

Supplementary Online Content

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

eTable 1. Risk Thresholds for the CXR-Risk Score.

Risk thresholds defining the CXR-risk score and percentage falling within each category. Thresholds were set in the PLCO development data set based on quantiles, then applied to the PLCO and NLST test data sets.

CXR-risk score	CNN probability threshold	PLCO development (n=41,856)	PLCO test (n=10,464)	NLST test (n=5,493)
Very low	0	25.0% (10,465)	24.3% (2,543)	13.7% (752)
Low	0.063583	25.0% (10,464)	26.5% (2,769)	30.6% (1,679)
Moderate	0.096197	25.0% (10,463)	25.6% (2,674)	31.4% (1,723)
High	0.1579735	20.0% (8,372)	19.2% (2,006)	21.1% (1,159)
Very high	0.34843	5.0% (2,092)	4.5% (472)	3.3% (180)

eTable 2. CXR-Risk Score Hazard Ratios for All-Cause Mortality, Unadjusted and Adjusted for Radiograph Findings, Risk Factors, and the Combination of Findings Plus Risk Factors.

PLCO test data set								
CXR-risk score	Unadjusted HR (95% CI)	P	HR adjusted for CXR findings (95% CI)	P	HR adjusted for risk factors (95% CI)	P	HR adjusted for findings & risk factors (95% CI)	P
Very low	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Low	2.0 (1.6-2.6)	<0.001	2.0 (1.6-2.5)	<0.001	1.5 (1.1-1.9)	0.002	1.4 (1.1-1.8)	0.003
Moderate	3.3 (2.7-4.2)	<0.001	3.2 (2.6-4.0)	<0.001	1.8 (1.4-2.2)	<0.001	1.7 (1.3-2.2)	<0.001
High	7.0 (5.6-8.6)	<0.001	6.5 (5.2-8.1)	<0.001	2.8 (2.2-3.6)	<0.001	2.6 (2.1-3.4)	<0.001
Very high	18.3 (14.5-23.2)	<0.001	16.1 (12.6-20.5)	<0.001	5.4 (4.1-7.1)	<0.001	4.8 (3.6-6.4)	<0.001
NLST test data set								
CXR-risk score	Unadjusted HR (95% CI)	P	HR adjusted for CXR findings (95% CI)	P	HR adjusted for risk factors (95% CI)	P	HR adjusted for findings & risk factors (95% CI)	P
Very low	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Low	1.4 (0.87-2.4)	0.158	1.4 (0.86-2.3)	0.17	1.2 (0.81-2.0)	0.53	1.2 (0.70-1.9)	0.56
Moderate	2.6 (1.6-4.1)	<0.001	2.5 (1.5-4.0)	<0.001	1.8 (1.1-2.9)	0.020	1.7 (1.0-2.8)	0.034
High	3.9 (2.4-6.3)	<0.001	3.5 (2.2-5.7)	<0.001	2.5 (1.5-4.1)	<0.001	2.3 (1.4-3.7)	0.002
Very high	15.2 (9.2-25.3)	<0.001	12.6 (7.5-21.1)	<0.001	8.3 (4.8-14.2)	<0.001	7.0 (4.0-12.1)	<0.001

CXR = chest radiograph, HR = hazard ratio, CI = confidence interval
Adjusted hazard ratios are adjusted for 9 chest radiograph findings (lung nodule, major atelectasis, pleural plaque or effusion, lymphadenopathy, chest wall or bony lesion, COPD/emphysema, cardiomegaly or other cardiovascular abnormality, and lung fibrosis), 10 risk factors (age, sex, smoking category, diabetes, hypertension, obesity, underweight, past myocardial infarction, past stroke, and past cancer), or the combination of findings plus risk factors.

eTable 3. Cox Model Including the CXR-Risk Score, Risk Factors, and Radiograph Findings With Adjusted Hazard Ratios for All-Cause Mortality

