Respiratory function in the very old and its impact on disability and mortality

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Doctor of Philosophy

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September 2017

Abstract

The aim of this PhD is to better understand the epidemiology of respiratory function in very old people and specifically examine the relationship between respiratory function and both cognitive function and disability in this age group. Data from the Newcastle 85+ study, a longitudinal cohort study of 85 year olds (born in 1921) were used in this thesis. Very few studies have investigated lung function and especially its impact on disability and mortality in the very old, and the unique point of this study was the multiple measurements of three lung function parameters: FEV_1, FVC and PEF, between the ages of 85 and 88 years.

Four sub-studies constituted the substantive results chapters of this thesis. The first sub-study described the prevalence of respiratory disease in the very old and the applicability of indicators of poor lung function and their cutpoints in this age group. The second sub-study explored the predictive ability of lung function for subsequent survival. The third sub-study quantified how lung function changes with further ageing in 85 year olds. The fourth sub-study examined the relationship between lung function and disability, particularly the direction of causality, and the potential mediating role of cognitive function.

In the very old significant differences were observed between physician-diagnosed COPD and the obstructive classification of spirometry using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global lung initiative (GLI) prediction models. Lung function was predictive of mortality in women only. When investigating lung function trajectories of change, smoking and cognitive impairment were associated with lower FEV_1. Bidirectional causality between lung function and disability revealed that higher FEV_1 at ages 85, 86.5 and 88 was associated with lower disability at subsequent follow-ups (ages 86.5, 88 and 90) whilst higher disability scores at age 85 were associated with lower FEV_1 at age 86.5.

To My Family:

Zahra Taheri, my truly remarkable mother and life mentor;

Ghasem Yadegarfar, my exceptional father and academic teacher;

Motahare Yadegarfar, my marvellous sister and ever-present confidant;

My achievements in life are a testament to your undying love and support.

Acknowledgements

I would like to thank my supervisors, Professor Carol Jagger, Professor Andrew Fisher and Professor Paul Corris for their invaluable knowledge, guidance and support during my PhD.

Furthermore, I am eternally grateful to Professor Carol Jagger, an exemplary role model and a selfless mentor who helped start my career in academia, encouraged its development and most importantly for being there through the highs and lows of my journey.

I would like to extend my thanks to my assessors, Professor John Simpson and Professor Mark Pearce for their invaluable guidance throughout this process. Credit also goes to my colleagues at the Newcastle University Institute for Ageing, especially Professor Tom Kirkwood, the Newcastle 85+ study research team and its participants for making all of this possible.

My wholehearted appreciation to my clubs, Newcastle University Athletics and Cross Country (NUAXC) and Newcastle University Taekwondo (NUTKD) for helping to keep my head, improve my physical fitness and the amazing teammates in helping me achieve what was once improbable. Special thanks to my coaches: Ian Whyte, Scott Abley and Sarah Broadaway.

Infinite thanks to the outstanding staff and friends at Quilliam Brothers' Tea House for making my day with their endless supply of tea and smiles over the years and many a time at the most ungodly hours, especially during the latter stages of this PhD.

Eternal debt of gratitude to L.C. for helping me through the most perilous predicament, exhibiting unparalleled levels of patience and guidance to guarantee me a brighter future.

Sincerest thanks to my brothers, Navid Rafatpanah, Navid Kabuli, Hadi Ziaei and Mahdi Ziaei whose presence provided me with irreplaceable memories, comedy and support over the past couple of decades and even more so during this PhD journey when it was most appreciated.

A heartfelt thank you to the wonderful friends I met in Newcastle for being there throughout the years, especially James Wordsworth, Yasamin Pishvaee, Diego Manni, Sarah Acey, Michelle Dorrington, Sarah Sexton, Kelsey Cairns and Bethany Bareham.

To my extended family, especially my grandparents (Khadijeh, Reza, Bibi-Soghra and Yadollah) and brother-in-law (Mohammadali), I send my love as you have throughout the years, making this journey as pleasant as the ones preceding it.

Last but foremost, I am forever thankful to my parents (Zahra and Ghasem) and sister (Motahare) for their unconditional love, continuous encouragement and wit accompanying me since day one.

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Abbreviations

ADL	Activities of daily living
AIC	Akaike information criterion
APEFR	Average peak expiratory flow rate
ATS	American Thoracic Society
BADL	Basic activities of daily living
BASE	The Berlin Aging Study
BIC	Bayesian information criterion
BLSA	Baltimore Longitudinal Study of Aging
BMI	Body mass index
BNF	British National Formulary
BODE	Body-mass index, airflow obstruction, dyspnoea, and exercise
CDR	Cognitive drug research
CFAS	Cognitive Function and Ageing Studies
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
DCS-1905	Danish 1905 Cohort Study
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ELSA	English Longitudinal Study of Ageing
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
FFM	Fat-free mass
FVC	Forced vital capacity
GLI	Global lung function initiative
GOLD	Global initiative for chronic obstructive lung disease

GP	General practitioner
GPRR	General practitioner record review
HRG	Healthy reference group
IADL	Instrumental activities of daily living
IL-6	Interleukin-6
JLCS	Jerusalem Longitudinal Cohort Study
LiLACS	Life and Living in Advance Age Study
LLN	Lower limits of normal
LSADT	Longitudinal Study of Aging Danish Twins
MDHA	Multidimensional health assessment
MMSE	Mini-Mental State Examination
MRC	Medical Research Council
N85+	Newcastle 85+ Study
NHANESIII	National Health and Nutrition Examination Survey III
NHS	National Health Service
NICE	National Institute for Clinical Excellence
PEF	Peak expiratory flow
SATSA	Swedish Adoption/Twin Study of Aging
SEM	Structural equation modelling
SMMSE	Standardised Mini-Mental State Examination
TB	Tuberculosis
TLC	Total lung capacity
TNFα	Tumour necrosis factor alpha
UK	United Kingdom
ULN	Upper limits of normal
VC	Vital Capacity
WHO	World Health Organisation

Chapter 1. Introduction

1.1 Ageing demography

The world's population and the UK in particular are facing challenging times. As life expectancy is increasing in combination with a decline in fertility rates we will be witnessing a higher proportion of older people in the future (United Nations, 2002). One sector of this population is the very old, referred to as those older than 85 years of age by some and above 80 by others, who are the fastest growing sector of our population. In 2014 this age group formed only 2.3% (1.5 million) of the population, but it is projected to rise to 4.8% (3.6 million) by 2039 (Office for National Statistics, 2015). Because of the strong relationship between most chronic diseases and age, the very old have a high burden of disease which includes multimorbidity (the presence of two or more conditions) and the highest health expenditure per capita compared to other age group (Summerfield and Babb, 2004). It is therefore crucial to understand the health and disease of this age group in order to recognise their needs for the future and to find ways to slow down functional decline. The World Health Organisation (WHO) has started this process in their healthy ageing strategy which focuses on extending healthy life expectancy rather than simply extending life expectancy (WHO, 2012). However, at least for the UK, gains in healthy life expectancy and disability-free years are progressing at a slower rate than life expectancy (Jagger *et al.*, 2016).

1.2 Functional capacity of the very old

The WHO healthy ageing concept is based on the relationship between an individual's intrinsic capacity and functional ability. Functional ability relates to a person's capacity to perform tasks they wish to do independently, often measured by the ability to carry out basic activities of daily living (BADLs) such as dressing, toileting, and instrumental activities of daily living (IADLs) such as shopping or housework (McGee *et al.*, 1998). The intrinsic capacity refers to objective measures of health such as strength, balance and which includes respiratory function. As intrinsic capacity declines with age, it becomes more difficult to sustain functional ability (Figure 1.1) (Beard *et al.*, 2016).

This relationship between respiratory function and functional ability is clearly shown by the development of scales such as the MRC breathlessness scale. This scale was devised to measure the exercise capacity of each subject and which grades patients from 1 to 5 with one meaning that the patient is not troubled by breathlessness and 5 indicating that patients are left

without breath whilst undressing, rendering them to be homebound (Fletcher *et al.*, 1959; Stenton, 2008).

1.3 The ageing lung

In keeping with respiratory function being part of the intrinsic capacity of an individual, previous studies have found that the lung's elastic and resistive properties decline with age (Pride, 2005; Vaz Fragoso and Gill, 2012). However total lung capacity does not appear to be affected by the ageing process, rather the functional residual capacity and residual volume change as people age (Pride, 2005). The physiological processes of ageing are associated with decreased lung function in three ways: decreased strength of the respiratory muscles; decrease in lung recoil; and increased stiffness of the chest wall (Vignola *et al.*, 2003). Moreover reduced chest wall compliance appears to cause an increase in the functional residual capacity (Janssens, 2005). In addition to this, the presence of certain ageing biomarkers and disease burden have been shown to be associated with lung function (Martin-Ruiz *et al.*, 2011).

Chronic Obstructive Pulmonary Disease (COPD) is one of the major challenges in the modern healthcare, ranked 4th in terms of mortality and leading cause of disease, and claiming 3 million lives annually (WHO, 2004). Its risk factors include a range of genetic, environmental and life style or behavioural factors. Age and sex also contribute to this although it may be argued that the reason behind this is the accumulation of exposures through life (Vestbo *et al.*, 2013) though pulmonary function may deteriorate as a result of the ageing process (Ito, 2007). As a result many studies have been conducted with subjects at the latter stages of their life in order to distinguish the effects and associations of ageing and COPD, although these have been predominantly in patients in hospital(Ranieri *et al.*, 2001; Ito, 2007; Almagro *et al.*, 2010).

1.4 Lung function measures

There are many different tests available for clinicians to identify lung efficiency. Tests can be used to check inspiration and expiration, airflow obstruction, gas transfer, lung volume, effect of medication and exercise on lungs and lung function during rest periods.

The main tests used to determine lung efficiency come under this heading and apply different measurement methods to the air exhaled by the patients after maximal inspiration (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2010). Peak Expiratory Flow (PEF) measures maximum speed of expiration and indicates if patients have constricted airways,

though this is not seen to be accurate as spirometry tests (Stephen J. Bourke, 2011). The main measures from spirometry tests are Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC). FEV_1 is the maximum amount of air that a patient forcefully exhales in 1 second. A reduction in this value is seen if the patient has either restrictive or obstructive lung disease. FVC is the total amount of air that patients expire and reduction in this is indicative of a patient with restrictive lung disease.

There have been studies exploring the age-related rate of lung function decline, expressing a faster decline in FEV_1 than FVC with higher rates observed for smokers (Beck *et al.*, 1981; Kerstjens *et al.*, 1997; Anthonisen *et al.*, 2002; Mannino and Davis, 2006; Yohannes and Tampubolon, 2014). A review of various studies of lung function decline reported yearly average reductions of between 10 and 35 ml in FEV_1 in both men and women (Kerstjens *et al.*, 1997). Age-related rate of decline from the English Longitudinal Study of Ageing (ELSA) reported a mean decline of 32.92 (SD: 0.96) ml per year for FEV_1 in a population of people aged 50 and over (Yohannes and Tampubolon, 2014). The most recent lung function equations from the Global Lung Initiative (GLI) reported marginally different rates of lung function decline between men and women aged 85 (Quanjer *et al.*, 2012). Men were observed to have a mean decline of 30 ml per year for both FEV_1 and FVC, whilst the mean rate of decline for women was reported as 30 ml per year for FEV_1 and 20 ml per year for FVC (Quanjer *et al.*, 2012).

The values obtained from these tests are used in various formulae to diagnose patients. Patient's height, age and sex are used to work out predicted or expected values for their FEV_1 and FVC (Table 1.1). Another parameter that aids this is the FEV_1 to FVC ratio (FEV_1/FVC). FEV_1 and FVC of above 80% predicted and a FEV_1/FVC value of above 0.7 indicates normal spirometry whilst FEV_1 below 80% of their predicted value, normal or reduced FVC and a FEV_1/FVC value of below 0.7 indicates obstructive spirometry. Normal or slightly reduced FEV_1, an FVC of below 80% predicted and a FEV_1/FVC of above 0.7 indicates restrictive spirometry (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2010).

Table 1.1: ERS 1993 formulae for predicted FEV_1 and FVC

FEV_1 (Females)	(3.95*(height$^{\#}$))-(0.025*age)-2.60
FEV_1 (Males)	(4.3*(height))-(0.029*age)-2.49
FVC (Females)	(4.66*(height))-(0.024*age)-3.28
FVC (Males)	(6.1*(height))-(0.028*age)-4.65

Height measured in metres; (Rabe et al., 2007)

1.5 Literature review of respiratory epidemiology in the very old

I addressed the issue of the current knowledge base on respiratory function in very old populations in two ways. Firstly, I reviewed the known studies of ageing that included very old participants (aged 85+ years) and ascertained which, if any, had lung function measures included. Secondly, I conducted a wider systematic literature review as described later.

As mentioned previously, few studies of very old populations include measures of respiratory function. Studies of older population more generally have included people aged 85+ but rarely in numbers large enough to draw robust conclusions. Such examples are: Baltimore Longitudinal Study of Aging (BLSA) (age range 17 – 96 years) (Shock, 1984); the Berlin Aging Study (BASE) (age range 70+) (Evans, 1999); the English Longitudinal Study of Ageing (ELSA) (age range 50+) (Higgs *et al.*, 2004); and the Longitudinal Study of Aging Danish Twins (LSADT) (age range 75 - 102) (Skytthe *et al.*, 2006). Of these only BLSA, LSADT and BLSA include respiratory function measures. There are 3 existing single birth cohort studies of those aged 85 years, with the first being the model for the others: the Leiden 85+ initiated in 1987 with a second cohort in 1997 (Lagaay *et al.*, 1992); the Newcastle 85+ study (N85+) initiated in 2006 (Collerton *et al.*, 2007); and the Life and Living in Advance Age study (LiLACS) in New Zealand (Hayman *et al.*, 2012). Of these, only the N85+ and LiLACS include respiratory function measures. Five other studies include a different age range but focus on the very old: the Tokyo Oldest Old Survey on Total Health study (Arai *et al.*, 2010); the Swedish Adoption/Twin Study of Aging (SATSA) (Finkel and Pedersen, 2004); the Jerusalem Longitudinal Cohort Study (JLCS) (Jacobs *et al.*, 2009); the Vitality 90+ study (age range 90 - 106) (Jylha and Hervonen, 1999) and Danish 1905-Cohort (DCS-1905) (age 93) (Nybo *et al.*, 2001). Of these SATSA, JLCS and DCS-1905 include respiratory function measures. Therefore, in total there are only 8 studies exclusively of the very old that have the potential to examine lung function, its determinants and its disabling consequences. This thesis is based on the most comprehensive of these, the Newcastle 85+ Study.

The focus of the literature review was research on respiratory epidemiology in the older population, specifically the very old. The search was focused on studies which either solely had participants of the age 75 and over or other studies which had an array of age categories including reasonable numbers aged 75+ and more importantly 85 year olds and over. Two article abstract and citation databases were utilised: Scopus and PubMed. The search began with just 3 terms, respiratory, old and epidemiology. The search parameters included the keywords: old, old age, oldest old, very old, geriatric and advanced age for returning relevant

samples for age. Epidemiology, lung function, COPD, respiratory, LLN, FEV_1, FVC, and PEFR were included to return research in this field. A 15-year limit was set at the start of this PhD meaning all publications since 1998 would be included. The search was not limited to longitudinal studies in order to be as comprehensive as possible and to identify subject areas which have been given varying degrees of exposure.

The search across both of the databases returned 929 articles and abstracts. In addition, further searches were made by referring to the bibliography of the more relevant articles. A total of 1199 articles, abstracts, reviews and study protocols were transferred into the citation manager EndNote and all of the abstracts were imported for ease of reviewing the papers.

Three main groups were created in EndNote: Guidelines/Reviews, Cross-sectional and longitudinal studies. For the latter two categories, sub-groups were created to differentiate between the studies and their outcomes/predictors. As an example, all studies which had associations with COPD either as outcome or predictor were grouped in a sub-folder titled with COPD.

All the abstracts were then reviewed and grouped according to relevance. There were 120 papers found to be within the scope of this literature review of which, 54 were from longitudinal studies and 66 reported cross-sectional findings. These papers will be discussed under three broad headings: lung function and lung disease; respiratory function as a predictor of other outcomes; predictors of respiratory function. As expected, papers in which COPD was used as a predictor or outcome formed the largest proportion of these papers (19/120 (16%)).

1.5.1 Lung function and lung disease

Whilst prediction models exist to evaluate how close a subject's lung function is to that predicted, these formulae rely on three non-respiratory parameters: age, sex and height. Race has also been suggested by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (Vestbo *et al.*, 2013), and other factors, such as Total lung capacity (TLC), nutrition, health and environmental status have been suggested (Pellegrino *et al.*, 2005). Such discussions may indicate that there may be a need for more comprehensive formulae that would be more accurate in predicting lung function. In a relatively large sample of 592 non-smokers population of 42 – 89 year olds quantile regression was used to produce equations for median and lower limit of normal lung function (Karrasch *et al.*, 2013). These formulae produced different results to other prediction formulae suggesting there may be

regional differences even within the Caucasian population of this age group in Europe (Gottdiener *et al.*, 2000). Additional measures to facilitate the identification of patients with Obstructive Lung Disease have been suggested, including diagnostic values of airway impedance (Z_{rs}) worked from forced oscillation technique, though these have been used exclusively in hospitalised patients (Janssens *et al.*, 2001).

Other studies have also investigated prediction methods and how the comparison to the GOLD guidelines. (Guder *et al.*, 2012; Runarsdottir *et al.*, 2013; Scholes *et al.*, 2014). Comparison of the difference in expert panel diagnosis with GOLD classification and Lower Limits of Normal (LLN) formulae found that GOLD criteria misclassified 28% of the patients whereas LLN equations misclassified COPD by at least 39% (Guder *et al.*, 2012). In addition the GOLD criteria led to more false positives whereas the LLN produces more false negative results when compared to the expert panel findings, with the expert panel classification seen to be most accurate (Guder *et al.*, 2012).

In a non-smoking Icelandic population of 66 – 92 year olds, the GOLD criteria identified a substantial number (38%) of non-symptomatic subjects as having COPD, and more than would have been identified if the LLN formulae had been used (Runarsdottir *et al.*, 2013). Similar findings were reported from wave 2 of the UK household survey where prevalence of obstruction was higher in 75 – 95 years old using GOLD (45.0%) in comparison to LLN (17.2%) (Scholes *et al.*, 2014). These findings have been confirmed in those aged 75 and over with higher COPD prevalence using GOLD (26.4%) than LLN (5.6%) (Karrasch *et al.*, 2016).

Almagro and colleagues investigated gender differences in COPD patients and found that men had a larger mean average FEV_1 but a lower FEV_1/FVC, higher number of comorbidities and they observed that more men had severe or very severe COPD compared to women (Almagro *et al.*, 2010).

1.5.2 Respiratory function as a predictor of other outcomes

Of the 120 studies reviewed, 30 examined respiratory function as a predictor of other outcomes. In eight of the studies the outcome was cognitive impairment (Schaub *et al.*, 2000; Murray *et al.*, 2005; Li *et al.*, 2006; Allaire *et al.*, 2007; Guo *et al.*, 2007a; Weuve *et al.*, 2011; Emery *et al.*, 2012; Vidal *et al.*, 2013); in a further 5 the outcome was disability (Ho *et al.*, 2001; Buchman *et al.*, 2009; Kingston *et al.*, 2014; Lahousse *et al.*, 2016; Hegendorfer *et al.*, 2017c); physical activity in three studies (Buchman *et al.*, 2008; Abe *et al.*, 2011; Nyssen *et al.*, 2013); 4 studied mortality (Cooper *et al.*, 2002; Lyyra *et al.*, 2005; Shipley *et al.*, 2007;

Buchman *et al.*, 2008; Buchman *et al.*, 2009); and a further two respiratory function as a cause of other morbidity (Bourdel-Marchasson *et al.*, 1998; Lawlor *et al.*, 2004). 8 studies investigated the different lung function formulae and their effectiveness in diagnosing COPD (Janssens *et al.*, 2001; Guder *et al.*, 2012; Karrasch *et al.*, 2013; Runarsdottir *et al.*, 2013; Miller *et al.*, 2014; Scholes *et al.*, 2014; Marcus *et al.*, 2015; Karrasch *et al.*, 2016). Brief details of the studies under these subheadings are given below.

From the literature, there seems to be a well-established link between lung function and cognitive impairment. Schaub et al using the Berlin Ageing Study (BASE) conducted a cross sectional analyses of demented and non-demented participants with mean age of 84.3 years whom 53.8% (235) were men. When looking at the two groups defined by dementia, they found differences between the groups in VC, FEV_1, PEFR, FVC and Maximal Expiratory Flow suggesting that those with dementia performed worse than those without (Schaub *et al.*, 2000). Analysis of the National Health and Nutrition Examination Survey III (NHANESIII) found no association between memory impairment and lung function though they did find an association between hearing impairment and poor lung function (Li *et al.*, 2006). Another study of older African American adults with an age range of 50-89 years of whom 38% were male, found a statistically significant inverse correlation between average PEFR (APEFR) and 6 cognitive tests (Immediate Memory, Delayed Memory, Backward Digit Span, Alpha Span, Digit Symbol and Telephone Interview of Cognitive Status (Allaire *et al.*, 2007)).

Brain White Matter Hyperintensities is a potential risk factor of cerebral ischemia and a study of 106 subjects of the 1921 birth cohort at age of 78-79 years found a negative correlation between white matter hyperintensity and three lung function measures (FEV_1, FVC and PEFR) suggesting that these measures could be predictors of cerebral ischemia (Murray *et al.*, 2005).

One of the shortcomings of cross sectional studies lies with the fact that they only indicate an association between outcomes and explanatory variables. However, longitudinal studies provide researchers with the ability to infer causation between two or more variables and thus produce causal pathways. In the Swedish Adoption/Twin Study of Aging, the relationship between pulmonary function and cognitive impairment was investigated by Structural Equation Modelling (SEM) in a sample of 832 (40% males) over a period of 19 years (Emery *et al.*, 2012). They concluded that decline in pulmonary measures FEV_1 and FVC leads to decline in cognitive function with a more pronounced decline in psychomotor speed and spatial abilities (Emery *et al.*, 2012).

Another study of multiple cohorts followed longitudinally, though using only female subjects, found that better lung function (FEV_1, FVC and PEFR) during midlife reduces the risk of dementia later in life (Guo *et al.*, 2007b). These associations remained significant even after adjusting for many potential confounders such that of age, height, Body Mass Index (BMI), physical activity, respiratory and cardiovascular related conditions. To show that this effect is not just found in females, Weuve et al (Weuve *et al.*, 2011) looked at FEV_1 and cognitive decline in ageing men and also confirmed that better lung function results in slower decline of cognitive abilities. Subjects with lower lung function (FEV_1 /height) during midlife have been shown to be more likely to develop mild cognitive impairment or dementia some 23 years after (Vidal *et al.*, 2013).

The association of respiratory function with living conditions, disability and care needs of the ageing population has been the subject of a number of studies (Ho *et al.*, 2001; Buchman *et al.*, 2009; Kingston *et al.*, 2014; Lahousse *et al.*, 2016; Hegendorfer *et al.*, 2017c). In a population aged 70 years and older, dyspnoeic subjects (compared to non-dyspnoeic) had significantly poorer functional status mean scores which included mobility (9.8 vs 14.5), kitchen duties (13.8 vs 14.5), domestic tasks (7.6 vs 10.2) and leisure activities (10.6 vs 13.3) (Ho *et al.*, 2001).

Pulmonary function, respiratory muscle strength and leg strength in a clinical population separately predicted incident mobility disability (gait) over 4 years after adjusting for certain confounders such as age, sex and education, although the effect of pulmonary function was lost later as more confounders were added (Buchman *et al.*, 2009). Furthermore, a study of those aged 80 years and older found that those with excessive respiratory function ($FEV_1/Height^3$) decline during an average follow-up period of 1.7 years revealed an increased risk (odds ratio:2.02, 95% CI: 1.10 – 3.68) of new or worsened activities of daily living (ADLs) in comparison to all other participants (Hegendorfer *et al.*, 2017c). The other studies in this subset confirmed similar findings in terms of respiratory disease and increased risk of becoming disabled (Kingston *et al.*, 2014) and those with COPD showing an increased risk of frailty prevalence (Lahousse *et al.*, 2016).

Physical activity is often used as a measure of wellbeing and thought to delay the effects or symptoms of ageing (Lacour *et al.*, 2002). A Portuguese study on respiratory function investigated the role of physical activity by dividing COPD patients into 2 groups defined by the average number of steps logged by a pedometer: with “severe physical inactivity” (<4580 steps) or without (≥4580 steps). The two groups did not differ on Body-mass index, airflow

Obstruction, Dyspnoea, and Exercise (BODE) index or percent predicted FEV_1. However no association was found, perhaps due to the small study size (n = 30) or the cut point used for physical inactivity (Nyssen *et al.*, 2013).

A number of studies have explored lung function as a predictor of other disease and conditions. FEV_1 and FVC have been found to be inversely related to insulin resistance and diabetes after adjusting for known and potential confounders (Lawlor *et al.*, 2004), although the authors also recognised that those of advanced age and/or having a history of smoking found it harder to provide adequate lung function and spirometry measures.

There have been studies investigating the associations between lung function and respiratory conditions with cardiovascular disease (Sin and Man, 2003; Sin *et al.*, 2005; Mannino and Davis, 2006; Agarwal *et al.*, 2012; Nilsson *et al.*, 2017). Reduced FEV_1 has been associated with increased risk of heart failure when comparing the lowest and highest quartiles (Agarwal *et al.*, 2012).Prevalence of COPD has been observed to be associated with increased risk of hypertension (OR: 1.6, 95% CI 1.3 – 1.9) and cardiovascular disease (OR: 24, 95% CI 1.9 – 3.0) (Mannino and Davis, 2006). Furthermore both reduced lung function and COPD prevalence has been found to be associated with increased rates of cardiovascular mortality (Sin and Man, 2003; Sin *et al.*, 2005; Nilsson *et al.*, 2017).

The only longitudinal study found examined the 5 year mortality of patients with or without diabetes (Bourdel-Marchasson *et al.*, 1998). As this study's main aim was to look at different predictors in diabetic patients, the only respiratory symptom investigated was dyspnoea. However this study reported that dyspnoea was associated with an increased relative risk of mortality in diabetic (RR=2.4 in 65-75 year olds, RR=1.9 in 75+) and non-diabetic patients (RR=1.5 for 65 – 75 year olds, RR=1.3 for 75+), although this appeared to be due to smoking since the association was lost once models were adjusted for smoking (Bourdel-Marchasson *et al.*, 1998).

Mortality has been looked at in conjunction with other outcomes in a number of studies already described. The relationship between pulmonary function and mortality of at least 2 years (mean 2.2 years) was investigated specifically in old age by Buchman (Buchman *et al.*, 2008) where the mean age of the subjects who died was 85.3 in contrast to 80.1 for the surviving subjects. VC, FEV_1 and PEF were converted into z-scores and combined to create a composite variable called pulmonary function. Cox Proportional hazard modelling using the 25^{th} and 75^{th} percentile was used to compare survival rates. Higher pulmonary function was associated with a lower risk (47% less) of death after adjustment for age, sex, education and

BMI (Buchman *et al.*, 2009). The same study found that extremity and respiratory muscle strength had no significant effect on survival once all covariates were adjusted for (Buchman *et al.*, 2008).

Respiratory related death as a specific cause of mortality was addressed in another study where a decline in different cognitive abilities over a long period of time (7 years of follow-up) was observed to increase the risk of death from respiratory disease (Shipley *et al.*, 2007).. Similar findings were confirmed when it reported that poor respiratory function in a cohort of 75 year olds increase the chance of death by 52% and 49% for lowest and middle tertile respectively when using the top tertile as reference (Lyyra *et al.*, 2005). Similar effects were seen in muscle strength and walking speed (Lyyra *et al.*, 2005).

1.5.3 Predictors of lung function, lung diseases and respiratory related mortality

The GOLD report recognises that nutritional state is linked to prognosis of COPD and that nutritional markers, such as BMI, are known to have an effect on the mortality of COPD patients (Vestbo *et al.*, 2013). Nutritional markers have been investigated in relation to lung function and respiratory related conditions cross-sectionally (Sergi *et al.*, 2006; van den Borst *et al.*, 2012; Abbatecola *et al.*, 2013). Resting energy expenditure has been found to be higher and Fat-Free Mass (FFM) lower in COPD patients (Sergi *et al.*, 2006). Abbatecola et al investigated this further in COPD patients only, and found as expected that men were heavier and had a higher lean mass than women (Abbatecola *et al.*, 2013). They also found that participants in the upper tertile of gait speed had lower BMI and fat mass and better respiratory function. They concluded that gait speed is directly related to FEV_1 (Abbatecola *et al.*, 2013). Visceral Fat Area has also been found to have an association when comparing patients with Obstructive Lung Disease and those without (van den Borst *et al.*, 2012). However, as these are cross-sectional studies, causality cannot be inferred.

There were only three longitudinal studies of the association between nutritional markers and pulmonary function with one of these only looking at ill health with pulmonary function as one of its outcome (Ramsay *et al.*, 2006). This study which re-examined participants 20 years after the first study (and aged 60 – 79 years at recall) observed reduced risk of low FEV_1 for those with a waist circumference of 89 – 94cm compared to the reference group (57 – 88cm) and they further confirmed previous findings of lower fat free index leading to lower lung function (Ramsay *et al.*, 2006).

The other two longitudinal studies were conducted by Rossi et al (Rossi *et al.,* 2008; Rossi *et al.,* 2011) and examined body composition. The first on only a sample of 77 (30/77, 39% men) subjects and the second on 1981 (957, 48% men) subjects, with the 7 and 5 year follow-up respectively. They confirmed previous findings between FEV_1 and FVC against Sagittal abdominal diameter, FFM, FM and waist size, with an increase in SAD predicting a decrease in FEV_1 and FVC and a decrease in FFM directly affecting FVC (Rossi *et al.,* 2008). The latter of the two studies, found that increased fat mass is a predictor of decline in FEV_1 and FVC (Rossi *et al.,* 2011).

Only five studies examined the effect of blood-based biomarkers on lung function, all longitudinal in design (Finkel *et al.,* 2003; Shaaban *et al.,* 2006; Gimeno *et al.,* 2011; Ahmadi-Abhari *et al.,* 2014; Hancox *et al.,* 2016). Finkel and colleagues used twin data to investigate whether there was any genetic influence on FEV_1. Using genetic latent growth models they reported gender differences in FEV_1 and found phenotypic correlations between the twins and their FEV_1, concluding that this was due to genetic and environmental influences (Finkel *et al.,* 2003).

Results from a longitudinal study with 8.5-year follow-up examined the relationship between C - reactive protein (CRP) and FEV_1 in 531 participants at two French centres for respiratory conditions. The study found that increases in CRP over time was associated with decline in FEV_1 levels (Shaaban *et al.,* 2006). Similarly, in the Whitehall II study, negative associations were revealed between CRP and Interleukin-6 (IL-6) over a 12-year period in participants with no self -reported respiratory problems at baseline (n=1,657) (Gimeno *et al.,* 2011).

Furthermore, the effect of CRP on lung function was investigated over a period of 13 years in 18,110 participants (age range 40 – 79 years) with findings that an increase in CRP levels was associated with a reduction in FEV_1 from the longitudinal data but this was not evident from the baseline data alone. They concluded that systemic inflammation resulted in a decrease in lung function (Ahmadi-Abhari *et al.,* 2014). A study investigated longitudinal change in FEV_1 as a predictor of CRP, finding that lower lung volumes were associated with higher CRP over a 6-year follow-up (Hancox *et al.,* 2016).

Respiratory medication use in the elderly has scarcely been investigated with only one study found which looked at inhaled anticholinergic in the elderly population with COPD and whether there was any increased risk of mortality. The study, a retrospective longitudinal panel data collected on 2610 individuals of 65 years and older, found an increased risk of

mortality before adjustment which was lost after accounting for the different confounders (Ajmera *et al.*, 2013).

Ranieri et al investigated one-year mortality differences supplemented by probing further into other socio-demographic and clinical associations. They found that patients with COPD were older and more likely to be men (Ranieri *et al.*, 2001). Patients without cor pulmonale (CP) had a 1.9 times higher risk of death after one year and those with cor pulmonale had were 4.2 times more likely to die (Ranieri *et al.*, 2001). The only other difference seen between the COPD and non-COPD group was the lower count of associated disease and lower medication use in the COPD group.

Smoking has long been known as a cause for many respiratory conditions and a contributor to poor physical and lung function. In 2001, 16% of the older population in the UK smoked, a large improvement on the 44% in 1974 (Allen, 2009). Allen also reported that mortality rates could be reduced if smoking cessation happened even at very old age and he believed that, with correct interventions, the prevalence of smoking amongst the older population could be reduced (Allen, 2009). Hsu et al took this one step further and investigated the effect of smoking cessation on both respiratory-related morbidity and mortality, in a cohort followed from 1989 and of whom 17.0% were 75 years of age and older. Smokers were found to have a higher relative risk of lower respiratory tract disease which was similar to that of former smokers (Hsu and Pwu, 2004).

1.6 Aim of this thesis

Given the paucity of studies examining lung function, its determinants and consequences in very old general populations, the primary aim of this study was to investigate the relationship of lung function with disability and mortality in the very old using the Newcastle 85+ study.

1.7 Specific objectives

In order to achieve the study aim, this thesis will:

1. Describe the study population of the Newcastle 85+ study.
2. Explore the sociodemographic characteristics, health behaviours, and lung function and disease prevalence of the very old.
3. Investigate whether longitudinal measures of lung function can still predict mortality at an advanced age whilst accounting for other sociodemographic and health characteristics.

4. Investigate how lung function changes with further ageing in the very old and the determinants of these changes.
5. Explore and investigate the causal pathways between lung function and disability in the very old and possible mediators.

1.8 Summary

This chapter has presented the clear need for further investigation of lung function determinants and consequences at a very old age. Although ageing studies have investigated the burden of disabling diseases and conditions in general, and certain conditions in particular (cardiovascular disease, cognition/dementia, arthritis, stroke), respiratory disease and respiratory function have been little studied. Moreover, associations between respiratory function and outcomes established in younger age groups may no longer hold, or hold differently, in the very old. An example of this is the relationship between telomere length and mortality with shorter telomere length predictive of mortality at younger ages (Cawthon *et al.*, 2003) but not in the very old (Martin-Ruiz *et al.*, 2005; Houben *et al.*, 2011).

The following chapter will describe the Newcastle 85+ study, its components and participants.

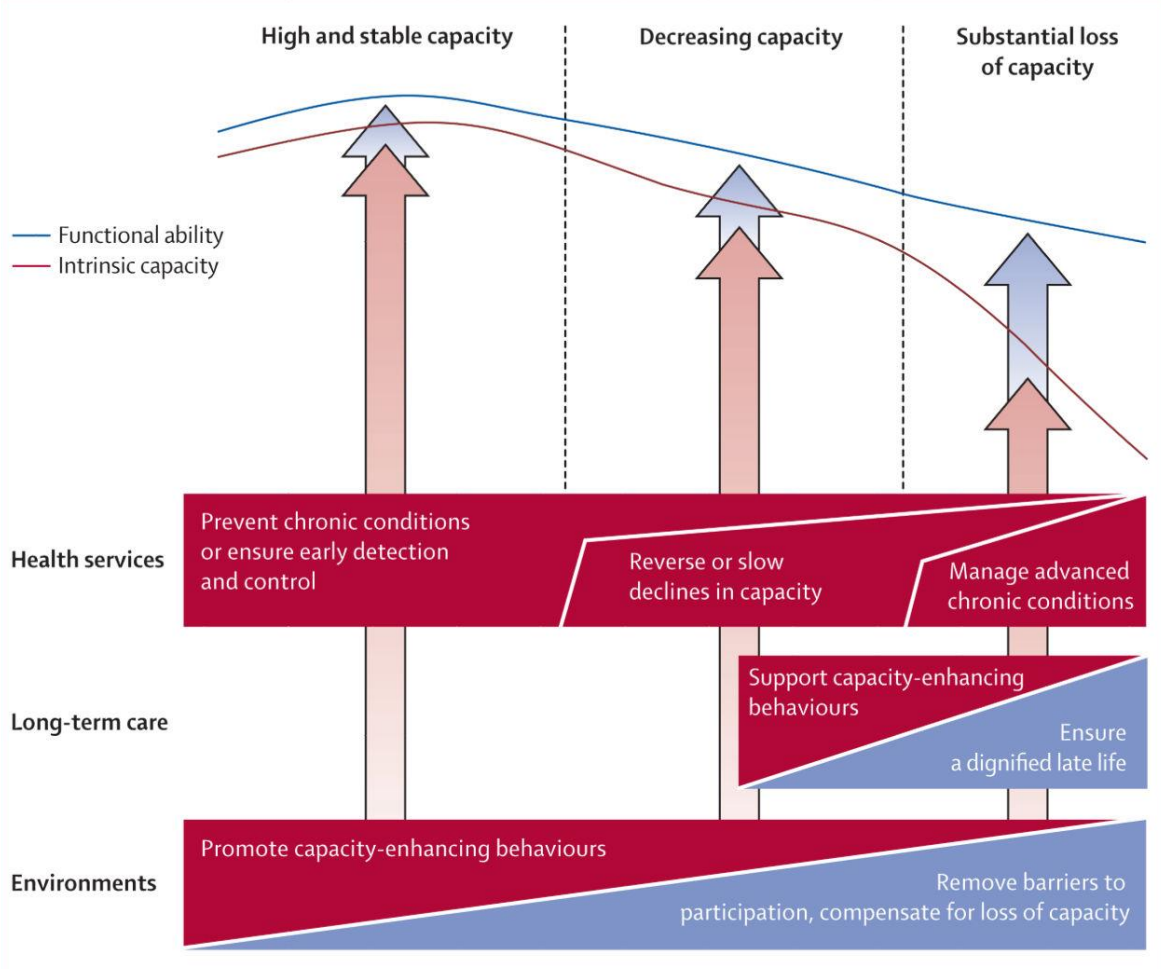


Figure 1.1: Physical functioning across the life course, stratified by ability to manage on current income (Beard et al., 2016)

Chapter 2. Newcastle 85+ Study

2.1 Aims of the chapter

This chapter aims to:

1. Outline the Newcastle 85+ study rationale, design and recruitment
2. Describe the two data collection components of the study
3. Describe in detail the available spirometric data
4. Discuss the creation of composite variables
5. Describe the overall sociodemographic characteristics of Newcastle 85+ population

2.2 Introduction

The literature review in the previous chapter highlighted the lack of research into lung function, its determinants and consequences in the very old. In order for society to adapt to the dynamic population progression, it is wise to try and understand the demands which it will face from the fastest growing sector of its population, those aged 85 years and older (United Nations, 2002). A prospective cohort study of the very old is an approach that can be taken to address this issue.

This chapter will describe in detail the Newcastle 85+ study from design to implementation providing a foundation for the subsequent chapters seeking to an answer to impact of lung function on disability and mortality.

2.3 Study rationale, design and recruitment

The Newcastle 85+ study (N85+) is a longitudinal cohort study of people born in 1921 and living in Newcastle and North Tyneside in the north east of the United Kingdom (UK) who were aged 85 years at study inception (2006) (Collerton *et al.*, 2007). The study was preceded by a pilot study conducted in 2003 – 2004 following a careful review of the Leiden 85+ study and collaboration with the Leiden group. The aims of the N85+ study were to "expose spectrum of health" and "examine, in unprecedented detail, health trajectories and outcomes as the cohort ages and their associations with underlying biological, medical and social factors"(Collerton *et al.*, 2007) (Bootsma-van der Wiel *et al.*, 2002).

The Newcastle 85+ study recruited participants by approaching general practices within Newcastle and North Tyneside Primary Care Trusts, to gain permission to contact participants. The inclusion criteria for participation required the participants to have been born

in 1921 and registered with a General Practitioner (GP). Invitation for participation were sent to those who met the inclusion criteria regardless of their living arrangement (home or institutional care) and included information pack with their GP's 'letter of support'. These were followed up by a research nurse through a phone call or a home visit for a detailed discussion about the study. Individuals who showed an interest in taking part were visited at their place of residence by a member of research team and written informed consent obtained. Individuals who were recognised to have end stage terminal illness by their GP were excluded

The study comprised of two parts, a multidimensional health assessment (MDHA) and the General Practitioner Record Review (GPRR). The MDHA included a series of questions to the participant (or their proxy) in addition to the administration of various functional tests. The baseline data was collected from 2006 – 2007 with three follow-ups at 18, 36 and 60 months (Appendix A). Complete health assessment was conducted at baseline, 18 and 36 months followed by a reduced health assessment at 60 months. The GPRR was conducted at baseline, phases 3 and 4 (Collerton *et al.*, 2007). Participants could opt in for either MDHA, GPRR or both.

2.3.1 Multidimensional health assessment

The MDHA including questionnaires, measurements, function tests and blood samples, was conducted by the study nurse over a series of visits. The questionnaires collected information about participant's "living arrangements, physical health, psychological health, disability, lifestyle, social support and participation and use of the social care" (Collerton *et al.*, 2007). The questionnaires thus had the following sections:

1) Sociodemographic factors: date of birth, sex, ethnic origin, and socio-economic status comprised of years in education, National Statistics Socio-economic Class and current financial income.
2) Lifestyle: smoking, alcohol consumption and exercise
3) Family data: marital status, age at parent's death, siblings and children with vital status
4) Physical health: self-rated health status, self-reported longstanding illness, angina, shortness of breath, generalised pain, joint pain, fractures, incontinence, falls, vision and hearing, and oral health
5) Non-prescribed medication
6) Depression: based on Geriatric Depression Scale
7) Disability: difficulty with instrumental/activities of daily living (I/ADLs)

8) Nutrition: two separate 24 hour multiple pass recall assessment
9) Social support and social participation
10) Use of health and social care

Data from measurements and function tests data collected from the participants included: anthropometrics: bio-impedance, weight, demispan, waist and hip circumference; tooth count; cognitive function tests: Mini-Mental State Examination (MMSE) and Cognitive Drug Research (CDR) computerised assessment system; 12 lead electrocardiogram (ECG); walking test (timed 'up and go'); handgrip strength, and spirometry and oximetry.

Blood samples were taken at the participant's home after an overnight fast at baseline and 36 months but not 18 months. The blood assays included (Collerton *et al.*, 2007):

1) Routine haematology and biochemistry: full blood count; creatinine and electrolytes; liver panel; bone panel; glucose; glycosylated haemoglobin.
2) Lipid profile: cholesterol, triglycerides, high and low-density lipoproteins, apolipoproteins (A1, B and E).
3) Thyroid function: free T4, free T3, reverse T3, TSH and TPO antibodies.
4) Inflammatory markers: High sensitivity CRP, rheumatoid factor, cytokines (TNFα and IL-6).
5) Cortisol
6) Nutritional markers: Vitamins B2, B6, B12, C and D, ferritin, red cell folate and homocysteine.
7) Biomarkers: Deoxyribonucleic acid (DNA) repair capacity, telomere length, F2-isoprostane (marker of oxidative stress).
8) Markers of immunosenescence: T cell oligoclonality and lymphocyte subpopulation distributions (senescent T-cells, memory T-cells and NKcells).

2.3.2 General practitioner record review

The GPRR comprised of four sections:

1) Medications list of participants were recorded with the drugs later coded to the British National Formulary (BNF). The drug dosage and duration were not collected.
2) Key diagnoses since birth and certain interventions were recorded with the date. The disease categories included cardiovascular, cancer, endocrine, eye disease, fractures (since 1971), liver disease, musculoskeletal disease, neurological disease, psychiatric and respiratory disease.

3) Last 40 consultations (date, professional seen and where seen.)

2.4 Health measures variables

2.4.1 Cognitive impairment

The Standardised Mini-Mental State examination (SMMSE) was administered with 12 questions and 30 point score (Molloy *et al.*, 1991; Molloy and Standish, 1997) with zero points awarded for wrong or missing items. The total score was categorised based on the Cognitive Function and Ageing Studies (CFAS) group to define cognitive impairment severity (Xie *et al.*, 2008):

i. 0 – 17: Severe cognitive impairment
ii. 18 – 21: Moderate cognitive impairment
iii. 22 – 25: Mild cognitive impairment
iv. 26 – 30: No cognitive impairment

2.4.2 Depression

Participants were screened for depression using the 15 Item Geriatric Depression Scale, a reduced version of the original questionnaire (Yesavage *et al.*, 1982). This version of the questionnaire has been found to be reliable in recognising depression within the very old (Alden *et al.*, 1989; Almeida and Almeida, 1999; Osborn *et al.*, 2002). If participants scored less than 15 on their SMMSE they were exempt from depression screening as it was deemed unreliable (Burke *et al.*, 1991). A three category variable was derived were participants were placed into these groups based on their score:

i. 0 - 5 : No Depression
ii. 6 - 7 : Mild Depression
iii. 8 – 15 : Severe Depression

2.4.3 Body mass index (BMI)

Demi-span was measured in centimetres (cm) and height was calculated from this using the two standard formulae for males [height = 1.40 x demi-span + 57.8] and females [height = 1.35 x demi-span +60.1]. The BMI was then derived by using the derived height converted to metres (m) variable and the participant's weight in kilograms (kg) measured during one of the interview visits using the standard equation [BMI = height^2/weight]. A categorical BMI

variable was also derived based on the World Health Organisation (WHO) classification (World Health Organisation, 2006) reduced to five main categories:

i. Underweight: up to 18.5
ii. Normal weight: 18.5 – 25
iii. Overweight: 25 – 30
iv. Obese: 30 – 40
v. Morbidly obese: 40+

2.4.4 Physical activity

Physical activity was measured through a self-report questionnaire based on three questions on frequency of very energetic, moderately energetic and mildly energetic activities. Participants were given a score of between zero and three based on the frequency of their activity for each question. A final physical activity score was calculated based on the sum of all three scores with a coefficient of 3, 2 and 1 being used for very, moderately and mildly energetic activity scores respectively as demonstrated below (Innerd *et al.*, 2015).

A categorical variable for physical activity was derived from this score with three bandings:

i. Low physical activity: 0 – 1
ii. Medium physical activity: 2 – 6
iii. High physical activity: 7 – 18

There was strong agreement between the subjective (questionnaire) and objective (accelerometer) at 36 months (only time point for accelerometry) (Innerd *et al.*, 2015).

2.4.5 Auditory and visual function

Participants were asked about everyday situations such as difficulty in following conversations in the background whilst wearing a hearing aid if they had one. The everyday situational questions asked about participant's ability to recognise friends across the road (whilst wearing glasses or contact lenses if necessary) or reading a newspaper.

2.4.6 Blood based biomarkers

Blood was drawn from participants with 95% of samples received by the laboratory for processing within an hour with over 72 biomarkers being profiled (Martin-Ruiz *et al.*, 2011). Three inflammatory markers which have previously been shown to be inversely associated

with lung function measures FEV_1 and FVC (Ahmadi-Abhari *et al.*, 2014) (Gimeno *et al.*, 2011) and a biomarker of ageing was included in respiratory analyses:

i. Interleukin-6 (IL-6)
ii. Tumour necrosis factor alpha (TNFα)
iii. C-Reactive Protein (CRP)
iv. Telomere length

2.4.7 Multimorbidity

Two separate disease burden measures were calculated, one based on a previously used disease count (Collerton *et al.*, 2009), with most of the prevalence derived from GPRR and others from the functional and blood tests performed during the interview stage, and the second disease count based solely on GPRR with the exception of cognitive impairment which used the SMMSE from the MDHA.

The first disease count was based on 18 diseases: hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial fibrillation, diabetes mellitus, thyroid disease, arthritis, osteoporosis, cancer excluding non-melanoma skin cancer, eye disease, dementia, Parkinson's disease, anaemia, renal impairment, COPD and other respiratory disease. A shortened version of this disease count was calculated, excluding COPD and other respiratory disease (maximum 16 diseases) (Collerton *et al.*, 2009) (Fisher *et al.*, 2016)

The second disease count variable was originally a sum of eight disease groups and thus participants could score a maximum of 8 (Table 2.1) (Kingston *et al.*, 2014). For this thesis, the respiratory disease group was removed and used separately for analysis and thus the maximum for this disease count was 7.

It is worth mentioning that due to the second disease count being solely based on GPRR, there were fewer missing values on this variable in comparison to the first where only 86.3% (729/845) of participants had complete data.

2.4.8 Spirometry

Spirometry and peak flow measurements were performed by a trained research nurse using the MicroLab Spirometer and Spida software (Micro Medical Ltd, Rochester, UK) at the participant's place of residence. Lung function measures were obtained at baseline, 18 and 36 months. "The aim was to obtain three technically satisfactory maximal effort 'blows' to

generate reproducible forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and peak flow measurement (PEF); blows were repeated until this was achieved or maximum effort reached" (Fisher *et al.*, 2016). Built-in Spida algorithms were used to assess technical adequacy of the each blow. The spirometry curves were independently assessed by a respiratory clinical physiologist and participants with at least two adequate blows were included in the analysis. However if this necessary quality was not achieved, the participants were excluded from the respiratory analysis. Participant's height was derived from demi-span measurements using standard equations as this has been found to be more accurate in those aged 65 and over (Hirani and Mindell, 2008).

Age, gender and height were used to calculate predicted FEV_1, FVC and peak flow values for each participants using the ERS 1993 (Quanjer et al., 1993) coefficients currently approved by the UK Department of Health (Department of Health, 2013). Spirometry classifications were based on the FEV_1/FVC ratio and percentage predicted values for FEV_1 and FVC. Participants classified with obstructive spirometry were subsequently categorised as mild, moderate, severe or very severe using the GOLD criteria (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2010) (Table 2.2) Lung function can also be classified using the LLN method which takes standardised values (z-scores) for each participant and places them within three groups; below lower limit of normal, normal and above upper limit of normal.

Furthermore, using the newer Global Lungs Initiative (GLI) prediction model equations (validated for ages 3 – 95 years) (Quanjer *et al.*, 2012), additional predicted values for FEV_1, FVC and PEF were calculated to enable comparison of methods and diagnosis of lung disease present in this cohort.

2.5 Newcastle 85+ population

2.5.1 Participant recruitment and retention

The study invited 1459 people and managed to make contact with 97% (1409/1459) of whom 74% (1042/1409) gave written informed consent to participate in the study (Davies *et al.*, 2010). In total 851 consented to both MDHA and GPRR, 188 to GPRR only and 3 to health assessment with the remaining 358 declining any participation.

Participant retention has been fully documented and a study of participant retention and the effectiveness of strategies employed around this was investigated (Davies *et al.*, 2014). In brief of the 854 participants at baseline 74% were retained for phase 2 (631/854) with 61% (135/223) of the attrition being due to death. 57% (484/854) were retained for phase 3 of the

study with an attrition rate of 17% (147/854) with 65% (95/147) being due to death. For phase 4, 40% (344/854) were retained. The attrition rate between phases 3 and 4 was 16% (141/854) of whom 81% (114/141) were death (Davies *et al.*, 2014). Factors which led to good retention rates included marginal loss to follow-up which was 0.5% (5/854) of participants through maintaining good relationship with their GP and where relevant their care home staff members in addition to maintaining contact with participants throughout the study (Davies *et al.*, 2014).

Of the 851 who agreed to MDHA and GPRR, six participants withdrew during the lifetime of the study and requested their data to be removed, leaving a complete cohort of 845 (526 women; 319 men) for the purpose of this thesis.

2.5.2 Sociodemography

Data from both the MDHA and GPRR was available for 845 participants, 58.2% (845/1453) of all those eligible, with a mean (standard deviation) age of 85.5 (0.4) years. Females accounted for 62.3% (526/845) of the participants and 99.6% (839/845) were of white ethnic group (Table 2.2). In terms of living arrangements, 77.0% (651/845) lived in standard housing, 12.8% (108/845) in sheltered accommodation and 10.2% (86/845) in institutional care. The proportion of males living in standard housing (83.4%, 266/319) was higher than that for women (73.2%, 385/526), lower for sheltered housing (men: 10.3%, 33/319; women: 14.3%, 75/526) and institutional care (men: 6.3%, 20/319; women: 12.6%, 66/526) (p-value= 0.002).

2.5.3 Baseline health behaviours

Examining the smoking history of the participants, 35.8% (301/845) reported themselves as never smokers with women (42.0%, 220/526) reporting a higher abstinence rate than men (25.6%, 81/316). Although almost three-quarters (74.4%, 235/316) of men and over half of women (58.0%, 304/524) had smoked in their lifetime, very few (men: 4.4%, 14/316; women: 6.5%, 34/524) were current smokers (Table 2.2).

