Supplementary File

Full search terms

1 (Alpha adj2 anti adj2 deficien$).tw.
2 A1AT.mp.
3 A1AT.ti,ab.
4 A1ATD.tw.
5 AAT.mp.
6 AAT.ti,ab.
7 AATD.mp.
8 AATD.ti,ab.
9 alfa 1 antitrypsin.ti,ab.
10 alpha 1 antitrypsin.ti,ab.
11 Alpha 1-Antitrypsin.mp.
12 Alpha 1-Antitrypsin Deficiency.mp.
13 (Alpha adj2 anti trypsin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14 alpha one antitrypsin.ti,ab.
15 alpha one-antitrypsin.ti,ab.
16 alpha1 antitrypsin.ti,ab.
17 alpha-1 antitrypsin.ti,ab.
18 alpha1-antitrypsin.mp. or alpha 1 antitrypsin/
19 alpha1-antitrypsin deficiency.mp.
20 alpha-1-antitrypsin.ti,ab.
21 alpha-1-at.ti,ab.
22 exp alpha 1 antitrypsin deficiency/
23 exp Bronchitis/
24 exp Pulmonary Disease, Chronic Obstructive/
25 chronic obstructive airway* disease.mp.
26 Chronic bronchitis.mp. or chronic bronchitis/
27 chronic obstructive pulmonary disease.mp.
28 chronic respiratory disorder.mp.
29 COPD.mp.
30 chronic obstructive lung disease/
31 deficien$.mp. or lack$.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
32 Smoking-related lung disease*$.mp.
33 Emphysema.mp. or emphysema/
34 Computed Tomography.mp.
35 Computerised axial tomography.mp.
36 Computerised axial tomography.mp.
37 computer assisted tomography/

38	ct.mp.
39	Tomography, X-Ray Computed.mp.
40	X-Ray computed.mp.
41	Lung density.mp.
42	Densitomet*.mp.
43	Lung attenuation.mp.
44	Lung densitometry.mp.
45	Lung function test/ or lung function/ or spirometry/ or forced expiratory volume/ or FEV1.mp.
46	Pulmonary function.mp.
47	Lung Volume Measurements.mp.
48	All alpha 1 terms. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
49	(excluding 31): all COPD terms: 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 32 or 33
50	All CT and CT densitometry terms: 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
51	Lung function terms: 45 or 46 or 47
52	alpha one AND CT: 48 and 50
53	alpha one AND CT and lung function: 48 and 50 and 51
54	COPD AND CT: 49 and 50
55	COPD AND CT AND lung function: 49 and 50 and 51
56	Sum of all COPD terms and CT/densitometry terms: 48 or 49
57	COPD OR alpha one AND CT: 50 and 56
58	COPD OR alpha one AND CT AND lung function: 51 and 57
59	Sum of 52 or 53 or 54 or 55 or 57 or 58
60	limit 59 to (human and (embase or medline) and (adolescent <13 to 17 years> or adult <18 to 64 years> or aged <65+ years>)

<u>Full inclusion and exclusion criteria</u>

Inclusion

- COPD/AATD and any reference linking lung density to clinical outcomes.

Exclusion

- Case study or studies with participant number less than 8.
- Surgical studies (i.e. those reporting density before and after surgical intervention)
- Other medical specialities
- Lab or animal based studies
- Paediatric studies
- Studies relating only to lung measurements including density with no clinical application.

Table S1. Risk of bias tool used in the systematic review

Patient Selection	
Source	How well defined was the source of information (survey, record review)
Inclusion/Exclusion	List inclusion and exclusion criteria for exposed and unexposed subjects?
Patient Selection	Was a consecutive or random sample of patients enrolled?
Applicability	Adequate representativeness of the sample: do they reflect all COPD/AATD patients rather than just one end of the spectrum e.g. NETT trial and LVRS
Duration of Study	Indicate time period used for identifying patients
Index and Reference Test	
Blinding	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants:
CT bias	Could conduct or interpretation of CT density have introduced bias? Was CT density measurement reliable
PFT Bias	Could conduct or interpretation of PFTs introduced bias: Was it done post-bronchodilator
Quality assurance	Was a phantom used or calibration performed?
Flow and Timing	
Flow and Timing	Was there an appropriate interval between the CT study and PFTs (within a year of each other?)
Reporting	
Confounding variables	Description of how confounding was assessed and/or controlled

Missing variables	If applicable, explain how missing data were handled in the analysis
Statistical methods	Adequate description of statistical methods and why.

