Exploring the currency of spirometric predictive equations from the viewpoint of the Lung Age concept.

Wendy Lynne Newbury

Discipline of General Practice

School of Population Health

Faculty of Health Sciences

The University of Adelaide

Australia

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Adelaide

June 2013

Table of Contents

Abstract

Spirometry is used to diagnose respiratory disease, to monitor disease progression and response to treatment, and in epidemiological surveys. As a large burden of disease is caused by cigarette smoking, spirometry has been incorporated in smoking cessation counselling in an attempt to improve quit rates. The concept of lung age (LA) was developed in 1985 in an effort to make spirometry results more easily understood by the lay person. Research results using LA to aid quitting remain inconclusive. This thesis investigates the need to update LA equations, as predictive equations based on old data may not be relevant for today's populations, and contemporary equations may result in a stronger message for smokers.

New LA equations were firstly developed using contemporary Australian data and four further LA equations were derived from previously published FEV_1 predictive equations. A series of comparisons of LA equations in contemporary Australian datasets followed.

The first project compared the original Morris LA equations with newly developed Australian LA equations in an independent workplace dataset (males only).

The second project compared four extra LA equations derived from previously published FEV_1 equations from Europe, the United Kingdom, America and Australia with the Morris and the new Australian equations. An independent dataset of randomly-selected males and females was used to compare these equations with the Morris LA equations and contemporary Australian LA equations.

Lastly, a different type of LA equation expressed as delta lung age (ΔLA), the difference between chronological age and lung age, based on the ratio of Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC), was compared with three other LA equations based on FEV_1 alone. This project used three independent datasets (urban, rural and a workplace) for added strength.

All LA equations confirmed poorer lung function in smokers than in never smokers in all 3 independent datasets. LA estimates were approximately 20 years lower using the original Morris equations when compared with the newest LA equations. The differences seen between estimated LA using all six equations were consistent in each analysis. The ΔLA equation gave extreme LA estimates in both the community-based datasets compared with the LA equations based on FEV_1 alone.

These results show that the Morris LA equations need to be updated. However, there appears to be no advantage in using the ΔLA equation. The differences between the older and the newer LA equations are most likely a result of cohort and period effects. This is also the case in the predictive equations themselves. Continuously updating predictive equations using recently acquired data will result in LA equations that are more relevant to contemporary populations.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Signed: _____ Date: 25th June 2013

Wendy Newbury (candidate)

Acknowledgements

I would like to thank the North West Adelaide Health Study team, the Whyalla Intergenerational Study of Health team, and the Metropolitan Fire Service Study team for generously providing access to their datasets. Obviously, this data would not exist without the hard work of the research and clinic teams, and the subjects themselves. I sincerely thank you all.

A special thank you is also due to the Port Lincoln subjects who kindly presented for spirometry and IOS tests in 2007.

I would like to thank the Discipline of Rural Health, University of Adelaide, for providing a workplace for me in Port Lincoln for the duration of my candidature. The support provided by their IT team is gratefully acknowledged.

Special thanks are also due to Nancy Briggs, and Michelle Lorimer, for statistical assistance and support.

To my supervisors, Alan Crockett and Richard Ruffin, I sincerely thank you both. In particular, Alan has been incredibly supportive, happy to share his knowledge of all things respiratory, and very generous with his time over the last six years. Thank you Alan for introducing me to a respiratory world very different to the one I knew from my nursing training many years ago.

To my husband Jonathan and our daughters, thank you all for helping me get through these last 4 years – and for every distraction away from my computer. Thanks for your belief that I could do this. Your encouragement helped me beyond belief.

Abbreviations

ATS	American Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
CS	Current Smokers
ECSC	European Community for Steel and Coal
ERS	European Respiratory Society
FEF_{50}	Forced Expiratory Flow at 50%
FEV_1	Forced expiratory volume in first second
FEV_1/FVC	ratio of FEV_1 to FVC
FVC	Forced Vital Capacity
IOS	Impulse Oscillometry System
LA	Lung Age
ΔLA	Delta Lung Age (Difference between LA and chronological age)
LLN	Lower Limit of Normal
MFS	Metropolitan Fire Service
NHANES III	Third National Health and Nutrition Examination Survey
NWAHS	North West Adelaide Health Study
PEF	Peak Expiratory Flow
RCT	Randomised Controlled Trial
SA	South Australia
SDL-age	Spirometry Derived Lung Age
UK	United Kingdom
ULN	Upper Limit of Normal
USA	United States of America
WISH	Whyalla Intergenerational Study of Health

Chapter 1: Introduction

This thesis investigates the currency of predictive equations for spirometry from the viewpoint of the lung age (LA) concept. It comprises a Literature Review, two published papers together with a third project of linked research where LA equations have been compared in multiple independent Australian datasets, a discussion, recommendations, a summary, Appendices and Bibliography.

