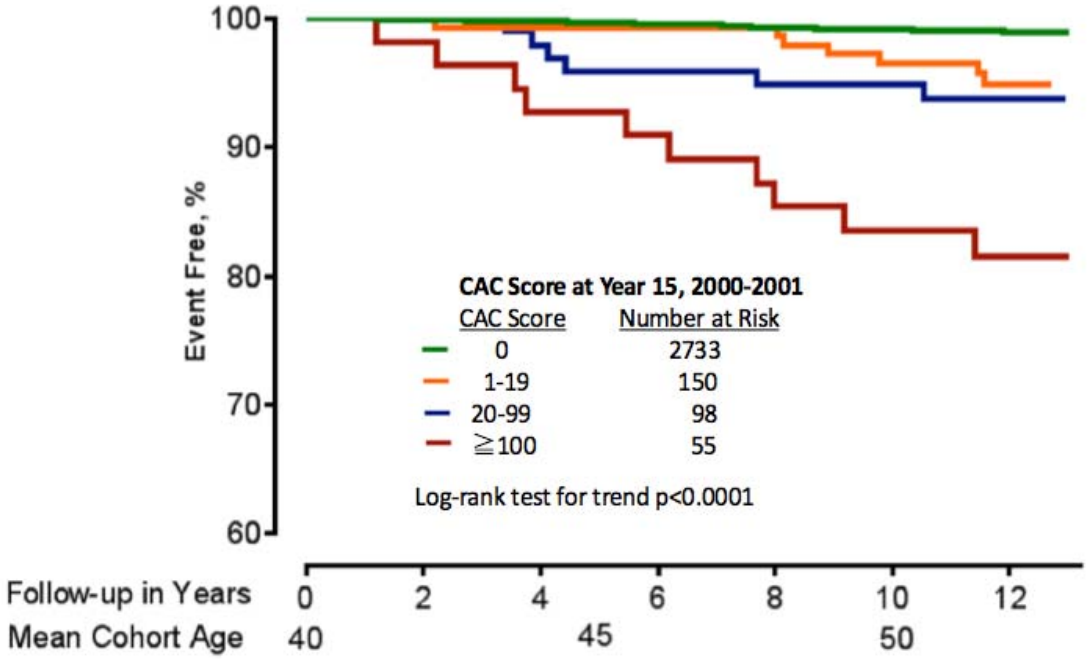
Supplementary Online Content

Carr JJ, Jacobs DR Jr, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. Published online February 8, 2017. doi:10.1001/jamacardio.2016.5493

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Cumulative Event-Free Survival for Incident Coronary Heart Disease, Unadjusted Among Participants 32 to 46 Years by CAC Score Categories



Unadjusted Kaplan-Meier cumulative-event curves for CHD events among participants with a CAC score of 0, 1-19, 20-99, and 100 and greater. The rates of fatal and non-fatal coronary heart disease (myocardial infarction, hospitalization for acute coronary syndrome, revascularization, or coronary heart disease death, including fatal myocardial infarction) are plotted by CAC score range and the differences among these curves were statistically significant (P<.001).

eTable 1. CT Scanners and Technical Parameters of the CARDIA CT Exams 2000-2011

Year **CARDIA Exam**	**2000-01** **Year 15**	**2005-06** **Year 20**	**2010-11** **Year 25**
Birmingham, AL			
Manufacturer Model CT type KVp Slice Thickness (mm)	GE LightSpeed Qxi MDCT-4 120 2.5	GE Lightspeed 16 MDCT-16 120 2.5	GE 750 HD MDCT-64 120 2.5
Chicago, IL			
Manufacturer Model CT type KVp Slice Thickness (mm)	GE Imatron C150 EBCT 130 3.0	GE Imatron C150 EBCT 130 3.0	Siemens Sensation 64 MDCT-64 120 3.0
Minneapolis, MN			
Manufacturer Model CT type KVp Slice Thickness (mm)	Siemens Volume Zoom MDCT-4 140 3.0	Siemens Sensation 16 MDCT-16 120 3.0	Siemens Sensation 64 MDCT-64 120 3.0
Oakland, CA			
Manufacturer Model CT type KVp Slice Thickness (mm)	GE Imatron C150 EBCT 130 3.0	GE Imatron C150 EBCT 130 3.0	GE LightSpeed VCT MDCT-64 120 2.5