Just over half of both men (51.5%, 151/293) and women (51.1, 218/427) were categorised as having normal weight with a normal BMI classification. The overweight BMI was the category with the second highest proportion of men (35.8%, 105/293) and women (30.7%, 131/427). The underweight category was only 6.5% (47/720) of the whole population with the obese/morbidly obese at 9.5% (68/720).

Exploring baseline physical activity levels, just under a quarter of women (24.8%, 124/501) and 21% (65/311) of men had low levels of physical activity. The highest proportion of women (49.5%, 248/501) were scored as having medium levels of physical activity compared to just 32.5% (101/311) of men. In men 46.6% (145/311) were categorised as having high levels of physical activity in comparison to women with just over a quarter (25.8%, 129/501) falling in the same category.

Over half (55.9%, 171/306) of men and almost a fifth (19.8%, 98/495) of women had occupational exposures which may have affected their respiratory health. This trend of higher occupational exposure prevalence was confirmed when detailing the different industries the participants were employed in (heavy industry: 41.2%, 126/306; coal mining: 11.4%, 35/307; chemical industry: 11.1%, 34/306; asbestos: 28.9%, 88/305), reflecting common historical occupations in this region of the UK (Table 2.2).

2.5.4 Baseline health

A higher proportion of men (31.6%, 100/317) had no disability at baseline compared to women (16.3%, 85/522). The majority of men (52.4%, 166/317) had a disability score between one and six, similar to that of women (57.5%, 300/522). Participants with the highest disability score (13 – 17) comprised of only 6.3% (53/839) of the whole population (men: 4.4%, 14/317; women: 7.5%, 39/522) (Table 2.3).

The majority (71.7%, 599/839) of the population had normal cognitive function (MMSE score of 26 – 30) at baseline with similar proportions between men (71.9%, 228/317) and women (71.1%, 371/522). Severe cognitive impairment was observed in 6.9% (58/839) of the population (men: 6.3%, 20/317; women: 7.3%, 38/522) (Table 2.3).

In terms of disease count, there was no difference observed in the median number of disease groups between men (Median: 2, IQR: 1 – 3) and women (Median: 2, IQR: 2 – 3). However, with the number of chronic diseases (comprehensive) at baseline, a statistically significant difference was observed between men (4, IQR: 3 – 6) and women (5, IQR: 4 – 6), with women having on average a higher number of diseases (Table 2.3).

With regard to gender differences in the systemic inflammatory biomarkers, men had a higher IL-6 (logarithmic mean, SD: 9.77, 0.89) compared to women (9.64, 0.90). A similar trend was observed for TNFα (men: 6.25, 1.19; women: 6.10, 1.22). Telomere length as a biomarker of ageing also presented a statistically significantly difference between men (8.28, 0.19) and

women (8.23, 0.19) ($p<0.001$) in line with previous findings (Table 2.3) (Gardner *et al.*, 2014).

2.6 Summary

This chapter described the design of the Newcastle 85+ study, and reported baseline prevalence of pertinent variables for subsequent chapters, The Newcastle 85+ Study was the first prospective longitudinal cohort study of 85 year olds conducted in the UK, with considerable success in recruiting and retaining participants over the period of three follow-up visits spanning 5 years. The study contained a quantitative component providing the study with vital information about the physical and mental well-being of the participants through health assessments and review of GP records. The study was found to be representative of the England and Wales population of this age group (Collerton *et al.*, 2009).

The main findings at baseline were:

1. The main cohort moving forward in this thesis comprised of 845 participants with 37.9% (323) men and 62.1% (529) women who agreed to both the health assessment and GPRR.
2. The retention rates were high between each phase and most of the attrition was due to death.
3. This population lived mainly in standard housing (77.0%), with higher proportion of women living in sheltered (14.3%) or were in institutional care (12.6%) compared to men.
4. Women had a higher proportion of never smokers (42.0%) and current smokers (6.5%) in comparison to men (25.6% and 4.4% respectively).
5. More men (46.6%) had high levels of physical activity in comparison to women (33.7%).
6. A higher proportion of men (55.9%) however worked in industries with respiratory related occupational exposures than women (19.8%).
7. Higher proportion of men (31.6%) reported no disability in comparison to women (22.1%).
8. On average, there was more chronic diseases observed in women (5, IQR: 4 – 6) than men (4, IQR: 3 – 6).

The following chapter will investigate lung function within the study's spirometric cohort, comparing different prediction formulae in assessing COPD.

Table 2.1: Disease groups and respective disease and conditions under each category

Disease group	Diseases and Conditions
Arthritis*	Generalised Osteoarthritis, Hand, Hip and Knee Osteoarthritis Rheumatoid, Degenerative, Poly, Gouty, Septic, Peri, Lumbar Spondylosis, Cervical Spondylosis, Ankylosing Spondylitis and Psoriatic Arthropathy
Cancer*	Any cancer diagnosis in past 5 years excluding non-melanoma skin cancer
Cardiac disease*	Heart Failure, Ischaemic heart disease (Angina, Myocardial Infarction, Coronary Artery Bypass Graft, Coronary Angioplasty/Stent)
Cerebrovascular disease*	Carotid Endarterectomy, Stroke, Transient Ischaemic Attack
Diabetes mellitus*	Type I, Type II and type unspecified
Hypertension*	Hypertension
Respiratory disease*	Bronchiectasis, Pulmonary Fibrosis, Fibrosing Alveolitis, Asbestosis, Pneumoconiosis, Asthma, Chronic Bronchitis, Emphysema, COPD
Cognitive Impairment**	Standardised Mini-Mental State Examination (sMMSE) score of ≤21

* Data from GPRR; ** Calculated using MDHA

Table 2.2: Sociodemographic, respiratory and health behaviour characteristics of total Newcastle 85+ cohort and by gender

% (N)		Men (n=319)	Women (n=526)	Overall (n=845)	p-value*
Ethnicity	White	99.4 (316)	99.8 (523)	99.6 (839)	0.272[1]
Living arrangements	Standard housing	83.4 (266)	73.2 (385)	77.0 (651)	
	Sheltered housing	10.3 (33)	14.3 (75)	12.8 (108)	0.002[1]
	Institutional care	6.3 (20)	12.6 (66)	10.2 (86)	
Education	9 Years	62.3 (195)	65.7 (339)	64.4 (534)	
	10 - 11 Years	24.6 (77)	21.7 (112)	22.8 (189)	0.576[1]
	12+ Years	13.1 (41)	12.6 (65)	12.8 (106)	
Smoking	Never	25.6 (81)	42.0 (220)	35.8 (301)	
	Former	69.9 (221)	51.5 (270)	58.5 (491)	<0.001[1]
	Current	4.4 (14)	6.5 (34)	5.7 (48)	
BMI	Underweight <18.5	4.4 (13)	8.0 (34)	6.5 (47)	
	Normal Weight (18.5 - 25)	51.5 (151)	51.1 (218)	51.3 (369)	0.161[2]
	Overweight (25 - 30)	35.8 (105)	30.7 (131)	32.8 (236)	
	Obese (30 - 40)	8.19 (24)	9.8 (42)	9.2 (66)	
	Morbidly Obese 40+	0.0 (0)	0.5 (2)	0.3 (2)	
Physical Activity	Low	20.9 (65)	24.8 (124)	23.3 (189)	
	Medium	32.5 (101)	49.5 (248)	43.0 (349)	<0.001[1]
	High	46.6 (145)	25.8 (129)	33.7 (274)	
Occupational Exposures	Any Respiratory Related occupations	55.9 (171)	19.8 (98)	33.6 (269)	<0.001[1]
	Heavy Industry	41.2 (126)	16.6 (83)	25.9 (209)	<0.001[1]
	Coal mining	11.4 (35)	0.0 (0)	4.3 (35)	<0.001[2]
	Chemical industry	11.1 (34)	4.0 (20)	6.7 (54)	<0.001[1]
	Asbestos exposure	28.9 (88)	1.6 (8)	12.0 (96)	<0.001[1]

*comparison of men and women; [1] Chi-Square test; [2] Fisher's exact test

Table 2.3: Health characteristics of total Newcastle 85+ cohort and by gender

		Men (n=319)	Women (n=526)	Overall (n=845)	p-value*
Disability	None	31.6 (100)	16.3 (85)	22.1 (185)	
% (N)	1 - 6	52.4 (166)	57.5 (300)	55.5 (466)	<0.001[1]
	7 - 12	11.7 (37)	18.8 (98)	16.1 (135)	
	13 - 17	4.4 (14)	7.5 (39)	6.3 (53)	
MMSE	Normal (26-30)	71.9 (228)	71.1 (371)	71.4 (599)	
% (N)	Mild (22-25)	18.3 (58)	14.8 (77)	16.1 (135)	0.111[1]
	Moderate (18-21)	3.5 (11)	6.9 (36)	5.6 (47)	
	Severe (0-17)	7.3 (38)	7.3 (38)	6.9 (58)	
Disease Count	GPRR	2 (1 - 3)	2 (2 - 3)	2 (1 - 3)	0.463[3]
Median (IQR)	Comprehensive	4 (3 - 6)	5 (4 - 6)	5 (3 - 6)	0.047[3]
Blood	CRP	1.09 (1.29)	0.97 (1.26)	1.02 (1.27)	0.184[3]
Biomarkers **	IL-6	9.77 (0.89)	9.64 (0.90)	9.69 (0.89)	0.026[3]
Mean (SD)	TNFα	6.25 (1.19)	6.10 (1.22)	6.16 (1.21)	0.038[3]
	Telomere Length	8.28 (0.19)	8.23 (0.19)	8.25 (0.19)	<0.001[3]

*comparison of men and women; [1] Chi-Square test; [2] Fisher's exact test;

[3] Mann-Whitney U test; ** log-transformed

Chapter 3. Lung function at age 85

3.1 Aims of the chapter

This chapter aims to:

1. Describe the respiratory health of the study cohort
2. Examine the difference between the spirometry cohort sub-group and those without
3. Describe baseline lung function of the spirometry cohort and sub-groups using GOLD and GLI prediction methods
    a. Spirometry cohort as a whole
    b. COPD group
    c. Healthy Reference Group (HRG)
4. Investigate the difference between GP diagnosed COPD and obstructive spirometry as determined using the GOLD and GLI formulae

3.2 Background

The lung function of very old individuals is affected by the accumulation of exposures throughout life and physiological changes with ageing such as loss of lung elasticity and reduced thoracic cage movement which has an effect on the objective lung function measures (Vaz Fragoso and Lee, 2012). This means that the risk of developing respiratory impairment increases in the older population, resulting in higher chronic respiratory disease prevalence and severity. Therefore it is expected that this population will present many respiratory symptoms such as dyspnoea, which has a prevalence of over 40% (Tessier *et al.*, 2001), leading to older people frequently seeking healthcare.

Objective lung function measures are used to classify and diagnose patients with respiratory conditions. The two main pulmonary function tests carried out for diagnosis of loss of lung function are: spirometry which measures Forced Expiratory Volume in 1 second (FEV_1) and Forced Vital Capacity (FVC); and Peak Expiratory Flow (PEF) which measures the highest forced expiratory flow measured using a peak flow meter. The current UK and international guidelines on Chronic Obstructive Pulmonary Disease (COPD) management use the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (as $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted) to define obstructive spirometry (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2010) and inform physicians on the use of specific respiratory

treatments. The predicted values used in the GOLD guidelines were derived from the 1993 European Respiratory Society (ERS) reference regression values (Quanjer *et al.*, 1993). The accuracy of GOLD lung function criteria in diagnosing airflow obstruction or restrictive lung disease in the very old has since been debated due to the physiological changes that occur in this group as part of normal ageing (Vaz Fragoso and Gill, 2012; Marcus *et al.*, 2015; Karrasch *et al.*, 2016).

Previously studies examining lung function in the older population defined this population as those aged 65 years and older (National Health Service, 2011; Guder *et al.*, 2012). The use of such an age cut off meant adequate sample size for answering the authors' research question. However, no meaningful inferences could be made about the lung function of the very old. This area of research, as previously discussed, lacks large cohort studies to extend our knowledge of respiratory health, and the prevalence of lung disease with ageing. Through investigation of lung function in the very old, this chapter will examine whether perceived norms of lung function measures using these prediction formulae corresponds with observed data.

Research in this area is further justified by findings from other studies that have suggested the likelihood of misdiagnosis and missed diagnosis in COPD (Guder *et al.*, 2012; Scholes *et al.*, 2014; Miller and Levy, 2015; Roberts *et al.*, 2015; Karrasch *et al.*, 2016). In those aged 65 years and over the use of GOLD diagnostic criteria led to over-diagnosis whilst Lower Limit of Normal (LLN) definitions resulted in the under-diagnosis of COPD (Guder *et al.*, 2012). Another study reported prevalence of airflow obstruction in those aged 40 – 95 years as 22.2% using GOLD and 13.1% when applying LLN definition (Scholes *et al.*, 2014). More recently, it was found that use of the GOLD criteria was responsible for increases in COPD prevalence (Karrasch *et al.*, 2016). In a younger population, from the Health Survey of England, GOLD criteria suggested airflow obstruction in 11.8% of participants leading to a third of this sample being false positives for COPD (Miller and Levy, 2015). In all these studies the very old (85+) numbered under 100 people.

The aim of this chapter is to address the lack of knowledge surrounding objective lung function measures, prevalence of respiratory symptoms and disease in the very old by examining their interrelationship in the N85+ study. My focus throughout this chapter will be on physician-diagnosed lung disease (available from the GPRR), in particular COPD, assessing its accuracy using the baseline spirometry data and comparing the COPD diagnosis with that obtained from the GOLD and LLN prediction formulae. I will investigate risk factors for respiratory ill health

and the appropriateness of prescribed respiratory medication. I will also identify a healthy reference group within this cohort in order to evaluate the application of the three standard methods of interpreting lung function measurements as normal or abnormal.

3.3 Methods

Details of the N85+ study have been comprehensively discussed in the previous chapter and publications (Collerton *et al.*, 2007; Collerton *et al.*, 2009). This study included baseline measures followed by three follow-ups at 18, 36 and 60 months. In this chapter I will concentrate on the baseline measures of FEV_1, FVC (including predicted values) and PEF.

In addition to the three observed measurements, spirometric ventilatory status, z-scores and LLN/ULN were derived using both GOLD and GLI prediction formulae Table 3.1. Agreement between the three different diagnosis methods (GP, GOLD and GLI) of COPD was also investigated.

3.3.1 Existing diagnoses of respiratory symptoms, disease, medications and environmental risk factors

A predetermined checklist was used to identify participants' current and past respiratory diagnoses from their GP records, including: asbestosis, asthma, bronchiectasis, COPD, pneumoconiosis, pulmonary fibrosis/fibrosing alveolitis and tuberculosis (TB). The data derived included date of diagnosis and medication use but not dosage. Respiratory medications included: inhaled short or long acting beta-2 adrenoreceptor agonists, inhaled short or long acting muscarinic antagonists, inhaled corticosteroids either as single agent or as part of a combination with long acting beta-2 adrenoreceptor agonists, oral corticosteroids, oral leukotriene receptor antagonists, oral theophylline and supplemental oxygen. Breathlessness, cough, wheeze and sputum production were the respiratory symptoms, which were identified as part of the health assessment interview conducted by the research nurse using a structured questionnaire. Medical Research Council (MRC) dyspnoea scores (range 1 – 5) were assigned to each participant based on their responses about the limitations they faced in carrying out day to day activities due to breathlessness (Appendix B: MRC Dyspnoea Questionnaire) (Fletcher *et al.*, 1959).

Relevant environmental exposures of each participant were obtained including: complete smoking history, relevant occupational exposures (including heavy industry, chemical industry, asbestos and coal mining).

3.3.2 Analytical methods

Participants with a GP diagnosis of COPD prior to the study were identified. A Healthy Reference Group of participants was identified who had none of the following; respiratory symptoms, respiratory disease diagnoses, respiratory medication use and respiratory related diagnoses which may influence their lung function such as Parkinson's disease, ankylosing spondylitis, heart failure and kyphoscoliosis. A sensitivity analysis was conducted to explore the need to exclude those with a BMI of over 30 from this group.

Gender differences in socio-demographic and health characteristics were explored by X^2 tests (ethnicity, living arrangements, smoking status, occupational exposures, respiratory diagnoses, medications), Kruskal Wallis tests (MRC dyspnoea scores) and Mann-Whitney U tests (total disease count and the disease count excluding respiratory). The disease count variable used in this section was the composite count derived from MDHA and GPRR.

Gender differences in lung functions measures (observed and predicted), spirometry classification, standardised FEV_1 and FVC z-scores and oxygen saturation were investigated within the whole sample, the COPD group and the HRG using X^2 and Fisher's exact tests for categorical measures, and Kruskal-Wallis tests for ordered categorical measures. Pearson correlation coefficients were used to investigate the relationship between FEV_1 and PEF scores. Sensitivity analyses were carried out to examine the effect of including participants with a Body Mass Index (BMI) score of 30 and over in the HRG, and the differences between those with and without spirometry measures and MRC dyspnoea scores within the total cohort.

The level of agreement between the three different COPD diagnosis methods (GP diagnosis, GOLD and GLI) was assessed by McNemar's and Cohen's Kappa test (Fleiss, 1981). All analyses were conducted using Stata 12.0 (StataCorp; College Station, TX).

3.4 Results

3.4.1 Respiratory symptomatology, diagnoses and medication use

Chronic cough was self-reported in 26.7% (217/812) and wheeze in 22.0% (179/812) of participants. Regular sputum production was more common in men (men: 40.7%, 127/312; women: 28.0%, 140/500; $p<0.001$). The MRC dyspnoea scores could be calculated for 70.8% (598/845) of participants, those without a score having their activity limited by other non-respiratory conditions. In men, 50.2% (123/245) and in women 40.5% (143/353) had an MRC

dyspnoea score of 1 and thus had no limitations to their daily activities due to breathlessness. At the other end of the spectrum, only 4.7% (28/598) of participants reported a score of 5 and were classed as too breathless to leave the house, or breathless when dressing/undressing (Table 3.2).

COPD was the most common respiratory diagnosis in the GPRR with a prevalence of 16.6% (140/845), with no significant difference (p-value=0.43) observed between men (17.9%, 57/319) and women (15.8%, 83/526). Asthma was the second most prevalent respiratory diagnosis at 10.5% (89/845), with men (6.9%, 22/319) reporting significantly lower prevalence than women (12.7%, 67/526) (p-value=0.007). Other respiratory conditions included bronchiectasis (1.9%, 16/845), pulmonary fibrosis (0.1%, 1/845), asbestosis (0.6%, 5/845), pneumoconiosis (0.5%, 4/845) and tuberculosis (4.7%, 40/845). Asbestosis and pneumoconiosis were only observed in male participants and the only pulmonary fibrosis diagnosis was seen in a female participant (Table 3.2).

The most frequently prescribed respiratory medications were inhaled short acting beta-2 adrenoreceptor agonists (10.5%, 89/845 of participants) followed by inhaled corticosteroids (6.9%, 58/845). Only 2.0% (17/845) were taking a combination inhaler containing corticosteroid and a long acting beta-2 adrenoreceptor agonist (Table 3.2).

3.4.2 Lung function measurements

Spirometry was performed by 93.0% (786/845) of participants of whom 98.2% (772/786) provided at least two adequate blows conforming to American Thoracic Society (ATS) and ERS guidelines. A further 14 participants did not have technically satisfactory blows for at least one of the spirometry measures and were excluded. Participants without adequate demispan measures (35/772) were also excluded with the remaining 87.2% (737/845) of the overall cohort forming the spirometry group (Figure 3.1). Sensitivity analysis was performed to compare the spirometry group against participants excluded (108/845) due to missing/inadequate spirometry and/or missing demispan. It was observed that those excluded were more likely to be females, living in an institution and previously exposed to the chemical industry but no significant differences were found in smoking history, respiratory symptoms, diagnoses or medications and dyspnoea scores (Table 3.2).

In the whole spirometry group, 31.1% (229/737) had a normal FEV_1/FVC ratio and 15.2% (112/737) presented with a restrictive pattern. Obstructive spirometry was the commonest finding (men: 58.7%, 172/293; women: 50.5%, 224/444) with 85.9% presenting with mild or

moderate levels of severity. No gender difference was observed in the spread of severity (Table 3.4). Measured values of FEV_1 and FVC in the spirometry group were normally distributed and had much wider range of values in comparison to the GOLD/ERS predicted values (Quanjer *et al.*, 1993) (Figure 3.2). The PEF median (IQR) was significantly higher in men (441 (323 - 604) litres/min) compared to that in women (283 (196 - 362) litres/min) but was highly correlated with measured FEV_1 in both sexes (Figure 3.3).

Scatter plots comparing the observed and predicted values of FEV_1 and FVC revealed more participants with measured values below the predicted values than above, with lung function being worse than expected according to the reference values (Figure 3.4 and Figure 3.5). The spread of FEV_1 and FVC measurements around the predicted values was much wider in men than women (Figure 3.4 and Figure 3.5 respectively). A higher proportion of women had normal or above Upper Limits of Normal (ULN) measurements (Table 3.4).

Predicted values using GLI prediction models were derived for the whole spirometry group to enable comparison with the GOLD criteria currently used within the National Health Service (NHS) (Table 3.4). More than half (52.7%, 388/737) of the cohort were deemed to have normal spirometry based on the GLI reference values (men: 52.9%, 155/293; women: 52.5%, 233/444) and under a quarter with restrictive (23.3%) or obstructive (24.0%) patterns. Based on z-scores for FEV_1, 59.7% (175/293) of men and 57.4% (255/444) women fell within the normal spirometric range (Table 3.4).

3.4.3 Prevalence and accuracy of physician-diagnosed COPD

Of the spirometry group, 16.7% (123/737) had a physician-diagnosed COPD (COPD group) of whom 57.7% (71/123) were female and 23.8% (29/123) reported as ‘never smokers’ (Table 3.5). Just over half (51.7%) of the non-smokers did not have any relevant occupational exposures.

Respiratory symptoms were common but not universal in this group with 50.4% (62/123) reporting cough and 58.2% (71/123) sputum production. Nevertheless 26.8% (11/52) of men and 12.5% (7/71) of women with a COPD diagnosis had only minimal breathlessness (MRC Dyspnoea score=1). In terms of co-morbid respiratory diagnosis, 39.0 % (48/123) were diagnosed with asthma, with other diagnoses including bronchiectasis (4.9%), asbestosis (3.3%), pneumoconiosis (1.6%) and TB (8.1%) (Table 3.6).

Based on the GOLD criteria, 75.6% (93/123) of the COPD group had obstructive spirometry (Table 3.6). A breakdown of obstructive severity showed that only 63.4% (78/123) of the COPD group fulfilled UK NICE guidelines definition of moderate, severe or very severe disease by spirometry. Classification of FEV_1 based on the z-score and LLN approach revealed that 48.1% (25/52) of men and 33.8% (24/71) of women from the COPD group fell below LLN, suggesting that a considerable proportion (60.2%, 74/123) of those with physician-diagnosed COPD had an FEV_1 within the normal range and/or no airflow obstruction on spirometric measurement (Table 3.6). These proportions were even higher when looking at those who were classed as having normal FVC (72.4 %, 89/123) with a gender difference observed for both set of measurements. The GLI prediction formulae were applied to the COPD group and obstructive spirometry criteria were satisfied in 48.1% (25/52) of men and 50.7% (36/71) of women (Table 3.7).

3.4.4 Agreement of classification methods for obstructive lung function

Agreement between the three methods was tested using the McNemar and Cohen's Kappa test (Fleiss, 1981). Varying levels of agreement were found between all three methods. The highest level of disagreement was between the GOLD and physician diagnosed COPD (Kappa agreement: good, 54.8%), with physician diagnosis only identifying 23.5% of those classed as GOLD obstructive with COPD. The highest level of agreement was found between the physician diagnosed and the GLI method (Kappa agreement: excellent, 75.9%). Although there was still a significant level of disagreement, all participants classed as obstructive by GLI were also recognised as such by the GOLD criteria. The GOLD method also recognised 38.9% of those with no GLI obstruction as having obstructive lung function (Kappa agreement: fair, 70.3%) (Table 3.8) (Fleiss, 1981).

3.4.5 Lung function of the healthy reference group (HRG)

Figure 3.1 shows the derivation of the HRG which comprised 20.5% (151/737) of the whole spirometry cohort. Measured values of FEV_1 and FVC in the HRG were normally distributed and had much wider range of values in comparison to the GOLD/ERS predicted values (Figure 3.6). In the HRG, just under half of men (49.1%, 28/57) and women (42.6%, 40/94) presented with airflow obstruction by GOLD criteria (Table 3.9). However they did not fulfil the requirements for a diagnosis of COPD through lack of symptoms, although 19.2% (29/151) fulfilled the spirometry definition of at least moderate COPD using National Institute for Clinical Excellence (NICE) criteria (obstructive spirometry and an FEV_1 <80% predicted).

The measured PEF median (IQR) of this group was 367 (263 – 515) litres/min, significantly higher in men (515 (340 – 647) litres/min) than in women (329.5 (243 – 417) litres/min) ($p<0.001$), and highly correlated with FEV_1 (men: r=0.82; women: r=0.74) (Figure 3.7).

Comparison of observed spirometric values and equation derived predicted values based on gender and height in the HRG were made using the three accepted methods: percent-predicted value, LLN and Z scores (Table 3.9). There was no difference observed in median (IQR) percent-predicted FEV_1 between men (90.1% (67.6-103.8%)) and women (93.8% (78.6-106.0%)) in the HRG. In total, 11.3% (17/151) had FEV_1 levels below LLN with a significant gender difference (men: 21.1%, 12/57; women: 5.3%, 5/94; p=0.008). A similar trend was also observed in measured FVC and the proportion of participants falling below the LLN (men: 29.8%, 17/57; women: 6.4%, 6/94; $p<0.001$).

GLI prediction models were used to calculate the spirometric percent predicted values and z-scores. Based on FEV_1 z-scores, 24.5% (37/151) had measured FEV_1 below LLN with no sex differences observed. These results were comparable to those based on FVC with 23.2% (35/151) of the HRG having below LLN values with again no sex differences found (Table 3.10).

3.5 Summary

This study showed that a high success rate of spirometry testing (87.2%, 737/845) with at least two adequate blows could be achieved even at an advanced age of 85 years. In this population, a quarter of participants (214/845) had at least one diagnosed respiratory condition in their GP records, with a similar proportion in the spirometry subset (186/737). However, the level of prescribed respiratory medication was much lower than diagnosis levels at 13.6% (115/845). The availability of the lung function measures allowed for a thorough examination of different prediction formulae in conjunction with the GP diagnosed COPD in this age group. The main findings of the baseline lung function were:

1. The expected spirometric differences between males and females, with larger lung and higher spirometric values in males across all three measures;
2. GOLD method identifying 53.7% (396/737) of the spirometry population with obstructive spirometry in comparison to 24.0% (177/737) for GLI;
3. Using FEV_1 the GOLD method over estimated normal lung function (80.9%, 596/737) in comparison to GLI (58.3%, 430/737) and the LLN.

4. Considerable differences between GP COPD diagnosis and the spirometric levels of that group using GLI and GOLD prediction formulae
    i. The GOLD method identified 75.6% (93/123) of this group as having obstructive spirometry with 63.4% (78/123) labelled as moderate, severe or very severe
    ii. The GLI identifying only 49.6% (61/123) of participants with obstructive spirometry
    iii. Based on FEV_1, GOLD estimated 60.2% (74/123) within normal range whilst GLI showed only 27.6% (34/123) falling within this boundary
    iv. Statistically significant ($p<0.001$) levels of disagreement between all three methods (GLI vs GOLD, GLI vs physician and GOLD vs physician).
    v. The highest level of agreement was found between the physician diagnosed and the GLI method (Kappa agreement: excellent, 75.9%)
    vi. Physician diagnosed COPD may be more useful as more information is available when making diagnosis.
    vii. There is a need for a more unified formula that accounts for additional information to reduce possible misdiagnosis.

This chapter has described in detail the respiratory function of people aged 85. Whilst this chapter has revealed the burden of respiratory symptom and disease in the very old, the next chapter will investigate whether lung function is still predictive of mortality in this age group.

Table 3.1: Formulae used for calculation of spirometric ventilatory status based on GOLD criteria and ERS predicted values

Spirometry Definition		
Normal	$FEV_1/FVC > 0.7$	FEV1 ≥ 80% predicted
Restrictive	$FEV_1/FVC > 0.7$	FEV1 ≤ 80% predicted
Obstructive	$FEV_1/FVC < 0.7$	

Obstructive Spirometry Grading Definition		
Mild	$FEV_1/FVC < 0.7$	$FEV_1 \geq$ 80% predicted
Moderate	$FEV_1/FVC < 0.7$	50% ≤ FEV_1 < 80% predicted
Severe	$FEV_1/FVC < 0.7$	30% ≤ FEV_1 < 50% predicted
Very Severe	$FEV_1/FVC < 0.7$	FEV_1 < 30% predicted

Limits of Normal*	FEV_1	FVC
Men	FEV_1Pred +/- (0.51*1.645)	FVCPred +/- (0.61*1.645)
Women	FEV_1 Pred +/- (0.38*1.645)	FVCPred +/- (0.43*1.645)

Z-Score	FEV_1	FVC
Men	(FEV_1Pred - FEV_1 Actual)/0.51	(FVCPred - FVCActual)/0.61
Women	(FEV_1Pred - FEV_1 Actual)/0.38	(FVCPred - FVCActual)/0.43
Range	Upper Limit of Normal > 1.645	Lower Limit of Normal < -1.645

*Use + for Upper Limit of Normal (ULN) and - for Lower Limit of Normal (LLN)

Table 3.2: Respiratory health characteristics of the total Newcastle 85+ cohort (n=845) and by gender

		Men (n=319)	Women (n=526)	Overall (n=845)	p-value*
Respiratory symptoms % (N)	Cough	28.3 (88)	25.8 (129)	26.7 (217)	0.425[2]
	Wheeze	25.0 (78)	20.2 (101)	22.0 (179)	0.109[2]
	Sputum production	40.7 (127)	28.0 (140)	32.9 (267)	<0.001
MRC Dyspnoea Score % (N)	1	50.2 (123)	40.5 (143)	44.5 (266)	
	2	11.4 (28)	19.0 (67)	15.9 (95)	
	3	20.4 (50)	17.6 (62)	18.7 (112)	0.048[1]
	4	15.1 (37)	17.0 (60)	16.2 (97)	
	5	2.9 (7)	6.0 (21)	4.7 (28)	
Respiratory diagnoses % (N)	COPD	17.9 (57)	15.8 (83)	16.6 (140)	0.429[2]
	Asthma	6.9 (22)	12.7 (67)	10.5 (89)	0.007[2]
	Bronchiectasis	2.5 (8)	1.5 (8)	1.9 (16)	0.308[2]
	Pulmonary Fibrosis	0.0 (0)	0.2 (1)	0.1 (1)	1.000 [3]
	Asbestosis	1.6 (5)	0.0 (0)	0.6 (5)	0.008 [3]
	Pneumoconiosis	1.3 (4)	0.0 (0)	0.5 (4)	0.020 [3]
	Tuberculosis	4.4 (14)	4.9 (26)	4.7 (40)	0.713[2]
Respiratory Medications - % (N)					
Inhaled short acting β-2 adrenoreceptor agonists		9.1 (29)	11.4 (60)	10.5 (89)	0.288[2]
Inhaled muscarinic antagonists		3.8 (12)	3.8 (20)	3.8 (32)	0.976[2]
Oral Theophylline		0.3 (1)	0.5 (3)	0.5 (4)	0.598 [3]
Combination short acting bronchodilators		0.6 (2)	0.0 (0)	0.2 (2)	0.142 [3]
Inhaled Corticosteroids		5.3 (17)	7.8 (41)	6.9 (58)	0.169[2]
Combination inhaled Corticosteroids and long acting β-2 adrenoreceptor agonists		1.9 (6)	2.1 (11)	2.0 (17)	0.833[2]
Oral leukotriene receptor antagonists		0.0 (0)	0.4 (2)	0.2 (2)	0.529 [3]
Oral mucolytics		0.6 (2)	0.2 (1)	0.4 (3)	0.560 [3]
At least one respiratory medication % (N)		12.2 (39)	14.5 (76)	13.6 (115)	0.361[2]
Disease count - Median (IQR)		4 (3 - 6)	5 (4 - 6)	5 (3 - 6)	0.074[1]
Co-morbid Disease Count Median (IQR)		4 (3 - 6)	5 (4 - 6)	5 (3 - 6)	0.047[1]

*comparison of men and women; ** Denominators vary due to missing values; [1] Mann-Whitney test; [2] Chi-square test

Table 3.3: Comparison of the groups included and excluded in the spirometry cohort

		Non-spirometry (n=108)	Spirometry (n=737)	p-value*
Sex	Female	75.9 (82)	60.2 (444)	0.002[2]
Ethnicity	White	98.1 (104)	99.9 (735)	0.043[2]
Living arrangements % (N)	Standard housing	46.3 (50)	81.6 (601)	<0.001[2]
	Sheltered housing	13.0 (14)	12.8 (94)	
	Institutional care	40.7 (44)	5.7 (42)	
Smoking % (N)	Never	41.9 (44)	35.0 (257)	0.375[2]
	Former	53.3 (56)	59.2 (435)	
	Current	4.8 (5)	5.9 (43)	
Occupational Exposures % (N)	Heavy Industry	18.1 (13)	26.7 (196)	0.111[2]
	Coal mining	2.7 (2)	4.5 (33)	0.763[3]
	Chemical industry	12.7 (9)	6.1 (45)	0.035[2]
	Asbestos exposure	5.7 (4)	12.6 (92)	0.121[3]
Respiratory symptoms % (N)	Cough	26.9 (21)	26.7 (196)	0.961[2]
	Wheeze	20.8 (16)	22.2 (163)	0.783[2]
	Sputum production	26.0 (20)	33.6 (247)	0.177[2]
MRC Dyspnoea Score % (N)	1	40.5 (15)	44.8 (251)	0.257[1]
	2	13.5 (5)	16.0 (90)	
	3	13.5 (5)	19.1 (107)	
	4	21.6 (8)	15.9 (89)	
	5	10.8 (4)	4.3 (24)	
Respiratory diagnoses % (N)	COPD	15.7 (17)	16.7 (123)	0.804[2]
	Asthma	7.4 (8)	4.1 (30)	0.118[2]
	Bronchiectasis	0.9 (1)	2.0 (15)	0.708[3]
	Pulmonary Fibrosis	0.9 (1)	0.0 (0)	0.128[3]
	Asbestosis	0.0 (0)	0.7 (5)	1.000[3]
	Pneumoconiosis	0.0 (0)	0.5 (4)	1.000[3]
	Tuberculosis	2.8 (3)	5.0 (37)	0.465[3]
Respiratory Medications - % (N)				
Inhaled short acting β-2 adrenoreceptor agonists		11.1 (12)	10.5 (77)	0.834[2]
Inhaled muscarinic antagonists		3.7 (4)	3.8 (28)	1.000[3]
Oral Theophylline		0.0 (0)	0.5 (4)	1.000[3]
Combination short acting bronchodilators		0.0 (0)	0.3 (2)	1.000[3]
Inhaled Corticosteroids		4.6 (5)	7.2 (53)	0.325[2]
Combination inhaled Corticosteroids and long acting β-2 adrenoreceptor agonists		0.9 (1)	2.2 (16)	0.712[3]
Oral leukotriene receptor antagonists		0.0 (0)	0.3 (2)	1.000[3]
Oral mucolytics		0.0 (0)	0.4 (3)	1.000[3]
At least 1 Respiratory Medication - % (N)		12.0 (13)	13.8 (102)	0.610[2]
Disease count - Median (IQR)		5 (4 - 6)	4 (3 - 6)	0.178[1]

* Comparison of Men and Women; ** Denominators may vary due to missing values; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher-exact test

Table 3.4: Results of Spirometry in the cohort completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows (n=737)

		Men (n=293)	Women (n=444)	All (n=737)	p-value*
Observed	FEV_1 (l)	1.8 (1.4 - 2.2)	1.2 (1.0 - 1.5)	1.4 (1.1 - 1.8)	<0.001[1]
Median (IQR)	FVC (l)	2.7 (2.2 - 3.2)	1.8 (1.4 - 2.1)	2.0 (1.6 - 2.6)	<0.001[1]
	FEV_1/FVC	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)	0.006[1]
	PEFR (l/m)	441 (323 - 604)	283 (196 - 362)	328 (233 - 450)	<0.001[1]
% predicted	FEV_1	78.8 (62.4 - 94.3)	83.4 (68.1 - 98.8)	81.5 (65.6 - 97.1)	0.008[1]
Median (IQR)	FVC	83.4 (70.3 - 99.6)	96.6 (79.1 - 113.7)	90.8 (74.1 - 108.4)	<0.001[1]
Spirometry	Normal	27.7 (81)	33.3 (148)	31.1 (229)	
% (N)	Restrictive	13.7 (40)	16.2 (72)	15.2 (112)	0.089[2]
	Obstructive	58.7 (172)	50.5 (224)	53.7 (396)	
Grading of obstructive	Mild	36.1 (62)	43.3 (97)	40.2 (159)	
spirometry[α]	Moderate	46.5 (80)	45.1 (101)	45.7 (181)	0.298[4]
% (N)	Severe	14.5 (25)	9.8 (22)	11.9 (47)	
	Very Severe	2.9 (5)	1.8 (4)	2.3 (9)	
FEV_1	Below LLN	25.9 (76)	13.3 (59)	18.3 (135)	
% (N)	Normal range	73.7 (216)	85.6 (380)	80.9 (596)	<0.001[3]
	Above ULN	0.3 (1)	1.1 (5)	0.8 (6)	
FEV_1 Z-Score	Median (IQR)	1.0 (0.2 - 1.7)	0.6 (0.0 - 1.2)	0.8 (0.1 - 1.4)	<0.001[1]
FVC	Below LLN	25.6 (75)	14.2 (63)	18.7 (138)	
% (N)	Normal range	73.4 (215)	84.0 (373)	79.8 (588)	<0.001[2]
	Above ULN	1.0 (3)	1.8 (8)	1.5 (11)	
FVC Z-Score	Median (IQR)	1.1 (0.2 - 1.7)	0.5 (-0.3 – 1.3)	0.7 (-0.1 - 1.4)	<0.001[1]
Oxygen Saturation	Median (IQR)	97 (96 - 98)	97 (96 - 98)	97 (96 - 98)	0.513[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher-exact test; [α] This is based on the 396 participant subsample with obstructive spirometry

Table 3.5: Results of Spirometry in the cohort completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows using GLI prediction models (n=737)

		Men (n=293)	Women (n=444)	All (n=737)	p-value*
Observed Spirometry Median (IQR)	FEV_1	1.8 (1.4 - 2.2)	1.2 (1.0 - 1.5)	1.4 (1.1 - 1.8)	<0.001[1]
	FVC	2.7 (2.2 - 3.2)	1.8 (1.4 - 2.1)	2.0 (1.6 - 2.6)	<0.001[1]
	FEV_1/FVC	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)	0.7 (0.6 - 0.8)	0.006[1]
	PEFR	441 (323 - 604)	283 (196 - 362)	328 (233 - 450)	<0.001[1]
% predicted Median (IQR)	FEV_1	74.3 (58.7 - 88.6)	72.4 (59.4 - 87.2)	73.2 (58.9 - 87.7)	0.457[1]
	FVC	80.8 (67.2 - 95.9)	80.4 (64.9 - 94.0)	80.6 (66.1 - 94.7)	0.162[1]
Spirometry % (N)	Normal	52.9 (155)	52.5 (233)	52.7 (388)	
	Restrictive	22.2 (65)	24.1 (107)	23.3 (172)	0.800[2]
	Obstructive	24.9 (73)	23.4 (104)	24.0 (177)	
FEV_1 % (N)	Below LLN	39.9 (117)	42.1 (187)	41.3 (304)	
	Normal range	59.7 (175)	57.4 (255)	58.3 (430)	0.812[3]
	Above ULN	0.3 (1)	0.5 (2)	0.4 (3)	
FEV_1 Z-Score	Median (IQR)	-1.3 (-2.1 - -0.6)	-1.4 (-2.1 - -0.7)	-1.4 (-2.1 - -0.6)	0.248[1]
FVC %(N)	Below LLN	31.4 (92)	31.5 (140)	31.5 (232)	
	Normal range	67.6 (198)	68.2 (303)	68.0 (501)	0.352[3]
	Above ULN	1.0 (3)	0.2 (1)	0.5 (4)	
FVC Z-Score	Median (IQR)	-1.1 (-1.9 - -0.2)	-1.0 (-1.8 - -0.3)	-1.1 (-1.8 - -0.3)	0.727[1]
Oxygen Saturation	Median (IQR)	97 (96 - 98)	97 (96 - 98)	97 (96 - 98)	0.513[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher-exact test;

Table 3.6: Descriptive characteristics of subset with physician-diagnosed COPD in GP records

		Men (n=52)	Women (n=71)	All (n=123)	p-value*
Smoking	Never	21.2 (11)	25.7 (18)	23.8 (29)	
% (N)	Former	67.3 (35)	67.1 (47)	67.2 (82)	0.637 [2]
	Current	11.5 (6)	7.1 (5)	9.0 (11)	
Occupational	Heavy Industry	49.0 (25)	19.7 (14)	32.0 (39)	0.001 [2]
Exposure	Coal Mining	17.7 (9)	0.0 (0)	7.4 (9)	<0.001[3]
% (N)	Chemical	13.7 (7)	2.8 (2)	7.4 (9)	0.034[3]
	Asbestos	33.3 (17)	7.1 (5)	18.2 (22)	<0.001[2]
Non-Smokers with no Occupational Exposures % (N)		3.9 (2)	18.3 (13)	12.2 (15)	0.023 [2]
Respiratory	Cough	46.2 (24)	53.5 (38)	50.4 (62)	0.419 [2]
symptoms	Wheeze	53.9 (28)	56.3 (40)	55.3 (68)	0.784[2]
% (N)	Sputum production	63.5 (33)	54.3 (38)	58.2 (71)	0.310[2]
MRC	1	26.8 (11)	12.5 (7)	18.6 (18)	
Dyspnoea	2	9.8 (4)	16.1 (9)	13.4 (13)	
Score	3	34.2 (14)	19.6 (11)	25.8 (25)	0.035[1]
% (N)	4	22.0 (9)	33.9 (19)	28.9 (28)	
	5	7.3 (3)	17.9 (10)	13.4 (13)	
Co-morbid	Asthma	25.0 (13)	49.3 (35)	39.0 (48)	0.006 [2]
respiratory	Bronchiectasis	7.7 (4)	2.8 (2)	4.9 (6)	0.240 [3]
diagnoses	Asbestosis	7.7 (4)	0.0 (0)	3.3 (4)	0.030 [3]
% (N)	Pulmonary Fibrosis	0.0 (0)	0.0 (0)	0.0 (0)	-
	Pneumoconiosis	3.9 (2)	0.0 (0)	1.6 (2)	0.177 [3]
	Tuberculosis	5.8 (3)	9.9 (7)	8.1 (10)	0.516 [3]
Respiratory Medications - % (N)					
Inhaled short acting β-2 adrenoreceptor agonists		36.5 (19)	52.1 (37)	45.5 (56)	0.087 [2]
Inhaled muscarinic antagonists		17.3 (9)	22.5 (16)	20.3 (25)	0.477[2]
Oral Theophylline		1.9 (1)	4.2 (3)	3.3 (4)	0.637 [3]
Combination short acting bronchodilators		1.9 (1)	0.0 (0)	0.8 (1)	0.423 [3]
Inhaled Corticosteroids		17.3 (9)	38.0 (27)	29.3 (36)	0.013[2]
Combination inhaled Corticosteroids and long acting β-2 adrenoreceptor agonists		11.5 (6)	12.7 (9)	12.2 (15)	0.849[2]
Oral leukotriene receptor antagonists		0.0 (0)	1.4 (1)	0.8 (1)	1.000 [3]
Oral mucolytics		1.9 (1)	1.4 (1)	1.6 (2)	1.000 [3]
Oral glucocorticoid therapy		5.8 (3)	4.2 (3)	4.9 (6)	0.697 [3]
At least 1 Respiratory Medication - % (N)		46.2 (24)	66.2 (47)	57.7 (71)	0.026 [2]
Disease count - Median (IQR)		5 (4 - 7)	6 (5 - 7)	6 (4 - 7)	0.156[1]
Non-respiratory Disease Count Median (IQR)		5 (4 - 6)	6 (5 - 7)	6 (4 - 7)	0.064[1]

*comparison of men and women; ** Denominators vary due to missing values;
[1] Mann-Whitney test; [2] Chi-square test; [3] Fisher's exact test

Table 3.7: Results of Spirometry in the COPD completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows (n=123)

		Men (n=52)	Women (n=71)	All (n=123)	p-value*
Observed	FEV_1	1.4 (1.1 - 1.8)	1.0 (0.7 - 1.1)	1.1 (0.8 - 1.4)	<0.001[1]
Median (IQR)	FVC	2.4 (2.0 - 3.1)	1.6 (1.3 - 1.9)	1.9 (1.5 - 2.3)	<0.001[1]
	FEV_1/FVC	0.6 (0.5 - 0.7)	0.6 (0.5 - 0.7)	0.6 (0.5 - 0.7)	0.591[1]
	PEFR	382.5 (243 - 519)	218 (144 - 290)	259 (191 - 380)	<0.001[1]
% predicted	FEV_1	63.5 (50.9 - 73.4)	64.2 (51.7 - 79.9)	64.2 (51.3 - 76.4)	0.609[1]
Median (IQR)	FVC	77.4 (64.2 - 94.1)	87.6 (70.4 - 101.0)	82.8 (68.2 - 99.8)	0.040[1]
Spirometry	Normal	7.7 (4)	8.5 (6)	8.1 (10)	
% (N)	Restrictive	15.4 (8)	16.9 (12)	16.3 (20)	0.959[2]
	Obstructive	76.9 (40)	74.7 (53)	75.6 (93)	
Obstructive spirometry[α]	Mild	10.0 (4)	20.8 (11)	16.1 (15)	
% (N)	Moderate	60.0 (24)	56.6 (30)	58.1 (54)	0.540[4]
	Severe	27.5 (11)	20.8 (11)	23.7 (22)	
	Very Severe	2.5 (1)	1.9 (1)	2.2 (2)	
FEV_1	Below LLN	48.1 (25)	33.8 (24)	39.8 (49)	
% (N)	Normal range	51.9 (27)	66.2 (47)	60.2 (74)	0.110[3]
	Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FEV_1 Z-Score	Median (IQR)	1.6 (1.2 - 2.2)	1.3 (0.7 - 2.0)	1.5 (0.9 - 2.0)	0.039[1]
FVC	Below LLN	38.5 (20)	19.7 (14)	27.6 (34)	
%(N)	Normal range	61.5 (32)	80.3 (57)	72.4 (89)	0.022[3]
	Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FVC Z-Score	Median (IQR)	1.3 (0.5 - 1.9)	0.9 (0.3 - 1.5)	1.1 (0.3 - 1.8)	0.060[1]
Oxygen Saturation	Median (IQR)	97 (96 - 98)	97 (95 - 98)	97 (95 - 98)	0.521[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher's exact test; [4] Kruskal-Wallis test; [α]This is based on the 93 participant subsample with obstructive spirometry;

Table 3.8: Results of Spirometry in the COPD completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows using GLI prediction models (n=123)

		Men (n=52)	Women (n=71)	All (n=123)	p-value*
Observed	FEV_1	1.4 (1.1 - 1.8)	1.0 (0.7 - 1.1)	1.1 (0.8 - 1.4)	<0.001[1]
Median (IQR)	FVC	2.4 (2.0 - 3.1)	1.6 (1.3 - 1.9)	1.9 (1.5 - 2.3)	<0.001[1]
	FEV_1/FVC	0.6 (0.5 - 0.7)	0.6 (0.5 - 0.7)	0.6 (0.5 - 0.7)	0.591[1]
	PEFR	382.5 (243 - 519)	218 (144 - 290)	259 (191 - 380)	<0.001[1]
% predicted	FEV_1	60.7 (48.8 - 69.1)	56.5 (43.4 - 68.9)	58.6 (44.8 - 69.0)	0.313[1]
Median (IQR)	FVC	73.8 (62.0 - 91.1)	71.8 (59.5 - 85.0)	73.2 (60.3 - 86.8)	0.221[1]
Spirometry	Normal	26.9 (14)	23.9 (17)	25.2 (31)	
% (N)	Restrictive	25.0 (13)	25.4 (18)	25.2 (31)	0.928[2]
	Obstructive	48.1 (25)	50.7 (36)	49.6 (61)	
FEV_1	Below LLN	69.2 (36)	74.7 (53)	72.4 (89)	
% (N)	Normal range	30.8 (16)	25.4 (18)	27.6 (34)	0.507[3]
	Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FEV_1 Z-Score	Median (IQR)	-2.0 (-2.5 - -1.6)	-2.3 (-2.9 - -1.6)	-2.1 (-2.8 - -1.6)	0.128[1]
FVC	Below LLN	46.2 (24)	45.1 (32)	45.5 (56)	
%(N)	Normal range	53.9 (28)	54.9 (39)	54.5 (67)	0.905[3]
	Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FVC Z-Score	Median (IQR)	-1.5 (-2.2 - -0.5)	-1.5 (-2.1 - -0.8)	-1.5 (-2.2 - -0.7)	0.560[1]
Oxygen Saturation	Median (IQR)	97 (96 - 98)	97 (95 - 98)	97 (95 - 98)	0.521[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher-exact test;

Table 3.9: Level of agreement between the three methods of obstructive lung function classification.