The LA concept remains controversial with many claiming it has no scientific basis and should not be used. Others see it as a simple method to show the damage to the lungs caused by cigarette smoke which can be used in conjunction with smoking cessation counselling. LA has inherent problems linked to the wide range of normal values for the spirometric indices derived from the predictive equations. However LA is easily understood by people with no medical or respiratory science background. Primary care providers generally have little understanding of the complexity of the interpretation of lung function tests, they seek something that is ready to use that will benefit their patients. LA output is available on many modern spirometers and can be readily incorporated into counselling sessions. It has also been made available through online websites and mobile phone 'applications'.

Research about the benefit of using lung age in smoking cessation counselling has been inconclusive and this is investigated further in the Literature Review. Possible explanations are discussed in the series of three projects that form the body of work for this thesis, as well as the following Discussion (Chapter 6). All are linked to the currency of the predictive equation on which LA is based. New LA equations have been

produced, based on newer data than that which informs the original LA equation. These new equations now give several up to date options for Europe and the United Kingdom, the USA, and Australia. Further research is needed to validate these new equations in appropriate populations.

The bibliography in Chapter 9 contains the references for Chapters 1-8, except for the published papers which contain their own references.

The LA equations developed as part of this thesis have already been translated to the patient care environment. They have informed the Lung Age Estimator in the Primary Care Respiratory Toolkit which appears on the Australian Lung Foundation website (see Appendix 6). They have also been incorporated into the COPD-6 screening device (Vitalograph) for use in Australian primary care settings.

This work has been presented at the 6th World Conference of the International Primary Care Respiratory Group (IPCRG), 25-28th April 2012, Edinburgh, UK.

Chapter 2: Literature Review

Background on spirometry

Spirometry is a non-invasive test that assesses lung function by measuring the volume of air that a person can fully exhale after maximal inhalation, as well as the rate of flow. The spirometer has become the standard tool for measuring basic respiratory function at a reasonable cost. It is used to assist in diagnosis of diseases that limit ventilatory function, to determine the severity of disease and to monitor both the response to treatment and progression of disease. It is also used in the monitoring of workers in hazardous workplace environments, and in epidemiological surveys.[1]

E.A. Spriggs provides an excellent history of the discoveries that led to the development of the spirometer[2] and some are described here. Borelli (in 1681) may have been the first to attempt to measure the volume of air inspired in one breath by sucking liquid up a tube. About 40 years later, in 1718, Jurin measured the volume of air exhaled into a bladder, by Archimedes' principle.[2] Others continued to add to knowledge throughout the 18th Century but it was in the early 19th Century that technology advanced in line with the Industrial Revolution.

Edward Kentish and Charles Turner Thackrah both worked in the United Kingdom (UK) in the early 1800s. Kentish measured what is now termed vital capacity with a 'pulmometer', consisting of a glass jar inverted in a trough of water; he recommended that this measurement would assist in the selection of recruits for the infantry, rather than basing their selection only on their height.[3] Thackrah also used a pulmometer to link ill-health to environmental conditions of the workplace at a time when there was no government control over exposures to occupational hazards. The increasingly industrialised workforce experienced conditions that were extremely poor.[4]

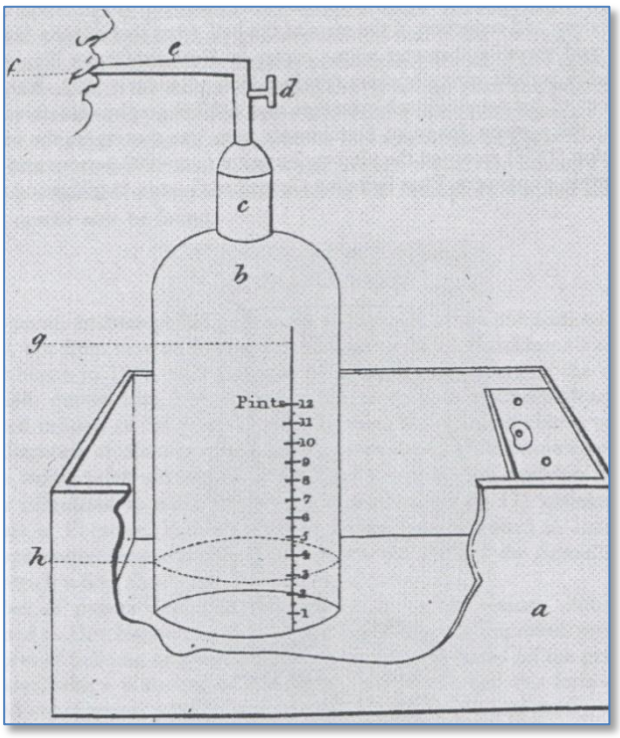

Figure 1: Kentish's pulmometer, 1814
From: Kentish, E. *An account of a pulmometer, by which may be known the power and the capacity of the lungs to receive the atmospheric air. An account of Baths, and of a Madeira-House at Bristol*. London: Longman, Hurst, Rees, Orme & Browne; 1814.