		PLCO Test (n=10,464)		NLST Test (n=5,493)	
		aHR (95% CI)	P	aHR (95% CI)	p
CXR-risk score	Very low	1 [Reference]		1 [Reference]	
	Low	1.4 (1.1-1.8)	0.003	1.2 (0.70-1.9)	0.56
	Moderate	1.7 (1.3-2.2)	<0.001	1.7 (1.0-2.8)	0.034
	High	2.6 (2.1-3.4)	<0.001	2.3 (1.4-3.7)	0.002
	Very high	4.8 (3.6-6.4)	<0.001	7.0 (4.0-12.1)	<0.001
Risk factors	Age (years)	1.1 (1.1-1.1)	<0.001	1.0 (1.0-1.1)	<0.001
	Male sex	1.5 (1.3-1.7)	<0.001	1.2 (0.93-1.5)	0.19
	Smoking	1 [Reference]		NA	
	Never	1.3 (1.2-1.5)	<0.001	1 [Reference]	
	Former	2.6 (2.2-3.1)	<0.001	1.6 (1.3-2.0)	<0.001
	Current				
	Diabetes	1.7 (1.5-2.0)	<0.001	1.5 (1.1-2.0)	0.016
	Hypertension	1.3 (1.2-1.5)	<0.001	1.4 (1.1-1.7)	0.004
	Obesity (BMI ≥30kg/m ²)	1.1 (0.98-1.3)	0.12	1.0 (0.82-1.3)	0.71
	Underweight (BMI <18.5 kg/m ²)	1.4 (0.89-2.3)	0.15	3.6 (1.9-6.8)	<0.001
	Past myocardial infarction	1.3 (1.2-1.5)	<0.001	1.3 (1.0-1.8)	0.032
	Past stroke	1.8 (1.5-2.3)	<0.001	1.3 (0.84-2.0)	0.24
	Past cancer	1.5 (1.2-1.9)	<0.001	1.1 (0.68-1.9)	0.65
	Radiograph findings	Lung nodule	1.3 (1.1-1.5)	0.006	1.6 (1.2-2.1)
Major atelectasis		1.8 (0.56-5.6)	0.33	1.2 (0.29-4.9)	0.81
Pleural plaque or effusion		0.88 (0.69-1.1)	0.30	1.1 (0.68-1.7)	0.78
Lymphadenopathy		1.0 (0.59-1.9)	0.87	3.0 (0.95-9.5)	0.060
Chest wall or bony abnormality		1.1 (0.83-1.4)	0.65	1.8 (0.64-4.8)	0.28
Lung opacity		1.4 (0.87-2.2)	0.16	3.6 (1.2-10.4)	0.018
COPD/emphysema		1.4 (1.1-1.7)	0.014	1.1 (0.85-1.5)	0.43
Cardiomegaly or other cardiovascular abnormality		1.4 (1.1-1.7)	0.004	1.8 (1.0-3.1)	0.045
Lung fibrosis	1.2 (1.0-1.4)	0.021	1.3 (0.94-1.9)	0.10	

BMI = body mass index, COPD = chronic obstructive pulmonary disease, aHR = adjusted hazard ratio, CI = confidence interval, NA = not applicable

Adjusted hazard ratios are adjusted for chest radiograph findings (lung nodule, major atelectasis, pleural plaque or effusion, lymphadenopathy, chest wall or bony lesion, COPD/emphysema, cardiomegaly or other cardiovascular abnormality, and lung fibrosis) and risk factors (age, sex, smoking category, diabetes, hypertension, obesity, underweight, past myocardial infarction, past stroke, and past cancer).

eTable 4. Cause-Specific Mortality by CXR-Risk Score

The CXR-risk score predicted multiple causes of death, including lung cancer death, cardiovascular death, and respiratory death. This association was robust to adjustment for the radiologists' findings (e.g. lung nodule) and standard risk factors (e.g. age, sex, diabetes).