Table S2. Summary of studies which subdivide the correlation between CT density (-950HU) and FEV_1/FVC into individual lobes.

Lobe	**Pooled correlation coefficient**	**95% CI**	**I^2 (%)**	**X^2**	**p**
LLL	-0.70	-0.83 to -0.57	86.20	10.00	0.0067
LUL	-0.33	-0.62 to -0.04	87.80	15.55	0.0004
RUL	-0.38	-0.56 to -0.20	71.20	6.60611	0.0368
RML	-0.33	-0.52 to -0.14	70.10	6.32	0.0424
RLL	-0.62	-0.69 to -0.54	20.80	2.21	0.3314

Table S3. Baseline Characteristics Table

Author, Year	**Participants (%male)**	**Age Mean (SD)**	**Baseline FEV_1 % Mean (SD)**	**Baseline DLCO % Mean (SD)**	**%LAA (HU)**	**Statistical methods**	**Reconstruction Algorithm**	**Software**	**Slice thickness**	**Recruitment procedures used**
Agusti, A. et al, 2010 [1]	2164 (48)	63.4 (7.1)			-950HU				low dose CT; 1mm thickness	From OPAs in participating hospitals. Smokers/non-smokers from site databases and local papers.
Akira et al, 2009 [2]	67(55)	70.7 (9.3)	24.4 (3.9)		-950HU	Correlation coefficient	not mentioned	Advantage Windows 3D	1.25mm	usual care
Alberti, P. et al 2012 [3]	1831 (66)	63.4(7.0)			-950HU				low dose CT	Via ECLIPSE: 3 year prospective non-interventional study in 12

										countries
Atta et al, 2015 [4]	63(58.7)	53 (8.9)	29.8 (18.4)		-950HU	Correlation coefficient	standard reconstruction algorithm	thoracic VCAR	5mm	usual care
Aziz, Z. A. et al, 2005 [5]	101 (65)	61 (26-86)	42.2 (26.7)	48.1 (20.8)	-950HU	Multivariate analysis and correlation coefficient	high spatial resolution algorithm	not mentioned	1-3mm	identified retrospectively
Baldi et al, 2001 [6]	24 (75)	61 (11)	35 (12)		-950HU	Correlation coefficient	bone algorithm	program developed at the research service branch of National institute of health	1mm	usual care
Barjaktarevic, I. et al	460(57)	64.2	30.6 (8)		-950HU	Correlation	B35f	Pulmonary	1.25mm	usual care

2015[7]		(6.8)				coefficient		Workstation		
Bastarrika, G. et al, 2009[8]	102 (80)	55 (7.5)	103 (23)		-950HU	Correlation coefficient	B30f		5mm	usual care
Bernspang, E. et al, 2011[9]	19 (61)	32	108(12)	92 (11)	PD15	Correlation coefficient	B10f	Pulmo	5mm	
Camiciottoli, G. et al, 2006[10]	51 (90)	64	52 (20)	68 (24)	-950HU	Correlation coefficient	High resolution	Pulmo	1mm	usual care
Camiciottoli, G. et al, 2012 [11]	72 (73)	66 (8)							5mm	
Castaldi, P. J. et al, 2013 [12]	9313 (54)	60 (9)	77 (25)		-910HU, -950HU	Multivariate analysis	B31f	Pulmonary Workstation	0.625, 0.75, 0.9	COPDGene

Chae et al, 2010 [13]	59(98)	65.71 (6.56)	45.79 (17.84)		-950HU	Correlation coefficient	B30	MATLAB and in house software	0.5-0.75mm	KOLD Cohort
Chapman, K. R. et al 2015 [14]	180 (54%)	53 (7)	43.3 (11.6)		PD15	mixed effects model and mITT	not mentioned	Pulmo	not mentioned	28 study centres in 13 countries
Chen et al, 2014 [15]	146 (83.6)	65			-950HU	Correlation coefficient	not mentioned	LungCAD	1mm	usual care
Cheng et al, 2015 [16]	103 (84)	75.8 (9.8)	44.77 (13.8)		-950HU	Logistic regression	Standard algorithm	Myrian	1.25mm	Usual care
Chierakul, N. et al, 2014 [17]	23(82)	73 (8)	67.8 (25.4)	56 (28.1)	-950HU	Correlation coefficient	not mentioned	Thoracic VCAR	not mentioned	usual care
Coxson, H. O. et al, 2013 [18]	2161 (64)	63.4 (7.1)	30.6 (8)	36.7 (13.1)	-950HU				1 or 1.25mm thickness	ECLIPSE