While not the first to measure lung capacity, John Hutchinson (a British surgeon) is credited with inventing, in the 1840s, what is considered to be the precursor to the modern spirometer.[5-8] This instrument consisted of a calibrated bell, suspended upside

down in water to allow measurement of the volume of exhaled air from fully inflated lungs, which he called the 'vital capacity' (VC).[9]

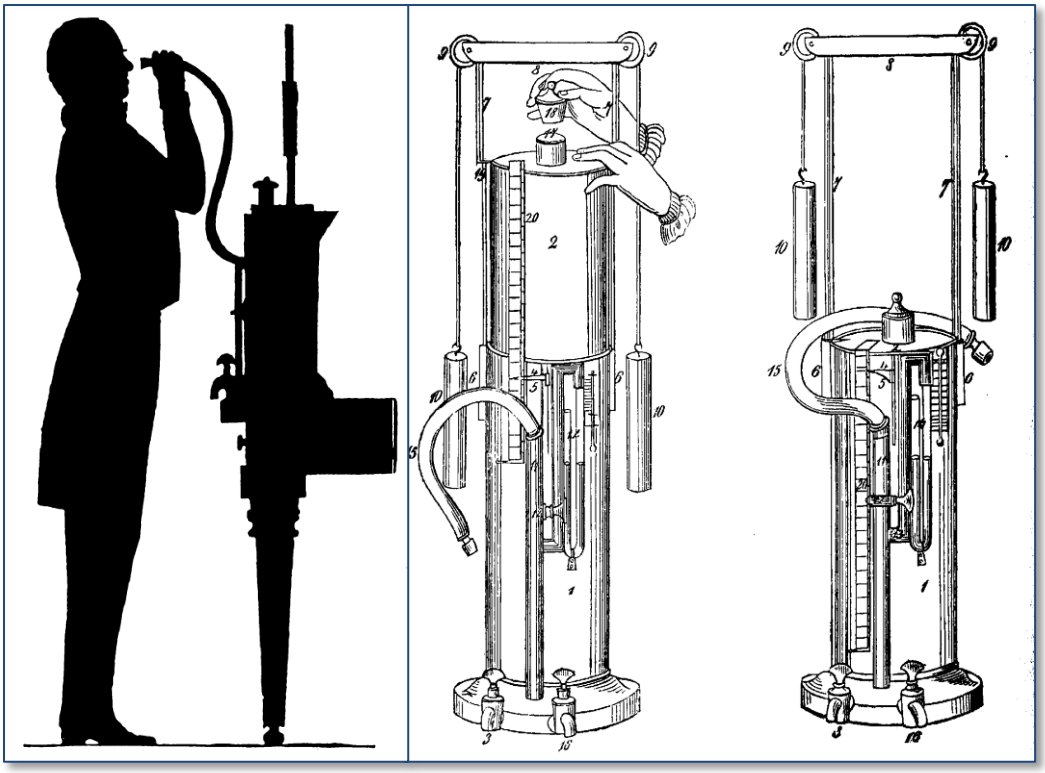

Figure 2: Hutchinson's spirometer
From: Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. *Medico-Chirurgical Transactions*. 1846;29:137-252. Copyright 1846, Royal Society of Medicine Press, UK. (Used with permission)

Hutchinson was part of a scientific group that believed there was a rule, or a reason, to explain all aspects of human physiology. Using his analysis of over 4000 measurements, mostly of male subjects from a wide variety of occupations, he

> *"… was able to link clinical medicine, with experimental physiology, the emerging field of statistics, and the social needs of industrializing Britain."*[10]

Hutchinson's careful analysis led him to determine that the main factors that influence vital capacity are height, age, and disease and created the first table of predictive

values. He also demonstrated that a fall in vital capacity preceded detection of lung disease by stethoscope (invented 30 years before), thus being possibly the first person to apply spirometry to the diagnosis of disease[11, 12] although some say that Kentish preceded him in this.[1, 13] Hutchinson claimed vital capacity was an indicator of longevity that would be of interest to the medical profession, the life insurance industry and could assist in determining the fitness of recruits for the army. He was also interested in workplace health issues, of coal miners in particular.[14]

The spirometer did not gain immediate widespread acceptance clinically, despite a more compact version being developed in 1852.[15] Physiologists however continued to work with the technology, and spirometry continued to be used in research in Europe and America. Spirometry did however have some early proponents. In 1864, Beigel expressed his opinion that spirometry deserved wider acceptance than it had thus far received,[16, 17] and that "…the spirometer promises to become one of the most excellent diagnostic helps in diseases of the chest"[17] as it allowed objectivity in diagnosis as well as the ability to monitor response to treatment.