A) PLCO test data set

Cause of death	CXR-risk score	Mortality	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Lung cancer	Very low	0.28% (7/2,543)	REF		REF	
	Low	0.61% (17/2,769)	2.2 (0.9-5.3)	0.078	1.8 (0.7-4.3)	0.198
	Moderate	1.4% (37/2,674)	5.1 (2.3-11.4)	<0.001	3.1 (1.3-7.2)	0.008
	High	3.2% (64/2,006)	12.5 (5.7-17.2)	<0.001	5.7 (2.4-13.1)	<0.001
	Very high	7.2% (34/472)	34.8 (15.4-78.5)	<0.001	11.1 (4.4-27.8)	<0.001
	All	1.5% (159/10,464)				
Non-lung cancer	Very low	1.7% (43/2,543)	REF		REF	
	Low	3.0% (82/2,769)	1.7 (1.2-2.5)	0.004	1.2 (0.8-1.8)	0.28
	Moderate	3.7% (99/2,674)	2.2 (1.5-3.1)	<0.001	1.1 (0.8-1.7)	0.48
	High	5.9% (118/2,006)	3.7 (2.6-5.3)	<0.001	1.6 (1.0-2.4)	0.029
	Very high	9.7% (46/472)	7.6 (5.0-11.6)	<0.001	2.5 (1.5-4.2)	<0.001
	All	3.7% (388/10,464)				
Cardiovascular illness	Very low	0.90% (23/2,543)	REF		REF	
	Low	2.3% (64/2,769)	2.5 (1.6-4.1)	<0.001	1.6 (1.0-2.5)	0.067
	Moderate	4.0% (107/2,674)	4.4 (2.8-7.0)	<0.001	1.8 (1.1-2.9)	0.018
	High	7.9% (159/2,006)	9.3 (6.0-14.4)	<0.001	2.4 (1.4-3.8)	0.001
	Very high	16.7% (79/472)	24.1 (15.2-38.4)	<0.001	3.6 (2.1-6.2)	<0.001
	All	4.1% (432/10,464)				
Respiratory illness	Very low	0.12% (3/2,543)	REF		REF	
	Low	0.47% (13/2,769)	3.9 (1.1-13.6)	0.034	2.9 (0.8-10.3)	0.096

	Moderate	0.79% (21/2,674)	6.6 (2.0-22.1)	0.002	3.5 (1.0-12.0)	0.051
	High	2.4% (48/2,006)	21.4 (6.7-68.7)	<0.001	8.3 (2.4-28.1)	0.001
	Very high	9.5% (45/472)	107.8 (33.5-347.0)	<0.001	27.5 (7.7-97.8)	<0.001
	All	1.2% (130/10,464)				
Other*	Very low	0.83% (21/2,543)	REF		REF	
	Low	1.4% (40/2,769)	1.7 (1.0-2.9)	0.047	1.3 (0.8-2.3)	0.28
	Moderate	2.8% (75/2,674)	3.4 (2.1-5.5)	<0.001	2.1 (1.2-3.5)	0.006
	High	5.5% (111/2,006)	7.1 (4.4-11.3)	<0.001	3.5 (2.1-6.0)	<0.001
	Very high	9.7% (46/472)	15.6 (9.3-26.1)	<0.001	6.2 (3.3-11.5)	<0.001
	All	2.8% (293/10,464)				