		Physician Diagnosed COPD	
		No	Yes
GOLD Obstructive	No	91.2 (312)	8.8 (30)
	Yes	76.5 (302)	23.5 (93)
	Total	83.3 (614)	16.7 (123)
McNemar test			p<0.001
Kappa agreement = 54.8%	Expected agreement = 47.5%	Kappa = 0.139	

		Physician Diagnosed COPD	
		No	Yes
GLI Obstructive	No	88.9 (498)	11.1 (62)
	Yes	65.5 (116)	34.5 (61)
	Total	83.3 (614)	16.7 (123)
McNemar test			p<0.001
Kappa agreement = 75.9%	Expected agreement = 67.3%	Kappa = 0.261	

		GOLD COPD	
		No	Yes
GLI Obstructive	No	61.1 (342)	38.9 (218)
	Yes	0.0 (0)	100.0 (177)
	Total	46.4 (342)	53.6 (395)
McNemar test			p<0.001
Kappa agreement = 70.3%	Expected agreement = 48.1%	Kappa = 0.428	

Table 3.10: Results of Spirometry in the HRG completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows (n=151)

		Men (n=57)	Women (n=94)	All (n=151)	p-value*
Observed	FEV_1	2.0 (1.7 - 2.4)	1.4 (1.2 - 1.6)	1.5 (1.2 - 2.0)	<0.001[1]
Median (IQR)	FVC	2.9 (2.4 - 3.5)	1.9 (1.6 - 2.2)	2.1 (1.8 - 2.8)	<0.001[1]
	FEV_1/FVC	0.7 (0.6 - 0.8)	0.7 (0.7 - 0.8)	0.7 (0.6 - 0.8)	0.244[1]
	PEFR	515 (340 - 647)	329.5 (243 - 417)	367 (263 - 515)	<0.001[1]
% predicted	FEV_1	90.1 (67.6 - 103.8)	93.8 (78.6 - 106.0)	91.6 (76.0 - 106.0)	0.154[1]
Median (IQR)	FVC	92.3 (72.0 - 107.7)	101.2 (85.2 - 121.7)	97.5 (80.6 - 115.2)	0.006[1]
Spirometry	Normal	36.8 (21)	44.7 (42)	41.7 (63)	
% (N)	Restrictive	14.0 (8)	12.8 (12)	13.3 (20)	0.636[2]
	Obstructive	49.1 (28)	42.6 (40)	45.0 (68)	
Obstructive	Mild	50.0 (14)	62.5 (25)	57.4 (39)	
spirometry [α]	Moderate	32.1 (9)	32.5 (13)	32.4 (22)	0.257[4]
% (N)	Severe	10.7 (3)	5.0 (2)	7.4 (5)	
	Very Severe	7.1 (2)	0.0 (0)	2.9 (2)	
FEV_1	Below LLN	21.1 (12)	5.3 (5)	11.3 (17)	
% (N)	Normal range	77.2 (44)	93.6 (88)	87.4 (132)	0.011[3]
	Above ULN	1.8 (1)	1.1 (1)	1.3 (2)	
FEV_1 Z-Score	Median (IQR)	0.5 (-0.2 - 1.6)	0.3 (-0.2 - 0.9)	0.3 (-0.2 - 1.0)	0.071[1]
FVC	Below LLN	29.8 (17)	6.4 (6)	15.2 (23)	
%(N)	Normal range	70.2 (40)	91.5 (86)	83.4 (126)	<0.001[3]
	Above ULN	0.0 (0)	2.1 (2)	1.3 (2)	
FVC Z-Score	Median (IQR)	0.6 (-0.2 - 1.7)	0.3 (-0.6 - 0.9)	0.4 (-0.4 – 1.2)	0.040[1]
Oxygen Saturation	Median (IQR)	98 (96 - 98)	98 (97 - 98)	98 (96 - 98)	0.970[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher-exact test; [α] This is based on the 68 participant subsample with obstructive spirometry

Table 3.11: Results of Spirometry in the HRG completing spirometry with adequate reproducible blows and demi-span available for calculation of predicted blows using GLI prediction models (n=151)

		Men (n=57)	Women (n=94)	All (n=151)	p-value*
Observed	FEV_1	2.0 (1.7 - 2.4)	1.4 (1.2 - 1.6)	1.5 (1.2 - 2.0)	<0.001[1]
Median (IQR)	FVC	2.9 (2.4 - 3.5)	1.9 (1.6 - 2.2)	2.1 (1.8 - 2.8)	<0.001[1]
	FEV_1/FVC	0.7 (0.6 - 0.8)	0.7 (0.7 - 0.8)	0.7 (0.6 - 0.8)	0.244[1]
	PEFR	515 (340 - 647)	329.5 (243 - 417)	367 (263 - 515)	<0.001[1]
% predicted	FEV_1	83.9 (65.7 - 97.5)	84.0 (69.7 - 93.3)	83.9 (69.0 - 94.2)	0.997[1]
Median (IQR)	FVC	90.3 (70.5 - 104.2)	85.0 (72.4 - 99.3)	86.4 (70.9 - 102.8)	0.602[1]
Spirometry	Normal	63.2 (36)	67.0 (63)	65.6 (99)	
% (N)	Restrictive	19.3 (11)	17.0 (16)	17.9 (27)	0.888[2]
	Obstructive	17.5 (10)	16.0 (15)	16.6 (25)	
FEV_1	Below LLN	26.3 (15)	23.4 (22)	24.5 (37)	
% (N)	Normal range	71.9 (41)	75.5 (71)	74.2 (112)	0.855[3]
	Above ULN	1.8 (1)	1.1 (1)	1.3 (2)	
FEV_1 Z-Score	Median (IQR)	-0.9 (-1.7 -0.1)	-0.9 (-1.6 - -0.4)	-0.9 (-1.6 - -0.3)	0.918[1]
FVC	Below LLN	26.3 (15)	21.3 (20)	23.2 (35)	
%(N)	Normal range	73.7 (42)	78.7 (74)	76.8 (116)	0.477[3]
	Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FVC Z-Score	Median (IQR)	-0.5 (-1.7 - 0.2)	-0.8 (-1.4 - 0.0)	-0.7 (-1.6 - 0.1)	0.845[1]
Oxygen Saturation	Median (IQR)	98 (96 - 98)	98 (97 - 98)	98 (96 - 98)	0.970[1]

* Comparison of Men and Women; [1] Mann-Whitney test; [2] Chi-square test; [3] Fisher's exact test; [4] Kruskal-Wallis test;

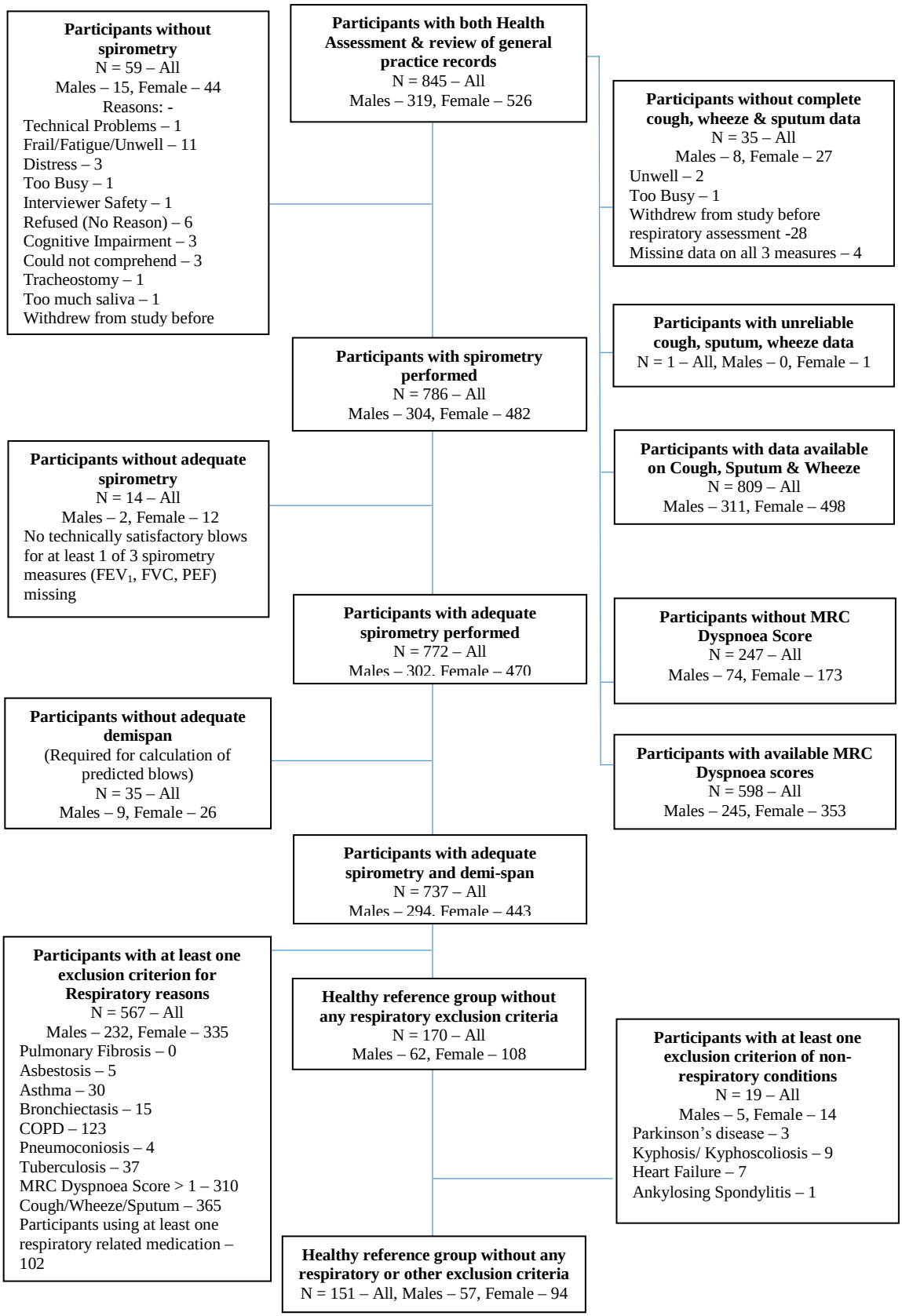


Figure 3.1: Flow chart illustrating how the total cohort of Newcastle 85+ Study participants was sub-divided in the respiratory study sample, demonstrating why different numbers of participants are included in the analyses.

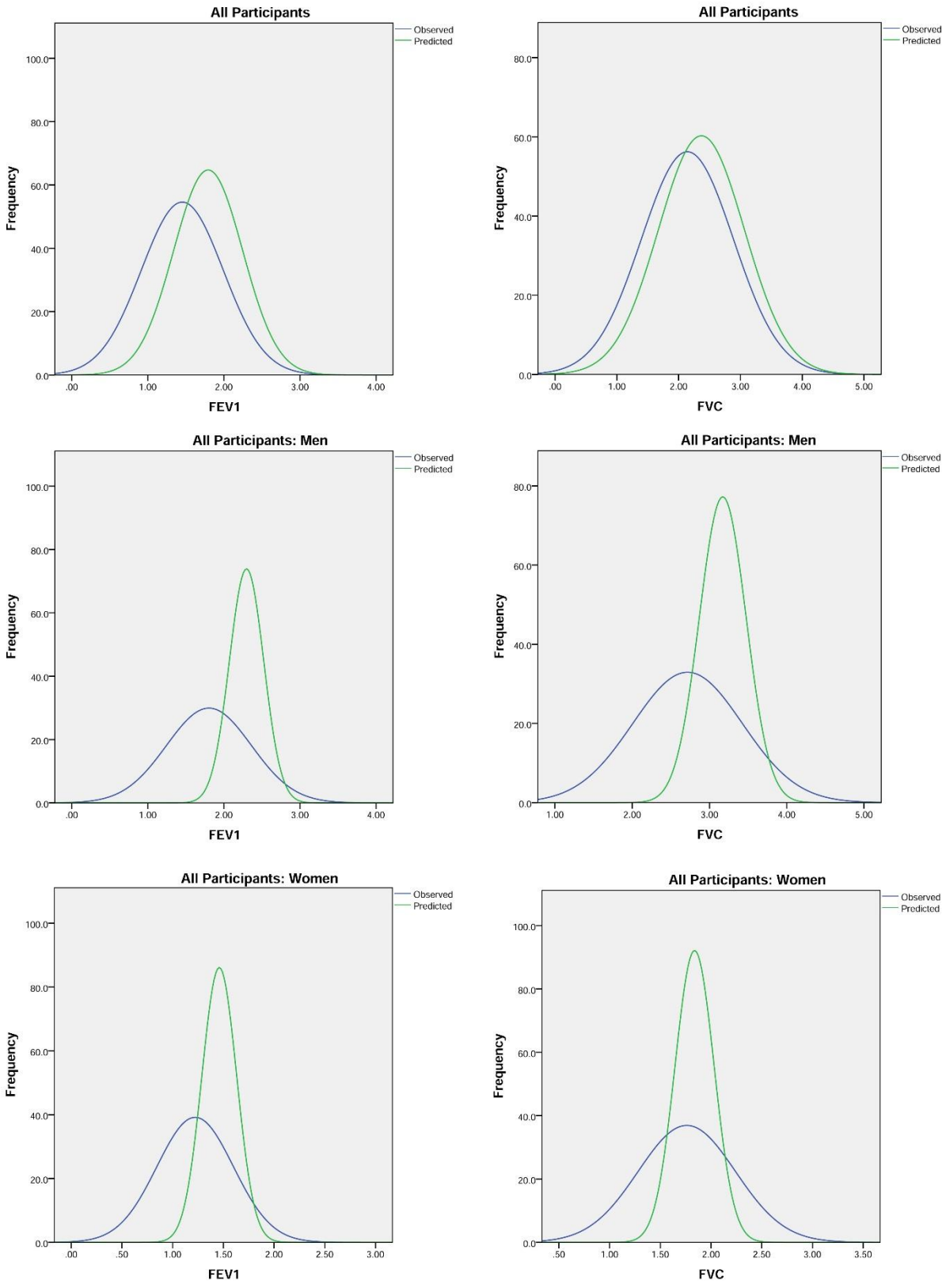


Figure 3.2: Distribution Curves of FEV_1 and FVC in all participants in spirometry cohort, measured (blue) and predicted (green)

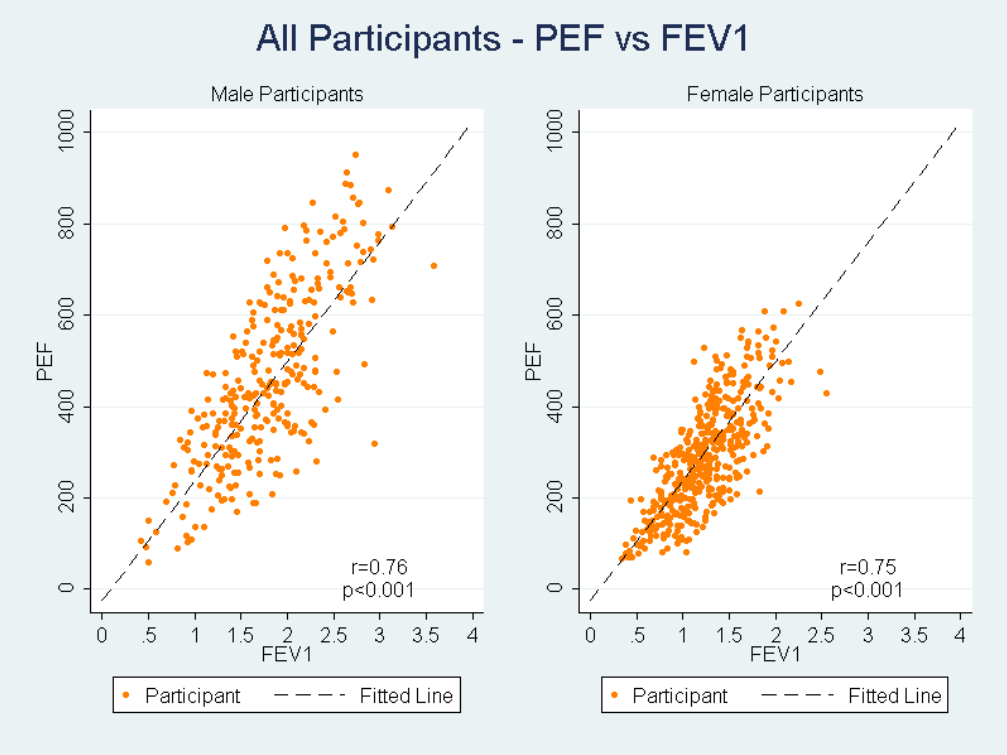


Figure 3.3: Scatter plot of measured PEF against FEV_1 showing the correlation between the two measures in whole spirometry cohort by sex

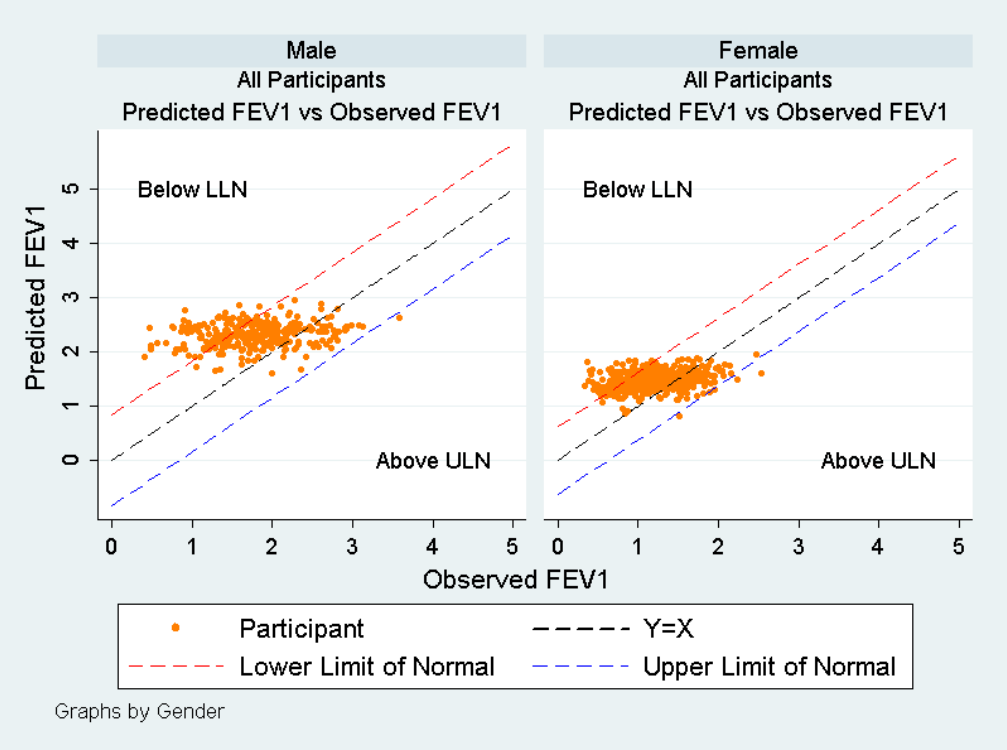


Figure 3.4: Scatter-plots of predicted and observed FEV_1 values by sex. The dots above the red line shows participants with lower than predicted FEV_1 and dots below the blue line suggest higher measured FEV_1 than expected.

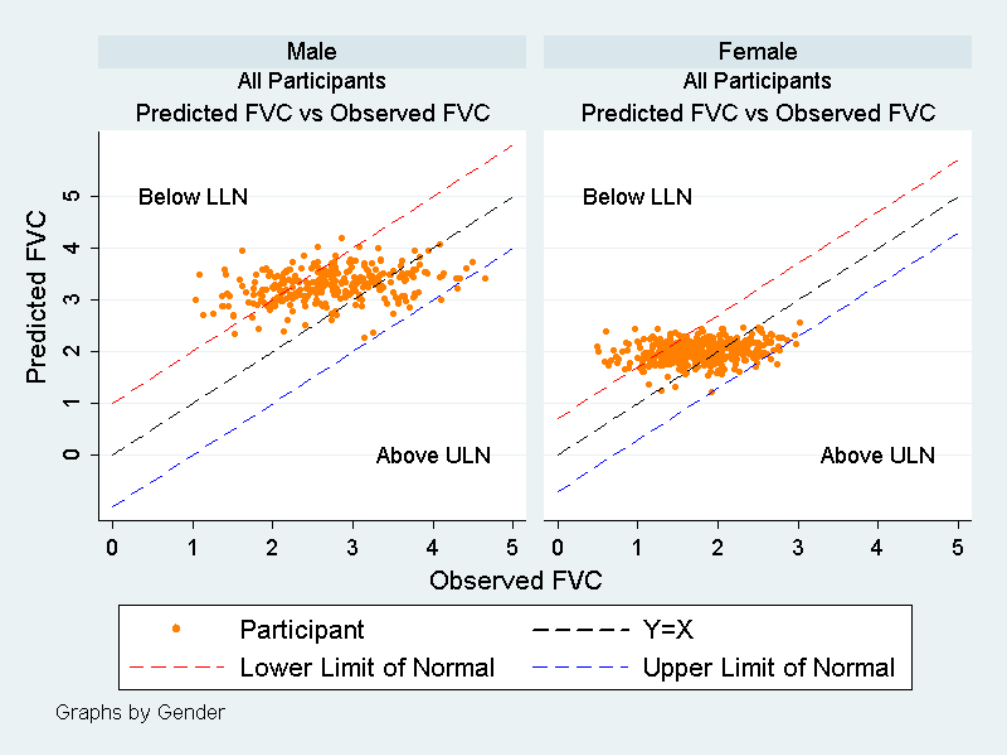


Figure 3.5: Scatter-plots of predicted and observed FVC values by sex. The dots above the red line shows participants with lower than predicted FVC and dots below the blue line suggest higher measured FVC than expected.

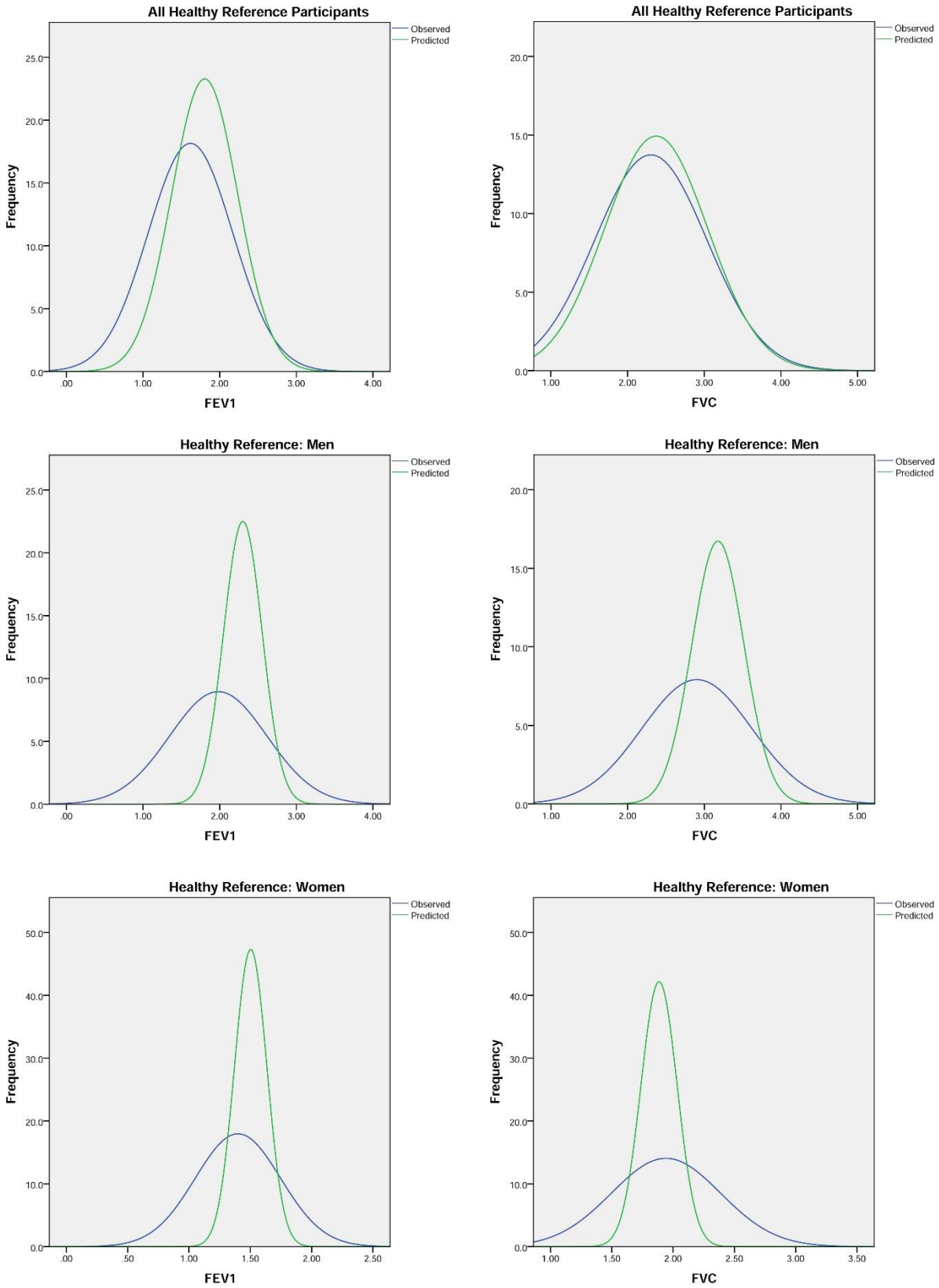


Figure 3.6: Distribution Curves of FEV_1 and FVC in HRG participants in spirometry cohort, measured (blue) and predicted (green)

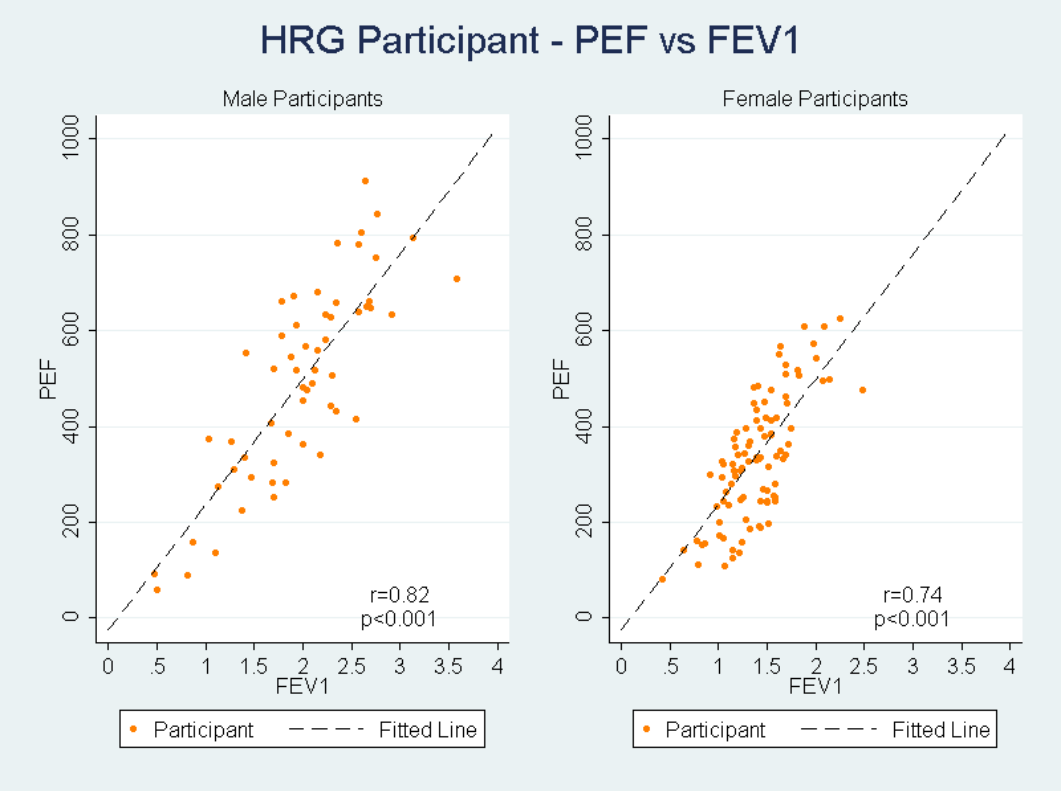


Figure 3.7 Scatter plot of measured PEF against FEV_1 showing the correlation between the two measures in HRG by sex.

Chapter 4. Lung function as a predictor of mortality in the very old

4.1 Aims of the chapter

This chapter aims to:

1. Investigate the relationship between both observed and percent predicted lung function measures at age 85 and subsequent mortality
2. Examine whether the inclusion of subsequent changes in lung function from baseline improves mortality prediction
3. Examine whether lung function predicts mortality in a healthy respiratory group

4.2 Background

Globally, respiratory disease is considered as one of the leading causes of years of life lost with lower respiratory infections being ranked 2nd, Chronic Pulmonary Obstructive Disease (COPD) ranked 12th, lung cancer ranked 15th and asthma ranked 32nd (Mortality and Causes of Death, 2014). In 2006, respiratory disease was reported as the second most common cause of hospital admissions accounting for 20% of all death in the UK (Hubbard, 2006). Age-standardised mortality of men aged 85 and in 2009 was 15 times higher than those aged 50 – 54 years (Sweet, 2011).

Mechanical properties of the lung and thoracic cage decline with age so that functional residual capacity and residual volume increase, with a resulting decrease in vital capacity (VC) (Pride, 2005). Since this population has a high disease burden, including respiratory disease, and the highest expenditure per capita on health care (Summerfield and Babb, 2004), it is important to understand how the level of lung function influences survival in this age group. However, for this age group there is little data on how lung function changes or whether measures that predict mortality at younger ages still do so in the very old.

Only one study has captured the predictive value of lung function measures on survival in the very old, the Danish 1905 cohort study, where participants had their FEV_1 recorded in 1998 at age 93 years, and were followed-up for 13 years until 2011 (Miller *et al.*, 2014). Applying prediction equations for survival from six different studies, they found those in the lowest quartile of FEV_1 had a 60% increased risk of mortality (Miller *et al.*, 2014).

The ability of lung function to predict mortality has been investigated in other studies in younger age groups (Hsu and Pwu, 2004; Lyyra *et al.*, 2005; van den Borst *et al.*, 2012). In

Finnish 75 year olds born in 1914 (Lyyra *et al.*, 2005), the lowest tertile of VC had an increased risk of mortality when compared to the highest tertile, but this was no longer significant after adjustment for other sensory and motor functions.

Another study of a younger population (mean age of 73) compared the effects of abdominal visceral fat on inflammatory pathways and mortality between those with and without obstructive lung disease defined by LLN cut-offs (van den Borst *et al.*, 2012). After adjustment for sociodemographic and health behaviour covariates, inflammatory marker (IL-6) and adiponectin they found that those with obstructive lung disease had a 52% higher risk of all-cause mortality (van den Borst *et al.*, 2012).

The Whitehall II study in particular made an in depth investigation of the relationship between FEV_1 and mortality in a population of civil servants with mean age of 60.8 years (SD, 5.9) and a mean follow-up period of 6.4 (SD, 5.9) years (Sabia *et al.*, 2010). Sociodemographic factors (age, sex and employment grade), health behaviours (smoking and alcohol consumption) and health characteristics (diseases, symptoms and blood biomarkers) were included as covariates in the cox regression models. After adjustment by all covariates, those in the lowest tertile of $FEV_1/height^2$ had a 52% increased risk of mortality compared to the other two tertiles (Sabia *et al.*, 2010).

Given the dearth of very old participants in previous studies, the aim of this chapter is to investigate whether lung function still predicts mortality at an advanced age, in particular using the same methods of the Whitehall II study. Previous studies will be extended by examining a fuller range of lung function measures (observed and predicted) collected at multiple time points, as well as examining a greater range of confounders that may affect this relationship. In addition, I will investigate whether lung function predicts mortality in a healthy respiratory group.

4.3 Analytical methods

4.3.1 Lung function measures

As discussed in previous chapters, FEV_1, FVC and PEF were collected and percent predicted values for FEV_1 and FVC calculated using both the GOLD and GLI methodology. Standardised z-scores for FEV_1, FVC and PEF were calculated, by subtracting the mean from the observed value and dividing the result by the standard deviation, within sex and sample (i.e. whole

spirometry cohort or the Healthy Reference Group). All ten measures were available at baseline, 18 months and 36 months follow-up.

4.3.2 Confounders

From a literature search, factors associated with lung function or mortality were identified (Veale *et al.*, 2000; Hsu and Pwu, 2004; Lyyra *et al.*, 2005; Sabia *et al.*, 2010) for inclusion in the analysis. These were: age; sex; smoking status (categorised as never, former and current smokers); years of education (categorised as 0-9 years, 10 – 11 years, 12+ years); occupational exposure; respiratory conditions; chronic disease count; and cognitive impairment. Occupational exposure was defined as having worked in any of heavy industry, coal mining, chemical works or asbestos related occupations. Respiratory disease was based on respiratory diagnoses from the GPRR. Disease count was the sum of 7 disease categories: arthritis, cancer, cardiac disease, cerebrovascular disease, diabetes, hypertension and cognitive impairment, all based on GPRR diagnoses with the exception of cognitive function which was ascertained from the MMSE in the MDHA. MMSE scores were categorised as normal (26-30), mild (22-25), moderate (18-21) and severe (0-17). Three serum biomarkers of inflammation were included: Interleukin 6 (IL-6), tumour necrosis factor alpha (TNFα), C-reactive protein (CRP), in addition to telomere length which has been identified as a biomarker for ageing (Gardner *et al.*, 2014) and associated with increased risk of mortality (Cawthon *et al.*, 2003).

4.3.3 Survival analysis

To assess the relationship between lung function measures and survival/mortality, Cox Proportional Hazards regression models were fitted for each of the lung function measures, updating the lung function measures at each assessment and thus treating them as time-varying. All confounders previously mentioned were also updated at each subsequent time point (18 and 36 months) apart from sex, smoking status, years of education and occupational exposures as these were fixed or considered to be fixed. PEF was transformed by dividing by 600 to allow for better interpretation and model convergence. Stepwise modelling was used with the Akaike Information Criterion (AIC) to identify the best fitting model. For observed measures, hazard ratios were reported for every 1 litre increase in FEV_1 and FVC, and every 10 decilitre/second increase in PEF Furthermore, hazard ratios were reported for every 10% increase in lung function for the percent predicted measures.

Survival models were fitted separately for men and women as there is a difference in lung function levels reported in previous chapters. The first model (unadjusted) had only the lung function measures as a predictor to inform of the univariate effects of these measures on survival. In model 2, smoking was added as it widely reported that smoking has an effect on lung function (Beck *et al.*, 1981; Anthonisen *et al.*, 2002). All further models were compared to Model 2 to replicate the analysis of the Whitehall II study (Sabia *et al.*, 2010) and to investigate whether the same factors act as confounders (e.g. socio-economic status) or mediators (e.g. physical activity) to the relationship between lung function and mortality at both younger ages and an advanced age. Model 3, added education and occupational history to model 2 since both are associated with mortality and lung function and may therefore be confounders. Model 4 adjusted for model 2 factors, physical activity and BMI investigating the effects of lung function on survival whilst adjusting for modifiable lifestyle characteristics. Model 5, adjusted for model 2 factors, respiratory disease, GP disease count and MMSE investigating effects of disease and cognitive ageing on lung function ability to predict mortality. Model 6, adjusted for model 2 factors and IL-6, TNFα, CRP and telomere length which were the inflammatory and ageing biomarkers which may be used as early indicators for disease onset. The final model, Model 7, contained all the covariates used in Models 2 – 6 adjusting for all possible confounders/mediators. Mortality data was available to 31st July 2014. The analysis was undertaken for men and women separately, on all participants and then repeated for the HRG group. The proportional hazards assumption of all Cox models was checked using Schoenfeld residuals.

One assumption of the Cox models previously described is that the relationship between lung function measures and mortality is linear. A sensitivity analysis was undertaken to test this assumption by fitting restricted cubic splines (Durrleman and Simon, 1989) in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). The only significant non-linear relationship between mortality and FEV_1 was observed in HRG women (p=0.028) (Figure 4.2). All other lung function measures were found to have a linear relationship with mortality for both sexes regardless of whether in the whole spirometry cohort or HRG (Figures 4.1 – 4.14). All other analyses were undertaken in Stata 12.0 (StataCorp; College Station, TX, USA).

4.4 Effects of lung function on mortality

Participants were followed for a median survival time of 5.4 years. Whilst all baseline observed and percent predicted lung function measures (adjusted for all confounders) were predictive of

survival in women (Figures 4.1 – 4.14), only FVC percent predicted (GOLD and GLI) were predictive of survival in men (p= 0.014 and p=0.021 respectively) (Figure 4.11 and Figure 4.13). FEV_1 percent predicted (GLI) for women was the only measure to predict survival in the HRG (p=0.026) (Figure 4.10).

In the complete spirometry sample (Table 4.1), FEV_1 was not predictive of survival for men (Models 1 -7). In women however, FEV_1 did predict survival with a 63% reduced risk of mortality (Model 1) for every litre increase. FVC and PEF were predictive of survival for men and women (Model 1) and remained so after adjustment for smoking status, education and occupational exposure (Model 3). At this stage, based on FVC, men had a 25% (HR: 0.75, 95% CI: 0.59 – 0.96) lower risk of mortality per litre increase in their FVC, whereas for women this was 54% (HR: 0.46, 95% CI: 0.31 – 0.67). For PEF, men showed a 67% (HR: 0.33, 95% CI: 0.18 – 0.62) reduced risk of mortality in comparison to women who had an 88% (HR: 0.12, 95% CI: 0.04 – 0.32) reduced risk of mortality (Model 3). In men, neither FVC nor PEF were predictive of survival once the models were fully adjusted (Model 7), most likely due to biomarkers, disease and physical activity attenuating the effect of lung function on survival. In women however, FEV_1 showed a 48% (HR: 0.52, 95% CI: 0.32 – 0.86) and FVC a 43% (HR: 0.57, 95% CI: 0.39 – 0.82) reduced risk of mortality for every one litre increase in each respective measure. For PEF a 76% (HR: 0.24, 95% CI: 0.09 – 0.70) reduced risk of mortality was also observed in women (Table 4.1).

Percent predicted FEV_1 for both the GOLD and GLI method were predictive of survival in the univariate models and when further adjusted for smoking and socioeconomic status (models 1 - 3); however these effects no longer held for men when models included physical activity and biomarkers (models 4 and 6) (Table 4.2). For the percent predicted FEV_1 and FVC (Table 4.2) none of the fully adjusted models (Model 7) were found to be predictive of survival in men, partly attributable to physical activity attenuating such effects for GOLD percent predicted values as lung function was predictive of survival in all other models. This was in contrast to the results for women where for every 10% increase in percent predicted FEV_1 (GOLD and GLI) there was an 11% (HR: 0.89, 95% CI: 0.83 – 0.96) reduced risk of mortality, indicating that both prediction method are similar in their ability to predict mortality in women. A similar trend was observed for FVC percent predicted measures in women (Table 4.2).

Results from the standardised values of the complete spirometry cohort (Table 4.3) were similar to those of the unstandardised values as they are derived from the same measures. However, the

standardised values allow comparison of the 3 measures on the same metric. Examining the fully adjusted models (Model 7) for women, all three measures were predictive of survival with similar hazard ratios (95% confidence interval) for FEV_1:0.79 (0.66 – 0.94), FVC: 0.76 (0.64 – 0.90) and PEF: 0.78 (0.65 – 0.95) (all $p<0.05$).

When analysis was restricted to the HRG (Table 4.4), none of the measures were predictive of survival in men. However, in women, although FEV_1 did not evidence of being predictive of survival, FVC and PEF were predictive of survival in unadjusted models (Model 1) and after adjusting for smoking, education and occupational history (Model 3). For a one litre increase in FVC at this point a 66% (HR: 0.34, 95% CI 0.13 – 0.88) reduced risk of mortality was observed (Model 3) in comparison to PEF which had a 96% (95% CI: 0 – 47) reduced risk of mortality for the same percentage increase. Nevertheless, when the models were fully adjusted for covariates (Model 7) neither FVC nor PEF remained predictive of survival in women in the HRG.

For the GOLD and GLI percent-predicted values in HRG women, only FVC measures were predictive of survival in unadjusted models (Model 1) and this effect was lost after complete adjustment for confounders (Model 7) (Table 4.5). Findings were similar for the standardised models (Table 4.6).

4.5 Summary

This chapter has confirmed that lung function still predicts survival as people reach an advanced age, albeit in women only. The effect of FVC and PEF on survival for men was mostly attenuated once the models adjusted for physical activity and biomarkers, which may be used as indicators of adverse health. Such findings could mean that some of the factors adjusted for in the models may act as mediators and not confounders. However, in a healthy group of the very old, with no previous respiratory symptoms, respiratory disease or respiratory related conditions, there was no evidence of the predictive ability of lung function for survival. The main findings of the chapter were:

1. FVC and PEF were predictive of survival before and after adjustment for sex and smoking.
2. FEV_1, FVC and PEF were predictive of survival women even after further adjustments for socioeconomic status, lifestyle behaviours, disease and biomarkers.
3. FEV_1, FVC and PEF did not predict survival in men after adjustment for all confounding factors regardless of whether or not they were healthy (i.e. had no respiratory related symptoms, disease or conditions) at baseline.
4. A litre increase in FEV_1 and FVC was associated with a 48% and 43% lower risk of mortality in women respectively.
5. FEV_1 and FVC percent predicted results were similar regardless of the calculation method (GOLD and GLI).

Whilst this chapter has revealed the relationship between lung function and mortality in the very old, the next chapter will investigate changes in lung function over time and the contributing factors (sociodemographic, health and lifestyle) to this.

Table 4.1: Effect of observed lung function measures on survival, Hazard Ratios (HR), 95% confidence interval for HR, p-value, whole spirometry cohort

Males		**FEV_1**			**FVC**			**PEF**	
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.74	(0.53 - 1.02)	0.064	0.75	(0.58 - 0.95)	0.019	0.35	(0.19 - 0.64)	0.001
2	0.76	(0.55 - 1.06)	0.109	0.76	(0.60 - 0.98)	0.031	0.36	(0.20 - 0.68)	0.001
3	0.73	(0.53 - 1.02)	0.067	0.75	(0.59 - 0.96)	0.021	0.33	(0.18 - 0.62)	0.001
4	0.95	(0.67 - 1.35)	0.781	0.86	(0.66 - 1.10)	0.230	0.60	(0.31 - 1.15)	0.124
5	0.78	(0.55 - 1.11)	0.168	0.79	(0.61 - 1.01)	0.057	0.40	(0.21 - 0.75)	0.005
6	0.91	(0.64 - 1.29)	0.583	0.86	(0.67 - 1.12)	0.268	0.45	(0.23 - 0.86)	0.015
7	1.06	(0.73 - 1.56)	0.749	0.96	(0.73 - 1.26)	0.769	0.63	(0.31 - 1.29)	0.210
Females		**FEV_1**			**FVC**			**PEF**	
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.37	(0.22 - 0.60)	<0.001	0.46	(0.31 - 0.67)	<0.001	*0.11*	*(0.04 - 0.29)*	*<0.001*
2	0.37	(0.22 - 0.60)	<0.001	0.46	(0.32 - 0.68)	<0.001	0.11	(0.04 - 0.31)	<0.001
3	0.36	(0.22 - 0.60)	<0.001	0.46	(0.31 - 0.67)	<0.001	0.12	(0.04 - 0.32)	<0.001
4	0.50	(0.31 - 0.80)	0.004	0.56	(0.39 - 0.81)	0.002	0.22	(0.08 - 0.59)	0.003
5	0.39	(0.24 - 0.65)	<0.001	0.50	(0.34 - 0.73)	<0.001	0.13	(0.05 - 0.36)	<0.001
6	0.39	(0.24 - 0.65)	<0.001	0.48	(0.33 - 0.71)	<0.001	0.12	(0.04 - 0.32)	<0.001
7	0.52	(0.32 - 0.86)	0.010	0.57	(0.39 - 0.82)	0.003	0.24	(0.09 - 0.70)	0.008

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6. Italic values indicate unmet proportional hazard assumptions in the modelling process.

Table 4.2: Effect of lung function on survival using percent predicted values, Hazard Ratios (HR), 95% confidence interval for HR, p-value, whole spirometry cohort

Males	**FEV_1 % Predicted (GOLD)**			**FEV_1 % Predicted (GLI)**			**FVC % Predicted (GOLD)**			**FVC % Predicted (GLI)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.92	(0.86 - 0.99)	0.033	*0.90*	*(0.84 - 0.97)*	*0.005*	*0.89*	*(0.82 - 0.96)*	*0.004*	*0.88*	*(0.82 - 0.95)*	*0.001*
2	0.93	(0.86 - 1.00)	0.062	0.91	(0.85 - 0.98)	0.010	0.90	(0.83 - 0.97)	0.008	*0.88*	*(0.82 - 0.95)*	*0.001*
3	0.92	(0.86 - 1.00)	0.041	0.91	(0.84 - 0.97)	0.006	0.89	(0.83 - 0.97)	0.006	0.88	(0.82 - 0.95)	0.001
4	0.97	(0.90 - 1.05)	0.432	0.95	(0.88 - 1.02)	0.150	0.92	(0.85 - 1.00)	0.055	0.91	(0.84 - 0.98)	0.011
5	0.93	(0.86 - 1.01)	0.870	0.91	(0.84 - 0.98	0.014	0.90	(0.83 - 0.98)	0.015	0.89	(0.83 - 0.96)	0.002
6	0.96	(0.89 - 1.05)	0.374	0.94	(0.87 - 1.01)	0.111	0.93	(0.85 - 1.01)	0.091	0.91	(0.84 - 0.99)	0.020
7	0.99	(0.91 - 1.08)	0.845	0.96	(0.88 - 1.04)	0.332	0.96	(0.88 - 1.04)	0.306	0.93	(0.86 - 1.01)	0.085
Females	**FEV_1 % Predicted (GOLD)**			**FEV_1 % Predicted (GLI)**			**FVC % Predicted (GOLD)**			**FVC % Predicted (GLI)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.84	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.91)	<0.001	0.85	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.90)	<0.001
2	0.84	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.91)	<0.001	0.85	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.90)	<0.001
3	0.84	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.91)	<0.001	0.85	(0.79 - 0.91)	<0.001	0.84	(0.78 - 0.90)	<0.001
4	0.89	(0.83 - 0.95)	0.001	0.88	(0.82 - 0.95)	0.001	0.88	(0.83 - 0.94)	<0.001	0.87	(0.82 - 0.94)	<0.001
5	0.85	(0.79 - 0.91)	<0.001	0.85	(0.78 - 0.91)	<0.001	0.85	(0.79 - 0.92)	<0.001	0.85	(0.78 - 0.91)	<0.001
6	0.85	(0.79 - 0.92)	<0.001	0.85	(0.79 - 0.92)	<0.001	0.85	(0.80 - 0.92)	<0.001	0.85	(0.79 - 0.91)	<0.001
7	0.89	(0.83 - 0.96)	0.002	0.89	(0.83 - 0.96)	0.002	0.88	(0.82 - 0.95)	0.001	0.88	(0.81 - 0.94)	0.001

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6. Italic values indicate unmet proportional hazard assumptions in the modelling process. HR Change for every 10% increase.

Table 4.3: Effect of standardised lung function measures on survival, Hazard Ratios (HR), 95% confidence interval for HR, p-value, whole spirometry cohort

Males	**FEV_1 (Standardised)**			**FVC (Standardised)**			**PEF (Standardised)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.85	(0.72 - 1.01)	0.072	0.80	(0.68 - 0.95)	0.012	0.75	(0.63 - 0.90)	0.002
2	0.87	(0.73 - 1.04)	0.122	0.81	(0.68 - 0.97)	0.019	0.76	(0.64 - 0.91)	0.004
3	0.85	(0.72 - 1.02)	0.075	0.80	(0.67 - 0.95)	0.013	0.74	(0.62 - 0.89)	0.001
4	0.98	(0.81 - 1.18)	0.826	0.88	(0.73 - 1.05)	0.163	0.89	(0.73 - 1.07)	0.218
5	0.88	(0.73 - 1.06)	0.184	0.83	(0.70 - 0.99)	0.037	0.78	(0.65 - 0.95)	0.011
6	0.95	(0.79 - 1.15)	0.623	0.89	(0.74 - 1.06)	0.194	0.81	(0.67 - 0.98)	0.033
7	1.04	(0.85 - 1.27)	0.716	0.95	(0.79 - 1.15)	0.614	0.90	(0.73 - 1.12)	0.347
Females	**FEV_1 (Standardised)**			**FVC (Standardised)**			**PEF (Standardised)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.70	(0.58 - 0.83)	<0.001	0.69	(0.58 - 0.82)	<0.001	*0.68*	*(0.57 - 0.81)*	*<0.001*
2	0.70	(0.58 - 0.83)	<0.001	0.69	(0.58 - 0.82)	<0.001	*0.68*	*(0.57 - 0.82)*	*<0.001*
3	0.69	(0.58 - 0.83)	<0.001	0.69	(0.58 - 0.82)	<0.001	0.69	(0.57 - 0.82)	<0.001
4	0.78	(0.65 - 0.92)	0.004	0.76	(0.64 - 0.89)	0.001	0.77	(0.64 - 0.92)	0.005
5	0.71	(0.59 - 0.86)	<0.001	0.71	(0.59 - 0.85)	<0.001	0.70	(0.58 - 0.85)	<0.001
6	0.72	(0.60 - 0.86)	<0.001	0.71	(0.59 - 0.85)	<0.001	0.68	(0.57 - 0.83)	<0.001
7	0.79	(0.66 - 0.94)	0.009	0.76	(0.64 - 0.90)	0.002	0.78	(0.65 - 0.95)	0.013

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6. Italic values indicate unmet proportional hazard assumptions in the modelling process.

Table 4.4: Effect of observed lung function measures on survival, Hazard Ratios (HR), 95% confidence interval for HR, p-value, HRG

Males		**FEV_1**			**FVC**			**PEF**	
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	1.12	(0.44 - 2.84)	0.811	1.08	(0.56 - 2.10)	0.819	0.61	(0.12 - 3.22)	0.562
2	1.13	(0.44 - 2.88)	0.799	1.09	(0.56 - 2.12)	0.802	0.61	(0.12 - 3.28)	0.568
3	1.02	(0.37- 2.82)	0.967	1.00	(0.49 - 2.05)	0.992	0.55	(0.10 - 3.08)	0.497
4	0.85	(0.30 - 2.41)	0.762	0.93	(0.46 - 1.90)	0.845	0.68	(0.10- 4.73)	0.694
5	1.23	(0.46 - 3.30)	0.682	1.26	(0.62 - 2.55)	0.523	0.64	(0.10 - 3.98)	0.633
6	1.84	(0.55 - 6.13)	0.320	1.41	(0.61 - 3.26)	0.423	1.04	(0.15 - 7.31)	0.972
7	1.44	(0.35 - 5.94)	0.612	1.32	(0.53 - 3.32)	0.555	1.38	(0.07 - 27.26)	0.832
Females		**FEV_1**			**FVC**			**PEF**	
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.37	(0.11 - 1.20)	0.098	0.37	(0.15 - 0.90)	0.028	0.05	(0.00- 0.60)	0.018
2	0.35	(0.11 - 1.14)	0.082	0.36	(0.15 - 0.89)	0.026	0.05	(0.00 - 0.51)	0.012
3	0.34	(0.10 - 1.15)	0.084	0.34	(0.13 - 0.88)	0.025	0.04	(0.00 - 0.47)	0.011
4	0.45	(0.14 - 1.41)	0.168	0.45	(0.18 - 1.14)	0.093	0.07	(0.00 - 1.02)	0.052
5	0.22	(0.06 - 0.81)	0.023	0.34	(0.13 - 0.88)	0.026	0.03	(0.00 - 0.38)	0.007
6	0.40	(0.13 - 1.29	0.126	0.38	(0.15 - 0.95)	0.039	0.07	(0.01 - 0.77)	0.030
7	0.67	(0.14 - 3.15)	0.613	0.67	(0.20 - 2.23)	0.510	0.41	(0.02 - 10.4)	0.591

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6.

Table 4.5: Effect of lung function on survival using percent predicted values, Hazard Ratios (HR), 95% confidence interval for HR, p-value, HRG

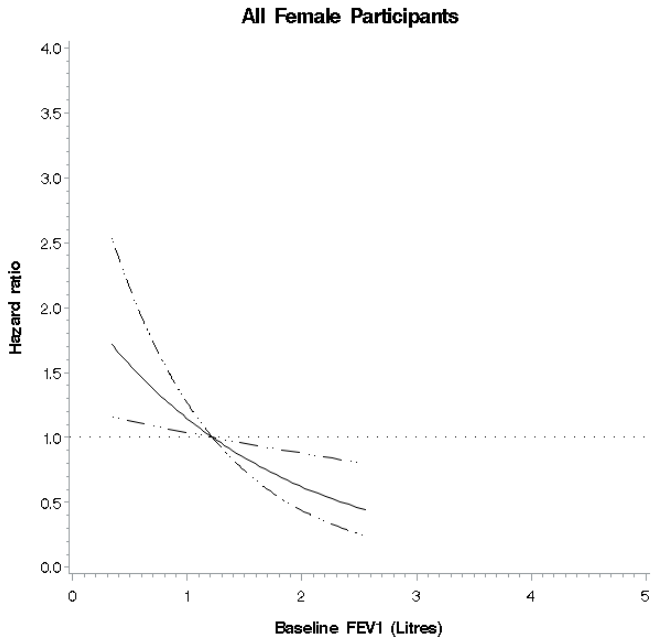
Males	**FEV_1 % Predicted (GOLD)**			**FEV_1 % Predicted (GLI)**			**FVC % Predicted (GOLD)**			**FVC % Predicted (GLI)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.94	(0.75 - 1.17)	0.570	0.94	(0.77 - 1.15)	0.550	0.94	(0.76 - 1.17)	0.576	0.94	(0.78 - 1.14)	0.543
2	0.94	(0.75 - 1.17)	0.571	0.94	(0.77 - 1.15)	0.552	0.94	(0.76 - 1.17)	0.582	0.94	(0.78 - 1.14)	0.550
3	0.89	(0.68 - 1.16)	0.397	0.90	(0.72 - 1.14)	0.390	0.90	(0.71 - 1.15)	0.411	0.91	(0.73 - 1.13)	0.379
4	0.91	(0.72 - 1.14)	0.408	0.91	(0.73 - 1.12)	0.363	0.92	(0.74 - 1.15)	0.476	0.92	(0.75 - 1.13)	0.432
5	0.95	(0.75 - 1.21)	0.700	0.95	(0.77 - 1.18)	0.636	0.99	(0.78 - 1.24)	0.902	0.98	(0.80 - 1.20)	0.821
6	0.99	(0.74 - 1.31)	0.928	0.99	(0.77 - 1.27)	0.920	0.96	(0.73 - 1.26)	0.783	0.96	(0.75 - 1.23)	0.768
7	1.00	(0.72 - 1.41)	0.980	0.98	(0.73 - 1.32)	0.894	1.02	(0.75 - 1.40)	0.876	1.00	(0.77 - 1.31)	0.990
Females	**FEV_1 % Predicted (GOLD)**			**FEV_1 % Predicted (GLI)**			**FVC % Predicted (GOLD)**			**FVC % Predicted (GLI)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.83	(0.69 - 1.00)	0.050	0.86	(0.71 - 1.03)	0.096	0.80	(0.68 - 0.96)	0.015	0.81	(0.68 - 0.97)	0.022
2	0.83	(0.69 - 0.99)	0.043	0.85	(0.71 - 1.02)	0.080	0.81	(0.68 - 0.96)	0.015	0.81	(0.68 - 0.97)	0.022
3	0.83	(0.69 - 1.00)	0.045	0.85	(0.70 - 1.02)	0.081	0.79	(0.66 - 0.96)	0.015	0.80	(0.66 - 0.97)	0.020
4	0.88	(0.73 - 1.04)	0.141	0.89	(0.75 - 1.06)	0.191	0.86	(0.72 - 1.02)	0.090	0.86	(0.72 - 1.03)	0.105
5	0.78	(0.63 - 0.96)	0.018	0.80	(0.65 - 0.98)	0.028	0.80	(0.67 - 0.97)	0.021	0.80	(0.66 - 0.98)	0.027
6	0.84	(0.70 - 1.01)	0.067	0.87	(0.73 - 1.04)	0.137	0.81	(0.68 - 0.97)	0.023	0.82	(0.68 - 0.99)	0.036
7	0.90	(0.70 - 1.17)	0.433	0.95	(0.74 - 1.21)	0.666	0.90	(0.71 - 1.15)	0.406	0.92	(0.72 - 1.19)	0.541

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6. HR Change for every 10% increase.