Crim, C. et al, 2011 [19]	2054 (65)	63.4 (7.1)			-950HU				1mm	ECLIPSE
Dawkins, P. et al, 2009 [20]	488 (60)	50 (0.48)	55.99 (1.4)		-910HU	Hazard Ratio			1mm	ADAPT
De Torres, J. P. et al, 2011 [21]	115 (84)	64 (10)	75 (15)	73 (20)	-960HU	Correlation coefficient	B40f	Leonardo	1mm	usual care
Desai et al, 2007 [22]	106 (66.9)	61	42.4 (26.7)	48.1 (20.8)	-950HU	Correlation coefficient	not mentioned	MagicView	1mm	usual care
Diaz et al, 2009 [23]	27 (33)	55 (12)	50 (10)	55 (16)	-950HU	Correlation coefficient	B10f	Pulmo	5mm	usual care
Diaz, A. A et al, 2015 [24]	102 (60)	66 (8.8)	68 (23.8)	71.5 (21.6)%	-960HU	MCID and C-statistic	B45f	not mentioned	1mm	PELE
Diaz, A. A.	109 (56)	61.2			-950HU					COPDGene

et al 2010 [25]		(7.9)								
Diaz, A. A. et al, 2010 [26]	93 (57)	66.7 (8.8)	57.1 (24.3)		-950HU	Correlation coefficient and multivariate linear regression	B46f	Airway inspector	1mm	LTRC
Diaz, A. A. et al, 2012 [27]	71 (45)	64.7 (10)	89 (7.5)	109 (22)	-960HU				not mentioned	From COPD longitudinal study (PELE)
Diaz, A. A. et al, 2013 [28]	2500	64 (8)	59 (23)		-950HU				0.75mm	COPDGene
Dijkstra, A. E. et al, 2013 [29]	492 (100)	59.4 (5.2)	98.2 (19.7)		PD15	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Dirksen, A. et al 1999 [30]	56 (61%)	47.6 (3)	48 (2.8)	60 (3)	PD15	random effects regression model, slope analysis and Pearson's	<5/10mm	not mentioned	8mm	alpha one registries in Netherlands and

						coefficient				Denmark
Dirksen, A. et al 2009 [31]	77 (53%)	55 (9)	46.5 (20)	51.5 (17)	PD15	ITT and mITT; slope analysis tested by linear regression with statistical or physiological adjustment	B30f	Pulmo	1mm	AATD registries Denmark, UK and Sweden
Dowson, L. J. et al, 2001 [32]	29 (65)	52 (46-60)	only raw value provided	only raw value provided	-910	correlation coefficient and multivariate linear regression	not mentioned	not mentioned	1mm	ADAPT
Garfield et al, 2012 [33]	59 (46)	63 (9)	41 (18)		-950HU	Multivariate analysis and correlation coefficient	not mentioned	pulmonary workstation	0.75 and 5mm	usual care

Gevenois, P. A. et al, 1996 [34]	37 (78.4)		72 (21)	65 (20)	-950HU	Correlation coefficient	not mentioned	pulmo	1mm	usual care
Gevenois, P. A. et al, 1996 [35]	59 (86.4)	62 (8)	73 (20)	66 (17)	-950HU	Correlation coefficient	not mentioned	pulmo	1mm	usual care
Gietema, H. A. et al, 2013 [36]	1778 (64)	63 (7)	48.4 (15.7)		-950HU	Multiple linear regression			1 or 1.25mm thickness	ECLIPSE
Grydeland, T. B. et al, 2010 [37]	463 (64)	65.2 (9.4)	52.6 (17.4)		-950HU		Standard algorithm	Not mentioned	1mm	GenKOLs
Han et al, 2011[38]	483 (53)	64 (8.5)	55 (22.7)		-950HU	multivariate analysis and forward selection regression	smooth reconstruction algorithm	VIVA Pulmonary Workstation version2		COPDGene