B) NLST test data set

Cause of death	CXR-risk score	Mortality	Unadjusted HR (95% CI)	P	Adjusted HR (95% CI)	P
Lung cancer	Very low	0.55% (4/732)	REF		REF	
	Low	1.7% (29/1,679)	3.2 (1.1-9.2)	0.027	3.0 (1.0-8.5)	0.041
	Moderate	2.0% (35/1,723)	3.9 (1.4-11.0)	0.010	3.1 (1.1-8.8)	0.039
	High	2.8% (33/1,159)	5.6 (2.0-15.9)	0.001	4.0 (1.4-11.8)	0.012
	Very high	6.7% (12/180)	14.9 (4.8-46.3)	<0.001	8.4 (2.5-28.0)	0.001
	All	2.1% (113/5,493)				
Non-lung cancer	Very low	1.6% (12/732)	REF		REF	
	Low	0.71% (12/1,679)	0.4 (0.2-1.0)	0.50	0.3 (0.0-0.7)	0.008
	Moderate	0.99% (17/1,723)	0.6 (0.3-1.3)	0.23	0.4 (0.2-0.8)	0.017
	High	2.0% (23/1,159)	1.3 (0.7-2.7)	0.43	0.7 (0.3-1.6)	0.41
	Very high	1.7% (3/180)	1.3 (0.4-4.5)	0.70	0.6 (0.2-2.4)	0.50
	All	1.2% (67/5,493)				
Cardiovascular illness	Very low	0.14% (1/732)	REF		REF	
	Low	0.83% (14/1,679)	6.3 (0.8-47.8)	0.076	4.9 (0.6-37.7)	0.13
	Moderate	1.3% (23/1,723)	10.3 (1.4-76.2)	0.022	6.5 (0.9-49.1)	0.069
	High	2.4% (28/1,159)	19.1 (2.6-140.5)	0.004	11.6 (1.5-87.7)	0.018
	Very high	10.0% (18/180)	89.7 (12.0-672.0)	<0.001	47.8 (6.1-374.9)	<0.001
	All					

	All	1.5% (84/5,493)				
Respiratory illness	Very low	0.14% (1/732)	REF		REF	
	Low	0.06% (1/1,679)	0.4 (0.03-7.2)	0.57	0.4 (0.02-5.6)	0.46
	Moderate	0.81% (14/1,723)	6.3 (0.8-47.6)	0.076	4.0 (0.5-31.6)	0.19
	High	1.1% (13/1,159)	8.8 (1.2-67.5)	0.036	4.6 (0.6-37.2)	0.16
	Very high	8.3% (15/180)	73.8 (9.7-558.5)	<0.001	31.9 (3.9-263.5)	0.001
	All	0.8% (44/5,493)				
Other*	Very low	0.27% (2/732)	REF		REF	
	Low	0.48% (8/1,679)	1.8 (0.4-8.5)	0.46	1.4 (0.3-6.5)	0.70
	Moderate	1.5% (26/1,723)	5.8 (1.4-24.6)	0.016	3.2 (0.7-13.9)	0.12
	High	1.5% (17/1,159)	5.8 (1.4-25.2)	0.018	2.4 (0.5-10.9)	0.27
	Very high	7.2% (13/180)	32.4 (7.3-143.6)	<0.001	8.1 (1.6-)	0.010
	All	1.1% (66/5,493)				

HR = hazard ratio, CI = confidence interval

Adjusted hazard ratios are adjusted for 9 chest radiograph findings (lung nodule, major atelectasis, pleural plaque or effusion, lymphadenopathy, chest wall or bony lesion, COPD/emphysema, cardiomegaly or other cardiovascular abnormality, and lung fibrosis) and 10 risk factors (age, sex, smoking category, diabetes, hypertension, obesity, underweight, past myocardial infarction, past stroke, and past cancer).

*One subject with a missing death certificate is graded as “Other” cause of death in both the PLCO and NLST data sets

eTable 5. Area Under the Receiver Operating Characteristic Curve (AUC) and Continuous Net Reclassification Index (NRI) for All-Cause Mortality

