THE RELEVANCE OF CT DENSITOMETRY DECLINE IN NEVER AND EX-SMOKERS WITH ALPHA ONE ANTITRYPSIN DEFICIENCY (AATD) AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD); A SYSTEMATIC REVIEW AND VALIDATION STUDY IN UNTREATED PATIENTS

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Abstract

CT densitometry is the method of quantifying emphysema using specialised software programs, and its ability to assess emphysema has been validated clinically and pathologically. However, the technique has yet to be standardised and its clinical utility remains unclear. The systematic review performed highlighted the strong relationship to clinically relevant parameters, but demonstrated that vast heterogeneity that exists between studies using CT Density. This heterogeneity was overcome when only studies using the same software program, reconstruction algorithm and slice thickness were meta-analysed.

The variability the two leading software programs, PULMO and Pulmonary Workstation was calculated, and showed that where the same slickness and reconstruction algorithms were used, the two programs showed directly comparable results for volume and PD15. The difference between -910HU and -950HU is likely clinically negligible but requires further consensus, and the difference between different slice thicknesses will require adjustment.

Analysis of CT scans performed within the Birmingham AAT registry confirmed the strong relationship between CT and lung function and quality of life measures. For the first time it was also shown that PD15 and -950HU whole lung are both predictive of mortality. Through a variety of methods the MCID for annual CT density decline was proposed as 2.89g/l/year.

Dedication

This thesis is dedicated to my mother Deborah Hansford

Acknowledgements

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List of Abbreviations

6MWD	6 Minute Walk Distance
AAT	Alpha One Antitrypsin
AATD	Alpha one Antitrypsin Deficiency
ADAPT	Antitrypsin Deficient Assessment and Programme for Treatment
ADC	Apparent Diffusion Coefficient
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of Variance
ATRA	All-Trans Retinoic Acid
ATS	American Thoracic Society
AWT	Airway Wall Thickness
BMI	Body Mass Index
BRVS	Bronchoscopic Lung Volume Reduction Surgery
BTS	British Thoracic Society
BWT	Bronchial Wall Thickening
CDSR	Cochrane Database of Systematic Reviews
CO2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPET	Cardio-Pulmonary Exercise Testing
CT	Computed Tomography
CTR	Computed Tomography emphysema Ratio
DARE	Database of Abstracts of Reviews of Effects
DCE	Dynamic Contrast Enhanced
DICOM	Digital Imaging and Communications in Medicine
DLCO	Diffusing capacity of the Lung for Carbon Monoxide
EBV	Endobronchial Valve
EED	Economic Evaluation Database
EFL	Expiratory Flow Limitation
EI	Emphysema Index
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in 1 second
FEV1/FVC	Forced Expiratory Volume in 1 second/Forced Vital Capacity
FVC	Forced Vital Capacity
FWHM	Full Width at Half Maximum
GOLD	Global Initiative for Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
He	Helium
HRCT	High Resolution Computed Tomography
HTA	Health Technology Assessment
HU	Hounsfield Units
I^2	Heterogeneity score
ICC	Intra-class Correlation Coefficient

ICS	Inhaled Corticosteroid
IL-6	Interleukin-6
IL-8	Interleukin-8
IQR	Interquartile Range
KCO	Carbon Monoxide transfer coefficient
KOLD	Korean Obstructive Lung Disease
LA	Luminal Area
LAA	Low Attenuation Area
LABA	Long Acting Beta Agonist
LAMA	Long Acting Muscarinic Antagonist
LTOT	Long Term Oxygen Therapy
LVRS	Lung Volume Reduction Surgery
mBODE	Modified (BMI, Airflow Obstruction, Dyspnoea and Exercise)
MCID	Minimal Clinically Important Difference
MDD	Minimal Detectable Difference
MLD	Mean Lung Density
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MWU	Mann-Whitney U
NE	Neutrophil Elastase
NETT	National Emphysema Treatment Trial
NICE	National Institute of Clinical Excellence
NIHR	National Institute of Health Research
NOTT	Nocturnal Oxygen Therapy Trial
O2	Oxygen
OSA	Obstructive Sleep Apnoea
PCA	Principal Component Analysis
pCO2	Partial pressure of Carbon Dioxide
PD15	15th Percentile Point
PD15	15th Percentile Point
PFTs	Pulmonary Function Tests
Pi10	10mm luminal perimeter
PMBF	Pulmonary Microvascular Blood Flow
pO2	Partial pressure of Oxygen
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
qCT	Quantitative CT
QOL	Quality of Life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
R5-R20	Measure of airway resistance at 5 and 20 Hz
RCI	Reliable Change Index
RCT	Randomised Controlled Trial
RV	Residual Volume
SABA	Short Acting Beta Agonist
SD	Standard Deviation
SE	Standard Error

SEM	Standard Error of Measurement
SERPIN	Serine Protease Inhibitor
SGRQ	St Georges Respiratory Questionnaire
SH	Schmidt-Hunter
SoC	Standard of Care
TLC	Total Lung Capacity
TNF	Tumour Necrosis Factor
VATS	Video Assisted Thorascopic Surgery
VI	Voxel Index
WA	Wall Area
X5	Airway reactance at 5Hz
Xe	Xenon
YACTA	Yet Another Computed Tomography Analyser
ZETOC	British Library's Electronic Table of Contents

Author's Declaration

All material within this thesis previously published has been indicated where appropriate. The contents of this thesis are all my own original work and any contributions by others have been clearly indicated. I can confirm that this thesis has not been submitted for a higher degree at any other university.

Chapter 1 **Introduction**

1.1. Chronic Obstructive Pulmonary Disease

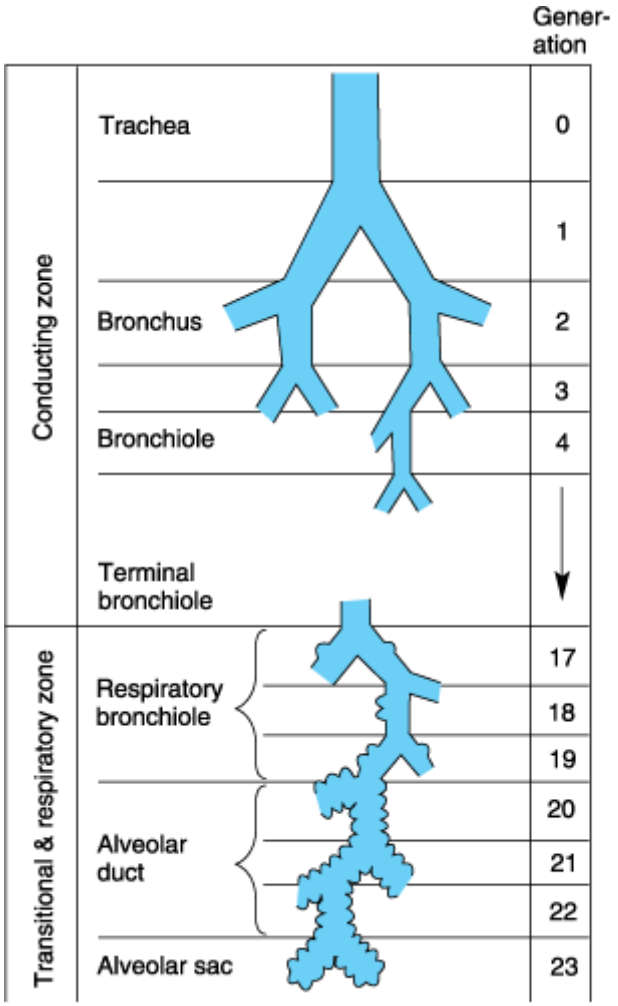
Chronic Obstructive Pulmonary Disease (COPD) is a common and preventable respiratory disease, characterised by a chronic inflammatory response in the lung tissue secondary to inhaled noxious gases or particles, most commonly tobacco smoke(1). It is currently the 4th leading cause of death worldwide and projected to be the third by 2020(2, 3). Diagnosis is made on the presence of symptoms of breathlessness, chronic cough and exacerbations together with spirometry. The degree of inflammatory response varies between patients, with only a few who smoke going on to develop severe airflow limitation and a diagnosis of COPD(4). There are multiple factors involved besides environmental exposure (e.g. cigarettes, air pollution) such as genetic abnormalities such as Alpha one Antitrypsin Deficiency (AATD) or abnormal lung development(5). Patients with COPD suffer the effects of chronic airway inflammation even after smoking cessation, which cause the symptoms of chronic bronchitis, airways obstruction and emphysema (6-8).

1.1.1. Anatomy of the airways

Moving distally from the trachea, the airways sequentially divide over 23 generations into smaller and smaller divisions down to the terminal and then respiratory bronchioles.16 divisions occur before the respiratory bronchioles,

constituting the conducting zone, and a further 7 more distally in the transitional and respiratory zones (see Figure 1.1)(9). High Resolution Computed Tomography (HRCT) is able to visualise to around 2mm, which equates to the 7th-9th order airway, or the inner two thirds (10).

Figure 1.1. Anatomy of the bronchial tree and its sequential divisions



(11)

1.1.2. Anatomy of the parenchyma

The lung parenchyma is the area of the lung responsible for gas exchange i.e. from the respiratory bronchioles down to the alveoli (pulmonary acinus). These are fenestrated with alveolar ducts , and continue to subdivide until the final alveolar ducts/sacs (12). Histologically in the centre of the acinus is the bronchiole and its adjacent bronchial artery, with the venous and lymphatic drainage on the periphery of the unit(13). The adjacent alveoli are separated by the interlobular septae with communicating fenestrations. The alveoli remain patent and compliant through trans-pulmonary pressures and the alveolar surfactant. Proteins including elastin, proteoglycans and collagen make up the alveolus and therefore the presence of proteases, and imbalance between proteases and anti-proteases, damages their structure and function(14); this leads to emphysema.

1.1.3. Spirometry

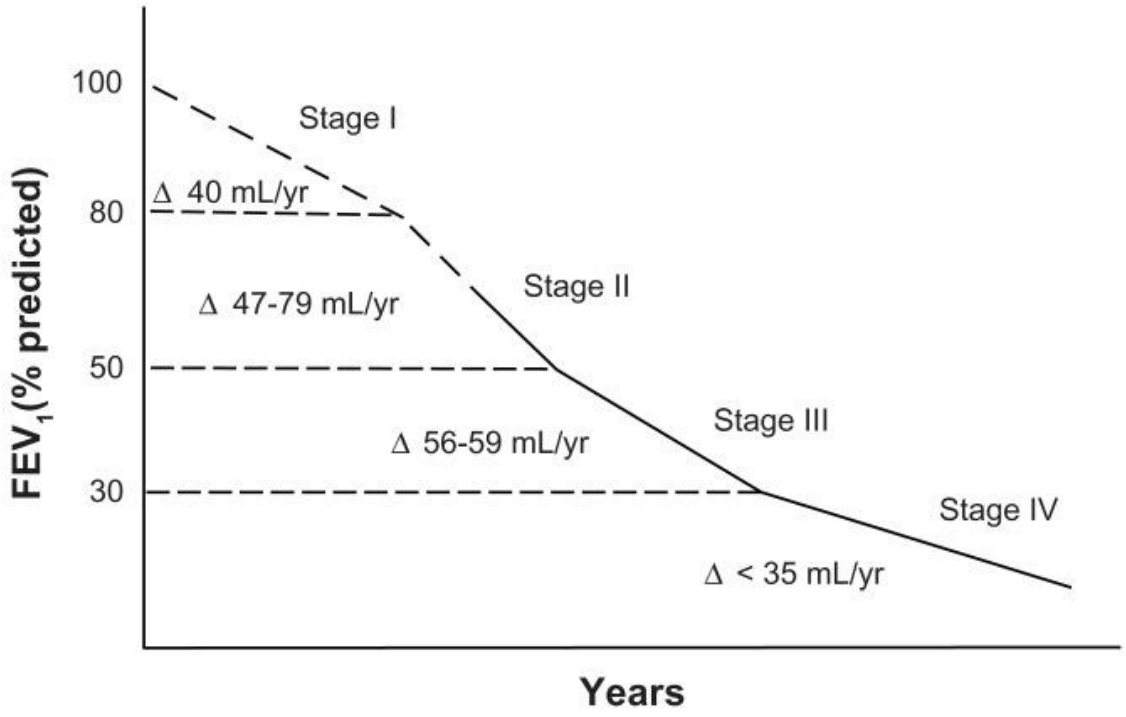
Spirometry measures volume of air over time during a forced expiratory manoeuvre. The Forced Expiratory Volume in 1 second/Forced Vital Capacity (FEV_1/FVC) ratio measures the degree of resistance to airflow during expiration over one second compared to their full capacity, and a ratio <70% indicates airflow obstruction. The FEV_1 alone is then used to grade the severity of the obstruction, with the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines using thresholds of 80%, 50% and 30% to diagnose mild, moderate and severe disease(1). Appendix 1

shows the formulae used to calculate predicted normal values, which vary with age, height and sex, and also show racial variation. Airways measuring less than 2mm have been shown to be the largest contributor to airflow resistance, likely due to the inflammation and elastin degradation overcoming the smaller airways' ability to maintain normal integrity and elastic recoil(15).

1.1.4. Gas Transfer

DLCO (Diffusing capacity of the Lung for Carbon Monoxide) measures the ability of gas to transfer across from the alveoli in to the circulation. Changes to alveolar ventilation and its blood supply, thickening of the interstitium or the haemoglobin can all affect it. KCO (Carbon Monoxide transfer coefficient) is calculated by DLCO divided by the alveolar volume (see also Appendix 1)(16). Breathless patients with parenchymal lung damage may sometimes exhibit a low DLCO with a relatively preserved FEV_1(17). In those with very severe COPD FEV_1 decline slows down (Figure 1.2) (18), making its use as a disease marker less relevant in the later stages of disease, particularly because DLCO continues to decline, and does so more rapidly in the later stages (19).

Figure 1.2. Rate of annual FEV_1 decline in patients with AATD



1.1.5. Lung Volumes

Where there is increased expiratory flow limitation (EFL) the length of time to complete lung emptying is prolonged, and if this time exceeds the drive to next the next breath in, the lungs do not fully empty such that the Residual Volume (RV) will rise (20). This effect is exacerbated by dynamic hyperventilation during episodes where the minute ventilation is increased (e.g. infective exacerbation, panic attacks) or where there is an increase in airflow resistance (e.g. bronchospasm). The volume of lung subsequently occupied by the RV reduces the inspiratory capacity, and increases the total lung capacity (TLC). Lung volumes increase even in the early stages of COPD and increase further with severity stages of disease (21). Air trapping is the radiological feature of increased RV seen on CT, more prominently seen in

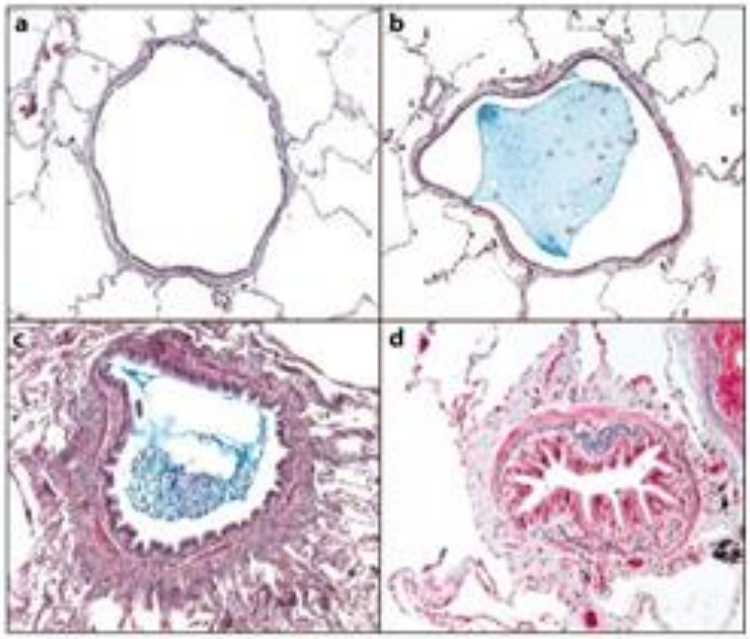
expiration; there is a decrease in the lung attenuation in a mosaic pattern relative to where there is regional small airways disease(22).

1.2. Pathology

1.2.1. Airways Disease

The pathology of airways disease seen in COPD consists of an exaggerated inflammatory response with abnormal tissue response to injury and airway remodelling (6, 23, 24). There is an accumulation of inflammatory cells within the airway wall contributing to increased airway wall thickening and airway resistance(25, 26). Proliferation of goblet cells and mucus glands also occurs which contributes to airway occlusion, and the hyper-proliferative state risks mucus and squamous cell metaplasia (25-27) (see Figure 1.3). This airway narrowing particularly affects the conducting airways measuring 2mm or less, and has been demonstrated in a multivariate analysis to be the largest contributor of FEV_1 decline (23).

Figure 1.3. Histology slides of small airways disease in COPD.



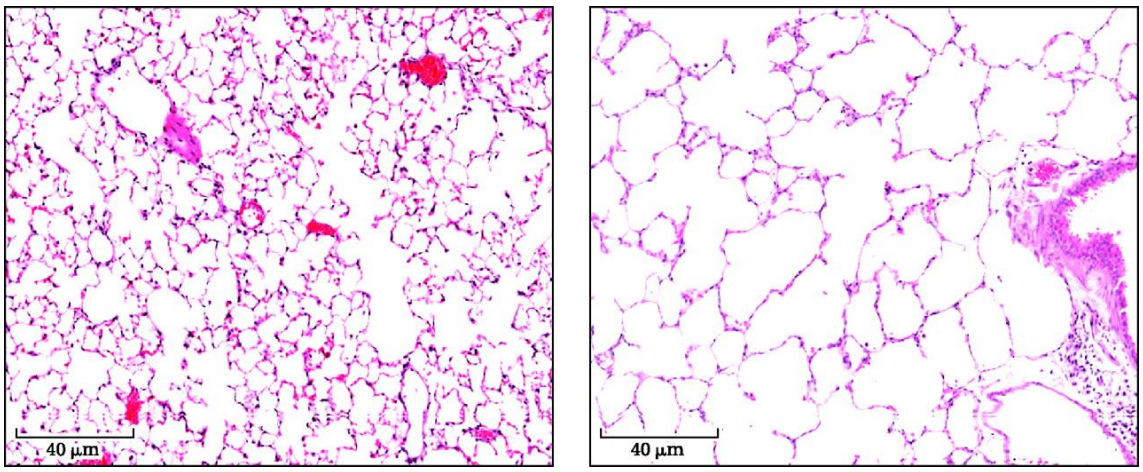
A) Airway with empty lumen for comparison. B) Lumen partially filled with mucus plug with a few epithelial cells. C) Active inflammatory process, exudate extends into the lumen. D) Narrowed airway from deposition of inflammatory infiltrate in the peri-bronchiolar space

1.2.2. Emphysema

Emphysema is the permanent abnormal dilatation of air spaces distal to the terminal bronchiole accompanied by destruction of their adjoining walls (28). The protease anti-protease theory addresses the direct tissue loss secondary to tobacco smoke, meaning there is destruction of the membranes responsible for gas transfer as well as the elastin that gives each alveolar duct/sac its structural integrity (29, 30). Inhalation of tobacco smoke is a noxious stimulus which triggers a subsequent

inflammatory cascade that involves the recruitment of neutrophils (31, 32). During the inflammatory process they release neutrophil elastase (NE) which if unopposed causes elastin breakdown in the lung tissue. Alpha one antitrypsin (AAT) is one of the key anti-proteinases, and if deficient, the individual has an increased risk of emphysema. The presence of elastases causes the collagen and elastin networks to become tortious and damaged in emphysema (see Figure 1.4)(33). The adjoining walls become degraded and airspaces coalesce causing airspace enlargement, which together with reduced elasticity of the tissues causes reduced elastic recoil (34, 35). The abnormal dilatation and hyperinflation reduces alveolar surface area, impacting on its ability to take part in oxygenation. In CT studies that account for the volume effects of hyperinflation, there is still a density reduction and therefore likely direct tissue loss(36).

Figure 1.4. Histology slides to demonstrate normal lung parenchyma and that affected by emphysema



Normal alveolar structure on the left and emphysematous changes on the right

1.2.3. Alpha One Anti-trypsin Deficiency

AAT is a type of serine protease inhibitor (SERPIN) coded for on SERPINA1 gene on chromosome 14q (37, 38). The enzyme has a major role in inactivating NE, and in AATD there is subsequent unopposed degradation of lung tissue by elastases resulting in emphysema(39). The enzyme additionally has anti-inflammatory properties, regulating pro-inflammatory cytokines such as TNF, IL-6 and IL-8(40). The M alleles indicate normal function, and the Z allele causes a severe deficiency in enzyme levels. Therefore MM represents a normal phenotype and ZZ would cause AATD(41). A number of other rarer alleles can cause deficiency and are summarised in Table 1.1. Specifically the mutation responsible for abnormal function in the Z allele is an amino acid substitution of lysine for glutamic acid on position 342, and accounts for 95% of the clinically significant cases(41). Levels of AAT above 11μmol/L are largely considered protective, and levels below are often associated with disease(42), however there is considerable debate about the minimum protective level.

Table 1.1. Rarer Alleles responsible for AATD

Allele	Genetic Defect	Cellular defect
Deficient		
Z	Amino acid substitution from glutamic acid to lysine	AAT polymers form inclusion bodies in the liver, instead of being released into circulation(38)
S	Slower polymer formation resulting from the same amino acid substitution	Slower rate of polymerisation as the structural change is not as profound(38)
Mmalton	Phenylalanine deleted position 52	Polymerisation of AAT(38)
Siiyama	Serine substitution from serine to phenylalanine position 53	Polymerisation of AAT(38)
Mprocida	Point mutation and an amino acid substation of proline for leucine and intracellular degradation	Mildly reduced neutrophil elastase function(43)
Mheerlen	Point mutation and an amino acid substation of leucine for proline and intracellular degradation	Abnormal processing of the secondary and tertiary structure of the AAT protein(44)
Null		
Null groups all result from mutations causing the formation of stop codons(45)		
QO granite falls	1 base pair deletion	Absence of AAT due to premature stop codon and unstable mRNA
QO hong kong	2 base pair deletions	Premature stop codon and truncated protein
QO Isola di procida	Deletion exons II-IV	Larger deletion and no detectable mRNA
Dysfunctional		
Pi mineral springs	Single amino acid substitution	Lack of neutrophil elastase inhibition, with intracellular aggregates
Pi Pittsburgh	Single amino acid substitution	Low NE activity and an anticoagulant effect.

1.3. Types of Emphysema

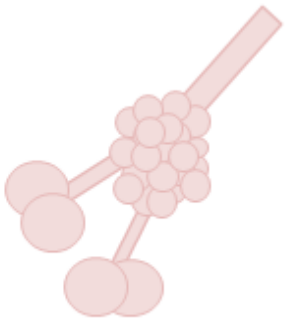
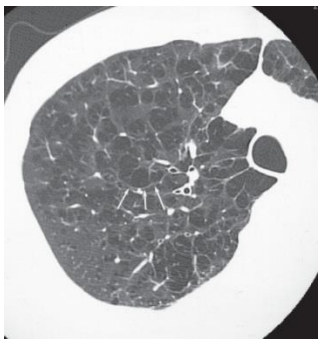
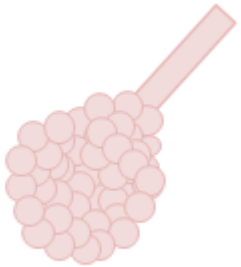
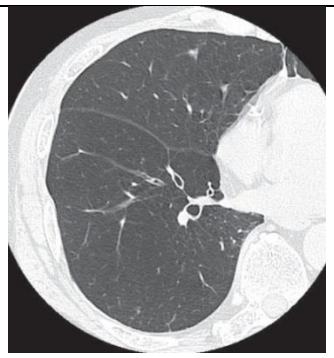
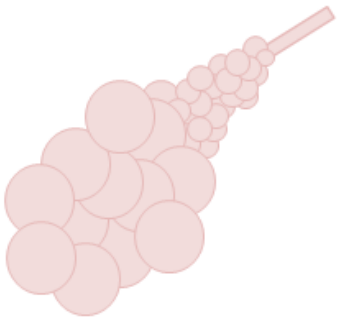
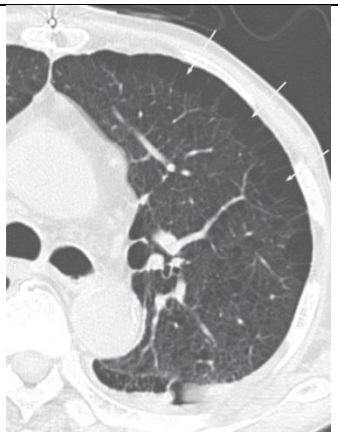
1.3.1. Centriacinar emphysema

In emphysema secondary to dust/smoke inhalation, there is an increase in the airspace of the proximal bronchioles, with relative sparing of the distal alveolar ducts/sacs (see Table 1.2) (25, 46). Airspaces this small cannot be visualised on CT but the adjacent bronchial artery can and therefore changes can be seen around the tip of the pulmonary artery (47). This type of emphysema is typically in the upper lobes or superior segment of the lower lobe, and is more core than peripheral (48, 49).

1.3.2. Panacinar emphysema

Unlike centriacinar emphysema where the airway dilatation is limited to the proximal element of the acinus, in panacinar emphysema there is dilatation of the respiratory bronchiole evenly distributed from the bronchiole to the alveolar ducts and sacs(50). The distribution of panacinar emphysema is more frequently in the lower lobes, and associated with more airway narrowing/inflammation(50, 51). Causes include alpha one antitrypsin deficiency as well as Swyer-James syndrome and Ritalin abuse (52, 53).

Table 1.2. Different types of emphysema as demonstrated pictorially and radiologically.

Type of emphysema	Pictoral representation	CT image	Description
Centrilobular			Enlargement of the respiratory bronchioles with relatively preserved distal alveolar sacs
Panlobular			Uniform dilatation of all air spaces from the respiratory bronchiole
Paraseptal			Predominantly enlarged airspaces at the periphery of each acini

1.3.3. Paraseptal/distal acinar.

This is the least common form of emphysema, and is characterised by enlarged airspaces at the periphery of the acinus usually on the dorsal surface of the upper

lobes(50). The main risk to the patient is due to the lesion adjacent to the pleura and disruption of the surrounding tissue can lead to pneumothoraces (54).

1.4. COPD and Phenotypes

1.4.1. Clinical Phenotypes

A phenotype in COPD is described as "a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes like symptoms, exacerbations, response to therapy, rate of disease progression, or death" (55). The aim of phenotyping is to be able to identify subgroups of patients who share similar underlying biological or physiological mechanisms and therefore targeted therapy can be prescribed(56). FEV_1 fails to describe the disease heterogeneity in COPD, and explains less than 25% of the disease impact on quality of life measures such as symptoms and quality of life (55). How best to include the heterogeneity into clinically useful phenotypes is still up for debate, with multiple methods of phenotyping proposed.

Historically "blue bloaters" and "pink puffers" identified those with hypoxaemia, CO2 retention and cor pulmonale versus breathlessness, hyper-inflated and low CO2 respectively (57, 58). Exacerbations in COPD are of particular interest as they are associated with accelerated decline in lung function, reduced quality of life and increased mortality(59) Certain patients exacerbate repeatedly whilst others do not suffer with any. The ECLIPSE study was a prospective observational study of 2138 patients with moderate to severe COPD followed up over 3 years. 23% of patients

did not suffer with any exacerbations whereas 60% of those with 2 or more exacerbations went on to have frequent exacerbations in the subsequent year. The stability of this 'exacerbator phenotype' indicates that this group may well have susceptibility to repeated exacerbations and therefore tailoring their investigations and management could improve care (60, 61).

1.4.2. Cluster analysis

Statistical modelling has been applied to patients with COPD in order to identify clusters and therefore phenotypes. An example of such a study that attempted this is by Burgel et al who performed a Principal Component Analysis (PCA) using 8 commonly used clinical variables in COPD was performed in 322 COPD patients(62). Variables used were age, cumulative smoking, FEV_1, BMI, exacerbations, the Medical Research Council (MRC) breathlessness score, St George's Respiratory Questionnaire (SGRQ) and Hospital Anxiety and Depression Score (HADS). 4 clinical phenotypes were identified, that would not have been found using GOLD classification, demonstrating that FEV_1 alone is ineffective for categorising patients who for the same value can have markedly different phenotypes.

A systematic review regarding the derivation and validation of clinical phenotypes in COPD by Pinto et al however demonstrated that the reproducibility and reliability of these clustering studies was only modest, with such a variety of methods used that a quantitative analysis was not possible(63). A large cohort study of COPD

heterogeneity and clustering was recently performed by Castaldi et al (64). This involved 17 countries, 146 individuals from 11 different cohorts including COPDGene and ECLIPSE and again showed only modest reproducibility of clustering analyses, and concluded the heterogeneity was better described as continuous disease rather than mutually exclusive groups. However the authors recognised that certain clusters do tend to reoccur. The first common cluster is that of with severe COPD with low FEV_1, low BMI, dyspnoea and extensive CT emphysema (LAA950 ≥19.7%). The other being an 'airway predominant' cluster have moderately impaired FEV1, elevated BMI and relatively little CT emphysema with thickened airway walls (LAA950 ≥4.7% and ≤Pi10 3.75% respectively). Other ways of phenotyping have been investigated such as resting inspiratory capacity and exercise tests, though this is beyond the scope of this chapter(65).

1.4.3. Radiological phenotyping

Imaging, and in particular CT, can be used to identify clinically important subgroups. For example those with upper vs lower zone emphysema or homogenous vs heterogeneous (see section 1.6.3 for further detail). Those with either predominant airways disease or emphysema can be identified using simply visual inspection or quantitative methods. Multiple studies have sub-grouped patients in to these radiologically defined phenotypes and demonstrated they have significant clinical difference between them (see Table 1.3). For example in the Emphysema versus Airways (EvA) trial (66) those with predominant airways disease had higher BMI, lesser degree of airflow obstruction, and less hyperinflation. In addition, there

was a negative correlation between CT lung density and airway wall thickening, which replicates similar findings from previous studies (67, 68). Therefore these two CT characteristics appear to be relatively independent of one another.

Table 1.3. Summary of studies dividing patients into HRCT defined phenotypes

Author and Year	HRCT defined phenotypes	Variables studied	Significant variable difference
Kitaguchi 2006 (69)	A: little or none of either emphysema or BWT E: emphysema but no BWT M: emphysema and BWT	Gas Exchange Gas Transfer Lung function Response to beta-agonist Response to treatment with ICS Sputum cell differentiation	A: ↑ BMI ↑DLCO ↓ hyperinflation. ↑reversibility. ↑response to ICS ↑ % of sputum eosinophils E: No response to ICS M: ↑response to ICS. ↑% of sputum eosinophils.
Fujimoto 2006(70)	A: little or none of either emphysema or BWT E: emphysema but no BWT M: emphysema and BWT	Exacerbation rates Gas Exchange Gas Transfer Hospital admissions Lung function Response to beta-agonist Symptoms	M: ↑ volume of sputum, exacerbation rate and admission to hospital
Pistolesi 2008(71)	From derivation set, created new validation set Group A and B	CT parameters Gas Exchange Gas Transfer Lung function	A: ↓ FEV_1, ↑ TLC ↓DLCO. ↑pixel index (threshold --950HU). B: ↑BMI purulent sputum worse bronchial wall thickening
Han 2011(72)	Emphysema Predominant or Airway Predominant	BWT Exacerbation rates Lung function % emphysema	Emphysema Predominant (>35% --950HU): ↓ FEV_1 and 6MWD. ↑SGRQ and MRC grade. For every 5% ↑ in emphysema, 1.18 fold ↑ exacerbation frequency. Airways Predominant: For 1mm ↑ in segmental BWT 1.84 fold ↑ in exacerbation frequency.

Subramanian 2016(66)	Emphysema dominant, airways disease dominant, mixed pathology and mild disease	Blood parameters CT parameters Gas Exchange Gas Transfer Lung Volumes Spirometry	Compared with airway disease dominant group, emphysema dominant group had ↑ lung volumes, ↓gas transfer ↓ pO2 +pCO2 ↓BMI ↑Hb No difference between age, and smoking history between the groups.
DaSilva 2016(73)	Emphysema or airways disease	Clinical +functional evaluation HRCT	Emphysema group: ↑ airflow obstruction ↓BMI ↓ 6MWD

The table shows significant differences in clinical and physiological parameters between the stated groups ($p<0.05$).

1.4.4. Management Guided by CT phenotypes

1.4.4.1. Medical Management

Table 1.4 summarises up to date evidence with regards to COPD management, subdivided into airways and emphysema predominant changes. These are subdivided into those clinical features shown to be statistically associated with one CT phenotype over the other.

Table 1.4. Treatment of COPD as defined by CT phenotypes.

CT Phenotype	CT feature	Clinical features	Management	Reference
Predominant Emphysema	↓ PD15 Emphysema • Centriacinar • Panacinar • Paraseptal • Bullous	Low BMI	Nutritional Support in a community rehabilitation program	Van Wetering et al 2010(74)
		Increased hyperinflation	Lung Volume Reduction Surgery	Cochrane Systematic Review Van Agteren et al 2016 (75) GOLD 2017(56)
			Bronchoscopic Valve Reduction Surgery	Sciurba et al, 2016(76) Davey et al 2015(77)
		Reduced exercise tolerance, and higher SGRQ	Pulmonary Rehabilitation	Cochrane Systematic Review, McCarthy et al 2015(78)
		Hypoxia	LTOT	NOTT trial(79) MRC trial(80)
		Lower FEV_1	Bronchodilators including LAMA +/-LABA	D'Urzo et al 2014 (81) Kerwin et al 2012 (82)

Predominant airways disease	Lower wall area/Body Surface Area ratio (WA/BSA) Lower luminal area/BSA Higher %WA	Higher BMI	Weight loss CPAP if associated OSA	OSA Taskforce 2009(83)
		Increased response to steroids	Inhaled steroids	Cochrane Systematic Review Yang et al 2007(84)
		Increased sputum eosinophils	Oral or inhaled steroid	Brightling CE et al 2005(85) Siva. R et al 2007 (86)
		Increased volume of sputum and exacerbation rate	Romiflumilast Mucolytics	Calverley et al 2009(87) Cochrane Systematic Review Poole et al 2006(88)
		Increased reversibility to SABA	Salbutamol	Tantucci et al 1998 (89)

1.4.4.2. Alpha One Augmentation Therapy

Unopposed NE in AATD produces emphysema like lesions, and therefore logically replacement of the enzyme might restore protective function in the lungs and slow down disease progression(90). Alpha one Proteinase Inhibitor given intravenously can increase serum levels of alpha one antitrypsin above 11μMol/L and a recent meta-analysis demonstrated slower disease progression in treatment vs placebo ($p=0.002$) as measured by CT density(91, 92). However, the outcome measures used in clinical trials of alpha one augmentation therapy still remain controversial. In the recent systematic review by Edgar et al, there was found to be no significant improvements in lung function (as measured by FEV_1 percent predicted and DLCO mmol/min/kPa) in those patients receiving augmentation therapy, and a small but significant increase in the annual exacerbation rate. The systematic review on intravenous alpha one augmentation therapy by Gotzche et al concluded further studies should aim to demonstrate a relevant clinical effect, namely reduction in mortality(93). However, most patients diagnosed with AATD are non-smokers, or stop smoking at diagnosis, and therefore rate of decline is reasonably slow. For this reason mortality cannot be expected to change within the short period of a trial, where patients are often very motivated and carefully selected(94).

The rate of decline seen on CT scanning is small but significant and evidence from the RAPID extension (RAPID-OLE (Open Label Extension)) indicates slowing of decline in density loss whether or not a patient has previously received alpha one augmentation therapy. The density loss in the placebo arm of the original RAPID

trial at TLC was -2.19/L/year versus -1.45g/L/year in the treatment arm. RAPID-OLE saw all patients receive active drug, with the two groups now defined as delayed and early start respectively. In both arms there was significant reduction in the annual density loss (-2.26g/L versus 1.51g/L) but the rate of tissue loss was slower in the early treatment group emphasising the importance of early initiation (95).

1.4.4.3. Lung Volume Reduction Surgery (LVRS)

Using CT measurements both visually and quantitatively allows for a more informed decision when considering patients with COPD for LVRS. By carefully selecting patients appropriately for surgical treatments who suffer with severe emphysema but remain dyspnoeic on maximal medical therapy, LVRS can reduce the associated symptoms and mortality. The surgery aims to resect areas of the lung most severely affected by emphysema, with a view to reducing reduce the total lung volume by up to 60% (96, 97). The mechanisms proposed are improved elastic recoil and expiratory airflow in the remaining lung (75, 98-100). Gas transfer is increased, dynamic hyperinflation is decreased, and an improvement in the movement and synchronicity of diaphragm and inspiratory muscle movements occurs (75, 101, 102).

The procedure is carried out via a median sternotomy, VATS or staged thoracotomy approach, with VATS now being the most common. The unwanted lung tissue is isolated and stapled using buttressed sutures with the remaining lung then allowed to re-inflate (See Figure 1.5)(97, 103, 104). The current NICE guidelines advise consideration of LVRS if still symptomatic despite maximum medical therapy, and

meeting all the recommended criteria: FEV1>20%, PCO2 <7.3, upper lobe predominant emphysema and TLCO >20%. (35) There is a pre-requisite that participants should have completed pulmonary rehabilitation first, and should have a TLC >100% predicted, and an RV >150%. (75)

Figure 1.5. Illustration of lung wedge resection performed during Lung Volume Reduction Surgery (LVRS).

1.4.4.3.1. LVRS Clinical trials

A systematic review was performed in 2016 of all RCTs examining the improvement of health outcomes in patients receiving LVRS vs standard medical therapy (75). This included the long term follow up outcomes from National Emphysema Treatment Trial (NETT) 2003, a large scale RCT comparing surgery with medical therapy,

which accounted for 68% of the patients included in the review (1218 participants). (96)

A meta-analysis of 5 clinical trials comparing LVRS versus standard medical care was performed to assess 90 day mortality, which showed a significantly higher number of deaths in the LVRS arm as a result of post-op complications (Odds Ratio 6.16, p<0.0001). However, the 36 month mortality favoured the LVRS arm; 307 events recorded in the LVRS arm versus 350 events in usual medical care respectively (OR 0.76, p=0.01).

The NETT authors re-analysed those patients at risk of early mortality by comparing high risk versus low risk patients. After identifying those at high risk i.e. FEV1<20% and/or DLCO<20% and homogenous emphysema, the 24 month mortality remained significantly high in the high risk group (OR 2.00, p=0.04), whereas there was no difference in mortality in the low risk group, (OR 0.86, p=0.29). The long term NETT data collected at 14 years showed that nearly all included patients randomised to either LVRS or usual care had died. Although 90 day mortality was higher in the LVRS group, the mortality curves of LVRS and usual care crossed at 4.4 years and showed a non-significant trend favouring the LVRS group.

The systematic review included analysis of change in SGRQ from baseline in surviving patients, combining data from the NETT study with a smaller study from 2005 of 83 patients(105). This demonstrated a mean change of -13.78 SGRQ units favouring LVRS (<0.0001). The NETT study alone chose a threshold of 8 points on the SGRQ scale to represent an improvement in quality of life. This was chosen over

the MCID of 4 points to justify the high risks of surgery. At 24 months, analysing all surviving patients, 121 patients out of 371 in the LVRS had an improvement of their SGRQ of 8 points or more, vs just 34 out of 378 in the usual medical care (OR 4.9, $p<0.001$).

1.4.4.4. Bronchoscopic valve reduction surgery (BRVS)

1.4.4.4.1. Endobronchial Valves

In an attempt to reduce the morbidity and mortality of LVRS, bronchoscopic techniques are being increasingly used. Zephyr valves are one way valves endoscopically placed under bronchoscopic vision (see Figure 1.6)(106). They allow trapped air and mucus to leave but not enter, and therefore cause distal collapse and atelectasis. The fissures must remain intact with no collateral ventilation from adjoining lobes so therapeutic collapse/atelectasis can take place, hence collateral ventilation must be actively assessed to determine eligibility (107). Figure 1.7 demonstrates a CT scan of a patient with severe AATD in whom the fissures can be seen to terminate early and therefore likely collateral ventilation is occurring.

Figure 1.6. Endoscopic view of Zephyr valve in situ.