Haruna, A. et al, 2010 [39]	65 (100)	71 (9)	58.8 (19.7)		-960HU		Lung algorithm	Not mentioned	0.5mm	kyoto
Haruna, A. et al, 2010[40]	251 (94)	68.7 (7)	50.3 (17)		-960HU	Hazard Ratio	lung reconstruction algorithm		2mm	Kyoto university
Hong, Y. et al, 2012 [41]	213 (96)	66.3 (7.3)	53.4 (16.5)	74 (58.4)	-950HU	Multivariate analysis	standard algorithm (??)	in house software	0.625-0.8mm	
Heussel et al, 2009 [42]	102	64			-950HU	Correlation coefficient	B40f	In house YACTA software	1.25mm	usual care
Johannessen, A. et al, 2013 [43]	947 (59)	60 (10)	77 (26)		-950HU	Multivariate analysis and Laplace regression	low spatial frequency algorithm for density	James Hogg iCAPTURE Centre	1mm	Norwegian GenKOLS study

Jung-Wan Yoo et al, 2011 [44]	260 (96.9)	66.2 (7.2)	53.1 (16.3)		-950HU	Logistic regression	Soft kernel (B30f)	Not mentioned	0.75mm	KOLD
Kim et al, 2010 [45]	200 (62.5)	64.6 (8.4)			-950HU	Multivariate analysis and correlation coefficient	different ones used in all different centres	pulmonary workstation and pulmo	0.625-0.9mm	COPDGene
Kim et al, 2014 [46]	78	65.3 (8.2)	49.6 (16.2)		-950HU	Correlation coefficient	reconstruction algorithm B	in house software	1mm	KOLD
Kim et al, 2015[47]	167	64.8 (8.2)			-950HU	Correlation coefficient	not mentioned	not mentioned	0.75mm	usual care
Koyama et al, 2010 [48]	25 (60)	67.6			-950HU	Correlation coefficient	FC51	doesn't specify	0.5mm	usual care
Koyama et al, 2012[49]	56 42	70.2 (8)	68.9 (19.6)		-950HU	Correlation coefficient	FC13	MATLAB	1mm	usual care

Kurashima, K. et al 2013[50]	70				-960HU	Correlation coefficient	from ultrahigh resolution (UHR) CT and noise reduction software	iDose	0.67mm	SCGOR
Kurashima, K. et al, 2015 [51]	62 (100)	70.8 (6.4)	62.9 (30.7)		-960HU	Correlation coefficient	Interactive reconstruction algorithm	Brilliance	0.67mm	Usual care
Lee, J. H. et al 2010 [52]	145 (98%)	66 (7)	47 (16)	78 (27)	-950HU		reconstruction algorithm B	in house software	1mm	KOLD
Lee, J. S. et al 2012 [53]	101 (92%)	65.5 (6.9)	50 (15.5)	75.7 (32.8)	-950HU	multi-variable linear regression and Pearson's correlation coefficient	reconstruction algorithm B	in house software	0.625-0.8	KOLD

Lee, J. S. et al, 2011 [54]	126 (98%)	65.5 (7.6)	47.9 (14.1)	74.6 (25.8)	-950HU	multiple, stepwise linear regression models and Pearson's correlation coefficient	reconstruction algorithm B	in house software	1mm	KOLD
Lutchmedial et al, 2015 [55]	274 (55)	66.9 (10.4)	50 (19)		-950HU	Correlation coefficient	not mentioned	not mentioned	Sub-mm, high spatial frequency algorithm	usual care
Martinez, C. H. et al 2012 [56]	1179 (53.3%)	65.0 (47.9, 70.6)			-950HU				not mentioned	COPDGene
Martinez, F. J. et al,	609	66.7 (5.9)	26.7 (7)	28.4 (9.7)	-950HU	Hazard Ratio	standard reconstruction	custom built		NETT