In 1865 a device known as a kymograph was added to the spirometer which enabled the recording of time in relation to measurement of air volumes, thus producing volume-time graphs.[18] This answered an earlier criticism in a report in 1860 which described use of the spirometer by the Grenadier Guards to assess the fitness of recruits.[19] It had been thought that it may be possible for unwilling recruits to avoid enlistment by performing at levels below the maximum effort. The addition of the kymograph meant that sub-maximal attempts could be detected.[18]

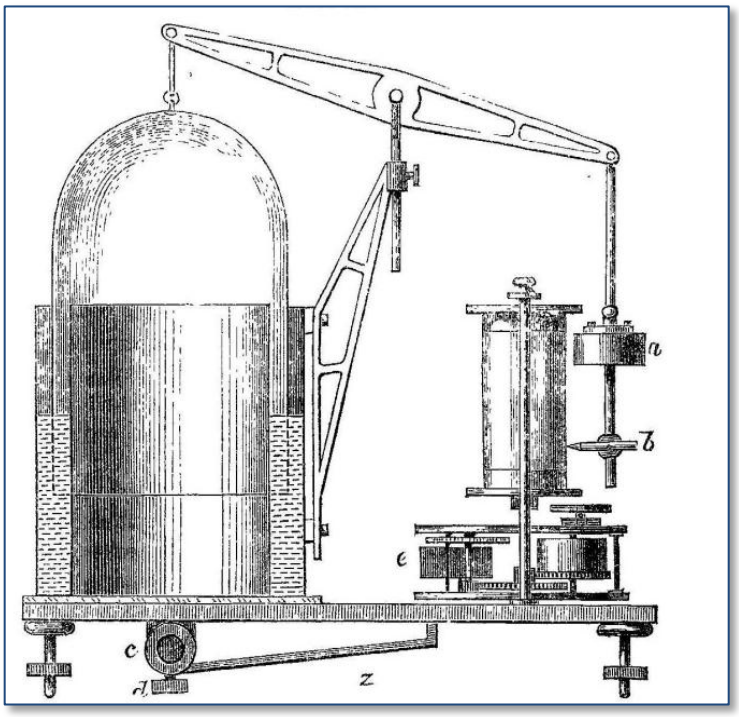

Figure 3: Salter's kymograph
From: H. Salter, Lectures on Dyspnoea, Lecture 3. 1865. The Lancet, Volume 86 (2200), p475-78. (Reproduced with permission from Elsevier Limited.)

In 1870 Bain described the development of a spirometer using dry bellows which was less complex, not requiring water or stopcocks.[20]

20th Century developments

Interest in the respiratory system burgeoned in the first half of the 20th Century, stimulated among other things by investigations into the effects of toxic gases in World War 1 (WW1) and the effects of altitude on pilots in World Wars 1 & 2.[21] Asthma, emphysema and diseases caused by industrial and environmental exposures had also stimulated interest in lung function, as did the developing specialty of thoracic surgery. Studies of ventilatory abnormalities had enabled recognition of 'obstructive' and 'restrictive' patterns while the effects of high cigarette use during WW1 were beginning to be observed.[1] One hundred years after Hutchinson measured what was essentially the Slow Vital Capacity, concurrent but independent work in Europe and America saw the development of the timed forced expiratory manoeuvre as published by Tiffeneau and Pinelli in 1947,[22] and Gaensler in 1951.[23] This manoeuvre made spirometry more applicable to clinical practice by providing a measurement that related to airways disease as it was observed that in disease the volume of air exhaled per unit of time was lower than in health.[22]

The spirometer itself has undergone frequent modification[2], has become more compact and easily portable and this has been accompanied by reduction in cost of purchase. As early as 1969 and into the 1970s and 1980s, computerisation of spirometry output increased accuracy and enabled more timely results to be available. This has also enabled instant feedback on the quality of the manoeuvre.[24-27] Office spirometers are now miniature in comparison to earlier models, with different types of transducers such as pneumotachographs, hot wire anemometers, ultra-sonic sensors that detect and record flow from which volume is then electronically differentiated.[28]

The small office spirometers are designed for use in the doctor's clinic rather than the respiratory laboratory and also enable easy measurement during fieldwork for epidemiological surveys or in the workplace.