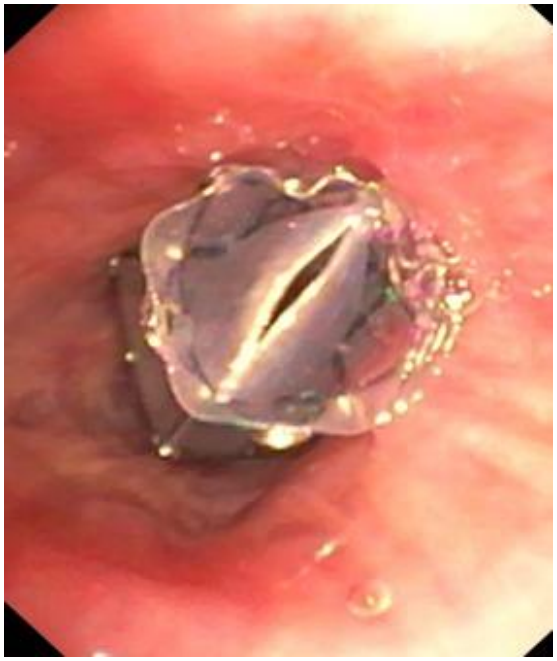
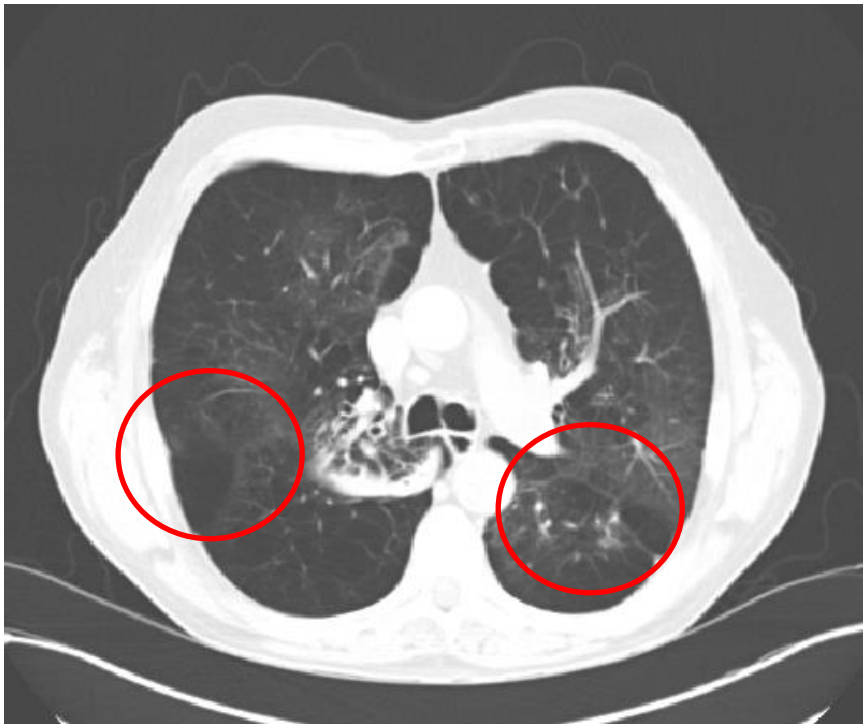


Figure 1.7. CT scan of a patient with severe AATD and incomplete fissures



The 2017 Cochrane systematic review of bronchoscopic volume reduction procedures meta-analysed 5 studies with a total of 703 participants (108). Table **1.5** lists all relevant endobronchial valve trials, with those included in the Cochrane review highlighted in bold. A more recent Endobronchial Valve (EBV) RCT has since been published (LIBERATE) that followed up randomised patients to EBV or Standard of Care (SOC) for a longer time period of 12 months (109). The Cochrane review concluded those patients who were randomised to EBV versus SoC had a significant improvement in FEV1, 6MWD, RV and SGRQ with no significant difference in mortality. However, adverse events such as pneumothorax were more common in the EBV group (OR 5.85). The NICE guidelines published in the same year were satisfied there was enough evidence to support their use clinically, and that patient selection should be done through an MDT (110). Patients are expected to have completed pulmonary rehabilitation first, and valves should only be placed in target lobes with no collateral ventilations. PFTs need to demonstrate severe obstruction and hyperinflation, and collateral ventilation should be assessed either by CT or by balloon catheter flow sensor.

Table 1.5. Summary of endobronchial valve trials since 2010.

Trial	Year of publication	Nº of patients	Duration of trial	Trial design	Primary outcome measures	Results
VENT US (111)	2010	220	6m	1:1 randomisation to unilateral EBV vs SoC in patients with heterogeneous emphysema	FEV1 and 6MWD	FEV1% increased by 4.3% in EBV group versus -2.5% in the control. 6MWD increased by 2.5% in EBV group, and decreased by 3.2% in control arm.
VENT EU (112)	2012	171	6m	1:1 randomisation to unilateral EBV vs SoC in patients with heterogeneous emphysema	FEV1 and 6MWD	EBV patients had a significant improvement in FEV1 compared to SoC (7% vs 0.5% change). The average distance change in 6MWD between groups was comparable (15m versus 10m for EBV and SOC respectively)
BeLieVeR-HIFi (107)	2015	50	3m	Single centre 1:1 double blind EBV vs sham controlled trial in patients with heterogeneous emphysema and intact	FEV1	FEV1 increased 8.77% in EBV arm vs 2.88% in control group. Significant complications including 2 deaths and a prolonged pneumothorax in EBV

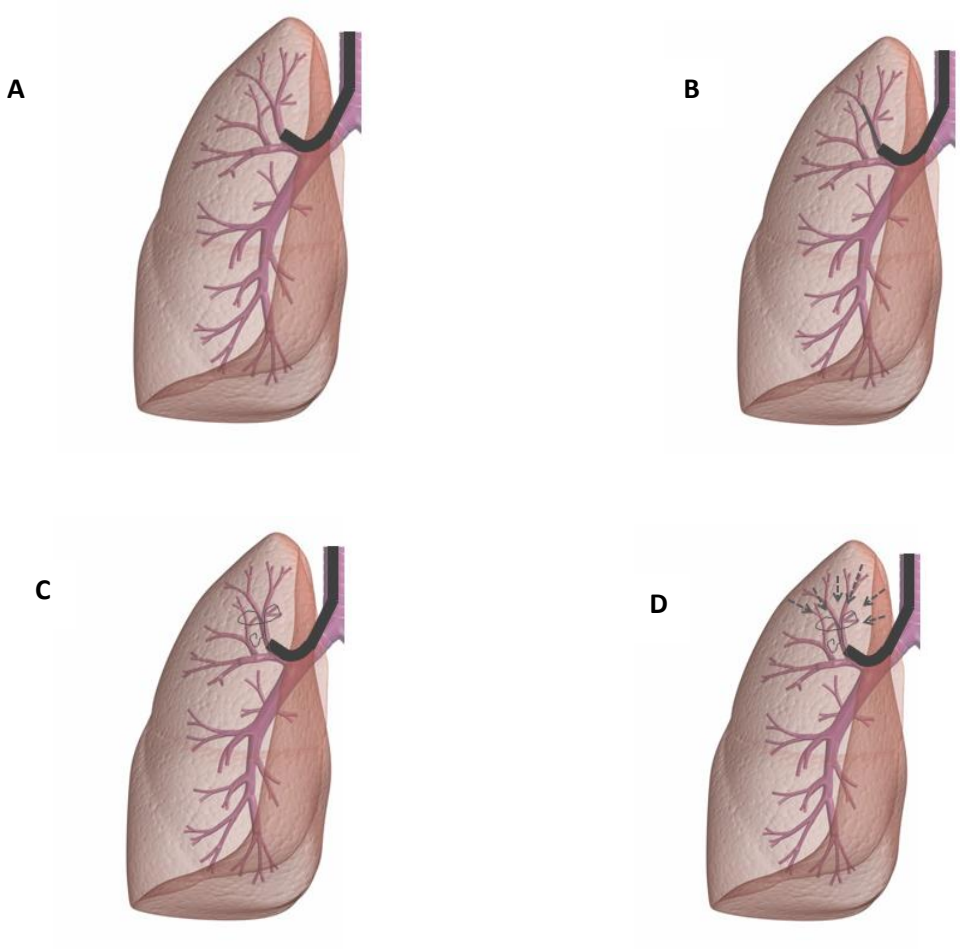
				interlobar fissures.		arm
LIBERATE (109)	2018	190	12m	2:1 randomisation (EBV to SoC) to assess effectiveness and safety of Zephyr valves in heterogeneous emphysema with little/no collateral ventilation	Difference of EBV-SoC post-bronchodilator FEV1 improvement from baseline of >15%	47.7% EBV patients vs 16.8% SoC had achieved change in FEV1 >15%. Differences between the two groups at 12m were also significant for 6MWD (+39.31) and SGRQ (-7.05).
TRANSFORM (113)	2017	97	3m	Single centre 2:1 RCT EBV vs SOC.	FEV1 improvement from baseline 12% or greater.	55.4% EBV group met sufficient FEV1 improvement, compared with 3.2% in SoC patients. Mean change of FEV1 at 6m was 20% vs -8.6%. 89.8% EBV patients at target volume reduction >350ml.
STELVIO (114)	2015	64	12m	Previously treated EBV patient were prospectively followed up for 1 year		EBV patients had a 17% improvement in FEV1, 687ml reduction in RV and 11 point reduction in SGRQ at 12m. 17% however underwent valve replacement and 22% needed valve removal.

IMPACT (115)	2016	93	3m	Prospective multicenter 1:1 RCT of EBV vs SoC., in patients with homogenous emphysema with absence of collateral ventilation assessed by Chartis	FEV1 at 3m related to baseline.	In the ITT population the improvement in FEV1 from baseline was 13.7% in EBV group versus -3.2% in SoC group. SGRQ change:-8.63 vs +11.25 in EBV/SoC groups. In the EBV group, 97.2% achieved volume reduction in the target lobe.

1.4.4.4.2. Endobronchial Nitinol Coils

Nitinol coils are passed through the bronchoscopic channel in a straightened position and once released into the lung tissue, they spring back into their coil shape, pulling in and collapsing surrounding tissue (See Figure 1.8). This aims to reduce the lung volume and therefore improve overall ventilation. Two RCTs published in 2016 randomised patients to either endobronchial coils or usual care (415 patients in total), both showing small improvement in FEV_1 that did not meet clinical significance (76, 116). There was a significant improvement of the SGRQ in the coils arm of the REVOLENS trial (-10.6 points at 12 months in the coil group) but for both studies, the rate of complications is as high as 35% and therefore this procedure is only recommend in the context of research as present by NICE (117).

Figure 1.8. Diagram of the mechanism of action of bronchoscopic coils.



A) Flexible bronchoscope is passed through and wedged into a segment of the RUL.

B) The coil which is held in the straightened position within the bronchoscopic channel is pushed out into the lobe

C) The coil quickly springs into its original shape

D) This pulls in surrounding lung tissue to reduce the volume of the segment of lung in which it was placed.

1.5. Prognosis as guided by Quantitative CT

1.5.1. Disease distribution

Emphysema as a result of smoking/inhalation of noxious gases most frequently results in the centriacinar distribution of emphysema which begins predominantly in the upper zones. Due to the nature of emphysema originating from inhalation and local destruction of lung tissue, there is a higher %LAA centrally rather than peripherally. When emphysema is divided into core and rind, studies show a higher association with predominant core emphysema and a lower FEV_1 and higher MRC (118). As the core has a greater %LAA this could also explain why there is a stronger association with gas transfer here versus peripherally (49). Findings by Parr et al demonstrated that in AATD patients basal distribution is associated with greater impairment of FEV_1 ($p=0.002$), but less impairment of gas exchange ($p=0.016$), and Aa gradient ($p=0.007$)(119). Given the lung function variation between different lung regions the authors warn of using a single physiological parameter as a measure of severity as it may introduce bias.

Castaldi et al found that panacinar rather than centriacinar distribution was associated with stronger associations with lung function and quality of life than CT lung density, demonstrating that the distribution of disease has an independent effect on severity (120). AATD typically occurs in a panacinar distribution with basal predominance, and Dawkins et al showed that for these patients, basal distribution carried a higher mortality risk (121). Finally, in patients randomised to the medical

arm of NETT, the authors demonstrated that a greater proportion of emphysema in the lower lung zone vs upper lung zone was predictive of mortality (p=0.005). (122)

1.5.2. Predicting post-operative FEV_1.

CT density masking to quantify the severity of emphysema is linked to favourable post-operative outcomes in a range of procedures. In a small study of 9 patients Sverzellati et al applied a density mask to COPD patients awaiting lobectomy for lung cancer, along with spirometry. With specific equations, they predicted the post-operative FEV1 using both values and found quantitative CT was superior to lung function (r=0.97)(123). Gierada et al used various LAA measurements and determined that a 75% LAA or greater for -900HU threshold, or 25% at --950HU were associated with improved outcomes post-operatively in patients undergoing LVRS, including a >50% improvement in FEV_1 and 2 fold increased six minute walk distance(124, 125).

Finally the ratio of upper to lower lobe emphysema is of particular importance in assessing predicted post-operative FEV_1 following bilateral LVRS. Consistent with the fact that upper lobe predominance is associated with better outcomes, Flaherty et al found that the CT emphysema ratio (CTR) was the best single predictor of a successful 12% increase in FEV_1 (absolute value 200ml). Importantly, the highest CTR scores (>2.5) were associated with a greater than 90% specificity at each time point up to 36 months, although the sensitivity was low (126). The positive predictive value (PPV) of this threshold was at least 75% up to 36 months after

surgery. The negative predictive value (NPV) remained moderate at all thresholds throughout 36 months of follow-up.

1.6. Quantifying Emphysema using Computed Tomography

1.6.1. Computed Tomography

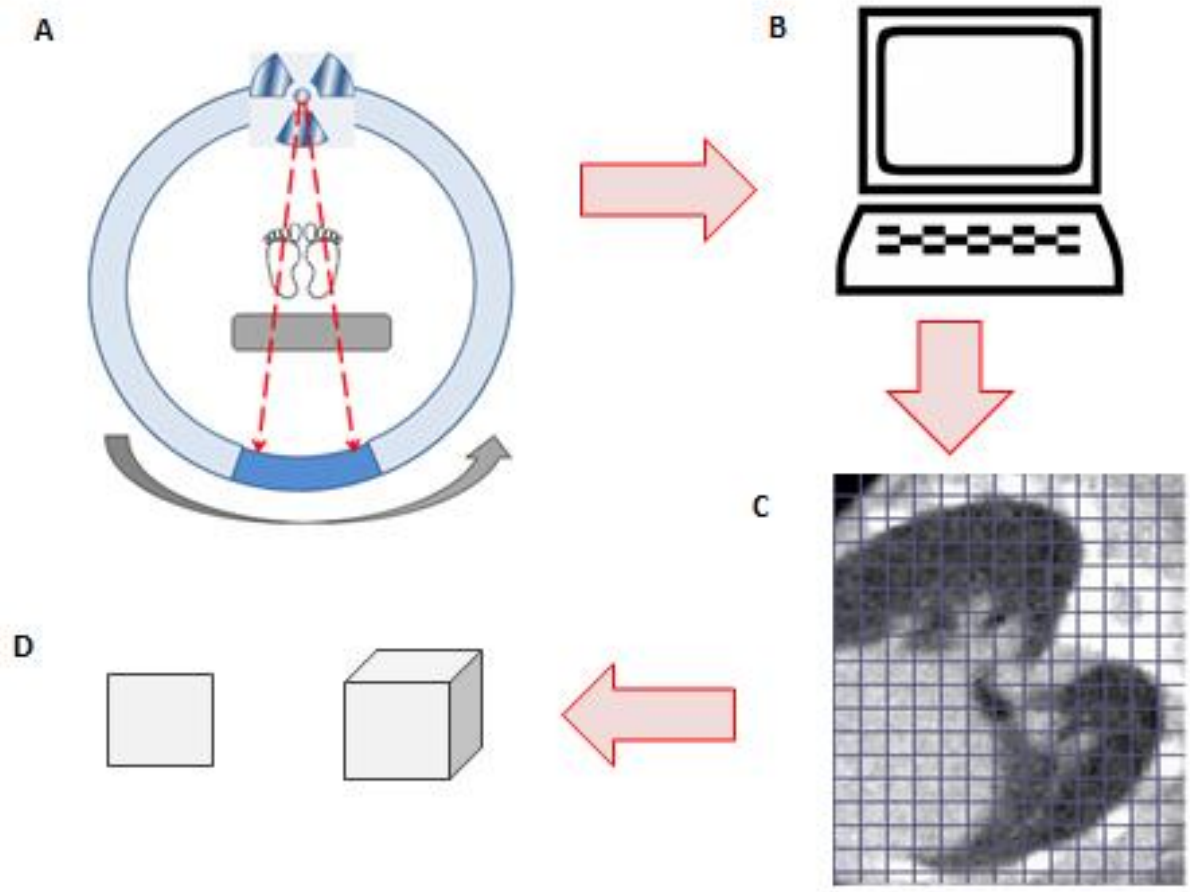
There was early recognition that CT scanning could provide useful information about the severity of COPD and before more sophisticated software was available to formally quantify the level of emphysema, there were numerous scoring systems to help visually grade disease. Two of the more commonly used methods are the Thurlbeck method and the modified Goddard system (127, 128). These score emphysema 0-100 and 0-4 respectively and correlate with pulmonary function tests. However the correlation is not as strong as that performed quantitatively with CT densitometry and the greater inter- and intra-observer variability means the results are less reliable and reproducible(129).

1.6.2. CT Densitometry.

CT densitometry is the method of quantifying the severity of emphysema using dedicated software. Figure 1.9 demonstrates how the CT images are digitally produced. X-rays are emitted and passed through the subject and received by detectors that calculate how much the intensity has been reduced by the tissue. These attenuation coefficients are then converted into a digital image in the form of a matrix consisting of many small data sets. Each small square in the matrix is a pixel,

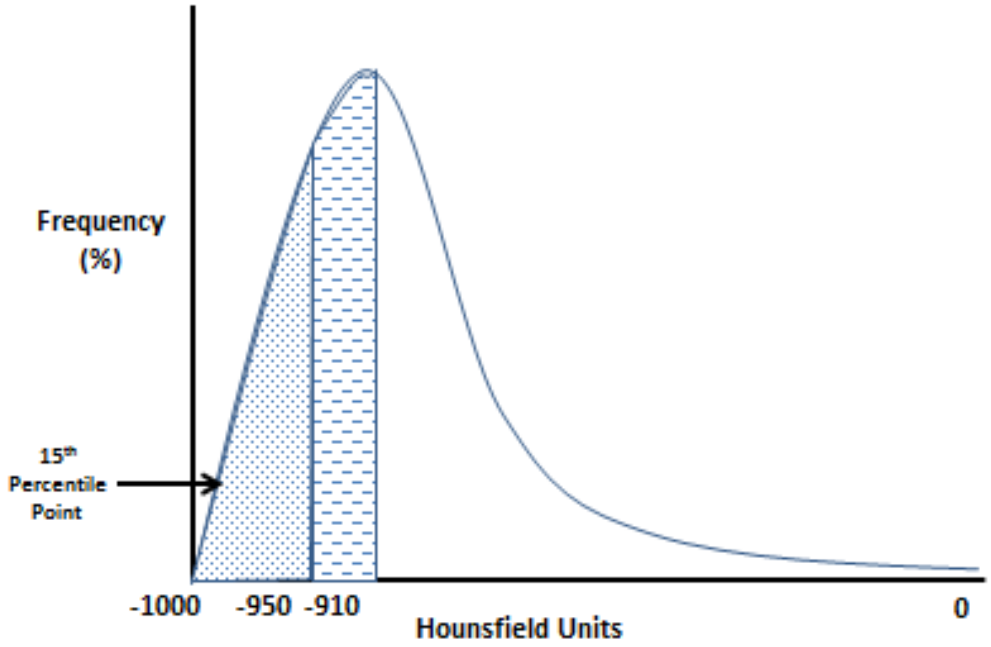
and in 3D with volume adjustment is a voxel. Each pixel is assigned a value in Hounsfield Units (HU) from -1000 representing the least possible density/attenuation i.e. air and 1000 representing the highest, i.e. solids. These pixels or voxels can be plotted on a histogram as shown in Figure 1.10. There are two ways of reading the severity from this histogram. The first is the value of where the 15th percentile point lies on the curve (PD15) and is the most preferred value in trials quoting density, as it is most accurate and sensitive to change(36, 119, 130, 131). The second method is to calculate the percentage under the curve that represents the low attenuation area for a selected threshold e.g. --910HU or --950HU. These and other values are used in studies quoting density, and Table 1.6 demonstrates trials that have sought to ascertain the most valid method in both AATD and COPD.

Figure 1.9. The process of CT scanning



X-rays are passed through the patient and received by the detectors that rotate 360^0 around the patient (A). The reduced intensity of the XR beam passed through the subject is calculated as an "attenuation coefficient" or a numerical value received by the computer (B). A software program will 'reconstruct' this data into a digital image (C). In the 2D format these individual units are known as pixels, and voxels when adjusted for volume (3D).

Figure 1.10. Calculation of densitometric indices.



Example of a density histogram, and how the area under the curve for a given threshold is calculated. As shown in the figure, where the 15th percentile point can be determined, or the area under the curve for given thresholds e.g. -950HU or -910HU

Table 1.6. Table to summarise studies performed in AATD and COPD directly comparing the most accurate measure of CT density.

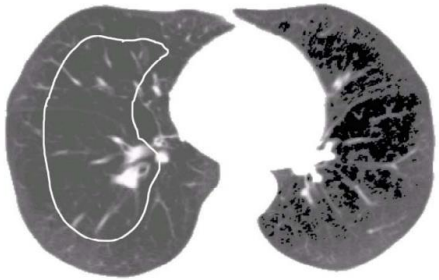
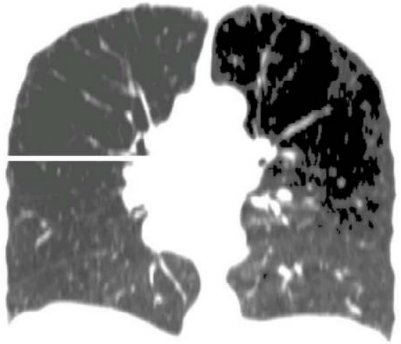
Condition	Type of study	910	950	PD15	Conclusion of superior measure	Reference
AATD	RCT	x	x		-950HU	Parr et al 2004(132)
	RCT		x	x	-950HU and PD15	Parr et al 2006(133)
	RCT	x	x	x	PD15	Parr et al 2008(36)
	Review	x	x	x	PD15	Newell, Hogg et al 2004(131)
COPD	RCT	x	x	x	PD15	Shaker et al 2004(134)
	Review	x		x	PD15	Dirksen 2008(130)
	RCT		x	x	-950HU	Chong et al 2012(135)
	Prospective observational study	x	X		-950HU	Gevenois et al 1995 (136)
	Prospective	x	x		-950HU	Gevenois et al

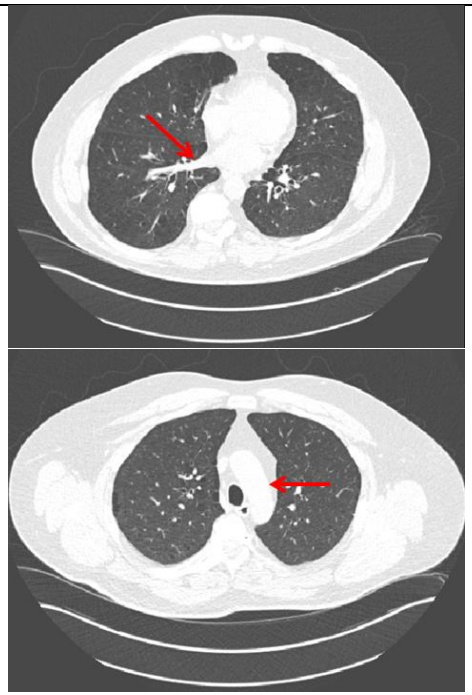
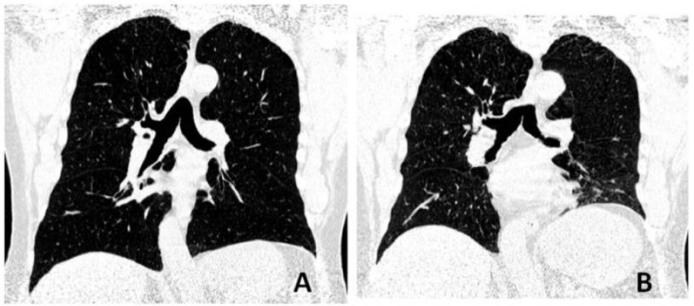
	observational study					1996 (137)

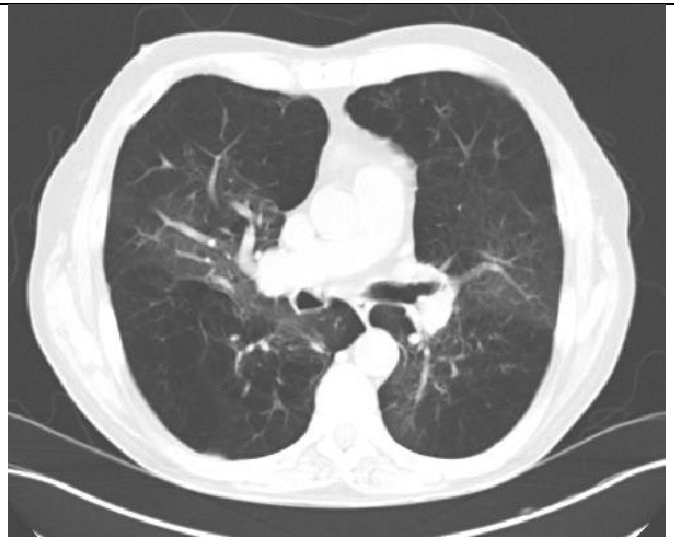
1.6.3. Other measures of emphysema quantification

Throughout the literature there are numerous other ways of describing or quantifying emphysema (see Table 1.7). However these measures are less widely used than CT density, which has been pathologically and clinically validated, and used as the outcome measure in therapeutic trials.

Table 1.7. Summary of alternative methods of quantifying emphysema

Measure	Description	CT image	Reference
Core vs Rind distribution	By dividing 50% of pixels into 'core' and 50% into 'rind', those with core predominant emphysema have a lower FEV1 and a higher BODE index.		Mair et al 2009 Nakano et al 2001 Aziz et al 2005 (118, 138, 139)
Cranio-caudal distribution	CT emphysema Ratio (CTR) is a measure of the cranio-caudal distribution, with a value>2.5 (representing upper lobe dominant emphysema) associated with an improved outcome following bilateral LVRS.		Flaherty et al 2001 (126) NETT (140)

Zones	In order to delineate upper zone from lower zone emphysema, studies have identified preferable landmarks as cut off values. Different studies use different anatomical landmarks e.g. mid-portion of the intrathoracic trachea or arch of the aorta for upper zone and therefore not identical method. Even within the same method there is still inter/intra-observer variability i.e. at least 4 slices include the arch of the aorta.		Soejima et al 2000 Dowson et al 2001 Dowson et al 2001(141-143)
Gas trapping	Ratio of expiratory CT density/inspiratory CT density to quantitatively assess lobar air trapping.		Nagatani et al 2015 Mets et al 2012 Zaporozhan et al 2005 (144-146) Yamashiro et al 2010(147)

Uniformity	Visual assessment of whether the distribution of emphysema is homogenous (shown on the right), heterogeneous or mixed. Both markedly heterogeneous and homogenous distributions were found to be protective, and therefore not an effective method of assessing risk prior to lung volume reduction surgery (LVRS).		Weder et al 1997 Hamacher et al 1999 Boutou et al 2015 (148-150)
Texture analysis	Uses automated software trained to identify certain patterns of emphysema on a CT scan (regions of interest-ROI).		Park et al 2008(151)

1.6.4. Validation

In order for a new technology such as CT densitometry to be deemed reliable, it requires validation against pre-existing methods of measuring emphysema, both pathological and clinical.

1.6.4.1. Pathological correlations

The ability of density analysis to accurately assess the degree of emphysema has been validated through pathological studies, using macroscopic and microscopic techniques. Muller et al in 1988 macroscopically assigned an emphysema pathology score (1 to 100) to 28 patients who had undergone lobar resection for a lung tumour, and showed a strong correlation with simple density mask results ($r=0.83$, $p<0.001$) (152).

Gevenois et al measured emphysema macroscopically using two further methods, point counting and panel grading, which both require investigators to manually estimating the amount of visible emphysema per section (136). Through this measure of emphysema, the authors did show -950HU was the only level for which no statistical significant difference was found between HRCT and morphometric data ($p=0.384$)

In 45 patients who had undergone lung resection of peripheral lung tumours, Gould et al compared CT density as measured by EMI units (EMI was the historic name for CT, Hounsfield was previously a scientist at EMI) with the resected pathological specimens. The mean value for the surface area of walls of the distal airspaces per

unit lung volume (AWUV) was measured in 1mm*1mm microscopic fields of lung from methacrylate-embedded blocks selected from inflation-fixed lobes. There was a strong correlation between EMI units and AWUV ($r=-0.77$, $p<0.001$), demonstrating the ability of CT to quantify emphysema (153).

Emphysema was measured microscopically by Gevenois et al by measuring the perimeter and the inter-wall distances within alveoli and the alveolar duct count on surgically resected specimens (137). The selected patients were undergoing resection for either primary lung cancer or transplant, and once resected, they were inflated with 10% buffer formalin overnight. 2cm*2cm blocks were then embedded in paraffin and cut into 5μm thin sections and stained with hematoxylin and eosin. CT density was measured and compared across numerous RA (relative area of emphysema) thresholds ranging from -900HU to -970HU. There were significant correlations with emphysema measured pathologically and CT density, with the strongest correlation between MIWD (mean inter-wall distance) and -950HU ($r=-0.7$, $p<0.001$) (compared with -910HU, $r=0.64$).

1.6.4.2. Clinical correlations

Numerous studies have shown significant correlations between CT measures of emphysema (PD15 and %LAA 950) and FEV_1 and DLCO (154-157), as well as measures of exercise tolerance e.g. MRC grade and 6 minute walk distance (6MWD)(158-162). There are also significant correlations with frequency of exacerbations and ultimately mortality (121, 158, 163-165) (see also chapter 4 for the systematic review). In the NELSON trial (Dutch and Belgium Lung Cancer Screening

Trial) Hoesein et al have shown that smokers with normal lung function demonstrated evidence of emphysema on CT, concluding that CT is a more sensitive in detecting emphysema than PFTs(166, 167). However, the R^2 value between CT density and FEV_1 even when adjusted for other variables remains 0.3-0.68 indicating that the parenchymal disease detected by CT density only contributes for 30 to 68% of the total variation(120, 168-170). Therefore other factors including small airways disease must additionally contribute to the altered lung function seen.

1.7. Airways disease

1.7.1. Quantification

There are several recognised methods of quantifying airway wall metrics, namely measurement of the airway lumen, the airway wall or the wall area expressed as a percentage. Semi-automated software programmes measure the luminal area (LA) and the wall area(WA) allowing the calculation of %WA (%WA=WA/LA +WA*100) (171). Alternatively the bronchial wall thickness (BWT) can be derived as the square root of WA adjusted for the internal perimeter (172, 173) (Figure 1.11).

Figure 1.11. Airways disease measurements

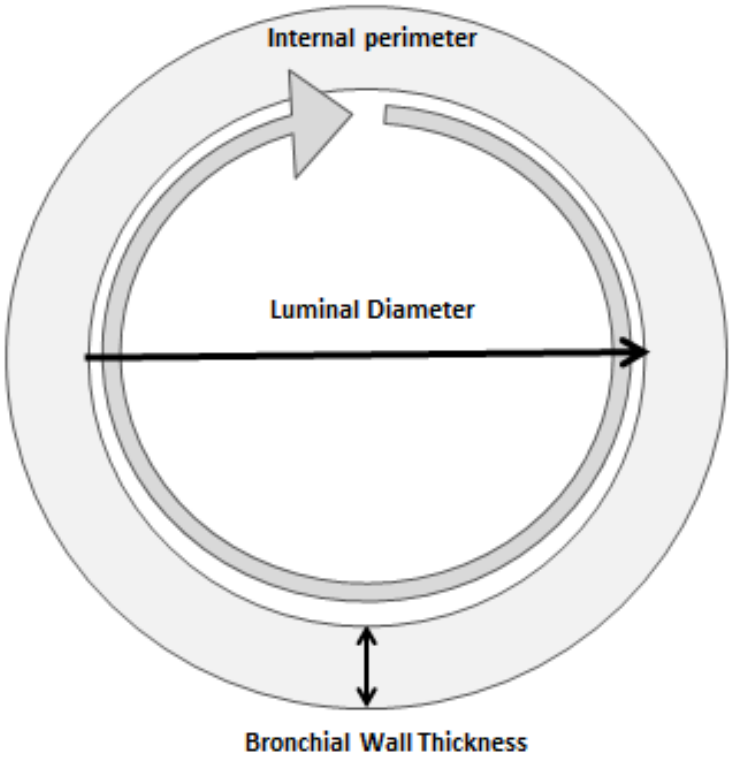


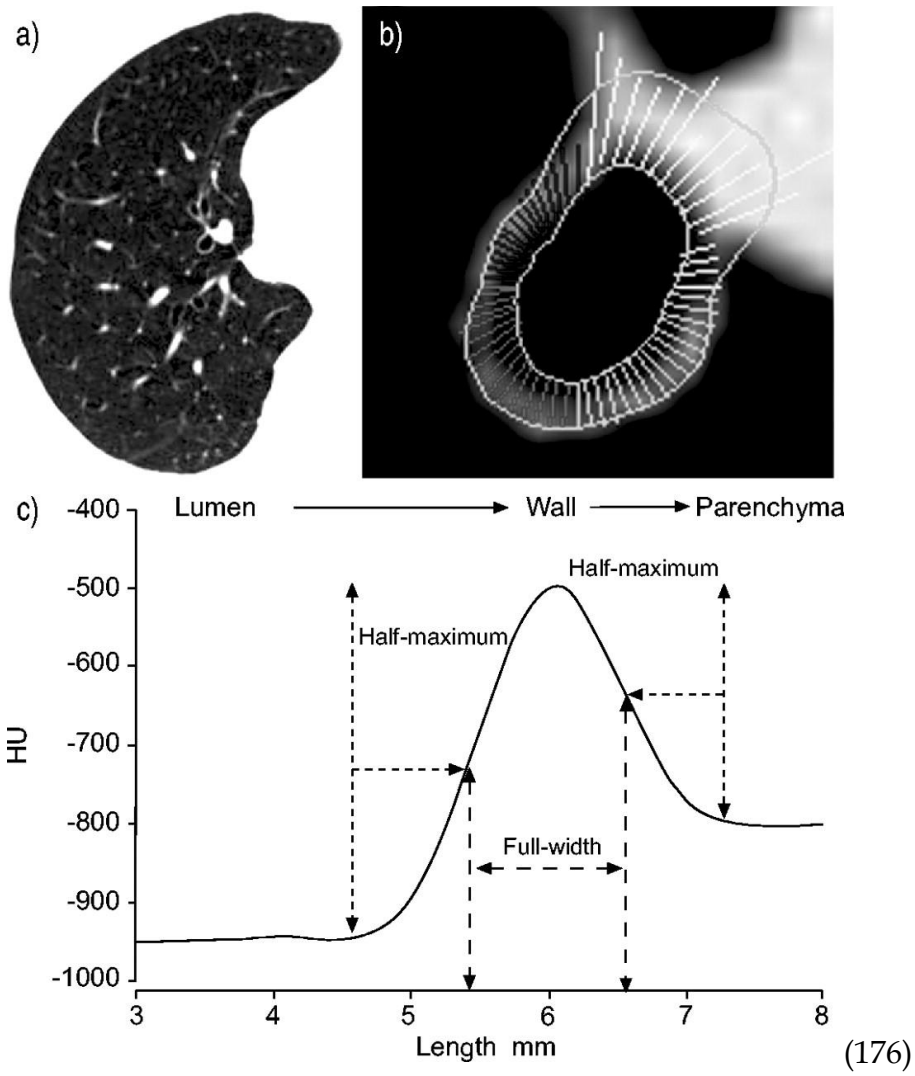
Diagram to demonstrate various values calculated in assessing either the luminal or wall contribution to airway thickening.

Airway wall measurements are often based on the full width at half maximum principle (FWHM) and modifications of it (174, 175). This technique estimates airway wall measurements by assessing the change of the XR attenuation along a XR beam as it travels from the lumen, through the airway wall and into the parenchyma. The change in attenuation as the XR enters the inner airway wall and leaves into the parenchyma is called the "full width". The FWHM principle then makes an assumption the true airway wall boundary is half the peak value (see Figure 1.12) (176). This method is known to overestimate the value of wall thickness

particularly in small airways due to influence of surrounding structures e.g blood vessels.

Table 1.8 summarises various algorithms proposed for quantification of airways disease, most of which are modifications of the FWHM principle (177, 178).

Figure 1.12. Demonstration of the Full Width at Half Maximum principle



(176)

Table 1.8. Summary of recognised methods to quantify airways disease.

Airway Measurement	Algorithm	Description	Reference
Airway lumen	Threshold-based	Uses a luminal seed point, and pixels detected within a given threshold (-500HU)	McNitt-Gray et al(179)
		Threshold refined to -577HU	King et al(180)
	Edge detection	Airway wall manually traced, and later smoothed out by computer software	Amirav et al(181)
	Region growing	Luminal seed point. Uses voxels rather than pixels	Wood et al(182)
Airway wall thickness	Full Width at Half maximum	Ray measured from inside to the outside of airway and the changes detected estimate the beginning and end of the wall.	Nakano et al(171)
	Best-fitting ellipse	Adjusts FWHM for airway orientation	Saba et al(177)
	Integral based	FWHM adjusted for a 3-dimensional approach	Achenbach et al(178)
Wall area percentage (%WA)		Measurement of the slope using internal perimeter along the X axis, and square root of wall area on the y axis	Grydeland TB et al(183)

1.7.2. Validation

Nakano et al measured the airway dimensions of intermediate and large sized airways on CT and compared them with measurements taken from histologic calculation in resected lung. They concluded that CT could be used to reliably estimate the diameter of small airways in vivo (CT airway with an internal diameter of greater than 0.75cm accurately predicts the dimensions of small conducting airways with an internal diameter of 1.27mm (r^2=0.57, $p<0.01$) (171, 174). Airway wall thickening as measured by CT is related to obstructive spirometry(184-187), and chronic sputum production is associated with increased likelihood of an exacerbation leading to a hospital admission(188), and death from a pulmonary infection(189). Chronic bronchitis (cough and sputum production for at least >3 months in 2 consecutive years)(56) has a greater mean %WA and internal perimeter, and is associated with higher exacerbation and mortality rates.(172, 190, 191) Thus CT defined airways disease is clinically relevant to measure.

1.8. CT Quantification Variability

The potential pitfall of CT analysis is that the various components of the technology must all be equal in order to compare study results. These factors include using the same software programme (192), the same reconstruction algorithm (193-195), appropriately calibrating the scanner (36, 132) and adjusting for volume (130, 135, 196) (see **Error! Reference source not found.**). CT phantoms should be used, which re models that contain manufactured rods of material which have identical CT density to air and water and are therefore used to calibrate the scanner. If CT density logistics are standardised, then scans may be compared longitudinally to measure treatment effect, and combined from different centres. A detailed review of CT noise reduction by Dirksen 2008 recommended using a soft reconstruction algorithm, with a slice thickness of 3-5mm, at a low radiation dose using a phantom(130).

Table 1.9. Summary of CT acquisition variables resulting in noise effects.

Factor	Effects	Reference
Software Programme	Significant variations in measurement of emphysema ($p<0.001$) therefore recommend when comparing results to use the same software	Wielputz et al 2014(192)
Reconstruction Algorithms	Trade off to be made between spatial and contrast resolution i.e. the sharper the image, the more noise and artefact created. In addition, selecting the wrong reconstruction algorithm can significantly overestimate the degree of emphysema	Shaker et al 2004(193) Kemerink GJ et al 1996(194) Gierada DS et al 2010(195)
Slice thickness	Thinner slices e.g. 1mm >5mm will give less detailed analysis for that slice and therefore values may differ	Shaker et al 2004(193)

Calibration	Calibrating for air and with a phantom essential as values differ significantly longitudinally if not.	Parr et al 2004(132) Parr et al 2008(197)
Radiation dose	Using a low radiation dose technically can overestimate the degree of emphysema. However the actual numbers are not clinically significant, and using low dose scans means it is more acceptable in terms of safety	Gierada DS et al 2008
Volume	Volume and level of inspiration must be adjusted for either statistically or physiologically. Difference of opinion of how reproducible a patient's breath hold is.	Dirksen 2008(130) Stoel B et al 2008(196)

1.8.1. Volume variability

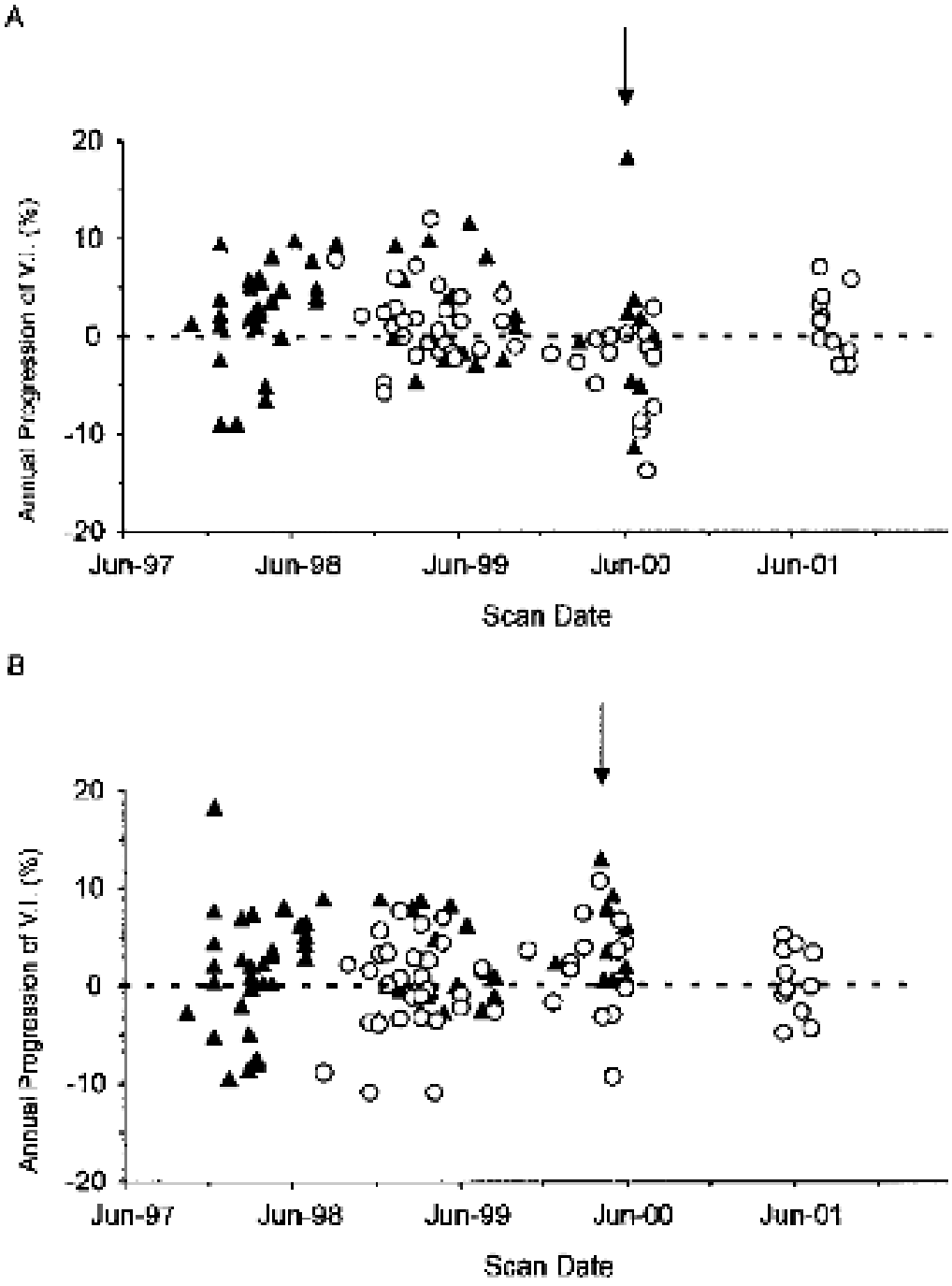
The principle of CT densitometry is to quantify the amount of alveolated tissue, and therefore arguably is a more precise measure of emphysema (lung tissue destruction) than pulmonary function tests. The amount of air that is within the alveolated tissue would be either due direct loss of alveolar tissue or increased inspired air, therefore eliminating the variability of the latter is crucial. Ideally every patient would always be examined at full inspiration each time, but especially in COPD patients who are already breathless, this is very difficult to do and needs a high level of patient compliance. Shaker et al demonstrated during their analyses of volume correction that even with patient coaching for deep inhalation, there was still a within-subject total lung volume (TLV) SD of 234ml (134). The weight of the lung however was more stable as would be expected with a SD of 21g.