2006[57]							kernel			
Martinez, F. J. et al, 2007 [58]	1053 (61)	66 (6)	27 (7)	28 (9.6)	-950HU		not mentioned	custom built software, pulmonary analysis software suite	5mm	NETT
Matsuoka, S. et al, 2007 [59]	32 (87)	72.8 (8.2)	56.2 (26.9)		-950HU	Correlation coefficient	not mentioned	ImageJ	2mm	usual care
McAllister, D. A. et al, 2014 [60]	521 (51)	68 (6)	76 (23)		-910HU	Multilinear analysis	B50f	Not mentioned	10mm	NLCST
Mets, O. M. et al, 2011 [61]	1140	62.5 (5.2)	94.8 (17.6)		-950HU	Multivariate analysis	smooth reconstruction filter (B filter)		1	Dutch and Belgian Lung Cancer Screening Trial.
Mets, O. M. et al, 2013 [62]	442	61.3 (5.5)	96.5 (18)		-950HU	Multivariate analysis	soft reconstruction	in house software	1mm	NELSON

							filter (B30f)			
Mohamed Hoesein, F. A. A. et al 2013 [63]	3670 (100)	59.8 (5.4)			-910HU, -950HU and PD15					from NELSON
Mohamed Hoesein, F. A. A. et al, 2011 [64]	522 (100)	60.1 (5.4)	97.6 (18.2)		PD15	Multivariate analysis and correlation coefficient	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A. et al, 2011 [65]	2085 (100)	59.8 (5.3)			PD15	Multivariate analysis	B30f	in house software	1	NELSON
Mohamed Hoesein, F.	2003 (100)	59.8	98.5 (18.5)		PD15	Multivariate	soft reconstruction	in house	1mm	NELSON

A. A. et al, 2012 [66]		(5.3)				analysis	filter (B30f)	software		
Mohamed Hoesein, F. A. A. et al, 2012 [67]	587 (100)		97.7 (18.1)		PD15	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A. et al, 2013 [68]	1108 (100)	60.4 (19.9)	94.8 (17.6)		-950HU and PD15	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A. et al, 2015 [69]	2021 (100)	59.8 (5.3)			PD15	Multivariate analysis	B30f	Cirrus Lung 12.03	1.0mm	nelson
Mohamed Hoesein, F. A. et al,		62.5 (5.2)	94.8 (17.6)		-950HU	Multivariate analysis	smooth reconstruction kernel	Cirrus	1mm	nelson trial, prospective

2014 [70]										
Motohashi, N. et al, 2009 [71]	125 (89)	71 (8)	51.5 (17.8)		-940HU	Correlation coefficient			1.25mm collimation	
Nakano, Y. et al, 1999[72]	73 (100)	68.7 (6.2)	46.1 (19.5)		-960HU	Correlation coefficient	high resolution reconstruction algorithm	C Programming language (Symantec C++)	2mm	usual care
Nakano, Y. et al, 2000 [73]	114	68 (9)	48 (28)		-960HU	Correlation coefficient	lung algorithm (FC 83)	C Programming language (Symantec C++)	2mm	usual care
Nambu et al, 2015 [74]	199 (50)	64.1 (8.4)	51.27 (23.1)		-910HU, -950HU and PD15	Multivariate analysis and correlation coefficient	not mentioned	VIDA Diagnostics	0.625mm	COPDGene

Nishio, M. et al, 2014 [75]	30 (83.3)	70.1 (12.2)	65.3 (20.6)	66.1 (23.6)	-900HU	Correlation coefficient	standard kernel FC 13	in house prototype software	1mm	not mentioned
O'Donnell, R. A. et al, 2004 [76]	65	55 (7)	56 (16)	56 (16)	-950HU	Correlation coefficient	not mentioned	not mentioned	1mm	usual care
Ogawa, E. et al, 2009 [77]	239 (100)	71 (7)	46 (18)		-960HU	Correlation coefficient	lung algorithm (FC38)	custom software written in C programming language (Symantec C++)	2mm	usual care
Orlandi et al 2005 [78]	42 (88)	63	49.09 (19.44)	67.57 (24.69)	-950HU	Correlation coefficient	not mentioned	Pulmo	1mm	usual care
Orlandi et al, 2004 [79]	11 (81)	68			-950HU	Correlation coefficient	not mentioned	Pulmo	1mm	usual care

Paoletti, M. et al 2015 [80]	169 (61)	66 (8)	54.1 (21.4)	69.6 (22.5)	-950HU	Multivariate analysis and correlation coefficient	B31f	Pulmonary Workstation Apollo. VIDA diagnostics	0.75mm	usual care
Park, M. J. et al 2014 [81]	98 (100)				-950HU					retrospectively recruited
Parr et al, 2004 [82]	100	52 (10.2)			-950HU	Correlation coefficient	smooth filter	Pulmo	5mm	ADAPT
Parr, D. G. et al 2009 [83]	77 (53%)	55 (9)	46.5 (20)	51.5 (17)	PD15, mld, 910 and -950HU	mITT and sensitivity ratios	not mentioned ?on supplemental information	Pulmo	5mm	alpha one registries from Demark, UK and Sweden
Pauls et al, 2010 [84]	474	60.4 (14.9)	60.7 (20.27)		-950HU	Correlation coefficient	not mentioned	"Lung Emphysema" application	2mm	usual care
Rambod, M.	2256 (52)	61.3	88.1 (24.3)	56.5	-950HU				1mm	COPDGene