The forced expiratory manoeuvre used in spirometry has 3 sequential components.

(1) a maximal inhalation

(2) maximal exhalation follows, where the air from the full lungs is exhaled (blasted out) as hard and as fast as possible and

(3) prolonged exhalation, or continuing to blow out until all the air is expelled.[29]

The forced vital capacity (FVC) measures the total volume of air forcibly exhaled over a minimum of 6 seconds or greater, following a maximal inhalation. The volume of air exhaled forcefully in the first second (FEV_1) relates to airway patency and lung elasticity. It has become the most common of the timed forced expiratory measures. The ratio of these two measures (FEV_1/FVC) is considered a measure of the degree of airflow obstruction when it is reduced below the current guidelines[30] or the lower limit of normal (LLN).[31]

Standardisation of spirometry

International guidelines published by the leading societies of respiratory medicine and respiratory science have produced, and regularly updated, standard specifications for

- spirometers
- the manoeuvres necessary for successful tests, and

- the interpretation of results.

Early guidelines attempted to clarify the terminology that had developed with regard to the measuring of lung volumes, firstly by physiologists in the United States of America (USA) in 1950[32], with the earliest British version dated 1957.[33] A report in 1963 by the American College of Chest Physicians included a discussion of types of instruments in use, a review of the standards applying to the prediction of normal values and notes on interpretation of results.[34] The American Thoracic Society (ATS) has produced regular updates on the standardisation of spirometry since 1979.[35-38] British[39] and European[36,37] statements have also been published. The most recent update appeared in 2005, as a joint statement between the ATS and the European Respiratory Society (ERS).[40-42] These are recognised globally as the most up to date recommendations for respiratory tests, for the respiratory laboratory as well as for epidemiological studies. Guidelines with respect to spirometry in the primary care setting have also been recently produced by the International Primary Care Respiratory Group.[43]

Predictive values

It is important to know what is normal in order to recognise results that might indicate presence of disease. Hutchinson himself produced a table of expected values for vital capacity.[8] He also reported measurements made on a particular person (a noteworthy American of great height) while healthy, and then several years later as the health of this person declined prior to his death due to tuberculosis.[8] This reflects what is considered to be the ideal situation, recognised soon after Hutchinson's paper[17], where a baseline measurement is made before the onset of disease, which would

allow each individual to act as his/her own control.[28, 44, 45] However, this is not usually possible and symptoms such as breathlessness on exertion are frequently already present when most people present to their physician for an assessment of their lung function. Diagnosis of disease therefore requires comparison of a subject's results with population norms determined by predictive equations with a defined lower level of normal, in combination with history of exposures and clinical examination.

Predictive equations define the range of normal values measured by spirometry based on results from studies of a healthy population; recommendations regarding these have also evolved with greater understanding of the effects of lung diseases and exposures that are harmful to lung function. The main predictors of lung function in adults are sex, height, and age, with weight contributing to a much lesser extent.[37] Ethnicity has also been thought to contribute because of differences in dimensions of the thorax and how this relates to standing height.[10, 37, 42, 46, 47] Together, these influences account for up to 70% of the value of FEV_1 or FVC in healthy adults; technical and other yet to be identified factors account for the remaining 30%.[37, 44, 48]

Lung function reaches a peak around early adulthood and then plateaus for several more years before declining with age. Cigarette smoking influences all three of the factors determining the level of FEV_1 at any time in adulthood: the peak attained in early adulthood, the length of the plateau phase and the rate of decline with age.[49] Other factors that affect the peak achieved at 20-25 years of age include in utero and/or early life exposure to cigarette smoke, premature birth, and low birth weight.[50] There are also genetic factors related to lung development as well as disorders such as

asthma and chronic obstructive pulmonary disease (COPD).[51] Early childhood respiratory illnesses and socioeconomic aspects may also contribute.[44, 52-54]

Current ATS/ERS guidelines for normal values recommend that the reference equations should be derived from a large representative sample of the general population, which should be composed of healthy rather than abnormal subjects, i.e. have no previously diagnosed respiratory disease or symptoms, be never-smokers, and have no workplace or environmental exposures to dust or fumes.[37, 42, 55] These guidelines also recommend that predictive equations be updated regularly, approximately every 10 years.[42] This recommendation aims to reduce the impact of the cohort effect and the period effect. The cohort effect describes how the lung function of a 50 year old today would be different to that of a 50 year old either 30 years ago or in 30 years' time due to changes in influences such as environment, nutrition and prevalence of smoking.[37, 49] The period effect describes advances in technology that result in measurement differences, including differences in recommended technique, improvements in equipment such as computerisation, and interpretation differences.[49]