1.8.2. Correction for air

The importance of air calibration was demonstrated by Parr et al 2004 (132). This two-part paper consisted of a validation study in order to propose a correction threshold, followed by application to AATD patients. 57 patients were recruited with 3 annual scans done 2 years apart and plotted the VI (voxel index) change against time, with comparisons made using the uncorrected and adjusted thresholds. The method of correction threshold calculation was = (air calibration-water calibration/-1000)*index threshold. Using this correction method, there a shift in the

observed VI progression from an apparent improvement of %VI before correction to no significant progression following correction (see Figure 1.13). By adjusting the analysis threshold there was improved detection of emphysema progression over the two years, and these results demonstrate the important of scanner and image calibration in longitudinal studies of CT density decline.

Figure 1.13. Annual progression of CT density with and without air calibration



(132)

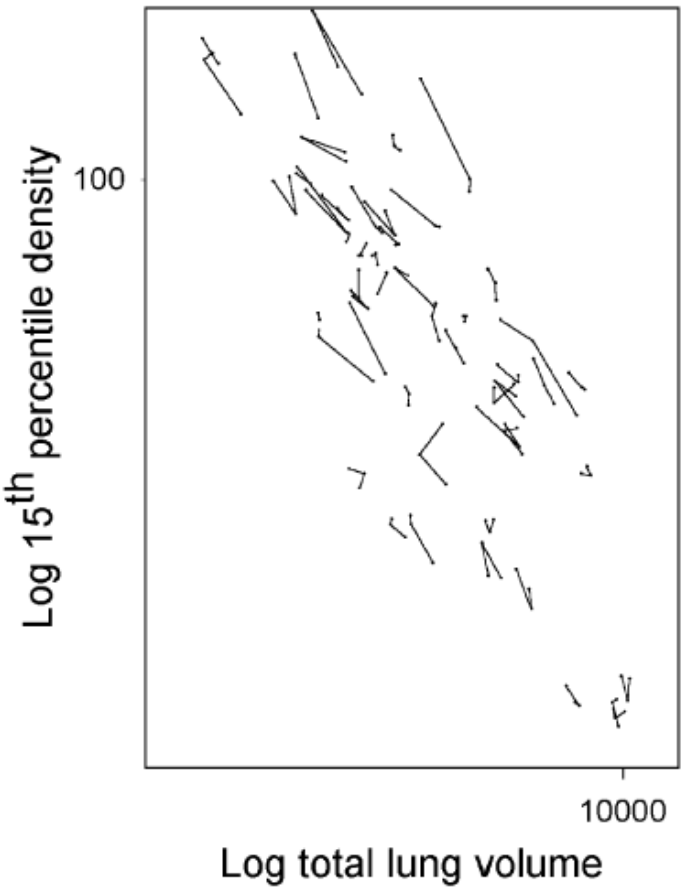
A) Before air calibration B) After air calibration.

1.8.3. Correction for volume

In theory the lungs may be considered sponge-like, i.e. a reduction in the lung volume would consolidate and increase the lung density, as the compression is mass preserving. How to adjust CT density for volume using the sponge model, or physiological adjustment, was explored by Shaker et al 2004(134). This is necessary so CT density may be use confidently in clinical trials and reassured that the changes seen are that of the patient and not variability in the instrument.

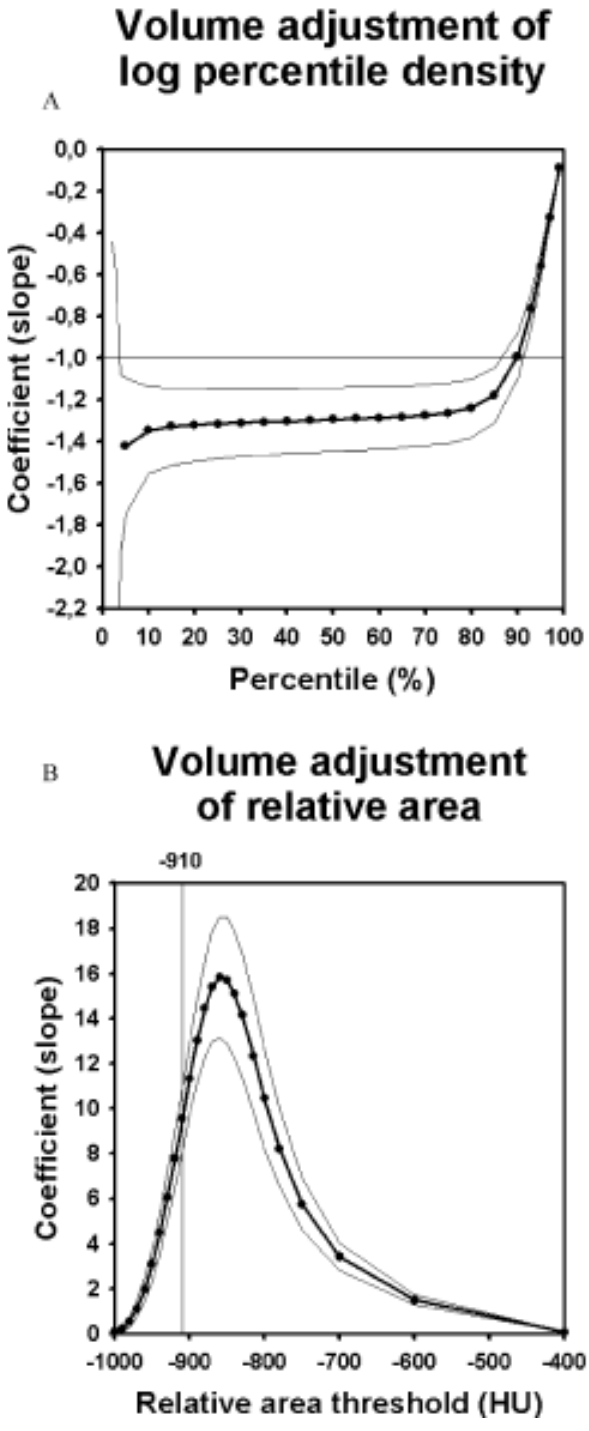
In this 2004 study 50 patients underwent 3 CT scans 2 weeks apart. Total lung volume (TLV) is the total measure of air and lung tissue combined (assuming air=-1000HU). In order to assess the variability of lung density for within-subject variability of TLV, TLV was plotted against percentile density (PD) and relative area of emphysema (RA), with the purpose of assessing the distribution of air at full inspiration and therefore how to adjust density measurements accordingly. Following double logarithmic transformation, the relationship of TLV against CT density was near to linear (see Figure 1.14) .The slope of the linear relationship gives a co-efficient, and when the co-efficients across the range of percentile densities was calculated, the slope lines were very stable across PD 10-75% whereas this was more variable in RA (Figure 1.15). For this reason, PD is the preferred method of density quantification.

Figure 1.14. Relationship of TLV to PD15 following logarithmic transformation



(134)

Figure 1.15. Co-effients for volume adjustment for PD and RA



(134)

Stoel et al further explored if the sensitivity of lung density could be improved by correcting for changes in lung volume based on the estimated relation between

density and lung volume (196). Two methods were explored; correcting CT density using an estimate for the entire patient group versus individual and patient specific volume adjustment. This was done by using a linear mixed effects model with CT density as the outcome, volume of lung, and time of CT scans as fixed effects. They found sensitivity was improved using repeated CT scans and by applying volume correction to individual patient data which decreased the SE of progression estimate by a factor of two.

Regarding the application of volume correction to clinical trials, the EXACTLE study used 2 methods to adjust for volume in this RCT of prolastin versus placebo; the 'physiological method' and 'statistical method'(198). Physiological 'sponge' method uses TLC-adjusted PD15 as the dependent variable; treatment and centre as fixed factors and baseline measurement as covariates. The statistical model used PD15 as the dependent variable; treatment and centre as fixed factors; and change in logarithm of CT-measured TLV and baseline measurement as covariates. Adjusting for volume and the level of inspiration is critical in standardisation of CT densitometry whether this be done as a physiological adjustment or statistically.

1.8.4. Clinical Trials using CT as an outcome measure.

CT has been used as an alternative outcome measure in therapeutic trials for patients with emphysema. When performing power calculations in the EXACTLE study using CT density as a measure of response to alpha one augmentation therapy, the author's calculated 494 patients would need to be recruited in each treatment arm

for 3 years using FEV_1 as the primary outcome measure (198). In the RAPID trial however, they calculated 180 patients distributed over the two treatment arms would provide a power of at least 80% using two sided p value of 0.05(92); this was possible because their primary outcome was CT density which is more sensitive to change.

CT has been used to measure treatment response in both usual COPD and AATD and a summary detailing CT measure used, outcomes and the strengths and weaknesses of each study are presented in Table 1.10. Notably, in AATD the recent RAPID trial was the first RCT to demonstrate a significant improvement in lung density with alpha one augmentation therapy. Stockley et al pooled the data from the two RCTs by Dirksen et al in 1999 and 2009 (EXACTLE), and with the increase in statistical power , augmentation therapy increased the lung density as measured by 2.997 g/L in comparison to the placebo arm (95% CI, 0.669 to 3.926, p=0.006)(199).

1.8.5. Development of reference values.

Now that we know CT density correlates with pathologically measured emphysema, lung function tests and other parameters such as mortality, how to we define thresholds beyond which we say a patient has clinically important emphysema and may need observation or treatment. An isolated value is meaningless without knowledge of what defines the healthy population and has the patient's measurement moved outside this. The mission to determine a range of CT density values in the normal population has shown there to be significant heterogeneity

even in the healthy population. For example, age, gender, ethnicity, BMI and even educational attainment are all known to significantly affect a person's CT density (200, 201). Reference or ROC derived intervals limits would be helpful in interpreting the sensitivity/specificity of test results and how they relate to our patients, and there have been attempts to define this in healthy populations (202, 203).

In my opinion there is a question about which anchors should be used to help determine a clinically important change in density i.e. quality of life measures or exacerbations or mortality are likely more pertinent to the patient than FEV_1. A reference value would help signpost clinicians towards someone who has pathologically more emphysema than a healthy individual and therefore may need more observation. The only current treatment for true emphysema progression in AATD at an alveolar level is augmentation therapy, and based on the publication by Dirksen et al and Chapman et al, one would argue that regardless of the baseline, it is the change in CT density over time that denotes a patient declining and in need of intervention. Therefore whilst work is in progress by groups such as MESA and SPIROMICS to create a reference range for CT density for healthy individuals, what we do with a patient who then has an out of range value is yet to be fully decided.

Table 1.10. Summary of interventional drug trials using CT measures as an outcome measure

Author	Study Design	Pt N⁰	Duration	CT measure	Drug	Result
Usual COPD						
Shaker 2009(204)	RCT	254	2-4 years	PD15 and --910HU.	Budesonide or placebo	Annual fall in PD15 ↑in the placebo arm vs budesonide (p=0.09). Annual increase in --910HU↓in the budesonide arm (p=0.02).
Hoshino et al 2014(205)	RCT	54	16 weeks	%WA, LA, BWT	Tiotropium, Indacaterol or both.	Combination therapy resulted in a ↓in %WA and wall thickness (p<0.01).
Nordenmark 2015(206)	RCT	36	12 weeks	BWT, air trapping index and %WA	Reversible neutrophil elastase inhibitor 60mg BD	No difference
Shimizu 2015(207)	Interventional trial	23	1 week	Airway inner luminal area	Salmeterol/Fluticisone (SFC)	Ct detected the significant change in airway inner luminal area r=0.65, p<0.001

Alpha 1 Antitrypsin Deficiency						
Stolk et al 2012(208)	RCT	262	1 year	PD15	Parlovarotene	no benefit on lung density
Mao et al 2002(209)	RCT-pilot study	20	9 months	--910HU	ATRA	No benefit
Roth et al 2006(210)	RCT feasibility study	148	9 months	--910HU	Patients received ATRA either low dose (LD), high dose (HD), 13-cis retinoic acid (13-cRA) or placebo	No definitive clinical benefits
Dirksen et al 1999(211)	RCT	32	3 years	PD15	Alpha1-antitrysin	CT analysis showed a non-significant trend towards a favourable effect. CT lung density twice as sensitive as PFTs
Dirksen et al 2009(198) (EXACTLE)	RCT	77	2-2.5 years	PD15	Prolastin	CT densitometry more sensitive measure for the detection of emphysema progression than PFTs or health status indices
Chapman et al 2015(92)	RCT	180	2 years	PD15.	Alpha 1 proteinase inhibitor	Annual rate of density decline at TLC ↓in treatment group (p=0.03)

1.9. Quantifying Emphysema using Magnetic Resonance Imaging (MRI)

1.9.1. Introduction to MRI

MRI measures the behaviour of protons once a strong magnetic force is applied. The lungs have therefore been notoriously difficult to image due to the abundance of air and low proton density. However, technology has advanced so that MRI may capture changes in a much shorter time window and use inhaled gases (oxygen and hyperpolarised helium/xenon) that alter the proton behaviour in different ways, so that disease and heterogeneity in the lung may be detected. The benefits of MRI over CT and PFTs are the ability to acquire functional information with regards to ventilation, perfusion and alveolar diffusion, and any regional differences. MRI therefore could offer an attractive solution to evaluating underlying pathology and targeting treatment.

1.9.2. Validation

1.9.2.1. Clinical Validation

MRI findings from the various modalities have been correlated with lung function and CT density in numerous studies (Table 1.11), r values for FEV_1 ranging from 0.61-0.72 and 0.45-0.9 for DLCO.

Table 1.11. Studies correlating MRI with other clinical variables

MRI modality	FEV_1	Gas Transfer	CT density (LAA% -950HU)
Hyperpolarised Gas	-0.632-0.76 (155, 212-215)	-0.45-0.82(155, 213, 216, 217)	0.8-0.9 (212, 218)
O2 enhanced	-0.74(219)	DLCO:0.911(220) KCO: 0.66(219)	
Dynamic contrast	0.677*(221)		
UTE-MRI**		0.6(222)	0.72(222)

*: Dynamic contrast measured by the signal intensity perfusion defect (SIpd).

**: Ultra-short echo time-MRI

1.9.2.2. Pathological Validation

One of the pathological hallmarks of emphysema is the destruction of alveolar walls and dilatation of respiratory bronchioles (223, 224). Histologically this may be measured by the surface area to volume ratio (SA/V) and this was compared with MRI findings in five patients who had undergone bilateral lung transplant for end-stage COPD. Using He-MRI and measuring the ADC, the correlation between histology and MRI findings was very strong (r=0.96)(225). Morino et al in an animal model measured the correlation between dynamic contrast MRI and alveolar

enlargement as defined by the mean linear intercept (Lm) and this demonstrated a slightly weaker correlation though still significant (r=-0.77, p<0.001)(226).

1.9.3. Oxygen enhanced MRI

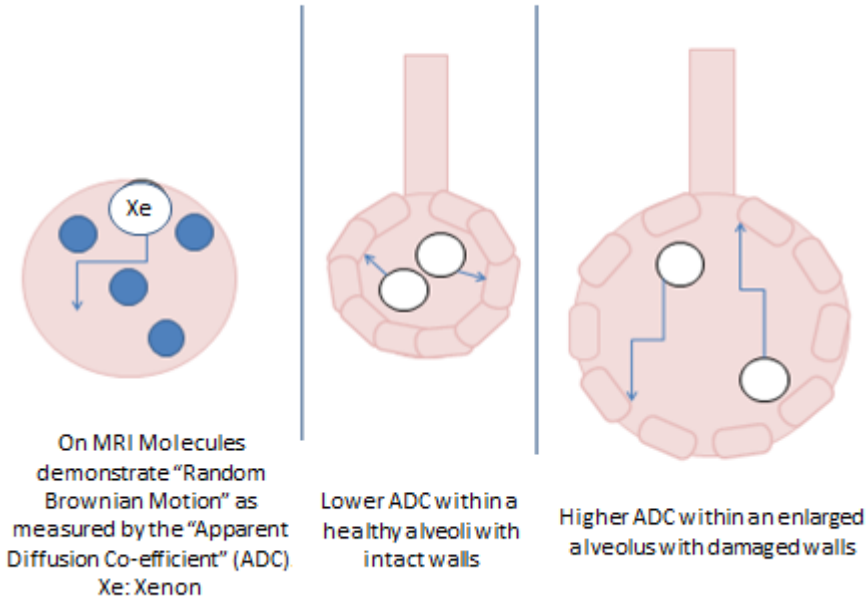
Proton MRI measures the longitudinal and transverse relaxation times (T1 and T2 respectively) after magnetic force has been applied(227). Oxygen molecules shorten the T1 relaxation time, and mapping the degree of change can depict the heterogeneity of ventilation within the lungs(228). The mean wash in time maps of oxygen created significantly correlates to FEV_1 and FEV_1/FVC ratio (-0.74 for both) demonstrating its strong relationship to current measures of ventilation (219). The degree of altered signal change as depicted by the mean relative enhancement signal has a stronger correlation with gas transfer (r=0.83) (220)and therefore as well as acting as a map of ventilation, oxygen enhanced MRI may also reflect alveolar-capillary gas transfer(219). Oxygen enhanced MRI has also been demonstrated to be able to separate emphysematous patients from asymptomatic smokers (213).

The benefits of offering oxygen enhanced MRI over other inhaled gases acting as a contrast is that it may be implemented at most centres without the need for specialist equipment, although it would still require specialist software(227). No breath holding manoeuvres are required, which is preferable in COPD patients, and the signal artefacts are relatively low, as is the overall cost. However, the scanning time is considerably longer (30mins vs 5 minutes) and the repeatability has not yet been confirmed. (229)

1.9.4. Hyperpolarised MRI

Using spin technology to hyperpolarise inhaled gases such as Xenon (129Xe) and Helium (3He) through polarised laser light, the nuclear polarisation is increased up to 10,000 times, and therefore can be detected and quantified by the MRI scanner. This is then amplified and then measured (228, 230) . The apparent diffusion coefficient (ADC) is a reflection of measured molecular movement, being enhanced in emphysema where there are larger air spaces and destroyed alveolar walls (Figure 1.16)(231). For this reason MRI using hyperpolarised gases yields information about alveolar anatomy unlike HRCT, and images produced of regional ventilation without ionising radiation and therefore no health risk to the patient of performing multiple scans. ADC correlates with lung function, and is sensitive at detecting differences between emphysematous and non-emphysematous patients(232).

Figure 1.16. Demonstration of Random Brownian Motion and Apparent Diffusion Coefficient (ADC) in emphysema

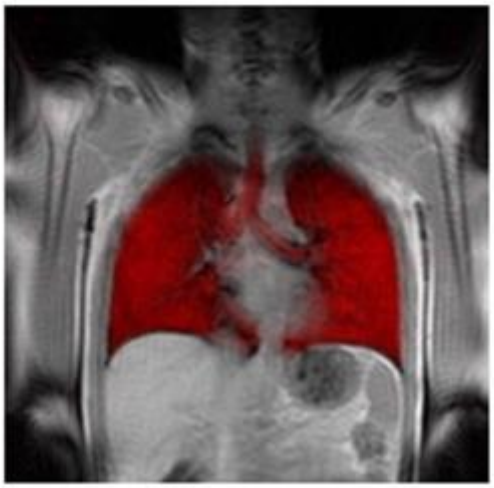


More recently a dwindling supply of helium has forced up the price, rendering it too expensive to be used for either clinical or research purposes(230). However, xenon is naturally abundant and therefore significantly cheaper; it also outperforms Helium in its ability to assess gas exchange and uptake (230, 233). Hyperpolarised 129Xe nuclei can remain dissolved in blood for around 4 seconds in venous blood (234) (235)(therefore potential use for examining the relationship between ventilation and perfusion), and in gaseous form for several hours(236, 237). The stability of hyperpolarised Xenon is therefore attractive in planning future clinical trials.

The main drawbacks of hyperpolarised Xenon and MRI are that the technique requires specialist centres with appropriately trained radiologists(227). Patients are required to breath hold for around 20 seconds, which is very challenging for patients with COPD, and at high doses Xenon has anaesthetic properties and therefore

caution following the procedure should be taken (e.g. driving and operating heavy machinery(234)). There needs to be the technology available to perform optical pumping of rubidium vapour, which in turn is used to excite nuclear spins of xenon/helium(234). However, hyperpolarised MRI has no radiation dose and gives high spatial resolution. It provides detailed regional information about gas exchange and ventilation, and its repeatability has been established (Figure 1.17). (229, 238)

Figure 1.17. MRI image of inhaled hyperpolarised xenon in a healthy subject.



1.9.5. Perfusion

Detecting early changes in the vascularity of patients at risk of developing emphysema could potentially act as another early biomarker of disease. Dynamic Contrast Enhanced MRI involves injecting contrast and measuring the amount of time taken for the contrast to pass through the pulmonary circulation, i.e. the longer the time taken, the more flow restriction there must be. Transit time of blood through the pulmonary circulation is notoriously rapid, though MRI with ultra-fast capabilities is able to capture this (239, 240). Not only is this technique feasible it also correlates to clinical parameters. Hueper et al demonstrated this is possible on a microvascular scale, and demonstrated evidence of disease in patients with COPD in areas of lung not emphysematous on CT (241).

1.9.6. Trials

Multiple studies have demonstrated that MRI correlates more strongly with PFTs than CT does (Table 1.12). However at this early stage it still remains unclear if MRI is more sensitive, as the literature is not as advanced.

Table 1.12. Summary of studies comparing MRI and CT in COPD.

Author	Year	Pt Nº	Variables	Results
Ley S (212)	2004	13	ADC and EI vs FEV_1	ADC vs FEV_1, R= 0.7 EI vs FEV_1 R= 0.5 MLD vs FEV_1 R=0.4
Ohno (219)	2008	71	O2 enhanced MRI (mean wash in time and relative enhancement ratio), CT defined lung volumes vs lung function	Mean wash in time vs FEV_1 r=-0.74 Relative Enhancement Ratio vs KCO r=0.66 CT lung volume vs FEV_1 r=0.61 CT lung volume vs KCO r=0.56
Van Beek (216)	2009	94	ADC and MLD vs FEV_1/FVC and DLCO	ADC vs FEV_1/FVC r=0.5 MLD vs FEV_1/FVC r= 0.52 ADC vs DLCO r=0.59 MLD vs DLCO r=0.29

Diaz S (155)	2009	27	ADC and EI vs FEV_1 and DLCO	ADC vs FEV_1 r=0.67 EI vs FEV_1 r=0.55 ADC vs DLCO r=-0.82 PD15 vs DLCO r=0.6
Quirk (242)	2011	30	Hyperpolarised He vs CT density in at risk smokers	Lung morphometry vs %LAA 950: Significant difference seen in those still smoke, not on CT
Xia (221)	2014	55	Positive rate of Perfusion defects vs CT changes	Early COPD: MRI detected 8/8, vs CT 3/8 P=0.003 Moderate COPD: MRI detected 9/9, vs CT 7/9 P=0.47
Hueper (241)	2015	144	DCE-MRI vs CT density	PMBF vs %LAA 950: Evidence of non-linearity, p=0.015

1.9.7. Phenotyping with MRI

1.9.7.1 Airways Disease

MRI is already used to visualise airway changes in more detail in Cystic Fibrosis including inflammation, mucus plugging and bronchiectasis (243). In this capacity, MRI is superior over CT with its ability to more accurately differentiate soft tissue such as remodelling/inflammation (227, 244). The increased airway resistance seen in small airways disease in asthma has also been evaluated by MRI. Where bronchoconstriction has resolved clinically MRI assessment of ventilation demonstrated focal, fixed obstructive defects that may be reversible with targeted therapies e.g. bronchothermoplasty (215). The ability of MRI to accurately measure the resultant degree of hyperinflation and air trapping has obvious potential clinical applications in COPD namely endobronchial valves and LVRS.

1.9.7.2. Emphysema

The ADC measured in MRI is a reflection of the amount of measured molecular movement, with more movement in emphysema where there are larger air sacs and destroyed alveolar walls(231). Therefore a high ADC indicates more severe emphysema and could be used either diagnostically or for assessment longitudinally. As there is increased interest in using CT density as a direct measure of parenchymal response to augmentation therapy in AATD, ADC would be another potential option of measuring alveolar changes.

Vascular remodelling secondary to hypoxic vasoconstriction is likely part of a more systemic process associated with COPD. Perfusion studies such as dynamic contrast enhanced MRI may therefore act as another useful imaging biomarker to detect and prevent further disease(245). For example where there is a perfusion defect with preserved ventilation, then this maybe a target for bronchodilators. Similarly where there is preserved perfusion, up to 20% have emphysematous regions which therefore may act as a map for targeted interventional therapies such as BVRS (246). Jobst et al showed a moderate relationship between oxygen enhanced MRI and contrast enhanced MRI (r value =0.52, $p<0.05$) therefore there is a link but one is not a surrogate for the other(247). A summary of how MRI can help phenotype COPD is given in Table 1.13.

Table 1.13. MRI modalities to phenotype and treat COPD.

Phenotype	MRI modality	Findings	Suggested treatments
Airways disease	Hyperpolarised MRI	Detailed anatomical information of airway inflammation, oedema and mucus plugging (227, 244)	Nebulised antibiotics Chest clearance techniques (243)
		Regional information re. lung volumes e.g. focal bronchoconstriction	Bronchothermoplasty (248) BVRS
Emphysema	Hyperpolarised MRI	Global high ADC(231) Low PaO2(213)	Early disease detection Future alpha one augmentation therapy*
	Oxygen enhanced MRI	↑↓Relative enhancement signal(219, 220)	Targets for resection. Early emphysema detection
	Dynamic contrast MRI	Global microvascular reduction blood flow(241)	Lifestyle moderation
		Focal defects, small pulmonary emboli	Anticoagulation
		Increased pulmonary pressure	Treat as pulmonary hypertension

Potential treatments based on the phenotypes identified by the technique, but that have not yet been tested are noted by * in the table. BVRS=bronchoscopic volume reduction surgery; ADC=apparent diffusion coefficient

1.10. Minimal Clinical Importance Difference (MCID)

1.10.1. MCID and COPD.

First described by Jaeschke et al, the Minimal Clinically Important Difference (MCID) is defined as the minimal amount of change to take place that is relevant to the patient (249, 250). Multiple validated MCIDs exist within COPD including health status (SGRQ 4 points), exercise capacity (47.5 m for incremental shuttle walk) (100ml at trough), dyspnoea (2 units Borg scale or 5-7 units on the UCSD questionnaire), and FEV_1 (100-140ml) (251-253). MCID are traditionally calculated one of two ways: the anchor method and the distribution method, though within this broad grouping, there is still upwards of 9 different methods used, and no consensus on the optimal technique (250, 254, 255).

1.10.2. Distribution Method

Distribution-based methods use the spread of the data to calculate the standard error of measurement, beyond which a significant change has occurred(250). The advantages of this technique are that they do remove some of the random variation. However, the disadvantage is that this is a statistically derived estimate and further removed from benefits observed by patients. Furthermore, there is a lack of consensus over the optimum tool, and there is a degree of lack of understanding in the literature between the minimal clinically important difference and the minimal detectable difference(250).

1.10.3. Anchor Method

Anchor-based methods examine the relationship between scores on the assessment instrument and other measures of impaired health (the anchors).i.e. using the already known MCID for FEV_1 of 100ml (251, 256, 257). Criticisms of this method surround using anchors that in themselves are effectively estimations, and that the lack of precision in the calculation means using the proposed MCID reduces its sensitivity and specificity (false negatives and positives respectively)(250).

The recommendations are to use a combination of approaches, narrowing down to a single figure or range, based on a triangulation process(257). Where triangulation cannot be performed then statisticians recommend using a modified Delphi method to order to achieve a consensus value. This vague approach to proposing an MCID produces a value that is in essence an estimate(251), and patients may describe feeling benefit without achieving the MCID. In summary, an MCID that uses patient reported outcomes as one of its anchors, plus multiple methods using the distribution technique should be used to give as narrow range of MCID as possible.

1.10.4. FEV1

Patients do not report an improvement in their FEV_1, rather their response to treatment will be judged by them by a reduction in breathless, exacerbations and mortality. However, these measurements remain relatively subjective, and therefore FEV_1 has continued to remain an endpoint in clinical trials due to its

reproducibility(251). The MCID needs to be beyond the noise of the instrument, and the repeatability of FEV1 testing itself can vary up to 150ml, requiring at least 3 measures are required to account for this variability (253, 258, 259). An American study of nearly 6000 patients with repeated spirometry 17 days apart demonstrated a difference in FEV1 of 110-123ml, and a larger 2004 study of 18,000 patients showed a variability of 120ml (260, 261).

The regularly cited review by Donohue recommends a proposed MCID for FEV1 of 100ml which has been used in subsequent trials (258, 262, 263). Using other methods of proposing an MCID including the anchor method and that of patient-opinion, other MCIDs proposed are 110ml and 122ml respectively(264) (265). However the ATS/ERS taskforce suggest a range of 100-140ml may be more appropriate but further work continues to needed (253). Of course the baseline FEV_1 measurement affects the decline over time, i.e. patients with the least and most severe COPD decline the least rapidly. Therefore FEV_1 change is relative to the baseline, not accounted for in the MCID(266). Finally, FEV_1 only correlates moderately with its anchors, re-affirming that multiple approaches should be used when calculating an MCID(251).

1.10.5. SGRQ

As the SGRQ is a validated tool to assess quality of life in COPD, it is more often used in COPD trials. Again, using a process of triangulation, the MCID for SGRQ is proposed at a decline by 4 units(267). Newer inhaled medications have been shown

to reach this MCID e.g. aclidinium (268) and indacterol(269, 270) as opposed to ipratropium (251, 271). However, as the SGRQ is a self-reporting technique, it is possible that patients will perceive benefit even when on placebo, and are more likely to be compliant with their medications than usual due to being observed (Hawthorn effect) (272).

Chapter 2 . Aims and Hypotheses

The studies presented in this thesis investigated the utility of CT density as an outcome measure in Chronic Obstructive Pulmonary Disease (COPD) and Alpha One Anti-Trypsin Deficiency (AATD). The aims and hypotheses are as follows.

Chapter 3 : The aim of the systematic review was to assess the validity of CT densitometry as an outcome measure of severity and progression of lung disease in emphysema specifically seeking relationship to lung function, mortality, hospital admissions and quality of life (QOL). The null hypothesis was there would be no significant relationship between CT density and other clinical parameters.

Chapter 4 : To aim was to assess the variability of CT measurements performed on the same CT scans by the same observer (intra-observer variability) and between observers (inter-observer variability) and between the two leading software programs. The null hypothesis was that measurements of the same scan performed by different observers or using different software programs would be incomparable.

Chapter 5 : The aim of this cross-sectional and longitudinal analysis was to assess the relationship between CT density and common clinical parameters including mortality using the Birmingham Alpha One Antitrypsin Deficiency cohort. The null hypothesis was CT density is not associated with other clinical parameters including mortality.

Chapter 6 : The aim of this study was to propose and validate an MCID for CT density annual decline. The null hypothesis was that a proposed MCID wouldn't be able to identify patients with worse lung function and nor those less likely to survive.

Chapter 3 . Methods

3.1. Systematic Review

This systematic review has been conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

3.1.1. Studies Included

This review is registered with Prospero (CRD42015024183). All papers concerning patients with clinically or spirometrically defined COPD or AATD which compared CT densitometry data with FEV_1, gas transfer (DLCO or KCO), quality of life (QOL), in the same study population were included. In addition any study in AATD or COPD patients which described longitudinal density change, irrespective of whether a direct relationship to one of our pre-specified outcomes was included.

3.1.2. Population

The following databases were searched with no date or language restrictions, confined to adults and human studies: MEDLINE (Ovid), MEDLINE In Process (Ovid), EMBASE (Ovid), Cochrane Library (Wiley) Cochrane Central Register of Controlled Trials (CENTRAL), CDSR, HTA, NHS EED and DARE. In addition Conference Proceedings Citation Index (CPCI) via Web of Science and British Library's ZETOC were searched for conference proceedings and abstracts and Clinical Trials.gov and WHO ICTRP (International Clinical Trials Registry Platform)

searched for ongoing trials. Search terms for COPD and AATD were combined with all search terms for CT or CT densitometry, and lung function (see Table 3.1)

Table 3.1. Search terms

Row Number	Search Terms	Row Number	Search Terms
1	(Alpha adj2 anti adj2 deficien$).tw.	31	deficien$.mp. or lack$.ti,ab. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2	A1AT.mp.	32	Smoking-related lung disease*$.mp.
3	A1AT.ti,ab.	33	Emphysema.mp. or emphysema/
4	A1ATD.tw.	34	Computed Tomography.mp.
5	AAT.mp.	35	Computerised axial tomography.mp.
6	AAT.ti,ab.	36	Computerised axial tomography.mp.
7	AATD.mp.	37	computer assisted tomography/
8	AATD.ti,ab.	38	ct.mp.
9	alfa 1 antitrypsin.ti,ab.	39	Tomography, X-Ray Computed.mp.
10	alpha 1 antitrypsin.ti,ab.	40	X-Ray computed.mp.
11	Alpha 1-Antitrypsin.mp.	41	Lung density.mp.
12	Alpha 1-Antitrypsin Deficiency.mp.	42	Densitomet*.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]	43	Lung attenuation.mp.
14	alpha one antitrypsin.ti,ab.	44	Lung densitometry.mp.
15	alpha one-antitrypsin.ti,ab.	45	Lung function test/ or lung function/ or spirometry/ or forced expiratory volume/ or FEV1.mp.
16	alpha1 antitrypsin.ti,ab.	46	Pulmonary function.mp.
17	alpha-1 antitrypsin.ti,ab.	47	Lung Volume Measurements.mp.
18	alpha1-antitrypsin.mp. or alpha 1 antitrypsin/	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
19	alpha1-antitrypsin deficiency.mp.	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
20	alpha-1-antitrypsin.ti,ab.	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
21	alpha-1-at.ti,ab.	51	Lung function terms: 45 or 46 or 47
22	exp alpha 1 antitrypsin deficiency/	52	alpha one AND CT: 48 and 50
23	exp Bronchitis/	53	alpha one AND CT and lung function: 48 and 50 and 51

24	exp Pulmonary Disease, Chronic Obstructive/	54	COPD AND CT: 49 and 50
25	chronic obstructive airway* disease.mp.	55	COPD AND CT AND lung function: 49 and 50 and 51
26	Chronic bronchitis.mp. or chronic bronchitis/	56	Sum of all COPD terms and CT/densitometry terms: 48 or 49
27	chronic obstructive pulmonary disease.mp.	57	COPD OR alpha one AND CT: 50 and 56
28	chronic respiratory disorder.mp.	58	COPD OR alpha one AND CT AND lung function: 51 and 57
29	COPD.mp.	59	Sum of 52 or 53 or 54 or 55 or 57 or 58
30	chronic obstructive lung disease/	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>)

3.1.3. Study Selection

Titles and abstracts of search yield were screened for relevance by two reviewers (DC and AT) independently and disagreements resolved by discussion, where required involving a third reviewer. Relevant articles were obtained and assessed against the full selection criteria in a similar manner. Studies which used visual scoring only were excluded, as were those that were measured in expiration only.

3.1.4. Inclusion and Exclusion Criteria

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.

3.1.5. Data Extraction

Data was extracted using the Cochrane model (273), and included general study information, specifics of CT acquisition (i.e. reconstruction algorithm, software and slice thickness), percentage Low Attenuation Area (%LAA), whether the scan was taken in full inspiration, use of bronchodilator during spirometry and a CT phantom for quality assurance. This process was performed by one reviewer (DC), and checked by another (AMT, EL, MT, MK).

3.1.6. Risk of bias

3.1.6.1. General Bias Assessment

Table 3.2 summarises the recommended risk of bias tool for each type of clinical study following a systematic review of methodological quality assessment tools by Zeng et al 2014(274). The majority of the studies we assessed were cross sectional with no intervention and therefore the risk of bias tool of choice was the Agency for Healthcare Research and Quality (AHRQ) tool. This consists of 11 items which examines the study population and the comparability of patients. The fairness of the outcome measure and appropriate statistical tests applied are assessed and whether there are any possible biases within the discussion. As CT density as an imaging biomarker is being compared with other disease measures such as lung function, including elements of the QUADAS 2 score allowed for assessment between the two tests to be performed i.e. asking questions about the index test plus the flow and timing. I created a specifically designed tool therefore to incorporate the strengths of

the AHRQ and QUADAS2 (see Table 3.3). Risk of bias was assessed by one reviewer (DC) and independently by another (AT, MR, EL, MK).

Table 3.2. Choice of risk of bias tool depending on the type of study

Study Type	Risk of Bias Tool	Reference
Randomised Control Trial	Cochranes Collaboration Tool	Higgins et al, 2011 (275)
Cohort and case control studies	Newcastle-Ottawa Scale	Stang et al, 2010 (276)
Non-randomised interventional studies	The Methodological Index for Non-Randomised Studies (MINORS)	Slim, K et al, 2003 (277)
Cross-sectional	Agency for Healthcare Research and Quality (AHRQ)	Viswanathan, M et al, 2008. (278)
Diagnostic accuracy tests	QUADAS-2	Whiting et al, 2011 (279)
Systematic reviews/meta-analysis	Assessment of Multiple Systematic Reviews (AMSTAR)	Shea, B.J. et al, 2007 (280)
Clinical practice guidelines	Appraisal of Guidelines, Research and Evaluation (AGREE)	Brouwers et al, 2010 (281)

Table 3.3. 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.

3.1.6.2. Publication Bias

Publication bias was assessed visually through funnel plots and the Egger test of significance applied. The Egger test was chosen to assess publication bias due to its high power and suitability for continuous/dichotomous outcomes. It is the most frequently used test though is limited by its type one error rate which can increase with the degree of heterogeneity (282).

3.1.7. Data Synthesis

Baseline characteristics are presented as mean (standard deviation), or median (interquartile range). Studies where density was taken from a single slice, where authors divided the patients into arbitrary thresholds or which only used Mean Lung Density (MLD) against clinical parameters were not included in meta-analysis as data reliability, quality or heterogeneity precluded this (283). Where meta-analysis of the relationship between CT density and one of our chosen outcomes was appropriate StatsDirect was used to estimate the Schmidt Hunter for Pearson's correlation coefficient alone, due to its high accuracy in heterogeneous populations (284). I^2 and Chi square analyses were performed to assess study heterogeneity. A narrative synthesis was conducted for all studies where meta-analysis was not possible.

3.2. CT Density Validation

3.2.1. Reader variability

3.2.1.1. Intra-observer variability

CT density analysis was performed twice, on two separate occasions three months apart by DC for 9 patients with varying severity of COPD as defined by the FEV_1. Volume, Mean Lung Density (MLD), and emphysema as defined by --910HU, --950HU and PD15 were measured each time and the correlation coefficient between the two sets of measurements calculated.