et al 2012 [85]		(9.3)		(21.5)						
Roth, M. D. et al, 2006 [86]	148 (58.1)	65.8 (7.45)	42.5 (13.7)	37.1 (12)	-910HU	ANOVA, chi square				from five university hospitals
Saitoh et al, 2000 [87]	50	68 (6)	54.9 (21.5)	66.4 (17.6)	-950HU	Correlation coefficient	Bone algorithm	a density mask program'	10mm	usual care
Sandek, K. et al, 2002 [88]	20 (40)	60 (8)	38.2 (15.5)	43.6 (23)	-910HU	Correlation coefficient	not mentioned	density mask-not specific software	1.5mm	usual care
Schroeder, J. D. et al, 2013 [89]	4062 (55)	60.8			-950HU and PD15	Multivariate analysis and correlation coefficient	B31f	Pulmonary Workstation	0.625, 0.75, 0.9mm	COPDGene
Schwaiblmair, M. et al, 1998 [90]	21 (61.9)	48 (2)	44.7 (3.3)	55.3 (4.1)	-950HU	Correlation coefficient	not mentioned	not mentioned	1mm	usual care
Shaker, S. B.	254 (58%)	63.6 (7)	52 (11)		PD15	mixed effects	low spatial (soft)	Pulmo	10mm	from OPA and

et 2009 [91]						regression model	frequency			local newspapers
Shaker, S. B. et al 2009 [92]	184 (59)	64.9 (7.1)	53 (13)	59 (17)	-910HU	Correlation coefficient	soft algorithm	pulmo	5mm	usual care
Shaker, S. B. et al, 2005 [93]	42 (38)	63 (7)	48 (13)	49 (16)	PD15	Correlation coefficient	low spatial resolution (soft)	Pulmo	5mm	
Stolk, J. et al 2012 [94]	227 (72%)	54 (8.7)	46.6 (16.7)	48 (14.8)	PD15	ANCOVA, Least mean squares, ITT, correlation coefficient	not mentioned	Pulmo	not mentioned	From 10 AAT registries
Stolk, J. et al, 2003 [95]	22 (45)	40.7 (9.2)	56 (32)		-950HU and PD15	Correlation coefficient				
Stolk, J. et al, 2007 [96]	87 (50.6)	58.6 (10.4)	50.2 (19.2)		PD15	Multivariate analysis and correlation	smooth reconstruction filter	pulmo	5mm	advertisement

						coefficient				
Sverzellati, N. et al, 2012 [97]	1159 (68)	57.5 (6)	97.1 (19.6)		-950HU	Multivariate logistic regression	B30f	MevisPULMO	5mm	MILD
Tanabe, N. et al 2012 [98]	53 (48)	65.5 (62-72.3)	71.2 (53.8-81.5)		-960HU	Multivariate analysis	FC56 (sharp kernel)	custom designed	5mm	kyoto university ongoing study
Tanabe, N. et al, 2011 [99]	60 (93)	73 (68.3-77.8)	50.6 (38.2-61.1)		-910HU, -930HU and -960HU	Multivariate analysis	Not mentioned	Not mentioned	0.5mm	Kyoto
Tanabe, N.et al, 2013 [100]	131 (100)	70.7 (8.8)	57.9 (19.8)		-960HU	Multivariate analysis	not mentioned	not mentioned	not mentioned	

Timmins, S. C. et al, 2012 [101]	26 (61.5)	69.6 (55-85)	64.8 (19.8)	50.7 (15.8)	-910HU	Multivariate analysis and correlation coefficient	lung reconstruction algorithm	osiriX	1.25	volunteer database and advertisements in newspaper
Tsushima, K. et al, 2010 [102]	48	61.1 (9.3)	77.5 (19.2)		-960HU	Correlation coefficient	not mentioned	not mentioned	5mm	lung screening cohort
Van der Lee et al, 2009 [103]	263	60.3 (5.4)	97.7 (16.8)	87.4 (16.1)	-950HU	Correlation coefficient	not mentioned	not mentioned	1mm	usual care
Vijayasarathy, K. et al, 2012 [104]	21 (81)	52.5 (2.1)	38.4 (3.1)		PD15	Multivariate analysis	Not mentioned	Pulmo	5mm	ADAPT
Wang et al	46(80.4)	67	72.56	69.38	-950HU	Correlation	standard	Thoracic VCAR	0.625mm	usual care