Table 4.6: Effect of standardised lung function measures on survival, Hazard Ratios (HR), 95% confidence interval for HR, p-value, HRG

Males	**FEV_1 (Standardised)**			**FVC (Standardised)**			**PEF (Standardised)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	1.04	(0.63 - 1.73)	0.868	1.05	(0.65 - 1.69)	0.857	0.85	(0.52 - 1.41)	0.540
2	1.05	(0.63 - 1.74)	0.857	1.05	(0.65 - 1.70)	0.840	0.86	(0.52 - 1.42)	0.547
3	0.99	(0.57 - 1.72)	0.974	0.99	(0.59 - 1.66)	0.964	0.83	(0.49 - 1.40)	0.480
4	0.89	(0.51 - 1.57)	0.689	0.94	(0.56 - 1.58)	0.815	0.87	(0.49 - 1.56)	0.642
5	1.10	(0.64 - 1.87)	0.730	1.16	(0.70 - 1.93)	0.563	0.88	(0.51 - 1.52)	0.639
6	1.35	(0.70 - 2.60)	0.362	1.26	(0.69 - 2.32)	0.453	1.00	(0.55 - 1.81)	0.994
7	1.18	(0.56 - 2.51)	0.666	1.20	(0.62 - 2.34)	0.586	1.08	(0.44 - 2.65)	0.860
Females	**FEV_1 (Standardised)**			**FVC (Standardised)**			**PEF (Standardised)**		
Model*	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
1	0.68	(0.43 - 1.06)	0.087	0.62	(0.41 - 0.95)	0.026	0.61	(0.39 - 0.94)	0.024
2	0.66	(0.42 - 1.03)	0.070	0.62	(0.41 - 0.94)	0.025	0.59	(0.39 - 0.91)	0.017
3	0.66	(0.41 - 1.04)	0.072	0.60	(0.39 - 0.93)	0.024	0.57	(0.36 - 0.90)	0.016
4	0.73	(0.47 - 1.12)	0.153	0.69	(0.45 - 1.06)	0.090	0.64	(0.40 - 1.04)	0.073
5	0.55	(0.34 - 0.91)	0.019	0.60	(0.39 - 0.94)	0.025	0.54	(0.34 - 0.87)	0.011
6	0.70	(0.45 - 1.09)	0.115	0.64	(0.42 - 0.98)	0.040	0.64	(0.42 - 0.98)	0.041
7	0.85	(0.48 - 1.53)	0.595	0.83	(0.48 - 1.46)	0.526	0.90	(0.51 - 1.60)	0.723

*Model 1 unadjusted. Model 2 adjusted for smoking status. Model 3 adjusted for model 2, education, and occupational exposure. Model 4 adjusted for model 2, physical activity and BMI. Model 5 adjusted for model 2, COPD, other respiratory disease, disease count excluding respiratory conditions and MMSE. Model 6 adjusted for model 2, IL-6, TNFα, CRP and Telomere length. Model 7 adjusted to include all parameters from models 2 to 6.



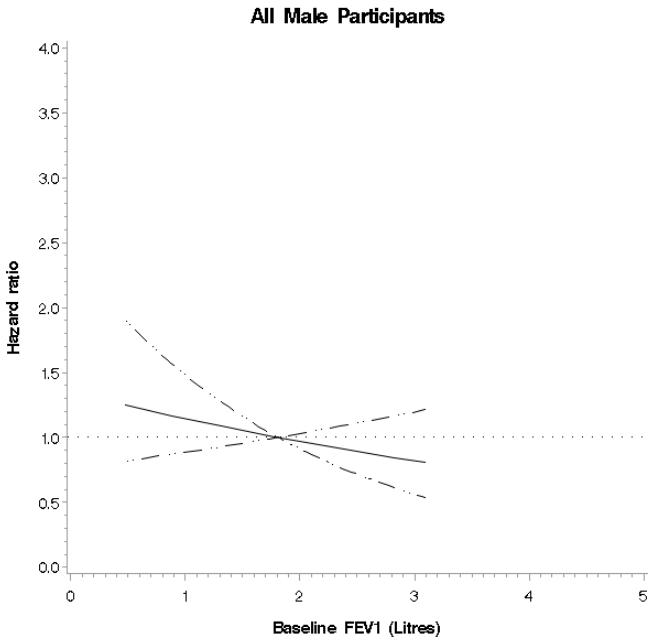
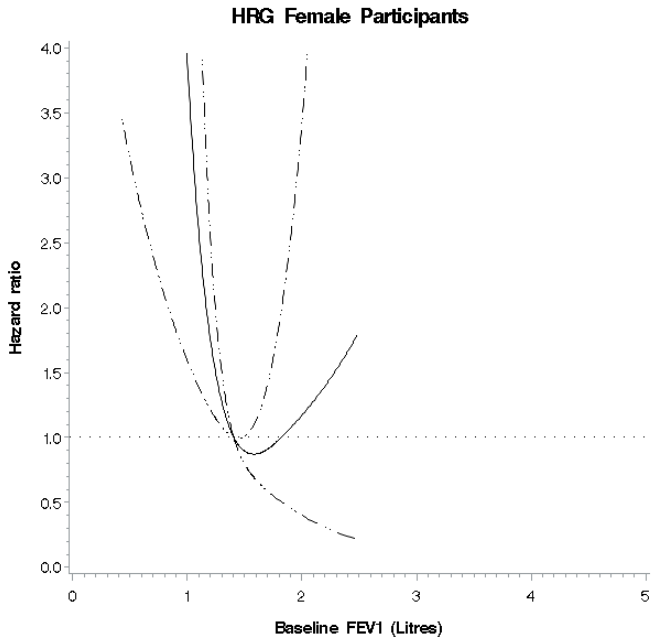


Figure 4.1: Restricted cubic spline curves of baseline FEV_1 (litres) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length



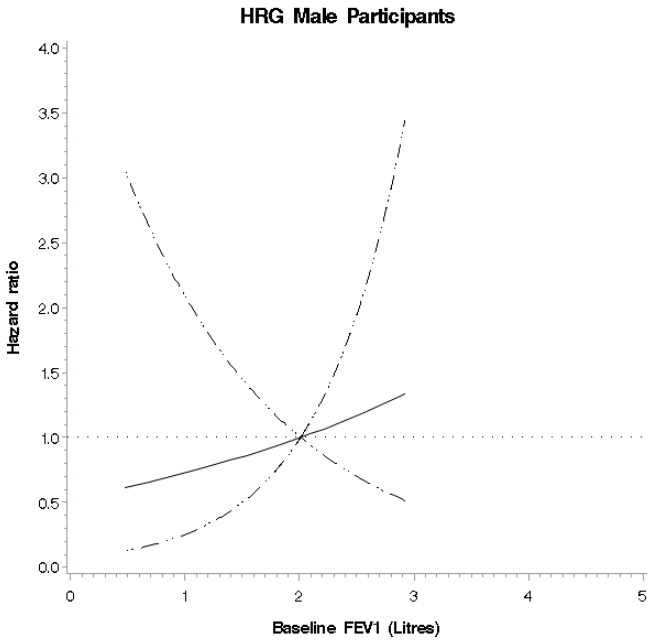


Figure 4.2: Restricted cubic spline curves of baseline FEV_1 (litres) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length

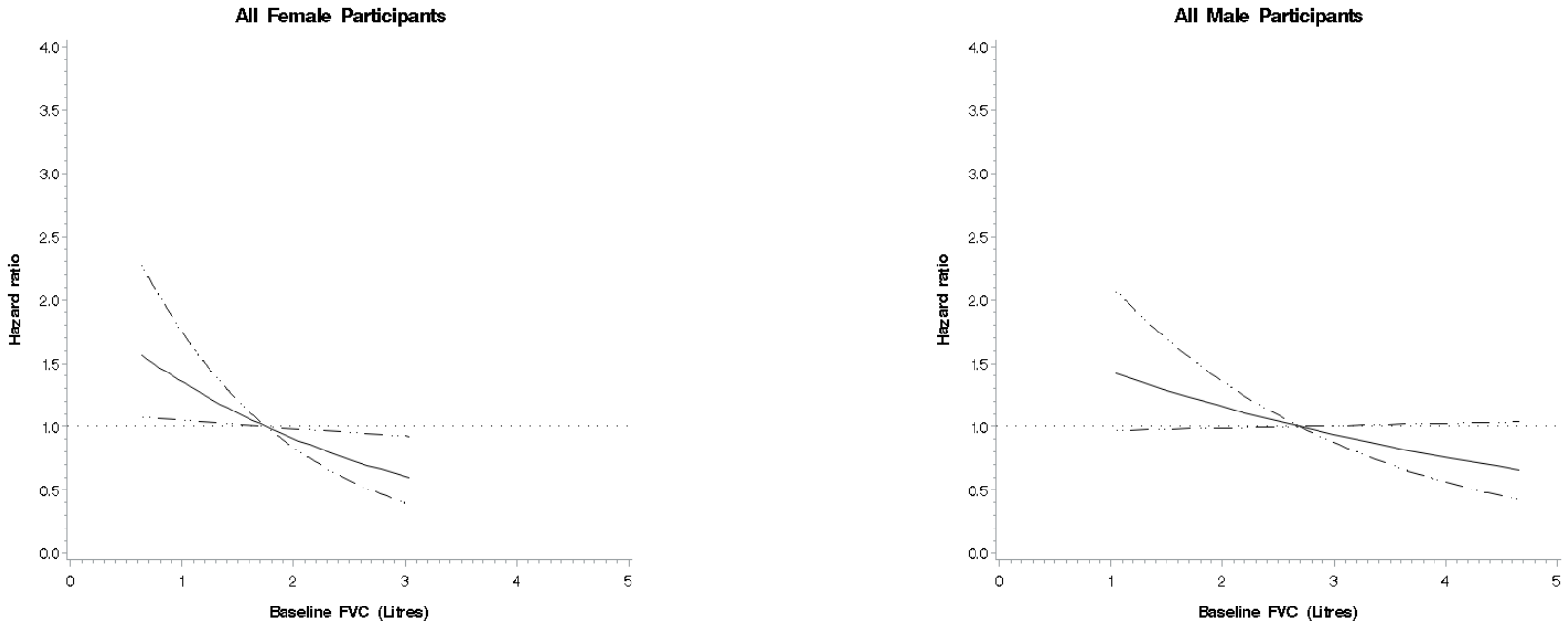


Figure 4.3: Restricted cubic spline curves of baseline FVC (litres) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length

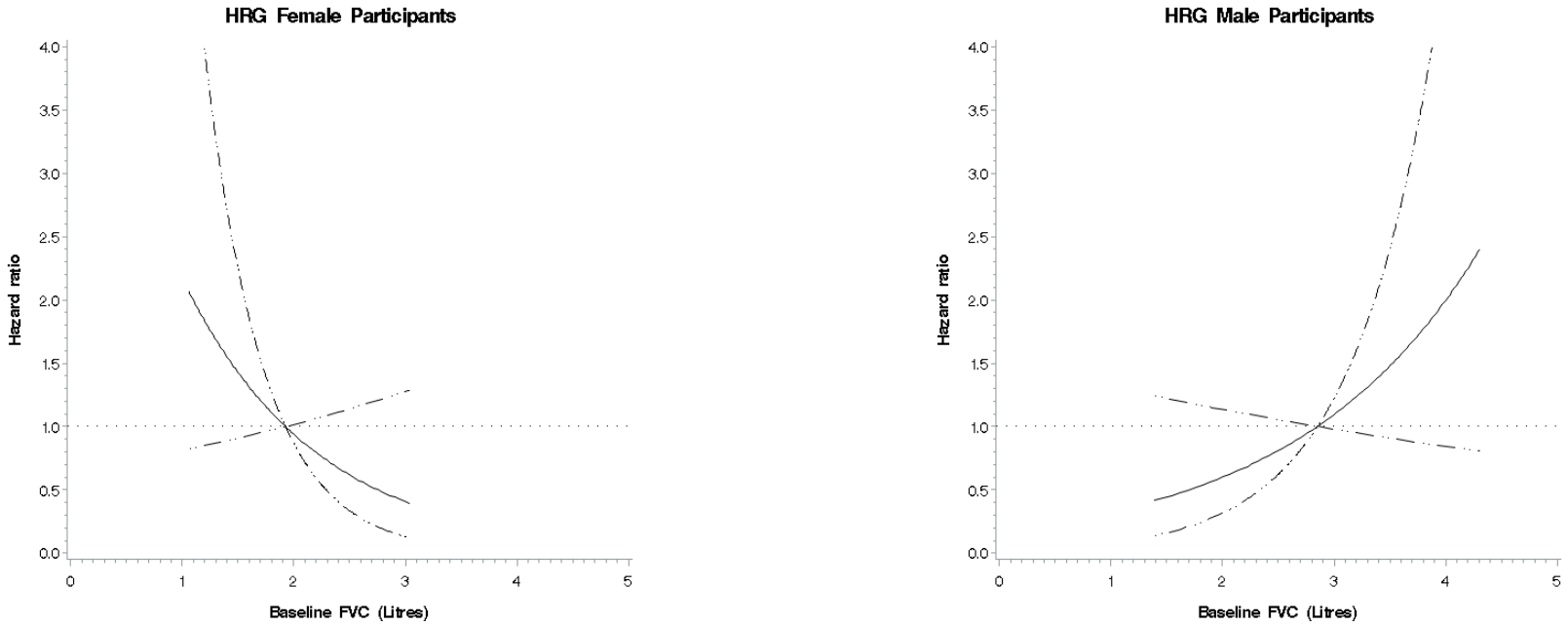
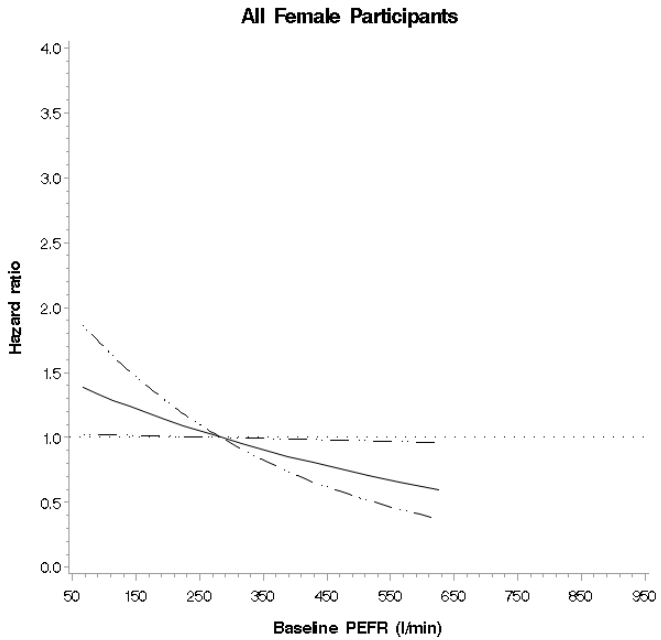


Figure 4.4: Restricted cubic spline curves of baseline FVC (litres) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length



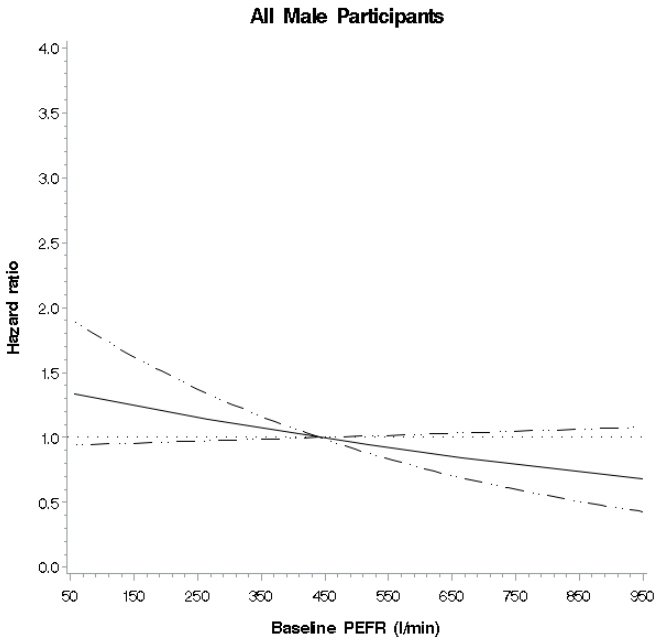


Figure 4.5: Restricted cubic spline curves of baseline PEF (litres) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length

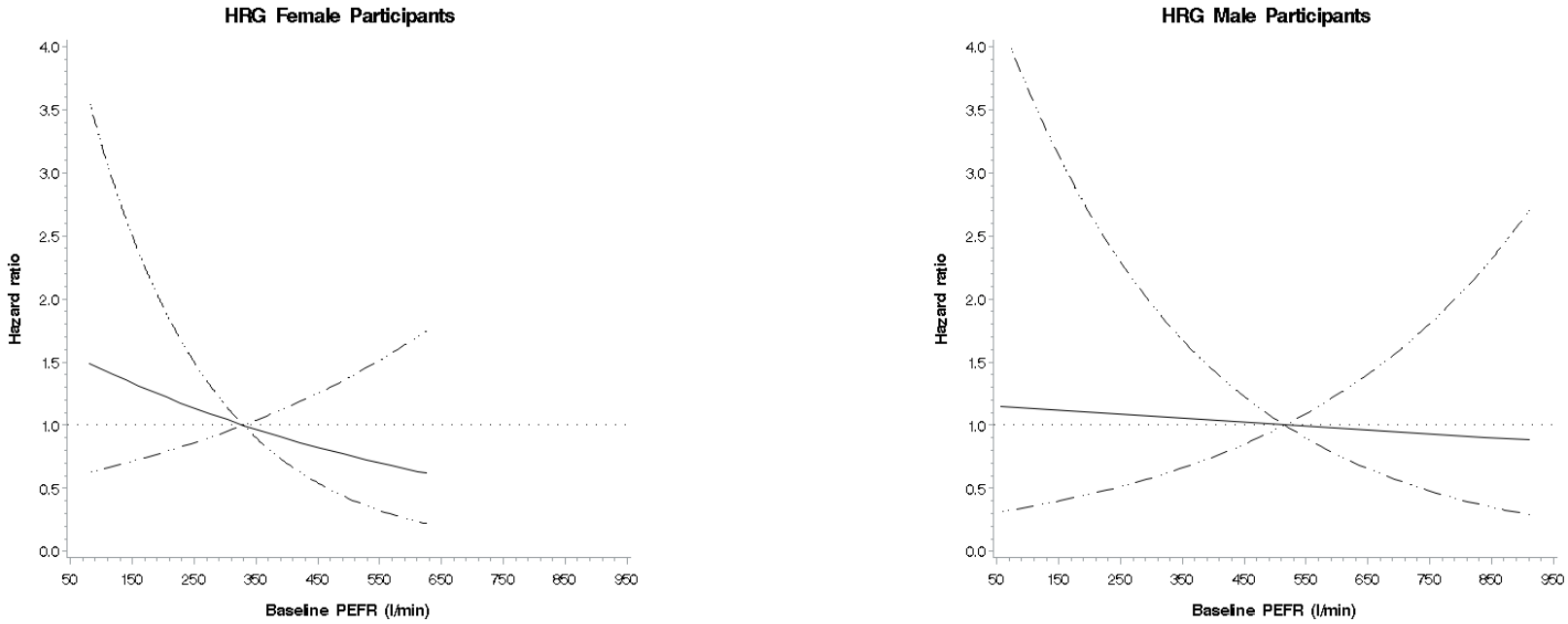


Figure 4.6: Restricted cubic spline curves of baseline PEF (litres) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length

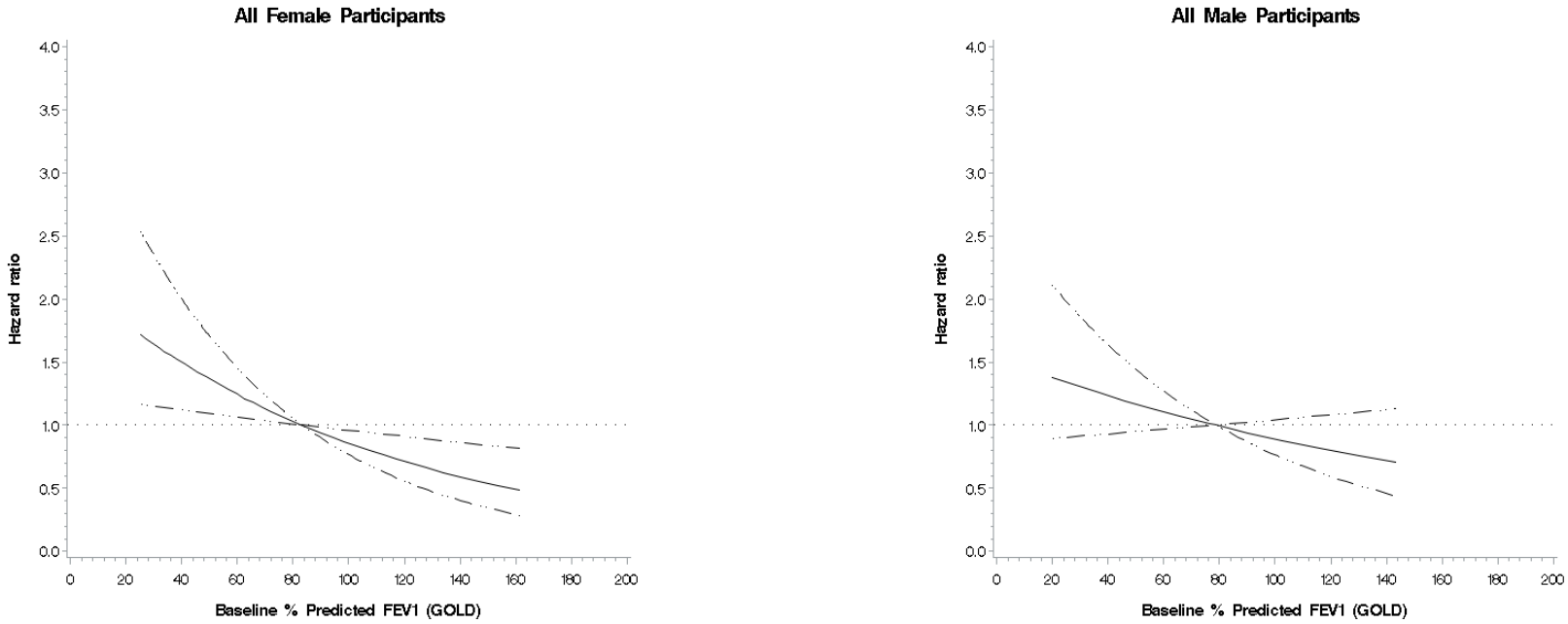


Figure 4.7: Restricted cubic spline curves of baseline GOLD FEV_1 Percent Predicted (%) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

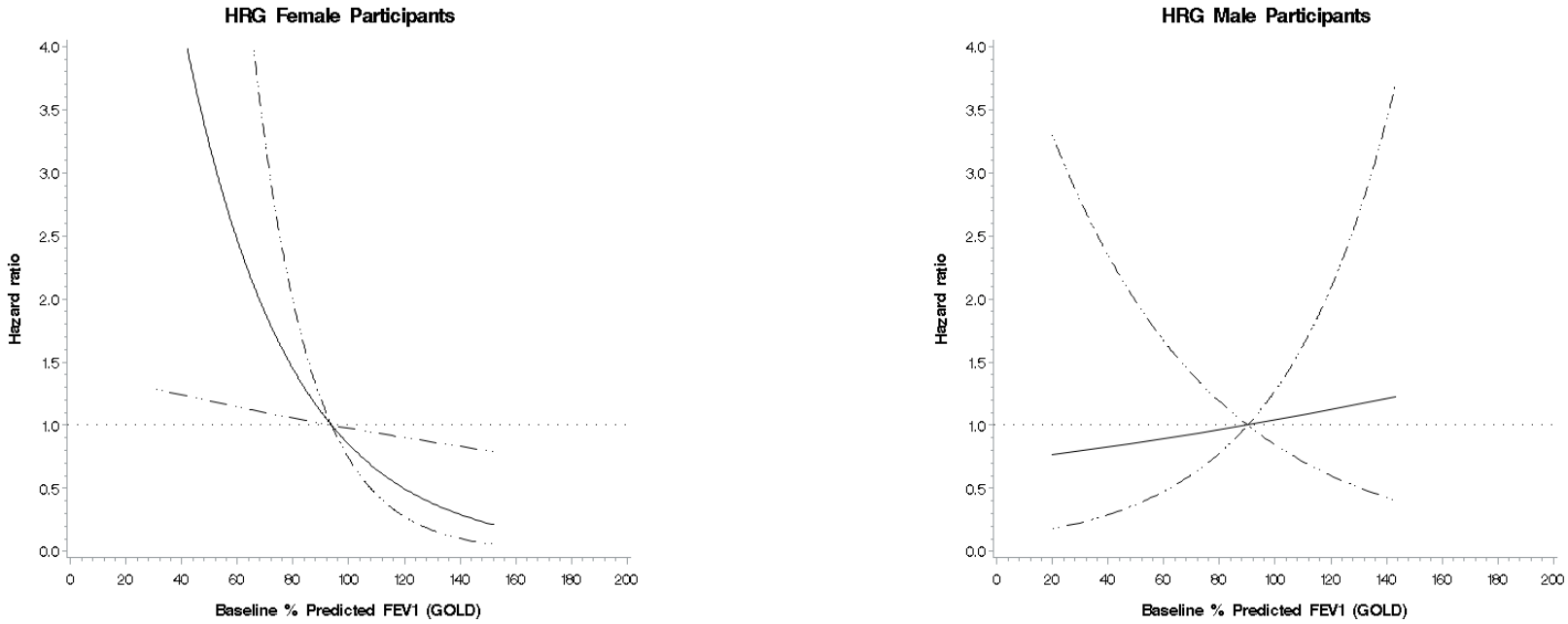


Figure 4.8: Restricted cubic spline curves of baseline GOLD FEV_1 Percent Predicted (%) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

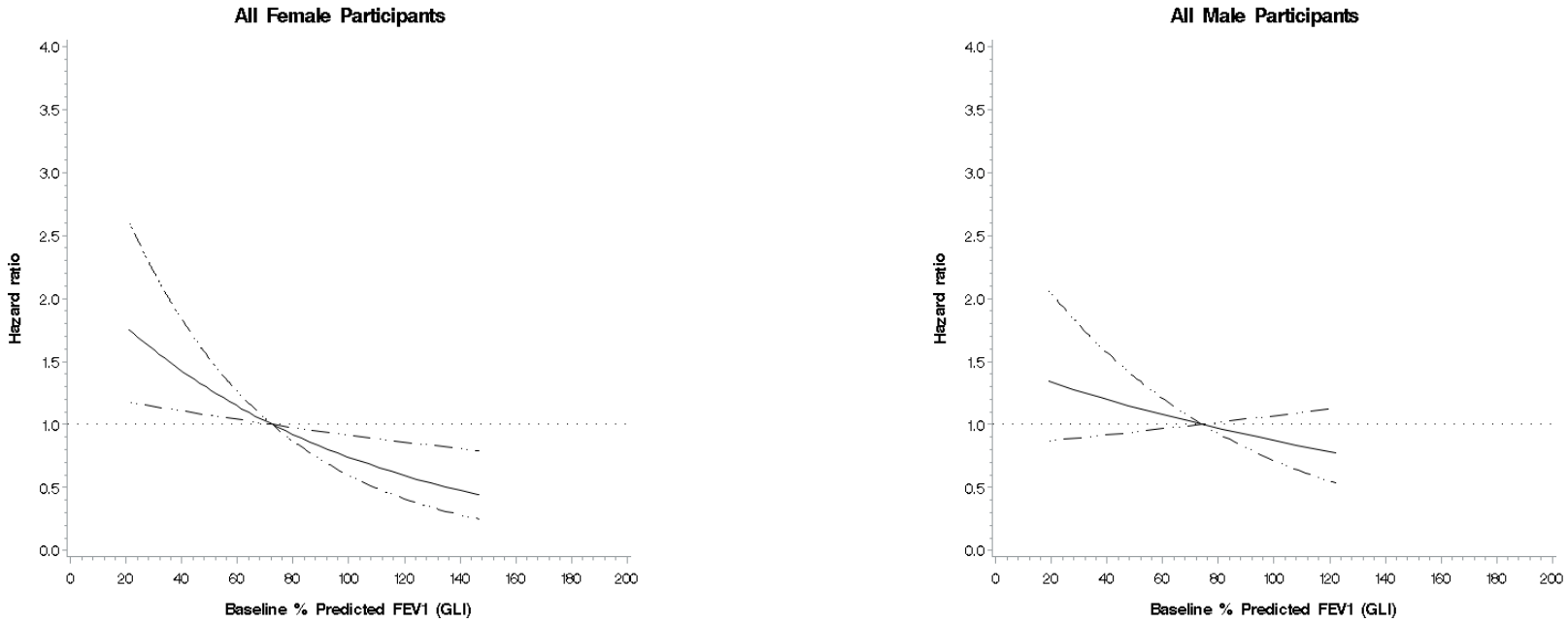


Figure 4.9: Restricted cubic spline curves of baseline GLI FEV_1 Percent Predicted (%) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

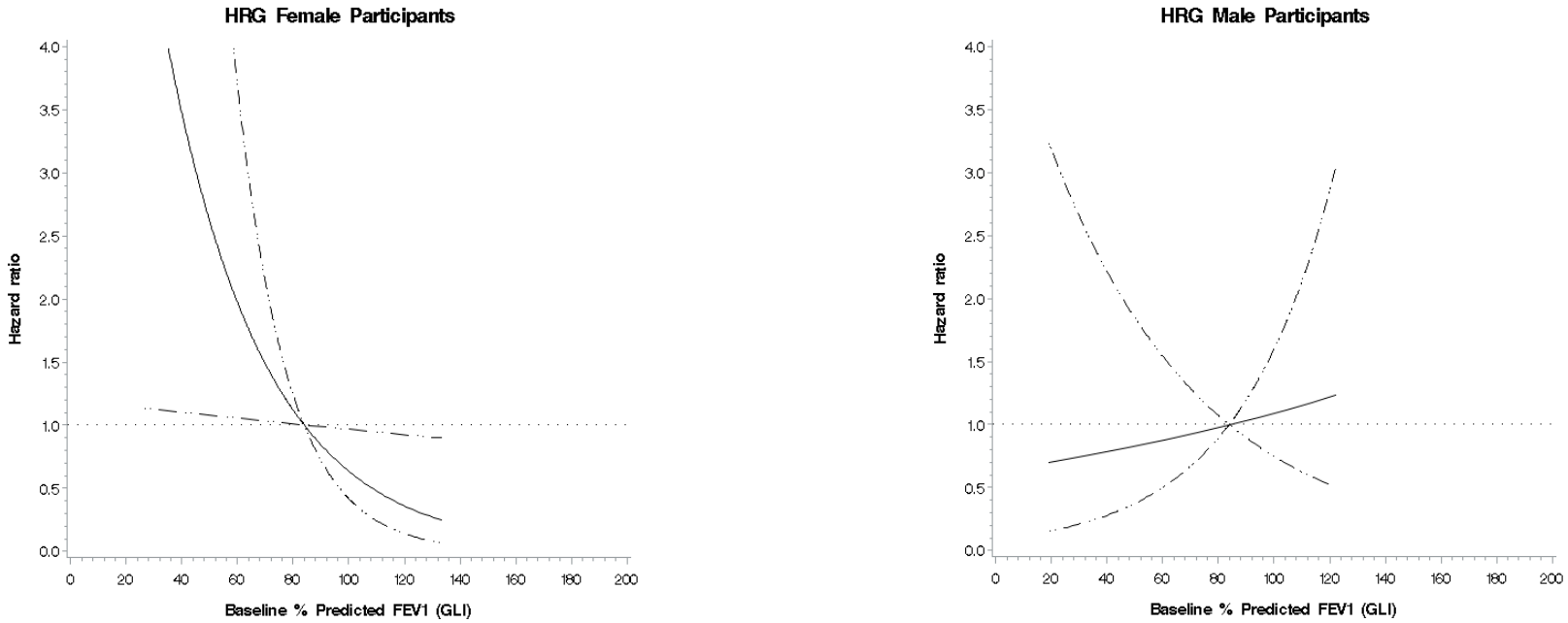


Figure 4.10: Restricted cubic spline curves of baseline GLI FEV_1 Percent Predicted (%) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

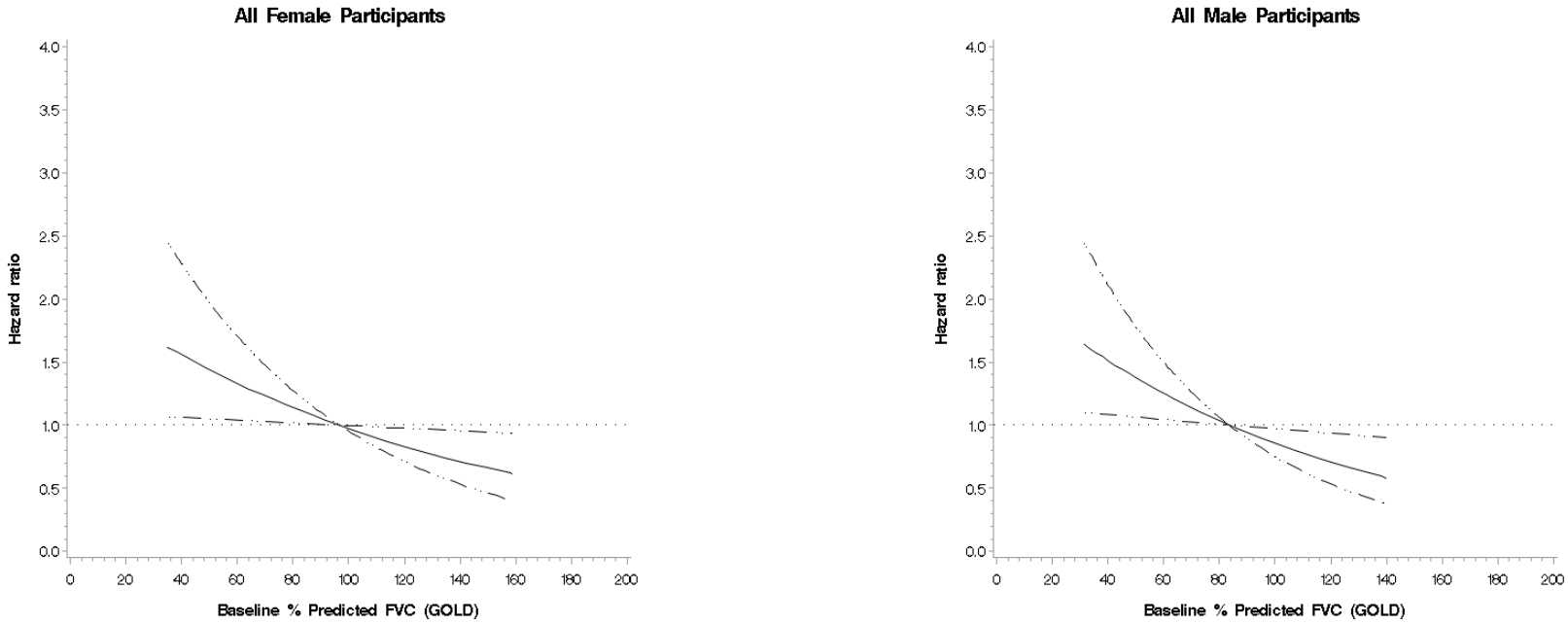


Figure 4.11: Restricted cubic spline curves of baseline GOLD FVC Percent Predicted (%) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

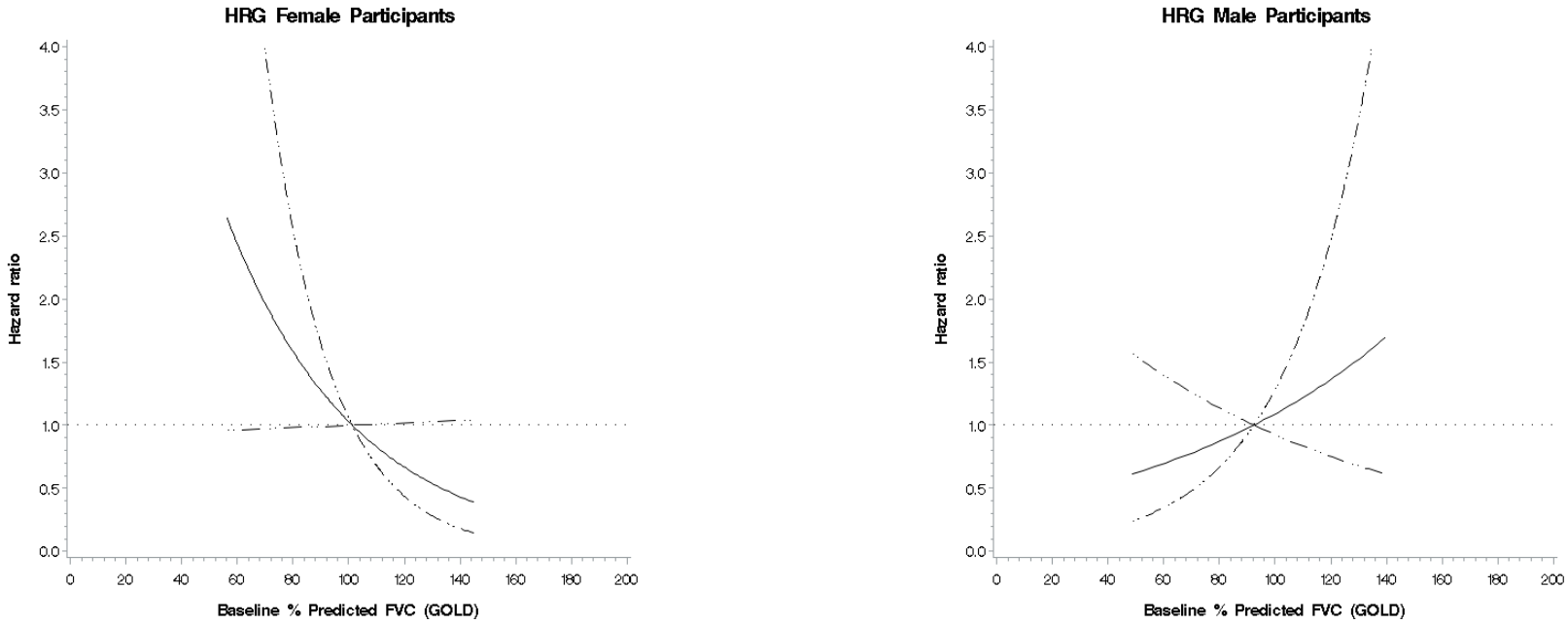


Figure 4.12: Restricted cubic spline curves of baseline GOLD FVC Percent Predicted (%) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

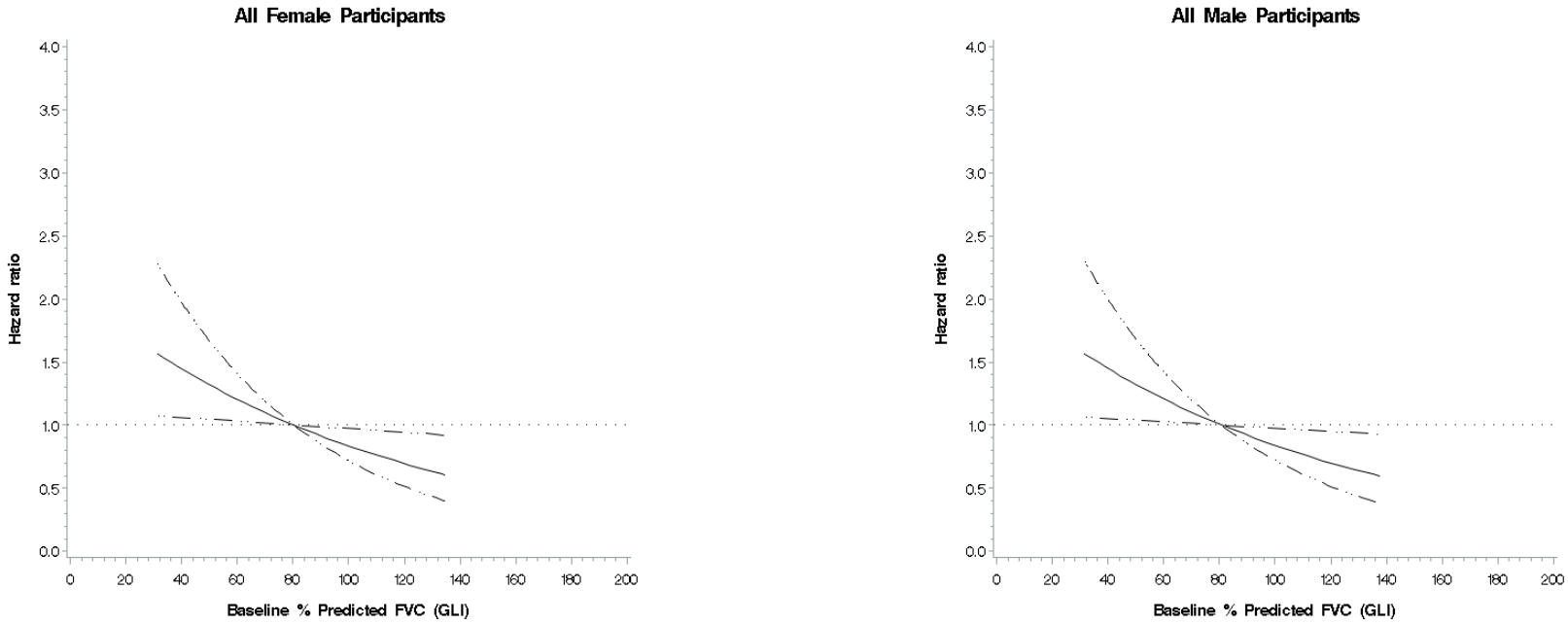


Figure 4.13: Restricted cubic spline curves of baseline GLI FVC Percent Predicted (%) levels and mortality in men and women in the whole spirometry cohort adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

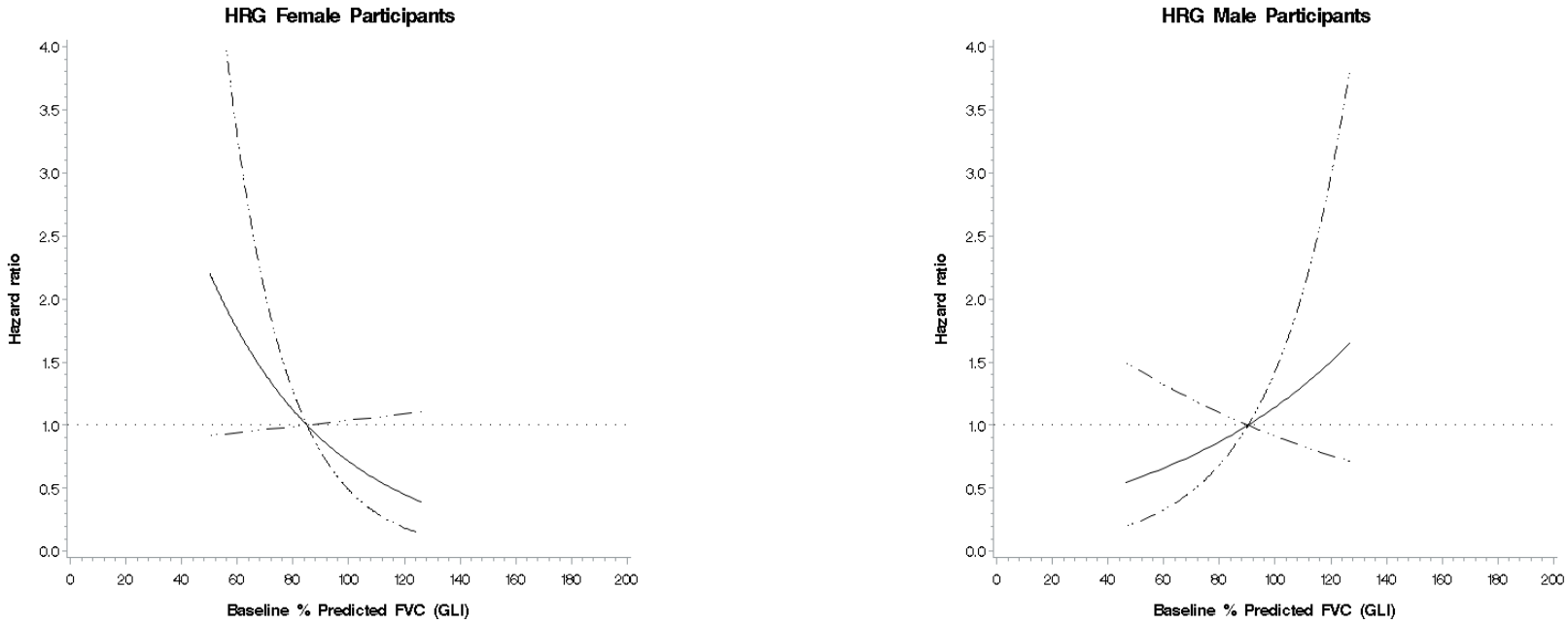


Figure 4.14: Restricted cubic spline curves of baseline GLI FVC Percent Predicted (%) levels and mortality in men and women in the HRG adjusted for smoking status, education, occupational exposure, physical activity, BMI, Respiratory disease, disease count excluding respiratory conditions, MMSE, IL-6, TNFα, CRP and Telomere length.

Chapter 5. Trajectories of lung function from age 85

In the previous chapter, the repeated measures of lung function obtained in the N85+ study were utilised to position the lung function measure closer to the event of death so that the effect of lung function on mortality could be estimated more precisely. This chapter will explore the pattern of change in lung function in 85 year olds as they age.

5.1 Aims of the chapter

Specifically this chapter will:

1. Describe lung function measures at baseline, 18 and 36 months
2. Quantify the extent of new cases of respiratory disease at 18 and 36 months
3. Investigate the lung function trajectories of change and their determinants within the
    a. Whole spirometry cohort
    b. HRG
    c. Survivor Group
4. Explore the relationship of inflammatory blood biomarkers to lung function over the 36 months period

5.2 Background

As discussed in the previous chapter, various studies have found reduced lung function to be a predictor of increased mortality in both younger and older populations (Lyyra *et al.*, 2005; Sabia *et al.*, 2010; Miller *et al.*, 2014). The N85+ study also confirmed that better lung function predicted lower risk of mortality but only in women in a general population. Earlier chapters have discussed that the ageing lung sees its function decrease over time (Pride, 2005; Vaz Fragoso and Lee, 2012). However, there have been few studies investigating lung function changes over time and specifically exploring the determinants and consequences of changes in lung function in the very old.

The literature review in Chapter 1 described the studies in older populations that have explored longitudinal changes in lung function. Findings from these included that decrease in fat free mass (FFM) decrease and increase in sagittal abdominal diameter were associated with decline in pulmonary function over a 7 year period (Rossi *et al.*, 2008); better pulmonary function resulting in slower cognitive decline (Weuve *et al.*, 2011; Emery *et al.*, 2012; Vidal *et al.*, 2013); and worse pulmonary function resulting in decline in cognitive function (Emery *et al.*,

2012). However, most longitudinal studies of lung function are in younger populations. In this age group socio-economic status (SES) at birth was found to be inversely associated with lung function during adolescence (Menezes *et al.*, 2011). As previously discussed, the longitudinal effect of inflammatory markers such as IL-6, TNFα and CRP on lung function has been extensively researched (Shaaban *et al.*, 2006; Gimeno *et al.*, 2011; Ahmadi-Abhari *et al.*, 2014; Hancox *et al.*, 2016).

In the Whitehall II study, an increase of 10 percent in baseline CRP was associated with a 4.7 ml decrease in FVC and 3.0 ml decrease in FEV_1 over a period of approximately 12 years. IL-6 followed a similar trend, but with a ten percent increase resulting in 12.6 ml decrease in FVC and 7.3 ml decrease in FEV_1 after adjusting for all covariates (Gimeno *et al.*, 2011). Analysis of the effect of CRP on both FEV_1 and FVC over a 13 year follow-up revealed an inverse association; however, CRP at baseline was not found to be predictive of lung function rate of change (Ahmadi-Abhari *et al.*, 2014). Another study of the association between CRP and FEV_1 over an 8.5 year follow-up period found a decline in lung function based on increasing tertiles of CRP after adjusting for sociodemographic (age and sex), life style (smoking habits and BMI) and health characteristics such as cholesterol levels, atopy and asthma (Shaaban *et al.*, 2006).

This brief review of longitudinal studies of lung function measures has revealed a gap which this chapter will address using the different lung function measures available in the N85+ study at two follow-ups covering a period of 36 months from age 85. Specifically, these analyses will explore the association between sociodemographic, health and lifestyle characteristics as well as blood biomarkers and changes in lung function measures.

5.3 Analytical methods

5.3.1 Lung function measures

The lung function measures collected remain the same throughout the study, however for the purpose of the analysis in this section, only observed measures will be investigated, specifically FEV_1, FVC, PEF and FEV_1/VC which were available at baseline, 18 months and 36 months follow-up.

5.3.2 Confounders

As previously mentioned in chapter 4, a series of factors were identified from the literature search for inclusion in the mortality analyses that were also relevant to trajectories of change.

These were: age; age^2; sex; smoking status (categorised as never, former and current smokers); years of education (categorised as 0-9 years, 10 – 11 years, 12+ years); BMI (categorised as underweight <18.5, normal 18.5 – 25, overweight 25 – 30, obese and morbidly obese 30+); physical activity (categorised as low, medium, high); occupational exposure; respiratory conditions; chronic disease count; and cognitive impairment. Occupational exposure was defined as having worked in any of heavy industry, coal mining, chemical works or asbestos related occupations. Respiratory disease was based on respiratory diagnoses from the GPRR. Disease count was the sum of 7 disease categories: arthritis, cancer, cardiac disease, cerebrovascular disease, diabetes, hypertension and cognitive impairment, also based GPRR diagnoses with the exception of cognitive impairment which was ascertained at interview. MMSE scores were categorised as normal (26-30), mild (22-25), moderate (18-21) and severe (0-17). Also included were three serum biomarkers of inflammation which had been explored in previous studies: Interleukin 6 (IL-6) , tumour necrosis factor alpha (TNFα), C-reactive protein (CRP), in addition to telomere length which has been identified as a biomarker for ageing (Shaaban *et al.*, 2006; Gimeno *et al.*, 2011; Ahmadi-Abhari *et al.*, 2014; Gardner *et al.*, 2014; Hancox *et al.*, 2016).

5.3.3 Longitudinal analysis

To model the trajectory of each lung function measure over the 36 months follow-up, multilevel random effects models were fitted with age as the time scale and including polynomial functions of age. The effect of key socio-demographic and health factors and biomarkers individually were assessed in subsequent models: sex; socio-economic status (education), occupational exposure, physical activity, BMI, respiratory diagnoses; chronic disease count; cognitive function (MMSE), IL-6, TNFα, CRP and telomere length. Due to skewed distribution, the biomarkers were log-transformed. Apart from education and smoking status, all other variables were updated. The analysis was performed for the whole spirometry cohort, HRG and the HRG survivor group (defined as those from the HRG who survived all 3 time points of the study and did not have a respiratory disease diagnoses at any point). A sensitivity analysis was performed using only survivors of all three times points to investigate the presence of survival bias affecting the findings. All analyses used Stata 12.0 (StataCorp; College Station, TX, USA).