3.2.1.2. Inter-observer variability

A further 9 different scans, with a mixed severity of COPD were analysed by DC and then independently re-analysed by one of my supervisors (Dr Subramanian) in order to determine the level of inter-observer agreement using a correlation coefficient.

Previously analysed scans performed between 2002 and 2004 as part of a previous fellow's thesis work (DP) were accessed and reanalysed. These scans were performed following the SPREAD trial (Software Performance and Reproducibility in Emphysema Assessment: Demonstration), where the CT slice thickness and increment were found to be inaccurate, and therefore repeated on 'Parr Protocol' on subsequent scans. The 'Parr protocol' was used through the remainder of this thesis i.e. B30f reconstruction algorithm, slice thickness 5mm and increment 2.5mm. These subsequent analyses by DP and those repeated by myself were compared. Between

the 2002/2004 scans and those performed by myself, there has been an update in the PULMO software program, which may introduce an element of variability.

3.2.2. Comparison and Evaluation of CT density analysis between the two leading software programs

18 patients with AATD and emphysema underwent CT scanning between May 2014 and February 2016 at the Queen Elizabeth Hospital Birmingham, recruited to the Birmingham AATD registry (processes for assessment being described in detail elsewhere and participating in the ongoing NIHR Rare Diseases Consortium). (285, 286) Informed consent was given and the parent studies approved by the local ethics committee. All scans were performed on a Siemens scanner during deep inspiration, using a smooth reconstruction filter (B30f) and both 1mm and 5mm slices. Images were analysed using PULMO CMS (developed at the Leiden University Medical Centre) in the UK and then the images sent by DICOM format to National Jewish Health for analysis by Pulmonary Workstation by a researcher blinded to the UK results.

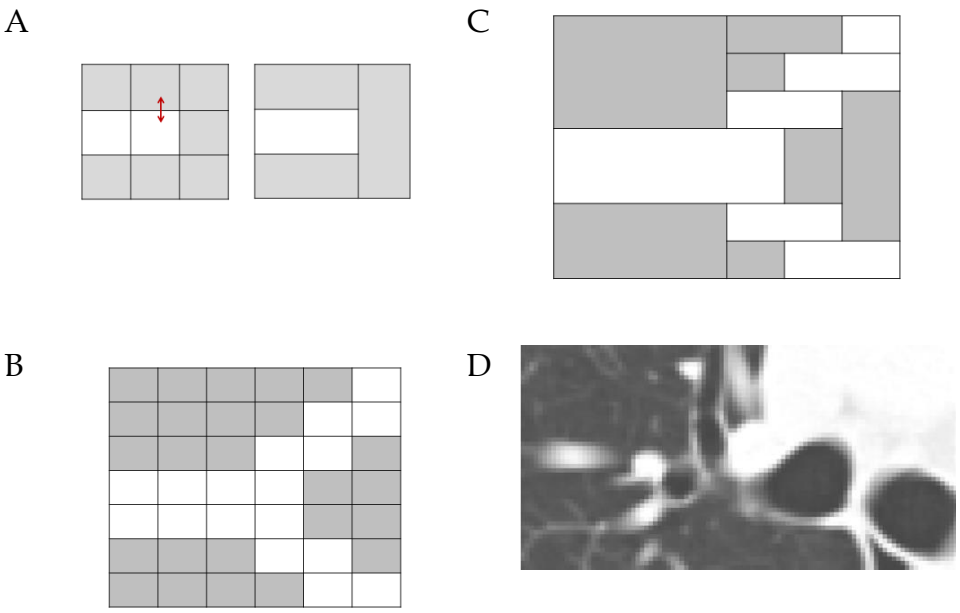
Linear regression was performed on volume and emphysema thresholds -910HU, -950HU and PD15 from both programs and the correlation coefficient calculated. Bland Altman plots were used to assess agreement. The level of significance was set at $p<0.05$ and all analyses were performed using IBM SPSS (version 22).

3.3. CT Density and the Birmingham AATD Registry

3.3.1 Introduction

The first thoracic CT scan analysed for densitometry within the Birmingham AATD registry was in 1994, and since then over 1100 CT scans have been performed and analysed. The nature of CT density analysis has evolved greatly over time, with modern techniques nearly fully automated and use sophisticated algorithms to delineate lung tissue from air (so called the region growing technique). PULMO (and Pulmonary Workstation, the second most frequently used software program) both use this technique as demonstrated in Figure 3.1. Between two adjacent voxels, the software program applies an algorithm to decide whether or not they are of the same density or different. If they are the same, the voxels will be connected to create a structure now 2 voxels wide. The software runs this program on all adjacent voxels until eventually an image is created that we recognise.

Figure 3.1. Region growing technique



A) The algorithm selects two adjacent voxels to determine if they are of the same density or not. B) Those voxels that are of the same density are combined to begin to create an image. C) This process continues until D) where an image recognisable as anatomical is created.

The slice thickness used by the Birmingham AATD registry changed from 6.5mm to 5mm in 2002, and for reasons detailed in the introduction, cannot be merged for meta-analysis. All scans performed from 2002 onwards were analysed using PULMO but prior to this, 'density mask analysis' was performed but without any further specifics given. Therefore all those scans performed before 2002 could not be included. 6 large databases existed with duplicate records and different formatting, which required extensive data 'cleaning' to finish with the most current version. 203 patients have had at least one CT scan, with 432 scans in total that have been analysed using the correct CT acquisition parameters. These were all performed during one of the below studies using B30f (soft) reconstruction algorithm, slice

thickness 5mm and increment 2.5mm on PULMO CMS. REPAIR and EXACTLE were RCT's with placebo and treatment arms; only those patients in the placebo arms were analysed.

- ADAPT (Antitrypsin Deficiency Assessment and Programme for Treatment)
- REPAIR (Retinoids in Emphysema Patients in the α1-Antitrypsin International Registry)
- EXACTLE (The Exacerbations and Computed Tomography scan as Lung End Points)
- NIHR (National Institute of Health Research) Rare Diseases Consortium.

3.3.2. CT density Analysis

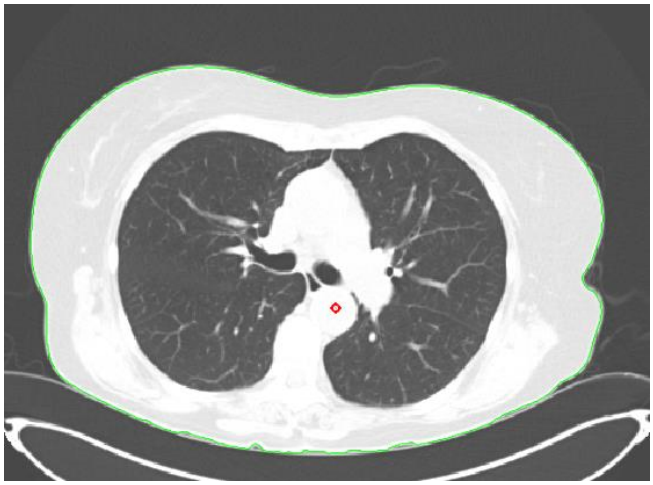
In order for PULMO to analyse the CT scans they must firstly be converted into DICOM (Digital Imaging and Communications in Medicine) format. The density of blood in the aorta can be calculated either manually or automatically. Two separate points are marked, at the proximal part of the aorta before the arch, and nearer to the diaphragm (see Figure 3.2a). The software program calibrates the density of the blood in subsequent slices until the standard error no longer changes. The same is repeated for air, though a manual scan through the slices is recommended to check any of the patient's clothes haven't been included in analysis for example (see Figure 3.2b). The seed point, and the starting point of analysis, is automatically detected by PULMO within the trachea and preliminary analysis will highlight the lung contours, i.e. boundaries within which it predicts the lungs lie and may be adjusted. If the seed point fails to be correctly detected by the software program, it will

subsequently fail to detect the lung contours. Common pitfalls during this stage of the segmentation include bowel or tracheal air being included and required manual deletion before density analysis is performed. The software program finally generates a histogram of voxel density, including the values for a given LAA% and percentile point (see Figure 3.2c, Figure 3.2d).

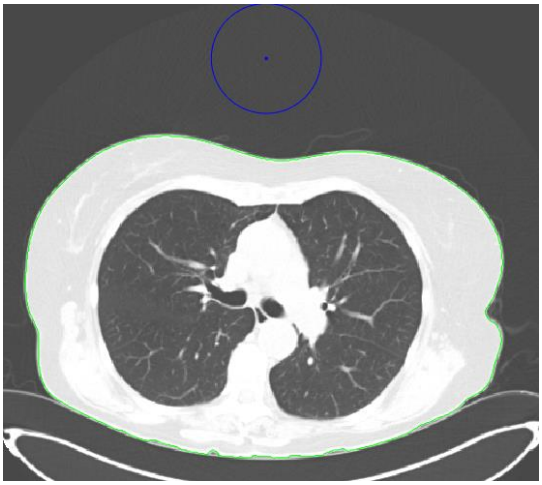
It is noteworthy the impact an incorrect reconstruction algorithm has on the density analysis of air. Figure 3.3a demonstrates the grainy quality of the appearance of air when a reconstruction algorithm of B50f was used instead of B30f. Figure 3.3b demonstrates the dramatic impact this then has on the density histogram with a left sided skew, and the results left uninterpretable.

Figure 3.2. Demonstration of CT density analysis using PULMO CMS.

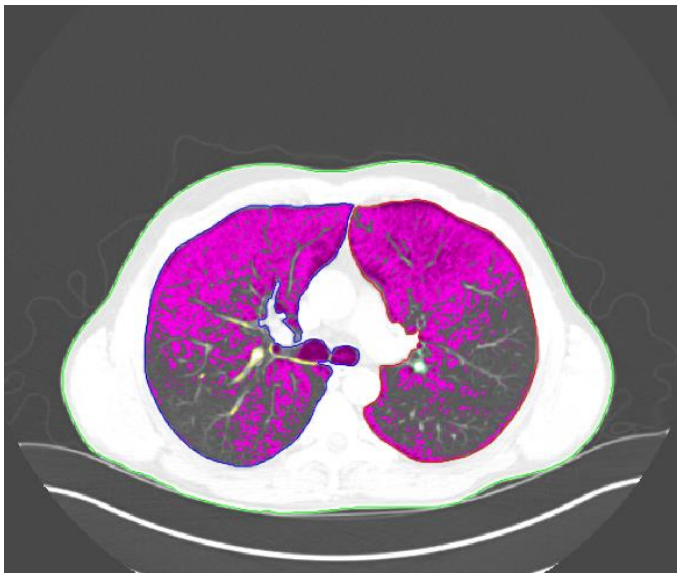
A



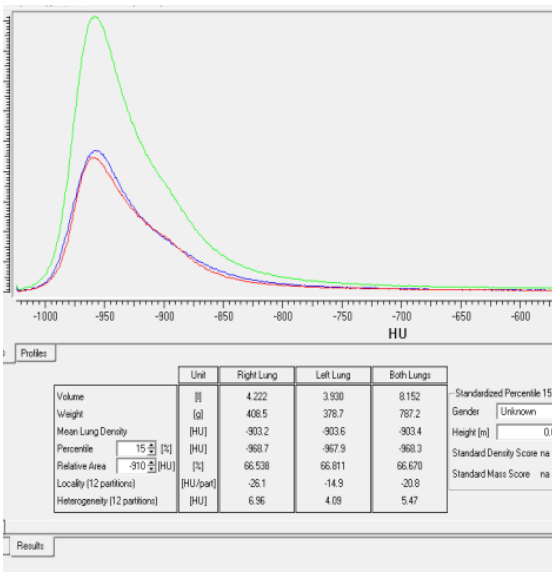
B



C

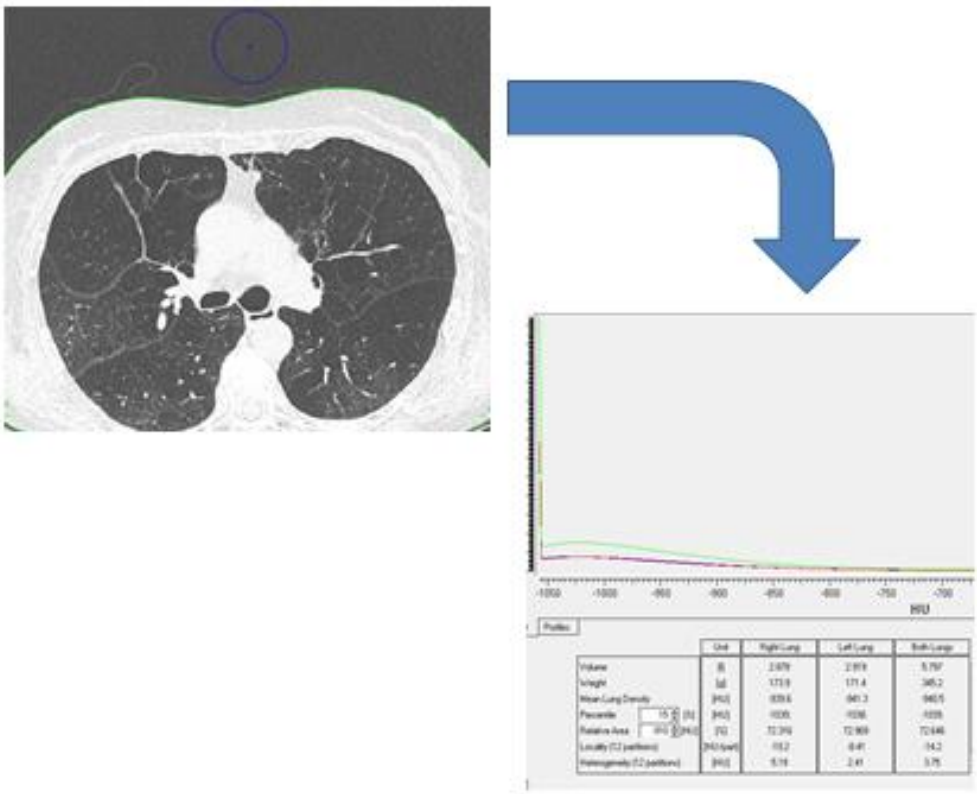


D



Firstly, blood in the aorta is detected B) secondly the density of air is determined. C) The software will detect all voxels within a specificied range D) These voxels are then plotted on a denisty histogram.

Figure 3.3. The effect of a sharper reconstruction algorithm on the CT density histogram.



A sharper reconstruction algorithm e.g. B50f causes the histogram to have a severe left sided skew and the results un-analysable.

3.3.3. Clinical Investigations

3.3.3.1. St George's Respiratory Questionnaire (SGRQ)

SGRQ is a validated 16 part questionnaire designed to measure quality of life in patients with COPD and asthma. Divided into two parts, part one (questions 1-8) are designed to assess respiratory symptoms and part two (sections 9-16) designed to assess the patient's activity and the impact this has on their day to day life. Ideally this should be completed by the patient in a quiet and undisturbed environment

with no input from friends and family. The answers are uniquely weighted and total score is out of one hundred, representing the maximum disability a patient may experience(287).

3.3.3.2. Lung Function

Spirometry measurements are performed in accordance with the British Thoracic Society (BTS) and the Association for Respiratory Technology and Physiology (ARTP) UK guidelines. FEV_1 and FVC are determined using a wedge-bellows spirometer following a 12 hour period without taking their usual long acting medication, and after 5mg nebulised salbutamol. Lung volumes are calculated by constant volume body plethysmography and gas transfers measured by the single breathe carbon monoxide technique (288). Subjects are trained to hold their breath for 10 seconds following deep inhalation, followed by full expiration. KCO (diffusing capacity of the lungs for carbon monoxide divided by the alveolar volume) was additionally calculated.

3.3.4. Statistical Analyses

3.3.4.1. Cross Sectional analysis

3.3.4.1.1. Univariate analysis

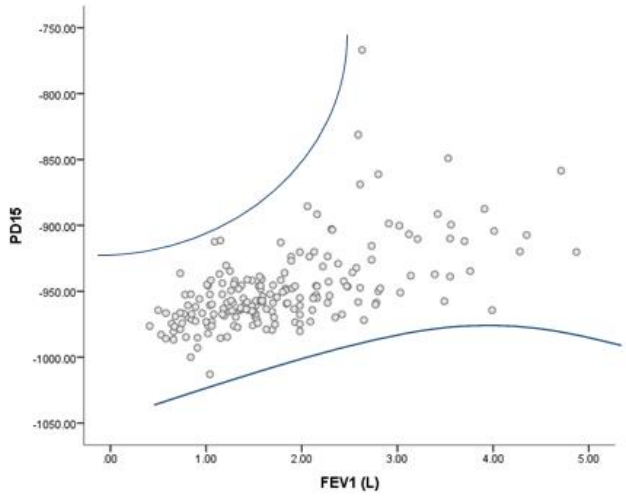
Baseline characteristics of the Birmingham AATD registry are presented as mean and standard deviation (SD) if normally distributed, or median and interquartile range (IQR) if non-normally distributed. The cohort was then subdivided into those

who have survived and those who have not, and test of significance performed by either an independent samples T test or Mann-Whitney U (MWU) test.

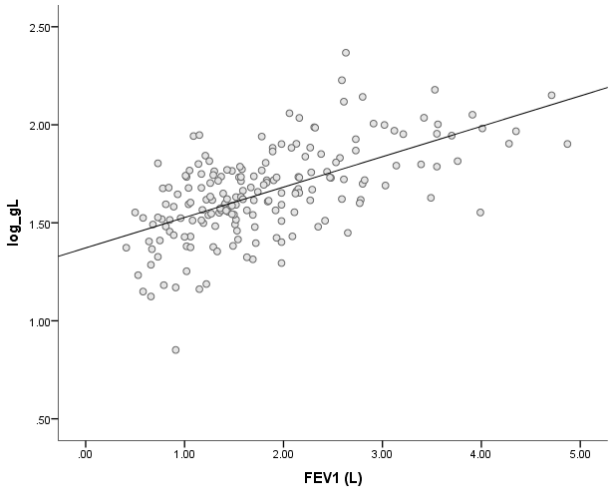
The Pearson's or Spearman rank correlation coefficient between CT density and PFTs was calculated, and analysis of variance (ANOVA) between CT density and GOLD stage groups. The strength of the correlation between FEV_1 and PD15 weakens with reduced severity of emphysema, and the scatter plot shows there is not a clear linear relationship between the two variables. PD15 may be expressed as g/L by the addition of 1000 to the PD15 in HU e.g. PD15 value of -900HU would equal 100 g/L (130). By then calculating the natural logarithm, the relationship with FEV1 (L) becomes linear and meets the assumptions of linear regression (see figure 3.4).

Figure 3.4. Logarithmic transformation of PD15

Before Logarithmic transformation



Following logarithmic transformation



In the Birmingham AATD registry lung volumes were largely non-normally distributed with the exception of Total Lung Capacity (TLC) percent predicted, and the Residual Volume (RV)/TLC ratio. Gas Transfer as measured by DLCO and KCO, both raw values and the percent predicted of each was correlated with CT density.

SGRQ is normally distributed and therefore Pearson's correlation coefficient applied where the dependant variable was normally distributed and Spearman rank correlation coefficient where the dependant variable non-normally distributed.

3.3.4.1.2. Multivariate analysis

Forward selection stepwise regression was performed between PD15 and SGRQ, KCO and FEV1 (L). The unstandardized beta coefficients with 95% confidence intervals are reported plus the level of significance. The r^2 value is reported between SGRQ and PD15 to demonstrate the amount of variability seen in CT density can be attributed to the SGRQ.

3.3.4.2. Longitudinal Analysis

3.3.4.2.1. Exacerbations and mortality

The annual exacerbation rate was drawn from the patient's electronic notes, and subdivided into those who frequently exacerbate (2 or more exacerbations per year) or not. Linear regression was subsequently performed between exacerbation rate and CT density to determine the effect of one variable on the other.

In order to determine an accurate date of death, patient's records were also accessed and the time to final analysis calculated. 193 patients in whom the CT density for each emphysema threshold and survival status was known was subdivided into four quartiles (see table 3.4). Kaplan Meier curves were created to demonstrate the mortality for each quartile, and tested statistically using the log-rank test.

Table 3.4. Quartiles used in the Kaplan Meier curves for each density measure

Quartile	**-910HU**	**-950HU**	**PD15**
Q1	<31%	<9.5%	>-939HU
Q2	31-45%	9.5-19%	-939HU to -956HU
Q3	46-55%	19.1-27.5%	-957HU to -966HU
Q4	>55%	>27.5%	<-967HU

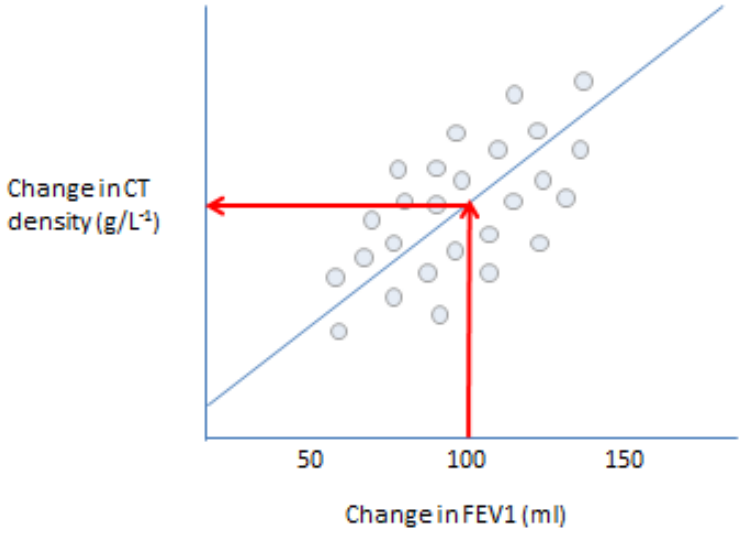
Cox regression analysis was subsequently performed in order to adjust survival for covariates: age, height, sex, pack years, FEV1 and KCO percent predicted. Multi-collinearity was assessed by linear regression and the variation inflation factors (VIFs). Each density quartile was converted into a categorical variable and separate plots created for each. Survival function and 95% confidence intervals were further calculated.

3.4. Proposal of MCID for Density Decline

3.4.1. Introduction

There are two recognised methods of proposing an MCID, the distribution and the anchor method. Both have their benefits and criticisms, and there is no clear consensus on which method is superior (see section 1.11.2 and 1.11.3). The anchor method uses an established MCID from a clinical parameter within the same field and plots the change of the known 'anchor' against the change in the parameter that is under review. In the case of proposing an MCID for CT change in density, the MCID of FEV_1 (100mls) is plotted against the annual change in CT density (see Figure 3.5).

Figure 3.5. Demonstration of the anchor method to propose an MCID



The distribution method, of which there are upwards of 6 different variations suggested, measures the standard deviation at baseline in order to determine a

threshold beyond which cannot be attributed to the noise of the instrument. For this reason, the distribution method may also be regarded as the Minimal Detectable Difference (MDD).

Statistical assistance and advice was provided by PN, a statistician employed within my hospital trust. The concept of proposing and validating a MCID was new to PN and therefore I needed to present the data and propose myself how I felt such analyses should be performed. A typical consult with the statistician would last around 30 minutes whilst we discussed potential techniques, and I would then proceed to perform the analysis and the outputs of the more difficult tests were cross checked by PN.

An MCID for CT density will bring clarity to an imaging modality and investigative tool that many perceive as potentially useful but uncertain how to interpret the result. We aim to propose and validate a MCID for CT density decline in patients with AATD using both recognised methods. This value could then be used to judge response to AAT, or to identify those declining rapidly in need of intervention.

3.4.2. Distribution Method

Studies that reported the mean and standard deviation of CT density (as measured by the 15th Percentile Point-PD15 g/L^{-1}) at baseline and annual change were sought. Table 3.5 summarises each method; the Reliable Change Index (RCI) and the Standard Error of Measurement (SEM) both require a test-retest correlation coefficient expressed as r. Using a random sample and two independent analysers, the calculated r value is 0.99 (see chapter 5). Given the sensitivity of CT density to

detect small changes, the MCID was calculated for small effects only. 95% confidence intervals for the true sample variance were further calculated for each individual method.

Table 3.5. Summary of proposed distribution methods to calculate the MCID

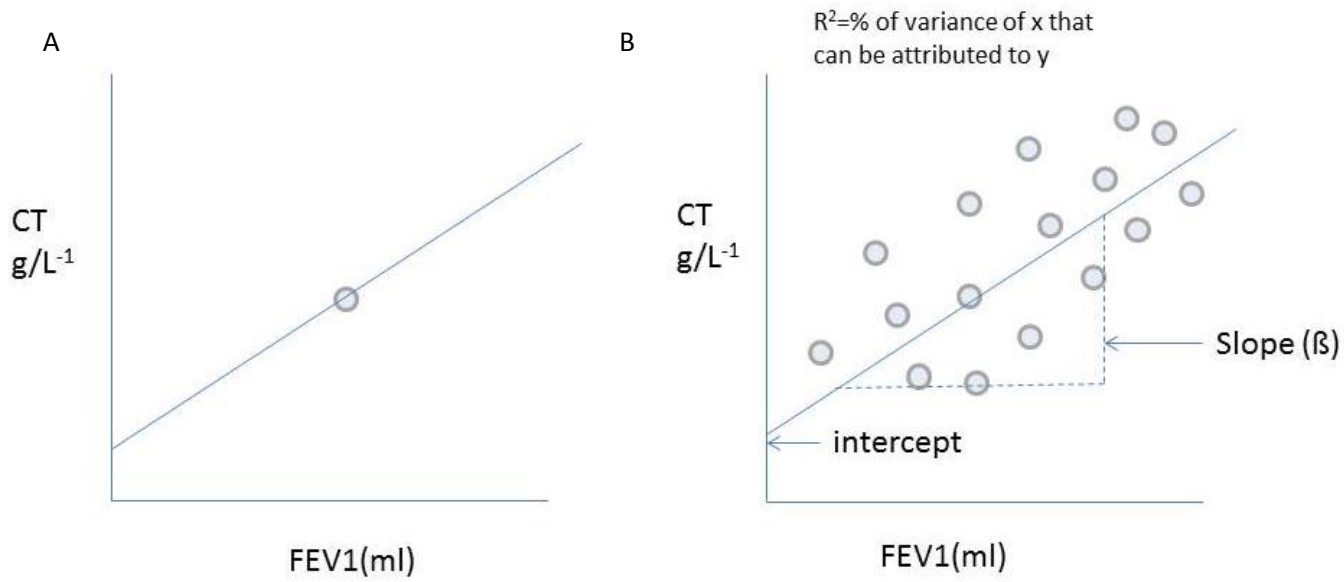
Distribution Method	Equation	Adjustments
Standard Error of Measurement (SEM).	MCID=X*SD $_{baseline}$[square root (1-r)]	X=1 for small effect 1.96 for moderate 2.77 for large
Reliable Change Index	MCID=X*SD $_{baseline}$ (154)	X=1 for small effect 1.96 for moderate 2.77 for large
Effect Size	MCID=X*SD baseline	small effect=0.2 moderate effect=0.5 large effect=0.8

3.4.3. Anchor Method

3.4.3.1. Placebo arms of AAT RCTs

The literature was searched for any papers that reported annual CT density change with the relative change in FEV_1 as measured in millilitres without exposure to an intervention i.e. the placebo arms. FEV_1 presented as a percent predicted only could not be used as the FEV_1 anchor is 100mls, with no alternative for percent predicted. We sought any papers that detailed the relationship between the two variables for all patients including the spread of data so that the sample variance may be deduced (see figure 3.6). After establishing the slope of the regression line, by taking known values of x and y at a certain time point (e.g. FEV_1 and CT change at one year), the regression equation can be built to establish the intercept. With a new estimated intercept and slope value, the MCID for CT density (y) can be calculated by knowing x (MCID for FEV_1, which equals 100mls). Using the sample variance, 95% confidence intervals could then be additionally calculated.

Figure 3.6. Demonstration of how scatter plots published in the literature differ, and what information was required to be able to establish a MCID



A) Most commonly a summary statistic is given i.e. overall FEV_1 and CT density at one year. B) Information regarding the variance of the data using each patient's measured values.

3.4.3.2. Birmingham AATD registry

423 scans have been performed on over 220 patients recruited into studies such as EXACTLE "Exacerbations and Computed Tomography scan as Lung End-points" and the ongoing NIHR (National Institute for Health Research) rare diseases consortium. These only include patients who had a CT scan as part of an observational study, or were in the placebo arm of an RCT. The CT scans have all been performed using the approved CT protocol of a smooth reconstruction algorithm (B30f), slice thickness 5mm and an increment of 2.5mm. The same

software programme (PULMO) was used throughout, and they were all analysed using the PD15 method.

Patients who had received 2 or more CT scans plus at least 3 FEV_1 measurements within the same time frame were identified. Annual slope FEV_1 (mls) was calculated and compared with the respective annual CT density in order to achieve the line of regression. Where patients had multiple CT scans performed over the time, the first and last scans were used to calculate the decline.

3.4.4. Validation of MCID

Mortality, time to death and time to transplant was established for each patient, alongside age, FEV_1, FEV_1/FVC, DLCO, KCO and baseline density. The cohort was then subdivided in to those that declined faster or slower than the proposed MCID, and either a t test (normal distribution) or Mann-Whitney-U (non-normal distribution) performed to identify any significant differences. All analyses have been reported as two tailed in order to reflect the novelty of this approach and not assuming it has a one way hypothesis. All those with a significance level <0.12 were then entered into a multivariate cox regression in order to determine to hazard ratios for each MCID.

Chapter 4 . CT densitometry in emphysema: a systematic review of its clinical utility

4.1. Introduction

The heterogeneity of COPD and AATD is well recognised, as is the need for more descriptive biomarkers beyond lung function.(289) CT has been used for many years to visually diagnose emphysema, providing the most direct assessment of its presence and distribution.(290) Software programs have since been developed which can objectively measure the severity of emphysema.(119) Quantitative CT, and in particular CT densitometry, is the method of quantifying emphysema using such software; its ability to assess emphysema has been validated clinically and pathologically (152, 160, 291) However, CT densitometry is yet to be standardised, with numerous factors impacting on the measurement of density and affecting results (195) Changes seen on CT predate those seen on spirometry, with pathological studies demonstrating that up to one third of the lung tissue is destroyed in emphysema before spirometry becomes abnormal. This suggests that CT densitometry may be a very important technique for detection of early disease, an area which is of increasing clinical interest.(292) CT densitometry was the primary outcome measure for registration level randomized clinical trials (RCTs) of augmentation therapy in AATD, where signals have been seen for this measure, and only trends in the same direction for other clinical outcomes(211) More recently large cross-sectional studies in COPD have been established (e.g. COPDGene) which

have collected data from quantitative measures on CT as well as extensive physiology.(293)

Understanding the implications of density data is complex for both clinicians and regulatory agencies and no systematic reviews of its utility have been undertaken. The purpose of our study is to assess the validity of CT densitometry as a measure of severity and progression of lung disease in emphysema specifically seeking relationship to lung function, mortality, hospital admissions and quality of life (QOL).

4.2. Methods

This systematic review has been conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. All papers concerning patients with clinically or spirometrically defined COPD which compared CT densitometry data with FEV_1, gas transfer (DLCO or KCO), quality of life (QOL), in the same study population were included. In addition any study that described longitudinal density change, irrespective of whether a direct relationship to one of our pre-specified outcomes was included. Studies where COPD was secondary to AATD were included. Details of data extraction, data analysis and meta-analysis can be found in section 3.1.

4.3. Results

4.3.1. Included Studies

The PRISMA flow diagram (Figure 4.1) demonstrates 112 papers were included in the overall narrative, and 82 papers could be combined by meta-analysis. Characteristics of all included papers can be found in the Table 4.1. 200 papers that met the initial inclusion criteria were later excluded followed a more detailed review. Clinical parameters that were felt not to be useful and beyond the scope of this review included chronic asthma/bronchitis, CPET (cardio-pulmonary exercise testing), tracheal and vascular indices or observed racial differences (294-297). A total of 35 papers were further excluded where the method of CT quantification was felt to be particularly experimental or unique and unrelated to CT densitometry. Such examples include those papers which discuss regions of interest (ROI) or image registration with biomechanical analysis (151, 298-300).

Figure 4.1. PRISMA Flow Diagram

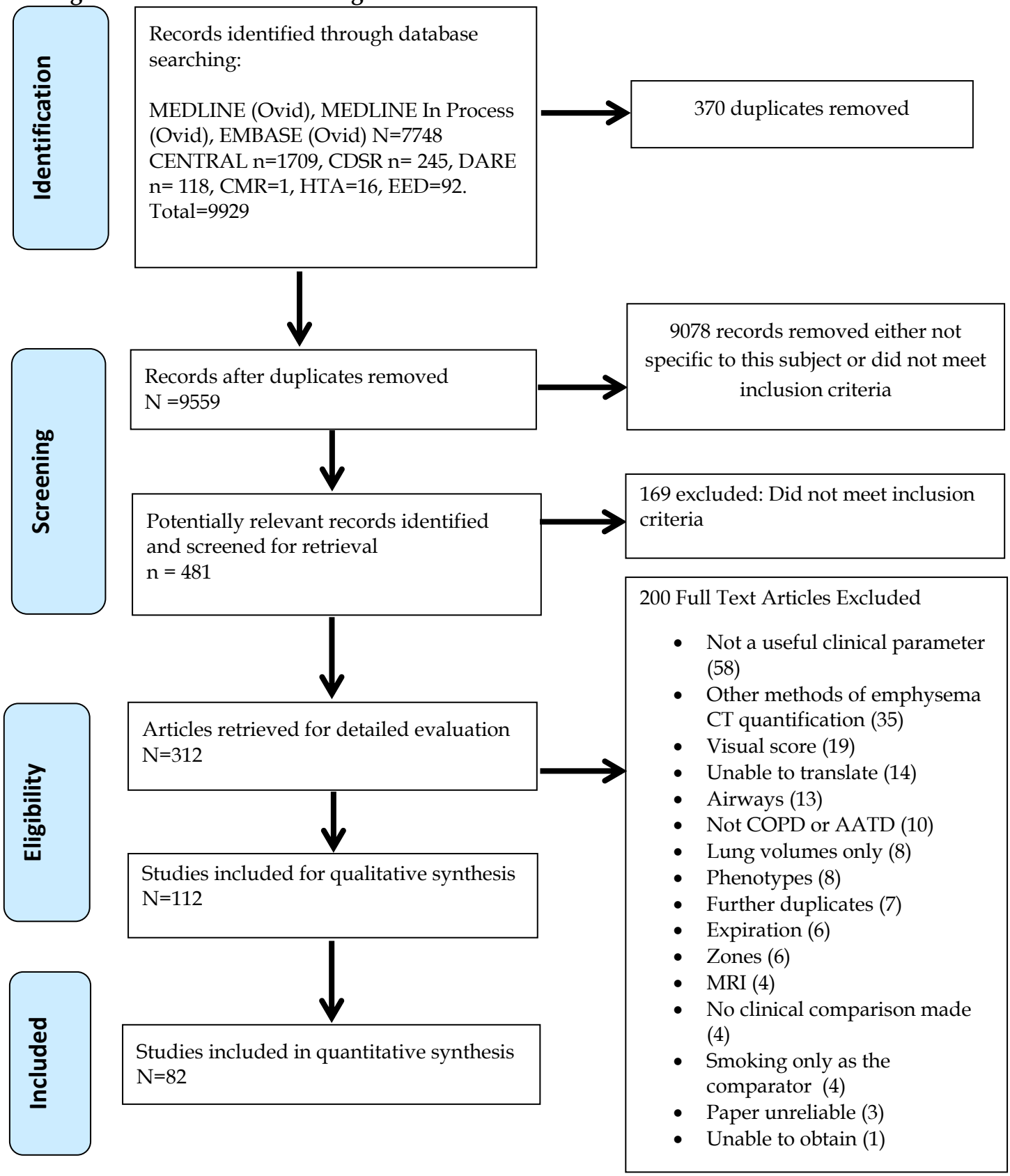


Table 4.1. Baseline Characteristics Table

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 (301)	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 (154)	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 (302)	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 (303)	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 (170)	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 (304)	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 2015(305)	460(57)	64.2 (6.8)	30.6 (8)		-950HU	Correlation coefficient	B35f	Pulmonary Workstation	1.25mm	usual care
Bastarrika, G. et al, 2009(306)	102 (80)	55 (7.5)	103 (23)		-950HU	Correlation coefficient	B30f		5mm	usual care
Bernspang, E. et al, 2011(307)	19 (61)	32	108(12)	92 (11)	PD15	Correlation coefficient	B10f	Pulmo	5mm	
Camiciottoli, G. et al, 2006(160)	51 (90)	64	52 (20)	68 (24)	-950HU	Correlation coefficient	High resolution	Pulmo	1mm	usual care
Camiciottoli, G. et al, 2012 (308)	72 (73)	66 (8)							5mm	
Castaldi, P. J. et al, 2013 (120)	9313 (54)	60 (9)	77 (25)		-910HU, -950HU	Multivariate analysis	B31f	Pulmonary Workstation	0.625, 0.75, 0.9	COPDGene
Chae et al, 2010 (309)	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 (92)	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 (310)	146 (83.6)	65			-950HU	Correlation coefficient	not mentioned	LungCAD	1mm	usual care
Cheng et al, 2015 (164)	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 (311)	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 (312)	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 (313)	2054 (65)	63.4 (7.1)			-950HU				1mm	ECLIPSE
Dawkins, P. et al, 2009 (121)	488 (60)	50 (0.48)	55.99 (1.4)		-910HU	Hazard Ratio			1mm	ADAPT
De Torres, J. P. et al, 2011 (314)	115 (84)	64 (10)	75 (15)	73 (20)	-960HU	Correlation coefficient	B40f	Leonardo	1mm	usual care
Desai et al, 2007 (315)	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 (155)	27 (33)	55 (12)	50 (10)	55 (16)	-950HU	Correlation coefficient	B10f	Pulmo	5mm	usual care

Diaz, A. A et al, 2015 (161)	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. et al 2010 (291)	109 (56)	61.2 (7.9)			-950HU					COPDGene
Diaz, A. A. et al, 2010 (162)	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 (316)	71 (45)	64.7 (10)	89 (7.5)	109 (22)	-960HU				not mentioned	From COPD longitudinal study (PELE)
Diaz, A. A. et al, 2013 (317)	2500	64 (8)	59 (23)		-950HU				0.75mm	COPDGene
Dijkstra, A. E. et al, 2013 (318)	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 (211)	56 (61%)	47.6 (3)	48 (2.8)	60 (3)	PD15	random effects regression model, slope analysis and Pearson's coefficient	<5/10mm	not mentioned	8mm	alpha one registries in Netherlands and Denmark
Dirksen, A. et al 2009 (319)	77 (53%)	55 (9)	46.5 (20)	51.5 (17)	PD15	ITT and mITT; slope analysis tested by linear regression with statistical or	B30f	Pulmo	1mm	AATD registries Denmark, UK and Sweden

						physiological adjustment				
Dowson, L. J. et al, 2001 (143)	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 (320)	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 (321)	37 (78.4)		72 (21)	65 (20)	-950HU	Correlation coefficient	not mentioned	pulmo	1mm	usual care
Gevenois, P. A. et al, 1996 (137)	59 (86.4)	62 (8)	73 (20)	66 (17)	-950HU	Correlation coefficient	not mentioned	pulmo	1mm	usual care
Gietema, H. A. et al, 2013 (322)	1778 (64)	63 (7)	48.4 (15.7)		-950HU	Multiple linear regression			1 or 1.25mm thickness	ECLIPSE
Grydeland, T. B. et al, 2010 (159)	463 (64)	65.2 (9.4)	52.6 (17.4)		-950HU		Standard algorithm	Not mentioned	1mm	GenKOLs
Han et al, 2011(72)	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,	65 (100)	71 (9)	58.8 (19.7)		-960HU		Lung algorithm	Not mentioned	0.5mm	kyoto

2010 (158)										
Haruna, A. et al, 2010(323)	251 (94)	68.7 (7)	50.3 (17)		-960HU	Hazard Ratio	lung reconstruction algorithm		2mm	Kyoto university
Hong, Y. et al, 2012 (169)	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 (324)	102	64			-950HU	Correlation coefficient	B40f	In house YACTA software	1.25mm	usual care
Johannessen, A. et al, 2013 (325)	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 (326)	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 (168)	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 (327)	78	65.3 (8.2)	49.6 (16.2)		-950HU	Correlation coefficient	reconstruction algorithm B	in house software	1mm	KOLD
Kim et al, 2015(328)	167	64.8 (8.2)			-950HU	Correlation coefficient	not mentioned	not mentioned	0.75mm	usual care

Koyama et al, 2010 (329)	25 (60)	67.6			-950HU	Correlation coefficient	FC51	doesn't specify	0.5mm	usual care
Koyama et al, 2012(330)	56 42	70.2 (8)	68.9 (19.6)		-950HU	Correlation coefficient	FC13	MATLAB	1mm	usual care
Kurashima, K. et al 2013(331)	70				-960HU	Correlation coefficient	from ultrahigh resolution (UHR) CT and noise reduction software	iDose	0.67mm	SCGOR
Kurashima, K. et al, 2015 (332)	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 (333)	145 (98%)	66 (7)	47 (16)	78 (27)	-950HU		reconstruction algorithm B	in house software	1mm	KOLD
Lee, J. S. et al 2012 (334)	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 (335)	126 (98%)	65.5 (7.6)	47.9 (14.1)	74.6 (25.8)	-950HU	multiple, stepwise linear regression	reconstruction algorithm B	in house software	1mm	KOLD

						models and Pearson's correlation coefficient				
Lutchmedial et al, 2015 (336)	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 (68)	1179 (53.3%)	65.0 (47.9, 70.6)			-950HU				not mentioned	COPDGene
Martinez, F. J. et al, 2006(165)	609	66.7 (5.9)	26.7 (7)	28.4 (9.7)	-950HU	Hazard Ratio	standard reconstruction kernel	custom built		NETT
Martinez, F. J. et al, 2007 (337)	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 (338)	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 (163)	521 (51)	68 (6)	76 (23)		-910HU	Multilinear analysis	B50f	Not mentioned	10mm	NLCST
Mets, O. M. et al, 2011 (339)	1140	62.5 (5.2)	94.8 (17.6)		-950HU	Multivariate analysis	smooth reconstruction filter		1	Dutch and Belgian Lung Cancer