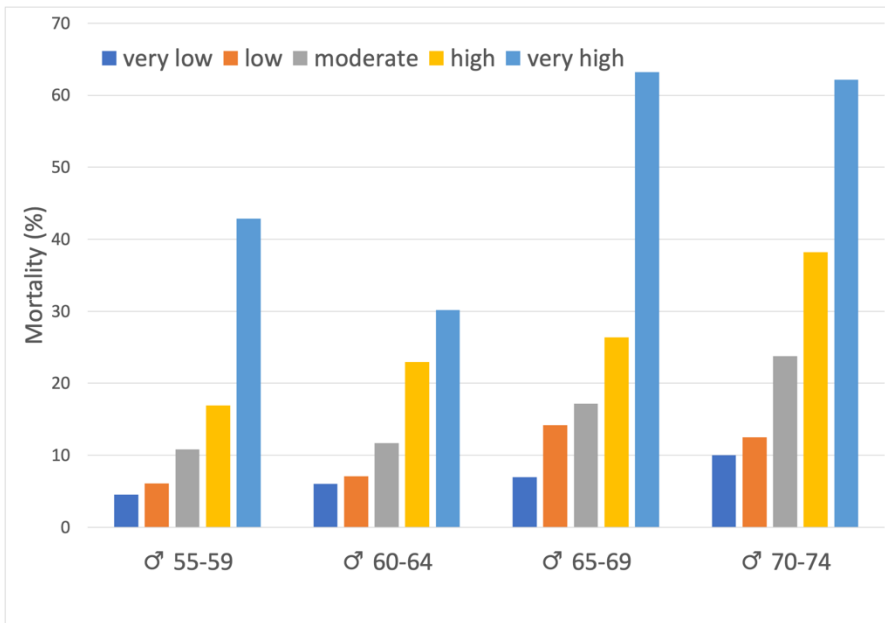
	PLCO Test (n=10,464, 12-year follow-up)					NLST Test (n=5,493, 6-year follow-up)				
	AUC alone (95% CI)	AUC with CXR-risk (95% CI)	P for ΔAUC	NRI (95% CI)	P for NRI	AUC alone (95% CI)	AUC with CXR-risk (95% CI)	P for ΔAUC	NRI (95% CI)	P for NRI
CXR-risk	0.75 (0.73-0.76)	NA	NA	NA	NA	0.68 (0.65-0.71)	NA	NA	NA	NA
Radiograph findings	0.58 (0.57-0.59)	0.74 (0.73-0.76)	<0.001	0.59 (0.53-0.65)	<0.001	0.59 (0.56-0.62)	0.70 (0.67-0.73)	<0.001	0.44 (0.33-0.55)	<0.001
Clinical risk factors	0.76 (0.75-0.78)	0.78 (0.77-0.79)	<0.001	0.21 (0.15-0.28)	<0.001	0.68 (0.65-0.71)	0.72 (0.69-0.75)	<0.001	0.32 (0.20-0.43)	<0.001
Risk factors + findings	0.76 (0.75-0.78)	0.78 (0.77-0.79)	<0.001	0.20 (0.13-0.27)	<0.001	0.70 (0.67-0.73)	0.73 (0.70-0.76)	<0.001	0.28 (0.17-0.41)	<0.001

Chest radiograph (CXR) findings include lung nodule, major atelectasis, pleural plaque or effusion, lymphadenopathy, chest wall or bony lesion, COPD/emphysema, cardiomegaly or other cardiovascular abnormality, and lung fibrosis. Risk factors include age, sex, smoking category, diabetes, hypertension, obesity, underweight, past myocardial infarction, past stroke, and past cancer.

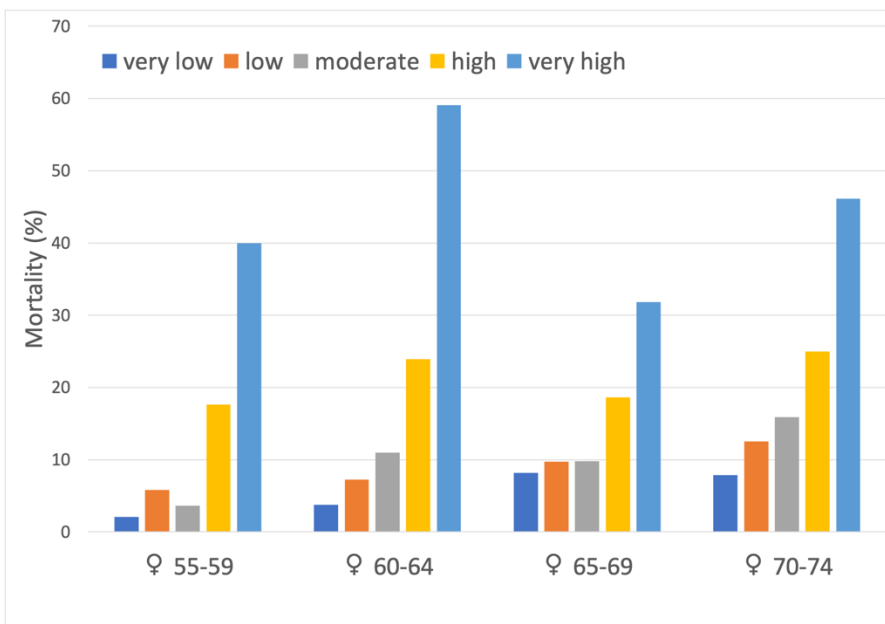
eFigure 1. CXR-Risk Score and 12-Year Mortality, Stratified by Sex and Age