Abbreviations: GE – GE Healthcare, Waukesha, WI Siemens – Siemens Medical Solutions USA, Malvern, PA, EBCT – electron beam computed tomography, MDCT – multi-detector computed tomography with the number representing the number of channels or slices per rotation (e.g. 4, 16 or 64 slice CT system). KVp – peak tube current in kilovolts.

eTable 2. CARDIA Participants' Framingham Risk Score, CAC Score Categories and Medications for High Blood Pressure and Elevated Cholesterol Over 10 Years From Age 32 to 46 Years to Age 42 to 56 Years

	Year 15 2000-01			Year 20 2005-06			Year 25 2010-11		
	% (N)[a]	Hypertension[b] Rx % (N)	Cholesterol[b] Rx % (N)	% (N)	Hypertension Rx % (N)	Cholesterol Rx % (N)	% (N)	Hypertension Rx % (N)	Cholesterol Rx % (N)
10-yr CHD Risk[c]	100 (3043)	7.6 (230)	2.6 (80)	100 (3076)	17.8 (546)	10.8 (331)	100 (3118)	28.1 (877)	18.0 (560)
<4%	80.1(2437)	6.4(156)	2.1 (51)	72.1 (2218)	14.3 (317)	8.7 (194)	55.3 (1723)	21.5 (371)	14.0 (242)
5-11%	17.9 (546)	11.0 (60)	4.8 (26)	24.7 (758)	24.4 (185)	16.1 (122)	37.2 (1159)	33.5 (388)	20.3 (235)
≥12%	2.0 (6)	23.3 (14)	5.0 (3)	3.3 (100)	44.0 (44)	15.0 (15)	7.6 (236)	50.0 (118)	35.2 (83)
CAC Score[d]									
0	89.8 (2734)	6.7 (183)	2.2 (61)	80.0 (2461)	14.7 (362)	7.8 (194)	71.7 (2237)	23.5 (525)	12.7 (284)
1-19	5.0(152)	13.2 (20)	4.6 (7)	10.1 (311)	26.1 (81)	13.8 (43)	9.5 (296)	32.4 (96)	21.6 (64)
20-99	3.3(99)	16.2 (16)	3.0 (3)	5.7 (176)	30.7 (54)	22.2 (39)	9.2 (287)	32.8 (94)	33.1 (95)
≥100	1.9 (58)	19.0 (11)	15.5 (9)	4.2 (128)	38.3 (49)	43.0 (55)	9.6 (298)	54.4 (162)	39.3 (117)
Any CAC	10.2(309)	15.2 (47)	6.1 (19)	20.0 (615)	29.9 (184)	22.3 (137)	28.3 (881)	40.0 (352)	31.3 (276)

[a]The number of participants in each exam year is reduced compared to table 1 because of missing data required for calculating the Framingham Risk Score or medications. Column percentages are shown in the N columns.
[b]Participants reporting taking medications for high blood pressure or to lower blood cholesterol.
[c]Framingham Risk Score for 10-year risk of coronary heart disease at the respective exams.
[d]CAC score – Total calcium score (Agatston Score), all coronary vessels.

eTable 3. Incident Cardiovascular Diseases Events by CAC Score for Individuals 32 to 46 Years in 2000-2001 and Followed Through 2013 (Ages 45 to 59 Years)