							(B filter)			Screening Trial.
Mets, O. M. et al, 2013 (340)	442	61.3 (5.5)	96.5 (18)		-950HU	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A. et al 2013 (341)	3670 (100)	59.8 (5.4)			-910HU, -950HU and PD15					from NELSON
Mohamed Hoesein, F. A. A. et al, 2011 (342)	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 (343)	2085 (100)	59.8 (5.3)			PD15	Multivariate analysis	B30f	in house software	1	NELSON
Mohamed Hoesein, F. A. A. et al, 2012 (344)	2003 (100)	59.8 (5.3)	98.5 (18.5)		PD15	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A. et al, 2012 (345)	587 (100)		97.7 (18.1)		PD15	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON
Mohamed Hoesein, F. A. A.	1108 (100)	60.4 (19.9)	94.8 (17.6)		-950HU and	Multivariate analysis	soft reconstruction filter (B30f)	in house software	1mm	NELSON

et al, 2013 (346)					PD15					
Mohamed Hoesein, F. A. A. et al, 2015 (187)	2021 (100)	59.8 (5.3)			PD15	Multivariate analysis	B30f	Cirrus Lung 12.03	1.0mm	nelson
Mohamed Hoesein, F. A. et al, 2014 (347)		62.5 (5.2)	94.8 (17.6)		-950HU	Multivariate analysis	smooth reconstruction kernel	Cirrus	1mm	nelson trial, prospective
Motohashi, N. et al, 2009 (348)	125 (89)	71 (8)	51.5 (17.8)		-940HU	Correlation coefficient			1.25mm collimation	
Nakano, Y. et al, 1999(49)	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 (174)	114	68 (9)	48 (28)		-960HU	Correlation coefficient	lung algorithm (FC 83)	C Programming language (Symantec C++)	2mm	usual care
Nambu et al, 2015 (349)	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 (350)	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 (351)	65	55 (7)	56 (16)	56 (16)	-950HU	Correlation coefficient	not mentioned	not mentioned	1mm	usual care
Ogawa, E. et al, 2009 (352)	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 (353)	42 (88)	63	49.09 (19.44)	67.57 (24.69)	-950HU	Correlation coefficient	not mentioned	Pulmo	1mm	usual care
Orlandi et al, 2004 (354)	11 (81)	68			-950HU	Correlation coefficient	not mentioned	Pulmo	1mm	usual care
Paoletti, M. et al 2015 (355)	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 (356)	98 (100)				-950HU					retrospectively recruited
Parr et al, 2004 (119)	100	52 (10.2)			-950HU	Correlation coefficient	smooth filter	Pulmo	5mm	ADAPT
Parr, D. G. et al	77 (53%)	55 (9)	46.5 (20)	51.5 (17)	PD15,	mITT and sensitivity	not mentioned ?on	Pulmo	5mm	alpha one registries

2009 (357)					mld, 910 and -950HU	ratios	supplemental information			from Demark, UK and Sweden
Pauls et al, 2010 (358)	474	60.4 (14.9)	60.7 (20.27)		-950HU	Correlation coefficient	not mentioned	"Lung Emphysema" application	2mm	usual care
Rambod, M. et al 2012 (359)	2256 (52)	61.3 (9.3)	88.1 (24.3)	56.5 (21.5)	-950HU				1mm	COPDGene
Roth, M. D. et al, 2006 (210)	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 (360)	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 (361)	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 (362)	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 (363)	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. et 2009 (364)	254 (58%)	63.6 (7)	52 (11)		PD15	mixed effects regression model	low spatial (soft) frequency	Pulmo	10mm	from OPA and local newspapers

Shaker, S. B. et al 2009 (156)	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 (157)	42 (38)	63 (7)	48 (13)	49 (16)	PD15	Correlation coefficient	low spatial resolution (soft)	Pulmo	5mm	
Stolk, J. et al 2012 (365)	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 (366)	22 (45)	40.7 (9.2)	56 (32)		-950HU and PD15	Correlation coefficient				
Stolk, J. et al, 2007 (367)	87 (50.6)	58.6 (10.4)	50.2 (19.2)		PD15	Multivariate analysis and correlation coefficient	smooth reconstruction filter	pulmo	5mm	advertisement
Sverzellati, N. et al, 2012 (368)	1159 (68)	57.5 (6)	97.1 (19.6)		-950HU	Multivariate logistic regression	B30f	MevisPULMO	5mm	MILD
Tanabe, N. et al 2012 (369)	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 (370)	60 (93)	73 (68.3-77.8)	50.6 (38.2-61.1)		-910HU, -930HU and -	Multivariate analysis	Not mentioned	Not mentioned	0.5mm	Kyoto

					960HU					
Tanabe, N.et al, 2013 (371)	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 (372)	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 (373)	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 (374)	263	60.3 (5.4)	97.7 (16.8)	87.4 (16.1)	-950HU	Correlation coefficient	not mentioned	not mentioned	1mm	usual care
Vijayasaratha, K. et al, 2012 (375)	21 (81)	52.5 (2.1)	38.4 (3.1)		PD15	Multivariate analysis	Not mentioned	Pulmo	5mm	ADAPT
Wang et al 2015 (376)	46(80.4)	67 (10.84)	72.56 (31.15)	69.38 (25.39)	-950HU	Correlation coefficient	standard algorithm	Thoracic VCAR software	0.625mm	usual care
Wang et al, 2013 (377)	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 (378)	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 (221)	51(100)				-950HU	Correlation coefficient	not mentioned	extended brilliance workspace	1mm	usual care
Yamashiro et al, 2010 (147)	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 al, 2009 (379)	143 (53)	59.5 (6.4)	99.4 (12.8)		-950HU	Multivariate analysis	Standard reconstruction kernel in 36 cases (25%) and B35f in 107 cases (75%)	custom software (Emphylxl)	1 and 1.25mm	British Columbia Cancer Agency (lung cancer screening programme)

4.3.2. Cross-sectional studies of CT Density

4.3.2.1. Baseline Characteristics

LAA% at --950HU was the most commonly used emphysematous threshold, with a total of 46 studies reporting a correlation coefficient and 23 of which were from larger cohort studies (e.g. COPDGene(293), KOLD(380)). The vast amount of papers in this particular sub-section was primarily due to the high number of publications produced whilst the knowledge base of the methodology and applicability of CT density was rapidly expanding. Eight papers were published in radiology journals exploring the optimum density analysis technique (e.g. factor analysis, histogram skewness/kurtosis)(309, 354, 381-383). The difference in the correlation between FEV1 using a high or low radiation dose was explored and the density results pre and post volume correction (329, 384). 5 papers examined the difference between inspiratory and expiratory CT scans (147, 154, 321, 328, 338), and 3 were assessing the additional impact of airway thickness or presence of bronchiectasis (330, 353, 362).

CT density was added to other clinical variables such as airway measures and lung function to try to use density measures to build effective prognostic models. (120, 355, 379) 4 studies adjusted CT density for airway wall thickness (AWT) so to elicit the contribution of parenchymal change over airway changes on PFTs, (170, 346, 347, 385)and a further three used a similar concept but simply used the inspiratory/expiratory ratio(169, 320, 386).

Table 4.2 summarises the baseline characteristics of studies and patients included in meta-analyses. Notably there were no two studies using the same statistical technique and emphysema threshold for mortality, exacerbations and all quality of life measures meaning that a quantitative meta-analysis would not be possible.

Table 4.2. Summary of all studies included in meta-analyses.

Statistical Method	Density Measure	N° studies	N° patients	Age	FEV_1pp	DLCOpp	KCOpp
Correlation Coefficients	900	7	551	66 (10)	54.96 (20.19)	65.47 (20.97)	63.73 (20.13)
	910	2	69	64.67 (8.34)	58.93 (24.27)	57.46 (19.63)	61.59 (22.47)
	950	46	10764	62.45 (10.77)	58.04 (33.59)	59.90 (31.43)	85.19 (21.86)
	960	6	639	67.96 (8.76)	54.86 (23.75)	---	---
	PD15	7	4544	60.91 (9.22)	53.99 (24.52)	---	67.16 (24.58)
Multivariate Regression	910	3	425	62.04 (8.93)	64.17 (27.27)	---	---
	950	14	18984	60.59 (9.56)	78.71 (26.29)	66.23 (23.44)	87.06 (18.07)
	960	2	161	70.33 (8.69)	54.81 (20.13)	---	---
	PD15	8	7251	59.89 (9.51)	93.06 (20.63)	---	85.19 (18.86)
Trials ICS+/-LABA	950	2	482	64.50 (7.37)	50.50 (12.21)	75.15 (29.50)	46.70 (39.08)
ATRA	PD15	2	375	58.83 (9.91)	44.99 (15.70)	43.82 (14.79)	43.70 (13.57)

Prolastin	PD15	4	369	51.83 (7.39)	47.39 (12.35)	36.14 (23.39)	54.70 (11.77)
Mortality	mixed	6	3584	61.66 (9.68)	69.39 (31.27)	----	----
Exacerbations	Mixed	7	2637	66.10 (8.22)	60.54 (25.44)	----	----
SGRQ	Mixed	8	4864	58.82 (13.75)	45.01 (19.03)	35.68 (18.17)	60.40 (22.22)
BODE	Mixed	4	2440	65.58 (6.44)	44.43 (21.19)	35.08 (19.87)	----
6MWT	Mixed	3	2481	61.63 (9.38)	56.03 (48.57)	----	----
MRC	Mixed	4	694	64.84 (10.85)	56.97 (18.99)	----	----

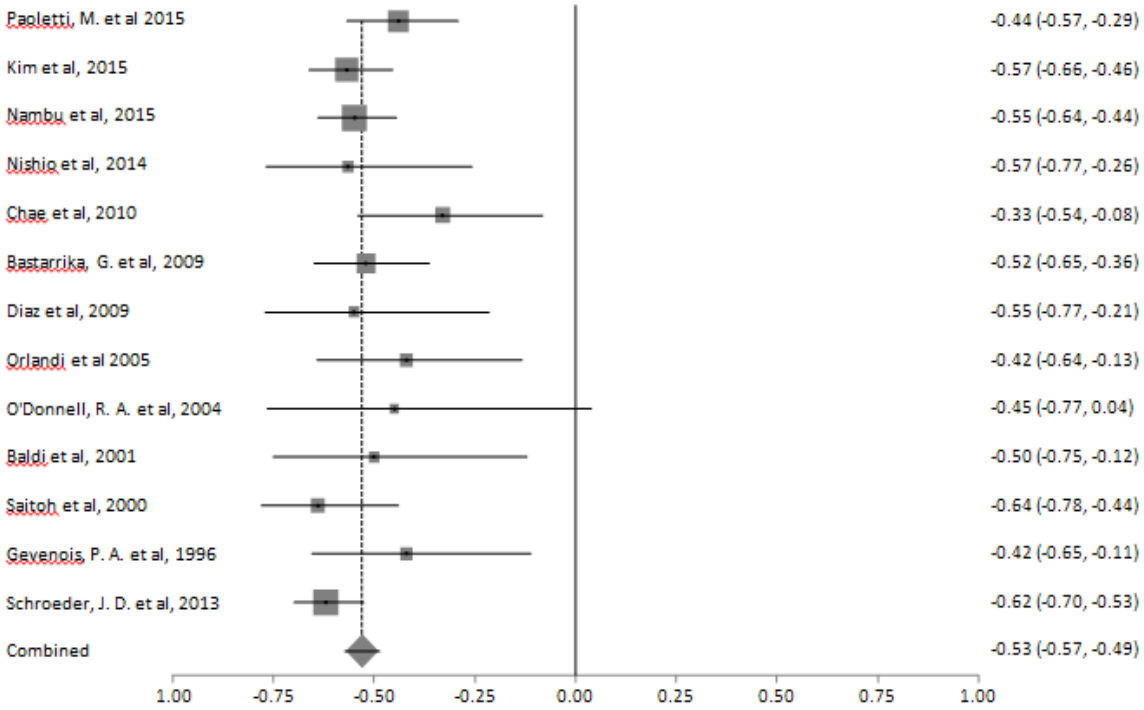
Studies of lung function, sub-divided by statistical techniques used to assess relationship to CT density, followed by trials, and those using quality of life measures. All quantitative measures are shown as mean (SD).

4.3.2.2. Spirometry

4.3.2.2.1. FEV1

A total of 36 studies compared FEV_1 percent predicted to CT density. The forest plot in Figure 4.2 demonstrates the correlation between FEV_1 percent predicted with CT density at--950HU and the variation seen within the included studies. The ranges of correlation coefficients are from -0.33 to -0.67; the pooled correlation coefficient is -0.53 (95% CI -0.57, -0.49) ($p<0.0001$). This data is further summarised in Table 4.3, which shows the meta-analyses of other CT parameters against FEV_1. The level of heterogeneity remained high in all sub-group analyses except 900HU v FEV_1 percent predicted which contained the smallest number of studies and thus could be less reliable.

Figure 4.2. Forest plot of all studies included in the meta-analysis that correlated FEV1 percent predicted with -950HU.



*X^2 test for heterogeneity=591, and I^2 score for inconsistency 97.2%. Pooled correlation co-efficient 0.53 (95% CI -0.57, -0.49)

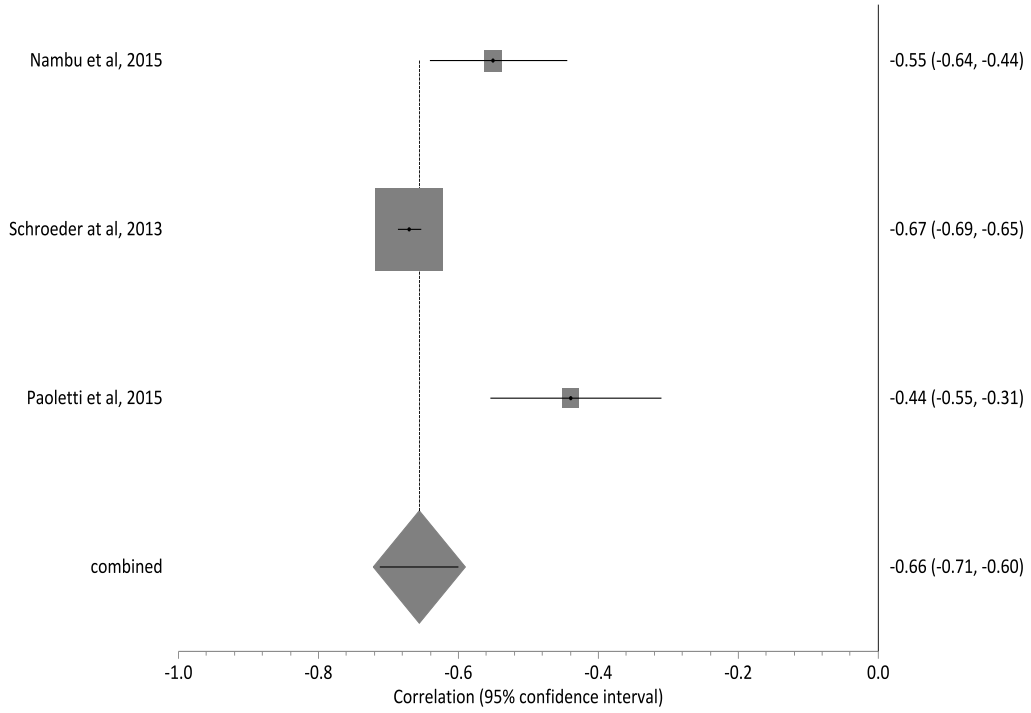
Table 4.3. Summary of meta-analyses performed on all studies using Pearson's correlation coefficient to compare FEV_1 and FEV_1 percent predicted with CT density.

PFT	Density Variable	N° of studies	SH* pooled correlation	Lower 95% CI	Higher 95%CI	P	I^2	X^2	p
FEV_1	950	6	-0.37	-0.53	-0.21	<0.0001	90.7	48.54	<0.0001
	960	3	-0.33	-0.43	-0.22	<0.0001	46.9	3.78	0.15
	PD15	4	0.40	0.20	0.59	<0.0001	84.9	18.90	0.0003
FEV_1pp	900	3	-0.53	-0.63	-0.43	<0.0001	0	1.96	0.37
	910	9	-0.29	-0.38	-0.20	<0.0001	80.5	36.45	<0.0001
	950	13	-0.54	-0.57	-0.49	<0.0001	97.2	591.46	<0.0001
	960	4	-0.35	-0.51	-0.19	0.0003	84.5	17.70	0.0005
	PD15	4	0.53	0.49	0.57	<0.0001	0	0.768	0.857

Further investigation into the cause of heterogeneity revealed major differences in the choice and combination of reconstruction algorithm, slice thickness and software program used by included studies. When the meta-analysis was restricted to 3 studies that used the same CT acquisition parameters, the forest plot became more uniform and heterogeneity as measured by X^2 decreased (**Error! Reference source ot found.**). Of note, in the Schroeder et al study, the box is larger than the line drawn through it. This can be explained as the size of the box over the stratum-specific point estimate (correlation coefficient) reflects the weight that study has on the pooled estimate. The confidence intervals for the point estimate are reflected by the

width of the line, and so for a study of larger power due to patient size for example, the box may be larger to reflect this and the CIs narrow.

Figure 4.3. Forest plot to demonstrate the effect on the forest plot once the same reconstruction algorithm, slice thickness, and software program are used.



Schmidt hunter (SH) weighted mean correlation coefficient=-0.66, I^2=91.8%, X^2=33.59

7 studies performed multivariate linear regression between FEV_1 and CT density (Table 4.4). However, for each density variable, all studies adjusted for different variables and therefore accurate meta-analysis could not be performed.

Table 4.4. Studies performing multivariate linear regression to examine the relationship between FEV_1 and CT density

Density Measure	Study	Variables adjusted for	Results for adjusted FEV1.	95 % Confidence Intervals (CI)
950	Kim et al, 2013(168)	Mean Wall Area Visual score of emphysema Visual score of lobe	β =-0.4726	-0.8215, -0.1238
	Hoesein et al, 2014(347)	Age Height Pack years Smoking status	β =-0.252	---
	Hong et al, 2012(169).	LAA% -950HU Mean Lung Density Mean Wall Area Smoking status	β =-0.24	---

	Aziz et al, 2005(170)	DLCO FEV_1	$_{\beta}$ =-1.27	-1.59, -0.94
PD15	Hoesein et al, 2012(345)	Age FEV_1/FVC Medical Centre Mucus Production Smoking Status	1 point change in PD 15 results in -0.824ml 3 year change FEV_1	-1.473 to -0.0174
	Hosein et al, 2011(343)	Age Height Medical Centre Smoking Status Years in Study	1 HU change in PD 15 results in -4.75 ml 3 year change FEV_1	- 3.3 to -6.1
	Hoesein et al, 2015(187)	Age FEV1 Pack Years	10 HU drop in PD15 caused a -10ml change in FEV_1	-15 to -5

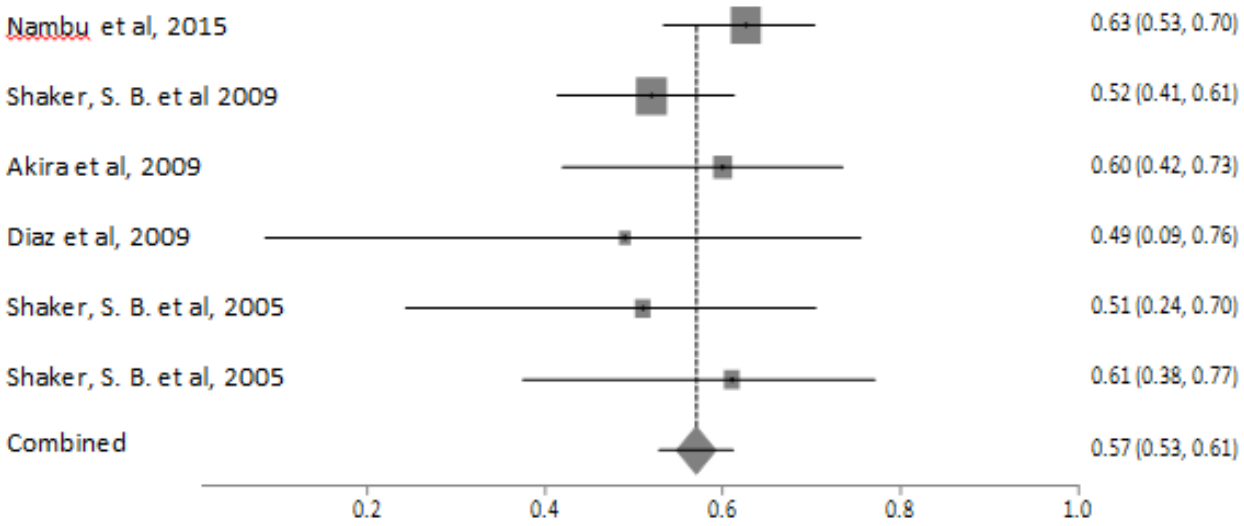
4.3.2.2.2. FEV_1/FVC

Akin to FEV_1, there was a significant correlation between each density variable and FEV_1/FVC ($p<0.0007$; Table 4.5). The forest plot demonstrating the meta-analysis of correlation co-efficients for PD15 and FEV_1/FVC is shown in Figure 4.4.

Table 4.5. Summary of studies comparing FEV_1/FVC with CT density, divided into the most commonly reported thresholds.

PFT	Density Variable	N° of studies	SH* pooled correlation	Lower 95%CI	Higher 95%CI	P value	I^2	X^2	P value
FEV_1/FVC	910	5	-0.33	-0.49	-0.16	<0.0001	95.5	75.72	<0.0001
	950	19	-0.56	-0.63	-0.49	<0.0001	86.2	114.35	<0.0001
	960	3	-0.48	-0.71	-0.25	<0.0001	88.9	18.73	<0.0001
	PD15	6	0.57	0.57	0.61	<0.001	0	3.4	0.6382

Figure 4.4. Forest plot of all studies comparing FEV1/FVC with PD15.

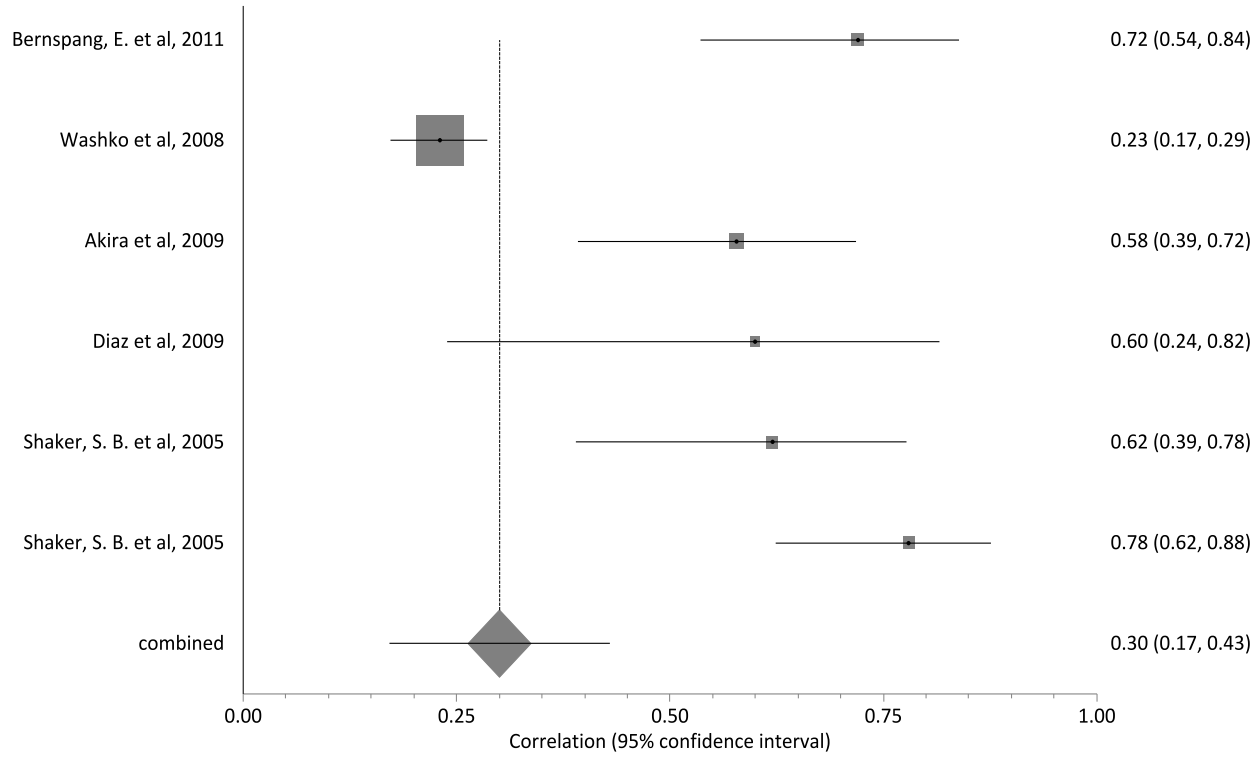


Schmidt hunter (SH) weighted mean correlation coefficient=-0.57, I^2=3.4%, X^2=3.4

4.3.2.2.3. Gas Transfer

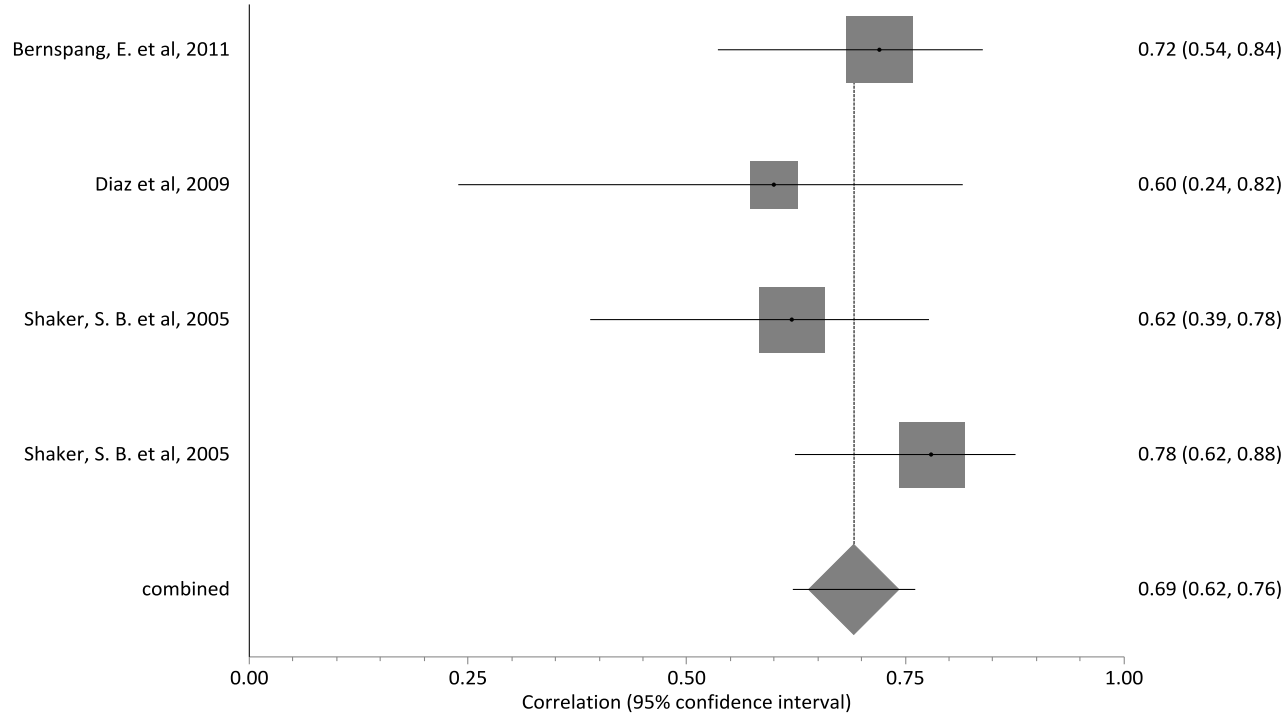
A total of 23 studies compared DLCO percent predicted to CT density. These studies tended to be as part of larger cohort studies examining the relationship between all PFTs and CT density (160, 311, 355). 4 studies reported the correlation between DLCO and CT density in order to help identify CT defined phenotypes and airways versus parenchymal disease (170, 353, 387). When exploring the utility of hyperpolarised helium and emphysema, DLCO was compared with the ADC from a MRI study that also quoted CT density (155). The pooled correlation coefficients were universally significant across individual density values, albeit slightly weaker than for FEV_1 and CT density (Table 4.7). The same pattern was seen regarding heterogeneity of results, with I^2 dropping from 91.5% to 0 once CT algorithm was taken into account (Figure 4.5 and Figure 4.6).

Figure 4.5. Forest plot demonstrating correlation co efficient confidence intervals and pooled correlation coefficient for those studies comparing DLCO percent predicted with PD15.



Schmidt hunter (SH) weighted mean correlation coefficient=0.3, I^2=91.5%, X^2=40.98

Figure 4.6. Forest plot of those studies comparing PD15 and DLCO percent predicted once all studies using the same CT variables has been re-analysed.



Schmidt hunter (SH) weighted mean correlation coefficient=0.69, I^2=0%, X^2=2.72

Table 4.6.Studies subdivided into density parameter used, that compare gas transfer to CT measured density.

PFT	Density Variable	N° of studies	SH* pooled correlation coefficient	Lower 95% CI	Higher 95% CI	p	I^2	X^2	p
DLCO	950	5	-0.42	-0.53	-0.32	<0.0001	77.8	15.538	0.0036
DLCOpp	910	3	-0.31	-0.40	-0.22	<0.0001	83.6	10.46	0.005
	950	16	-0.43	-0.52	-0.34	<0.0001	88	100.34	<0.0001
	PD15	5	0.29	0.15	0.42	<0.0001	92.2	33.79	<0.0001
KCO	950	3	-0.63	-0.71	-0.54	<0.0001	49.9	4.43	0.1091
	PD15	3	0.38	0.15	0.61	0.0012	96.4	45.67	<0.0001
KCOpp	910	3	-0.61	-0.63	-0.59	<0.0001	0	0.29	0.8658
	950	6	-0.42	-0.6	-0.25	<0.0001	78.6	22.47	0.0004

4.3.2.2.4. Lobar analyses

Table 4.7 summarises the results of three papers that subdivided the correlation between LAA --950HU and FEV_1/FVC into the individual lobes in patients with usual COPD (303, 360, 376). The total number of patients included was 189, and there remained a significant correlation between spirometry and CT density, though no stronger than whole lung density. The lower lobes appeared to have a stronger correlation than the upper lobes.

Table 4.7. 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

4.3.2.2.5. Quality of Life, symptom and composite scores

SGRQ was the most frequently reported QOL compared with CT density. 2 studies recruited patients with AATD (genotype PiZZ); Stolk et al found that when those

patients with normal lung function were removed from analysis, the correlation coefficient improved from 0.56 to 0.74 with CT density as measured by PD15, highlighting the same change was not seen with --950HU and that the former method is better able detect early emphysema changes than --950HU (366). Of the 4 studies comparing SGRQ to COPD, Motohashi et al was the only publication to detail the relationship across each sub-component i.e. impact, activity, symptoms and total score (348).

2 out of 5 studies using correlation coefficients showed no relationship between the two measures, whilst the other 3 showed a strong association ($p<0.003$) (Table 4.8). There was variability in the density threshold and patient groups used (e.g. cancer screening populations or those being considered for lung volume reduction surgery), thus precluding meta-analysis. Nevertheless, studies that performed multivariate analyses consistently showed a significant association between density and SGRQ.

Table 4.8. Summary of studies that correlate CT density with SGRQ.

Univariate Analysis					
Reference	COPD or AATD	LAA% parameter	Statistical technique	Results	P value
Stolk et al, 2003 (366)	AATD	PD15	Spearman's CC	-0.56	<0.007
		-950HU		0.6	0.003
Dowson et al, 2001(143)	AATD	-910	Spearman's CC	0.39	<0.001
Barjaktarevic, I. et al 2015 (305)	COPD	-950	Pearson's CC	0.028	0.572
Motohashi, N et al, 2010 (348)	COPD	-940	Pearson's CC	0.501	<0.001
De Torres, J. P. et al, 2011 (314)	COPD	-960	Pearson's CC	-0.12	0.39
Martinez, C. H. et al, 2012(68)	COPD	-950	Un-normalised and Normalised (value-mean/SD) parameters in univariate analysis	Un-normalised estimate 0.53 (95% CI 0.45 to 0.61)	<0.001
				Normalised estimate 5.82 (95% CI 4.91-6.72)	<0.001

Multivariate analysis					
Martinez, F. J et al 2007(337)	COPD	-950	Adjusted for Age, pack years and FEV1%predicted	Beta value=-7.69 (95% CI -14.09, -1.3)	0.02
Gietema, H. A. et al, 2013(322)	COPD	-950	Adjusted for Gender, Age, smoking status, pack years, BMI and FEV% predicted and Pi10	Coefficient=1.43 SE=0.57	P<0.05

Studies comparing BODE (BMI, Airflow Obstruction, Dyspnoea, Exercise Capacity) with CT density were particularly heterogeneous in their methods and analyses. Camiciolotti et al compared CT density as measured by --950HU with the modified BODE index (mBODE), Martinez et al presented all their results as parameter estimates, and De Torres et al compared BODE indexes across those with predominant core versus rind disease and upper versus lower predominance(68, 160, 314).

2 studies examined the relationship between CT density and MRC grade using multivariate analysis. Camiciolotti et al performed logistic regression in order to establish an odds ratio for presence of dyspnoea using inspiratory and expiratory CT scans. (308)Haruna et al assessed MRC grade whilst examining CT defined emphysema and mortality from cardiac and respiratory causes (323). The relationship between MRC, BODE and CT density was particularly significant once adjusted for other variables including lung function (Table 4.9).

Table 4.9. Summary of studies that compare BODE and MRC with CT density.

Subdivided into univariate or multivariate models used.

Univariate Analysis						
Reference	**COPD or AATD**	**Severity measure**	**LAA%**	**Statistical technique**	**Results**	**P value**
Camiciottoli, G. et al, 2012(308)	COPD	BODE	-950	Pearson's CC	R=0.58	<0.0001
Camiciottoli, G. et al, 2006 (160)	COPD	MRC	-950	Odds ratio	1.41 (95% CI 1.11-1.78)	<0.005
Martinez, C. H. et al, 2012(68)	COPD	BODE	-950	Un-normalised and Normalised (value-mean/SD) parameters in univariate analysis	Unnormalised estimate 1.02 (95% CI 1.02-1.02)	<0.001
					Normalised estimate 1.23 (95% CI 1.2-1.26)	<0.001
De Torres, J. P. et al, 2011(314)	COPD	BODE	-960	Pearson's CC	R=-0.08	0.53
Haruna et al, 2010 (323)	COPD	MRC	-960	Pearson's CC	R=0.41	<0.05
De Torres, J. P. et al 2011 (314)	COPD	MRC	-960	Pearson's CC	R=-0.19	0.14

Multivariate analysis						
Martinez, F. J. et al, 2007(337)	COPD	BODE	-910	Adjusted for Age, pack years and FEV_1%predicted	Beta value=0.01 7.69 (95% CI 0.005, 0.02)	0.002
Camiciottoli, G. et al, 2012(308)	COPD	BODE	-950	Adjusted for FEV_1, BMI, MRC, 6MWT	R=0.61	<0.0001
Haruna et al, 2010 (323)	COPD	MRC	-960	Adjusted for FEV_1, RV/TLC. R5-R20, X5	R=0.06	<0.05

4.3.3. Longitudinal studies of CT density

4.3.3.1. Introduction

Understanding the nature and prognostic value of CT density decline is imperative if it is to be used in the future as an imaging biomarker. For this reason, studies which reported longitudinal outcomes such as exacerbations and mortality were sought in addition to cross-sectional studies. These clinically relevant end points allow for appreciation of how an intervention is like to impact patient's quality of life, as opposed to a decline in FEV_1(or other physiological measures) which patients may not perceive as important for them(388). As interventional trials of alpha one augmentation therapy report annual change in lung function and CT density, these were also included in the analyses.

4.3.3.2. Mortality

6 papers reported the relationship between CT density and mortality, 3 of which reported a hazard ratio (HR) for all-cause mortality (Table 4.10) generated by multi-variable logistic regression. However, it was inappropriate to combine them statistically due to differing emphysematous thresholds and confounding variables included in their models. Emphysema as defined by CT density remained a significant independent predictor for mortality throughout.

Table 4.10. Studies reporting an all-cause mortality HR for emphysema as defined by CT density.

Reference	Patient Source	LAA%	Statistical technique	Confounding variables in model	Results	HR	Lower 95% CI	Upper 95% CI	P value
Haruna et al, 2009(158)	COPD OPA clinic	-960	Univariate and multivariate Cox proportional hazards	Univariate analysis therefore N/A	↑LAA% significantly related to mortality	1.52	1.2	1.91	<0.001
					Upper lung field	1.55	1.22	1.95	<0.001
					Lower lung field	1.41	1.09	1.78	0.009
				Age, BMI, FEV1, RV/TLC and KCO	LAA% independent predictor of mortality	1.74	1.18	2.54	<0.01
Martinez 2006(165)	NETT	-950	Univariate and multivariate Cox proportional hazards	N/A	Whole lung %emphysema not associated with mortality	1.14	0.85	1.52	0.38
					Lower zone emphysema associated with ↑mortality	1.39	1.04	1.85	0.02
				Age, LTOT, Hb, BODE, RV%, TLC%, DLCO%, maximal CPET workload, lower lung emphysema and nuclear perfusion scan result.	Difference between upper and lower lungs% emphysema remained predictive in multivariate model	1.80	1.22	2.66	0.003
Dawkins 2009(121)	ADAPT	-910	Univariate Cox proportional hazards	Age. Hazard ratio for mortality (Exp B) comparing those with FEV1 >80pp with FEV1<30pp.	Survival curves indicate a relationship of ↑VI to ↑mortality				
					↑%LAA associated with ↑mortality	0.111	0.026	0.473	0.003

4.3.3.3. Exacerbations

4 studies investigated severity of emphysema, as measured by CT density, as a risk factor for COPD exacerbations, using multiple regression analyses in order to independently attribute exacerbations to density loss (Table 4.11). Due to different regression methods, variables and presentation a statistical meta-analysis could not be performed. All but one study showed a significant relationship between CT density and exacerbations; Yoo et al found that the ability for emphysema index to predict exacerbations did not remain significant when multiple variables including age and exercise tolerance were adjusted for.(326) Cheng et al performed a multivariate ordinal logistic regression to demonstrate a LAA%>7.5 was associated with worse performance status and MRC grade if they presented to Accident and Emergency with an infective exacerbation of COPD.(164)

Table 4.11. Summary of papers describing the association between CT density and exacerbations.

Subdivided into the risk of exacerbations from a low density score, and the impact exacerbations have on CT density decline.

Reference	LAA% parameter	Statistical technique	Variable adjusted for	Results	p value
Yoo et al 2011(326)	-950	Univariate logistic regression		OR=1.02 (95% CI 1.01-1.04)	0.01
		Multiple logistic regression	Age, gender, current smoker, exacerbation leading to hospitalisation in past year; Charlson index, BMI, MMRCS, 6MWD, SGRQ, FEV1%, CT wall area %, CT air trapping index	OR=1.01 (95% CI 0.987-1.034)	0.39
Vijaysaratha et al 2012 (375)	PD15	stepwise linear regression; spearman's CC	FEV1, FEV/FVC, KCO% predicted, delay in treatment initiation in days, Anthonisen criteria, cold symptoms	PD15 associated with exacerbation length and (r=-0.361)	0.003
				PD15 associated with treatment delay (r=-0.786)	0.004
McAllister et al(163)	-910	Multivariate rate ratios (RR)	Age, sex, race/ethnicity and cotinine	%emphysema predicts episodes of care RR1.45 (95% CI 1.04-2.03)	0.03
				↑hospital; admissions RR 1.62 (95% CI 1.08-2.44)	0.02

Reference	LAA% parameter	Statistical technique	Variable adjusted for	Results	p value
Han et al 2011(72)	-950	multivariate analyses and forward selection regression	Scanner model, age, sex, smoking status and FEV1	>35% emphysema associated with a 1.18 fold increase in exacerbation	0.047
				5% ↑ in emphysema associated with a 0.86 fold ↑ in exacerbation frequency	0.001
Cheng et al 2015(164)	-950	ANOVA		No difference in CT density before and after exacerbation (13.38%+/-9.04% vs 11.43%+/-7.1%)	0.135
Tanabe et al 2011 (370)	-960	Multivariate regression	Exacerbations, change in CT derived lung volume and baseline LAA%	exacerbations independently contributed to changes in LAA (R2=0.41)	0.0001
				Significant change in %LAA in those that exacerbated and those that didn't	0.0001
				Baseline scan result made no difference to those that went on to exacerbate	0.54

4.3.3.4. Interventional studies reporting CT density

4.3.3.4.1. Alpha One Augmentation Therapy

3 RCTs used CT density as an outcome measure for augmentation therapy in AATD patients (92, 198, 211). The first two, "A randomized clinical trial of alpha 1-antitrypsin augmentation therapy" and "Exacerbations and Computed Tomography scan as Lung End-points" (EXACTLE) trial both by Dirksen et al in 1999 and 2009 respectively followed by "Randomized Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency" (RAPID) by Chapman et al in 2015. The annual change in CT density was a secondary outcome in the first RCT by Dirksen et al, and the primary outcome in subsequent 2 studies. A final paper was not included in the quantitative synthesis as it simply explored statistical approaches in data from the EXACTLE trial (357). In all papers CT density was log transformed and volume adjusted (see table 4.1 for CT acquisition parameters), study duration was 2-3 years, and the rate of density decline was measured in g/l^{-1} per year. A recent meta-analysis of this data by our group has been reported separately (389), which demonstrates slower density decline in those receiving augmentation therapy than those receiving placebo (p=0.002). The 3 papers analysed also report overall low to moderate correlation coefficients between CT density and FEV_1, KCO and exercise tolerance (0.31, 0.47 and 0.21 respectively).

