**Table S1.** Agreement between baseline and 3-month automated CAC scores in a subgroup of 100 randomly selected BioMILD volunteers

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Total** | **3-month CAC** | | | |
|  | | **N (%)** | **0-99** | **100-399** | **≥400** | **Weighted Kappa** |
| **Total** | | 100 | **79 (79%)** | **15 (15%)** | **6 (6%)** | 0.87 (0.76-0.97) |
| **Baseline CAC** | **0-99** | 82 (82%) | 77 (93.9%) | 5 (6.1%) | 0 |
|  | **100-399** | 13 (13%) | 2 (15.4%) | 10 (76.9%) | 1 (7.7%) |
|  | **≥400** | 5 (5%) | 0 | 0 | 5 (100%) |

CAC, coronary artery calcium by pre-specified Agatston score strata.

**Table S2.** Agreement between automated and manual CAC scores in a subgroup of 100 randomly selected BioMILD volunteers

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Total** | **Automated CAC** | | | |
|  | | **N (%)** | **0-99** | **100-399** | **≥400** | **Weighted Kappa** |
| **Total** | | 100 | **79 (79%)** | **15 (15%)** | **6 (6%)** | 0.92 (0.85-1.00) |
| **\*Manual CAC** | **0-99** | 76 (76%) | 75 (94.9%) | 1 (6.7%) | 0 |
|  | **100-399** | 18 (18%) | 4 (5.1%) | 14 (93.3%) | 0 |
|  | **≥400** | 6 (6%) | 0 | 0 | 6 (100%) |

CAC, coronary artery calcium by pre-specified Agatston score strata.

\*Computed by a 5-years experienced thoracic radiologist blinded to demographic, clinical, and pulmonary function data.

**Table S3.** Distribution of %LAA and CAC to 6-year all-cause deaths, cause-specific deaths, and lung cancer incidence

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Total** | **Alive** | **6-year All-Cause deaths** | | **6-year Non-Cancer deaths** | | **6-year CV deaths** | | **6-year LC deaths** | | **6-year LC incidence** | |
| **N** | **N** | **N** | **p-value** | **N (%)** | **p-value** | **N** | **p-value** | **N** | **p-value** | **N** | **p-value** |
| **Total** | | **4098** | **3957 (96.6%)** | **141 (3.4%)** |  | **55 (1.3%)** |  | **27 (0.7%)** |  | **38 (0.9%)** |  | **112 (2.8%)a** |  |
|  |  | 5.9x1000 py |  | 2.3x1000 py |  | 1.1x1000 py |  | 1.6x1000 py |  | 4.8x1000 py |  |
| **%LAA** | **Median (IQR)** | 1.2 (0.5-2.8) | 1.2 (0.5-2.7) | 2.0 (0.7-4.9) | <0.0001 | 1.6 (0.6-5.4) | 0.0468 | 2.0 (0.7-5.2) | 0.0482 | 2.1 (1.2-3.3) | 0.0074 | 1.7 (0.8-3.2) | 0.0035 |
| **CAC** | **0-99** | 2995 (73.1%) | 2923 (97.6%) | 72 (2.4%) | <0.0001 | 23 (0.8%) | <0.0001 | 9 (0.3%) | <0.0001 | 23 (0.8%) | 0.1115 | 72 (2.4%) | 0.0755 |
| **100-399** | 652 (15.9%) | 623 (95.6%) | 29 (4.5%) | 10 (1.5%) | 4 (0.6%) | 9 (1.4%) | 25 (3.9%) |
| **≥400** | 451 (11.0%) | 411 (91.1%) | 40 (8.9%) | 22 (4.9%) | 14 (3.1%) | 6 (1.3%) | 15 (3.4%) |

%LAA, percentage of lung volume occupied by voxels with attenuation of –950 Hounsfield units or less; CAC, coronary artery calcium by pre-specified Agatston score strata; CV, cardiovascular; LC, lung cancer.

Data are presented as n (%) or median (interquartile range).

a% on 4051 volunteers without prevalent lung cancer.

**Table S4.** Association between CAC and self-reported statin therapy

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Total** | **CAC** | | | |
|  | | **N (%)** | **0-99** | **100-399** | **≥400** | **Trend p-value** |
| **Total** | | **4098** | **2995 (73.1%)** | **652 (15.9%)** | **451 (11.0%)** |  |
| **Statins** | **No** | 3280 (80.0%) | 2571 (78.3%) | 477 (14.5%) | 232 (7.1%) | <0.0001 |
|  | **Yes** | 818 (20.0%) | 424 (51.8%) | 175 (21.4%) | 219 (26.8%) |  |

CAC, coronary artery calcium by pre-specified Agatston score strata.