	Cardiovascular Disease (CVD) – All[e]							Cardiovascular Disease (CVD) – excluding CHD[f]						
CAC Score[a]	N[b]	p-y	events	ID[c]	HR[d]	95% CI	pvalue	N[b]	p-y	events	ID[c]	HR[d]	95% CI	pvalue
None	2717	34,045	70	2.6	1		NA	2719	34,204	44	1.6	1		NA
Any(>0)	300	3,555	38	13.4	3.0	1.9-4.7	<0.0001	306	3,768	8	1.7	1.2	0.5-2.6	0.64
Score Ranges														
1-19	149	1,814	11	7.6	1.8	0.9-3.4	0.07	151	1,868	4	2.7	1.3	0.4-3.6	0.61
20-99	98	1,150	13	14.1	3.6	1.8-6.5	<0.0001	99	1,223	3	3.1	1.3	0.3-3.7	0.68
≥100	53	591	14	29.6	5.7	2.8-10.9	<0.0001	56	677	1	1.8	0.8	0.1-4.2	0.86
Total	3017	37,599	108	3.6				3025	37,972	52	2.7			

[a]CAC score – Total calcium score (Agatston Score), all coronary vessels at year 15 exam(2000-01) by presence and score categories.
[b]N: number of participants at risk at year 15 exam, 2000-01; 26 and 18 of the 3043 participants who had a CT at year 15 had a prior CVD or CVD other than CHD event and were excluded from the respective analyses.
[c]ID: incidence density, the number of adjudicated CHD events per 100 people followed for 11.6 years.
[d]HR: hazard ratio; CI: confidence interval; Hazard ratios in proportional hazards regression, adjusted for age, race, gender, field center, smoking status, maximum educational attainment, systolic blood pressure, treatment for hypertension, cholesterol, triglycerides, HDL-C, treatment for dyslipidemia, diabetes and BMI.
[e]CVD: cardiovascular disease, included CHD, hospitalization for heart failure, stroke, transient ischemic attack, or intervention for peripheral artery disease.
[f]CHD: coronary heart disease, included hospitalization for myocardial infarction, hospitalization for acute coronary syndrome with increasing symptoms consistent with ischemia but without evidence of myocardial necrosis, or CHD death (including fatal myocardial infarction) (n=46) or coronary revascularization (n=11).

eTable 4. Prediction of CAC Presence at Any of Years 15, 20, and/or 25 in a Linear Model Using Year 0 and Year 7 Risk Factor Predictors

Parameter	β	Standard error	t Value	Pr > |t|
Intercept	-0.9388	0.13046	-7.2	<.0001
Age at year 0 (years)	**0.01748**	**0.00208**	**8.4**	**<0.0001**
Black race (vs white)	**-0.0594**	**0.01629**	**-3.65**	**0.0003**
Female sex (vs male)	**-0.1859**	**0.01632**	**-11.39**	**<0.0001**
Clinical center (vs Oakland)				
Birmingham	-0.0019	0.02067	-0.09	0.9284
Chicago	0.02488	0.02059	1.21	0.2269
Minneapolis	0.0153	0.02016	0.76	0.448
Education, maximum attained (vs did not complete high school)				
More than college	-0.1066	0.05602	-1.9	0.0572
College	-0.0846	0.0561	-1.51	0.1317
Some post-secondary	-0.0774	0.05502	-1.41	0.1595
High school	-0.0969	0.05678	-1.71	0.0881
Year 0 cigarette smoking (vs never)				
Current	0.02983	0.03037	0.98	0.3261
Former	-0.036	0.03018	-1.19	0.2324
Year 7 cigarette smoking (vs never)				
Current	**0.10904**	**0.03099**	**3.52**	**0.0004**
Former	0.02303	0.02937	0.78	0.433
Year 0 LDL-C (mg/dL)	**0.00127**	**0.00034**	**3.68**	**0.0002**
Year 7 LDL-C (mg/dL)	**0.00141**	**0.00034**	**4.08**	**<0.0001**
Year 0 BMI **(kg/m^2)**	0.0041	0.00326	1.26	0.2083
Year 7 BMI **(kg/m^2)**	0.00514	0.00267	1.93	0.0539
Year 0 SBP **(mmHg)**	0.00148	0.0009	1.64	0.101
Year 7 SBP (mmHg)	**0.00251**	**0.00081**	**3.1**	**0.002**
Use of antihypertensive medication (vs nonuse)	-0.0219	0.0391	-0.56	0.5747
Use of lipid lowering medication (vs nonuse)	0.00164	0.04562	0.04	0.9712
Ever diabetes by year 7 (vs never)	0.13521	0.06928	1.95	0.0511