4.3.3.4.2. All-trans-retinoic acid (ATRA)

ATRA was shown to promote alveolar repair in animal models by upregulating RARγ leading to decrease in alveolar area by up to 50% through improved alveolar

septation and a subsequent increase in oxygenation (390). In 2011 Stolk et al randomised 262 patients with AATD to either Palovarotene or placebo, using volume adjusted CT density as their primary outcome(391). The results of this study showed no significant benefit in the treatment arm, and the authors postulated that perhaps due to the severity of the patients selected, there was little available tissue to repair, or that perhaps a larger study was required. However, retinoids have not been further investigated since this RCT.

4.3.3.4.3. Inhaled LABA/ICS

2 studies from South Korea and the KOLD study collected longitudinal data on spirometric change over 3 months with ICS/LABA treatment and demonstrated a significant correlation between FEV_1 and baseline CT density, using--950HU as the emphysematous threshold (333, 392). Shaker et al performed annual CT densitometry in a RCT conducted in patients with COPD which demonstrated significantly slower decline in emphysema (using --910HU; p=0.02) in those randomised to budesonide compared to placebo (364)).

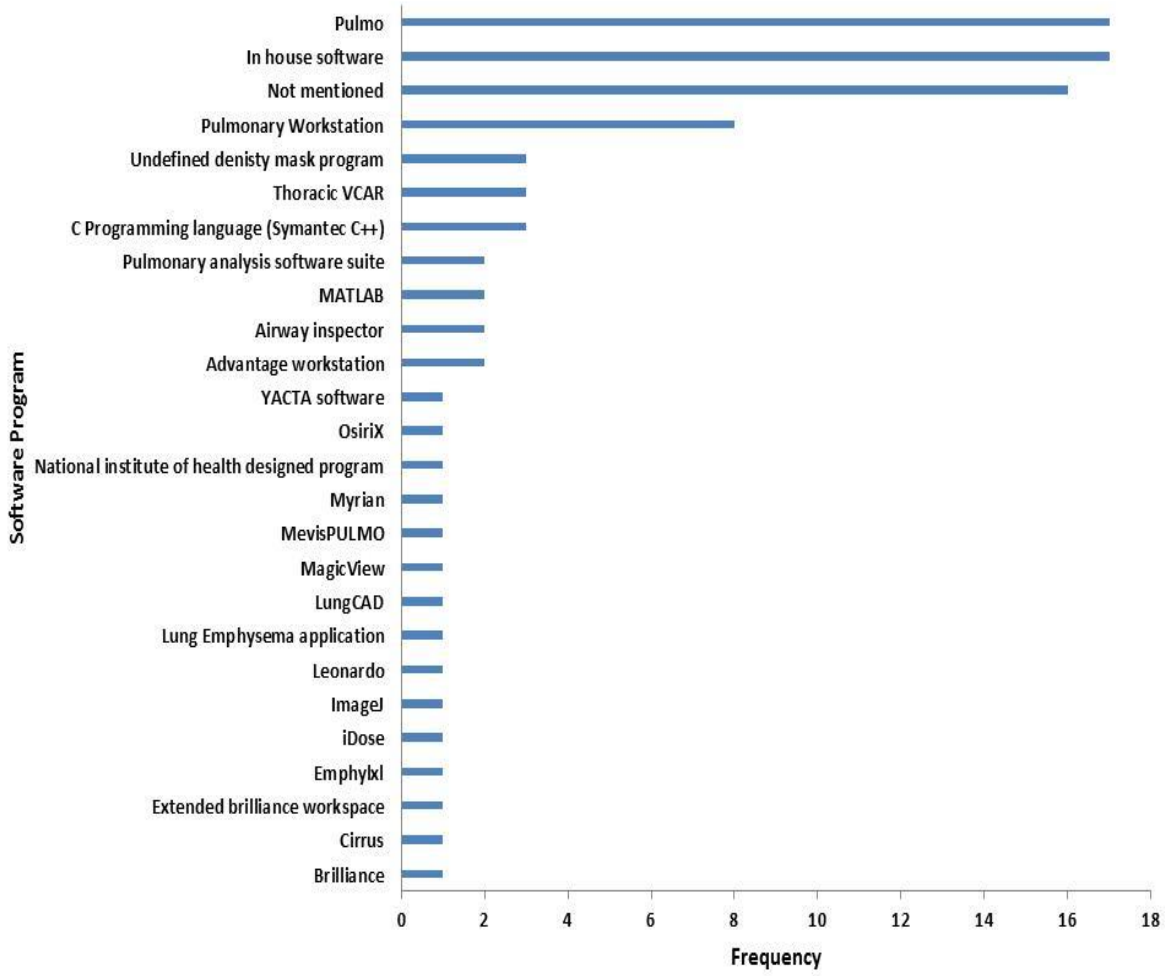
4.4. Standardising studies for equal CT variables

Since there were clear differences in the meta-analyses regarding the relationship between CT density and outcome when stratified by CT acquisition parameters, a separate summary was performed to illustrate the extent of the heterogeneity.

4.4.1. Software Programs

PULMO was the most frequently used software program (used in EXACTLE and RAPID trials), and the same number of publication again used an 'in house' software program (see Figure 4.7)(324, 377). Many papers did not report which program they had used, with a staggering 23 different programs reported. Pulmonary Workstation is the principle software program used by COPDGene and does use the same 'region growing technique' as PULMO (72, 120). This heterogeneity of software programs is likely be a frequently recurring problem in respiratory imaging (e.g. in other conditions such as Interstitial Lung Disease (ILD)) as there is a shift towards quantitative imaging, and one that should be addressed sooner rather than later (393, 394).

Figure 4.7. Frequency Histogram to demonstrate the variety of software programs reported

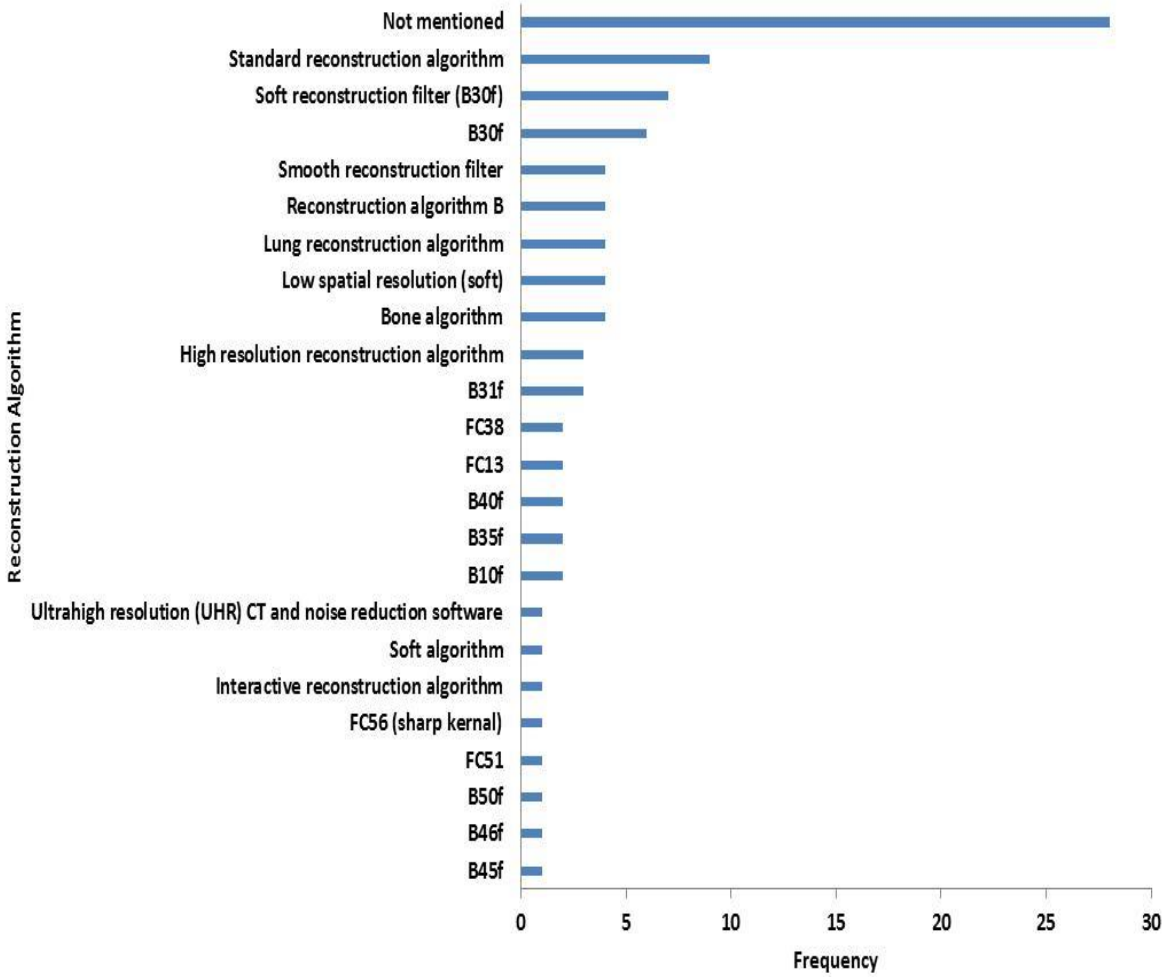


4.4.2. Reconstruction Algorithms

There is a clear consensus that a soft or smooth reconstruction algorithm is most appropriate for parenchymal/density analysis whereas a sharper algorithm is more suitable for airways analysis (130, 194). There is however no global definition for the exact reconstruction that constitutes a 'soft filter' with algorithms used varying between B10f and B45f. The most frequently reported algorithm was a 'standard algorithm' followed by 'soft' and then 'smooth' with no more detail regarding the resolution given. To add to the heterogeneity, 'B' algorithms are used by Siemens

scanners and 'FC' by Toshiba. Figure 4.8 summarises the different reconstruction algorithms reported throughout this review.

Figure 4.8. Frequency Histogram to demonstrate the variety of reconstruction algorithms reported

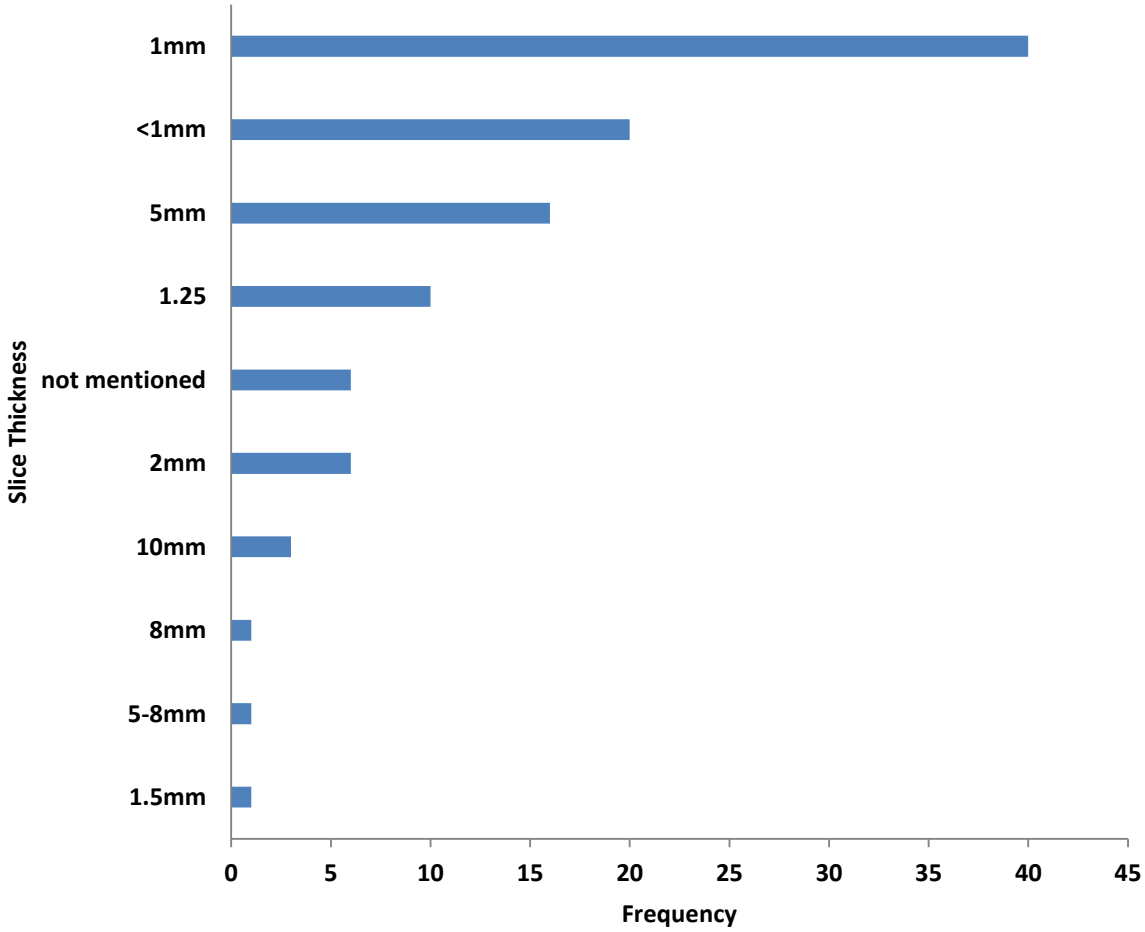


4.4.2. Slice Thickness

Varying slice thicknesses were used throughout with 1mm or less being the most commonly reported. 1mm is the choice of slice thickness used by Pulmonary Workstation which allows for airway and parenchymal measurement and is likely the reason why many other authors have chosen to use the same thickness. PULMO on the other hand uses 5mm as it is solely used to measure CT density. Thinner

slices however sacrifice the accuracy of the emphysema due to the fewer number of pixels, broadening the density histogram and over estimating the severity of emphysema(130). Figure 4.9 demonstrates the variety of slice thicknesses reported.

Figure 4.9. Frequency Histogram to the demonstrate variety of slice thicknesses reported



4.5. Bias assessment

4.5.1. Study Quality

Risk of bias is detailed in Table 4.12. Risk bias for all included studies and a summary is provided in Figure 4.10. Risk of Bias Summary The risk of bias tool was designed to ascertain the CT acquisition parameters and those relating to lung

function (e.g. were the PFTs performed before or after bronchodilation). Where there was no concern across each subheading, the paper was considered to be at low risk of bias. If two or more domains were determined to high risk, then the paper was described as high risk of bias, and then a pragmatic decision was taken on the remainder of papers whether they were felt to be medium risk. Two reviewers independently assessed the risk of bias for all 112 papers; none were considered to be high risk for all 4 domains and therefore were all included in the overall bias assessment. A key finding was that less than 40% of the papers reported the CT and PFT acquisition method adequately. Flow and timing was of high concern in 20% of the papers analysed. Ideally the two diagnostic tests, that is, CT and another clinical parameter, should be measured on the same day but there were a large number of papers where this could not be ascertained.

Table 4.12. Risk bias for all included studies

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

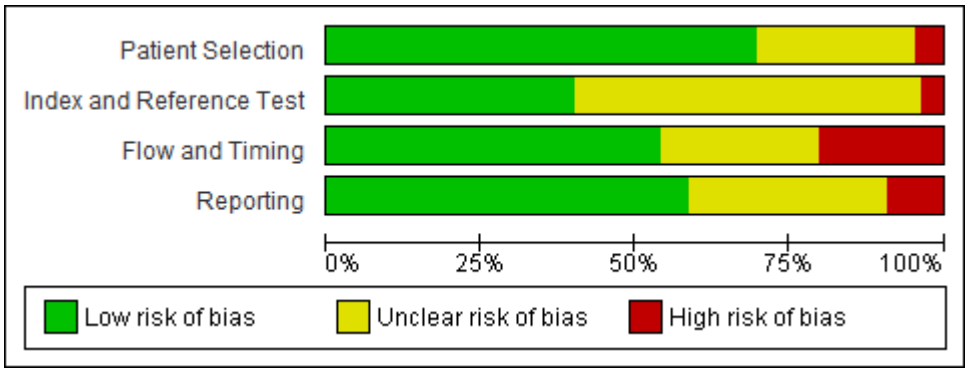
Kim et al, 2010	medium	medium	high	medium
Stolk, J. et al, 2007	medium	medium	high	medium
Johannessen, A. et al, 2013	low	medium	high	medium
Garfield et al, 2012	low	medium	high	medium
Pauls et al, 2010	low	medium	high	medium
Mohamed Hoesein, F. A. A. et al, 2011	low	low	high	medium
Stolk, J. et al, 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

Figure 4.10. Risk of Bias Summary



4.5.2. Publication bias

The funnel plots for --950HU versus FEV_1 percent predicted and DLCO percent predicted are presented in Figure 4.11and Figure 4.12, chosen as these were the most frequently reported values. Both show a significant degree of publication bias on initial inspection, though one study with a low standard error and large population (Washko et al 2008) causes the funnel to shift to the right.(378). Without this study, it stands to reason that the funnel would be more inclusive of the studies within the plot and would result in statistically less publication bias.

Figure 4.11. Funnel plot for studies correlating --950HU with FEV_1 percent predicted

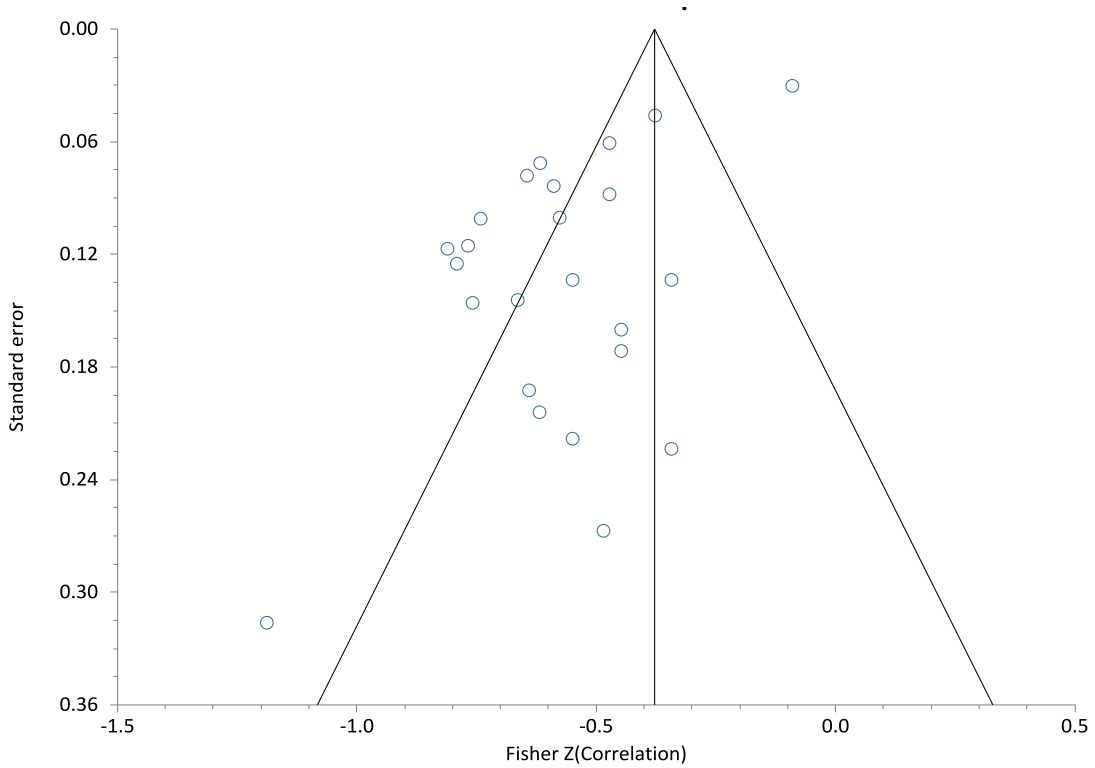
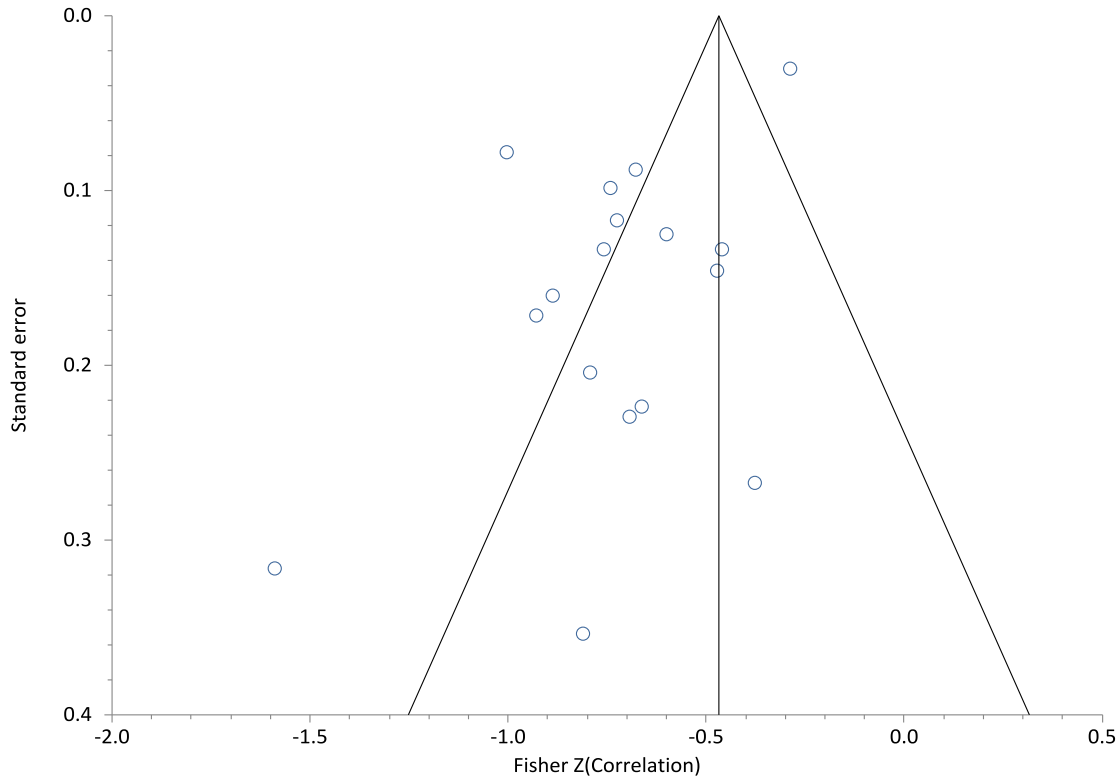


Figure 4.12. Funnel plot for studies correlating --950HU with DLCO percent predicted



4.6. Discussion

The purpose of this review was to summarise all the currently available literature regarding CT density and its association with commonly used clinical parameters to develop a clear understanding of for the utility of CT density measures for current and future clinical practice. This is particularly important as CT density has been used as a primary outcome in registration level clinical trials in AATD, but doubt has been cast by some authors as to its relevance as a surrogate outcome. (92),(93) Our data showed that association between CT density and other clinical parameters deemed suitable as outcomes for airways disease trials (e.g. FEV_1, SGRQ) was consistently significant, and furthermore there was a clear and consistent relationship to mortality. This suggests that CT density is an appropriate surrogate outcome measure in studies of emphysema, like those conducted in AATD. However, publication and other biases as well as study heterogeneity makes it more difficult to draw conclusions regarding the precise strength of each relationship.

Over half of the included studies were from larger cohort studies and subsequent retrospective/cross sectional analysis. The nature of these cohorts introduces heterogeneity in the types of patients recruited, i.e. lung cancer screening studies (NELSON)(395), alpha one cohorts, (319) COPD (e.g. COPDGene,KOLD(380, 396)), and end stage disease (e.g. NETT) (397).The consistency of direction of the relationship between density and lung function across diverse patient groups is reassuring and suggests density could be a valid surrogate outcome across the spectrum of disease severity. However, the wide range of values seen for the CT versus FEV_1 correlations meant that defining the exact level of CT density that

relates to, for instance, the Minimally Clinically Important Difference (MCID) for FEV_1 was difficult.

The chosen CT parameter (eg --950HU, PD15), software programme, reconstruction algorithm and slice thickness varied widely throughout. This level of heterogeneity was far greater than we had anticipated and made combination of all data via meta-analysis potentially less valid. The broad range of published correlation coefficients seen between --950HU and FEV_1% (Figure 4.2) (-0.1 to -0.8) demonstrated this well, and when variables during the CT acquisition process were adjusted for, the level of heterogeneity fell dramatically.

Besides the previously mentioned 3 variables, there are others that we did not account for. For example, the current and age of the XR tube, methods of volume adjustment or table height (132, 196). These further factors are known to have a significant impact on density values. To account for all possible variables would have been overly cumbersome and beyond the scope of this review which has demonstrated the impact parameter heterogeneity has on density analysis. However, it should be noted that whether emphysema is measured by PD or RA, without detailed description of corrections made, for example for volume, there must remain a reservation when considering the validity of CT density data.

This implies that future CT density studies should have a standardised approach. Despite PD15 being established as the most reliable and sensitive measure, we have seen many studies that do not use this parameter, and would encourage authors to report this value so that data can be combined and our knowledge can grow.

The most appropriate CT algorithm would be a soft reconstruction algorithm (e.g. B30f), slice thickness 2.5-5mm and a software programme that yields reliable and repeatable results. This algorithm and slice thickness is optimal due to minimal technical noise. Sharper algorithms and thinner slices have been demonstrated to overestimate the amount of emphysema.(194) Many publications used in-house software that, whilst producing useful data, may not be comparable to one another.(192) For example, Pulmo and Pulmonary Workstation are two of the most commonly used software programs (used in RAPID trial and COPDGene cohort studies respectively), and if identical and repeatable results can be produced by both programmes then cohort studies using them can then be combined and meta-analysed to increase power (92, 396). This requires direct comparison of the software on the same scans; a similar approach would be needed for slice thickness, reconstruction and so on. There are limited studies of this nature to date (195).

There was a paucity of longitudinal CT density data in the included studies, which precluded conclusions about the sensitivity and specificity of CT density change over time with respect to our chosen outcomes. This has meant we are unable to assess the relationship between CT density and clinical parameters over time for which there a known MCID (e.g. FEV_1 of 100mls), and therefore a proposal of a MCID for CT density was not possible. This would be of particular use for registration level trials which have used or intend to use this as their primary outcome. (398)

The key strengths of this review are that it was very broad; therefore all potential papers were captured. Rigorous checking of data extracted from the large number of

included studies occurred, and the statistical analyses were conducted with help from an experienced statistician.

Limitations were largely centred on the quality and heterogeneity of the included studies. There are other CT scanner variables we did not examine in more detail as their impact was considered less relevant, e.g. scanner type and radiation dose. Finally, there were 14 papers in languages to which we did not have access to a translator such as Japanese and Korean. This was due to funding limitations, and ideally all studies would have been translated. In some cases the abstract alone was translated by the publisher, so we can be reasonably confident that no major omissions have resulted from this limited assessment of the data.

4.7. Conclusion

This evidence synthesis has demonstrated that CT density relates significantly to all commonly used clinical parameters. However, the large amount of heterogeneity and lack of longitudinal data means that how sensitive and specific CT density is to change relating to time or interventions is not clear. We recommend that international consensus is reached to standardise CT conduct and analysis in future emphysema studies.

Chapter 5 . Exploration of the variability between observers analysing CT density and between the two leading software programs

5.1. Introduction

Quantitative Computed Tomography (qCT) exemplifies how pulmonary imaging in is evolving towards precision medicine for assessment and treatment of emphysema. The sensitivity index of qCT is greater than that of lung function or Quality of Life (QoL) questionnaires, and the ability to demonstrate the type and distribution of emphysema is an attractive feature not possible with other modalities (142, 399). However, in order to have confidence in the results generated there needs to be proven reliability and repeatability of the instrument. The lack of consensus over the optimal CT acquisition parameters, and the lack of standardisation currently stands in the way of qCT being used in clinical care.

There is an important difference to distinguish between repeatability measured by the intra-class correlation coefficient (ICC) and the level of agreement. The ICC measures the relative consistency of the measure and any differences may be ascribed to the error of measurement process (400). To put this into context of other respiratory investigations, the ICC for FEV_1 (L) is 0.97 and MRC grade is 0.82(401). Agreement quantifies how similar the two measurements are and the precision of the instrument. This 'true variance' reflects associated factors including biological noise, error on behalf of the subject or the examiner and so on(400).

Ensuring equal results are produced when the same scan is analysed repeatedly will evidence the reproducibility of CT densitometry. There will always be an element of

technical noise associated with a measurement tool, but this variability should remain within the set confidence limits. The intra-observer variability has not been reported for thoracic CT density specifically but a study measuring diameter and attenuation of renal cell carcinomas reported the intra-class correlation coefficient (ICC) as 0.998 (402). Inter-observer variability has been investigated to a greater extent in the literature and an ICC >0.9 reported(292).

By assessing the intra- and inter observer variability within our cohort we will in parallel validate my own analyses of CT scans. One of my supervisors (DS) reanalysed a subset of CT scans in order to determine the correlation coefficient and the level of agreement. In addition, CT scans analysed by a previous fellow (DP) in 2002-2004 were sourced and reanalysed, and the results of his comparisons and mine compared. Providing the results of the analyses were equal, we would have confidence in my ability to accurately analyse the CT scans and proceed further.

The software programs used for CT density measurement have recently been reviewed in chapter 4. We found that most frequently the software programme was either not mentioned, or was 'custom built'. Wielputz et al previously compared the analyses of three software programmes (YACTA, LowATT and Pulmo 3D) finding marked differences between the measurements of emphysema, concluding that this hampered qCT becoming an accepted biomarker in COPD (192).

Since this time 2 density analysis programs are emerging as leaders in the field. The most frequently reported program PULMO has been used in the "Exacerbations and Computed Tomography scan as Lung End-points" (EXACTLE) trial and

"Randomized Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency" (RAPID) (92, 319). Both trials reported change in CT density as their primary outcome measure, and used CT slices of 5mm thickness. Pulmonary Workstation, a product of VIDA diagnostics founded at the University of Iowa, is designed to analyse airways and parenchymal density. Used by the COPDGene authors to analyse CT scans, numerous publications have arisen that cross-sectionally examine the associations between CT density and lung physiology or quality of life (72, 349, 378). Pulmonary Workstation uses 1mm slices which allows for airway and parenchymal measurement, whereas PULMO is used solely to measure CT density. Thinner slices sacrifice the accuracy of the emphysema due to the fewer number of pixels, broadening the density histogram and over estimating the severity of emphysema.

5.2. Methods

5.2.1. Internal Validation and the generation of an intra-class correlation coefficient

CT density analysis was performed on 15 scans twice by myself (DC) on two separate occasions three months apart, from patients with COPD with varying severity as defined by the FEV1. 9 CT scans were analysed by DC and then independently re-analysed by one of my supervisors (DS) in order to determine the level of inter-observer agreement. A further 17 CT scans previously performed and analysed by a previous fellow (DP) between 2002 and 2004 studies were additionally accessed. They were analysed by a previous fellow (DP), and the results from these

historic analyses and those repeated by myself were compared. Between the 2002/2004 scans and those performed by myself, there has been an update in the PULMO software program, which may introduce an element of variability.

The mean and SD, or median and IQR, depending on the normality of each variable was calculated and expressed as percent predicted for age, sex, race and height (see appendix). Bland Altman plots were created using SPSS (version 22) by establishing the mean difference between the sets of results and 95% confidence intervals. If the true differences between two sets of measurements have a normal distribution, 95% of differences will lie within 1.96*standard deviations of the mean. In general though, the 95% limits of agreement from a Bland-Altman analysis will not contain 95% of true differences, because both the mean and standard deviation used in the calculation of the limits of agreement are estimates rather than true values. Therefore in order to determine confidence in the findings, Monte Carlo methods were used to establish the true limits of agreement.

5.2.2. Comparison and Evaluation of CT density analysis between the two leading software programs

50 patients underwent CT scanning between May 2014 and February 2016 at the Queen Elizabeth Hospital Birmingham, recruited to ADAPT programme and participating in the ongoing NIHR Rare Diseases Consortium. (285, 286) All scans were performed on a Siemens scanner during deep inspiration. A smooth reconstruction filter (B30f) was used and both 1mm and 5mm slices created. Air and water calibration are performed on a daily basis as part of routine CT conduct. Images were analysed using PULMO CMS (developed at the Leiden University

Medical Centre) in the UK and then the images sent by DICOM format to National Jewish Health for analysis by Chest Imaging Platform (CIP). Linear regression was performed and the correlation coefficient calculated. Bland Altman plots were used to confirm any agreement. A t test or a Mann Whitney U depending on normality distribution was performed and the level of significance set at $p<0.05$.

5.3. Results

5.3.1. Internal Validation

5.3.1.1. Intra-observer validation

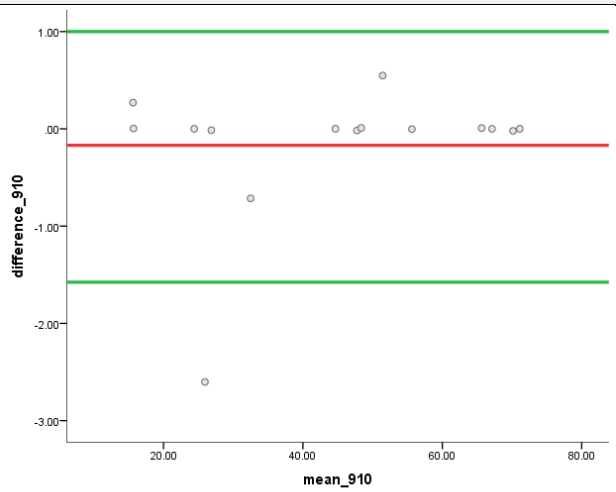
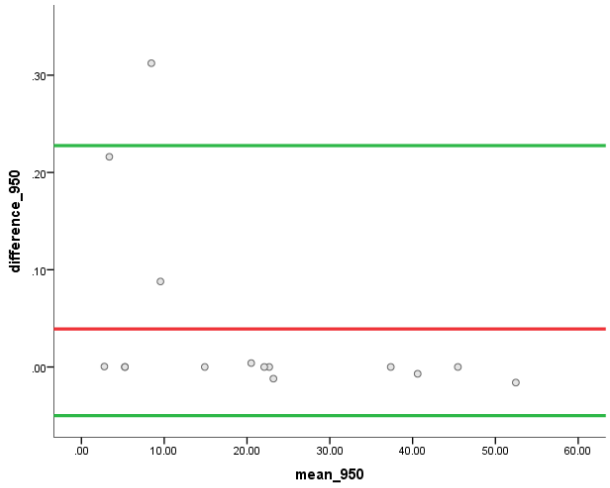
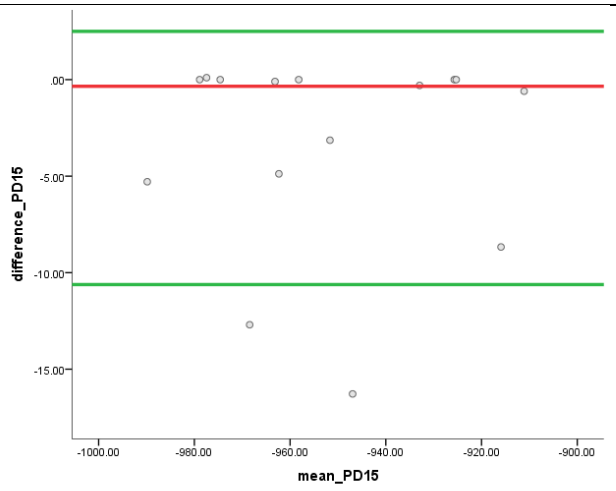
Table 5.1 details the clinical characteristics of the 17 patients included in the analysis. The mean FEV_1 percent predicted was 52.97% (GOLD stage 2), with evidence of hyperinflation within the cohort confirmed by the elevated TLC and RV percent predicted (117% for each).

Table 5.1. Patient Characteristics Table

Clinical Parameter	**Mean (SD)**
Age	62.34 (11.3)
Sex	9 M 8 F
FEV_1pp	52.97 (22.53)
FEV_1/FVC (%)	39.15 (13.4)
KCOpp	70.3 (8.05)
TLCpp	117.4 (18.1)
RVpp	117.19 (18.22)

Figure 5.1 demonstrates the Bland Altman plots for repeated measurements by the same observer and show that nearly all measurements lay within the expected levels of agreement, with only one or two outliers within each CT density parameter. As Bland Altman plots use 95% limits of agreement, certainly one outlier could be expected.

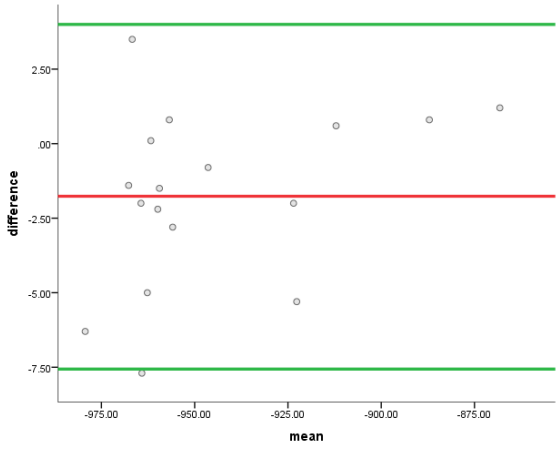
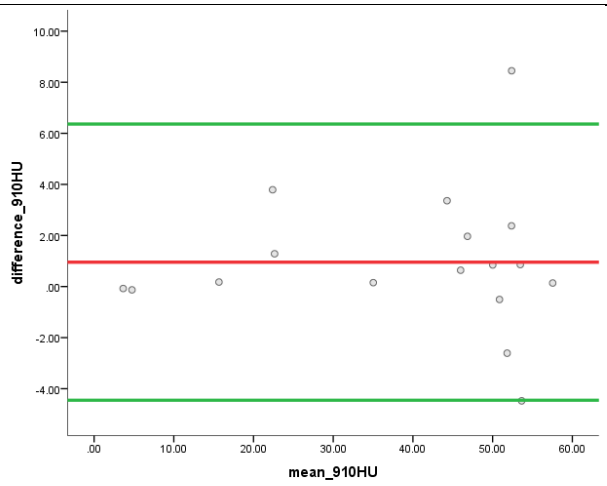
Figure 5.1. Bland Altman plots of the intra-observer variability

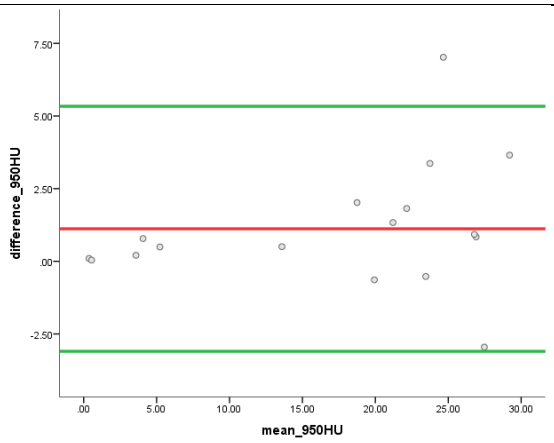
CT Density Measure	Bland Altman Plot
-910HU	
-950HU	
PD15	

5.3.1.2. Inter-observer validation

The correlation between these analyses performed by DC and DS was very strong with r values for -910, -950 and PD15 of 0.981, 1.0 and 0.995 respectively. The Bland-Altman plots in Figure 5.2 demonstrate good agreement between the results between observers, with just one outlier on each plot, and no proportional bias.

Figure 5.2. Bland Altman plots to demonstrate the inter-observer agreement

CT Density Measure	Bland Altman Plot
PD15	
-910HU	

-950HU	

5.3.3. Comparison of the two leading software programs

5.3.3.1. Patient Characteristics

It was not possible to analyse 3 out of 50 scans due to issues with automatic segmentation. For the remaining 47 patients, a summary of the baseline patient characteristics is shown in Table 5.2. The mean FEV_1 percent predicted was 63.89% (GOLD stage 2), with evidence of hyperinflation within the cohort confirmed by the elevated TLC and RV expressed as percent predicted for age, sex, race and height (259).