2015 [105]		(10.84)	(31.15)	(25.39)		coefficient	algorithm	software		
Wang et al, 2013 [106]	573 (36.6)	63.9 (5.4)	74.8 (28.5)		-950HU	Correlation coefficient	bone kernel, due to its ability to analyse airways and parenchyma	in house software	0.625mm	SCGOR
Washko et al, 2008 [107]	1094 (60.9)	67 (6.2)	26.9 (7.2)	28.5 (9.7)	-950HU	Correlation coefficient	lung algorithm	Pulmonary Analysis Software Suite	5-8mm	NETT
Xia et al, 2014 [108]	51(100)				-950HU	Correlation coefficient	not mentioned	extended brilliance workspace	1mm	usual care
Yamashiro et al, 2010 [109]	46 (56.5)	67.7 (7.9)	57.9 (24.6)		-950HU	Correlation coefficient	bone algorithm	Airway Inspector	1.25mm	lung tissue research consortium
Yuan, R. et	143 (53)	59.5	99.4 (12.8)		-950HU	Multivariate	Standard	custom software	1 and	British Columbia

al, 2009 [110]		(6.4)				analysis	reconstruction kernel in 36 cases (25%) and B35f in 107 cases (75%)	(Emphylxl)	1.25mm	Cancer Agency (lung cancer screening programme)

Table S4. Full risk of bias table

Author, Year	Patient Selection	Index and Reference Test	Flow and Timing	Reporting
Nakano, Y. et al, 2000	high	medium	high	high
Wang et al 2015	low	medium	high	high
Chapman, K. R. et al 2015	low	medium	high	high
Koyama et al, 2012	low	high	medium	high
Schroeder, J. D. et al, 2013	low	medium	low	high
Castaldi, P. J. et al, 2013	low	medium	low	high
Dijkstra, A. E. et al, 2013	low	medium	low	high
Bernspang, E. et al, 2011	low	medium	low	high
Haruna, A. et al, 2010	low	medium	low	high
Diaz, A. A. et al, 2010	low	low	low	high
Shaker, S. B. et al, 2005	high	medium	high	medium
Stolk, J. et al 2012	high	medium	high	medium
Kim et al, 2010	medium	medium	high	medium
Stolk, J. et al, 2007	medium	medium	high	medium
Johannessen, A. et al, 2013	low	medium	high	medium
Garfield et al, 2012	low	medium	high	medium
Pauls et al, 2010	low	medium	high	medium
Mohamed Hoesein, F. A. A. et al, 2011	low	low	high	medium
Stolk, J. et al, 2003	low	low	high	medium
Diaz, A. A et al, 2015	medium	medium	high	low
Lee, J. S. et al, 2011	medium	medium	high	low
Nambu et al, 2015	medium	medium	high	low
Chierakul, N. et al, 2014	medium	medium	high	low
Nakano, Y. et al, 1999	low	medium	high	low
Lee, J. H. et al 2010	low	medium	high	low
Lutchmedial et al, 2015	medium	low	high	low
Haruna, A. et al, 2010	low	low	high	low