5.4 Lung function trajectories of change

5.4.1 Respiratory disease diagnoses

From the respiratory diagnoses in the GPRR at 18 months in the whole spirometry cohort, 5 new cases of COPD were found, along with 2 cases of asthma, pulmonary fibrosis, asbestosis and one case of bronchiectasis and TB each (Table 5.1). A further 7 cases of COPD were found by 36 months in addition to 3 bronchiectasis and 1 pulmonary fibrosis diagnoses. Overall, there were 24 new diagnoses of respiratory disease over the 36 months follow-up period. This was in contrast to the number of cases diagnosed in the HRG with only 1 case of bronchiectasis and 1 of pulmonary fibrosis over the same period (Table 5.1). The incidence rate for COPD in this cohort was 7.8 cases per 1000 persons per year.

5.4.2 Changes in lung function measures over time

In the spirometry cohort, mean FEV_1 for men was 1.80 litres at baseline, 1.85 litres at 18 months and 1.80 litres at 36 months.In women mean FEV_1 was 1.22 litres at baseline, 1.21 litres at 18 months and 1.20 litres at 36 months (Table 5.2). For FVC, both men and women saw an overall decline with overall mean of 2.14 (SD: 0.75) decreasing to 2.02 (SD: 0.74) over the 36 months follow-up (Table 5.2). Mean PEF increased over the 36 months period for both men (461, SD: 188 to 488, SD: 171) and women (287, SD: 117 to 309, SD: 106) and the FEV_1/FVC ratio had a similar trend to that of FEV_1 for both men and women (Table 5.2). Similar trends were observed for the HRG lung function in both men and women (Table 5.2).

In the HRG survivor group a gradual decrease was observed in both FEV_1 and FVC. It is worth noting that PEF did actually decrease overall between baseline (423, SD: 169) and 36 months (411, SD: 165) though this was mostly between 18 and 36 months (Table 5.3). The average FEV_1/FVC ratio did not change for men between baseline and 36 months though a slight but non-significant increase was observed for women for the same period (Table 5.3).

5.4.3 Lung function trajectories of change

The FEV_1 trajectories of change are shown graphically in Figure 5.1. For the whole spirometry cohort. In men, there was a significant effect of time suggesting a non-linear trajectory whilst current smoking, cognitive impairment and higher CRP were associated with lower FEV_1 trajectories and higher education with higher FEV_1 trajectories (Table 5.4). In contrast, women's FEV_1 did not change significantly over time, although current smoking, respiratory

disease and cognitive impairment resulted in significantly lower FEV_1 (Table 5.4). Sensitivity analysis was performed based on the spirometry cohort participants who survived all three time points to investigate the possibility of survival bias (Table 5.5). Similar conclusions were drawn for the majority of variables with the exception of smoking status (no longer associated), TNF alpha (men) and CRP (women) (Table 5.5).

In the HRG men, higher education levels and lower disease count resulted in significantly higher FEV_1 whereas in women, medium physical activity, BMI of over 30, respiratory disease and higher disease count resulted in lower FEV_1 (Table 5.6). In the HRG survivor group, mild and moderate cognitive impairment and raised TNFα resulted in lower FEV_1 and in women medium physical activity and increased disease count resulted in lower FEV_1 (Table 5.7).

The FVC trajectories for the whole spirometry cohort are shown graphically in Figure 5.2. FVC did not change significantly over time in men or women (Table 5.8). However, men with greater cognitive impairment, higher CRP and longer telomere length had significantly lower FVC whilst higher BMI, the presence of respiratory disease and higher CRP in women resulted in significantly lower FVC (Table 5.8). In the HRG, none of the covariates impacted men's FVC trajectory in contrast to women where lower physical activity and higher BMI were associated with lower FVC (Table 5.9). In the HRG survivor group, physical activity in women was the only covariate found to impact FVC (Table 5.10).

PEF trajectories are shown graphically for the whole spirometry cohort in Figure 5.3. PEF in men showed a non-linear relationship with time (β:-1.02, SE: 0.50) (Table 5.11). Current smokers (β:-0.25, SE: 0.08) compared to never smokers, medium (β:-0.10, SE: 0.03) and low (β:-0.06, SE: 0.02) physical activity compared to high levels and being underweight (β:-0.12, SE: 0.05) were all associated with lower PEF (Table 5.11). Lower cognitive function and higher CRP levels were also associated with lower PEF in men (Table 5.11). In women current smoking, lower physical activity, being underweight, respiratory disease, cognitive impairment and longer telomere length all resulted in lower PEF (Table 5.11). In the HRG, no associations were found between the covariates and PEF for men, though in women medium physical activity (β:-0.14, SE: 0.04) compared to high levels and IL-6 (β:-0.03, SE: 0.01) were inversely associated with PEF (Table 5.12). In the HRG survivor group, only physical activity and BMI impacted PEF trajectories in women (Table 5.13).

The FEV_1/FVC ratio trajectories (Figure 5.4) for whole spirometry cohort (Table 5.14), the HRG (Table 5.15) and HRG survivor group (Table 5.16) presented similar findings to that of

FEV_1 and PEF trajectories.

5.4.4 Lung function and biomarkers of inflammation

This section will consolidate all significant findings for biomarkers of inflammation on all lung function measures. IL-6, TNFα and CRP were the three biomarkers of systemic inflammation investigated against the lung function trajectories. Increased IL-6 level was associated with lower PEF levels in HRG women (β:-0.04, SE: 0.02) and women in the HRG survivor group (β:-0.04, SE: 0.02) (Table 5.12, Table 5.13, Figure 5.6). Higher levels of TNFα (β:-0.05, SE: 0.02) were associated with lower FEV_1 levels of men in the HRG survivor groups (Figure 5.7, Table 5.7). In the whole spirometry group, increases in CRP (β:-0.05, SE: 0.01) had was associated with lower FEV_1 in men of the whole spirometry cohort (Table 5.4, Figure 5.8). Increased CRP was associated with lower FVC levels in both men (β:-0.05, SE: 0.02) and women (β:-0.03, SE: 0.01) of the whole spirometry group (Table 5.8, Figure 5.8). Similar results were found in PEF for men in the whole spirometry group (Table 5.11, Figure 5.8) and the HRG survivor group (Table 5.13, Figure 5.8).

5.5 Summary

This chapter explored lung function trajectories over time and investigated lifestyle and health characteristics which may influence them. There were similarities in FEV_1, PEF and FEV_1/FVC trajectories of men in whole spirometry group where change was non-linear over the 36 months period. However, in contrast, women's lung function showed little evidence of change over time. Sensitivity analysis revealed minor differences between the whole spirometry cohort and its survivors. The effect of health characteristics were more pronounced in the whole spirometry groups and such effects were diminished when investigated in the HRG or the HRG survivor group indicating a survivor effect.

The main findings of a longitudinal survival analysis were:

1. There were 24 new cases of lung disease over the 36 month follow-up, and COPD accounted for 50% of all new lung disease diagnoses.
2. The incidence rate of COPD in this cohort was 7.8 cases per 1000 per year.
3. FEV_1 for the whole spirometry group was lower for current smokers and the cognitively impaired in both men and women.
4. Smoking was no longer associated with FEV_1 in whole spirometry cohort survivors.
5. Cognitive impairment had an adverse effect on FEV_1 levels for men in both the whole spirometry group and the HRG survivor group.
6. BMI and physical activity had the most influence on lung function levels in women in the HRG and HRG survivor groups.
7. Lower physical activity was associated with lower FEV_1, FVC and PEF in women of the HRG survivor group.
8. Increased IL-6 was associated with lower PEF levels in the HRG and HRG survivor group but only for women.
9. Higher TNFα was associated with lower FEV_1 in men in the HRG survivor group.
10. Higher CRP was associated with lower FEV_1, FVC and PEF for men in the whole spirometry group.

Whilst this chapter has explored lung function trajectories between the ages of 85 and 88 and factors influencing them, the next chapter will investigate causal pathways between lung function and disability between ages 85 and 90.

Table 5.1: New cases of respiratory disease GP diagnoses at each time point by sex, whole spirometry cohort and HRG

Spirometry Cohort	Baseline			18 Months			36 Months		
Disease	Male (293)	Female (444)	All (737)	Male (214)	Female (337)	All (551)	Male (157)	Female (255)	All (412)
COPD	17.8 (52)	16.0 (71)	16.7 (123)	0.6 (1)	1.4 (4)	1.0 (5)	1.6 (2)	2.3 (5)	2.0 (7)
Asthma	6.8 (20)	13.1 (58)	10.6 (78)	0.0 (0)	0.7 (2)	0.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Bronchiectasis	2.4 (7)	1.8 (8)	2.0 (15)	0.0 (0)	0.3 (1)	0.2 (1)	0.7 (1)	0.8 (2)	0.7 (3)
Pulmonary Fibrosis	0.0 (0)	0.0 (0)	0.0 (0)	0.5 (1)	0.3 (1)	0.4 (2)	0.0 (0)	0.4 (1)	0.2 (1)
Asbestosis	1.7 (5)	0.0 (0)	0.7 (5)	1.0 (2)	0.0 (0)	0.4 (2)	0.0 (0)	0.0 (0)	0.0 (0)
Pneumoconiosis	1.4 (4)	0.0 (0)	0.5 (4)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Tuberculosis	4.4 (13)	5.4 (24)	5.0 (37)	0.0 (0)	0.3 (1)	0.2 (1)	0.0 (0)	0.0 (0)	0.0 (0)

HRG	Baseline			18 Months			36 Months		
Disease	Male (57)	Female (94)	All (151)	Male (46)	Female (80)	All (126)	Male (39)	Female (68)	All (107)
COPD	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Asthma	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Bronchiectasis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.6 (1)	0.0 (0)	0.9 (1)
Pulmonary Fibrosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	1.5 (1)	0.9 (1)
Asbestosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Pneumoconiosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)
Tuberculosis	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)

Table 5.2: Summary statistics of lung function measures over time by sex, whole spirometry cohort and HRG

Whole Spirometry Group	**Male**		**Female**		**All**	
	Mean (SD)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**
FEV_1						
Baseline	1.80 (0.56)	293	1.22 (0.38)	444	1.45 (0.54)	737
18 Months	1.85 (0.52)	214	1.21 (0.37)	337	1.45 (0.53)	551
36 Months	1.80 (0.52)	157	1.20 (0.36)	255	1.43 (0.52)	412
FVC						
Baseline	2.72 (0.71)	293	1.76 (0.48)	444	2.14 (0.75)	737
18 Months	2.67 (0.66)	214	1.67 (0.46)	337	2.05 (0.73)	551
36 Months	2.62 (0.71)	157	1.65 (0.46)	255	2.02 (0.74)	412
PEF						
Baseline	461 (188)	293	287 (117)	444	356 (172)	737
18 Months	487 (178)	214	303 (115)	337	374 (168)	551
36 Months	488 (171)	152	309 (106)	238	379 (161)	390
FEV_1/FVC						
Baseline	0.67 (0.13)	293	0.70 (0.13)	444	0.69 (0.13)	737
18 Months	0.70 (0.11)	214	0.73 (0.12)	337	0.71 (0.12)	551
36 Months	0.69 (0.11)	157	0.73 (0.12)	255	0.72 (0.12)	412

HRG	**Male**		**Female**		**All**	
	Mean (SD)	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**
FEV_1						
Baseline	1.98 (0.63)	57	1.40 (0.35)	94	1.62 (0.55)	151
18 Months	2.06 (0.51)	46	1.35 (0.37)	80	1.61 (0.55)	126
36 Months	2.00 (0.53)	39	1.32 (0.38)	68	1.57 (0.55)	107
FVC						
Baseline	2.90 (0.72)	57	1.94 (0.44)	94	2.30 (0.73)	151
18 Months	2.86 (0.68)	46	1.78 (0.43)	80	2.17 (0.74)	126
36 Months	2.79 (0.72)	39	1.77 (0.46)	68	2.14 (0.75)	107
PEF						
Baseline	493 (204)	57	332 (129)	94	393 (179)	151
18 Months	507 (195)	46	337 (119)	80	399 (172)	126
36 Months	536 (174)	38	335 (104)	63	411 (166)	101
FEV_1/FVC						
Baseline	0.69 (0.15)	57	0.73 (0.12)	94	0.71 (0.13)	151
18 Months	0.73 (0.09)	46	0.76 (0.11)	80	0.74 (0.10)	126
36 Months	0.72 (0.07)	39	0.75 (0.11)	68	0.74 (0.10)	107

Table 5.3: Summary statistics of lung function measures over time by sex, survivor group

Survivor Group	Male		Female		All	
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
FEV_1						
Baseline	2.15 (0.57)	36	1.45 (0.31)	62	1.71 (0.54)	98
18 Months	2.12 (0.50)	36	1.40 (0.34)	62	1.66 (0.53)	98
36 Months	2.00 (0.55)	36	1.32 (0.39)	62	1.57 (0.56)	98
FVC						
Baseline	3.00 (0.73)	36	2.01 (0.44)	62	2.37 (0.73)	98
18 Months	2.92 (0.68)	36	1.86 (0.39)	62	2.25 (0.72)	98
36 Months	2.79 (0.75)	36	1.78 (0.47)	62	2.15 (0.76)	98
PEF						
Baseline	538 (182)	36	356 (119)	62	423 (169)	98
18 Months	539 (184)	36	350 (107)	62	419 (167)	98
36 Months	527 (179)	35	340 (106)	57	411 (165)	92
FEV_1/FVC						
Baseline	0.72 (0.10)	36	0.73 (0.12)	62	0.73 (0.11)	98
18 Months	0.73 (0.08)	36	0.75 (0.11)	62	0.74 (0.10)	98
36 Months	0.72 (0.07)	36	0.74 (0.12)	62	0.74 (0.10)	98

Table 5.4: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1 adjusted for all covariates by sex, whole spirometry cohort

Whole spirometry group	**Male**			**Female**		
FEV_1	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-127.79	48.72	0.009	-7.06	31.80	0.824
Age/10	30.18	11.25	0.007	2.17	7.33	0.767
$(Age/10)^2$	-1.75	0.65	0.007	-0.14	0.42	0.744
Smoking Status			0.013			0.011
Never	0 (Ref)			0 (Ref)		
Former	-0.11	0.06	0.075	-0.10	0.04	0.007
Current	-0.44	0.16	0.005	-0.15	0.07	0.031
Education			0.029			0.580
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.01	0.07	0.837	0.00	0.04	0.928
12+ Years	0.19	0.09	0.032	0.05	0.05	0.323
Occupational Exposure	-0.02	0.06	0.713	-0.02	0.04	0.662
Physical Activity			0.109			0.355
High	0 (Ref)			0 (Ref)		
Medium	-0.01	0.04	0.800	-0.03	0.03	0.296
Low	-0.04	0.03	0.135	0.00	0.02	0.924
BMI			0.567			0.173
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.05	0.08	0.530	-0.04	0.03	0.218
Overweight (25 - 30)	0.03	0.04	0.524	-0.03	0.03	0.247
Obese (30+)	-0.02	0.07	0.798	-0.08	0.04	0.055
Respiratory Disease	-0.11	0.06	0.053	-0.14	0.03	<0.001
Disease Count	0.02	0.02	0.434	0.00	0.01	0.787
Categorised MMSE			<0.001			0.001
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.02	0.04	0.559	-0.04	0.03	0.182
Moderate (18-21)	-0.25	0.08	0.001	-0.15	0.05	0.002
Severe (0-17)	-0.39	0.12	0.001	-0.24	0.07	<0.001
IL-6*	0.01	0.02	0.706	0.01	0.01	0.324
TNFα *	-0.03	0.01	0.059	0.00	0.01	0.878
CRP*	-0.05	0.01	<0.001	-0.01	0.01	0.145
Telomere Length*	-0.01	0.05	0.816	-0.02	0.03	0.477

* log-transformed

Table 5.5: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1 adjusted for all covariates by sex, whole spirometry cohort survivors

Whole Spirometry Cohort Survivors	**Male**			**Female**		
FEV1	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-119.32	49.47	0.016	-34.83	32.68	0.287
Age/10	28.45	11.41	0.013	8.50	7.53	0.259
$(Age/10)^2$	-1.66	0.66	0.011	-0.50	0.43	0.247
Smoking Status			0.148			0.498
Never	Ref			Ref		
Former	-0.05	0.09	0.555	-0.04	0.04	0.293
Current	-0.51	0.23	0.027	0.00	0.09	0.978
Education			0.033			0.965
0 - 9 Years	Ref			Ref		
10 - 11 Years	0.17	0.10	0.086	-0.01	0.05	0.805
12+ Years	0.14	0.11	0.203	-0.03	0.06	0.661
Occupational Exposure	-0.07	0.08	0.404	-0.07	0.05	0.207
Physical Activity			0.927			0.892
High	Ref			Ref		
Medium	0.05	0.05	0.275	0.01	0.03	0.771
Low	0.01	0.03	0.825	0.00	0.02	0.878
BMI			0.266			0.348
Normal (18.5 - 25)	Ref			Ref		
Underweight (<18.5)	0.03	0.09	0.732	-0.02	0.03	0.492
Overweight (25 - 30)	-0.05	0.04	0.295	-0.03	0.03	0.318
Obese and Morbidly Obese (30+)	-0.11	0.08	0.143	-0.06	0.05	0.205
Respiratory Disease	-0.06	0.07	0.370	-0.10	0.04	0.008
Disease Count	0.03	0.02	0.239	0.02	0.02	0.314
Categorised MMSE			<0.001			0.010
Normal (26-30)	Ref			Ref		
Mild (22-25)	-0.05	0.04	0.209	-0.03	0.03	0.277
Moderate (18-21)	-0.25	0.08	0.001	-0.14	0.05	0.008
Severe (0-17)	-0.40	0.14	0.005	-0.23	0.08	0.003
IL6 (log-transformed)	0.01	0.02	0.557	0.02	0.01	0.122
TNF Alpha (log-transformed)	-0.04	0.01	0.012	0.00	0.01	0.646
CRP (log-transformed)	-0.02	0.01	0.134	-0.02	0.01	0.047
Telomere Length (log-transformed)	-0.04	0.05	0.445	0.01	0.04	0.829

Table 5.6: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1 adjusted for all covariates by sex, HRG

HRG	**Male**			**Female**		
FEV_1	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-120.55	104.12	0.247	-7.86	53.66	0.884
Age/10	28.41	24.07	0.238	2.55	12.38	0.837
$(Age/10)^2$	-1.64	1.39	0.236	-0.17	0.71	0.808
Smoking Status			0.996			0.097
Never	0 (Ref)			0 (Ref)		
Former	0.00	0.15	0.996	-0.12	0.07	0.075
Current	-	-	-	-0.51	0.24	0.036
Education			0.011			0.546
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.42	0.17	0.013	-0.08	0.09	0.353
12+ Years	0.49	0.21	0.020	-0.08	0.10	0.416
Occupational Exposure	0.18	0.14	0.193	0.06	0.09	0.523
Physical Activity			0.398			<0.001
High	0 (Ref)			0 (Ref)		
Medium	-0.16	0.12	0.181	-0.21	0.05	<0.001
Low	-0.05	0.06	0.442	0.01	0.03	0.767
BMI			0.553			0.002
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.01	0.11	0.931	0.02	0.05	0.727
Overweight (25 - 30)	0.06	0.10	0.556	0.06	0.05	0.294
Obese (30+)	-0.49	0.37	0.186	-0.39	0.12	0.001
Respiratory Disease	0.21	0.25	0.401	-0.06	0.16	0.714
Disease Count	0.12	0.05	0.008	0.07	0.03	0.012
Categorised MMSE			0.088			0.125
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.11	0.07	0.146	-0.09	0.05	0.067
Moderate (18-21)	-0.52	0.29	0.072	-0.01	0.09	0.873
Severe (0-17)	-0.84	0.37	0.023	0.15	0.14	0.268
IL-6*	-0.01	0.03	0.783	-0.01	0.02	0.682
TNFα *	-0.05	0.03	0.054	0.02	0.02	0.231
CRP*	-0.04	0.03	0.147	-0.02	0.02	0.154
Telomere Length*	-0.03	0.11	0.792	0.01	0.06	0.869

* log-transformed

Table 5.7: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1 adjusted for all covariates by sex, survivor group

Survivor Group	**Male**			**Female**		
FEV_1	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-64.93	92.95	0.485	-4.11	56.81	0.942
Age/10	15.98	21.48	0.457	1.81	13.11	0.890
$(Age/10)^2$	-0.94	1.24	0.448	-0.14	0.76	0.857
Smoking Status			0.576			0.371
Never	0 (Ref)			0 (Ref)		
Former	-0.12	0.21	0.576	-0.11	0.09	0.190
Current	-	-	-	-0.24	0.34	0.475
Education			0.081			0.960
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.50	0.22	0.021	-0.06	0.11	0.586
12+ Years	0.11	0.28	0.699	-0.02	0.11	0.833
Occupational Exposure	0.16	0.16	0.342	0.02	0.11	0.873
Physical Activity			0.910			0.002
High	0 (Ref)			0 (Ref)		
Medium	-0.05	0.11	0.633	-0.16	0.06	0.003
Low	-0.04	0.05	0.482	0.02	0.03	0.527
BMI			0.916			0.048
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	0.04	0.11	0.731	0.02	0.05	0.668
Overweight (25 - 30)	-0.02	0.10	0.821	0.06	0.06	0.381
Obese (30+)	-	-	-	-0.39	0.17	0.021
Disease Count	0.05	0.06	0.400	0.08	0.03	0.013
Categorised MMSE			0.043			0.142
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.13	0.06	0.044	-0.10	0.05	0.070
Moderate (18-21)	-0.56	0.25	0.025	-0.02	0.10	0.803
Severe (0-17)	-	-	-	0.14	0.14	0.306
IL-6*	0.01	0.03	0.723	-0.01	0.02	0.715
TNFα *	-0.05	0.02	0.022	0.02	0.02	0.413
CRP*	0.00	0.03	0.893	-0.03	0.02	0.146
Telomere Length*	-0.11	0.09	0.229	-0.01	0.06	0.935

* log-transformed

Table 5.8: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FVC adjusted for all covariates by sex, whole spirometry cohort

Whole spirometry group	**Male**			**Female**		
FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-22.73	77.04	0.768	19.32	44.78	0.666
Age/10	6.92	17.79	0.697	-3.38	10.33	0.744
$(Age/10)^2$	-0.44	1.02	0.670	0.16	0.59	0.788
Smoking Status			0.695			0.277
Never	0 (Ref)			0 (Ref)		
Former	0.01	0.08	0.952	0.00	0.04	0.985
Current	-0.17	0.21	0.424	-0.13	0.09	0.124
Education			0.203			0.911
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	-0.03	0.09	0.781	0.02	0.05	0.669
12+ Years	0.19	0.12	0.106	0.00	0.07	0.962
Occupational Exposure	-0.04	0.08	0.647	-0.02	0.05	0.764
Physical Activity			0.258			0.362
High	0 (Ref)			0 (Ref)		
Medium	-0.07	0.07	0.311	-0.03	0.04	0.384
Low	-0.08	0.05	0.092	0.01	0.03	0.746
BMI			0.713			0.016
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.08	0.12	0.506	-0.07	0.04	0.119
Overweight (25 - 30)	-0.02	0.06	0.731	-0.09	0.03	0.009
Obese (30+)	-0.10	0.10	0.319	-0.14	0.06	0.017
Respiratory Disease	-0.01	0.08	0.876	-0.18	0.04	<0.001
Disease Count	-0.04	0.03	0.152	-0.01	0.02	0.672
Categorised MMSE			0.019			0.121
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.04	0.06	0.444	-0.03	0.04	0.438
Moderate (18-21)	-0.31	0.12	0.008	-0.11	0.06	0.085
Severe (0-17)	-0.37	0.17	0.032	-0.20	0.09	0.030
IL-6*	0.01	0.03	0.748	0.01	0.02	0.467
TNFα *	-0.04	0.02	0.069	0.01	0.01	0.306
CRP*	-0.05	0.02	0.008	-0.03	0.01	0.025
Telomere Length*	-0.17	0.08	0.036	-0.04	0.05	0.348

* log-transformed

Table 5.9: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FVC adjusted for all covariates by sex, HRG

HRG	**Male**			**Female**		
FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-25.72	162.50	0.874	65.35	84.59	0.440
Age/10	7.83	37.56	0.835	-13.72	19.52	0.482
$(Age/10)^2$	-0.49	2.16	0.823	0.74	1.12	0.510
Smoking Status			0.889			0.746
Never	0 (Ref)			0 (Ref)		
Former	0.03	0.19	0.889	-0.01	0.08	0.938
Current	-	-	-	-0.23	0.30	0.443
Education			0.072			0.466
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.46	0.22	0.036	-0.11	0.10	0.279
12+ Years	0.40	0.27	0.139	-0.11	0.12	0.390
Occupational Exposure	0.13	0.17	0.445	0.08	0.11	0.435
Physical Activity			0.479			0.002
High	0 (Ref)			0 (Ref)		
Medium	-0.12	0.18	0.486	-0.28	0.08	<0.001
Low	-0.11	0.10	0.236	-0.03	0.05	0.494
BMI			0.799			0.035
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	0.11	0.17	0.514	0.08	0.08	0.280
Overweight (25 - 30)	0.00	0.14	0.984	-0.10	0.08	0.207
Obese (30+)	-0.36	0.47	0.444	-0.46	0.17	0.007
Respiratory Disease	0.69	0.39	0.078	-0.28	0.26	0.274
Disease Count	-0.04	0.06	0.538	0.07	0.04	0.067
Categorised MMSE			0.089			0.791
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.17	0.11	0.117	0.03	0.07	0.666
Moderate (18-21)	-0.79	0.45	0.077	0.14	0.14	0.304
Severe (0-17)	-0.87	0.49	0.079	0.09	0.20	0.673
IL-6*	-0.05	0.05	0.343	0.01	0.03	0.836
TNFα *	-0.03	0.04	0.528	0.04	0.03	0.196
CRP*	-0.03	0.04	0.436	-0.03	0.02	0.166
Telomere Length*	-0.27	0.16	0.098	-0.06	0.09	0.480

* log-transformed

Table 5.10: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FVC adjusted for all covariates by sex, survivor group

Survivor Group	**Male**			**Female**		
FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-31.27	167.27	0.852	68.26	91.12	0.454
Age/10	9.15	38.65	0.813	-14.34	21.02	0.495
$(Age/10)^2$	-0.57	2.23	0.800	0.77	1.21	0.522
Smoking Status			0.545			0.968
Never	0 (Ref)			0 (Ref)		
Former	-0.16	0.27	0.545	0.00	0.10	0.976
Current	-	-	-	-0.01	0.42	0.976
Education			0.058			0.910
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.69	0.28	0.013	-0.06	0.13	0.674
12+ Years	0.05	0.36	0.898	-0.03	0.14	0.840
Occupational Exposure	0.11	0.21	0.584	0.03	0.13	0.795
Physical Activity			0.639			0.005
High	0 (Ref)			0 (Ref)		
Medium	-0.01	0.19	0.952	-0.25	0.09	0.005
Low	-0.09	0.10	0.368	-0.03	0.05	0.542
BMI			0.857			0.478
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	0.10	0.20	0.621	0.09	0.08	0.268
Overweight (25 - 30)	-0.03	0.16	0.831	-0.02	0.09	0.823
Obese (30+)	-	-	-	-0.11	0.25	0.666
Disease Count	-0.04	0.09	0.667	0.07	0.04	0.093
Categorised MMSE			0.113			0.609
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.17	0.11	0.126	0.04	0.08	0.632
Moderate (18-21)	-0.85	0.44	0.053	0.15	0.15	0.313
Severe (0-17)	-	-	-	0.10	0.22	0.647
IL-6*	-0.03	0.05	0.492	-0.01	0.04	0.749
TNFα *	-0.04	0.04	0.370	0.03	0.03	0.364
CRP*	-0.01	0.05	0.898	-0.04	0.03	0.127
Telomere Length*	-0.25	0.16	0.126	-0.05	0.10	0.631

* log-transformed

Table 5.11: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of PEF adjusted for all covariates by sex, whole spirometry cohort

Whole spirometry group	**Male**			**Female**		
PEF	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-76.86	37.57	0.041	-38.37	22.32	0.086
Age/10	17.83	8.67	0.040	9.01	5.15	0.080
$(Age/10)^2$	-1.02	0.50	0.041	-0.52	0.30	0.082
Smoking Status			0.002			0.004
Never	0 (Ref)			0 (Ref)		
Former	-0.04	0.03	0.257	-0.04	0.02	0.031
Current	-0.25	0.08	0.002	-0.10	0.03	0.002
Education			0.090			0.070
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.04	0.04	0.285	0.02	0.02	0.412
12+ Years	0.07	0.05	0.118	0.06	0.03	0.022
Occupational Exposure	0.00	0.03	0.900	-0.01	0.02	0.776
Physical Activity			<0.001			0.049
High	0 (Ref)			0 (Ref)		
Medium	-0.10	0.03	0.001	-0.04	0.02	0.018
Low	-0.06	0.02	0.004	-0.01	0.01	0.363
BMI			0.015			0.023
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.12	0.05	0.020	-0.06	0.02	0.002
Overweight (25 - 30)	0.04	0.03	0.137	-0.01	0.02	0.431
Obese (30+)	0.04	0.05	0.349	-0.01	0.03	0.644
Respiratory Disease	0.00	0.03	0.883	-0.07	0.02	<0.001
Disease Count	0.01	0.01	0.423	0.00	0.01	0.653
Categorised MMSE			<0.001			0.007
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.05	0.03	0.064	-0.02	0.02	0.408
Moderate (18-21)	-0.20	0.05	<0.001	-0.08	0.03	0.005
Severe (0-17)	-0.26	0.08	0.002	-0.12	0.04	0.006
IL-6*	0.00	0.01	0.902	0.00	0.01	0.897
TNFα *	-0.01	0.01	0.489	-0.01	0.01	0.421
CRP*	-0.03	0.01	<0.001	-0.01	0.01	0.189
Telomere Length*	0.01	0.04	0.888	-0.05	0.02	0.029

* log-transformed

Table 5.12: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of PEF adjusted for all covariates by sex, HRG

HRG	**Male**			**Female**		
PEF	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	54.55	85.80	0.525	21.38	43.26	0.621
Age/10	-12.46	19.83	0.530	-4.58	9.98	0.646
$(Age/10)^2$	0.73	1.14	0.525	0.26	0.57	0.654
Smoking Status			0.723			0.122
Never	0 (Ref)			0 (Ref)		
Former	0.03	0.08	0.721	-0.03	0.04	0.487
Current	-	-	-	-0.21	0.14	0.142
Education			0.774			0.465
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.07	0.09	0.425	-0.03	0.05	0.570
12+ Years	0.10	0.11	0.390	0.02	0.05	0.761
Occupational Exposure	-0.02	0.07	0.786	0.04	0.05	0.418
Physical Activity			0.056			<0.001
High	0 (Ref)			0 (Ref)		
Medium	-0.16	0.09	0.062	-0.14	0.04	0.001
Low	-0.10	0.05	0.035	-0.01	0.02	0.564
BMI			0.328			0.087
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.07	0.08	0.414	-0.06	0.04	0.106
Overweight (25 - 30)	0.13	0.07	0.048	0.06	0.04	0.089
Obese (30+)	0.06	0.20	0.747	-0.15	0.08	0.064
Respiratory Disease	0.17	0.21	0.415	-0.06	0.13	0.654
Disease Count	0.03	0.03	0.232	0.03	0.02	0.095
Categorised MMSE			0.179			0.817
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.08	0.06	0.148	0.02	0.04	0.575
Moderate (18-21)	-0.05	0.23	0.841	0.02	0.07	0.734
Severe (0-17)	-0.40	0.22	0.067	0.05	0.13	0.685
IL-6*	-0.03	0.03	0.206	-0.04	0.02	0.010
TNFα *	-0.02	0.02	0.350	0.03	0.02	0.057
CRP*	-0.04	0.02	0.050	-0.02	0.01	0.184
Telomere Length*	0.02	0.09	0.850	-0.03	0.04	0.494

* log-transformed

Table 5.13: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of PEF adjusted for all covariates by sex, survivor group

Survivor Group	**Male**			**Female**		
PEF	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	25.87	95.43	0.786	21.23	45.30	0.639
Age/10	-5.70	22.05	0.796	-4.50	10.45	0.666
$(Age/10)^2$	0.33	1.27	0.794	0.25	0.60	0.678
Smoking Status			0.272			0.510
Never	0 (Ref)			0 (Ref)		
Former	-0.11	0.10	0.272	-0.02	0.04	0.709
Current	-	-	-	-0.19	0.16	0.251
Education			0.172			0.422
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.15	0.11	0.162	-0.06	0.05	0.283
12+ Years	-0.16	0.14	0.264	0.03	0.05	0.617
Occupational Exposure	-0.03	0.08	0.697	0.02	0.05	0.623
Physical Activity			0.178			0.019
High	0 (Ref)			0 (Ref)		
Medium	-0.05	0.10	0.621	-0.12	0.04	0.006
Low	-0.10	0.05	0.058	-0.01	0.02	0.736
BMI			0.771			0.002
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.01	0.10	0.960	-0.06	0.04	0.143
Overweight (25 - 30)	0.06	0.08	0.467	0.07	0.04	0.088
Obese (30+)	-	-	-	-0.29	0.11	0.009
Disease Count	0.05	0.04	0.231	0.03	0.02	0.064
Categorised MMSE			0.743			0.872
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	-0.07	0.06	0.268	0.02	0.04	0.626
Moderate (18-21)	-0.04	0.24	0.872	0.06	0.08	0.459
Severe (0-17)	-	-	-	0.10	0.14	0.499
IL-6*	-0.03	0.03	0.238	-0.04	0.02	0.016
TNFα *	-0.02	0.02	0.421	0.03	0.02	0.058
CRP*	-0.05	0.02	0.045	-0.01	0.01	0.425
Telomere Length*	0.00	0.09	0.981	-0.03	0.05	0.594

* log-transformed

Table 5.14: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1/FVC adjusted for all covariates by sex, whole spirometry cohort

Whole spirometry group	**Male**			**Female**		
FEV_1/FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-41.67	15.53	0.007	0.13	15.39	0.993
Age/10	9.65	3.59	0.007	0.01	3.55	0.998
$(Age/10)^2$	-0.55	0.21	0.008	0.01	0.20	0.972
Smoking Status			0.001			<0.001
Never	0 (Ref)			0 (Ref)		
Former	-0.04	0.01	0.008	-0.05	0.01	<0.001
Current	-0.12	0.04	0.002	-0.04	0.02	0.096
Education			0.887			0.097
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.01	0.02	0.633	-0.01	0.01	0.250
12+ Years	0.00	0.02	0.811	0.03	0.02	0.133
Occupational Exposure	0.00	0.01	0.858	0.00	0.01	0.728
Physical Activity			0.373			0.498
High	0 (Ref)			0 (Ref)		
Medium	0.01	0.01	0.624	-0.01	0.01	0.294
Low	-0.01	0.01	0.368	-0.01	0.01	0.282
BMI			0.086			0.048
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.02	0.02	0.454	-0.02	0.01	0.232
Overweight (25 - 30)	0.02	0.01	0.066	0.02	0.01	0.028
Obese (30+)	0.04	0.02	0.035	0.02	0.02	0.145
Respiratory Disease	-0.05	0.01	<0.001	-0.02	0.01	0.045
Disease Count	0.01	0.01	0.008	0.00	0.00	0.507
Categorised MMSE			0.205			0.104
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	0.01	0.01	0.319	-0.01	0.01	0.253
Moderate (18-21)	-0.01	0.02	0.556	-0.04	0.02	0.054
Severe (0-17)	-0.05	0.03	0.092	-0.05	0.03	0.056
IL-6*	0.00	0.01	0.950	0.00	0.01	0.787
TNFα *	0.00	0.00	0.892	0.00	0.00	0.933
CRP*	-0.01	0.00	0.051	0.00	0.00	0.860
Telomere Length*	0.02	0.02	0.146	0.00	0.02	0.921

* log-transformed

Table 5.15: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1/FVC adjusted for all covariates by sex, HRG

HRG	**Male**			**Female**		
FEV_1/FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-40.80	40.67	0.316	-17.59	26.06	0.500
Age/10	9.41	9.39	0.316	4.07	6.01	0.499
$(Age/10)^2$	-0.54	0.54	0.320	-0.23	0.35	0.510
Smoking Status			0.382			0.001
Never	0 (Ref)			0 (Ref)		
Former	-0.02	0.03	0.378	-0.07	0.02	0.002
Current	-	-	-	-0.23	0.08	0.003
Education			0.616			0.868
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	0.02	0.03	0.537	-0.01	0.03	0.634
12+ Years	0.03	0.04	0.372	-0.01	0.03	0.723
Occupational Exposure	0.01	0.02	0.578	0.00	0.03	0.963
Physical Activity			0.132			0.216
High	0 (Ref)			0 (Ref)		
Medium	-0.06	0.04	0.113	-0.03	0.02	0.243
Low	0.02	0.02	0.482	0.01	0.01	0.459
BMI			0.065			<0.001
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.02	0.03	0.477	-0.05	0.02	0.023
Overweight (25 - 30)	0.06	0.02	0.016	0.07	0.02	0.001
Obese (30+)	-0.05	0.06	0.430	-0.02	0.05	0.708
Respiratory Disease	-0.09	0.10	0.371	0.09	0.08	0.264
Disease Count	0.03	0.01	0.003	0.00	0.01	0.744
Categorised MMSE			0.259			0.003
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	0.02	0.02	0.329	-0.06	0.02	0.003
Moderate (18-21)	0.08	0.10	0.448	-0.06	0.04	0.153
Severe (0-17)	-0.12	0.08	0.159	0.10	0.06	0.093
IL-6*	0.00	0.01	0.711	0.00	0.01	0.685
TNFα *	0.00	0.01	0.942	0.00	0.01	0.729
CRP*	-0.01	0.01	0.330	0.00	0.01	0.569
Telomere Length*	0.04	0.04	0.279	0.04	0.03	0.171

* log-transformed

Table 5.16: Association of socio-demographic, socio-economic, health and biomarkers on trajectories of FEV_1/FVC adjusted for all covariates by sex, survivor group

Survivor Group	**Male**			**Female**		
FEV_1/FVC	**Coeff**	**SE**	**p-value**	**Coeff**	**SE**	**p-value**
Intercept	-26.23	35.07	0.455	-16.55	24.75	0.504
Age/10	6.09	8.10	0.452	3.86	5.71	0.499
$(Age/10)^2$	-0.35	0.47	0.456	-0.22	0.33	0.507
Smoking Status			0.704			0.026
Never	0 (Ref)			0 (Ref)		
Former	-0.01	0.02	0.704	-0.07	0.03	0.009
Current	-	-	-	-0.13	0.10	0.188
Education			0.613			0.883
0 - 9 Years	0 (Ref)			0 (Ref)		
10 - 11 Years	-0.02	0.03	0.340	-0.02	0.03	0.618
12+ Years	0.01	0.03	0.858	-0.01	0.03	0.867
Occupational Exposure	0.01	0.02	0.648	0.00	0.03	0.938
Physical Activity			0.311			0.316
High	0 (Ref)			0 (Ref)		
Medium	-0.03	0.04	0.387	0.00	0.02	0.956
Low	0.02	0.02	0.348	0.02	0.01	0.172
BMI			0.041			<0.001
Normal (18.5 - 25)	0 (Ref)			0 (Ref)		
Underweight (<18.5)	-0.03	0.03	0.373	-0.05	0.02	0.024
Overweight (25 - 30)	0.05	0.02	0.017	0.06	0.02	0.020
Obese (30+)	-	-	-	-0.16	0.07	0.016
Disease Count	0.00	0.01	0.919	0.00	0.01	0.775
Categorised MMSE			0.979			<0.001
Normal (26-30)	0 (Ref)			0 (Ref)		
Mild (22-25)	0.00	0.02	0.951	-0.07	0.02	0.001
Moderate (18-21)	0.01	0.08	0.857	-0.06	0.04	0.154
Severe (0-17)	-	-	-	0.11	0.06	0.048
IL-6*	0.01	0.01	0.588	0.00	0.01	0.828
TNFα *	0.00	0.01	0.921	0.00	0.01	0.873
CRP*	0.00	0.01	0.849	0.00	0.01	0.788
Telomere Length*	0.03	0.03	0.378	0.03	0.03	0.201

* log-transformed

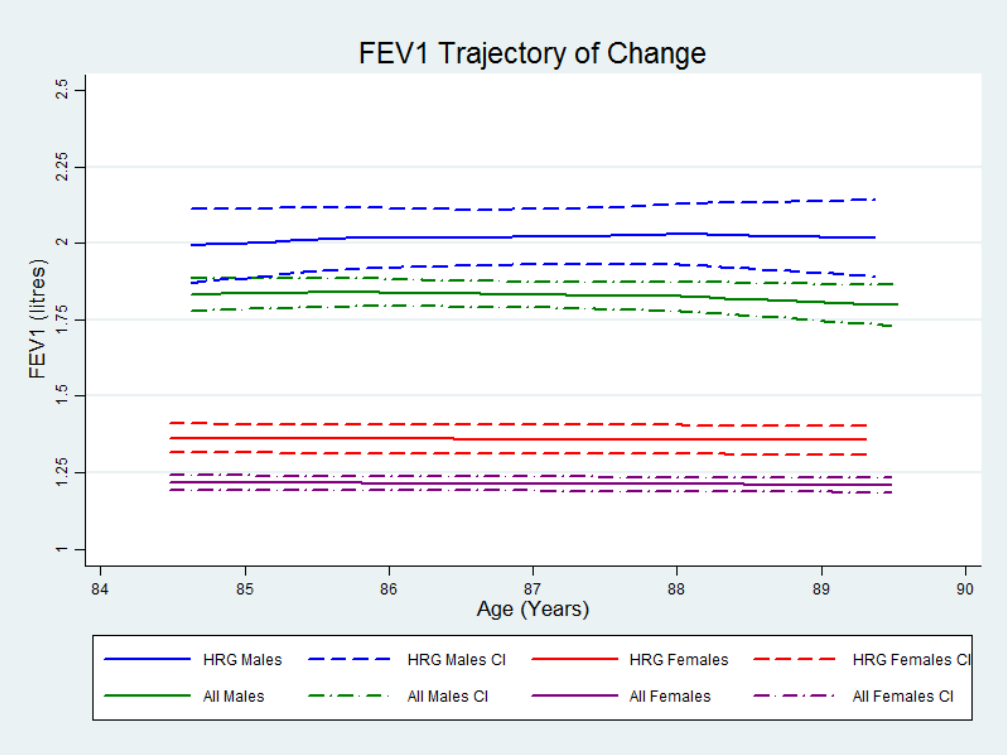


Figure 5.1: FEV_1 trajectory of change adjusted for smoking status, education, occupational exposure, respiratory disease, disease count, categorised MMSE, IL-6, TNFα, CRP and Telomere length

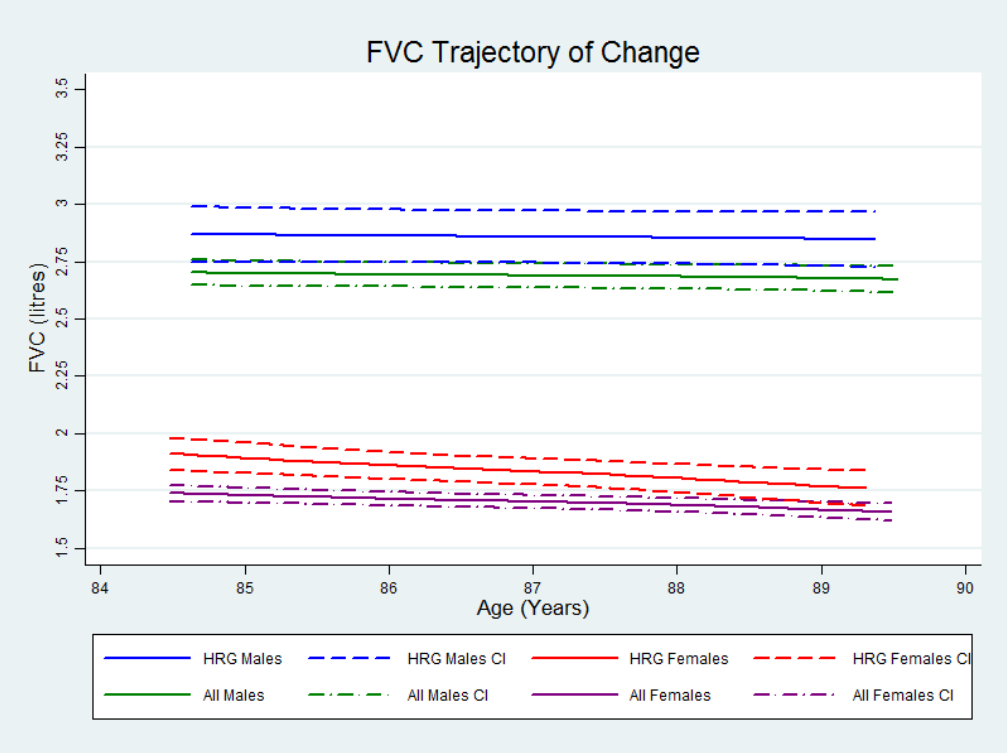


Figure 5.2: FVC trajectory of change adjusted for smoking status, education, occupational exposure, respiratory disease, disease count, categorised MMSE, IL-6, TNFα, CRP and Telomere length.

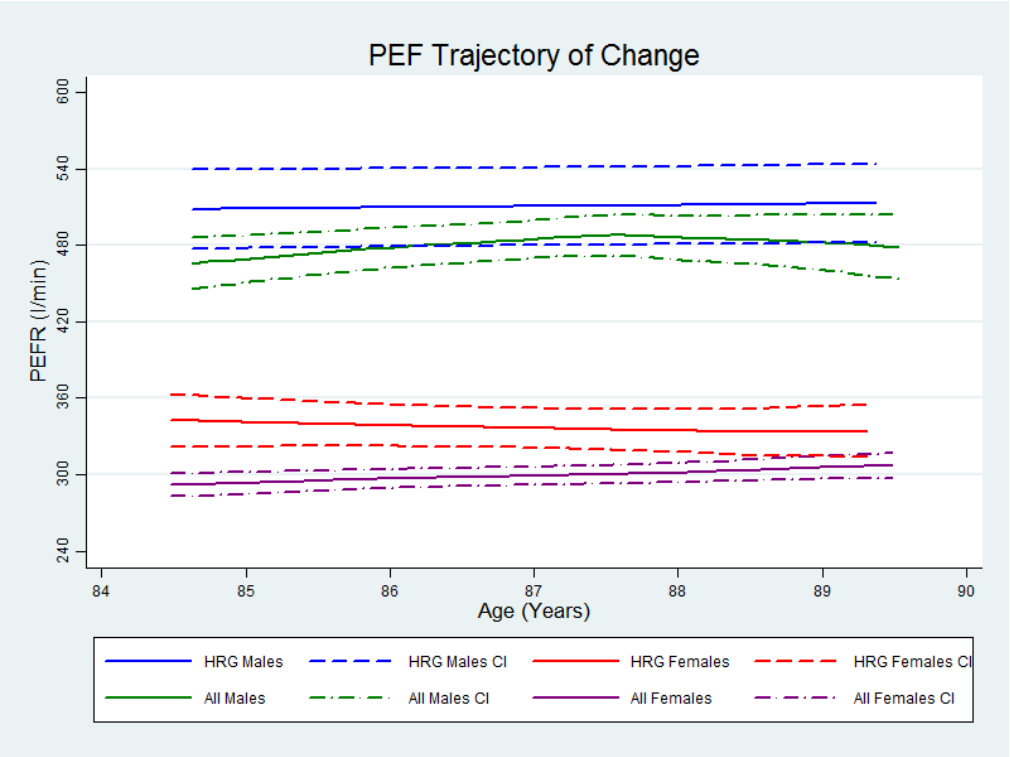


Figure 5.3: PEF trajectory of change adjusted for smoking status, education, occupational exposure, respiratory disease, disease count, categorised MMSE, IL-6, TNFα, CRP and Telomere length.

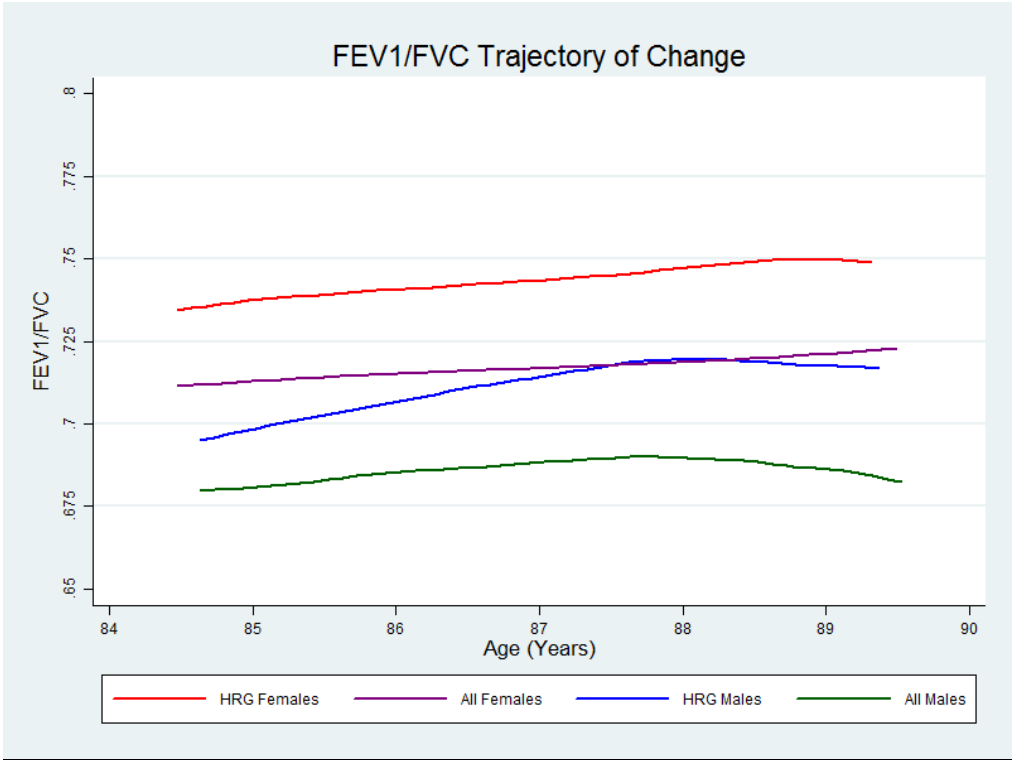


Figure 5.4: FEV_1/FVC trajectory of change adjusted for smoking status, education, occupational exposure, respiratory disease, disease count, categorised MMSE, IL-6, TNFα, CRP and Telomere length.