Table 5.2. Patient Characteristics Table

Clinical Parameter	**Mean (SE)**
Age	61.53 (11.3)
Sex	26 M 21 F
FEV_1pp	63.89 (6.93)

FEV_1/FVC (%)	44.87 (20.08)
KCOpp	70.2 (3.04)
TLCpp	111.35 (3.85)
RVpp	107.03 (6.19)

5.3.3.1. 1mm slices Pulmonary Workstation versus PULMO

Table 5.3 demonstrates the overall mean assessment of density and inspiratory volume for the two programs. There is an average (though non-significant difference) of 110ml difference in the inspiratory volume and no significant difference between the two programs for each measure of emphysema.

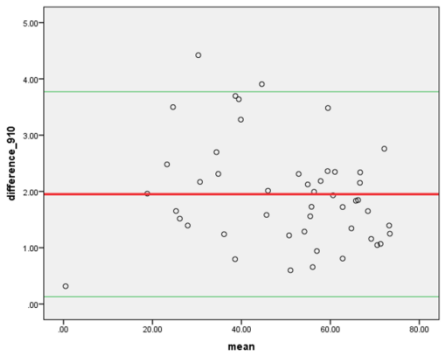
Table 5.3. Comparison of lung volume (inspiratory) and emphysema estimation between PULMO and CIP using the same slickness

	PULMO 1mm	**CIP 1mm**	**P value**
-910HU (%)	51.85 (15.51)	49.96 (15.75)	0.554
-950HU (%)	27.36 (14.37)	25.57 (13.98)	0.49
PD15 (HU)	-970 (31.18)	-969 (-32)	0.631
Volume (L)	6.6 (1.47)	6.71 (1.43)	0.853

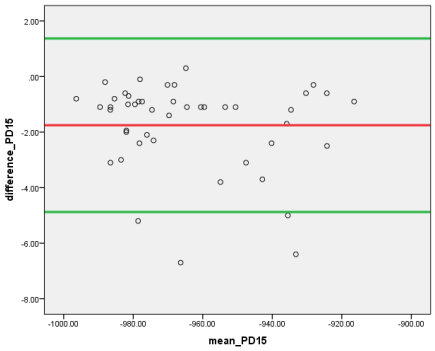
Figure 5.3 demonstrates the Bland Altman plots for the two programs. For volume, -910HU and -950HU all but two data points are within the limits of agreement. The mean difference for PD15 estimation was 1.8HU and 66ml for volume estimation performed on CT. These similar results indicate that a correction could and should also be made for these parameters. There were 4 out 47 data points beyond the limits of agreement for PD15 though no significant bias and the outliers did not have extremes of lung function or disease.

Figure 5.3. Bland Altman plots between the two software programs for volume and emphysema estimation using same slice thickness.

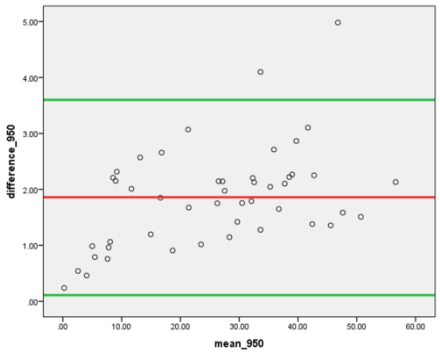
910HU



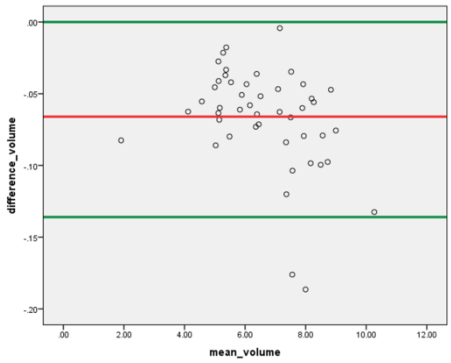
PD15



950HU



Volume



5.3.3.2. 1mm Pulmonary Workstation vs 5mm PULMO

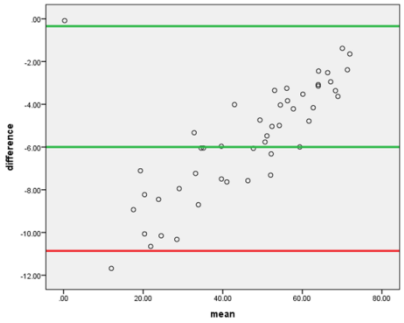
Table 5.4 demonstrates larger differences in the emphysema assessment between the two programs for the different slice parameters used especially for PD15 (p=0.005). Figure 5.4 shows the Bland Altman plots for each emphysema measurement and volume with the slice differences. There is clear proportional bias demonstrated for emphysema measurement with one of the programmes consistently overestimating the degree of emphysema especially at the extremes of measurement.

Table 5.4. Comparison of mean assessment of volume and emphysema between PULMO and CIP using different slice thicknesses

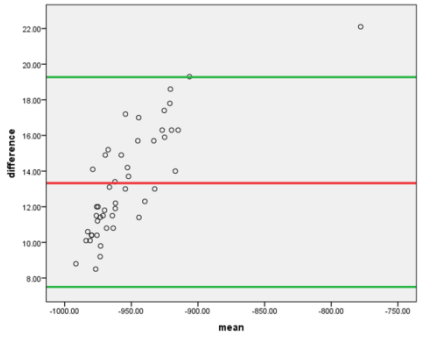
	PULMO 5mm	**CIP**	**P value**
-910HU (%)	43.37 (18.94)	49.96 (15.75)	0.66
-950HU (%)	19.31 (13.7)	25.57 (13.98)	0.60
PD15 (HU)	-957 (-35.3)	-969 (-32)	0.005
Volume (L)	6.66 (1.65)	6.71 (1.43)	0.977

Figure 5.4. Bland Altman plots between the two software programs for volume and emphysema estimation using the different slice thicknesses reported for each programme

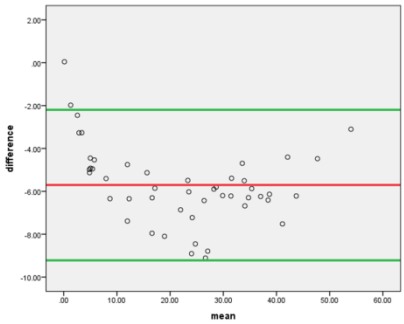
910HU



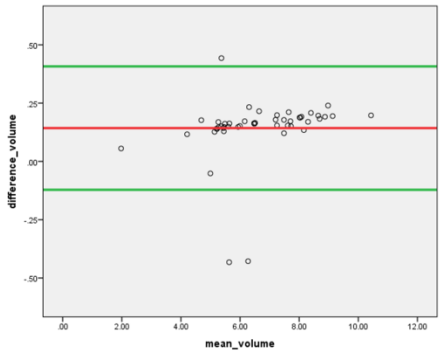
PD15



950HU



Volume



5.4. Discussion

The results of the validation work for both intra and inter-observer analyses demonstrated there was strong agreement and therefore appropriate to proceed with further analyses. The Bland Altman plots in Figure 5.1 and Figure 5.2 show the agreement, with one or two outliers' only and no proportional bias. By using Monte Carlo technique, there was an 80% chance that the 95% limits of agreement estimated from a sample of 17 pairs of measurements will contain 90% or more of the true differences. It would be arguably inappropriate however to calculate power at this

point, as with no reasonable prior knowledge of the relationship between the two sets of analyses then estimates cannot be built in to the calculation.

The summary ICC for each CT density threshold based on the observed variability is 0.99 which can be used for future work applying the standard error of the mean (SEM) calculations. That is when assessing CT density, there is only 1% error that can be attributed to the noise of the instrument and the remainder is that reflective of disease.

The software comparison data compares the 2 most widely used software programmes for assessing pulmonary emphysema quantitatively(91). We have demonstrated that analysing CT scans with either programme but with the same slice thickness, produces comparable results for volume and for emphysema estimation as -910HU, -950HU and PD15 with only minor and insignificant differences. For emphysema estimation, based on our results we would recommend a minor correction factor of 2.47% for -910HU, 1.18% for -950HU, or 1.8HU for PD15.

However, when using the different slice thicknesses the Bland Altman plots showed consistent proportional bias in emphysema quantification and therefore no suitable agreement. This is consistent with the previous literature recommending use of the same slice thickness due to the recognised over-estimation of emphysema with thinner slices (195). There is currently an international consensus to address this (Quantitative Imaging Biomarker Alliance) (403) which may address this issue as raised in the recent CT density systematic review and is clearly essential for acceptance of this biomarker as a key outcome measure for future treatments. .

The most recent similar publication to our analyses was that by Wielputz et al in 2014 (192) that compared 3 different software programmes (YACTA, lowATT and Pulmo3D). These 3 programs are, however, infrequently used in the literature and it was only possible to analyse 43% of scans for CT density with all 3 programs due to segmentation errors(404). The authors found a significant difference in both the emphysema and volume estimation between each of the three programs ($p<0.001$). By comparison we were able to analyse 94% scans using PULMO and CIP, demonstrating better reproducibility. PULMO and CIP produced similar results for volume and emphysema estimation using both the same and different slice thicknesses, with the exception of PD15 comparing 1mm vs 5mm slices ($p=0.005$). This difference is likely due to higher sensitivity of PD15 for emphysema quantification as previously described(131). Both PULMO and CIP showed identical and significant correlations of density to lung function not seen by Weilputz et al providing further support for the results reported here. The strength of the current study is that the scans were analysed independently by physicians with a specialist interest in quantitative CT and a depth of experience in the field. A wide range of severity (as defined by FEV_1) was included and therefore the results are generalizable for all stages of emphysema. One minor limitation of our study was perhaps the sample size, although the tight correlations seen suggest confidence in the result. Inter-observer variability invariably exists, though the published literature regarding the test retest intra-class correlation coefficient for qCT analysis suggests this is greater than 0.9 (292).

5.5. Conclusion

In conclusion, the ICC for CT density analysis using --910HU, --950HU and PD15 is 0.99. Emphysema and volume estimation between PULMO and CIP using the same slice thickness is comparable and could be combined using the recommended adjustment factors. However, attention must be paid to the slice thickness used in emphysema quantification as this will produce significant differences between cohorts.

Chapter 6 Evaluation of the relationship between CT density and common clinical parameters using the Birmingham Alpha one Antitrypsin Deficiency cohort.

6.1. Introduction

The Antitrypsin Deficient Assessment and Programme for Treatment (ADAPT) was established in 1996, recruiting patients with AATD into the research registry in order to further understanding and management of the disease. Research that has arisen from the registry spans multiple sub-specialities including neutrophil studies, lung physiology and small airways disease, and COPD biomarkers. Quantitative CT has been performed as an imaging biomarker of emphysema severity by the ADAPT group since 2002, with 423 scans have been performed on over 220 patients. These included patients recruited into studies such as EXACTLE (Exacerbations and Computed Tomography scan as Lung End-points) and NIHR Translational Research rare disease consortium. Prior to 2002, density mask analysis had been performed on a small number of scans, but was done so on a software program and slice thickness incomparable with scans performed post 2002. All scans included in subsequent analyses have all been performed using the approved CT protocol of a smooth reconstruction algorithm (B30f), slice thickness 5mm and an increment of 2.5mm. The same software programme (PULMO) was used throughout, and they were all analysed using three emphysema thresholds: -910HU, -950HU and the PD15 method.

The systematic review (chapter 4) concluded that despite an overall significant association between CT density and clinical parameters, there was marked heterogeneity throughout, meaning a meta-analysis was only possible for those studies reporting a correlation coefficient. With regards to mortality, there were three studies which reported a hazard ratio for %LAA and risk of death, but none of them reported mortality with respect to PD15. Several publications regarding mortality and PD15 once divided into upper and lower zone have been produced from the ADAPT group, but none regarding whole lung PD15.

6.2. Methods

Multiple databases have produced independently by different clinical fellows over the past 10 years, and therefore the first hurdle to overcome was to combine these and then 'clean' the database so that one up to date comprehensive database now exists. Added to these previous analyses were all those analysed by myself as part of the NIHR rare diseases consortium, and scans analysed during the validation work, where the results were previously either not reported or were in paper format. In order to describe the cohort with regards to the associations with clinical parameters such as lung function and mortality, the results have been subdivided into cross sectional analyses and longitudinal analyses. Full details on the statistical methods may be found in chapter 3.3.

6.3. Results

6.3.1. Cross-Sectional Analysis

6.3.1.1. Baseline Characteristics

204 patients have received at least 1 CT scan using the recommended CT acquisition parameters (i.e. smooth reconstruction algorithm, 5mm slice thickness with 2.5mm increment). Table 6.1 summarises the patient characteristics as assessed within a mean of 63 days of their baseline scan. FEV_1 measured in litres and as a percent predicted was found to be significantly different between survivors and non-survivors, as was the FEV_1/FVC. KCO was significantly lower in non-survivors as was (RV and pack year history. All 3 measurements of CT density (-910HU, -950HU and PD15) showed no difference between in those alive and those who had died.

Table 6.1. Baseline Characteristics Table

	Whole Group	**Alive**	**Dead**	**Significance**
Age	64.8 (11.48)	62.18 (10.7)	72.18 (10.26)	0.0001
FEV1	1.58 (1.11)	1.67 (1.21)	1.55 (0.85)	0.032
FEV1%	55.39 (38.34)	57.86 (39.03)	46.94 (29.79)	0.007
PD15	-957.1 (26.65)	-954.64 (28.46)	-958.8 (25.45)	0.446
-910HU	43.13 (19.41)	43.06 (18.28)	43.28 (16.67)	0.949
-950HU	19.41 (13.11)	19.06 (13.5)	20.14 (12.34)	0.53
FVC	4.13 (1.22)	4.08 (1.18)	4.21 (1.31)	0.851
FVC%	107.3 (20.72)	107.55 (20.1)	106.76 (22.13)	0.473
FEV/FVC	44.02 (17.73)	46.17 (17.91)	39.39 (16.54)	0.005
TLCO	5.72 (2.28)	5.68 (2.18)	5.8 (2.47)	0.994
TLCO%	61.83 (20.55)	62.27 (20.39)	61.02 (21.02)	0.603
KCO	1.03 (0.34)	1.09 (0.36)	0.97 (0.3)	0.036
KCO%	64.76 (19.08)	67.39 (20.65)	61.66 (16.69)	0.08
RV	2.42 (1.1)	2.29 (0.95)	2.78 (3.47)	0.028
RV%	115.16 (40.67)	110.46 (32.24)	127.74 (43.42)	0.036
TLC	7.24 (1.68)	6.98 (1.55)	7.55 (1.8)	0.117
TLC%	112.48 (17.26)	110.98 (17.5)	115.50 (16.5)	0.095
RV/TLC	36.81 (11.3)	36.20 (10.07)	38.02 (13.47)	0.338
RV/TLC%	102.4 (41.8)	99.671 (36.68)	109.14 (54.26)	0.158
Pack Years	19.48 (13.62)	17.22 (12.98)	24.06 (13.87)	0.004

*presented at mean (SD) or median (IQR).

6.3.1.2. Spirometry

6.3.1.2.1. Univariate Analysis

Table 6.2 summarises the correlation coefficients between the three measures of CT density and spirometric measures. The strongest correlation can be seen between PD15 and FEV_1 percent predicted, with 87.8% of the variability of FEV_1 percent predicted accounted for.

Table 6.2. Summary of correlation coefficients between spirometry and CT density

Variable	PD15	p value	950	p value	910	p value
FEV1	0.604	<0.0001	0.59	<0.0001	0.570	<0.0001
FEV1pp	0.937	<0.0001	0.646	<0.0001	-0.663	<0.0001
FVC	0.093	0.101	-0.07	0.166	0.063	0.195
FVCpp	0.144	0.023	0.179	0.007	-0.084	0.123
FEV/FVC	0.712	<0.0001	0.697	<0.0001	0.774	<0.0001

Figure 6.1 demonstrates the significant differences in CT density between each of the GOLD stage groups. Figure 6.2 shows the individual scatter plots between FEV1 (L) and -910HU, -950HU and PD15.

Figure 6.1. Box plots to demonstrate differences in CT density as subdivided into GOLD stage groups.

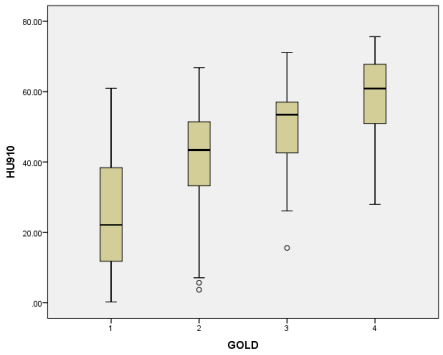
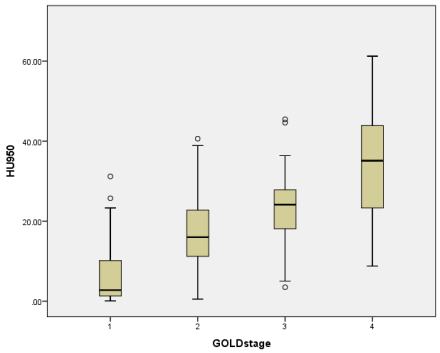
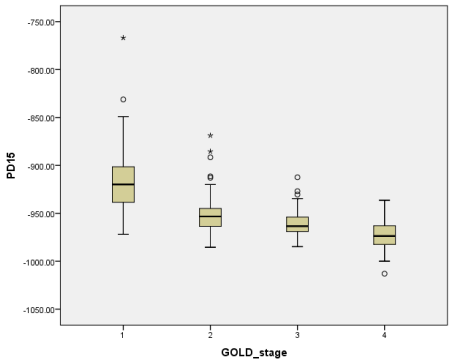
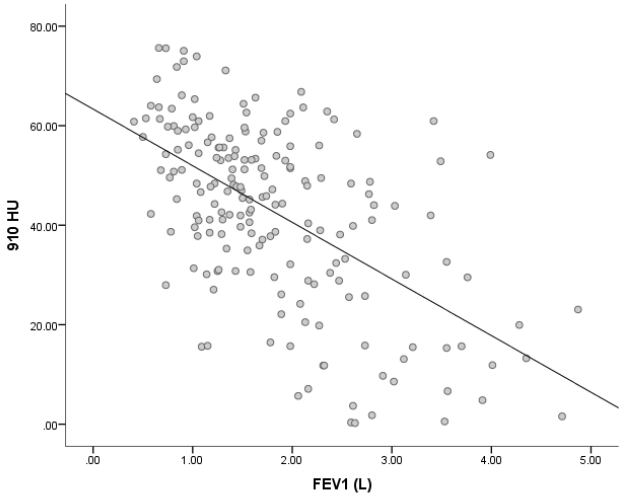
	GOLD and CT density box plot	P value*
A -910HU		<0.0001
B -950HU		<0.0001
C PD15		<0.0001

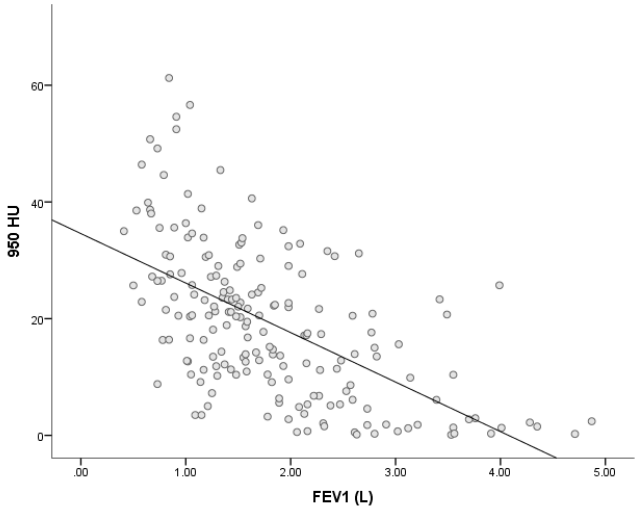
Figure 6.2. Scatter plots between each CT density threshold and FEV_1 (L)

A - 910HU



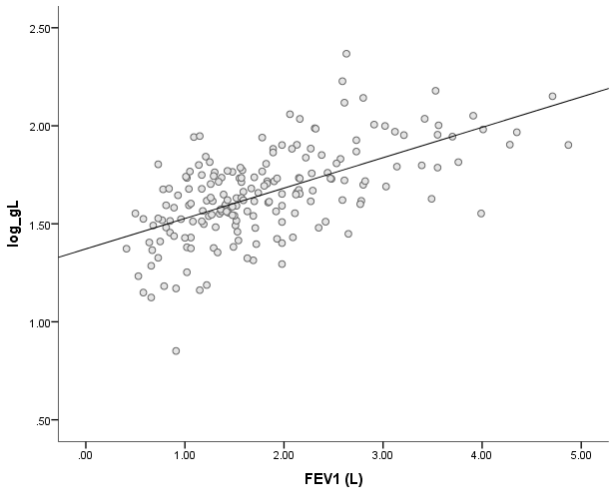
p<0.0001

B - 950HU



p<0.0001

C PD15



p<0.0001

6.3.1.2.2. Multivariate analysis

Table 6.3 demonstrates the sequential adjustment of FEV_1 against PD15 for age, height, sex and pack years, which remains significant throughout. The r2 value for PD15 and FEV_1 strengthened with each variable included (r^2 for FEV_1 adjusted for age, height, sex and pack years equals 0.407), reiterating the strength of the relationship.

Table 6.3. Forward step multi-linear regression between PD15 and FEV_1 (L)

	Unstandardized Beta Coefficient	Constant	Lower Bound 95% Confidence Interval	Upper Bound 95% Confidence Interval	P value
FEV_1	0.155	1.372	0.125	0.185	<0.001
Adjusted for age	0.151	1.458	0.120	0.182	<0.001
Adjusted for age and sex	0.162	1.233	0.132	0.192	<0.001
Adjusted for age, sex and height	0.17	1.958	0.14	2.01	<0.001
Adjusted for age, sex, height and pack years	0.17	2.136	0.131	0.208	<0.001

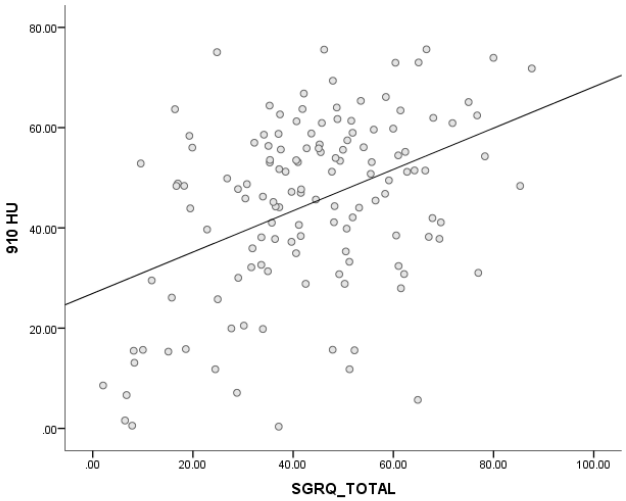
6.3.1.3. St George's Respiratory Questionnaire (SGRQ)

6.3.1.3.1. Univariate Analysis

There is a significant relationship between CT density and SGRQ as measured by Pearson's correlation coefficient (Figure 6.4). The association is marginally stronger between PD15 and SGRQ though all are significant, with a p value <0.001.

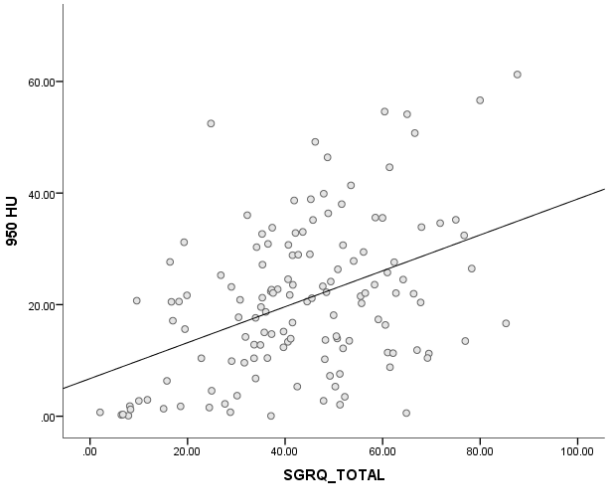
Figure 6.3. Scatter plots between each CT density threshold and SGRQ

A



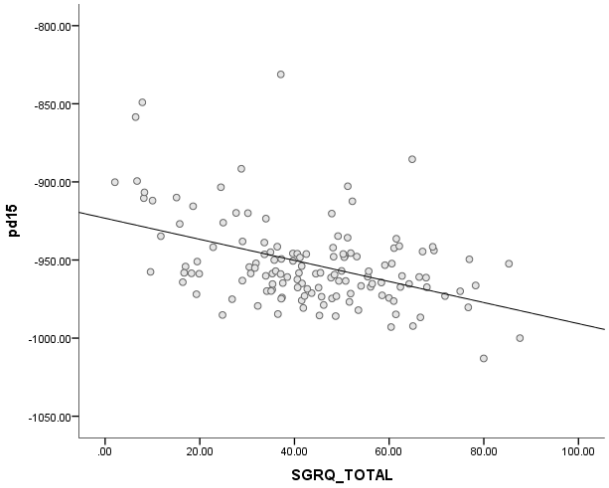
R=0.423 p<0.001

B



R=0.429 <0.001

C



R=-0.442 <0.001

6.3.1.3.2. Multivariate Analysis

The relationship between SGRQ and PD15 remained significant following adjustment for age, sex, height and pack years (table 6.4). In the same manner as FEV_1, the r^2 value improved once adjustments had been made.

Table 6.4. Summary of the r^2 values between SGRQ and PD15 following sequential adjustment

	Adjusted r^2 value	**P value**
SGRQ	0.196	<0.001
Adjusted for age	0.189	<0.001
Adjusted for age and height	0.190	<0.001
Adjusted for age, sex and height	0.184	<0.001
Adjusted for age, sex, height and pack years	0.223	<0.001

6.3.1.4. Gas Transfer

There is a significant correlation between each of the measures of gas transfer and CT density, albeit slightly less significant than for FEV_1 (see table 6.5). The relationship between KCO and PD15 remains significant even after adjustment for FEV1 (L) and the adjusted r^2 value of 0.44 indicates CT density can explain approaching 50% of the variability seen in KCO (see table 6.6).

Table 6.5. Summary of correlation coefficients between gas transfer and CT density

Measurement	PD15	P value	--950HU	P value	--910HU	P value
TLCO	0.513	<0.001	0.532	<0.001	0.482	<0.001
TLCOpp	0.604	<0.001	0.640	<0.001	0.608	<0.001
KCO	0.679	<0.001	-0.606	<0.001	-0.677	<0.001
KCOpp	0.598	<0.001	0.588	<0.001	0.628	<0.001

Table 6.6. Forward step multi-linear regression between KCO and FEV_1 (L)

	Unstandardized Beta Coefficient	Constant	Lower Bound 95% Confidence Interval	Upper Bound 95% Confidence Interval	P value
KCO	0.402	1.291	0.301	0.495	<0.001
Adjusted for age	0.421	1.182	0.319	0.523	<0.001
Adjusted for age and sex	0.415	1.179	0.307	0.523	<0.001
Adjusted for age, sex and height	0.416	1.341	0.308	0.525	<0.001
Adjusted for age, sex, height and pack years	0.419	1.617	0.299	0.539	<0.001
Adjustment for age, sex, height, pack years, FEV_1	0.222	2.023	0.086	0.359	0.002

6.3.1.5. Lung Volumes

RV and TLC both significantly correlated with CT density, though this appears to be the weakest association of the clinical parameters thus far (see table 6.7). Both TLC measured as percent predicted, or RV/TLC percent predicted had no association with CT density.

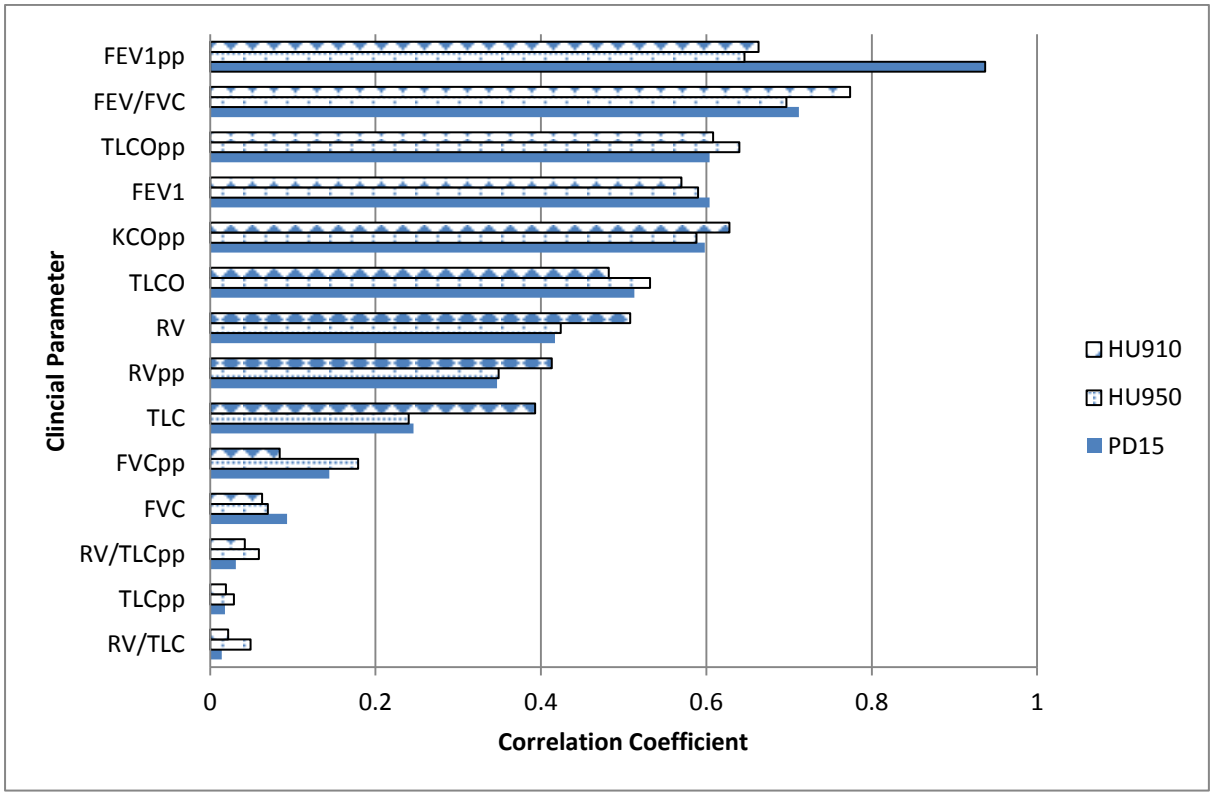
Table 6.7. Summary of correlation coefficients between volumes and CT density

	PD15	p value	--950HU	p value	--910HU	p value
RV	0.417	0.000	0.424	0.000	0.508	0.000
RV%	0.347	0.000	0.349	0.000	0.413	0.000
TLC	0.246	0.003	0.240	0.005	0.393	0.000
TLC%	0.018	0.411	-0.029	0.361	-0.019	0.405
RV/TLC	-0.014	0.430	0.049	0.271	0.022	0.393
RV/TLC%	-0.031	0.353	0.059	0.236	0.042	0.304

6.3.1.6. Summary

FEV_1 measured as a percent predicted showed the strongest correlation with CT density, and in particular FEV_1 (r=0.937) (see figure 6.5). Measures of volume including FVC demonstrated the weakest relationship with CT density, with either minimal or no significance between the two variables.

Figure 6.4. Summary of the correlation coefficients between each CT density measure and clinical parameters



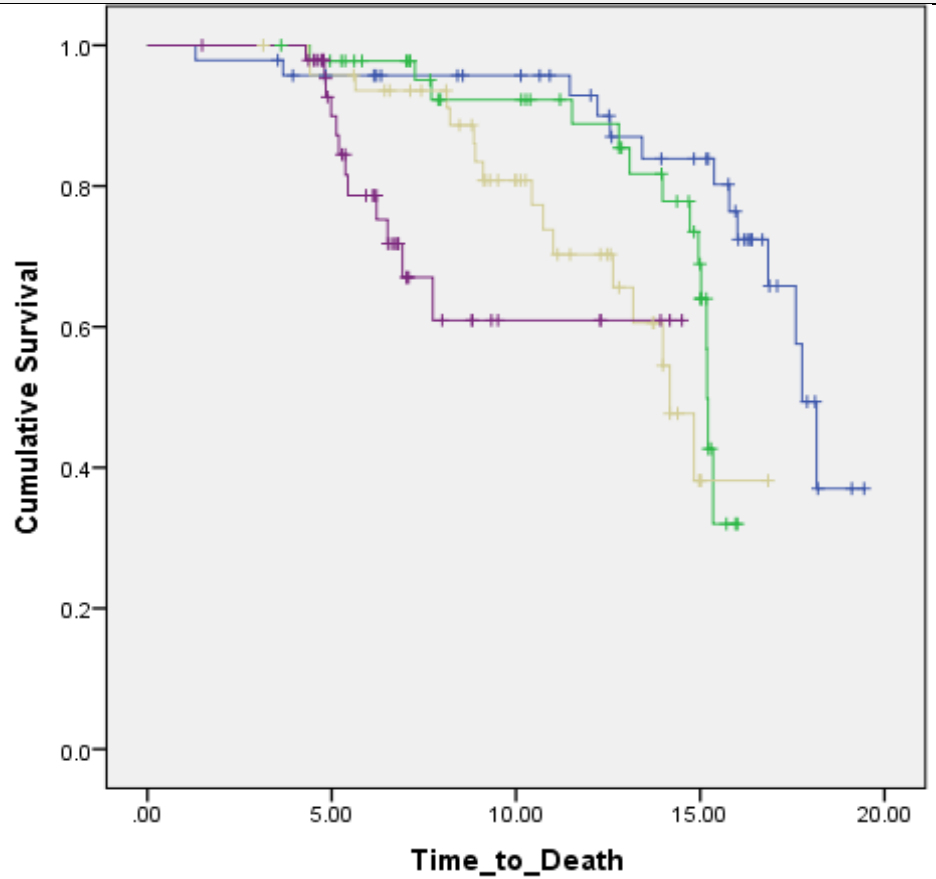
6.3.2. Longitudinal analysis

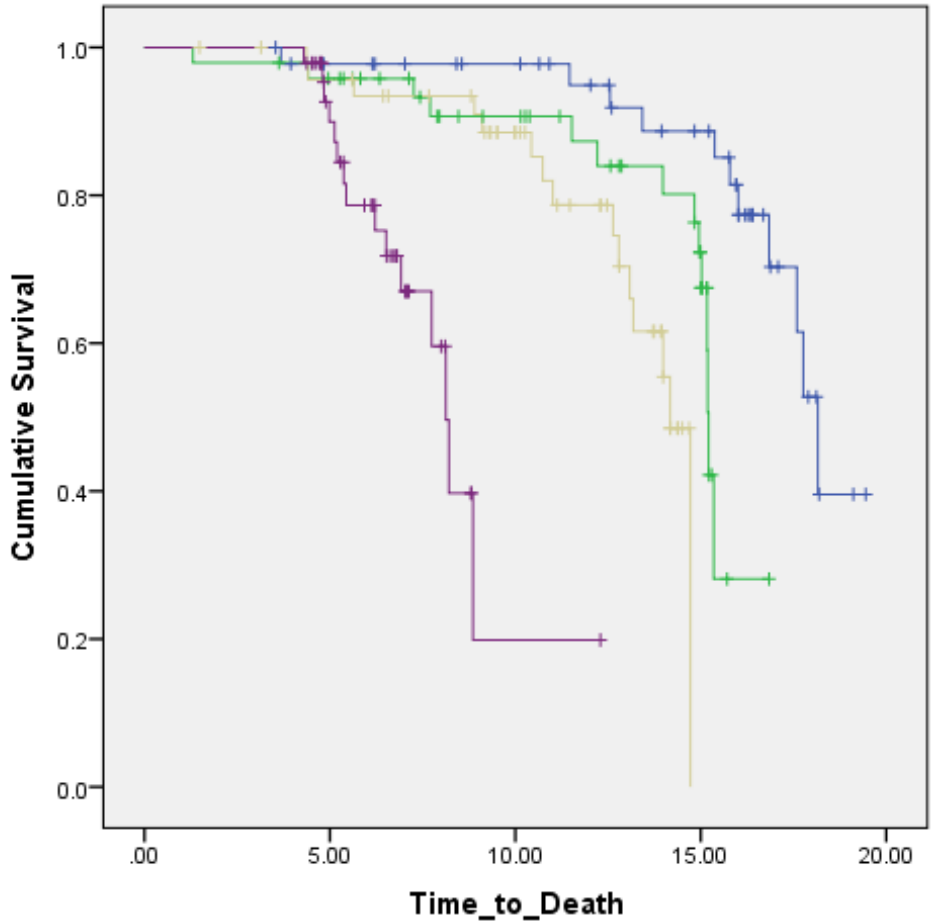
6.3.2.1. Mortality

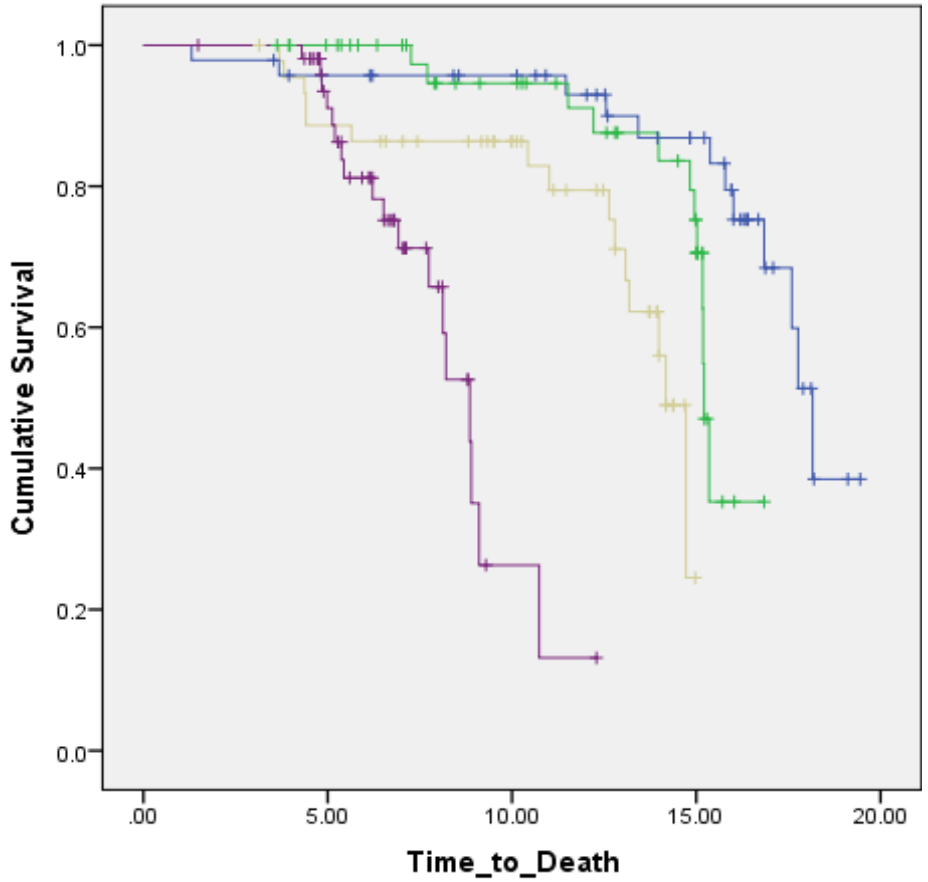
6.3.2.1.1. Kaplan-Meier Plots

The ADAPT cohort was subdivided into 4 quartiles of worsening emphysema severity as measured by PD15. These quartiles were (1) >-940HU (2) -940 to -956HU (3) -957 to -966HU and (4) <-967HU. Table 6.8 demonstrates the Kaplan Meier plot with each quartile shown. The estimated time to death for those in the 4th quartile is 9.9 years, compared with 13.1 years for those in the first quartile (Log Rank chi square value 13.691, p=0.003).