N=3330 with CT done at least once and no missing predictor variables which were measured in CARDIA year 0 (1985-86) and year 7 (1992-93). The most contributory predictor rows are in bold. The predicted score for ever CAC presence is computed as the sum of cross products of variable values time coefficients in the β column.

eTable 5. Actually Observed CAC at Years 15, 20, and/or 25 According to Prediction Decile in the Linear Model Presented in eTable 4

Decile of predicted CAC	Never CAC	Ever CAC	% Ever CAC	Total
0	319	14	4.2	333
1	301	38	11.21	339
2	303	34	10.09	337
3	279	61	17.94	340
4	259	72	21.75	331
5	237	100	29.67	337
6	212	116	35.37	328
7	205	123	37.5	328
8	148	189	56.08	337
9	103	217	67.81	320
Total	2366	964	100.00	3330

eAppendix. Methods for CAC Prediction During Middle Age (All Participants Prior to Age 56 Years)

We investigated a method for a tiered strategy to identify individuals at high risk for premature clinical CHD or death by combining demographics and traditional risk factors measured in early adult life with information from predictive modeling of developing CAC during middle age in CARDIA. The intention was to develop a model that identifies those individuals at elevated risk of developing premature coronary artery disease as indicated by the presence of CAC based on commonly measured risk factors in early adult life. We note that this is only one of many potential strategies and that any algorithm to risk stratify should be thoroughly vetted prior to applying in clinical practice. We present these computations as an example that will hopefully inform future algorithms using risk factors, CAC and events data. Standard risk measurements were mean age, race, sex, educational attainment, field center, smoking status, LDL-C, BMI, systolic BP, use of antihypertensive medication, use of lipid lowering medication, and presence of diabetes, formed into a CAC risk score based on two measurements of risk factors, at about ages 25 and 32. As presented, the patient and healthcare provider would complete a shared decision making visit between the ages 32-45 years to determine if further CHD risk assessment with a CT screening program for CAC should be considered, comparable to that currently performed prior to CT screening for lung cancer. There were 3980 CARDIA participants who participated in any CT exam with 650 having missing data at baseline or the year 7 exam resulting in a sample size of 3330 with all of the measurements and at least one CT measurement in years 15, 20, and/or 25. We used a linear model to provide a direct and unbiased estimate of percent of people with CAC present (that is, the linear estimate is the mean of the distribution of possible estimates of CAC presence); however, the linear model predicted value can be less than zero or greater than one, the variance structure violates homoscedasticity, and the model does

not distinguish time of follow-up after risk factor measurements until CAC measurements. A Poisson regression model with person time offset addresses all of these issues, estimating CAC presence as 1 – probability of CAC not found. However, the Poisson model is on the natural logarithm scale. Exponentiation of the predicted Poisson mean λ and using it in the formula 1 – exp(-exp(λ)) as the predicted probability for CAC presence gives the geometric mean of the distribution of possible estimates of CAC presence, which is difficult to interpret. In the case of the Poisson model, this estimate is a substantially lower number than is the unbiased mean value of the linear model. We computed percentage of people with CAC in the Poisson prediction and it was close to identical to the findings for the linear model, correlation 0.94. Therefore, we used the linear model for the predictive model presented in eTable 4 and to then calculate the deciles of predicted CAC presented in eTable 5.