It has been suggested that the use of predictive equations alone to diagnose disease is flawed. Subject exclusion criteria for developing normal values include a positive respiratory disease status, respiratory symptoms, and current smoking status as well as the inability to perform reproducible spirometry. Marks suggests that the selection of only healthy subjects to generate predictive equations could result in bias and compromise the generalisability of the sample.[56] This has been addressed previously with the ATS guidelines as early as 1991[37] recommending that abnormal subjects, with

abnormality defined by taking into account the smoking habits, environmental or occupational exposures, disease status or respiratory symptoms, being excluded from general population samples. This will make the remainder of the sample a 'normal' or healthy population as opposed to a 'general' population.[42, 55] Clinicians shouldn't rely solely on results of pulmonary function tests, but should also consider a patient's history, signs and symptoms before making a diagnosis.[30, 57]

New predictive equations for spirometry have been recently made available and have been implemented on some spirometers.[58] These have been developed from the collating of different existing datasets from many centres around the world. Equations compiled from different separate studies in different countries are not new, the equations that have been long-used in Europe were compiled from data from different projects spanning 20 years, and utilised varied equipment (European Community for Steel and Coal (ECSC)/ERS).[59] These however are now approximately 40 years old. The new equations have been developed using new, complex statistical methods to enable them to cover a single age-range of 3-95 years. However, the utility of this equation has not yet been fully investigated.

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD) is a preventable, chronic and debilitating respiratory disease characterised by airflow limitation, including reduced maximum expiratory flow and slow forced emptying of the lungs, which is not fully reversible with bronchodilation.[60, 61,62] It is usually diagnosed later in life as it has an insidious onset with those affected often mistaking early symptoms for the assumed

decline in function associated with normal ageing. COPD usually goes undiagnosed until symptoms worsen, in later stages of the disease.[30] According to the Global Initiative for Obstructive Lung Disease (GOLD) definition, limitation is

> *"…usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases."*[30]

COPD covers chronic obstructive bronchitis, where remodelling of the airway walls and mucus in the lumen obstruct the airways, and emphysema where airspaces become enlarged because lung parenchyma is destroyed, and lung elasticity is lost resulting in closure of the small airways. Mucus hypersecretion (which causes a productive cough of more than 3 months duration for more than 2 consecutive years) is not always associated with airflow limitation, however all 3 conditions tend to be seen together.[63] Some childhood respiratory illnesses, including bronchopulmonary dysplasia and bronchiolitis as well as untreated asthma, may also lead to COPD in later life in the absence of a personal smoking history, although cigarette smoking has an added effect on top of these conditions.

The FEV_1 and the FEV_1/FVC ratio are used to assess airflow limitation. There has been ongoing debate for decades about the accepted method to define abnormal results. This is not helped by different guidelines that are not consistent in their recommendations, with the ATS/ERS statement on interpretation of lung function tests[39] differing from its statement on diagnosis/management of COPD.[64] The use of a fixed ratio of FEV_1/FVC below 80% dates from around 1954.[22] It was originally conceived as a rough guide, and continues to be recommended as a simple method to

define abnormal results.[56,58,59] The COPD guidelines by National Institute for Health and Clinical Excellence (NICE) [62], the Global Initiative for Chronic Obstructive Lund Disease (GOLD)[59] and ATS/ERS Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease[61] all use a FEV_1/FVC ratio of 0.7 (or 70%) to establish airflow limitation, and <80% of the predicted value for FEV_1 to determine the degree of impairment. The COPD-X Plan, the Australian and New Zealand Guidelines for the Management of Chronic Obstructive Pulmonary Disease[65], currently uses the guidelines from the GOLD initiative. As the FEV_1/FVC normally decreases with age, those with lower predicted values (e.g. shorter, older, females) will be more likely to fall below the 70% cut off.[66] This may result in asymptomatic older people with no smoking history or exposure to noxious particles or gases being erroneously determined to have airflow limitation, a false-positive diagnosis. At the same time, young people who actually have airflow limitation are more likely to be missed, creating false-negatives.