Table 6.8. Kaplan Meir plots to demonstrate the influence of CT density on mortality

Emphysema threshold	Kaplan Meier Plot	Quartile	Time to death (years)	Log rank p value
-910HU		1: (Blue) <31%	16.842	<0.0001
		2: (Green) 31-45%	14.433	
		3: (Yellow) 46-55%	13.451	
		4: (Purple) >55%	11.151	

-950HU		1: (Blue) <9.5%	17.382	<0.0001
		2: (Green) 9.5-19%	14.463	
		3: (Yellow) 19.1-27.5%	13.007	
		4: (Purple) >27.5%	8.241	

PD15		1: (Blue) >-939HU	12.8	<0.0001
		2: (Green) -939HU to -956HU	11.97	
		3: (Yellow) -957HU to -966HU	11.12	
		4: (Purple) <-967HU	9.94	

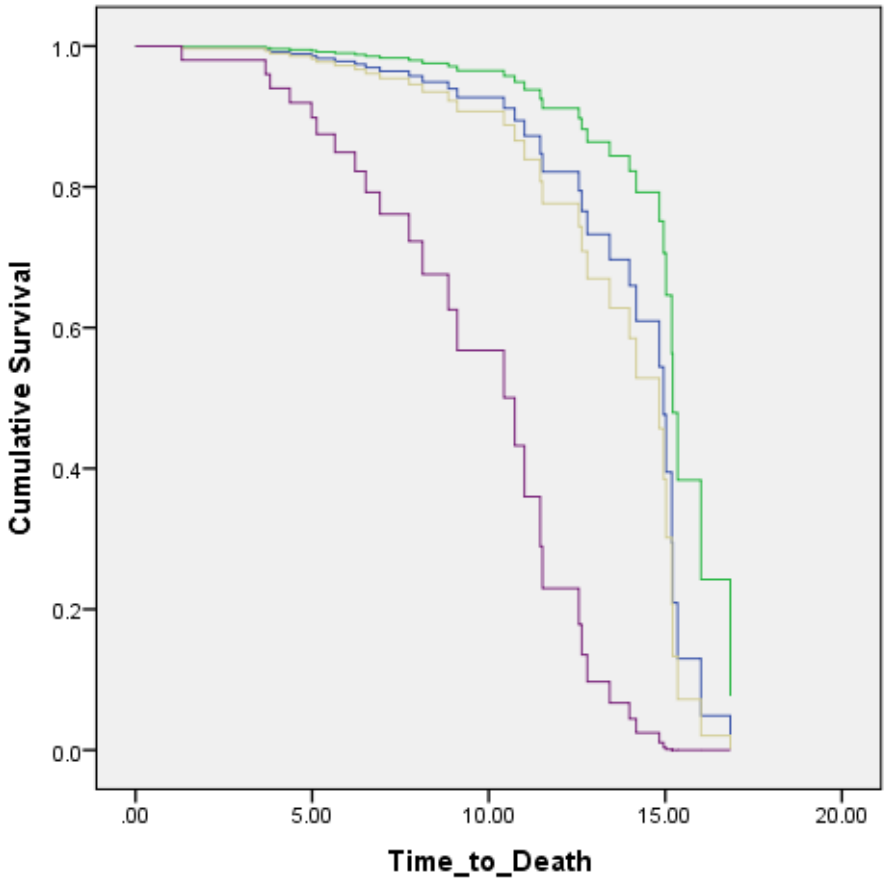
6.3.2.1.2. Cox Regression

Out of 193 patients that were included in the longitudinal analysis there were 57 deaths that occurred. 6 variables were adjusted for: Age, height, sex, pack years, FEV_1 and KCO percent predicted, none of which demonstrated multi-collinearity with one another (VIF collinearity statistic remained <2.0 throughout). Considering PD15, each of the first 3 quartiles remained significantly different to the fourth and final quartile (see table 6.9). The fourth quartile, i.e. those with PD15 < -967HU does have a strikingly worse time to death than the other three quartiles. Therefore, if a patient's baseline CT scan shows a <-967HU there is a significant faster time to death than those with less emphysema (see figure 6.5). This pattern held true when the cohort was divided into quartiles for -950HU with same adjustments including FEV_1 and KCOpp. There was a significant difference between quartile 2 and quartile 4 using -910HU, there was no difference between quartile 4 and 1 or 3. Therefore following adjustment, -950HU and PD15 quartiles remained significant with regards to predicting time to death, but -910HU did not. In those with a CT density measure of -967HU or lower as measured by the 15^{th} percentile point, there is an estimated time of 8.485 years to death versus 17 years if the PD15 measure is greater than -939HU

Table 6.9. Summary of multivariate cox regression analyses for each CT density measure

Quartile	B	HR	Lower 95% CI	Upper 95% CI	P value
PD15					
Quartile 4 (control)					
Quartile 3	-1.76	0.172	0.043	0.688	0.013
Quartile 2	-2.768	0.063	0.014	0.277	0.000
Quartile 1	-2.013	0.134	0.021	0.866	0.035
-910HU					
Quartile 4 (control)					
Quartile 3	-0.942	0.390	0.072	2.111	0.274
Quartile 2	-1.99	0.137	0.022	0.846	0.032
Quartile 1	-1.181	0.307	0.024	3.956	0.365
-950HU					
Quartile 4 (control)					
Quartile 3	-1.847	0.158	0.037	0.667	0.012
Quartile 2	-2.84	0.058	0.012	0.285	0.000
Quartile 1	-2.83	0.059	0.007	0.499	0.009

Figure 6.5. Survival plots for each PD15 quartile once adjusted for age, sex, height, pack years, FEV_1 and KCO percent predicted.



1: (Blue)

>-939HU

2: (Green)

-939HU to -956HU

3: (Yellow)

-957HU to -966HU

4: (Purple)

<-967HU

6.3.2.2. Exacerbations

There was no significant difference in CT density as measured by -910HU, -950HU or PD15 between those with 1 or no exacerbations per year versus 2 or more (p=0.94, 0.47, 0.87 respectively).

6.4. Discussion

This study of CT scans performed and quantitatively analysed on 204 patients recruited to ADAPT has shown for the first time CT density as measured by PD15 is

significantly associated with mortality, including after adjustment for FEV_1 and KCO. Previous studies have shown such an association with other CT measures i.e. -910HU and -950HU, and upper zone PD15 but not whole lung. Age, height, sex, pack years, FEV_1 and KCO percent predicted were all included in the adjusted multivariate analyses. FEV_1 and KCO were both included as they predominantly represent predominant airways versus emphysematous disease and therefore a statistical conclusion regarding mortality adjusted for each of the predominant phenotypes was felt to increase the applicability. As lung function declines naturally with age, and is accelerated by the number of pack years their impact on mortality was adjusted for. With the addition of age and height, 6 variables were adjusted for in this model, which slightly surpasses the traditional recommendation of adjusting for one variable per every event. However, given the impact each variable is likely to have on mortality, it was felt appropriate to include a 6^{th} variable, and a highly cited publication by Charles McCulloch suggests the rule of 10 can be relaxed to 5-9 events per predictor variable (EPVs) (405). Furthermore, the absence of multicollinearity between each of the independent variables means a 6^{th} variable is unlikely to have had a detrimental statistical effect.

The analyses performed showed a higher correlation with FEV_1 and FEV_1pp than the pooled correlation coefficient form the systematic review (0.64 and 0.937 respectively). By taking the unstandardized coefficient and constant reported following the multivariate linear regression, in a similar manner to the Hoesein et 2015 paper, a 10HU difference in PD15 would results in a 0.46L change in FEV_1 (following adjustment for age, height, sex and pack year history) (187). Alternatively,

a 0.1L change in FEV1 would results in a 2.153HU change in PD15. The association with gas transfer and PD15 was stronger within the ADAPT cohort than the pooled correlation coefficient from the systematic review, likely related to the homogeneity of the patient cohort. For KCO, in the review the overall CC was reported as 0.38 in 3 studies, but the results from this stud show a CC of 0.679. For KCO percent predicted, 0.42 (from 6 studies) was the pooled correlation coefficient, but in this analysis the CC is 0.598.

These results confirm the significant relationship between CT density and other clinical parameters seen in the systematic review. In a large study with the same CT acquisition parameters used throughout and therefore any heterogeneity minimalised, these results should add further to growing appreciation of CT density as a biomarker of measure of emphysema progression. Exacerbations were not significantly associated with patient's baseline CT scan and therefore should not at present be used as part of a predictive model. A CT scan before and after an infective episode would allow for a greater understanding of the impact on parenchymal change, but the risks from the radiation dose probably outweigh the benefits.

Patients included in this cross sectional analysis were participating in either an observational cohort study or in the placebo arm of a RCT. This usually involved multiple patient visits, and where ideally all of their investigations would be done on the same day, this was not always possible. The radiology department and lung function department used for CT scans and lung function tests respectively are not exclusive research facilities, and therefore it is difficult to coordinate investigations

such as the CT scan and lung function to happen on the same day. This is less than ideal, and a mean time of 63 days between the two investigations in this cohort is longer than we would like. The mean FEV1 percent predicted is 55% (GOLD stage 2) and FEV1 (L) 1.58. The mean decline in FEV1 in GOLD stage 2 patients with AATD and COPD may be as rapid as 4.7%/year (406). Over the 63 days that our patients were seen, it stands to reason that over 2 months (one 1 sixth of a year), even in a rapid declining population, there could be a loss 0.8% FEV1 percent predicted in this time. This is not an insignificant amount, and over time would accumulate to a damaging loss of lung function. However, in the context of this population over this amount of time, whilst I accept there could have been some change in lung function between visit days I do not feel it is enough to warrant removing these values from the analysis.

The limitation of this study is that these results are only comparable for those patients with AATD and more work needs to be done to help understand the relationship in COPD. However, the size and the robust conduct of this study add gravity to an argument for using CT density in the management of AATD, and particularly so alpha one augmentation therapy. The alpha one augmentation therapy systematic review recommended mortality should be used as an outcome measure in future studies. By dividing the cohort into quartiles, we have shown CT density at baseline may be used as a prognostic measure. However, by dividing the cohort into quartiles, I recognise that this does reduce the statistical meaningfulness. Further work still needs to be done with regards to longitudinal CT scans so that density change and how it relates to clinical parameters maybe further understood.

In conclusion, PD15 at baseline is significantly associated with all clinical parameters, with a density measure of -967HU or less associated with increased mortality.

Chapter 7 Proposal and validation of a Minimal Clinically Important Difference (MCID) for Annual CT density decline.

7.1. Introduction

CT densitometry offers a precise method of quantifying emphysema that would enable tailored treatment of emphysema in patients with AATD. It is more sensitive to disease change than PFTs or QoL questionnaires, is objective, and highly repeatable (167, 343). Alpha one augmentation therapy (AAT) improves the deficient levels of alpha one antitrypsin, to boost the neutrophil elastase activity and prevent (or at least reduce) further parenchymal damage(90). Placebo-controlled RCTs have demonstrated improvement of CT measured density with AAT, with the recent RAPID-OLE (Randomized Placebo-controlled Trial of Augmentation Therapy in Alpha-1 Proteinase Inhibitor Deficiency-Open Label Extension) trial showing that even when previously on the placebo arm, once patients are switched to AAT, their CT density decline slows down (95). The 2010 systematic review of AAT recommended the future outcome measures of augmentation trials be simply mortality(93). Power calculations demonstrate the length of time to power a study for FEV1 is at least three years and 494 patients, nearly three times that required that of CT density, and inevitably outcomes such as time to transplant or death would be even longer(319). This makes such studies highly unlikely to occur due to cost limitations and recruitment difficulties.

An MCID is defined as "the smallest change in an outcome that a patient would identify as important"(407). It represents a move away from simply being

statistically significant towards a threshold beyond which patients would notice an improvement.

7.2. Methods

Two methods were used to propose the MCID for CT density decline; the anchor method and the distribution method. The anchor method observes the line of regression between the change in one variable versus another, and where the MCID for FEV1 is known (100mls or 0.1L), the corresponding MCID for CT density can be determined. The line of regression was calculated by using the slope and/or intercept with relation to CT density and FEV_1 that had been previously been reported, and replace the x value with the MCID for FEV_1 (100ml). The relationship and the line of regression were additionally calculated using Birmingham AAT registry's CT data (section 6.3.1.1. for a description of the cohort). All patients who had received 2 or more CT scans on the same CT protocol were sought and their annual decline calculated. Where there was more than one CT scan, the first and last CT scan were used, and the difference in density calculated. Annual decline in FEV_1 was determined by calculating the slope which requires at least 3 measurements within the same time period(258). By plotting one against the other, the linear regression equation was calculated, into which the known MCID for FEV_1 is inputted to determine the corresponding decline in CT density.

The distribution method is better termed the "minimal detectable difference" (MDD), and is designed to predict a threshold based on the variance of the sample beyond which any changes seen cannot be attributed the noise of the instrument.

There are numerous proposed methods of calculating the MCID using the distribution method; the three most applicable methods may be found in section 3.4. 95% confidence intervals for each proposed MCID were calculated and then each proposed value plotted for illustrative purposes.

The proposed value for the MCID was then used to subdivide the ADAPT cohort into those above or below it to determine if there was any survival differences using Kaplan Meier plots and Cox regression. In addition any changes in the time to transplant were calculated and if there were any differences in the exacerbation rates.

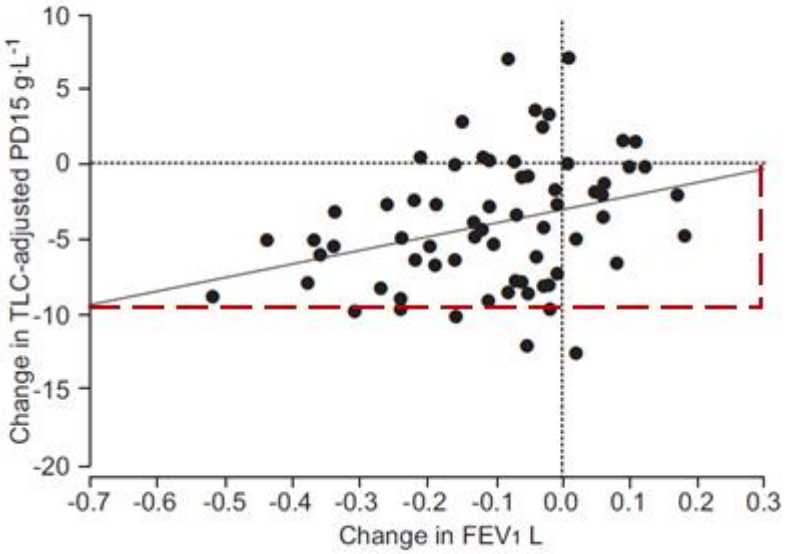
7.3. Results

7.3.1. Anchor Method

7.3.1.1. Reported annual change between FEV_1 and CT density

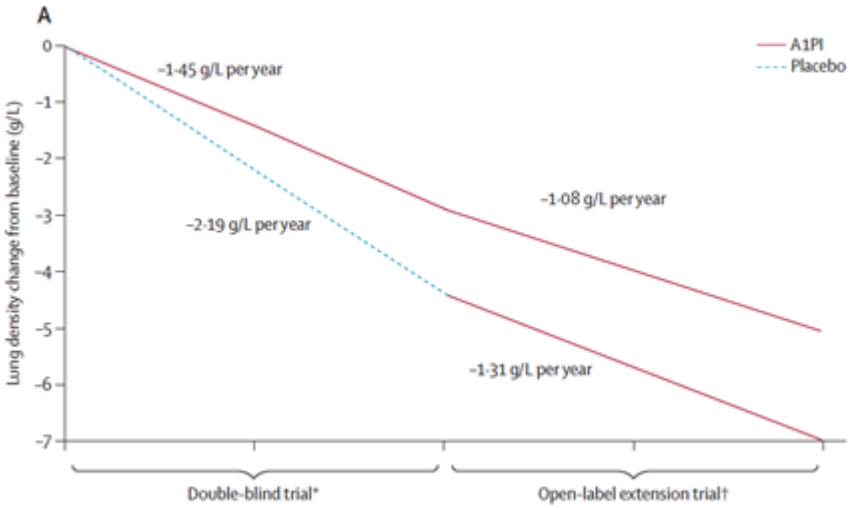
Only one study reported the FEV_1 change in litres against CT density decline for all participants, including the spread of the data. Dirksen et al produced a figure that plotted one against the other, quoting a correlation coefficient of 0.316 (figure 7.1) (319).

Figure 7.1. Correlation between change in PD15 and FEV1 (L) for Prolastin and placebo groups combined



However, this was a combined scatter plot for all patients regardless of whether they were receiving Prolastin or placebo, and therefore certain assumptions needed to be made. Firstly, by referring to the RAPID RCT, Chapman et al 2015 showed there was approximately a 50% faster decline in density in those receiving placebo versus those receiving Prolastin (figure 7.2) (92).

Figure 7.2. Rates of density decline in patients receiving Prolastin and placebo.



The slope from the graph in the Dirsken et al 2009 paper shows an approximate slope of the line of regression of 8.5. From here, in order to deduce how two lines may appear with a 50% difference between them, and solving simultaneous equations, the intercept of the placebo and treatments arms would be 6.8 and 10.2 respectively. By inputting the new slope, and using two known values of x and y into the linear regression equation y=a+bx we can calculate the intercept. In the Dirksen 2009 paper, the annual change in FEV_1 and CT was 0.023 $L/yr^{-1}$and 1.3848g/L^{-1} respectively. Below is the bullet pointed demonstration of how the MCID was then calculated.

Step One: Establishing the intercept

- Y=a+bx
- ΔDensity=intercept+slope*ΔFEV_1
- 1.3848=a+10.2*0.023
- a=1.3848-(10.2*0.023)
- a(intercept)=1.15

Step Two: Use new equation to propose MCID

- Y=a+bx
- ΔDensity=intercept+slope*ΔFEV_1
- ΔDensity=1.15+10.2*0.1
- MCID=2.17

Regarding confidence intervals, the correlation coefficient of 0.316 and therefore the r^2 value and the amount of variability on CT density attributed to FEV_1 is 0.098 (rounded up to 0.1). The total variance in the sample, i.e. SD of CT density change squared is 30.25 (5.536^2). Therefore the residual variance is 30.25*0.9=27.225, and the residual standard deviation the square root of this (5.218). By then converting to the standard error and multiplying by 2, the 95% CIs are +/- 1.76.

7.3.1.2. Changes between FEV_1 and CT density within the ADAPT cohort

39 patients received at least 2 CT scans analysed using identical CT parameters and PD15, plus at least 3 FEV_1 measurements within the same time frame. Figure 7.3 demonstrates the resultant correlation and line of regression, and the MCID for CT density using our cohort would be -1.59HU. This is over 1 HU less than our proposed MCID from the literature. However, table 7.1 highlights how different the two cohorts are, particularly with regards to age and baseline FEV1.

Figure 7.3. Proposal of MCID using ADAPT data

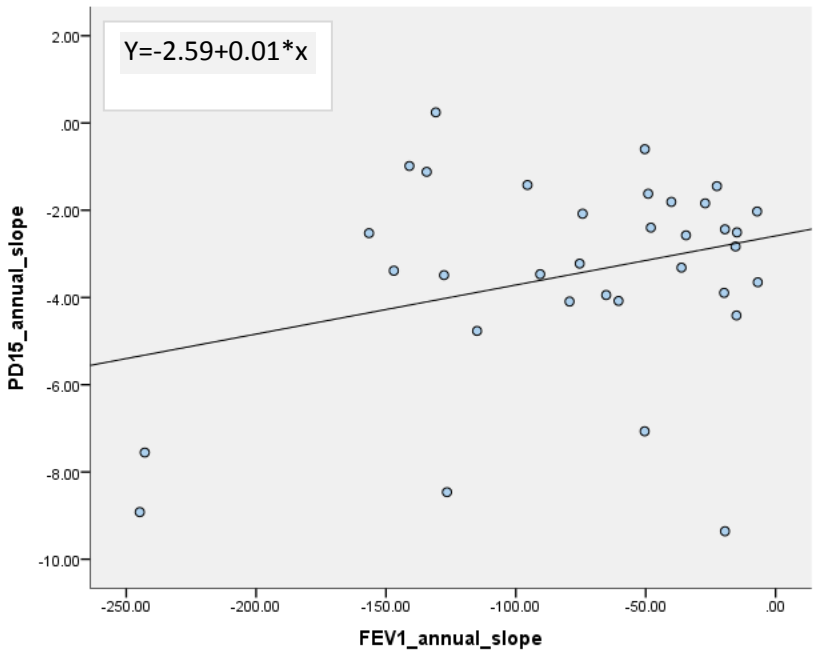
A) Scatter Plot between FEV1 and PD15	
B) Calculation of MCID	Y=a+bx Y=-2.59+0.01*MCID for FEV(ml) Y=-2.59+0.01*100 Y=-2.59+1 Y=-1.59HU

Table 7.1. Comparison of baseline characteristics from the placebo arms of AAT RCTs and the ADAPT cohort.

	ADAPT cohort (n=39)		AAT RCTs* (n=67)		
Variable	Mean	SD	Mean	SD	p value
Age	69.72	11.41	50.74	9.41	<0.0001
FEV1 (L)	1.76	0.87	1.51	2.55	0.556
FEV1/FVC (% predicted)	47.1	1.23	---	---	
DLCO mmol/min/kPa	5.89	1.77	5.39	1.88	0.181
KCO mmol/min/kPa/VA	1.00	0.26	0.91	0.26	0.089
Baseline Density (PD15)	-945.12	27.05	-934.4	22.47	0.03

*Dirksen et a 1999 and 2009

7.3.2. Distribution Method

Three studies reported the baseline and annual change in CT density (See table 7.2). The overall baseline density SD was 20.399 g/L, and annual change SD 3.402. The 95% confidence limits for the baseline standard deviation using n=154 were 18.347 and 22.972.

Table 7.2. Summary of baseline CT density and annual change in the 3 AAT RCTs.

Study	No of patients	Baseline Density (mean)	Baseline Density (SD)	Annual Density Loss (mean)	Annual Density Loss (SD)
Dirksen et al 1999	28	73.0	25.29	-2.57	2.17
Dirksen et al 2009	39	45.48	16.95	-1.38	5.5
Chapman et al 2015	87	48.9	15.5	-2.19	2.33
Average	154	52.42	20.399	-2.0552	3.402

Table 7.3 details how each proposed MCID was reached using the 3 different methods. The 95% confidence intervals were calculated by simply replacing the standard deviation with the confidence limits.

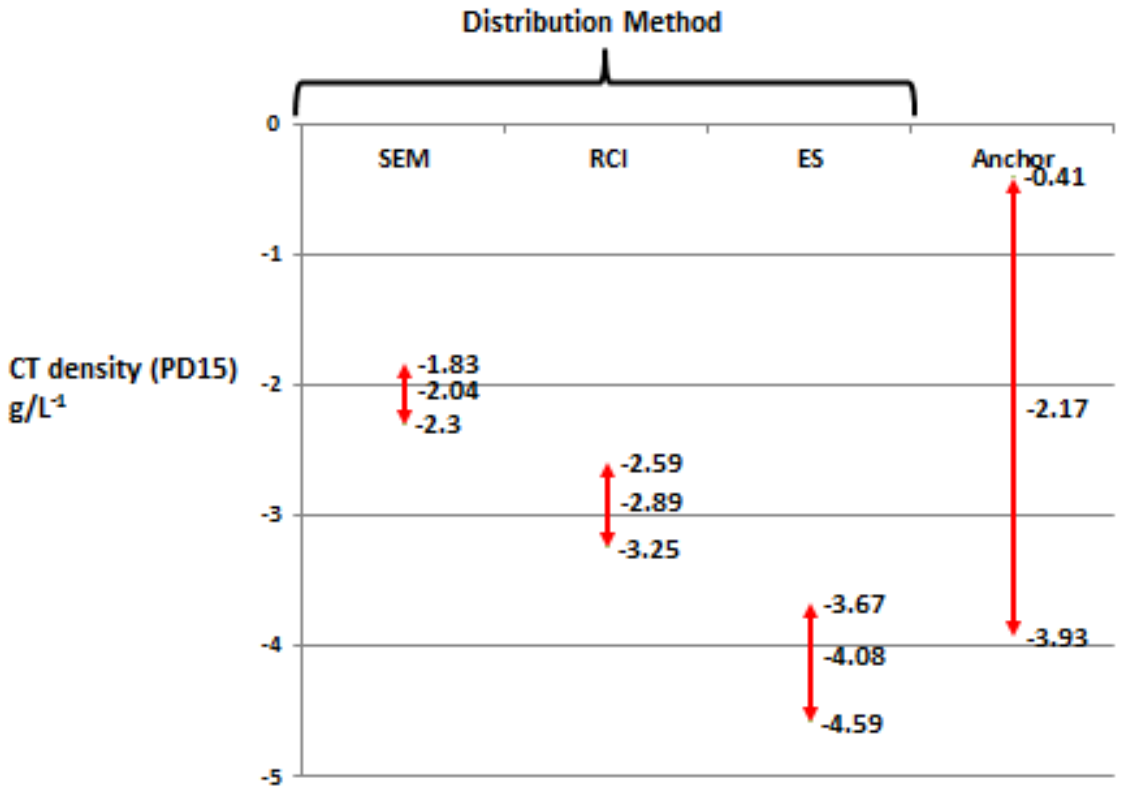
Table 7.3. Summary of proposed MCIDs through Distribution method.

Distribution Method	Description	Results
Standard Error of Measurement	MCID=X*$SD_{baseline}$[sqrt(1-r)] =1*20.399[sqrt(1-0.99)] 95% CI=X*CI[sqrt(1-r)] =1*-18.347[sqrt(1-0.99)] =1*-22.972 [sqrt(1-0.99)]	-2.04 (-1.83- -2.3) (small effect)
Reliable Change Index	MCID=X*SDbaseline{sqrt[2*(1-r)]} =1*20.399sqrt[2*(1-0.99)] 95% CI= X*CI{sqrt[2*(1-r)]} =1*-18.347sqrt[2*(1-0.99)] =1*-22.972sqrt[2*(1-0.99)]	-2.89 (-2.59- -3.25) (small effect)
Effect Size	MCID=X*SDbaseline =0.2*20.399 95%CI=0.2*CI =0.2*18.347 =0.2*22.972	-4.08 (-3.67- -4.59)

7.3.3. Proposal of MCID

Figure 7.4 illustrates each MCID and their confidence intervals. The first three are each of the distribution methods and the final MCID derived from the anchor method.

Figure 7.4. Summary of each MCID and corresponding 95% confidence intervals



The 95% confidence intervals from the anchor method encompass those of the standard error of measurement (SEM) and reliability change index (RCI) with the effect size being outside of this range. Given that a proposed MCID should originate from a variety of methods, it is reasonable to propose the MCID for CT density as -2.89g/L^{-1}, as this is the middle estimate from the three distribution methods, and still within the confidence intervals of the anchor method.

7.3.4. Validation of the MCID

7.3.4.1. Survival

Table 7.4 summarises the patient characteristics from the cohort once they have been subdivided into those with CT decline faster or slower than the MCID. Variables that were different between those above/below each MCID as determined by the threshold of $p<0.12$ are highlighted in bold, which were then used as part of the multivariate cox regression analysis. The univariate and multivariate cox regression models showed no effect of the proposed MCID on determining mortality (Table 7.5).

Table 7.4. Demonstration of the differences in clinical parameters for patients with CT density decline faster or slower than the proposed MCID

Variable	**MCID decline slower than -2.89g/L^{-1}/year**	**MCID decline greater than -2.89g/L^{-1}/year**	**p value**
Age	69.93	65.84	0.117*
FEV_1 (L)	1.53	1.70	0.23
FEV_1/FVC (pp)	43.8	4.13	0.417
DLCO (mmol/min/kPa)	6.19	6.30	0.849
KCO (mmol/min/kPa/VA)	0.94	1.06	0.052*

Baseline Density (PD15)	-959.45	-938.45	<0.001*

*p values less than 0.12 used in the cox regression model.

Table 7.5. Summary of univariate and multivariate cox regression analyses to establish the prognostic benefit of the proposed MCID.

Univariate Analysis				
Variables	HR	Lower 95% CI	Upper 95% CI	p value
	1.12	0.616	2.037	0.711
Multivariate analysis				
Variables	HR	Lower 95% CI	Upper 95% CI	p value
Age	0.879	0.466	1.646	0.68
Age and KCO	0.696	0.344	1.408	0.313
Age, KCO and Baseline density	0.614	0.301	1.256	0.182

7.3.4.2. Exacerbations

Using a multivariate linear regression, each MCID had no impact on exacerbation rate following adjustment for age and baseline density (Hazard Ratio=0.116).

7.3.4.3. Time to transplant.

By altering the outcome in a cox regression analysis to time to death or time to transplant instead of time to death alone, this made no significant impact on the survival analysis.

7.4. Implications of MCID for future trial design

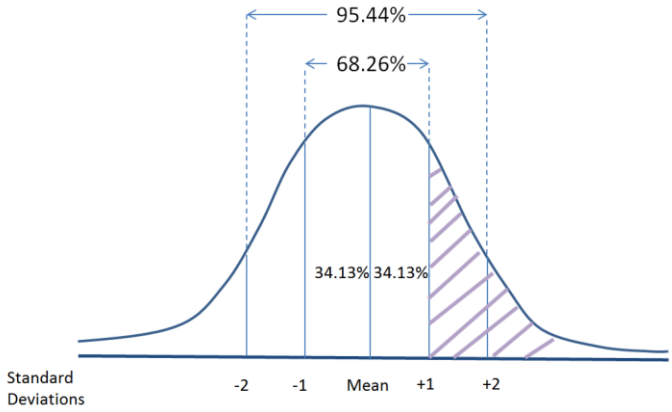
7.4.1 Utility of MCID

Through a variety of methods we have proposed an MCID of -2.89g/L and therefore density change beyond this may represent a change that is clinically appreciable by the patient. The MCID value proposed with the reliable change index uses the density at baseline and therefore any change beyond this is likely due to actual changes rather than the noise of the instrument. This represents an absolute value which can be used to design a trial and establish how long it should last and how many patients would be recruited.

7.4.2. Study length

We can assume the natural density decline in AATD patients is approximately -2.06g/L/yr (standard deviation 3.40g/L/yr) based on the known density decline in in the placebo arms of augmentation trials (table 7.2). For a trial including AATD patients who are 'rapidly declining' (i.e. more than expected) who are potential candidates for augmentation therapy, it would be important to know the natural rate of decline. There have been no specific studies that have reported data for rapid decline in AATD patients. In order to determine a reasonable estimate, it is possible to define a rapid decliner if the mean and SD of the whole group are known. In figure 7.5, the marked area under the curve represents those who have CT density decline greater than the mean +1 SD, i.e. the top 16%.

Figure 7.5. Normal Distribution Bell Curve



The hashed area under the curve represents those patients with density greater than the mean +1 SD

By estimating those within the top 16% of the overall natural decline, we can define rapid density decline in an untreated AATD population. The annual rate of decline in this 'rapid group' would be 2.06+3.40=5.46g/L. If the mean rate of 'natural decline' is subtracted (-2.06g/L), the remaining rate of change would be approximately 3.40g/L. (As this is derived from the same population, we can assume the SD remains constant).

Using the MCID -2.89g/L plus natural rate of decline (total -4.95g/L), it would take a "rapid decliner" as defined here approximately 1.4 years to reach the MCID. This would be assuming 100% power and rapid decliners in the top 16%, therefore it would probably be more reasonable to suggest at least a 2 year study.

7.4.3 Sample Size

A power calculation was performed to estimate the required sample size required to demonstrate this difference. 'Group A' is mean density of natural decliners (-

2.06g/L/yr), 'group B' the mean density of 'rapid decliners' (3.46g/L/yr), and the SD is 3.46g/L. Using a power of 0.8, a type 1 error rate of 5% and sampling ratio 1:1, the study would require 93 participants.

7.5. Discussion

CT densitometry is undoubtedly an attractive solution to quantifying emphysema due to its objectivity, repeatability and sensitivity. Understanding how it can be used in a clinical context or as an outcome measure in clinical trials is still not fully appreciated. The proposal and validation of an MCID offers a threshold to which investigators can power studies, and clinicians can use to identify those rapid decliners. This is the first time a MCID has been proposed for CT density, and validation work performed. Though the validation failed to show a difference in mortality for the MCID, perhaps this is not entirely unexpected. Given the sensitivity of the tool to small changes not seen with other clinical parameters such as lung function over a short space of time, it is perhaps not surprising that the MCID failed to show prognostic value with regards to survival. Furthermore, as the MCID should, in theory, relate to a parameter that patients appreciate a difference in. Therefore there is an argument that it would be better to relate to QOL score or other patient reported outcomes (PROs). However, lack of longitudinal data on these over the same time period as CT scans were done limited my ability to conduct such analyses. Notably QOL and the other measures assessed have been related to one another in prior studies. The 2011 systematic review by Westwood et al quoted an r value between FEV1 and SGRQ of -0.46, and the relationship seemed to strengthen with a larger increase in FEV1 associated with a greater improvement in the

SGRQ(263). Therefore, although we were unable to use SGRQ to propose a MCID, its significant relationship to FEV1 means there is still likely to be an impact of achieving the MCID and QOL features.

Within the ADAPT cohort, most patients who had 2 or more scans performed had them done so between 2002 and 2004 as part of the ADAPT project and REPAIR (Retinoids in Emphysema Patients in the α1-Antitrypsin International Registry) studies (143 out of 155 scans performed 2004 or earlier). Although quantitative CT has been performed within the ADAPT group on many patients particularly as part of the NIHR rare diseases collaboration, most of these patients did not have a previous scan to compare to. Only 12 scans used in this longitudinal analysis were performed and analysed since 2014. In a bid to reduce the impact of the time between scans, only those which used the same CT acquisition parameters were used. At least 2 different versions of PULMO have been used over time and a change in CT scanner will have inevitably introduced some changes differences difficult to account for. As demonstrated in table 7.1 there are significant differences between our cohort and those patients used within the two trials by Dirksen et al, namely age and FEV_1. Our patients were more likely to be older with worse COPD as measured by FEV1. However, the MCID proposed sits between those receiving placebo in 1999 Dirksen et al study and our cohort, which is likely to indicate this value relevancies generalizable outside those carefully selected for RCTs.

The strengths of this study include the uniformity with regards to CT acquisition parameters, the importance of which was outlined in section 1.8. Care and time have been spent with help of a statistician to ensure the methods and results are robust, and a variety of methods to propose an MCID employed. One limitation would be that the MCID proposed using the distribution method was done primarily from 3 studies, all of which were placebo controlled RCTS of alpha one augmentation therapy. The proposed MCID -2.89g/L represents one of four calculated values, and the true value is likely to lie within the proposed range of values (2.04g/L - 4.08g/L, 95% CIs -0.41to -4.59). Each method used has both inherent strengths and weaknesses, and the RCI which we used in the analyses is a distribution method and therefore signifies the minimal detectable difference (MDD). In order to increase confidence in the proposed MCID we should re-evaluate the value with the results of other such RCTS if and when they are published. The current MCID is taken from AATD patients and therefore is not generalisable to the usual non deficient COPD population. There is no equivalent parenchymal therapy in usual COPD, but we would urge caution in using this value outside -an AATD population.

7.6. Conclusion

In conclusion, the proposed MCID for CT density in patients with AATD is -2.89g/L. This value is derived but may act as guidance for powering trials assessing therapeutic interventions to alter CT density decline, and identifying patients who may benefit from alpha one augmentation therapy.

Chapter 8 Overall conclusions from this thesis relating to the original hypotheses

Chapter 4 : The systematic review demonstrated that CT density relates significantly to all commonly used clinical parameters. The large amount of heterogeneity and lack of longitudinal data means that the sensitivity and specificity of CT density change, relating to time or interventions is not clear. International consensus is required to standardise CT conduct and analysis in future emphysema studies. The null hypothesis was rejected.

Chapter 5 : There was no significant inter-observer variability detected, and therefore CT density analysis technique by DC successfully validation. Following assessment of intra-observer variability, the intra-class correlation coefficient for future work within this thesis in 0.99. As all repeated scans were comparable, the null hypothesis was rejected.

Chapter 6 : Volume and PD15 when analysed using the same slice thickness were identical for the two most frequently used software programs in CT densitometry (Pulmonary Workstation and PULMO) and can be directly meta-analysed. The difference between results for -910HU and -950HU using the same slice thickness is negligible, and all measurements using different slice thicknesses require application of a correction factor. The null hypothesis is

rejected for both analyses of CT scans using the same and different slice thickness as a correction factor can be applied.

Chapter 7 : Each measure of CT density i.e. RA-910HU, RA-950HU and PD15 was significantly associated with lung function and quality of life measures. Following adjustment for variables including age and lung function, RA-950HU and PD15 were both predictive of mortality but RA-910HU was not. Given the clear strongly significant association between CT density and other clinical measures, the null hypothesis was rejected.

Chapter 8 : The proposed MCID for CT density in patients with AATD is -2.89g/L^{-1}/year and may act as a guide for those patients under CT surveillance. However, the MCID failed to identify those patients more likely to die and therefore the null hypothesis is accepted.

Where there is appropriate standardisation of CT acquisition parameters heterogeneity between CT density analyses may be eliminated, and the inter-reader variability is negligible. CT density is strongly associated with clinical parameters including mortality, but the proposed MCID failed to have significant prognostic value.

Chapter 9 General discussion and future directions

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality. The pathophysiology is increasingly recognised as complex, with some patients remaining stable whilst others show more rapid decline. The most used biomarker for disease change in COPD remains the FEV_1, but has been demonstrated to only detect disease once a third of the lung has been affected by COPD(292). Evidence presented in this thesis has demonstrated that the relationship of CT density to all other clinical parameters deemed suitable as outcomes for airways disease trials (e.g. FEV_1, SGRQ) was consistently significant, and furthermore there was a clear and consistent relationship to mortality. This suggests that CT density is an appropriate surrogate outcome measure in studies of emphysema, like those conducted in AATD. However, the large amount of heterogeneity and lack of longitudinal data means that how sensitive and specific CT density is to change relating to time or interventions is not clear. Further international collaboration is required to reach a unified consensus regarding CT standardisation in order to reduce the heterogeneity that is currently hampering its development as a biomarker within COPD.

The systematic review presented in the chapter four demonstrates statistically the reduction in heterogeneity once the same reconstruction algorithm, slice thickness and software program is used. In chapter five we showed that where the same slice thickness and reconstruction algorithm are used, the agreement between the two leading software programs is strong and identical values for volume and PD15 are

produced. However, whether the 1-3% difference in relative area seen for emphysema thresholds --910HU and --950HU is clinically significant or not remains to be determined. When 1mm and 5mm slice thicknesses are compared, the difference in values is greater again and if/how to adjust for this needs further consideration. These two slice thicknesses used by the two most frequently software programs (PULMO and Pulmonary Workstation), and realistically unlikely to change in the near future.

Through the analyses performed using patients recruited to the Birmingham AAT registry, chapter six shows we were able to validate the association between CT and clinical parameters presented in the literature. Each measure of CT density i.e. RA-910HU, RA-950HU and PD15 was significantly associated with lung function and quality of life measures. Furthermore, for the first time CT density as measured by PD15 is significantly associated with mortality, including after adjustment for FEV_1 and KCO

Taking the concept of CT density and its clinical utility forward, in chapter 7 we proposed an MCID of -2.89g/L^{-1}/year for CT density decline in patients with AATD. Am annual density decline value beyond this may indicate patients who are declining rapidly and could possibly benefit from alpha one augmentation therapy. This value was proposed using available data from three alpha one augmentation trials that use CT density as an outcome measure, and patients who had received 2 or more CT scans as part of the Birmingham AAT registry. Further work is still required to fully understand the utility of CT density longitudinally and its role as an outcome measure.

The problem with CT as a biomarker and its use in serial repeat measurements is the associated radiation dose. At 80 times the radiation dose of that associated with a plain chest x-ray, the combined dose over 2 or more CT scans is not negligible therefore MRI as a non-ionising imaging modality has been considered(408). The lungs have historically been notoriously difficult to image but by hyperpolarising inhaled gases to alter the proton behaviours accordingly, direct visualisation of the airspaces can be obtained. There is renewed interest in therapeutic options available in advanced COPD such as endobronchial valves (EBV)/coils for the purpose of lung volume reduction, which remains an attractive option for AATD patients in whom standard Lung Volume Reduction Surgery (LVRS) is not currently recommended due to adverse outcomes in the National Emphysema Treatment Trial (NETT) (140). MRI has the potential to define patients who could benefit from valves/coils by defining the areas of ventilation more accurately than CT and therefore offering prospects for direct and imminent patient benefit. A small pilot study has been organised in collaboration with the University of Nottingham who are already performing MRI with hyperpolarised Xenon in patients with usual COPD. Our aim is to conduct the first study of the utility of lung imaging by hyperpolarised xenon MRI for quantifying emphysema in AATD patients. To date 10 AATD patients have been successfully recruited with a view to start scanning in October 2017.

We plan to perform functional MRI scans in Nottingham using inhaled hyperpolarised xenon to produce novel and clinically relevant data regarding

emphysema in AATD identified from the UHB data base. All patients already have PFTs, Quality of Life (QoL) scores and CT scans for comparison with the MRI scans. Understanding regional gas trapping in AATD will likely enable therapeutic interventions that target hyperinflation, such as endobronchial valves and coils, to be targeted in appropriate patients. Thus our specific objectives are:

1. Acquire 129Xe MRI in AATD patients to estimate lung volumes and regional ventilation to provide baseline data for future clinical studies
2. Use the images obtained to establish standard sequencing protocols, define algorithms and inform power calculations for future interventional studies
3. Compare MRI results with routine PFTs, composite health scores (e.g. SGRQ)
4. Validate MRI emphysema quantification by comparison to emphysema severity determined from CT density, measured using the software program Pulmo (including, but not limited to the most standardised PD15 assessment).

In summary, this MD thesis has proven the clinical utility of CT density as a biomarker in COPD but more work needs to be done to understand its role longitudinally, and to standardise the technology to reduce heterogeneity. Functional MRI may offer an attractive non-ionising alternative that images ventilation in great detail, and a pilot study is under way to explore this in more detail.

Appendix 1.

Reference equations that generate predicted lung function values are available from the Association for Respiratory Technology and Physiology in the UK (www.artp.org.uk). These were generated using regression models from a cohort of subjects aged 18-60, and include height, age and gender components. The equations are as follows.

	Unit	Regression equation	
		Male	Female
FEV1	l	4.30H - 0.029A - 2.49	3.95H - 0.025A - 2.60
FVC	l	5.76H - 0.026A - 4.34	4.43H - 0.026A - 2.89
TLC	l	7.99H - 7.08	6.60H - 5.79
RV	l	1.31H + 0.22A -1.23	1.81H + 0.016A - 2.00
TLCO	$mmol.min^{-1}.kPa^{-1}$	11.11H - 0.066A - 6.03	8.18H - 0.049A - 2.74
KCO	$mmol.min^{-1}.kPa^{-1}.l^{-1}$	predTLCO/predTLC	

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