CXR-risk score and 12-year mortality rate in the PLCO test data set, stratified by A) male and B) female sex and age in years

A) Men

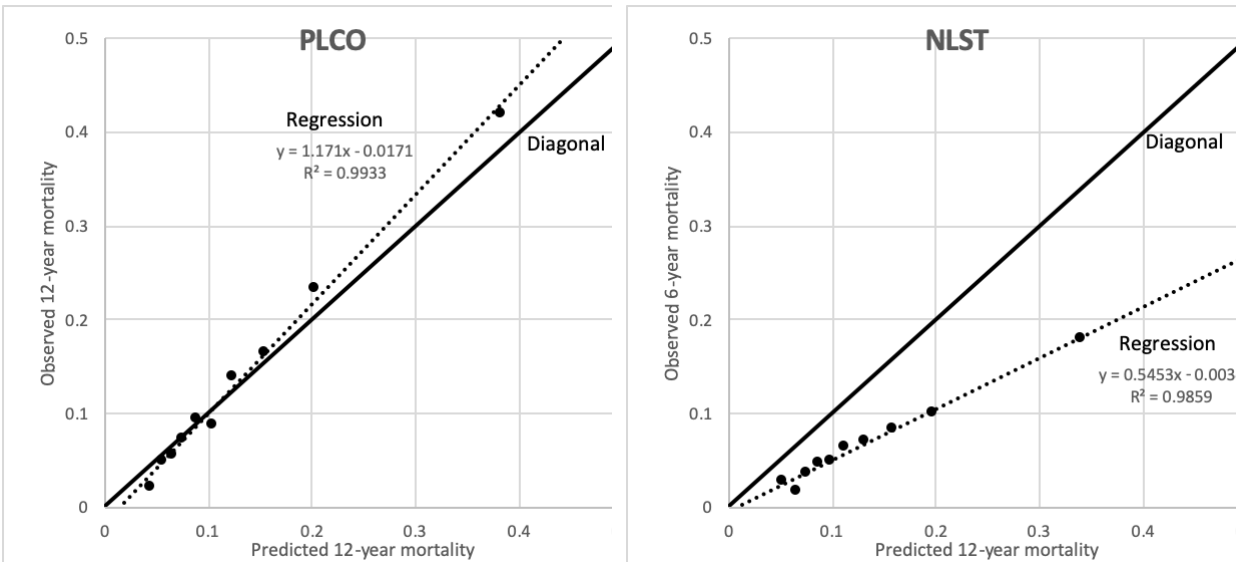


B) Women



eFigure 2. CXR-Risk Calibration Plots

Calibration plots of CXR-risk predicted 12-year mortality versus observed 12-year (PLCO test data set) and 6-year (NLST test data set) mortality.



eMethods. Determination of Cause of Death; Model Development; Chest Radiograph Image Processing and Data Augmentation; Classifier, Architecture and Training; Implementation