The opposing view is that values below the statistically derived 5th percentile should be considered to be abnormal.[42] The 5th percentile lower limit of normal (LLN) declines with age and therefore the problems associated with using a fixed cut-off may be avoided.[66] Using the 5th percentile of measurements from a normally distributed sample of a healthy population means that 5% of subjects without disease would be misclassified, i.e. would be false positives.[37] Modern computerised equipment is able to promptly calculate and display a statistically derived LLN, as well as include it in the printed report, which should negate the argument about the ease of use of the fixed cut-off.[66] The ATS/ERS Interpretive Strategies for Lung Function Tests (1991)

recommend that values below the 5th percentile should be considered to be outside the range of normal and that using both 80% of the predicted value for FEV_1 and 0.7 of FEV_1/FVC ratio will lead to errors including false-positives in both sexes, as well as over-diagnosis of COPD in asymptomatic elderly never-smokers[37] and this is repeated in the 2005 ATS/ERS guidelines for Interpretative Strategies for Lung Function Tests.[42] In response to the ongoing international debate, the latest GOLD guidelines acknowledge that

> *"…use of the fixed FEV_1/FVC ratio… will result in more frequent diagnosis of COPD in the elderly and less frequent diagnosis in adults younger than 45 years compared to using a cut-off based on the lower limit of normal (LLN) values for FEV_1/FVC."*[30(p viii)]

Both the fixed ratio and the statistically derived LLN depend on the use of appropriate predictive equations for the local population as discussed in 2005 ATS/ERS guidelines on Interpretative Strategies for Lung Function Tests.[42] Important considerations in the selection of appropriate predictive equations include matching age-range, anthropometric measurements, ethnicity, even socio-economic and environmental aspects. The type of instrument as well as the statistical model used to derive the predictive equation should also be considered.[42]

A recent review of publications where FEV_1/FVC below LLN was compared with FEV_1/FVC less than 70% concluded that the prevalence of COPD detected by spirometry was greater when using the fixed cut-off of 70% FEV_1/FVC than when using the LLN.[67] However, the authors note that one longitudinal study showed that subjects who were defined as normal using LLN but abnormal using the fixed cut-off had higher

rates of mortality and COPD-related hospitalisation than healthy subjects, but lower than those with values below the LLN during the 11 years of follow-up.[68] This clearly needs further investigation.

Historically, the 19th Century saw rapid industrialisation originally in the United Kingdom (UK), which was followed by Europe and America. Power for the burgeoning

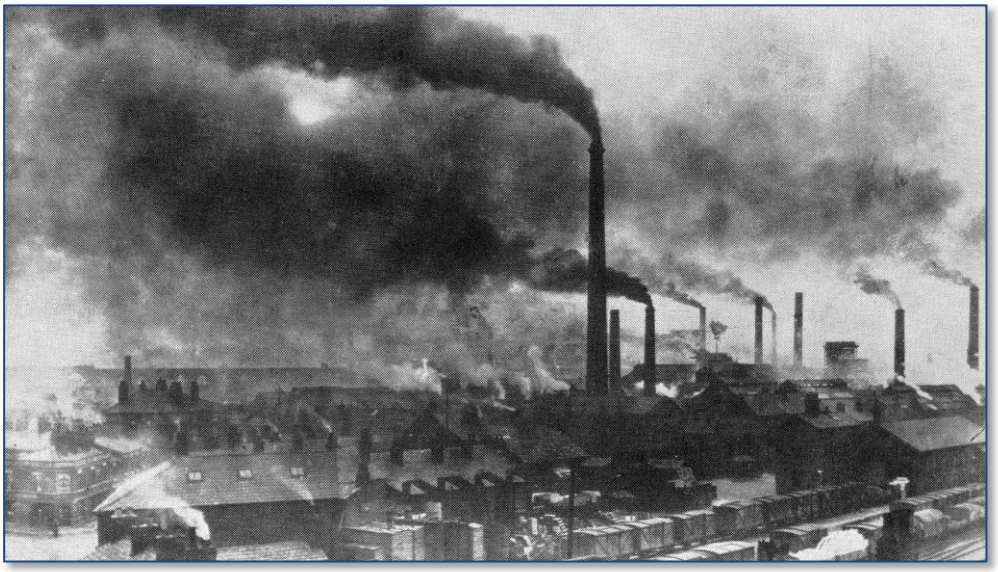

Figure 4: Photograph of Widnes, Cheshire, UK, in the late 19th century showing the effects of industrial pollution.
From: Hardie, D. A history of the Chemical Industry in Widnes, Imperial Chemical Industries Limited, 1950. Source: Wikimedia Commons: http://commons.wikimedia.org/wiki/File:Widnes_Smoke.jpg

factories was supplied by coal-burning plants, while the burning of coal also provided heating inside the home.[62] Together these factors caused appalling pollution in the cities which, combined with the workplace dust exposures in the mills and the mines, contributed to the development of emphysema and chronic bronchitis, especially in the UK. Improvements in both workplace dust exposures and outdoor pollution coincided with the dramatic increase in the prevalence of cigarette consumption around the times of the two World Wars.