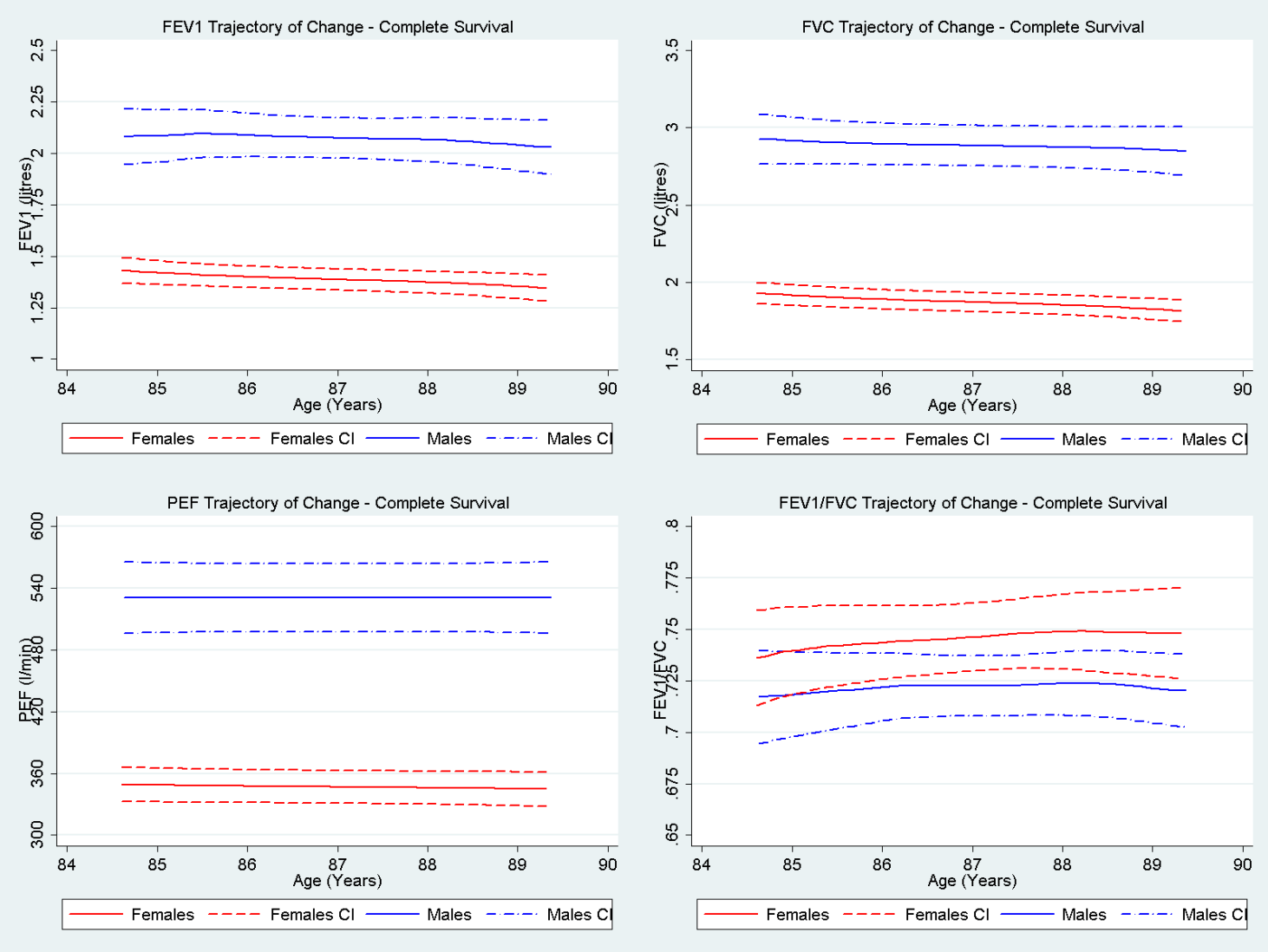


Figure 5.5: Lung function measurements trajectory of change by sex, survivor group

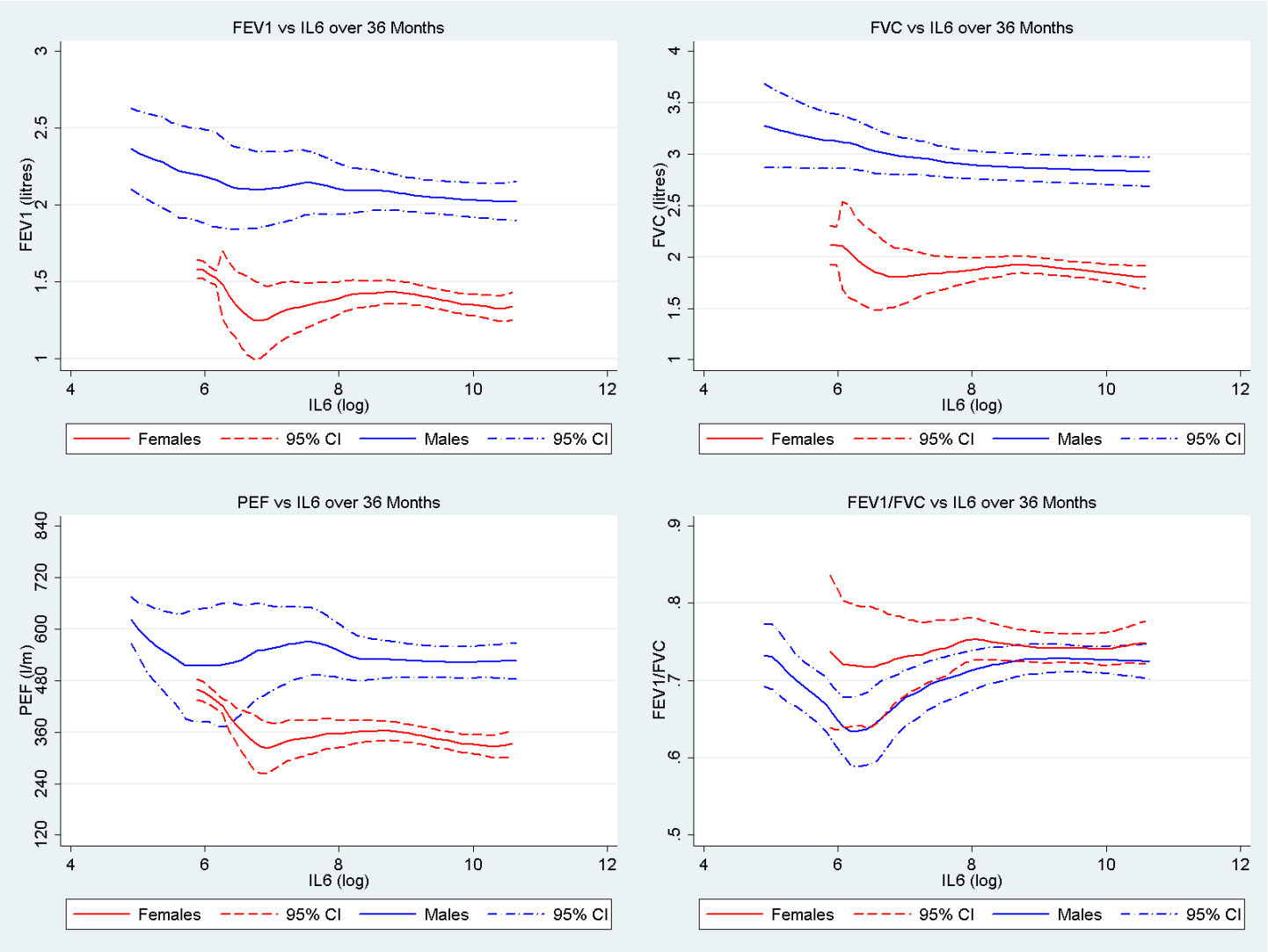


Figure 5.6: Graphs showing effect of IL-6 on lung function measures over time by sex, survivor group

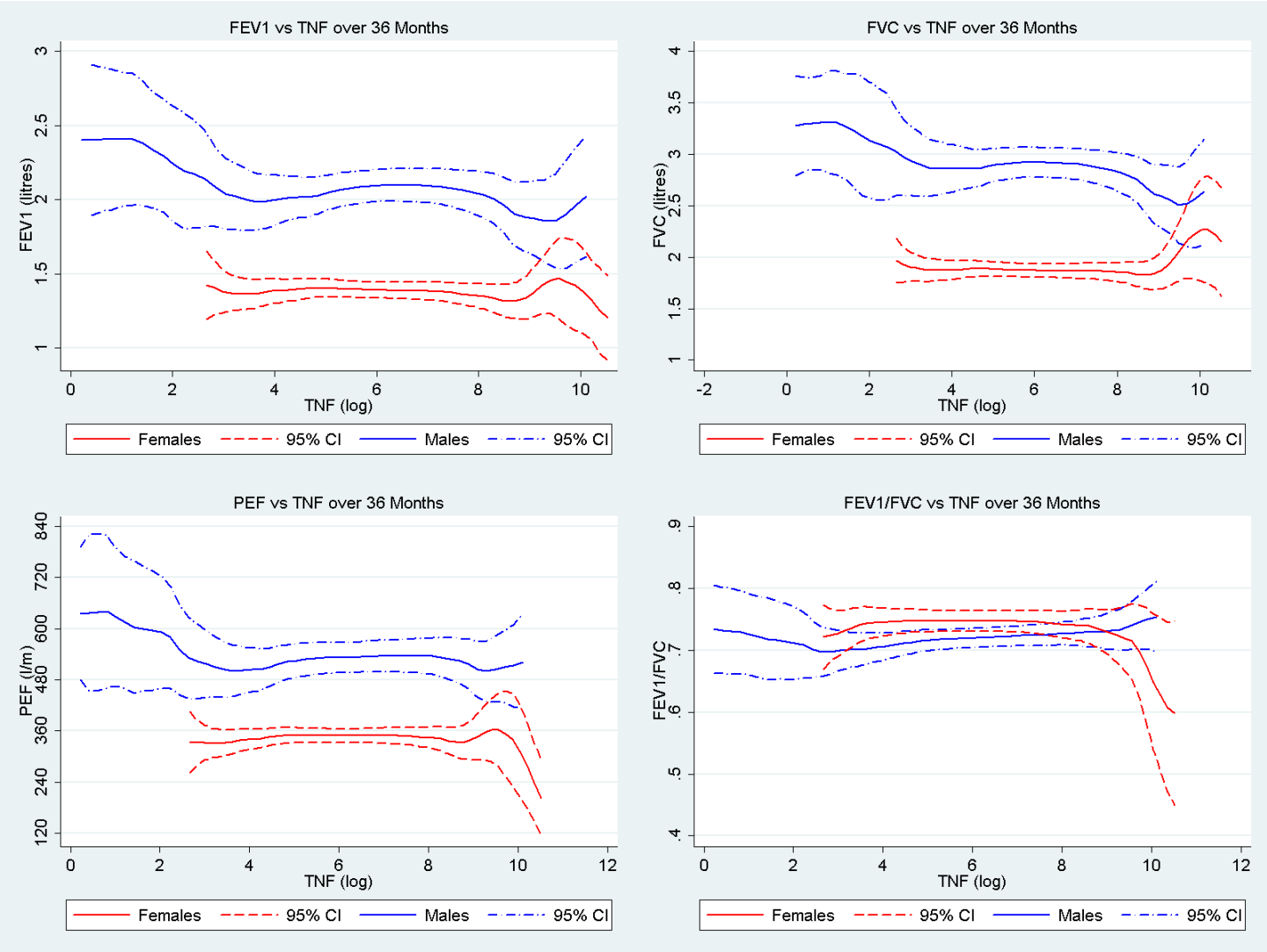


Figure 5.7: Graphs showing effect of TNF on lung function measures over time by sex, survivor group

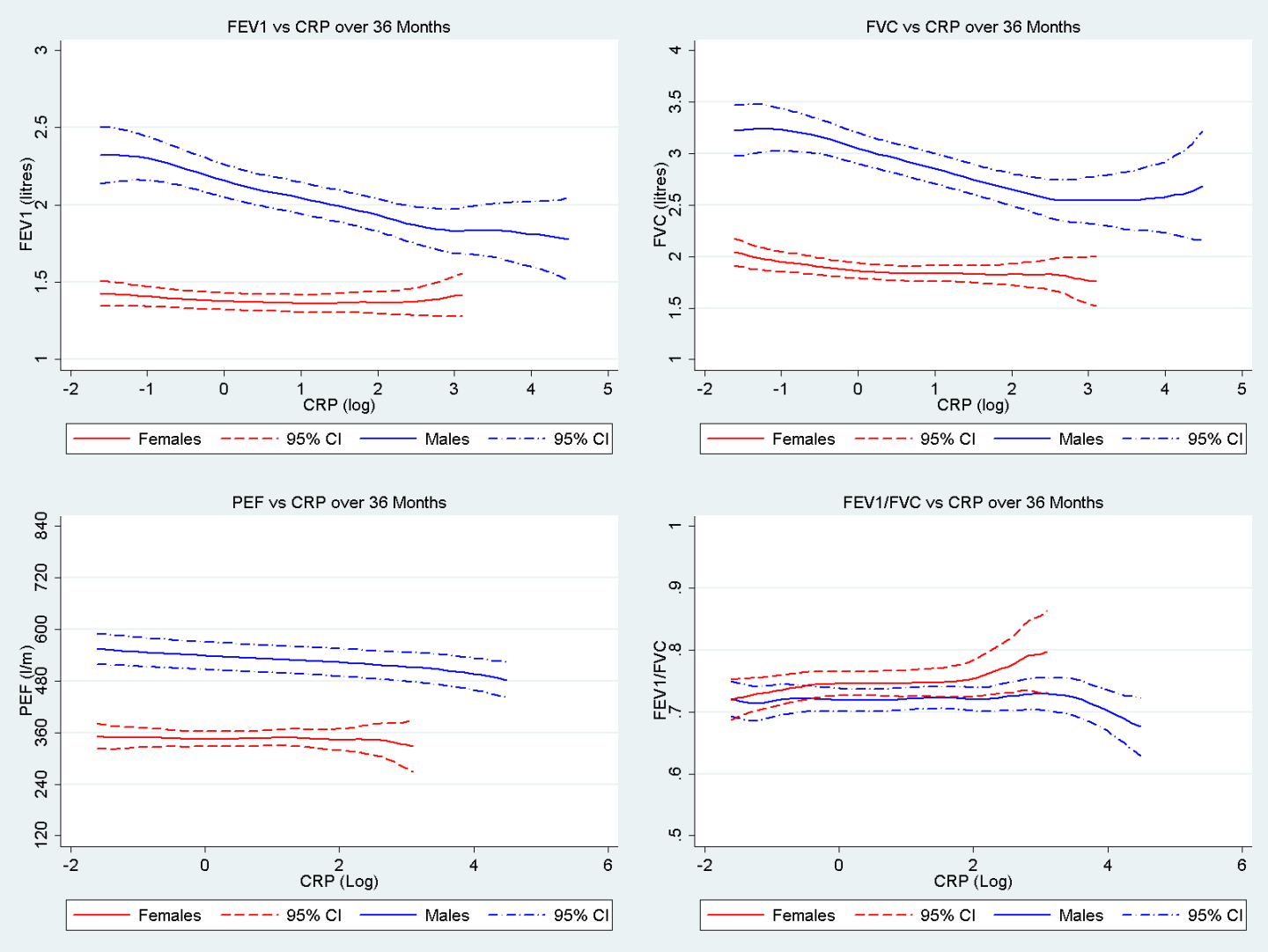


Figure 5.8: Graphs showing effect of CRP on lung function measures over time by sex, survivor group

Chapter 6. Relationship between lung function and disability

The previous chapter investigated how lung function, its potential confounders and possible determinants changed between ages 85 and 88 years in the N85+ study. This chapter will investigate the pathways between lung function and disability exploring potential mediators of the relationship. Disability is an important outcome for the very old, being a predictor of mortality as well as the need for social care. However, this chapter will not prejudge the causal link between lung function and disability but will use path models, a variant of structural equation modelling (SEM), to ascertain the direction of the relationship.

6.1 Aims of the chapter

Specifically this chapter will:

1. Describe the disability measures used:
    a. Basic Activities of daily living (BADLs)
    b. Instrumental activities of daily living (IADLs)
    c. Mobility score
2. Investigate the relationship between FEV_1 and disability through SEM by:
    a. Exploring the pathways between FEV_1 and each separate disability measures
    b. Exploring the effect of confounders whose effects may be mediated through this pathway

6.2 Background

Disability is an important indicator for independent living and a predictor of admissions to care home, hospitalisation and other health care services (Kingston *et al.*, 2017). Disability is usually measured by BADLs (such as feeding oneself, washing face and hands and washing all over) and IADLs (e.g. laundry, light and heavy housework (Table 6.1). These have been shown by both cross-sectional and longitudinal studies to be lost in a particular order, broadly with IADLs first followed by BADLs (Dunlop *et al.*, 1997; Ferrucci *et al.*, 1998; Kingston *et al.*, 2012). If both are available, as in the N85+ study, a severity scale for disability can be determined.

The relationship between disability and cognitive impairment has been extensively researched in older people with studies finding a strong association between increased disability and decline in cognitive function including studies of the UK populations (N85+ cohort and CFAS) (Kingston *et al.*, 2012) (Spiers *et al.*, 2005; Seidel *et al.*, 2009).

There have been few studies of the relationship between lung function and disability but all have hypothesised that lung function affects functional ability (Lahaije *et al.*, 2010; Kingston *et al.*, 2012; van Helvoort *et al.*, 2016; Hegendorfer *et al.*, 2017b). A case-control study of patients with early-stage COPD and its constraints on ADLs, found that patients "had greater ventilatory inefficiency and higher ventilatory requirements during ADL" and increased Dyspnoea scores (van Helvoort *et al.*, 2016).

In a longitudinal study of the very old, participants with excessive deterioration in their lung function ($FEV_1/height^3$) had an increased risk (odds ratio: 2.02, 95% CI: 1.10 – 3.68) of decline in functional ability (ADL score) (Hegendorfer *et al.*, 2017a). A further study used gait speed rather than self-reported ADL and found that increased pulmonary function predicted lower risk of disability, though the ability to predict disability was lost after adjusting for physical activity, BMI, vascular risk factors and diseases (Buchman *et al.*, 2009).

More studies have explored the link between lung function and cognitive function or dementia, predominantly, though not exclusively assuming lung function impacts cognitive function. A cross-sectional study found that those in the lowest group of lung function performance had more dementia compared to those with best lung function (Schaub *et al.*, 2000). Better respiratory function has been found to reduce the risk of developing Alzheimer's disease (Guo *et al.*, 2007a), whilst a longitudinal study of African American adults showed that lung function was a significant predictor of cognitive status in older adults but not the younger population (Allaire *et al.*, 2007). Other studies have reported similar findings (Weuve *et al.*, 2011; Vidal *et al.*, 2013).

Only one previous study has explored the direction of the causal link between lung function (FEV_1 and FVC) and cognitive impairment (verbal ability; spatial ability; processing speed; and memory) using SEM (Emery *et al.*, 2012), and found that decreases in lung function resulted in decline in cognitive functions including spatial performance, processing speeds and verbal ability (Emery *et al.*, 2012).

Despite previous studies, there is a lack of research investigating the direction of the relationship between lung function and disability in the very old. Moreover, given the increased risk of cognitive impairment in this age group and the known relationship between cognitive impairment and both lung function and disability, there is merit in investigating the role of cognitive impairment in modifying the lung function/disability relationship. To address this I shall use path models (a variant of SEM) to analyse the causal pathways between lung function,

cognitive function and disability to discern the direction of the causal pathway and explore possible mediators.

6.3 Analytical methods

6.3.1 Measures of functional status

In the N85+ study, a 17 item ADL questionnaire was adapted based on the Groningen Activity Restriction Scale to calculate the participants' disability, scoring 0 for performing each item without disability and 1 if there was any difficulty, with a maximum score of 15 (complete dependency) (Kempen et al., 1996) (Jagger et al., 2011). For the purposes of this thesis, three disability scores were derived from the 17 functional ability items: 8 items of basic activities of daily living (BADL), 6 instrumental activities of daily living (IADL) and 3 mobility items (Table 6.1) (Jagger et al., 2011). All three measures of functional status were calculated for baseline, 18 months, 36 months and 60 months follow-up.

6.3.2 Statistical analysis

Univariate regression models were fitted separately with each of the 3 measures of disability and FEV_1 as dependent variables against these potential variables to explore quantitative associations. Models were fitted for baseline values and all 3 follow-up periods (except 60 months for FEV_1). Variables which could be part of the causal pathway were identified from the literature search,,results of analyses from previous chapters and the univariate models in investigating associations between different time points. Variables included: sex; smoking status (categorised as never, former and current smokers); years of education (categorised as 0-9 years, 10 – 11 years, 12+ years); BMI (categorised as underweight <18.5, normal 18.5 – 25, overweight 25 – 30, obese and morbidly obese 30+); physical activity (categorised as low, medium, high); occupational exposure; respiratory conditions; chronic disease count; and cognitive impairment.

Path analysis, a version of SEM, is often used in the analysis of causal pathways where it explores the relationship between variables without imposing a direction for the relationship in the presence of intervening (mediating or confounding) variables. This analysis would therefore allow a life course epidemiological approach in investigating whether lung function had an effect on disability or vice versa answering the main research question of this thesis.

For path analysis, all possible variables were included in the model for all 4 time points, linking the factors to both the disability and FEV_1 variables. The disability measure and FEV_1 were also linked to each other at the subsequent time point (e.g. baseline FEV_1 linked to 18 months BADL) and vice versa. Once the path diagram was constructed, the models were executed. Those factors which were no longer statistically significant were eliminated from the models in a stepwise manner to obtain the final model and odds ratios (OR) obtained. Three separate path models (diagrams) were constructed, one for each disability measure: BADL, IADL and mobility. This modelling method would allow better understanding of how poorer lung function could, for example, lead to difficulty for a person to do their shopping (IADL) or how cognitive impairment could result in a person's inability to get dressed (BADL). The Akaike information criterion (AIC) and Bayesian information criterion (BIC) were used to assess model fit. All analyses were completed using Stata 14.0 (StataCorp; College Station, TX, USA).

6.4 Results

6.4.1 Path models

All the disability scores increased significantly over time, after adjustment for age and sex (Table 6.2). At baseline (age 85) higher disability scores were evident for women, participants with respiratory disease and those with higher disease count (Table 6.3). Analysis of the impact of baseline (age 85) factors on disability scores at age 86.5 found that physical activity, respiratory disease, disease count and FEV_1 affected all the three disability measures (Table 6.4). Baseline cognitive impairment had an effect on all disability measures, though there was no difference found in mobility for those with mild cognitive impairment (Table 6.4). BMI only affected mobility and only for those underweight (β: 0.36, 95% CI: 0.00 – 0.72) and obese (β: 0.72, 95% CI: 0.37 – 1.06) (Table 6.4).

At age 86.5 years disability scores, physical activity, BMI, cognitive impairment, disease count and FEV_1 were all predictive of disability scores at age 88 (Table 6.5). Similar patterns were also observed for factors at age 88 affecting disability at age 90 (Table 6.6).

Once the path models were constructed and analysis performed, odds ratios were obtained for factors affecting both FEV_1 and disability scores. Exploring the BADL path model at baseline, the effect of sex, education, smoking status and respiratory disease were mediated through FEV_1 (Table 6.7, Figure 6.1). Those who never smoked were more likely to have better lung function compared to former smokers (OR: 0.90, 95% CI: 0.85 – 0.97) or current smokers (OR:

0.76, 95% CI: 0.66 – 0.88); participants with 0-9 years of education were more likely to have poorer lung function than those with 12+ years of education (OR: 1.15, 95% CI: 1.04 – 1.26) (Table 6.7, Figure 6.1). Disease count was the only factor which affected BADL directly with an increased risk of higher BADL score for each additional disease group diagnosis (OR: 1.37, 95% CI: 1.25 – 1.50) (Table 6.7, Figure 6.1).

Physical activity levels measured at baseline were predictive of both FEV_1 and BADL score at 18 months follow-up (Table 6.7, Figure 6.1). For the same time period severe cognitive impairment (MMSE<18) increased the risk of disability more than five fold (OR: 5.80, 95% CI: 2.83 – 11.86) compared to those with normal cognition. Disease count also increased the risk of disability (OR: 1.24, 95% CI: 1.11 – 1.38) while increased FEV_1 reduced the risk of disability (OR: 0.75, 95% CI: 0.60 – 0.95) (Table 6.7, Figure 6.1). BADL score at baseline was predictive of FEV_1 with increased risk of lower FEV_1 with every additional BADL item (OR: 0.96, 95% CI: 0.93 – 0.99) that participants had difficulty performing on their own (Table 6.7, Figure 6.1).

Physical activity at age 86.5 was predictive of both FEV_1 and BADL at age 88, whilst respiratory disease and BMI predictive of FEV_1 only (Table 6.7, Figure 6.1). Higher FEV_1 at ages 85 and 86.5 was predictive of a reduced risk for BADL both at age 86.5 (OR: 0.69, 95% CI: 0.53 – 90) and at age 88 (OR: 0.59, 95% CI: 0.43 – 82) respectively (Table 6.7, Figure 6.1). Worsening cognitive function and lower physical activity at age 88 predicted higher risk of BADL score at age 90 (Table 6.7, Figure 6.1).

For IADL, patterns were similar to BADL, whereby FEV_1 was predictive of IADL at every age but IADL only predicted FEV_1 from 85 to 86.5 years (Table 6.8, Figure 6.2).

Differences were observed in the mobility pathway (Table 6.9, Figure 6.3) compared to the BADL (Table 6.7, Figure 6.1) and IADL (Table 6.8, Figure 6.2) pathways. Cognitive impairment did not affect the mobility pathway (Table 6.9, Figure 6.3). However, being overweight or obese (compared to normal weight) at 85 and 88 years was predictive of higher mobility scores at subsequent follow-ups (Table 6.9, Figure 6.3). Increased disease count predicted higher mobility score whilst high physical activity predicted lower mobility scores in line with previous findings (Table 6.9, Figure 6.3). Better FEV_1 at 85 years (OR: 0.75, 95% CI: 0.64 - 0.89) and 86.5 (OR: 0.77, 95% CI: 0.65 - 0.91) was predictive of reduced risk of mobility problems (Table 6.9, Figure 6.3). Between ages 88 and 90, all the effects of FEV_1 on mobility were mediated through physical activity, BMI and disease count (Table 6.9, Figure 6.3).

6.5 Summary

This chapter has demonstrated the causal pathways between lung function and different measures of disability (BADL, IADL and mobility). The use of path analysis informed by univariate models investigating the association of potential confounders and mediators has provided novel findings about the disability and lung function causal pathway. The N85+ study has provided information that within the complete spirometric cohort, lung function and disability have a bidirectional cause and effect pathway and, depending on the type of activities, different factors act as mediators. Furthermore it has shown that only long term accumulation of disabilities are associated with lung function whereas even a short term decline of lung function has an adverse effect on disability.

The major findings of this analysis were:

1. Higher FEV_1 at each time point was associated with lower BADL and IADL scores at subsequent follow-ups.
2. All three disability measures at baseline (age 85) predicted an increased risk of lower FEV_1 at age 86.5.
3. Cognitive impairment significantly affects the BADL and IADL pathways but not mobility.
4. Lower levels of physical activity at ages 85 and 86.5 predicted an increased risk of lower FEV_1 at subsequent follow-up for all disability pathways.
5. Higher BMI at age 86.5 was associated with an increased risk of lower FEV_1 at age 88 in all disability pathways.

This chapter aimed to investigate and address one of the main aims of this thesis by investigating the relationship between lung function and disability. The next and final chapter discusses each of the sub-studies reported in Chapters 3-6 in relation to other literature and details the contribution of the work as a whole.

Table 6.1: Activities of Daily Living items in the Newcastle 85+ Study

Activities of Daily Living (Newcastle 85+ Study)		
Basic Activities of Daily Living (BADL)	**Instrumental Activities of Daily Living (IADL)**	**Mobility**
feeding self - including cutting up of food	light housework	getting around the house going up and down stairs/steps
washing face and hands	heavy housework	
washing all over	preparing and cooking a hot meal	walking at least 400 yards
getting in and out of bed	shopping for groceries	
getting on and off the toilet	taking medication	
getting in and out of a chair	managing money	
dressing and undressing		
cutting own toenails		

Table 6.2: Disability category scores over time, by sex

	Men	Women	All	P-value*
BADL Score				
85 Years	1.2 (1.5)	1.5 (1.6)	1.4 (1.6)	<0.001
86.5 Years	1.7 (1.7)	2.1 (1.8)	1.9 (1.8)	
88 Years	1.9 (1.9)	2.4 (1.8)	2.2 (1.8)	
90 Years	1.9 (1.9)	2.5 (1.8)	2.3 (1.9)	
IADL Score				
85 Years	1.2 (1.8)	1.8 (1.8)	1.6 (1.8)	<0.001
86.5 Years	1.8 (2.0)	2.7 (1.9)	2.3 (2.0)	
88 Years	2.4 (2.2)	2.9 (1.9)	2.7 (2.0)	
90 Years	2.3 (2.2)	3.0 (2.0)	2.8 (2.1)	
Mobility Score				
85 Years	0.9 (1.1)	1.2 (1.2)	1.1 (1.16)	<0.001
86.5 Years	1.2 (1.1)	1.6 (1.2)	1.4 (1.2)	
88 Years	1.5 (1.2)	1.8 (1.1)	1.7 (1.1)	
90 Years	1.5 (1.3)	1.8 (1.2)	1.7 (1.2)	

* trend over time adjusted for age and sex

BADL: Basic activities of daily living

IADL: Instrumental activities of daily living

Table 6.3: Univariate analysis of Disability outcomes at 85 years against sociodemographic, lifestyle and health characteristics in early life

	Age 85 - BADL		Age 85 - IADL		Age 85 - Mobility	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Earlier Life						
Sex	0.28 (0.05 - 0.51)	0.015	0.65 (0.38 - 0.92)	<0.001	0.30 (0.13 - 0.47)	0.001
Smoking Status		0.225		0.067		0.921
Never	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Former	-0.13 (-0.37 - 0.11)	0.295	-0.17 (-0.46 - 0.11)	0.231	0.02 (-0.16 - 0.20)	0.812
Current	0.25 (-0.25 - 0.76)	0.322	0.47 (-0.13 - 1.06)	0.124	0.07 (-0.30 - 0.45)	0.701
Education		0.666		0.051		0.666
0 - 9 Years	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
10 - 11 Years	-0.11 (-0.38 - 1.65)	0.443	-0.17 (-0.49 - 0.15)	0.287	-0.13 (-0.33 - 0.08)	0.221
12+ Years	-0.11 (-0.45 - 0.24)	0.534	-0.49 (-0.90 - -0.08)	0.018	-0.39 (-0.65 - -0.13)	0.003
Occupational Exposure	0.12 (-0.12 - 0.36)	0.342	-0.10 (-0.39 - 0.18)	0.471	0.00(-0.17 - 0.18)	0.967
Respiratory Disease	0.33 (0.08 - 0.59)	0.012	0.31(0.22 - 0.41)	<0.001	0.39 (0.08 - 0.69)	0.014
Disease Count	0.41 (0.30 - 0.52)	<0.001	0.42 (0.22 - 0.61)	<0.001	0.26 (0.19 - 0.33)	<0.001

Table 6.4: Univariate analysis of Disability outcomes at 86.5 years against lifestyle and health characteristics in between ages 85 and 86.5

	Age 86.5 - BADL		Age 86.5 - IADL		Age 86.5 - Mobility	
Aged 85 years old	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Physical Activity		<0.001		<0.001		<0.001
High	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Low	2.14 (2.14 - 2.93)	<0.001	3.27 (2.84 - 3.71)	<0.001	1.61 (1.33 - 1.88)	<0.001
Medium	1.23 (0.97 - 1.49)	<0.001	1.56 (1.27 - 1.85)	<0.001	0.87 (0.69 - 1.06)	<0.001
BMI		0.067		0.069		<0.001
Normal (18.5 - 25)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Underweight (<18.5)	-0.00 (-0.59 - 0.58)	0.989	0.51 (-0.18 - 1.20)	0.149	0.26 (-0.16 - 0.68)	0.217
Overweight (25 - 30)	0.20 (-0.11 - 0.50)	0.202	0.14 (-0.22 - 0.49)	0.452	0.34 (0.12 - 0.55)	0.002
Obese (30+)	0.63 (0.15 - 1.11)	0.011	0.70 (0.13 - 1.27)	0.017	0.72 (0.37 - 1.06)	<0.001
Respiratory Disease	0.36 (0.03 - 0.69)	0.031	0.53 (0.15 - 0.90)	0.006	0.38 (0.16 - 0.61)	0.001
Disease Count	0.40 (0.28 - 0.51)	<0.001	0.39 (0.26 - 0.53)	<0.001	0.29 (0.21 - 0.37)	<0.001
Categorised MMSE		<0.001		<0.001		<0.001
Normal (26-30)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Mild (22-25)	0.50 (0.10 - 0.91)	0.014	1.08 (0.64 - 1.52)	<0.001	0.15 (-0.14 - 0.43)	0.315
Moderate (18-21)	1.08 (0.40 - 1.76)	0.002	2.66 (1.92 - 3.40)	<0.001	0.61 (0.12 - 1.09)	0.014
Severe (0-17)	3.34 (2.37 - 4.31)	<0.001	4.09 (3.04 - 5.15)	<0.001	1.15 (0.46 - 1.84)	0.001
FEV_1	-0.66 (-0.92 - -0.40)	<0.001	-1.00 (-1.29 - -0.70)	<0.001	-0.51(-0.69 - -0.33)	<0.001

Table 6.5: Univariate analysis of Disability outcomes at age 88 against lifestyle and health characteristics between ages 86.5 and 88

	Age 88 - BADL		Age 88 - IADL		Age 88 - Mobility	
Aged 86.5 years	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Physical Activity		<0.001		<0.001		<0.001
High	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Low	2.91(2.53 - 3.30)	<0.001	3.27(2.82 - 3.71)	<0.001	1.72 (1.47 - 1.98)	<0.001
Medium	0.96 (0.66 - 1.26)	<0.001	1.59 (1.24 - 1.93)	<0.001	0.97 (0.77 - 1.17)	<0.001
BMI		<0.001		0.009		0.001
Normal (18.5 - 25)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Underweight (<18.5)	0.40 (-0.12 - 0.93)	0.134	0.93 (0.30 - 1.56)	0.004	0.36 (0.00 - 0.72)	0.048
Overweight (25 - 30)	0.35 (-0.00 - 0.70)	0.053	0.08 (-0.34 - 0.50)	0.711	0.12 (-0.12 - 0.36)	0.317
Obese (30+)	1.33 (0.74 - 1.92)	<0.001	0.74 (0.04 - 1.45)	0.039	0.77 (0.37 - 1.18)	<0.001
Respiratory Disease	0.17 (-0.55 - 0.55)	0.381	0.17 (-0.26 - 0.60)	0.436	0.19 (-0.05 - 0.43)	0.123
Disease Group	0.46 (0.32 - 0.59)	<0.001	0.52 (0.36 - 0.67)	<0.001	0.28 (0.19 - 0.37)	<0.001
Categorised MMSE		<0.001		<0.001		0.027
Normal (26-30)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Mild (22-25)	0.73 (0.26 - 1.19)	0.002	1.52 (1.01 - 2.03)	<0.001	0.28 (-0.03 - 0.58)	0.073
Moderate (18-21)	1.57 (0.66 - 2.49)	0.001	2.79 (1.79 - 3.80)	<0.001	0.57 (-0.03 - 1.17)	0.063
Severe (0-17)	3.57 (1.19 - 5.96)	0.003	3.65 (1.04 - 6.26)	0.006	1.43 (-0.14 - 2.99)	0.074
FEV_1	-0.84 (-1.15 - -0.54)	<0.001	-1.04 (-1.38 - -0.69)	<0.001	-0.58 (-0.77 - -0.39)	<0.001

Table 6.6: Univariate analysis of Disability outcomes at age 90 against lifestyle and health characteristics between ages 88 and 90

	Age 90 - BADL		Age 90 - IADL		Age 90 - Mobility	
Aged 88 years	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Physical Activity		<0.001		<0.001		<0.001
High	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Low	2.55 (2.06 - 3.03)	<0.001	2.89 (2.34 - 3.44)	<0.001	1.67 (1.35 - 1.99)	<0.001
Medium	0.92 (0.50 - 1.34)	<0.001	1.30 (0.82 - 1.78)	<0.001	0.81 (0.53 - 1.09)	<0.001
BMI		<0.001		<0.001		0.007
Normal (18.5 - 25)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Underweight (<18.5)	0.54 (-0.09 - 1.17)	0.091	0.84 (0.10 - 1.58)	0.026	0.35 (-0.09 - 0.79)	0.120
Overweight (25 - 30)	0.02 (-0.41 - 0.45)	0.925	-0.15 (-0.65 - 0.36)	0.570	-0.03 (-0.34 - 0.27)	0.834
Obese (30+)	1.91 (1.14 - 2.68)	<0.001	1.60 (0.70 - 2.51)	0.001	0.85 (0.31 - 1.39)	0.002
Respiratory Disease	-0.02 (-0.49 - 0.44)	0.922	0.08 (-0.45 - 0.61)	0.764	0.06 (-0.24 - 0.37)	0.688
Disease Group	0.47 (0.31 - 0.62)	<0.001	0.51 (0.33 - 0.69)	<0.001	0.26 (0.15 - 0.37)	<0.001
Categorised MMSE		<0.001		<0.001		0.018
Normal (26-30)	1 (Ref)	-	1 (Ref)	-	1 (Ref)	-
Mild (22-25)	0.02 (-0.49 - 0.54)	0.926	1.13 (0.55 - 1.70)	<0.001	0.08 (-0.28 - 0.45)	0.652
Moderate (18-21)	1.55 (0.81 - 2.29)	<0.001	2.48 (1.56 - 3.19)	<0.001	0.59 (0.06 - 1.11)	0.028
Severe (0-17)	3.63 (2.44 - 4.82)	<0.001	3.79 (2.47 - 5.10)	<0.001	1.03 (0.19 - 1.87)	0.016
FEV_1	-0.78 (-1.17 - -0.39)	<0.001	-1.08 (-1.51 - -0.64)	<0.001	-0.46 (-0.72 - -0.20)	<0.001

Table 6.7: Path analysis of BADL score and FEV_1 from ages 85 to 90

	FEV_1		BADL Score	
Earlier Life on age 85	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Sex				
Female	0.56 (0.52 - 0.59)	<0.001		
Education				
0 - 9 Years	1 (Ref)			
10 - 11 Years	1.02 (0.95 - 1.10)	0.568		
12+ Years	1.15 (1.04 - 1.26)	0.006		
Smoking Status				
Never	1 (Ref)			
Former Smoker	0.90 (0.85 - 0.97)	0.004		
Current Smoker	0.76 (0.66 - 0.88)	<0.001		
Respiratory Disease	0.77 (0.71 - 0.83)	<0.001		
GP Disease Count	-	-	1.37 (1.25 - 1.50)	<0.001
Age 85 on age 86.5				
FEV_1			0.75 (0.60 - 0.95)	<0.001
BADL Score	0.96 (0.93 - 0.99)	0.005	-	-
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.72 (0.65 - 0.87)	<0.001	2.74 (2.10 - 3.58)	<0.001
Low	0.75 (0.65 - 0.78)	<0.001	9.13 (6.13 - 13.59)	<0.001
MMSE Score				
Normal (26-30)			1 (Ref)	
Mild (22-25)			1.40 (0.99 - 1.98)	0.061
Moderate (18-21)			1.28 (0.72 - 2.29)	0.403
Severe (0-17)			5.80 (2.83 - 11.86)	<0.001
GP Disease Count			1.24 (1.11 - 1.38)	<0.001
Respiratory Disease	0.77 (0.70 - 0.85)	<0.001	-	-
Age 86.5 on age 88				
FEV_1			0.69 (0.53 - 0.90)	0.006
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.77 (0.69 - 0.86)	<0.001	2.21 (1.63 - 3.00)	<0.001
Low	0.74 (0.63 - 0.86)	<0.001	12.51 (8.27 - 18.90)	<0.001
GP Disease Count			1.26 (1.12 - 1.42)	<0.001
Respiratory Disease	0.76 (0.68 - 0.85)	<0.001	-	-
BMI			-	-
Underweight (<18.5)	0.82 (0.70 - 0.97)	0.022		
Normal (18.5 - 25)	1 (Ref)			
Overweight (25 - 30)	1.05 (0.95 - 1.17)	0.324		
Obese (30+)	1.20 (1.00 - 1.43)	0.053		

Age 88 on age 90		
FEV_1	0.59 (0.43 - 0.82)	0.002
Physical Activity		
High	1 (Ref)	
Medium	1.87 (1.25 - 2.80)	0.002
Low	6.98 (4.32 - 11.27)	<0.001
MMSE Score		
Normal (26-30)	1 (Ref)	
Mild (22-25)	0.71 (0.46 - 1.10)	0.128
Moderate (18-21)	2.02 (1.06 - 3.83)	0.032
Severe (0-17)	11.79 (4.24 - 32.81)	<0.001
GP Disease Count	1.31 (1.14 - 1.51)	<0.001

Table 6.8: Path analysis of IADL score and FEV_1 from ages 85 to 90

	FEV_1		IADL Score	
Earlier Life on age 85	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Sex				
Female	0.56 (0.52 - 0.59)	<0.001		
Education				
0 - 9 Years	1 (Ref)			
10 - 11 Years	1.02 (0.95 - 1.10)	0.568		
12+ Years	1.15 (1.04 - 1.26)	0.006		
Smoking Status				
Never	1 (Ref)			
Former Smoker	0.90 (0.85 - 0.97)	0.004		
Current Smoker	0.76 (0.66 - 0.88)	<0.001		
Respiratory Disease	0.77 (0.71 - 0.83)	<0.001		
GP Disease Count	-	-	1.51 (1.35 - 1.68)	<0.001
Age 85 on age 86.5				
FEV_1			0.66 (0.52 - 0.84)	<0.001
IADL Score	0.92 (0.89 - 0.95)	<0.001	-	-
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.76 (0.69 - 0.83)	<0.001	3.59 (2.72 - 4.75)	<0.001
Low	0.90 (0.77 - 1.06)	0.200	15.30 (10.11 - 23.17)	<0.001
MMSE Score				
Normal (26-30)			1 (Ref)	
Mild (22-25)			2.21 (1.53 - 3.18)	<0.001
Moderate (18-21)			4.74 (2.59 - 8.69)	<0.001
Severe (0-17)			9.07 (4.30 - 19.12)	<0.001
GP Disease Count			1.16 (1.04 - 1.29)	0.009
Respiratory Disease	0.78 (0.71 - 0.85)	<0.001	-	-
Age 86.5 on age 88				
FEV_1			0.64 (0.47 - 0.86)	0.003
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.77 (0.69 - 0.86)	<0.001	4.02 (2.84 - 5.69)	<0.001
Low	0.74 (0.63 - 0.86)	<0.001	16.48 (10.30 - 26.35)	<0.001
GP Disease Count			1.32 (1.15 - 1.51)	<0.001
Respiratory Disease	0.76 (0.68 - 0.85)	<0.001	-	-
BMI			-	-
Underweight (<18.5)	0.82 (0.70 - 0.97)	0.022		
Normal (18.5 - 25)	1 (Ref)			
Overweight (25 - 30)	1.05 (0.95 - 1.17)	0.324		
Obese (30+)	1.20 (1.00 - 1.43)	0.053		

Age 88 on age 90		
FEV_1	0.46 (0.32 - 0.67)	<0.001
Physical Activity		
High	1 (Ref)	
Medium	2.32 (1.47 - 3.64)	<0.001
Low	7.47 (4.36 - 12.78)	<0.001
MMSE Score		
Normal (26-30)	1 (Ref)	
Mild (22-25)	2.13 (1.30 - 3.49)	0.003
Moderate (18-21)	4.40 (2.15 - 9.03)	<0.001
Severe (0-17)	14.16 (4.49 - 44.63)	<0.001
GP Disease Count	1.29 (1.10 - 1.51)	0.001

Table 6.9: Path analysis of Mobility score and FEV_1 from ages 85 to 90

	FEV_1		Mobility Score	
Earlier life on age 85	**OR (95% CI)**	**P-Value**	**OR (95% CI)**	**P-Value**
Sex				
Female	0.56 (0.52 - 0.59)	<0.001		
Education				
0 - 9 Years	1 (Ref)			
10 - 11 Years	1.02 (0.95 - 1.10)	0.568		
12+ Years	1.15 (1.04 - 1.26)	0.006		
Smoking Status				
Never	1 (Ref)			
Former Smoker	0.90 (0.85 - 0.97)	0.004		
Current Smoker	0.76 (0.66 - 0.88)	<0.001		
Respiratory Disease	0.77 (0.71 - 0.83)	<0.001		
GP Disease Count	-	-	1.529 (1.21 - 1.39)	<0.001
Age 85 on age 86.5				
FEV_1			0.75 (0.64 - 0.89)	0.001
Mobility Score	0.94 (0.90 - 0.98)	0.005	-	-
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.72 (0.66 - 0.79)	<0.001	2.02 (1.68 - 2.43)	<0.001
Low	0.76 (0.66 - 0.88)	<0.001	3.52 (2.66 - 4.66)	<0.001
BMI				
Underweight (<18.5)			1.19 (0.83 - 1.69)	0.343
Normal (18.5 - 25)			1 (Ref)	
Overweight (25 - 30)			1.41 (1.78 - 1.69)	<0.001
Obese (30+)			1.60 (1.20 - 2.13)	0.001
GP Disease Count			1.19 (1.11 - 1.28)	<0.001
Respiratory Disease	0.78 (0.71 - 0.86)	<0.001	-	-
Age 86.5 on age 88				
FEV_1			0.77 (0.65 - 0.91)	0.003
Physical Activity				
High	1 (Ref)		1 (Ref)	
Medium	0.77 (0.69 - 0.86)	<0.001	2.35 (1.92 - 2.86)	<0.001
Low	0.74 (0.63 - 0.86)	<0.001	4.28 (3.27 - 5.61)	<0.001
GP Disease Count			1.17 (1.08 - 1.27)	<0.001
Respiratory Disease	0.76 (0.68 - 0.85)	<0.001	-	-
BMI			-	-
Underweight (<18.5)	0.82 (0.70 - 0.97)	0.022		
Normal (18.5 - 25)	1 (Ref)			
Overweight (25 - 30)	1.05 (0.95 - 1.17)	0.324		
Obese (30+)	1.20 (1.00 - 1.43)	0.053		

Age 88 on age 90		
FEV_1		
Physical Activity		
High	1 (Ref)	
Medium	1.88 (1.40 - 2.52)	<0.001
Low	3.96 (2.77 - 5.65)	<0.001
BMI		
Underweight (<18.5)	1.24 (0.84 - 1.83)	0.288
Normal (18.5 - 25)	1 (Ref)	
Overweight (25 - 30)	1.01 (0.77 - 1.31)	0.969
Obese (30+)	1.66 (1.03 - 2.67)	0.036
GP Disease Count	1.14 (1.03 - 1.27)	0.016

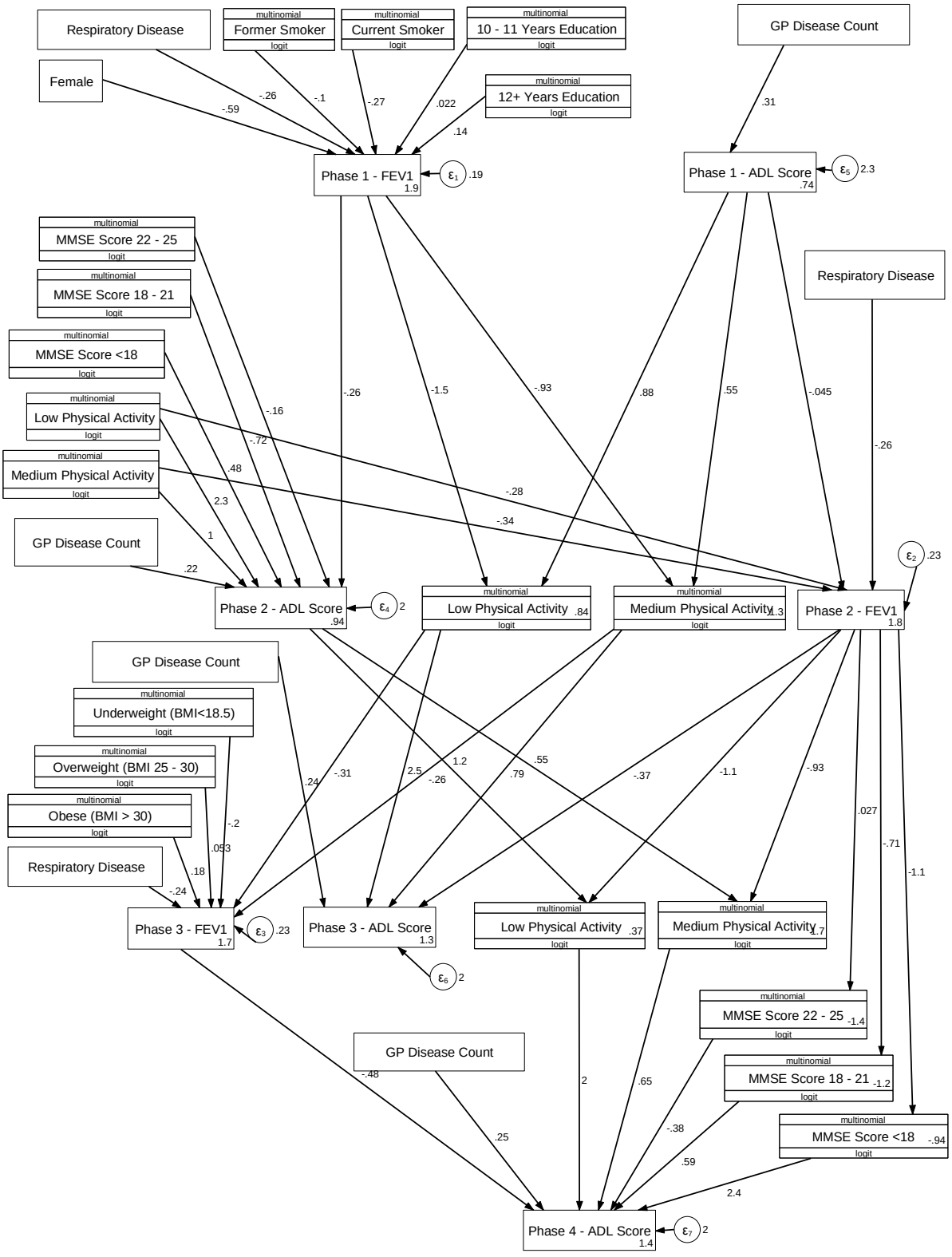


Figure 6.1: Path diagram showing the direct and indirect predictors of Basic Activities of Daily Living (BADLs) score and FEV_1 from age 85 to 90

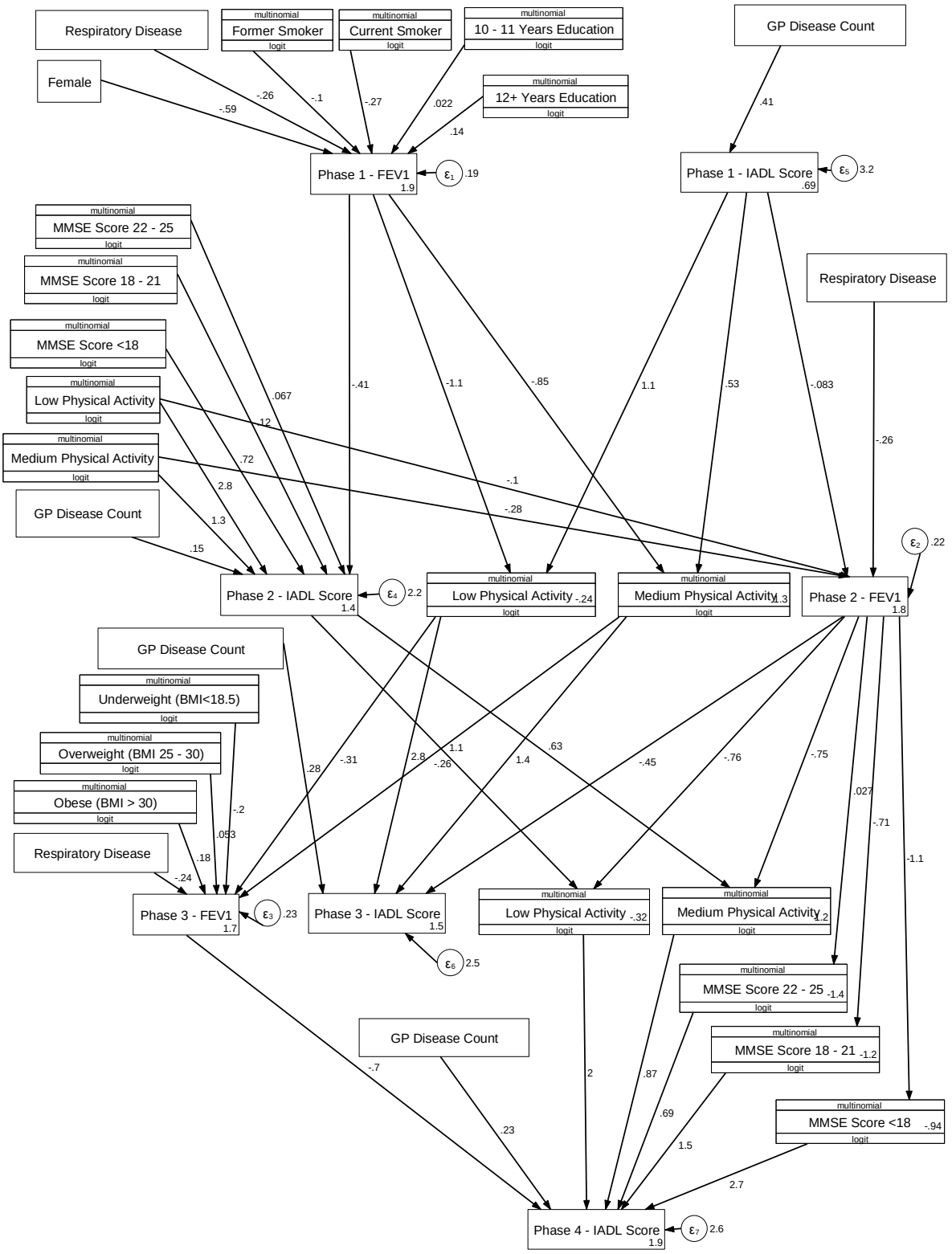


Figure 6.2: Path diagram showing the direct and indirect predictors of Instrumental Activities of Daily Living (IADLs) score and FEV_1 from age 85 to 90

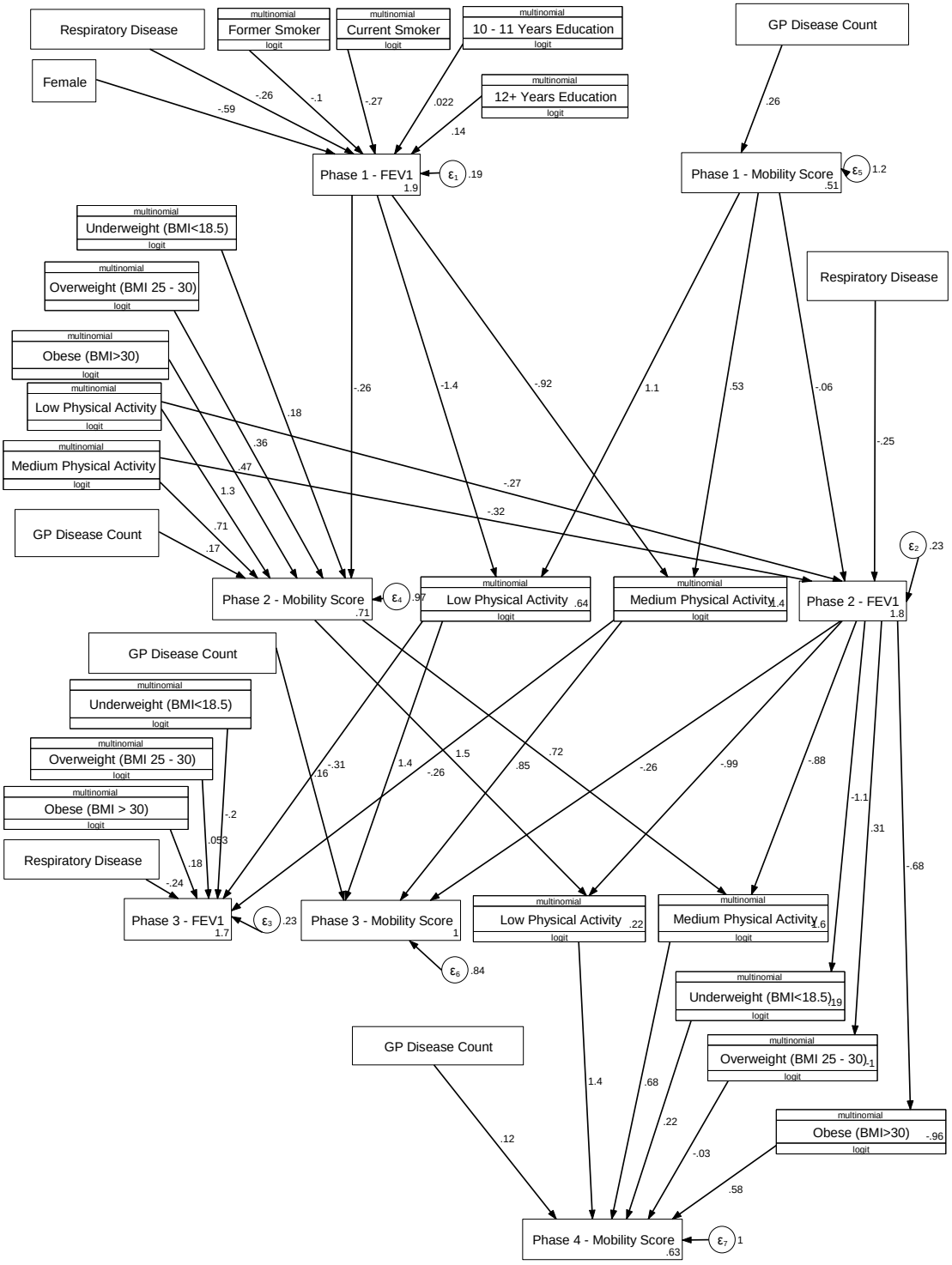


Figure 6.3: Path diagram showing the direct and indirect predictors of Mobility score and FEV_1 from age 85 to 90

Chapter 7. Discussion

This section aims to provide an overarching response to the research questions posed at the conception of this thesis.