Koyama et al, 2010	low	low	high	low
Aziz, Z. A. et al, 2005	low	low	high	low
Nishio, M. et al, 2014	high	high	low	medium
Parr et al, 2004	high	high	low	low
Gevenois, P. A. et al, 1996	medium	high	low	medium
Mohamed Hoesein, F. A. A. et al, 2015	medium	high	low	low
Kim et al, 2014	high	medium	medium	low
Saitoh et al, 2000	medium	medium	medium	medium
Washko et al, 2008	medium	medium	medium	medium
Diaz et al, 2009	low	medium	medium	medium
Matsuoka, S. et al, 2007	low	medium	medium	medium
Martinez, C. H. et al 2012	low	medium	medium	medium
Diaz, A. A. et al, 2013	low	medium	medium	medium
Diaz, A. A. et al, 2012	low	medium	medium	medium
Roth, M. D. et al, 2006	low	medium	medium	medium
Kim et al, 2015	low	low	medium	medium
Jung-Wan Yoo et al, 2011	low	low	medium	medium
Shaker, S. B. et 2009	low	low	medium	medium
McAllister, D. A. et al, 2014	medium	medium	low	medium
O'Donnell, R. A. et al, 2004	medium	medium	low	medium
Dowson, L. J. et al, 2001	medium	medium	low	medium
Park, M. J. et al 2014	medium	medium	low	medium
Barjaktarevic, I. et al 2015	low	medium	low	medium
Atta et al, 2015	low	medium	low	medium
Mohamed Hoesein, F. A. A. et al, 2012	low	medium	low	medium
Han et al, 2011	low	medium	low	medium
Yamashiro et al, 2010	low	medium	low	medium
Desai et al, 2007	medium	low	low	medium
Gietema, H. A. et al, 2013	low	low	low	medium

Tanabe, N. et al 2012	low	low	low	medium
Chae et al, 2010	low	low	low	medium
Camiciottoli, G. et al, 2006	low	low	low	medium
Cheng et al, 2015	medium	medium	medium	low
Mohamed Hoesein, F. A. A. et al, 2013	medium	medium	medium	low
Vijayasaratha, K. et al, 2012	medium	medium	medium	low
Mets, O. M. et al, 2011	medium	medium	medium	low
Hong, Y. et al, 2012	low	medium	medium	low
Akira et al, 2009	low	medium	medium	low
Baldi et al, 2001	low	medium	medium	low
Gevenois, P. A. et al, 1996	low	medium	medium	low
Crim, C. et al, 2011	low	medium	medium	low
Dirksen, A. et al 1999	low	medium	medium	low
Paoletti, M. et al 2015	medium	low	medium	low
Xia et al, 2014	medium	low	medium	low
Mohamed Hoesein, F. A. A. et al, 2012	low	low	medium	low
Mohamed Hoesein, F. A. A. et al, 2011	low	low	medium	low
De Torres, J. P. et al, 2011	low	low	medium	low
Huessel et al, 2009	low	low	medium	low
Orlandi et al, 2004	low	low	medium	low
Atta et al, 2015	medium	medium	low	low
Mohamed Hoesein, F. A. et al, 2014	medium	medium	low	low
Coxson, H. O. et al, 2013	low	medium	low	low
Mets, O. M. et al, 2013	low	medium	low	low
Motohashi, N. et al, 2009	low	medium	low	low
Shaker, S. B. et al 2009	low	medium	low	low
Ogawa, E. et al, 2009	low	medium	low	low
Dawkins, P. et al, 2009	low	medium	low	low
Martinez, F. J. et al, 2006	low	medium	low	low

Orlandi et al 2005	low	medium	low	low
Rambod, M. et al 2012	low	medium	low	low
Albert, P. et al 2012	low	medium	low	low
Mohamed Hoesein, F. A. A. et al 2013	low	medium	low	low
Martinez, F. J. et al, 2007	low	medium	low	low
Chen et al, 2014	medium	low	low	low
Schwaiblmair, M. et al, 1998	medium	low	low	low
Camiciottoli, G. et al, 2012	medium	low	low	low
Kurashima, K. et al, 2015	medium	low	low	low
Nishio et al, 2014	medium	low	low	low
Kurashima, K. et al 2013	low	low	low	low
Tanabe, N.et al, 2013	low	low	low	low
Wang et al, 2013	low	low	low	low
Timmins, S. C. et al, 2012	low	low	low	low
Sverzellati, N. et al, 2012	low	low	low	low
Tanabe, N. et al, 2011	low	low	low	low
Tsushima, K. et al, 2010	low	low	low	low
Grydeland, T. B. et al, 2010	low	low	low	low
Yuan, R. et al, 2009	low	low	low	low
Bastarrika, G. et al, 2009	low	low	low	low
Van der Lee et al, 2009	low	low	low	low
Sandek, K. et al, 2002	low	low	low	low
Agusti, A. et al, 2010	low	low	low	low
Diaz, A. A. et al 2010	low	low	low	low
Dirksen, A. et al 2009	low	low	low	low
Parr, D. G. et al 2009	low	low	low	low
Lee, J. S. et al 2012	low	low	low	low

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