Determination of cause of death

Cause of death was reported according to the guidelines of the parent PLCO and NLST trials.^{1,2} In PLCO, deaths possibly related to a PLCO cancer were reviewed by an independent adjudication committee who had access to death certificates, medical records, and autopsy reports.¹ Other causes of death were assigned based on review of death certificates.^{3,4} In NLST, incident lung cancer was likewise reviewed by an independent adjudication committee. Cause of death was based on the death certificate's International Classification of Diseases, 10th Revision (ICD-10) code as defined in the parent trial publication: lung cancer (C33-C34), non-lung cancer (C00-D48 excluding C33-C34), cardiovascular illness (I00-I99), respiratory illness (J00-J99), and other.²

Model development

Chest radiograph image processing and data augmentation

PLCO chest radiographs were scanned at sites and collected by the NCI as tagged image format (.tif) files, with black bars redacting protected health information (PHI). The NLST chest radiographs available for our study were collected by ACRIN as anonymized Digital Imaging and Communications in Medicine (DICOM) files, with no black bars. PLCO and NLST chest radiographs were converted to portable network

graphics (.png) format. For the PLCO development (training and tuning) data sets, each participant's baseline (T0) and year 1 (T1) chest radiographs were included and treated independently. For the PLCO test and NSLT test data sets, only the first baseline chest radiograph was included, to reflect the anticipated clinical use case.

For regularization, geometric data augmentation of the images included random rotation up to ± 2.5 degrees, brightness $\pm 15\%$, and zoom factor up to 20%. The image was then resized to the target resolution along its lesser dimension and randomly cropped to a square.⁵ No flipping augmentation was performed, to preserve the anatomic situs of the heart and mediastinum. Images were progressively resized during model development, starting with 128x128 pixel images with a batch size of 512 and ending with 224x224 pixel images with a batch size of 368.² The mixup data augmentation principle, where the model was trained using combinations of images and their labels, was employed for the training images only with an alpha of 0.4.⁶ Test time augmentation was performed, with a reduced scaling factor of 5% followed by a resize and random square crop to 224x224 pixels including each of the four corners of the image.⁷

Classifier, architecture and training

The goal was to predict all-cause mortality. However only 13% of PLCO participants died. Due to this unbalanced distribution of the desired classifier (death), we chose to train with a staged classifier. In the first stage of training, the CNN was trained against a composite binary classifier of death or incident cancer, which occurred in 25% of PLCO development data set participants. In epidemiology, a composite outcome including

both nonfatal endpoints (e.g. incident cancer) and death is commonly used when the primary outcome (death) is rare.⁸ The rationale is that these nonfatal outcomes are along the causal pathway towards death and can be considered as a surrogate endpoint. We extend this intuition to the classifier, under the assumption that persons who develop cancer share similar underlying risk to those who died. In the second stage of training, the classifier was narrowed to death. Results from the final model are reported for death only. The model was developed using the chest radiograph images and the classifier only—no other information, including age, sex, risk factors, radiographic findings, duration of follow-up, or censoring was available to the CNN.

A PyTorch implementation⁹ of the Inception v4 architecture¹⁰ was modified by replacing the final “head” of average pooling and linear layers with a “custom head” of adaptive concatenation pooling, batch normalization, dropout, linear, ReLU, batch normalization, dropout and a final linear layer.⁷ The “body” of the network was initialized with pre-trained weights from the 2015 ImageNet classification challenge as a starting point.^{9,11} Mixed precision training¹² using the ADAM optimizer¹³ was employed, with the one cycle policy to govern learning rate and momentum.¹⁴ Differential learning rates were used, with a maximum learning rate of up to 1e-02 in the head and lesser learning rates in the body.^{7,15-17}

Implementation

The CXR-risk model was developed using open source and/or freely available software with off-the-shelf consumer-grade hardware. Software included PyTorch 1.0, Python

3.7, and the fastai deep learning libraries.⁷ The final CNN was developed using a Nvidia Titan RTX graphics processing unit (GPU) with 24 GB of video RAM on an AMD 1950x platform with Ubuntu Linux 16.04. Image pre-processing was performed with ImageMagick (ImageMagick Studio, Landenberg PA) and DCMTK (OFFIS, Oldenburg Germany).

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