7.1 Summary of main findings

This thesis was driven by the inadequate research conducted on lung function, its impact and implications in the very old. The data from the Newcastle 85+ (N85+) study, a longitudinal cohort study of 85 year olds, provided the means to address the research aim and objectives of this thesis. Lung function measured at age 85 provided the answer to the question, 'Are lung function prediction methods applicable and appropriate at this advanced age?' Adequate spirometry data was available for 87.3% (737/845) of the N85+ cohort, demonstrating that lung function tests can be performed by this age group. From the spirometry data, participants were assigned obstructive lung status using the standard criteria of GOLD (Wen and He, 2012) and GLI (Quanjer *et al.*, 2012) in addition to their GP diagnosed COPD, and comparison of all three methods revealed an over diagnosis of COPD from GP records compared to GOLD and GLI. Furthermore, GOLD overestimated obstructive spirometry when compared to GLI prediction in the N85+ cohort.

Spirometry was also measured at 18 months and 36 months follow-up in addition to the available death data (median survival 5.4 years). Investigating the observed lung function measures (FEV_1, FVC and PEF) along with GLI and GOLD predicted (percent predicted FEV_1 and FVC) values both in the whole spirometry cohort and a healthy reference group (HRG) with no respiratory related symptoms, disease or conditions, generated interesting results. The observed measures all predicted survival in women in the overall spirometry cohort, but not in men. Furthermore, none of the lung function measures observed or otherwise, predicted survival in either men or women of the HRG.

Examination of lung function trajectories between ages 85 and 88 years found that men's lung function declined significantly (though non-linearly) whilst there was no significant change over time for women. Smoking and cognitive impairment were associated with worsening FEV_1 in both men and women of the whole spirometry cohort, with cognitive impairment also being associated with worsening FEV_1 in the survivor group. Body mass index (BMI) and physical activity had the strongest association with lung function in women. With regard to

biomarkers of ageing, higher CRP was associated with lower FEV_1, FVC and PEF in men of the whole spirometry cohort.

These findings contributed to the final research question examining the direction of the relationship between lung function and disability, using three disability measures that differentiate severity: basic activities of daily living (BADL); instrumental activities of daily living (IADL) and mobility. Higher levels of FEV_1 were found to predict better BADL and IADL scores at later follow-ups, but, additionally, all three measures of disability at baseline (age 85) predicted an increased risk of lower FEV_1. Thus, the relationship between FEV_1 and disability is bidirectional. Cognitive impairment mediated the FEV_1- BADL and FEV_1- IADL pathways but not the FEV_1-mobility pathway.

7.2 Lung function at age 85

The objective in this section of the study was to assess the respiratory symptoms, disease prevalence and objective measures of lung function of the very old for the first time using a single year birth cohort of 85 year olds in the UK, the N85+ study data. The study population had success in challenging the misconception that the very old cannot perform spirometry successfully with 93% undertaking the test with a 93% success rate (Fisher *et al.*, 2016).

There is an increased risk of respiratory impairment associated with age due to the accumulation of environmental insults experienced over the life course such as air pollution, occupational dusts, smoking and infections (Vaz Fragoso and Lee, 2012). This risk is compounded further by the changes in lung function as part of normal ageing including reduction in muscle strength, ventilatory control, movement of chest wall and increased compliance (Vignola *et al.*, 2003) and it is therefore anticipated that symptoms of wheeze, cough and dyspnoea will be common amongst older people. However, it was discovered that despite the high prevalence of chronic lung disease and respiratory symptoms in this cohort, significant proportions of men (50%) and women (40%) reported no limitations due to breathlessness (MRC dyspnoea score of 1) which suggested that they were either able to function very well or had a poor perception of symptoms.

The participants of this study have survived significant historical events, born not long after WW1 and the 1918 Spanish Flu pandemic. This was a time of high depravation levels with unemployment having reached 17% in 1921. They lived through WW2 and witnessed the introduction of legislation aimed to improve living standards such that of the Housing Act

(1930) and the Clean Air Act (1956). Most of these participants were close to retirement before the 1986 WHO: Ottawa Charter for Health Promotion and as already observed quite a high proportion of this population were smokers, especially men. The experience of such major events by the N85+ cohort led to plausible findings such as the high prevalence of physician-diagnosed COPD (16.7%) compared to the national average of 10% in 65-74 year olds based on self-reported COPD in the 2010 Health Survey for England (Miller and Levy, 2015).

Further investigation of the subgroup with physician-diagnosed COPD revealed that just under 25% of this group showed no sign obstructive spirometry, with a significant proportion exhibiting no evidence of smoking or occupational history with minimal symptoms (Fisher *et al.*, 2016). Such findings suggested potential COPD misdiagnosis in this age group, confirming the findings from a community Respiratory Assessment unit (Roberts et al., 2015). This led to the examination of the GOLD/NICE guidelines (Vestbo *et al.*, 2012) and the GLI prediction models and lower limits of normal (LLN) (Quanjer *et al.*, 2012) methodology in the whole cohort and the HRG (n=151) and the physician diagnosed COPD (n=123) subgroups. In the COPD subgroup, just over 75% presented with obstructive spirometry when using GOLD criteria and about half using the GLI prediction and LLN criteria. The highest level of agreement was between the physician diagnosed COPD and GLI obstructive classification (Kappa = excellent, 75.9%), perhaps in part because the GLI coefficients were derived to include people up to age of 95 whereas the ERS 1993 (Quanjer *et al.*, 1993) coefficients used by the GOLD criteria were derived for a population up to the age of 69. COPD diagnosis by a physician may be more useful as they have access to more information about a patient's health than the few indicators GLI and GOLD methods rely on.

A review of people aged 40 and over in England and Wales found evidence of over diagnosis of COPD by up to 13% when using GOLD instead of LLN methodology (Miller and Levy, 2015). Interestingly, in the N85+ study, a higher proportion of the HRG fulfilled spirometry criteria for COPD using current GOLD/NICE guidelines, whilst the use of GLI prediction models and LLN methodology of identifying airflow obstruction may reduce chances of misdiagnosis. The results from this study gives further evidence that the use of current NICE guidelines may no longer be adequate and the more recent GLI prediction formulae and LLN definition should be adapted through a more unified process, especially in this age group to increase accuracy of COPD diagnosis.

7.3 Lung function as a predictor of mortality in the very old

It has previously been established that lung function is a predictor of mortality at a younger ages on its own (Sabia *et al.*, 2010) or mediated through respiratory disease (Romme *et al.*, 2013) (Ranieri *et al.*, 2001; Gudmundsson *et al.*, 2006; van den Borst *et al.*, 2012; Ajmera *et al.*, 2013). Vital capacity (VC) and mortality was explored in a Finnish cohort (n=388) of 75 year olds revealing an increased risk of mortality for the middle VC tertile (compared to highest) of 49% in men and 25% in women, and an even higher risk for those in the lowest VC tertile (compared to the highest) of 52% in men and 49% in women (Lyyra *et al.*, 2005).

An investigation of lung function equations and their suitability in an older cohort explored the relationship between observed and predicted values mortality using the Danish 1905 cohort (Miller et al., 2014). Lung function was found to inversely predict mortality using either standardised residual values using all prediction formulae and as a proportion of height (FEV_1/height^2 and FEV_1/height^3) after controlling for sex, MMSE and grip strength (Miller *et al.*, 2014). The effect of FEV_1/height^3 as a predictor was further explored in a cohort of 80 years and older adults in Belgium. It was found that those in the lowest quartile had increased risk of all-cause mortality (HR: 1.69, 95% CI: 1.10 – 2.60) after adjusting for age, sex, smoking status, co-morbidities, anaemia, CRP and creatinine levels (Turkeshi *et al.*, 2015). These results were similar to the N85+ study though only for women and not in men.

The aforementioned studies of lung function and mortality all showed lung function to be predictive of mortality in the very old, however they all employed different confounding factors hindering comparisons. The Finnish cohort were aged 10 years younger in comparison to the N85+ cohort and only adjusted for the number of fatal diseases and cognitive capacity (Lyyra *et al.*, 2005). The Danish 1905 cohort, similar to the N85+ study, found the GLI predicted values to be a predictor of mortality (Miller *et al.*, 2014).

The Whitehall II study investigated the link between FEV_1 and mortality in a population of civil servants aged 35 – 55 years old and found that people in the lowest tertile of FEV_1/height^2 had an increased risk of mortality (HR: 1.52, 95% CI: 1.05 – 2.19) compared to rest of the study population (Sabia *et al.*, 2010). Although Whitehall II was a study of a younger age group, it had a more complete set of confounders, and it therefore formed the model analysis for the N85+ study in order to examine whether the Whitehall II study findings held true for very old age. The two differences between the methodological approaches was that in the N85+ analyses

lung function measures were updated at each follow-up prior to death, and secondly, observed values were used as continuous measures rather than tertiles.

The major difference in findings between the N85+ study and Whitehall II was that FEV_1 was only predictive of mortality in women in the former compared to the latter after adjusting for all potential factors which may have acted as confounders or mediators (Sabia *et al.*, 2010). A major advantage of the N85+ study was the ability to update measurements during the follow-up period, in comparison to Whitehall II where they only used baseline measures (Sabia *et al.*, 2010). Indeed all other very old cohorts, as Whitehall II, adjusted for sex rather than analysing men and women separately as the N85+ study. Thus, the N85+ study has added to the knowledge base in finding that lung function was only predictive of survival in very old women. Analysing men and women separately was considered a better approach as it has already been established, especially in this cohort, that lung function is significantly different between the sexes at baseline (Fisher *et al.*, 2016) and mortality rates are known to be higher in men than women, even at very old ages (Miller *et al.*, 2014). However, despite the smaller number of men than women in the N85+ cohort, and therefore wider confidence intervals around the hazard ratios for mortality, the same effects were observed in the HRG men but not women. This is indicative of existing diseases diluting the effect of mortality as higher proportion of women had a respiratory diseases diagnosis and higher disease count in general.

7.4 Trajectories of lung function from age 85

Exploring lung function changes over time in the very old and its potential predictors could lead to better understanding of early indicators of respiratory decline at this age, and, as previously mentioned, possibly reduction of the risk of mortality in women. As previously demonstrated, studies of lung function and its predictors have been scarce in the very old. The use of potential predictors was informed from similar studies of all older people (aged 65 years and over) in addition to the findings from previous chapters of this thesis.

It is interesting to note that even at age 85, new lung disease was diagnosed, with 13 new physician diagnosis between ages 85 and 86.5 and with COPD accounting for just over a third (5/13). Between ages 86.5 and 88 years, a further 11 physician diagnoses were made of which 64% were COPD. However, in the healthy group who had no respiratory symptoms, disease or related conditions at age 85, there was only three new diagnoses over the 36 months follow-up with no cases of COPD (1 bronchiectasis and 1 pulmonary fibrosis).

Lung function measures included FEV_1, FVC and PEF with the addition of FEV_1/FVC to investigate changes in lung physiology. Multilevel modelling was employed to account for the multiple measures over time and men and women were analysed separately as previously since they had significantly different lung function at baseline. Separate analyses for HRG and survivor groups (those who were present at all three time points) allowed the examination of a survivor effect and the strength of association between certain predictors if they were significant in the overall population and these subgroups. The non-linear decline over time found for FEV_1, PEF and FEV_1/FVC in men overall is indicative of significant change in lung physiology at advanced age , although these associations did not hold for the HRG or the survivor group, perhaps because of smaller numbers.

Lower fat free mass (FFM) and higher sagittal abdominal diameter (SAG) were found to be associated with lower lung function (FEV_1 and FVC) over a 7 year follow-up of a cohort of old adults (mean age of 71) (Rossi *et al.*, 2008). This was confirmed in the N85+ whole spirometry cohort, although with BMI rather than FFM or SAG, and with being underweight associated with lower PEF in both men and women, although this only held true in the whole spirometry cohort. Compared to the N85+, Rossi et al followed their participants for 7 years rather than five, although they had a total population sample of 77 to this study's 737 at baseline (Rossi *et al.*, 2008).

Education was used as a proxy for socio-economic status (SES) in the N85+ analyses with higher education being associated with higher FEV_1 levels in men of both the complete spirometry cohort and the HRG. Socio-economic status has also been found to be a predictor of better lung function at 15 years old in both boys and girls (Menezes *et al.*, 2011), suggesting that socio-economic status might act on lung function throughout the life course.

Cognitive impairment was associated with poorer lung function (FEV_1, FVC and PEF) in the complete spirometry cohort in both men and women, except for FVC in women. This confirms other studies that have shown significant association between higher FEV_1 levels and better cognitive function or lower incidence of Alzheimer's disease, (Weuve *et al.*, 2011; Emery *et al.*, 2012; Vidal *et al.*, 2013), although all presumed a pathway from lung function to cognitive function. These together with the findings in this thesis suggests a possible bidirectional relationship between pulmonary and cognitive function. Cognitive impairment may be an early sign of a neurodegenerative process that ultimately affects pulmonary function, or, more likely, lower pulmonary function may result from those with cognitive impairment not performing

tests as well. The N85+ study gives credence to the latter since those unable to provide adequate spirometry were more cognitively impaired (32.4% with severe cognitive impairment in the whole N85+ study, as opposed to 3.4% in spirometry cohort).

In the N85+ study, three biomarkers of systemic inflammation, tumour necrosis factor alpha (TNFα), interleukin-6 (IL-6) and C-reactive protein (CRP) were among those collected in addition to telomere length which is a biomarker of ageing (Martin-Ruiz *et al.*, 2011). These were used to validate associations with lung function based on previous literature which was mostly on younger populations (Katz *et al.*, 1963; Gimeno *et al.*, 2011; Ahmadi-Abhari *et al.*, 2014; Baldi *et al.*, 2014; Hancox *et al.*, 2016).

Telomere length in the N85+ study was inversely associated with FVC in men and PEF in women of whole spirometry cohort. Examination of 386 Danish twins revealed no association between telomere length and FEV_1 in keeping with the N85+ results, although both were of these measures were found to be affected by genetic factors (Sillanpaa *et al.*, 2016). However, associations between short telomere length and decreased FEV_1 and FVC were observed in participants of two prospective observational studies in Denmark (Rode *et al.*, 2013). This can be explained by the large sample (n=46396) allowing for more power in the analysis of such associations (Rode *et al.*, 2013).

CRP was inversely associated with FEV_1 for men and FVC for men and women of the whole spirometry cohort, and PEF of men in all three groups (whole cohort, HRG, survivor group), confirming the inverse relation that others have found (Gimeno *et al.*, 2011; Ahmadi-Abhari *et al.*, 2014; Hancox *et al.*, 2016) (Baldi *et al.*, 2014). Findings of N85+ study and association of lung function measures with IL-6 and TNFα were inconsistent as the effect was not carried through all three groups. Since IL-6 was only associated with PEF in the HRG and the survivor group but not the whole spirometry cohort, it can be argued that the effect of IL-6 was attenuated due to existing respiratory disease which was significantly associated with PEF in the whole spirometry cohort. Similarly, disease count could be attributed to diluting the effect of TNFα in the whole spirometry cohort. However, the associations observed were which indicated increased inflammation with lower lung function were akin to other findings (Gimeno *et al.*, 2011; Baldi *et al.*, 2014).

The major difference between this study and other literature was the method of analysis by multilevel modelling, separate analysis for men and women (which allows an assumption of different intercepts as well as different functional forms with time and covariate effects), as

well as the older age group and shorter follow-up of 3 years in the N85+study compared to minimum of 6 years in other studies (Gimeno *et al.*, 2011; Ahmadi-Abhari *et al.*, 2014; Baldi *et al.*, 2014; Hancox *et al.*, 2016).

7.5 Relationship between lung function and disability

Previous chapters explored the baseline lung function at age 85, its impact on mortality and potential predictors of lung function using multiple lung function measures. In the N85+ study, we could examine how lung function, as one measure of intrinsic capacity, related to functional ability, measured by the self-report of 17 different activities participants would carry out on a daily basis (Jagger *et al.*, 2011).

The effect of poor lung function through breathlessness on carrying out certain tasks that are part of the ADLs has been explored with The MRC Dyspnoea score (Fletcher *et al.*, 1959). A large cohort of old adults aged 70 years and over (n=5002) who were breathless (scores 3 – 5 on dyspnoea scale) had poorer quality of life, physically and mentally with higher risk of depression and anxiety (Ho *et al.*, 2001). In the N85+ study, just under 40% of the spirometry cohort scored 3 and over on the MRC dyspnoea scale. Other studies found associations between COPD and reduction in ability to perform ADLs (Pitta *et al.*, 2008; Lahaije *et al.*, 2010; Locke *et al.*, 2013; van Helvoort *et al.*, 2016), but all were cross-sectional in design.

Few longitudinal studies have investigated the association of lung function on activity limitations and all assuming lung function decline precedes disability (Ahacic *et al.*, 2007; Buchman *et al.*, 2009; Locke *et al.*, 2013; Hegendorfer *et al.*, 2017a). The N85+ study analysis tried to take this a step further and analyse the cause and effect pathway between lung function and disability without prior assumption of direction through Structural Equation Modelling (SEM). Only a few studies have used SEM, and then to investigate lung function and cognitive impairment (Finkel and Pedersen, 2004; Emery *et al.*, 2012; Finkel *et al.*, 2013) or cognitive impairment and disability (Infurna *et al.*, 2011). Moreover three separate disability scores (BADL, IADL and mobility) were derived from the ADL questionnaire items in the N85+ study, to allow for different severity levels of disability to be explored; separate models were fitted for each score.

The main finding was bidirectional cause and effect pathways. Lower BADL, IADL and mobility scores at age 85 were predictive of higher FEV_1 levels at age 86.5. The BADL and IADL models had very similar cause and effect pathways with higher FEV_1 at each time point

(ages 85, 86.5 and 88) predicting lower disability at each subsequent follow-up (ages 86.5, 88 and 90), whereas higher FEV_1 levels (at age 85 and 86.5) was predictive of better mobility at ages 86.5 and 88 respectively. Cognitive impairment, physical activity and disease count were also predictors of BADL and IADL scores between baseline and age 86.5. FEV_1 was predictive of mobility up to age 88 whilst physical ability, BMI and disease count were also predictive of mobility at subsequent follow-up. Sex, smoking, education and respiratory disease earlier in life mediated through FEV_1 at baseline (age 85) and early life disease count had a direct effect on disability at baseline. These findings were true for all three of the disability measures.

This study had the ability to apply the findings from the other studies of cognitive impairment with disability or lung function and incorporate them all into one pathway (Finkel and Pedersen, 2004; Infurna *et al.*, 2011; Emery *et al.*, 2012; Finkel *et al.*, 2013). Study of the SATSA population revealed the association between decline in lung function where they found lower respiratory function to be associated with subsequent poorer spatial performance and processing speed (Emery *et al.*, 2012). Direct links between cognition and functional limitations were observed in that better memory reduces functional limitations both at intercept and over time (Infurna *et al.*, 2011). Furthermore they found that the effect size was larger in adults aged 80 – 95 when compared to those aged 70 – 79 (Infurna *et al.*, 2011). The N85+ study pathways showed cognitive impairment to have no direct effect on lung function, whereas the effect of lung function at age 86.5 mediated through cognitive impairment at age 88 to disability at age 90 for BADL and IADL but not mobility. This suggests that some of the relationship between impaired cognition affecting the ability to perform daily tasks such as shopping or dressing, is due to worsening lung function adversely affecting brain function. The direct (inverse) relationship between lung function and mobility score adds further credence since cognitive function has little effect on mobility. The advantage of the SATSA and the AHEAD studies was the larger cohorts and seven waves of data collected over at least 12 years in comparison to the N85+ study with only three time points for lung function and four for disability (Finkel and Pedersen, 2004; Collerton *et al.*, 2009; Infurna *et al.*, 2011; Emery *et al.*, 2012; Finkel *et al.*, 2013; Fisher *et al.*, 2016).

7.6 Implications of the findings and further research

Respiratory diseases is a major health concern in the world accounting for just over 15% of all death worldwide and a burden on the health services with over 6 million hospital admission in EU amounting to a total cost of just under €380 billion with €200 billion being COPD related

(Gibson *et al.*, 2013). The cost of respiratory disease to the UK in 2004 was £6.6 billion of which £1.9 billion was mortality cost and £1.7 billion spent on morbidity with the remainder spent on NHS care (Hubbard, 2006). The cost difference between primary and secondary care is over £1700 (Punekar et al., 2015) with medications ranging anywhere between £3.30 and £48.64, further supporting the importance of correct and early diagnosis. Our study, as others (Roberts et al., 2015) have established that misdiagnosis of COPD in the very old may be contributing to these high costs. Furthermore, removal of the misconception that the very old are unable to perform spirometry, as well as the use of correct prediction methodology, could lead to diagnosis that is more accurate and reduced healthcare costs. Further research is recommended to examine the cost effectiveness of providing regular spirometry for patients that present with symptoms of restrictive and more so obstructive lung function. Our findings that lower lung function predicts later disability partly through cognitive impairment may also provide an impetus for regular lung function tests for older people, since this may also be indicative of early cognitive decline.

Smoking rates in Great Britain have been on the decline in adults aged 16 and over since 1974, however 2014 saw an slight increase in prevalence for women in two youngest age groups (16-24 and 25-34)(ONS, 2016). In the N85+ study up to 65% of participants had a history of smoking and smoking remained a predictor of mortality and lower lung function even in this cohort who had survived to age 85.

The implication and clinical relevance of such finding can be related to the fact that worsening or faster decline in lung function results in more hospital admissions (Mannino and Davis, 2006; Garcia-Aymerich *et al.*, 2011). There is a clear message that protection of good lung function leads to favourable health outcomes at older ages. Good lung function at older ages can be attained by maintenance of healthy behaviours (not smoking, increasing physical activity) from a young age. This is especially true for women where lung function was predictive of mortality even when adjusting for all potential confounders.

Increases in biomarkers of systemic inflammations were consistently associated with lower lung function (Finkel *et al.*, 2003; Ahmadi-Abhari *et al.*, 2014; Baldi *et al.*, 2014). In line with the findings from the N85+ study, this merits the use of CRP as an indicator of worsening lung function in the very old. Replication of the survival analysis and the trajectories of change in a larger cohort where there is enough power to investigate the interaction of time with predictors

of lung function and also where there is a large enough cohort to meet the proportional hazard assumption would be worthy to explore whether these findings hold true or not.

Since the population is ageing with increased life expectancy, it would be an advantage to focus on both intrinsic and functional ability to live longer without disability (Office for National Statistics, 2015). The findings in this study found that better lung function reduced the risk of disability. Furthermore, higher levels of physical activity and normal BMI were associated with reduced disability and increased lung function levels. These are modifiable health behaviours in addition to smoking which can improved at any stage of life.

7.7 Strengths and limitations

The main strengths of this study are the high participation and retention, the disease and spirometry measures and multiple time points, the advanced analytical methods and the different severity levels for disability. The N85+ study provided a comprehensive assessment of respiratory health and lung disease in the very old that was socio-demographically representative of England and Wales birth cohort of 845 participants (Collerton et al., 2009). Participants were interviewed in their homes achieving higher participation and retention rates. , and there was little withdrawal other than death and withdrawal did not appear to be linked to any particular participant health or demographic characteristic (Davies *et al.*, 2014).

Disease was ascertained from general practice record instead of self-report of doctor diagnoses thereby removing the risk of recall bias in this age group with higher rates of cognitive impairment. A key strength of this study was the uptake of spirometry conducted at the participants' place of residence with multiple tests performed by a trained research nurse and later individually validated by an experienced physiology nurse (Fisher *et al.*, 2016). Although the participants opting in were not a random sample, there was little evidence to suggest any difference in respiratory disease between the two groups (Fisher *et al.*, 2016). The availability of multiple longitudinal measures of health behaviours and characteristics in addition to spirometry was a major strength which enabled this study to investigate the role of lung function and its predictors over a three-year period and even longer follow-up for mortality (median 5.4 years).

The survival analysis used for the N85+ data was more precise in estimating mortality as the lung function measures and most covariates (except early life fixed such as education) were updated for each follow-up until death compared to other studies where only baseline measures

were used (Sabia *et al.*, 2010). A possible limitation of this analysis was that, in the earlier models before adjusting for all covariates, some models did not meet the proportional hazards assumption due to the spread of results for in certain covariates.

Multilevel modelling was used to analyse how lung function changes over time from age 85 years and path analysis to investigate the direction of the relationship between lung function and disability and how cognitive impairment may impact this. Few studies have been able to use these advanced statistical techniques, partly because of the lack of sufficient repeated measures of lung function. However, one limitation with the multilevel modelling undertaken was that, since men and women were analysed separately to allow for different functional forms of lung function over time (including baseline values at age 85). The relatively low numbers in each group did not allow the testing of interactions between time and potential predictors since models would not converge due to lack of statistical power.

As there were 17 ADL items available at each follow-up including 60 months (where spirometry was not) used to calculate three different measures of disability in investigating different aspects of capability and dependency in participants. The use of path models in comparison to standard regression model is the ability to quantify the influence of both direct and indirect variables. The availability of more than one follow-up allowed this study not to assume the direction of relationship between lung function and disability is a strength compared to other studies with only one follow-up period, which proved crucial as the study revealed bidirectional associations between lung function and disability.

A further limitation of this study is that those who agreed to participate may be comparatively healthier and less frail than those refusing to take part with a possible under-representation of those with cognitive impairment. The ability to opt in or out of the GPRR allowed for some investigation of participation to whole study (MDHA and GPRR) or part (GPRR only) and it was revealed that the rate for non-response and refusal to take part due to poor health was 30% for health assessment and 28% for GPRR (Collerton *et al.*, 2009).

7.8 Conclusion

The ageing population worldwide is placing an enormous burden on health care systems. Poor respiratory function is adding more strain and there are opportunities to lift some of this burden through better prediction and diagnosis of costly diseases such as COPD. As lung function is a predictor of both clinical and social care outcomes such as hospital admissions, disability and

mortality frequent lung function test could used to prevent or reduce the burden on the health and social care systems.There is a need for recognition that the modification of certain health and lifestyle behaviours could improve quality of life through maintenance of good lung function which leads to better cognitive and function al status during an individual’s lifetime.

Appendices

Appendix A: Excerpts of Newcastle 85+ Study Questionnaire

Complete questionnaires available at: https://research.ncl.ac.uk/85plus/

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The Newcastle

Study

Phase 1
Interview 1

The Institute for Ageing and Health

INTERVIEWER NOTES

- Interview 1 is the most important interview.
- For those participants who are particularly frail, the interview may need to be split over several visits or completed with the help of a proxy; use your judgement.

INTERVIEWS WITH A PROXY

- If you judge that a participant is too cognitively impaired to give reliable answers, you should carry out the interview with a proxy instead.
- In all other circumstances it is preferable to interview the participant directly. Where this is not possible an interview with a proxy is acceptable.
- If both participant and proxy are present and give conflicting responses, take the participant's answer, unless you have judged them too cognitively impaired to give reliable answers.
- The majority of the interview can be conducted with a proxy; those questions not possible with a proxy are clearly marked.
- Please note whether relevant sections were answered by participant, proxy or both by marking the appropriate code at the end of each section.

INTERVIEWER INSTRUCTIONS

- All interviewer instructions within the interview schedule will be in ***bold italics***.

TYPES OF QUESTIONS

- **Closed questions**: in these, a range of possible responses has been identified by the research team and are printed on the questionnaire. The interviewer should mark the appropriate box for the selected response. There will be an "other" category where necessary; please specify what the "other" is.
- **Numeric response questions**
    - If the numeric answer is actually zero this should be entered as such.
    - If the answer is 'missing', the interviewer should note the most appropriate missing value.
        - **'don't know'** response from the participant.
        - **'refused to answer'** from participant.
        - **'not applicable'** to this respondent because of an answer to a previous question. This code would be inserted where questions have been skipped.
        - **'not asked'** by interviewer (usually omitted in error)

PAPER QUESTIONNAIRES

- Use only blue or black biro to mark responses and pencil for interviewer notes.

Zeros, Z and 7 should all be crossed to avoid confusion with letter O, 2 and 1.

Attach bar code label

DATE OF BIRTH D D M M Y Y

Double check that they were born in 1921 and check any discrepancies

SEX MALE.....1
FEMALE.....2

RESEARCH NURSE ID

DATE OF 1st VISIT FOR INTERVIEW 1 D D M M Y Y

START TIME FOR 1ST VISIT

FINISH TIME FOR 1ST VISIT

DATE OF 2ND VISIT FOR INTERVIEW 1 D D M M Y Y

START TIME FOR 2ND VISIT

FINISH TIME FOR 2ND VISIT

DATE OF 3RD VISIT FOR INTERVIEW 1 D D M M Y Y

START TIME FOR 3RD VISIT

FINISH TIME FOR 3RD VISIT

DATE OF 4TH VISIT FOR INTERVIEW 1 D D M M Y Y

START TIME FOR 4TH VISIT

FINISH TIME FOR 4TH VISIT

TOTAL TIME FOR INTERVIEW 1 (MINS)

Interview 1

O. SMOKING

Possible with a proxy

This section asks about smoking.

1 Have you ever smoked a cigarette, cigar or pipe?

- Yes
- No **SKIP O2 to O23**
- *Don't know*
- *Refused to answer*
- *Not asked*

2 Do you smoke cigarettes at all nowadays?

- Yes **SKIP O10 to O17**
- No **SKIP O3 to O9**
- *Don't know* **SKIP O3 to O9**
- *Not applicable*
- *Refused to answer* **SKIP O3 to O9**
- *Not asked*

3 Do you mainly smoke:

- Filter tipped cigarettes **SKIP O6 to O9**
- Plain or untipped cigarettes **SKIP O6 to O9**
- Roll ups? **SKIP O4 O5**
- *Don't know* **SKIP O4 to O9**
- *Not applicable*
- *Refused to answer* **SKIP O4 to O9**
- *Not asked*

4 About how many cigarettes a day do you usually smoke on weekdays

5 About how many cigarettes a day do you usually smoke on weekends

6 About how much tobacco do you normally smoke on weekdays? (in oz)

7 ***If not in oz, enter details of amount***

8 About how much tobacco do you normally smoke per day on weekends? (in oz)

9 ***If not in oz, enter details of amount***

10 Have you ever smoked cigarettes ?

- Yes
- No **SKIP O11 to O18**
- *Don't know* **SKIP O11 to O18**
- *Not applicable*
- *Refused to answer* **SKIP O11 to O18**
- *Not asked*

11 Did you smoke cigarettes regularly, that is at least 1 cigarette a day, or did you smoke them only occasionally?

- Smoked cigarettes regularly, at least 1 a day
- Smoked them only occasionally **SKIP O12 to O18**
- Never really smoked cigarettes, just tried them once or twice **SKIP O12 to O18**
- *Don't know* **SKIP O12 to 18**
- *Not applicable*
- *Refused to answer* **SKIP O12 to O18**
- *Not asked*

12 Did you mainly smoke:

- ☐ Filter tipped cigarettes **SKIP O14 O15**
- ☐ Plain or untipped cigarettes **SKIP O14 O15**
- ☐ Roll ups? **SKIP O13**
- ☐ *Don't know* **SKIP O13 to O15**
- ☐ *Not applicable*
- ☐ *Refused to answer* **SKIP O13 to O15**
- ☐ *Not asked*

13 About how many cigarettes did you smoke in a day

14 About how much tobacco did you normally smoke a day? (in oz)

15 *If not in oz, enter details of amount*

16 How long ago did you stop smoking cigarettes?

- ☐ Less than 6 months ago
- ☐ More than 6 months but less than one year
- ☐ 1 or more years - specify
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

17 For approximately how many years did you smoke cigarettes regularly

18 How old were you when you started to smoke cigarettes regularly?

19 Do you smoke at least 1 cigar of any kind per month nowadays?

- Yes **SKIP O21**
- No **SKIP O20**
- *Don't know* **SKIP O20**
- *Not applicable*
- *Refused to answer* **SKIP O20**
- *Not asked*

20 About how many cigars do you usually smoke in a week?

21 Have you ever regularly smoked at least 1 cigar of any kind per month?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

22 Do you smoke a pipe at all nowadays?

- Yes **SKIP O23**
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

23 Have you ever smoked a pipe regularly?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

24 ***Smoking section answered by***

- ☐ Participant alone **SKIP O25**
- ☐ Proxy alone **SKIP O25**
- ☐ Participant and proxy
- ☐ *Item not completed*

25 ***If participant and proxy was this***

- ☐ Mainly participant
- ☐ Mainly proxy
- ☐ Equal contribution
- ☐ *Not applicable*
- ☐ *Item not completed*

26 Was this section omitted?

- ☐ Yes
- ☐ No **SKIP O27**
- ☐ *Item not completed*

27 Why was it omitted?

- ☐ Participant frailty/fatigue
- ☐ Participant distress
- ☐ Participant busy
- ☐ Proxy only interview - section not possible by proxy
- ☐ Proxy only interview - proxy didn't know
- ☐ Concern re interviewer safety
- ☐ Interviewer error
- ☐ Other reason (specify) ☐
- ☐ *Not applicable*
- ☐ *Item not completed*

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The Newcastle

Study

Phase 1
Interview 2

The Institute for Ageing and Health

GENERAL INFORMATION

- For those participants who are particularly frail, the interview may need to be split over several visits or completed with the help of a proxy; use your judgement.

INTERVIEWS WITH A PROXY

- If you judge that a participant is too cognitively impaired to give reliable answers, you should carry out the interview with a proxy instead.
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- Please note whether relevant sections were answered by participant, proxy or both by marking the appropriate code at the end of each section.

INTERVIEWER INSTRUCTIONS

- All interviewer instructions within the interview schedule will be in ***bold italics***

TYPES OF QUESTIONS

- **Closed questions**: in these, a range of possible responses has been identified by the research team and are printed on the questionnaire. The interviewer should mark the appropriate code number for the selected response. There will be an "other" category where necessary; please specify what the "other" is.
- **Numeric response questions**
    - If the numeric answer is actually zero this should be entered as such.
    - If the answer is 'missing', the interviewer should note the most appropriate missing value code.
        - **'don't know'** response from the participant.
        - **'refused to answer'** from participant.
        - **'not applicable'** to this respondent because of an answer to a previous question. This code would be inserted where questions have been skipped.
        - **'not asked'** by interviewer (usually omitted in error)

PAPER QUESTIONNAIRES

- Use only blue or black biro to mark responses and pencil for interviewer notes.

Zeros, Z and 7 should all be crossed to avoid confusion with letter O, 2 and 1.**Attach bar code label**

DATE OF BIRTH | | | | | | | (D D M M Y Y)

SEX **MALE……1**
FEMALE……2

RESEARCH NURSE ID | |

DATE OF 1st VISIT FOR INTERVIEW 2 | | | | | | | (D D M M Y Y)

START TIME FOR 1ST VISIT | | | |

FINISH TIME FOR 1ST VISIT | | | |

DATE OF 2ND VISIT FOR INTERVIEW 2 | | | | | | | (D D M M Y Y)

START TIME FOR 2ND VISIT | | | |

FINISH TIME FOR 2ND VISIT | | | |

DATE OF 3RD VISIT FOR INTERVIEW 2 | | | | | | | (D D M M Y Y)

START TIME FOR 3RD VISIT | | | |

FINISH TIME FOR 3RD VISIT | | | |

DATE OF 4TH VISIT FOR INTERVIEW 2 | | | | | | | (D D M M Y Y)

START TIME FOR 4TH VISIT | | | |

FINISH TIME FOR 4TH VISIT | | | |

TOTAL TIME FOR INTERVIEW 2 (MINS) | | |

Interview 2

Either ECG plus Waist/Hip Circumference or Spirometry and Oximetry will be done in Interview 2 with the converse in interview 3

II. SPIROMETRY and OXIMETRY

Questions 1-7 possible with a proxy

I would like to ask you some questions about your chest. Please answer yes or no where possible.

0 Is this section scheduled for Interview 3?

- ☐ Yes **SKIP II1 to II16**
- ☐ No
- ☐ *Item not completed*

1 Do you usually have a cough?

- ☐ Yes
- ☐ No **SKIP II2**
- ☐ *Don't know* **SKIP II2**
- ☐ *Not applicable*
- ☐ *Refused to answer* **SKIP II2**
- ☐ *Not asked*

2 *If yes, ask* Is it worse in the mornings?

- ☐ Yes
- ☐ No
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

3 Do you usually bring up phlegm from your chest?

- ☐ Yes
- ☐ No **SKIP II4**
- ☐ *Don't know* **SKIP II4**
- ☐ *Refused to answer* **SKIP II4**
- ☐ *Not asked*

4 *If yes, ask* Is it worse in the mornings?

- ☐ Yes
- ☐ No
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

5 Do you ever wheeze?

- ☐ Yes
- ☐ No **SKIP II6**
- ☐ *Don't know* **SKIP II6**
- ☐ *Not applicable*
- ☐ *Refused to answer* **SKIP II6**
- ☐ *Not asked*

6 *If yes, ask* Is it worse in the mornings?

- ☐ Yes
- ☐ No
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

7 Have you ever worked in any of the following

	Yes	No	*Don't know*	*Not applicable*	*Refused to answer*	*Not asked*
Heavy industry	☐	☐	☐	☐	☐	☐
Coal mining	☐	☐	☐	☐	☐	☐
Chemical works	☐	☐	☐	☐	☐	☐
Anywhere where you worked with asbestos	☐	☐	☐	☐	☐	☐

8 *HEIGHT* (cm): Women: Height= 1.35 x demi-span + 60.1

9 *HEIGHT* (cm): Men: Height= 1.40 x demi-span + 57.8

10 Was spirometry performed?

- Yes **SKIP II11**
- No **SKIP II12 II13**
- *Not applicable*
- *Item not completed*

11 If spirometry was not performed state reason

- Scheduled for interview 3
- Interviewer decision - Technical problem
- Interviewer omitted - Participant frailty/fatigue
- Interviewer omitted - Participant distress
- Interviewer omitted - Participant too busy
- Interviewer omitted - Concern re interviewer safety
- Omitted in error
- Interviewer decision - other reason (specify)
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

12 Were 3 good blows obtained?

- Yes **SKIP II13**
- No
- *Not applicable*
- *Item not completed*

13 If No, state reason

- Technical problem
- Unable to comprehend task
- Distress
- Fatigue
- Other: Specify
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

14 Was oximetry performed?

- Yes **SKIP II16**
- No **SKIP II15**
- *Not applicable*
- *Item not completed*

15 Oxygen saturation (%)

Min 93 Max 100 Omitted 990

16 If oximetry not performed, state reason

- Scheduled for interview 3
- Interviewer decision - Technical problem
- Interviewer omitted - Participant frailty/fatigue
- Interviewer omitted - Participant distress
- Interviewer omitted - Participant too busy
- Interviewer omitted - Concern re interviewer safety
- Omitted in error
- Interviewer decision - other reason (specify)
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

Attach Bar Code Label

The Newcastle

Study

Phase 1
Interview 3

The Institute for Ageing and Health

GENERAL INFORMATION

- For those participants who are particularly frail, the interview may need to be split over several visits or completed with the help of a proxy; use your judgement.

INTERVIEWS WITH A PROXY

- If you judge that a participant is too cognitively impaired to give reliable answers, you should carry out the interview with a proxy instead.
- In all other circumstances it is preferable to interview the participant directly. Where this is not possible an interview with a proxy is acceptable.
- If both participant and proxy are present and give conflicting responses, take the participant's answer, unless you have judged them too cognitively impaired to give reliable answers.
- The majority of the interview can be conducted with a proxy; those questions not possible with a proxy are clearly marked.
- Please note whether relevant sections were answered by participant, proxy or both by marking the appropriate code at the end of each section.

INTERVIEWER INSTRUCTIONS

- All interviewer instructions within the interview schedule will be in ***bold italics***

TYPES OF QUESTIONS

- **Closed questions**: in these, a range of possible responses has been identified by the research team and are printed on the questionnaire. The interviewer should mark the appropriate code number for the selected response. There will be an "other" category where necessary; please specify what the "other" is.
- **Numeric response questions**
    - If the numeric answer is actually zero this should be entered as such.
    - If the answer is 'missing', the interviewer should note the most appropriate missing value code.
        - **'don't know'** response from the participant.
        - **'refused to answer'** from participant.
        - **'not applicable'** to this respondent because of an answer to a previous question. This code would be inserted where questions have been skipped.
        - **'not asked'** by interviewer (usually omitted in error)

PAPER QUESTIONNAIRES

- Use only blue or black biro to mark responses and pencil for interviewer notes.
- Zeros, Z and 7 should all be crossed to avoid confusion with letter O, 2 and 1.

Attach Bar Code Label

DATE OF BIRTH | | | | | | |
D D M M Y Y

SEX MALE.....1
FEMALE.....2

RESEARCH NURSE ID | |

DATE OF 1st VISIT FOR INTERVIEW 3 | | | | | | |
D D M M Y Y

START TIME FOR 1ST VISIT | | | |

FINISH TIME FOR 1ST VISIT | | | |

DATE OF 2ND VISIT FOR INTERVIEW 3 | | | | | | |
D D M M Y Y

START TIME FOR 2ND VISIT | | | |

FINISH TIME FOR 2ND VISIT | | | |

DATE OF 3RD VISIT FOR INTERVIEW 3 | | | | | | |
D D M M Y Y

START TIME FOR 3RD VISIT | | | |

FINISH TIME FOR 3RD VISIT | | | |

DATE OF 4TH VISIT FOR INTERVIEW 3 | | | | | | |
D D M M Y Y

START TIME FOR 4TH VISIT | | | |

FINISH TIME FOR 4TH VISIT | | | |

TOTAL TIME FOR INTERVIEW 3 (MINS) | | |

Interview 3

Either ECG plus Waist and Hip Circumference or Spirometry and Oximetry will be done depending on what was carried out on Interview 2.

EEE. SHORTNESS OF BREATH

Possible with a proxy

I would now like to find out whether shortness of breath limits your day to day activities. I am not just asking whether or not you get short of breath when you do each activity but whether the shortness of breath limits you. I am interested in how you have been over the last 4 weeks, that is since ***(State date 4 weeks previously)***

1 So in the last 4 weeks, has shortness of breath limited your ability to move around your home (on one level)?

Do not include stairs

- ☐ Yes
- ☐ No **SKIP EEE2**
- ☐ Limited for reason(s) unrelated to shortness of breath **SKIP EEE2**
- ☐ *Don't know* **SKIP EEE2**
- ☐ *Refused to answer* **SKIP EEE2**
- ☐ *Not asked*

2 How much has shortness of breath limited your ability to move around your home (on one level)?

- ☐ A bit
- ☐ A lot
- ☐ Completely unable to move around the home due to shortness of breath
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

3 In the last 4 weeks, has shortness of breath limited your ability to walk outdoors, on the level, at your own pace?

- ☐ Yes
- ☐ No **SKIP EEE4**
- ☐ Limited for reason(s) unrelated to shortness of breath **SKIP EEE4**
- ☐ *Don't know* **SKIP EEE4**
- ☐ *Refused to answer* **SKIP EEE4**
- ☐ *Not asked*

4 How much has shortness of breath limited your ability to walk outdoors, on the level, at your own pace?

- A bit
- A lot
- Completely unable to walk outdoors, on the level, at own pace due to shortness of breath
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

5 In the last 4 weeks, has shortness of breath limited your ability to hurry on the level?

- Yes
- No **SKIP EEE6**
- Limited for reason(s) unrelated to shortness of breath **SKIP EEE6**
- *Don't know* **SKIP EEE6**
- *Refused to answer* **SKIP EEE6**
- *Not asked*

6 How much has shortness of breath limited your ability to hurry on the level?

- A bit
- A lot
- Completely unable to hurry on the level due to shortness of breath
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

7 Over the past 4 weeks, have you had any swelling in your feet, ankles or legs?
Only record bilateral swelling

- Yes
- No **SKIP EEE8**
- *Don't know* **SKIP EEE8**
- *Refused to answer* **SKIP EEE8**
- *Not asked*

8 Was this swelling ever so bad that you were unable to put on your shoes?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

9 Shortness of breath section answered by

- ☐ Participant alone **SKIP EEE10**
- ☐ Proxy alone **SKIP EEE10**
- ☐ Participant and proxy
- ☐ *Item not completed* **SKIP EEE10**

10 If participant and proxy

- ☐ Mainly participant
- ☐ Mainly proxy
- ☐ Equal contribution
- ☐ *Not applicable*
- ☐ *Item not completed*

11 Was this section omitted?

- ☐ Yes
- ☐ No **SKIP EEE12**
- ☐ *Item not completed*

12 Why was it omitted?

- ☐ Participant frailty/fatigue
- ☐ Participant distress
- ☐ Participant busy
- ☐ Proxy only interview - section not possible by proxy
- ☐ Proxy only interview - proxy didn't know
- ☐ Concern re interviewer safety
- ☐ Interviewer error
- ☐ Other reason (specify) ☒
- ☐ *Not applicable*
- ☐ *Item not completed*

MMM. SPIROMETRY AND OXIMETRY

I would like to ask you some questions about your chest. Please answer yes or no where possible.

0 Was this section completed on Interview 2?

- Yes **SKIP MMM1 to MMM16**
- No
- *Not applicable*

1 Do you usually have a cough?

- Yes
- No **SKIP MMM2**
- *Don't know* **SKIP MMM2**
- *Refused to answer* **SKIP MMM2**
- *Not asked*

2 *If yes, ask* Is it worse in the mornings?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

3 Do you usually bring up phlegm from your chest?

- Yes
- No **SKIP MMM4**
- *Don't know* **SKIP MMM4**
- *Not applicable*
- *Refused to answer* **SKIP MMM4**
- *Not asked*

4 *If yes, ask* Is it worse in the mornings?

- Yes
- No
- *Don't know*
- *Not applicable*
- *Refused to answer*
- *Not asked*

5 Do you ever wheeze?

- ☐ Yes
- ☐ No **SKIP MMM6**
- ☐ *Don't know* **SKIP MMM6**
- ☐ *Not applicable*
- ☐ *Refused to answer* **SKIP MMM6**
- ☐ *Not asked*

6 *If yes, ask* Is it worse in the mornings?

- ☐ Yes
- ☐ No
- ☐ *Don't know*
- ☐ *Not applicable*
- ☐ *Refused to answer*
- ☐ *Not asked*

7 Have you ever worked in any of the following

	Yes	No	*Don't know*	*Not applicable*	*Refused to answer*	*Not asked*
Heavy industry	☐	☐	☐	☐	☐	☐
Coal mining	☐	☐	☐	☐	☐	☐
Chemical works	☐	☐	☐	☐	☐	☐
Anywhere where you worked with asbestos	☐	☐	☐	☐	☐	☐

8 *HEIGHT* (cm): Women: Height= 1.35 x demi-span + 60.1

ENTER FROM INTERVIEW 1

9 *HEIGHT* (cm): Men: Height= 1.40 x demi-span + 57.8

ENTER FROM INTERVIEW 1

10 Was spirometry performed?

- Yes **SKIP MMM11**
- No **SKIP MMM12 MMM13**
- *Not applicable*
- *Item not completed*

11 If spirometry was not performed state reason

- Conducted in interview 2
- Interviewer decision - Technical problem
- Interviewer omitted - Participant frailty/fatigue
- Interviewer omitted - Participant distress
- Interviewer omitted - Participant too busy
- Interviewer omitted - Concern re interviewer safety
- Omitted in error
- Interviewer decision - other reason (specify)
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

12 Were 3 good blows obtained?

- Yes **SKIP MMM13**
- No
- *Not applicable*
- *Item not completed*

13 If No, state reason

- Technical problem
- Unable to comprehend task
- Distress
- Fatigue
- Other Reason: Specify
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

14 Was oximetry performed?

- Yes **SKIP MMM16**
- No **SKIP MMM15**
- *Not applicable*
- *Item not completed*

15 Oxygen saturation (%)

Min 93 Max 100 Omitted 990

16 If oximetry not performed, state reason

- Conducted in interview 2
- Interviewer decision - Technical problem
- Interviewer omitted - Participant frailty/fatigue
- Interviewer omitted - Participant distress
- Interviewer omitted - Participant too busy
- Interviewer omitted - Concern re interviewer safety
- Omitted in error
- Interviewer decision - other reason (specify)
- Participant or relative/carer refused - no reason
- Participant or relative/carer refused - other reason (specify)
- *Not applicable*
- *Reason not entered*

Appendix B: MRC Dyspnoea Questionnaire

1959 MRC Breathlessness Scale	
Grade 1	**Are you ever troubled by breathlessness except on strenuous exertion?**
Grade 2	**(If yes) Are you short of breath when hurrying on the level or walking up a slight hill?**
Grade 3	**Do you have to walk slower than most people on the level? Do you have to stop after a mile or so (or after ¼ hour) on the level at your own pace?**
Grade 4	**(If yes to either) Do you have to stop for breath after walking about 100 yds. (or after a few minutes) on the level?**
Grade 5	**(If yes) Are you too breathless to leave the house, or breathless after undressing?**

(Fletcher *et al.*, 1959)

Appendix C: Journal article emanating from this PhD

OPEN ACCESS

ORIGINAL ARTICLE

Respiratory health and disease in a UK population-based cohort of 85 year olds: The Newcastle 85+ Study

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► Additional material is published online only. To view this file please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2015-207249)

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Received 30 April 2015
Revised 11 November 2015
Accepted 18 November 2015
Published Online First 5 January 2016

CrossMark

To cite: Fisher AJ, Yadegarfar ME, Collerton J, *et al*. *Thorax* 2016;**71**:255–266.