**Table S5**. Univariate and multivariate Cox models for 6-year all-cause mortality in volunteers with ≥ 30 pack years

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **%LAA** | **CAC** | | |
| **median (IQR)** | **0-99** | **100-399** | **≥400** |
| **1.2 (0.5-2.8)** | **2774 (72.4%)** | **624 (16.3%)** | **436 (11.4%)** |
| **All-Cause Mortality** | 2.0 (0.7-4.9) | 71 (2.6%) | 29 (4.7%) | 40 (9.2%) |
| **HRcrude (95%CI)** | 1.24 (1.16-1.30) | Ref. | 1.86 (1.19-2.82) | 3.75 (2.53-5.49) |
|
| **p-value** | <0.0001 |  | 0.0049 | <0.0001 |
| **HRadjusted1 (95%CI)** | 1.24 (1.16-1.31) | Ref. | 1.74 (1.12-2.64) | 3.62 (2.44-5.30) |
| **p-value** | <0.0001 |  | 0.0120 | <0.0001 |
| **HRadjusted2 (95%CI)** | 1.17 (1.09-1.25) | Ref. | 1.29 (0.82-1.99) | 2.32 (1.52-3.51) |
| **p-value** | <0.0001 |  | 0.2645 | <0.0001 |
| **HRadjusted3 (95%CI)** | 1.15 (1.06-1.24) | Ref. | 1.18 (0.74-1.84) | 2.17 (1.39 – 3.35) |
| **p-value** | 0.0007 |  | 0.4674 | 0.0006 |

%LAA, percentage of lung volume occupied by voxels with attenuation of –950 Hounsfield units or less; CAC, coronary artery calcium by pre-specified Agatston strata; IQR, Interquartile Range; HR, hazard ratio; CI, Confidence Interval.

1Multivariable model including %LAA and CAC; 2adjusted for age, sex, and pack-years (Modelsurvey-LDCT); 3adjusted for age, sex, pack-years, body mass index, self-reported chronic obstructed pulmonary disease, history of cardiovascular disease (defined as myocardial infarction, stroke, thrombosis, or angina), hypertension, diabetes, statins, and respiratory function (Modelfinal).

**Table S6.** Univariate and multivariate Cox models for 6-year lung cancer mortality

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **%LAA** | **CAC** | | |
| **median (IQR)** | **0-99** | **100-399** | **≥400** |
| **1.2 (0.5-2.8)** | **2995 (73.1%)** | **652 (15.9%)** | **451 (11.0%)** |
| **Lung Cancer Mortality** | 2.1 (1.2-3.3) | 23 (0.8%) | 9 (1.4%) | 6 (1.3%) |
| **HRcrude (95%CI)** | 1.20 (1.03-1.33) | Ref. | 1.88 (0.84-3.87) | 1.90 (0.73-4.28) |
|
| **p-value** | 0.0034 |  | 0.1081 | 0.1551 |
| **HRadjusted1 (95%CI)** | 1.19 (1.02-1.33) | Ref. | 1.78 (0.80-3.68) | 1.82 (0.70-4.10) |
| **p-value** | 0.0064 |  | 0.1405 | 0.1856 |
| **HRadjusted2 (95%CI)** | 1.09 (0.91-1.24) | Ref. | 1.11 (0.48-2.37) | 0.93 (0.35-2.21) |
| **p-value** | 0.2781 |  | 0.7950 | 0.8814 |
| **HRadjusted3 (95%CI)** | 1.01 (0.82-1.18) | Ref. | 1.08 (0.47-2.32) | 1.08 (0.40-2.54) |
| **p-value** | 0.9556 |  | 0.8518 | 0.8769 |

%LAA, percentage of lung volume occupied by voxels with attenuation of –950 Hounsfield units or less; CAC, coronary artery calcium by pre-specified Agatston strata; IQR, Interquartile Range; HR, hazard ratio; CI, Confidence Interval.

1Multivariable model including %LAA and CAC; 2adjusted for age, sex, and pack-years (Modelsurvey-LDCT); 3adjusted for age, sex, pack-years, asbestos exposure, self-reported chronic obstructed pulmonary disease, and respiratory function (Modelfinal).

**Table S7.** Univariate and multivariate Cox models for 6-year lung cancer incidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **%LAA** | **CAC** | | |
| **median (IQR)** | **0-99** | **100-399** | **≥400** |
| **1.2 (0.5-2.8)** | **2958 (73.0%)** | **649 (16.0%)** | **444 (11.0%)** |
| **Lung Cancer Incidence** | 1.7 (0.8-3.2) | 72 (2.45) | 25 (3.9%) | 15 (3.4%) |
| **HRcrude (95%CI)** | 1.10 (0.98-1.20) | Ref. | 1.63 (1.02-2.52) | 1.49 (0.83-2.50) |
|
| **p-value** | 0.0678 |  | 0.0362 | 0.1595 |
| **HRadjusted1 (95%CI)** | 1.09 (0.97-1.20) | Ref. | 1.59 (0.99-2.47) | 1.46 (0.81-2.45) |
| **p-value** | 0.1023 |  | 0.0454 | 0.1830 |
| **HRadjusted2 (95%CI)** | 1.04 (0.92-1.15) | Ref. | 1.38 (0.84-2.18) | 1.16 (0.63-2.04) |
| **p-value** | 0.4520 |  | 0.1902 | 0.6142 |
| **HRadjusted3 (95%CI)** | 0.94 (0.82-1.07) | Ref. | 1.44 (0.88-2.30) | 1.23 (0.66-2.16) |
| **p-value** | 0.3790 |  | 0.1349 | 0.4946 |

%LAA, percentage of lung volume occupied by voxels with attenuation of –950 Hounsfield units or less; CAC, coronary artery calcium by pre-specified Agatston strata; IQR, Interquartile Range; HR, hazard ratio; CI, Confidence Interval.