ABSTRACT

Background People aged 85 years and older are the fastest growing age group worldwide. This study assessed respiratory health, prevalence of respiratory disease and use of spirometry in respiratory diagnosis in a population-based cohort of 85 year olds to better understand respiratory health and disease in this sector of society.

Methods A single year birth-cohort of 85 year olds participated in a respiratory assessment at their home or residential institution including self-reporting of symptoms and measurement of spirometry. General practice medical records were reviewed for respiratory diagnoses and treatments.

Findings In the 845 participants, a substantial burden of respiratory disease was seen with a prevalence of COPD in medical records of 16.6% (n=140). A large proportion of the cohort had environmental exposures through past or current smoking (64.2%, n=539) and occupational risk factors (33.6%, n=269). Spirometry meeting reliability criteria was performed in 87% (n=737) of participants. In the subgroup with a diagnosis of COPD (n=123), only 75.6% (n=93) satisfied Global Initiative in Obstructive Lung Disease (GOLD) criteria for airflow obstruction, and in a healthy subgroup without respiratory symptoms or diagnoses (n=151), 44.4% (n=67) reached GOLD criteria for airflow obstruction and 43.3% (n=29) National Institute of Health and Care Excellence criteria for at least moderate COPD.

Interpretation Spirometry can be successfully performed in the very old, aged 85 years, and may help identify respiratory diseases such as COPD. However interpretation in this age group using current definitions of COPD based on spirometry indices may be difficult and lead to overdiagnosis in a healthy group with transient symptoms.

Key messages

What is the key question?
- What is the burden of respiratory disease and utility of spirometry in aiding assessment of respiratory health and diagnosis of respiratory disease in community-living 85 year olds in the UK?

What is the bottom line?
- The study reveals a substantial burden of respiratory disease and symptoms in 85 year olds but also considerable discordance between physician-diagnosed COPD and confirmatory spirometry evidence in the very old that have important implications for clinical practice.

Why read on?
- This study represents the largest and most detailed assessment to date of respiratory health status and challenges of using spirometry criteria in respiratory diagnosis in the very old, aged 85 years and over, which are now the fastest growing sector of the population.

INTRODUCTION

The very old, aged 85 years and older, are now the most rapidly expanding age sector of most populations worldwide.[1] Data from the 2011 England and Wales Census showed a doubling of the over 85 years age group between 1985 and 2010, from nearly 0.7 million to over 1.4 million,[2] and numbers are projected to double again between 2010 and 2030.[3] This age group frequently uses healthcare resource in primary and secondary care,[4] and therefore understanding their health status and burden of disease is important for training of health professionals and for organisation of healthcare provision.

Symptoms relating to the respiratory system, in particular dyspnoea, are common in those 85 years and older with a prevalence of over 40%,[5] and are frequently a reason for older people to seek healthcare. Although it is recognised that many chronic respiratory diseases increase in prevalence and severity with age, it is also clear that dyspnoea is non-specific and may be associated with non-pulmonary morbidities.[6] In the very old, assessment of respiratory health is further complicated by the physiological changes that occur as part of 'normal' or 'healthy' ageing, such as loss of lung elasticity and reduced thoracic cage movement, which will have an effect on objective measures of lung function.[7]

Current national and international guidelines on the management of COPD have obstructive spirometry (FEV_1/FVC ratio <0.7) as a key diagnostic test directing physicians towards the use of specific

respiratory medications.[8 9] However, the accuracy of lung function criteria for the diagnosis of airflow obstruction or restrictive lung disease in very old people has been questioned due to the intrapulmonary and extrapulmonary physiological changes that occur in this age group as part of normal ageing.[10] This may cause misdiagnosis and inappropriate use of medications in this population. Moreover, a previous study in a population with a mean age of 73 years suggested that COPD may be either overdiagnosed or underdiagnosed depending on the approach taken to defining abnormal lung function.[11]

This study aimed to address the lack of knowledge about respiratory health, prevalence of lung disease and objective measures of lung function in the very old using baseline data from the Newcastle 85+ Study,[4 12] a large population-based cohort of 85 year olds. Specifically the study aimed to: assess the extent of common respiratory symptoms and the prevalence of physician-diagnosed lung disease, particularly COPD; and to assess the accuracy of COPD diagnosis based on lung function measurements, respiratory symptoms and identification of risk factors, and the degree to which respiratory medication was appropriately prescribed. Finally, in a healthy reference group (HRG), the study aimed to evaluate the applicability of three standard methods of interpreting lung function measurements as normal or abnormal to disentangle the effects of lung disease and 'normal' or 'healthy' ageing on measured lung function.

METHODS

Full details of the Newcastle 85+ Study methodology have been reported.[12] In brief, members of the 1921 birth cohort living in Newcastle upon Tyne or North Tyneside (North-East England) were recruited around their 85th birthday over a 17-month-period spanning 2006 and 2007. Participants included people living at home or in institutional care and regardless of their current health status. More detailed methods are available as online supplementary materials.

Existing diagnoses of respiratory disease, respiratory symptoms, respiratory medications and environmental risk factors

Current and past respiratory diagnoses were identified from a general practice records review (GPRR) using a predetermined checklist of chronic respiratory diseases. Data on use, but not doses, of respiratory medications were also obtained from GPRR. Data on symptoms of breathlessness, cough, wheeze and sputum production were obtained by a structured questionnaire administered as part of a domiciliary multidimensional health assessment (MDHA) conducted by a research nurse in the participant's home or institution. Specifically, participants were asked whether shortness of breath limited their day-to-day activities and responses were then used to assign an Medical Research Council (MRC) dyspnoea score.[8] Participants were asked about any relevant environmental exposure in their occupation or at home, specifically detailed smoking history and relevant occupational history (including exposure to heavy industry generally as well as the chemical industry, asbestos and coal mining). Two measures of disease burden were used: a disease count (maximum 18 diseases) previously determined in the cohort; and a non-respiratory disease count excluding COPD and other respiratory disease (maximum 16 diseases).[4] Further details of the individual respiratory diagnoses, medications and chronic non-respiratory diseases included in the disease count are provided (see online supplementary methods).

Lung function measurements

Spirometry and peak flow measurements were performed at the participant's place of residence by a trained research nurse using MicroLab Spirometer and Spida V.5 software (Micro Medical, Rochester, UK). The aim was to obtain three technically satisfactory maximal effort 'blows' to generate reproducible FEV_1, FVC and peak expiratory flow measurement (PEF); blows were repeated until this was achieved or maximum effort reached. Blows were assessed for technical adequacy using in-built Spida algorithms. All spirometry curves were assessed independently by a respiratory clinical physiologist and those able to produce at least two adequate blows were included in the analysis. If the necessary quality was lacking they were excluded from analysis. Demispan was measured as a surrogate for height[13] (calculated using standard equations) and height used with age and gender to calculate predicted values for FEV_1, FVC and peak flow using equations in the UK Department of Health guide.[9] Spirometry was classified (see online supplementary table S2) as normal, obstructive or restrictive based on the FEV_1/FVC ratio of 0.7 and the percentage of predicted values for FEV_1 and FVC, with obstructive spirometry further classified as mild, moderate or severe based on Global Initiative in Obstructive Lung Disease (GOLD) criteria.[10] In addition, we reanalysed the data using criteria presented by the Global Lung Function Initiative (GLI)[14] which provides alternative prediction model equations validated for ages 3 years to 95 years (see online supplementary tables S3–S5).

Healthy reference group

To establish the distribution of normal lung function in people aged 85 years, we identified a HRG of participants with no respiratory symptoms, no respiratory diagnoses, no current use of respiratory medications and no non-respiratory diagnosis which might influence lung function (eg, Parkinson's disease, kyphoscoliosis, heart failure, ankylosing spondylitis) in their GPRR. Those with a BMI >30 were also excluded from HRG. Lung function in the HRG was compared against equation derived[15] predicted values based on gender and height by three accepted methods: percentage predicted value; lower limit of normal (LLN) using American Thoracic Society/European Respiratory Society (ATS/ERS) criteria;[16] and Z scores.

Statistical methods

Gender differences in respiratory symptoms, diagnoses, environmental exposures and medications were examined using χ^2 and Mann-Whitney U tests. Gender differences in lung function were investigated in the whole sample, COPD group and the HRG using Mann-Whitney U test for continuous measures, χ^2 and Fisher's exact tests for categorised measures and Kruskal-Wallis test for ordered categorised measures. The relationship between FEV_1 and PEF scores was assessed using Pearson's correlation coefficients. Sensitivity analyses were carried out to examine differences between those included and excluded from analysis due to lack of spirometry measures and those with and without an MRC dyspnoea score. All analyses were conducted using Stata V.12.0 (StataCorp; College Station, Texas, USA).

RESULTS

Sociodemographic, non-respiratory health characteristics and environmental exposures of the study population

Details of the Newcastle 85+ Study population have been reported previously, and the study population was broadly

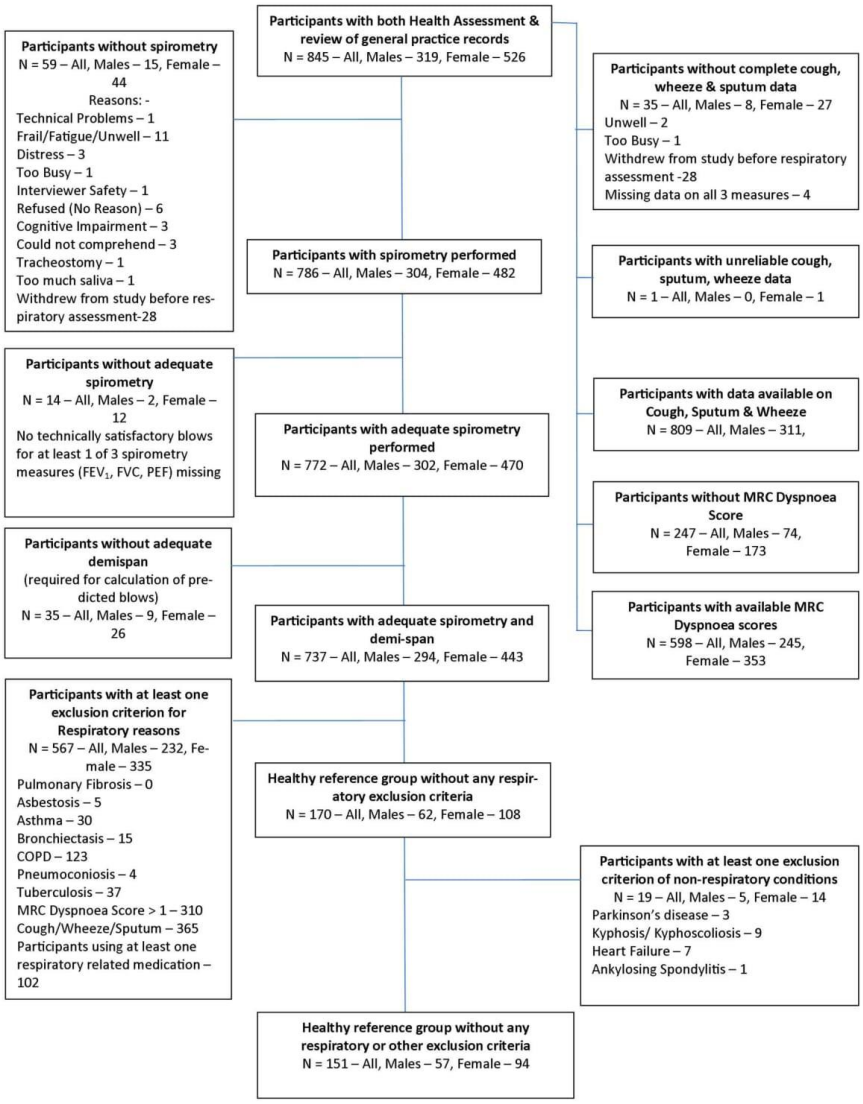

Figure 1 Flow chart illustrating how the total cohort of Newcastle 85+ Study participants was subdivided in the respiratory study sample, demonstrating why different numbers of participants are included in the analyses. The derivation of the study groups are shown in the flow chart; note that for some variables the number of participants included is less than 845 due to missing data, the reasons for which are detailed. The basis for the healthy reference group (HRG) was the 845 participants who had multidimensional health assessment (MDHA) and general practice records review (GPRR) conducted. Of these, 786 (93.0%) had spirometry performed of whom 772 performed it adequately; a further 35 participants with missing demispan were removed (unable to calculate predicted blows), resulting in 737. Participants with at least one respiratory condition, those with respiratory symptoms and those on respiratory medication were excluded which reduced the group size to 170. Other conditions which have an effect on spirometry values were also taken into account leading to exclusion of a further 19 participants. The remaining 151 (17.9% of 845) participants formed the HRG.

sociodemographically representative of the local population, and of England and Wales, including the proportion in institutional care.[4] Data from MDHA and GPRR was available for 845 participants, 58.2% (845/1453) of those eligible (figure 1); their mean (SD) age was 85.5 (0.4) years, 62.3% (526/845) were female and 99.6% (839/845) were of white ethnic group (table 1). Three-quarters were living in standard housing, 12.8% (108/845) in warden-supported accommodation and 10.2% (86/845) in institutional care. The median (IQR) chronic disease count was 5(3–6) with no significant gender difference

Table 1 Sociodemographic and health characteristics of the total Newcastle 85+ cohort (n=845) and by gender

	Men (n=319)	Women (n=526)	Overall cohort (n=845)	p Value*
Ethnicity % (N)				
White	99.4 (316)	99.8 (523)	99.6 (839)	0.272†
Living arrangements % (N)				
Standard housing	83.4 (266)	73.2 (385)	77.0 (651)	0.002†
Sheltered housing	10.3 (33)	14.3 (75)	12.8 (108)	
Institutional care	6.3 (20)	12.6 (66)	10.2 (86)	
Smoking % (N)				
Never	25.6 (81)	42.0 (220)	35.8 (301)	<0.001†
Former	69.9 (221)	51.5 (270)	58.5 (491)	
Current	4.4 (14)	6.5 (34)	5.7 (48)	
Occupational exposures % (N)				
Heavy industry	41.2 (126)	16.6 (83)	25.9 (209)	<0.001†
Coal mining	11.4 (35)	0.0 (0)	4.3 (35)	<0.001‡
Chemical industry	11.1 (34)	4.0 (20)	6.7 (54)	<0.001†
Asbestos exposure	28.9 (88)	1.6 (8)	12.0 (96)	<0.001†
Respiratory symptoms % (N)				
Cough	28.3 (88)	25.8 (129)	26.7 (217)	0.425†
Wheeze	25.0 (78)	20.2 (101)	22.0 (179)	0.109†
Sputum production	40.7 (127)	28.0 (140)	32.9 (267)	<0.001
MRC dyspnoea score % (N)				
1	50.2 (123)	40.5 (143)	44.5 (266)	0.048§
2	11.4 (28)	19.0 (67)	15.9 (95)	
3	20.4 (50)	17.6 (62)	18.7 (112)	
4	15.1 (37)	17.0 (60)	16.2 (97)	
5	2.9 (7)	6.0 (21)	4.7 (28)	
Respiratory diagnoses % (N)				
COPD	17.9 (57)	15.8 (83)	16.6 (140)	0.429†
Asthma	6.9 (22)	12.7 (67)	10.5 (89)	0.007†
Bronchiectasis	2.5 (8)	1.5 (8)	1.9 (16)	0.308†
Pulmonary fibrosis	0.0 (0)	0.2 (1)	0.1 (1)	1.000‡
Asbestosis	1.6 (5)	0.0 (0)	0.6 (5)	0.008‡
Pneumoconiosis	1.3 (4)	0.0 (0)	0.5 (4)	0.020‡
TB	4.4 (14)	4.9 (26)	4.7 (40)	0.713†
Respiratory medications				
Inhaled short-acting β-2 adrenoreceptor agonists	9.1 (29)	11.4 (60)	10.5 (89)	0.288†
Inhaled muscarinic antagonists	3.8 (12)	3.8 (20)	3.8 (32)	0.976†
Oral theophylline	0.3 (1)	0.5 (3)	0.5 (4)	0.598‡
Combination short-acting bronchodilators	0.6 (2)	0.0 (0)	0.2 (2)	0.142‡
Inhaled corticosteroids	5.3 (17)	7.8 (41)	6.9 (58)	0.169†
Combination inhaled Corticosteroids and long-acting β-2 adrenoreceptor agonists	1.9 (6)	2.1 (11)	2.0 (17)	0.833†
Oral leukotriene receptor antagonists	0.0 (0)	0.4 (2)	0.2 (2)	0.529‡
Oral mucolytics	0.6 (2)	0.2 (1)	0.4 (3)	0.560‡
At least one respiratory medication				
% (N)	12.2 (39)	14.5 (76)	13.6 (115)	0.361†
Disease count				
median (IQR)	4 (3–6)	5 (4–6)	5 (3–6)	0.074§
Comorbid disease count				
median (IQR)	4 (3–6)	5 (4–6)	5 (3–6)	0.047§

*Comparison of men and women.
§Mann–Whitney U test.
†χ^2 test.
‡Fisher's exact test,.
Denominators vary due to missing values.

(p=0.074). Although the 845 participants were a non-random sample of the eligible population, data from an additional 188 participants (18%) who opted for GPRR only showed no difference in respiratory diagnoses compared with those who participated fully.

Almost three quarters (74.4%, 235/316) of men and over half of women (58.0%, 304/524) had smoked in their lifetime, although very few (men: 4.4%, 14/316; women: 6.5%, 34/524) were current smokers. A significant proportion of men and women had occupational exposures which may have influenced respiratory health, with much higher prevalence in men (heavy industry: 41.2%, 126/306; coal mining: 11.4%, 35/307; chemical industry: 11.1%, 34/306; asbestos: 28.9%, 88/305), reflecting common historical occupations in this region of the UK (table 1).

Respiratory diagnoses, symptomatology and medication use

The most common physician-diagnosed respiratory condition was COPD with a prevalence of 16.6% (140/845) and no significant gender difference (p=0.43) (table 1). A diagnosis of asthma had been made in 10.5% (89/845) with a predominance in women (men: 6.9%; women: 12.7%; p=0.007). Other respiratory diagnoses were rare.

Chronic cough was self-reported in 26.7% (217/812) and wheeze in 22.0% (179/812) of participants. Regular sputum production was more common in men (men: 40.7%, 127/312; women: 28.0%, 140/500; p<0.001). An MRC dyspnoea score was assigned in 598 (70.8%) participants since in the other participants their activity could be limited by other non-respiratory conditions. Half (123/245) of the men and 40.5% (143/353) of the women allocated an MRC dyspnoea score had no limitations to their daily activities due to breathlessness.

The most frequently prescribed respiratory medications were inhaled short-acting β-2 adrenoreceptor agonists (10.5%, 89/845 of participants) followed by inhaled corticosteroids (6.9%, 58/845) (table 1). Only 2.0% (17/845) were taking a combination inhaler containing corticosteroid and a long-acting β-2 adrenoreceptor agonist. The use of other respiratory medications was unusual (table 1).

Lung function measurements

Spirometry was performed by 786 (93.0%) participants (figure 1), most of whom (98.2%, 772/786) provided at least two adequate blows conforming to ATS/ERS guidelines. Demispan was available for 737 participants with adequate expiratory effort and consistency allowing calculation of predicted spirometry values, with these 737 forming the spirometry group (table 2). Comparison of the spirometry group (n=737) with those excluded due to missing/inadequate spirometry and/or missing demispan (n=108) showed those excluded were more likely to be female, living in an institution and with previous exposure to the chemical industry, but not significantly different in smoking history; respiratory symptoms, diagnoses or medications; or dyspnoea scores (see online supplementary table S1).

Of the whole spirometry group, 31.2% (230/737) had a normal FEV_1/FVC ratio and 15.2% (112/737) had a restrictive

Table 2 Results of spirometry in the cohort completing spirometry with adequate reproducible blows and demispan available for calculation of predicted blows (n=737)

	Men (n=293)	Women (n=444)	All (n=737)	p Value*
Actual spirometry median (IQR)				
FEV_1 (l/s)	1.8 (1.4–2.2)	1.2 (1.0–1.5)	1.4 (1.1–1.8)	<0.001†
FVC (l/s)	2.7 (2.2–3.2)	1.8 (1.4–2.1)	2.0 (1.6–2.6)	<0.001†
FEV_1/FVC	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.006†
PEF (L/m)	441 (323–604)	283 (196–362)	328 (233–450)	<0.001†
% predicted median (IQR)				
FEV_1	78.8 (62.4–94.3)	83.4 (68.1–98.8)	81.5 (65.6–97.1)	0.008†
FVC	83.4 (70.3–99.6)	96.6 (79.1–113.7)	90.8 (74.1–108.4)	<0.001†
Spirometry % (N)				
Normal	28.0 (82)	33.3 (148)	31.2 (230)	0.108‡
Restrictive	13.7 (40)	16.2 (72)	15.2 (112)	
Obstructive	58.4 (171)	50.5 (224)	53.6 (395)	
Grading of obstructive spirometry§ % (N)				
Mild	35.7 (61)	43.3 (97)	40.0 (158)	0.059¶
Moderate	46.8 (80)	45.1 (101)	45.8 (181)	
Severe	14.6 (25)	9.8 (22)	11.9 (47)	
Very severe	2.9 (5)	1.8 (4)	2.3 (9)	
FEV_1 % (N)				
Below LLN	25.9 (76)	13.3 (59)	18.3 (135)	<0.001**
Normal range	73.7 (216)	85.6 (380)	80.9 (596)	
Above ULN	0.3 (1)	1.1 (5)	0.8 (6)	
FEV_1 Z-score				
median (IQR)	1.0 (0.2–1.7)	0.6 (0.0–1.2)	0.8 (0.1–1.4)	<0.001†
FVC % (N)				
Below LLN	21.2 (62)	9.2 (41)	14.0 (103)	<0.001‡
Normal range	77.1 (226)	86.3 (383)	82.6 (609)	
Above ULN	1.7 (5)	4.5 (20)	3.4 (25)	
FVC Z-score				
median (IQR)	0.9 (0.0–1.5)	0.1 (−0.6–0.9)	0.4 (−0.4–1.2)	<0.001†
Oxygen saturation				
median (IQR)	97 (96–98)	97 (96–98)	97 (96–98)	0.513†

*Comparison of men and women.
†Mann–Whitney U test.
‡χ^2 test.
§This is based on the 395 participant subsample with obstructive spirometry.
¶Kruskal–Wallis test.
**Fisher's exact test.
LLN, lower limit of normal; PEF, peak expiratory flow; ULN, upper limit of normal.

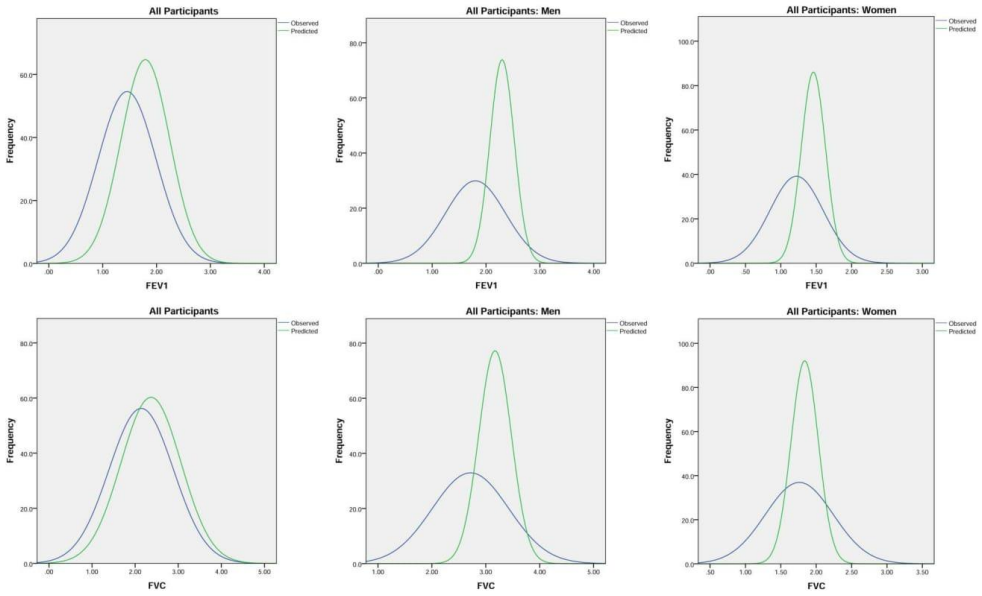

Figure 2 Distribution curves of FEV_1 and FVC in all participants in spirometry cohort (all, men and women) measured (blue) and predicted (green).

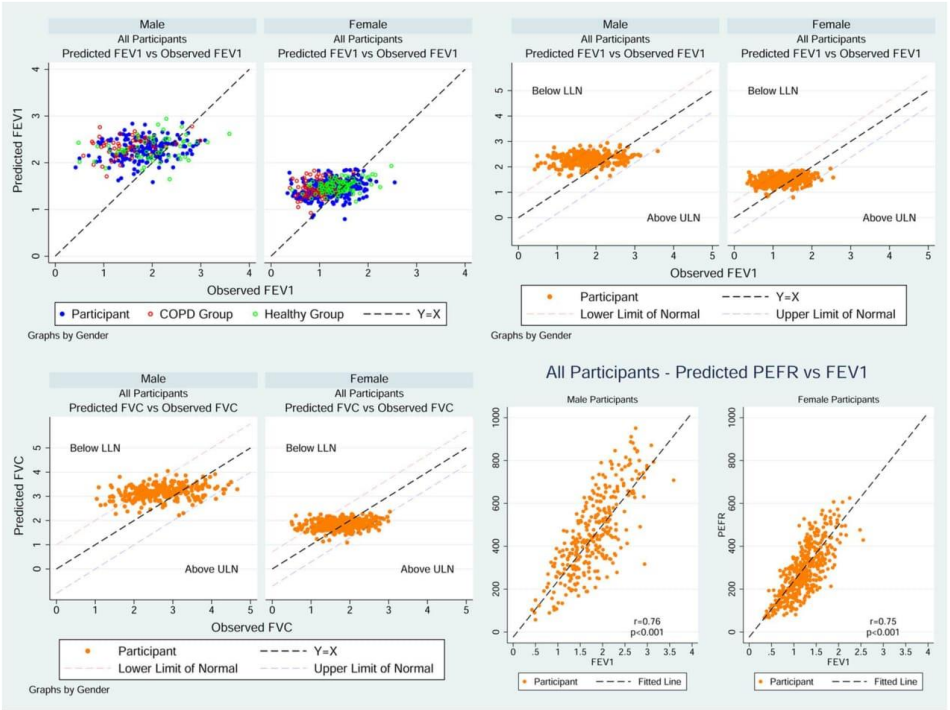

Figure 3 Scatter plots of spirometry and peak expiratory flow in all participants in spirometry cohort.

Table 3 Descriptive characteristics of subset with physician-diagnosed COPD in general practitioner records

	Men (n=52)	Women (n=71)	All (n=123)	p Value*
Smoking % (N)				
Never	21.2 (11)	25.7 (18)	23.8 (29)	0.637†
Former	67.3 (35)	67.1 (47)	67.2 (82)	
Current	11.5 (6)	7.1 (5)	9.0 (11)	
Occupational exposure % (N)				
Heavy industry	49.0 (25)	19.7 (14)	32.0 (39)	0.001†
Coal mining	17.7 (9)	0.0 (0)	7.4 (9)	<0.001‡
Chemical	13.7 (7)	2.8 (2)	7.4 (9)	0.034‡
Asbestos	33.3 (17)	7.1 (5)	18.2 (22)	<0.001†
Non-smokers with no occupational exposures % (N)	3.9 (2)	18.3 (13)	12.2 (15)	0.023†
Respiratory symptoms % (N)				
Cough	46.2 (24)	53.5 (38)	50.4 (62)	0.419†
Wheeze	53.9 (28)	56.3 (40)	55.3 (68)	0.784†
Sputum production	63.5 (33)	54.3 (38)	58.2 (71)	0.310†
MRC dyspnoea score % (N)				
1	26.8 (11)	12.5 (7)	18.6 (18)	0.035§
2	9.8 (4)	16.1 (9)	13.4 (13)	
3	34.2 (14)	19.6 (11)	25.8 (25)	
4	22.0 (9)	33.9 (19)	28.9 (28)	
5	7.3 (3)	17.9 (10)	13.4 (13)	
Comorbid respiratory diagnoses % (N)				
Asthma	25.0 (13)	49.3 (35)	39.0 (48)	0.006†
Bronchiectasis	7.7 (4)	2.8 (2)	4.9 (6)	0.240‡
Asbestosis	7.7 (4)	0.0 (0)	3.3 (4)	0.030‡
Pulmonary fibrosis	0.0 (0)	0.0 (0)	0.0 (0)	–
Pneumoconiosis	3.9 (2)	0.0 (0)	1.6 (2)	0.177‡
TB	5.8 (3)	9.9 (7)	8.1 (10)	0.516‡
Medications % (N)				
Inhaled short-acting β-2 adrenoreceptor agonists	36.5 (19)	52.1 (37)	45.5 (56)	0.087†
Inhaled muscarinic antagonists	17.3 (9)	22.5 (16)	20.3 (25)	0.477†
Oral theophylline	1.9 (1)	4.2 (3)	3.3 (4)	0.637‡
Combination short-acting bronchodilators	1.9 (1)	0.0 (0)	0.8 (1)	0.423‡
Inhaled corticosteroids	17.3 (9)	38.0 (27)	29.3 (36)	0.013†
Combination inhaled corticosteroids and long-acting β-2 adrenoreceptor agonists	11.5 (6)	12.7 (9)	12.2 (15)	0.849†
Oral leukotriene receptor antagonists	0.0 (0)	1.4 (1)	0.8 (1)	1.000‡
Oral mucolytics	1.9 (1)	1.4 (1)	1.6 (2)	1.000‡
Oral glucocorticoid therapy	5.8 (3)	4.2 (3)	4.9 (6)	0.697‡
At least 1 respiratory medication % (N)	46.2 (24)	66.2 (47)	57.7 (71)	0.026†
Disease count				
median (IQR)	5 (4–7)	6 (5–7)	6 (4–7)	0.156§
Non-respiratory disease count				
median (IQR)	5 (4–6)	6 (5–7)	6 (4–7)	0.064§

*Comparison of men and women.
†χ^2 test.
‡Fisher's exact test.
§Mann–Whitney U test.
Denominators vary due to missing values.

pattern. Obstructive spirometry was the most common finding (men: 58.4%, 171/293; women: 50.5%, 224/444) but with no gender difference in the spread of severity (table 2). Measured values of FEV_1, FVC and PEF in the spirometry group were normally distributed but with a much wider distribution range than that of the predicted values (figure 2). Scatter plots of the measured FEV_1 and FVC against the predicted values showed more participants with measured values below the predicted values than above suggesting a downward shift in the population as a whole (figure 3). The spread of FEV_1 measurements around the predicted values was much wider in men than women.

Prevalence and accuracy of physician-diagnosed COPD

Of the spirometry group, 16.7% (123/737) had physician-diagnosed COPD (COPD group) of whom 57.7% (71/123) were female and 23.8% (29/123) reported being 'never smokers' (table 3). More than half of the 'never smokers' with a COPD diagnosis had no occupational exposures either.

In the COPD group, only 45.5% (56/123) were taking short-acting inhaled β-2 adrenoreceptor agonist bronchodilator therapy, 20.3% (25/123) were taking inhaled long-acting muscarinic antagonists, 41.5% (51/123) were on inhaled corticosteroids either as monotherapy (36/51) or in combination with a

Table 4 Results of spirometry in the subgroup with physician-diagnosed COPD (n=123)

	Men (n=52)	Women (n=71)	All (n=123)	p Value*
Actual median (IQR)				
FEV_1	1.4 (1.1–1.8)	1.0 (0.7–1.1)	1.1 (0.8–1.4)	<0.001†
FVC	2.4 (2.0–3.1)	1.6 (1.3–1.9)	1.9 (1.5–2.3)	<0.001†
FEV_1/FVC	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.591†
PEF	382.5 (243–519)	218 (144–290)	259 (191–380)	<0.001†
%predicted median (IQR)				
FEV_1	63.5 (50.9–73.4)	64.2 (51.7–79.9)	64.2 (51.3–76.4)	0.609†
FVC	77.4 (64.2–94.1)	87.6 (70.4–101.0)	82.8 (68.2–99.8)	0.040†
Spirometry %(N)				
Normal	7.7 (4)	8.5 (6)	8.1 (10)	0.959‡
Restrictive	15.4 (8)	16.9 (12)	16.3 (20)	
Obstructive	76.9 (40)	74.7 (53)	75.6 (93)	
Obstructive spirometry§ %(N)				
Mild	10.0 (4)	20.8 (11)	16.1 (15)	0.190¶
Moderate	60.0 (24)	56.6 (30)	58.1 (54)	
Severe	27.5 (11)	20.8 (11)	23.7 (22)	
Very severe	2.5 (1)	1.9 (1)	2.2 (2)	
FEV_1 %(N)				
Below LLN	48.1 (25)	33.8 (24)	39.8 (49)	0.137**
Normal range	51.9 (27)	66.2 (47)	60.2 (74)	
Above ULN	0.0 (0)	0.0 (0)	0.0 (0)	
FEV_1 Z-score				
median (IQR)	1.6 (1.2–2.2)	1.3 (0.7–2.0)	1.5 (0.9–2.0)	0.039†
FVC %(N)				
Below LLN	30.8 (16)	14.1 (10)	21.1 (26)	0.043**
Normal range	69.2 (36)	84.5 (60)	78.1 (96)	
Above ULN	0.0 (0)	1.4 (1)	0.8 (1)	
FVC Z-score				
median (IQR)	1.1 (0.3–1.8)	0.6 (0.0–1.2)	0.8 (0.0–1.6)	0.008†
Oxygen saturation				
median (IQR)	97 (96–98)	97 (95–98)	97 (95–98)	0.521†

*Comparison of men and women.
†Mann–Whitney U test.
‡χ^2 test.
§This is based on the 93 participant subsample with obstructive spirometry.
¶Kruskal–Wallis test.
**Fisher's exact test.
LLN, lower limit of normal; PEF, peak expiratory flow; ULN, upper limit of normal.

long-acting β-agonist (15/51). There was minimal use of theophylline preparations, oral mucolytics or oral leukotriene receptor antagonists and none of the COPD group used home oxygen (table 3). The proportion of the COPD group that were on at least one respiratory medication differed significantly between men and women (men: 46.2%, 24/52; women: 66.2%, 47/71; p=0.026), although a sizeable proportion (42.3%, 52/123) of those with a COPD diagnosis were not on any (table 3). There was a significant overlap in the diagnoses of asthma and COPD with 61% (48/78) of those with an asthma diagnosis also being diagnosed with COPD.

Respiratory symptoms were common but not universal in the COPD group with 50.4% (62/123) reporting cough and 58.2% (71/123) sputum production. Nevertheless 26.8% (11/52) of men and 12.5% (7/71) of women with a COPD diagnosis had only minimal breathlessness (MRC dyspnoea score=1).

Only 75.6% (93/123) of the COPD group had obstructive spirometry by GOLD criteria (table 4). There was no gender difference in severity of airflow obstruction (based on % predicted FEV_1) and only 63.4% (78/123) of the COPD group fulfilled the UK National Institute of Health and Care Excellence (NICE) guidelines spirometry definition of moderate, severe or very severe disease (table 4). Furthermore, only 63.4% (78/123) of the COPD group fulfilled the UK NICE guidelines spirometry definition of moderate, severe or very severe disease. When FEV_1 was classified by the LLN approach, 48.1% (25/52) of men and 33.8% (24/71) of women from the COPD group fell below the LLN with all other participants falling between the LLN and upper limit of normal, suggesting that a substantial proportion (60.2%, 74/123) of those with physician-diagnosed COPD had an FEV_1 in the normal range and/or no airflow obstruction on spirometry measurement. When applying the GLI prediction models to the COPD group, 48.1% (25/52) men and 50.7% (36/71) women satisfied criteria for airflow obstruction (see online supplementary table S4). The degree of agreement between physician-diagnosed COPD and spirometric evidence of airflow obstruction using either GOLD or GLI criteria is poor when assessed by the McNemar test (see online supplementary table S6).

Assessment of lung function in an HRG

Figure 1 shows the derivation of the HRG which comprised 20.5% (151/737) of the spirometry cohort (table 5). The distribution of measured and predicted FEV_1, FVC and PEF in this

Table 5 Results of spirometry in healthy reference group of participants (n=151)

	Men (n=57)	Women (n=94)	All (n=151)	p Value*
Actual median (IQR)				
FEV_1	2.0 (1.7–2.4)	1.4 (1.2–1.6)	1.5 (1.2–2.0)	<0.001†
FVC	2.9 (2.4–3.5)	1.9 (1.6–2.2)	2.1 (1.8–2.8)	<0.001†
FEV_1/FVC	0.7 (0.6–0.8)	0.7 (0.7–0.8)	0.7 (0.6–0.8)	0.244†
PEF	515 (340–647)	329.5 (243–417)	367 (263–515)	<0.001†
%predicted median (IQR)				
FEV_1	90.1 (67.6–103.8)	93.8 (78.6–106.0)	91.6 (76.0–106.0)	0.154†
FVC	92.3 (72.0–107.7)	101.2 (85.2–121.7)	97.5 (80.6–115.2)	0.006†
Spirometry %(N)				
Normal	38.6 (22)	44.7 (42)	42.4 (64)	0.764‡
Restrictive	14.0 (98)	12.8 (12)	13.3 (20)	
Obstructive	47.4 (27)	42.6 (40)	44.4 (67)	
Obstructive spirometry§ %(N)				
Mild	48.2 (13)	62.5 (25)	56.7 (38)	0.137¶
Moderate	33.3 (9)	32.5 (13)	32.8 (22)	
Severe	11.1 (3)	5.0 (2)	7.5 (5)	
Very severe	7.4 (2)	0.0 (0)	3.0 (2)	
FEV_1 %(N)				
Below LLN	21.1 (12)	5.3 (5)	11.3 (17)	0.008**
Normal range	77.2 (44)	93.6 (88)	87.4 (132)	
Above ULN	1.8 (1)	1.1 (1)	1.3 (2)	
FEV_1 Z-score				
median (IQR)	0.5 (−0.2–1.6)	0.3 (−0.2–0.9)	0.3 (−0.2–1.0)	0.071†
FVC %(N)				
Below LLN	19.3 (11)	1.1 (1)	8.0 (12)	<0.001**
Normal range	79.0 (45)	91.5 (86)	86.8 (131)	
Above ULN	1.8 (1)	7.5 (7)	5.3 (8)	
FVC Z-score				
median (IQR)	0.4 (−0.4–1.5)	−0.1 (−0.9–0.6)	0.1 (−0.7–0.9)	0.004†
Oxygen saturation				
median (IQR)	98 (96–98)	98 (97–98)	98 (96–98)	0.970†

*Comparison of men and women.
†Mann–Whitney U test.
‡χ^2 test.
§This is based on the 67 participant subsample with obstructive spirometry.
¶Kruskal–Wallis test.
**Fisher's exact test.
LLN, lower limit of normal; PEF, peak expiratory flow; ULN, upper limit of normal.

group, by gender, are shown in figure 4 and table 5, with scatter plots of measured versus predicted FEV_1 and FVC by gender in figure 5.

Approximately half of the HRG (men: 47.4%, 27/57; women: 42.6%, 40/94) had a spirometry definition of airflow obstruction by GOLD criteria (table 5) yet did not fulfil the requirements for a diagnosis of COPD through lack of symptoms. Interestingly 19.2% (29/151) fulfilled a spirometry definition of at least moderate COPD using NICE criteria (obstructive spirometry and an FEV_1 <80% predicted). The measured best PEF median (IQR) for this group was 367 (263–515) L/min, significantly higher in men (515 (340–647) L/min) than in women (329.5 (243–417) L/min) (p<0.001), and highly correlated with FEV_1 (figure 5). When applying the GLI criteria to HRG only 17.5% (10/57) men and 16% (15/94) women (see online supplementary table 5) fulfilled criteria for airflow obstruction suggesting that GLI offered superiority to GOLD in spirometry interpretation in this age group.

The measured spirometry values in HRG were compared with equation-derived[15] predicted values based on gender and height using three different accepted approaches: percentage predicted value, LLN and Z scores (table 5). The median (IQR) percentage predicted value FEV_1 in HRG was 90.1% (67.6–103.8%) in men and 93.8% (78.6–106.0%) in women. The measured FEV_1 fell below LLN in 11.3% (17/151) of participants with a large gender difference (men: 21.1%, 12/57; women: 5.3%, 5/94; p=0.008). A significant gender difference was also found for the proportion of measured FVC falling below LLN with observed gender difference in the median Z-scores (table 5).

DISCUSSION

This study presents the first evaluation of respiratory symptomatology, respiratory disease prevalence and objectively measured lung function in a large UK population-based single-year birth cohort of 85 year olds. It provides insight into the burden of respiratory disease and degree of respiratory impairment in very old people in an urban setting, and illustrates a population with substantial environmental exposures and smoking history, even in women. Furthermore, despite the higher rate of cognitive impairment with age, 93% of our cohort performed spirometry and of these 98% did so successfully which challenges reluctance to use spirometry in the very old and

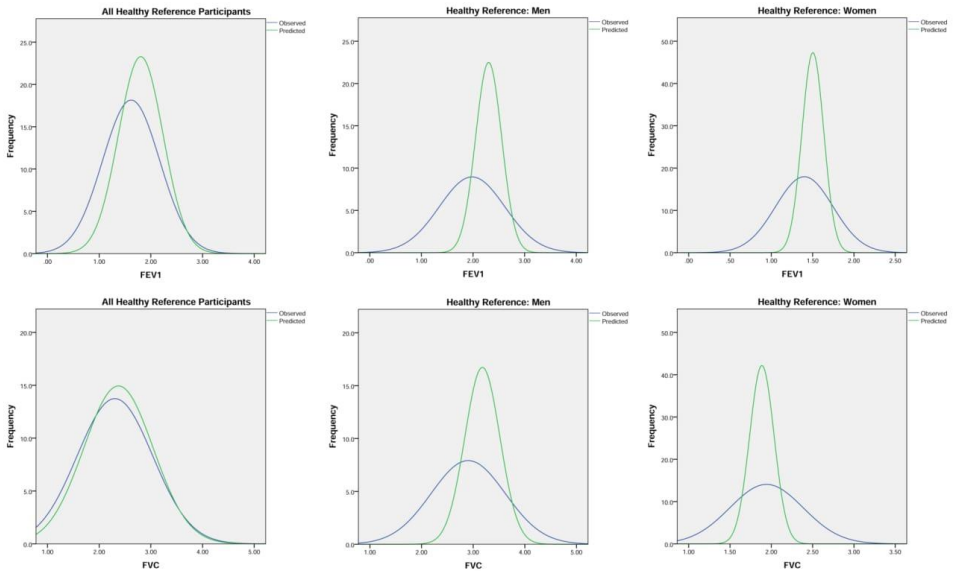

Figure 4 Distribution curves of FEV_1 and FVC of participants in the healthy reference group (all, men and women) measured (blue) and predicted (green).

dispels misconceptions that they cannot perform spirometry successfully.

The participants are long-lived, and survivors of some of the most remarkable historical periods of our time, starting in the year of their birth immediately post World War I and the 1918 Spanish influenza pandemic. There were high levels of deprivation, and unemployment across Britain reached 17% in 1921. This period was pre welfare state, Housing Act (1930), Clean Air Act and widespread use of penicillin (1940). Many of the participants would have been nearing retirement age when the 1986 WHO: Ottawa Charter for Health Promotion was introduced—smoking rates are particularly high for men.

It is therefore not unexpected that a high prevalence of physician-diagnosed COPD (16.7%) was identified compared with previous self-reports of COPD of 10% in 65–74 year olds in the 2010 Health Survey for England.[17] Nevertheless there were signs of potential misdiagnosis of COPD with a significant proportion of those with physician-diagnosed COPD having no evidence of airflow obstruction on spirometry, no smoking or occupational history and minimal symptoms. At the same time, a high proportion of our HRG fulfilled spirometry criteria for COPD using current GOLD/NICE guidelines, though use of LLN and GLI criteria rather than GOLD or NICE guidelines might reduce levels of misdiagnosis.

The risk of respiratory impairment increases with age due to the cumulative lifetime effect of environmental insults from active and passive cigarette smoking, air pollution, occupational dusts and infections.[18 19] When this risk is added to the changes which occur in the respiratory system as part of normal ageing, including reduced ventilatory control, reduced respiratory muscle strength, increased compliance and less favourable respiratory mechanics due to reduced movement of the chest wall,[7] it is not surprising that symptoms of cough, wheeze and dyspnoea are common in older people. All of these factors are likely to reduce measured lung function, which has been shown to be an independent risk factor for frailty and death.[20–22] Distinguishing physiological age-related loss of lung function from a pathological disease process in the lungs is further complicated by a reduced perception of respiratory symptoms that occurs with increasing age as demonstrated by significantly reduced awareness of measured bronchospasm after a methacholine challenge in older compared with younger patients.[23] Despite the high prevalence of chronic lung disease and respiratory symptoms, we found a significant proportion, 50% of men and 40% of women, with no reported limitations due to breathlessness suggesting many are either able to function very well or have a poor perception of symptoms.

The strengths of this work are the comprehensive assessment of respiratory health and lung disease in a large population-based cohort of 85 year olds, including those in institutional care and those with cognitive impairment, in a stable urban setting and with little ethnic diversity. The cohort of >800 participants was achieved through engagement with 83% of the general practices in the area and a consent rate of almost 60% in those approached to participate. Previous studies of respiratory health in older subjects have relied on self-reported diagnoses whereas in our study the use of general practice records significantly improves the validity of our findings.[24 25] Furthermore by conducting spirometry in the participant's place of residence using trained research nurses we were able to achieve a very high uptake of this assessment, in contrast to the known selection bias if participants had been required to attend a clinic for assessment. Although participants opting in for the health assessment were not a random sample of those eligible, there was little evidence to suggest they had more or less respiratory disease than those refusing the health assessment. In

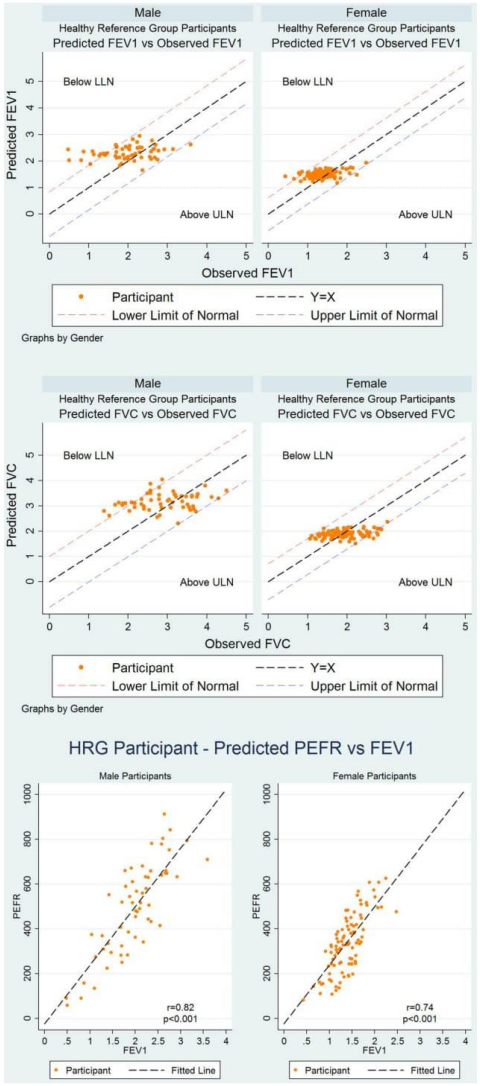

Figure 5 Scatter plots of spirometry and peak expiratory flow in the healthy reference group.

addition they were sociodemographically representative of their England and Wales birth cohort.[4] A potential limitation of the study is that those who agreed to participate may be healthier and less frail than those who declined to participate and those with cognitive impairment may have been under-represented. Although some information was collected about why those invited declined to participate, we obviously do not have objective data on their respiratory health or disease burden. However the prevalence of COPD of 16.7% in those who agreed to MDHA and GPRR (n=845) was very similar to the prevalence of 16.5% reported previously in all participants with GPRR data (n=1030),[4] suggesting that in terms of COPD, those agreeing to MDHA had similar respiratory health profiles to the larger study population. While 85 year olds in this urban area in North-East England are sociodemographically and ethnically similar to the same birth cohort in England and Wales as a whole, they may differ from those in other parts of the world.

This study has revealed a substantial burden of respiratory symptoms and respiratory disease, particularly COPD, in a cohort of the very old aged 85 years; a group with substantial environmental exposures recorded through smoking and occupational exposure, which are known risk factors for lung disease. Despite these observations, we show a good proportion of participants functioning well with no respiratory symptoms or diagnoses. Lung function tests revealed only 75.6% of the COPD group satisfied spirometry criteria whereas 44% of the healthy group satisfied spirometry criteria for COPD using GOLD criteria. Healthcare professionals need to recognise that spirometry can be reliably assessed in the vast majority of this age group but care is needed as to how this is interpreted. Current definitions of COPD based on spirometry may lead to overdiagnosis in a group with transient symptoms and 'normal' lung ageing, whereas at the same time failure to use spirometry to assess symptoms in this age group may lead to mislabelling those with breathlessness or cough as having COPD when there are other explanations.

Acknowledgements The authors thank the 85 year olds of Newcastle and North Tyneside, and their families and carers, for the generous donation of their time and personal information. The authors also thank the research nurses, data manager, project secretary, and the North of England Commissioning Support Unit and local general practitioners and their staff.

Contributors AJF: study design; data preparation; literature review; data analysis and interpretation; development and writing of the paper. MEY: literature review, statistical analysis and interpretation of data; development and critical review of paper drafts. JC: study design; supervision of data collection; data preparation; literature review; data analysis and interpretation; and the development and writing of the paper. TS: study design; supervision of data collection; literature review; development of paper and critical review of paper drafts. TBLK: overall leadership of the Newcastle 85+ Study; study design; and critical review of paper drafts. KD: study design; participant recruitment; supervision of data collection; data preparation; and critical review of paper drafts. CJ: study design; supervision of statistical analysis; data interpretation; and critical review of paper drafts. PAC: study design; data interpretation; and critical review of paper drafts.

Funding UK Medical Research Council and Biotechnology and Biological Sciences Research Council (G0500997), Dunhill Medical Trust (R124/0509); Newcastle Healthcare Charity; NIHR Newcastle Biomedical Research Centre.

Competing interests The authors declare: the authors' institution had financial support from the UK Medical Research Council and the Biotechnology and Biological Sciences Research Council (G0500997), the Dunhill Medical Trust (a privately endowed foundation having no connection with tobacco industries) and the Newcastle Healthcare Charity in terms of funding the submitted work; CJ was supported by the AXA Research Fund from 2010 to 2015.

Patient consent Obtained.

Ethics approval The research complied with the requirements of the Declaration of Helsinki. Ethical approval was obtained from the Newcastle and North Tyneside 1 Research Ethics Committee (reference number 06/Q0905/2).

Provenance and peer review Not commissioned; externally peer reviewed.

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