1Multivariable model including %LAA and CAC; 2adjusted for age, sex, and pack-years (Modelsurvey-LDCT); 3adjusted for age, sex, pack-years, body mass index, personal history of cancer, self-reported chronic obstructed pulmonary disease, and respiratory function (Modelfinal).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | **Total** | **Alive** | **6-year All-cause deaths** | | **6-year Non-cancer deaths** | | **6-year CV deaths** | | **6-year LC deaths** | | **6-year LC incidence** | |
| **N** | **N** | **N** | **p-value** | **N (%)** | **p-value** | **N** | **p-value** | **N** | **p-value** | **N** | **p-value** |
| **%LAA < 1.3** | | | | | | | | | | | | | |
| **Respiratory Function** | | **2135** | **2083 (97.6%)** | **52 (2.4%)** |  | **22 (1.0%)** |  | **9 (0.4%)** |  | **10 (0.5%)** |  | **42 (2.0%)** |  |
|  | **Control** | 1686 (79%) | 1650 (97.9%) | 36 (2.1%) | 0.22741  0.08102 | 14 (0.8%) | 0.39361  0.07612 | 6 (0.4%) | 0.74961  0.40812 | 5 (0.3%) | 0.00061  0.03972 | 29 (1.7%) | 0.05091  0.10412 |
| **PRISm** | 110 (5.25) | 102 (92.7%) | 8 (7.3%) | 5 (4.6%) | 3 (2.7%) | 0 | 1 (0.9%) |
| **GOLD I** | 217 (10.2%) | 214 (98.6%) | 3 (1.4%) | 1 (0.5%) | 0 | 2 (0.9%) | 9 (4.2%) |
| **GOLD II** | 117 (5.5%) | 113 (96.6%) | 4 (3.4%) | 2 (1.7%) | 0 | 2 (1.7%) | 2 (1.7%) |
| **GOLD III** | 5 (0.2%) | 4 (80%) | 1 (20%) | 0 | 0 | 1 (20.0%) | 1 (25%) |
| **GOLD IV** | // |  |  |  |  |  |  |
| **%LAA** ≥ **1.3** | | | | | | | | | | | | | |
| **Respiratory Function** | | **1963** | **1874 (95.5%)** | **89 (4.5%)** |  | **33 (1.7%)** |  | **18 (0.9%)** |  | **28 (1.4%)** |  | **70 (3.6%)** |  |
|  | **Control** | 1045 (53.2%) | 1011 (96.8%) | 34 (3.3%) | 0.00031  0.00362 | 16 (1.5%) | 0.20241  0.58132 | 10 (10.0%) | 0.86241  0.84292 | 11 (1.1%) | 0.05501  0.13622 | 30 (2.9%) | 0.02561  0.07172 |
|  | **PRISm** | 33 (1.7%) | 31 (93.4%) | 2 (6.1%) | 1 (3.0%) | 1 (3.0%) | 0 | 0 |
|  | **GOLD I** | 541 (27.6%) | 514 (95.0%) | 27 (5.0%) | 7 (1.3%) | 3 (0.6%) | 9 (1.7%) | 21 (4.0%) |
|  | **GOLD II** | 305 (15.5%) | 286 (93.8%) | 19 (6.2%) | 5 (1.6%) | 2 (0.7%) | 7 (2.3%) | 17 (5.6%) |
|  | **GOLD III** | 36 (1.8%) | 30 (83.3%) | 6 (16.7%) | 4 (11.1%) | 2 (5.7%) | 0 | 2 (5.6%) |
|  | **GOLD IV** | 3 (0.2%) | 2 (66.7%) | 1 (33.3%) | 0 | 0 | 1 (33.3%) | 0 |

**Table S8**. Distribution of respiratory function stratified by %LAA < 1.3 and %LAA ≥ 1.3

CV, cardiovascular; %LAA, percentage of lung volume occupied by voxels with attenuation of –950 Hounsfield units or less; GOLD, Global Initiative for Obstructive Lung Disease; LC, lung cancer; PRISm, preserved ratio impaired spirometry.

The %LAA cut-off 1.3 was defined by maximization of Youden index to predict abnormal respiratory function.

1trend test p-value all categories.

2p-value for control vs others.