The major risk factor for COPD in the developed world is cigarette smoking. Other risk factors include exposure to both indoor and outdoor air pollution (including from the burning of biomass fuels), occupational and environmental exposures to toxic dust and fumes, and exposure to second-hand smoke. Genetic risk factors, such as α-1 anti-trypsin deficiency, are rare but recent studies of the human genome have identified regions on chromosomes 4 and 15 that are associated with susceptibility to COPD.[60]

Effects of smoking

Smoking has long been thought to be deleterious to health, with the first published anti-smoking comment in English possibly being that by King James I of England in 1604. 'A Counter-blaste to Tobacco'[69] followed the popularisation of tobacco smoking in England by Sir Walter Raleigh, in the late 1500s.[70] James I described smoking as:

> *"A custome loathsome to the eye, hatefull to the Nose, harmefull to the braine, dangerous to the Lungs , and in the blacke stinking fume thereof, nearest resembling the horrible Stigian smoke of the pit that is bottomlesse."*[69]

Tobacco was originally smoked in pipes or used as snuff; cigars followed around the end of the 18th Century. The 19th Century saw the introduction of the ready-made cigarette with mass production starting around 1880.[62, 70, 71] In males, the popularity of cigarettes was greatly influenced by World War 1 when cigarettes were distributed to soldiers to help them to cope with the stress of the battlefield. It is disappointing that heavily subsidised cigarettes are still available to the armed forces in combat zones to this day. By the end of World War 2, 80% of British men were regular smokers.[70] Increased prevalence of smoking in females followed that of males, particularly during

and after World War 2 when women were increasingly earning their own money when employed outside the home.

Around the time that it became apparent that poor air quality was linked with respiratory deaths (the infamous London smog of 1952 caused at least 4000 deaths due to cardiac or respiratory problems) research into causes of lung cancer deaths was underway. Lung cancer had been an extremely rare disease around 1880, with increased prevalence from the turn of the century and after World War 1, in women as well as men.[72] With the benefit of hindsight, this was related to the introduction and rapid increase in popularity of the cigarette, although at the time other possibilities such as increased air pollution from industrial sources as well as from domestic coal fires, the sealing of roads with asphalt, the increase in use of motor vehicles were all considered to be possible causes.[71, 72] Research prior to 1950s consisted mostly of case-control studies, and included work by Richard Doll and Bradford Hill which had originated in London but had later expanded to include other cities around the UK,[73] and in USA by Wynder and Graham.[74] Together with results from large prospective cohort studies that followed soon after, such as the British doctor cohort of Doll and Hill[75], these provided evidence that smoking not only caused lung cancer, but also was associated with chronic bronchitis and coronary thrombosis. The British doctor cohort was followed from 1951 for more than 50 years.[76] This work is the keystone of all anti-tobacco initiatives.

Cigarette contents can be readily manipulated by the manufacturers, and some additives are known to dilate the airways, which facilitates increased smoke intake and nicotine absorption.[77, 78] Nicotine is a naturally occurring substance in tobacco; it is

highly addictive and is the reason that most smokers continue to smoke.[79] Cigarette smoke has a lower pH than that of pipes or cigars; this inhibits nicotine absorption via the oral mucosa therefore a deeper inhalation is required to deliver the smoke to where nicotine is readily absorbed, the lower airways and alveoli. This results in the extremely large surface area of respiratory epithelium being exposed to the highly toxic products of combustion.[80, 81]

Repeated, chronic exposure to the huge number of toxic chemicals and gases in cigarette smoke causes damage to the airways at the cellular level as well as reducing the effect of the body's anti-aging defence mechanisms.[82]

After the nasal hairs, the next line of defence in healthy lungs is the mucociliary escalator. This is severely compromised by exposure to cigarette smoke. Mucus normally traps bacteria and particles which are then swept up the bronchial tree by the regular beating action of the cilia; but mucus production is increased and the action of the cilia is adversely affected due to damage caused by the toxicity of the chemicals in cigarette smoke – the beat frequency of the cilia is reduced, the length of the cilia is decreased and the number of cilia are all greatly reduced in regular smokers.[83-87]

At the same time, damage occurs to the junctions between the cells in the epithelium, allowing toxic particles to cross the membrane into the lung tissue. Lung inflammation results via a very complex mechanism involving increased numbers of inflammatory cells such as leucocytes (macrophages and neutrophils) and lymphocytes. Inflammatory mediators secreted by these cells cause recruitment of further

inflammatory cells from the circulation, structural changes in the airways and parenchyma with associated vascular changes, together with increased mucus secretion.[84, 88-90]

Oxidative stress from cigarette smoke as well as from activated inflammatory cells causes further inflammation as well as a protease-antiprotease imbalance. Matrix metalloproteinase, from macrophages as well as the small airways, attacks the complex matrix that forms the alveolar wall, as well as further increasing the inflammatory response.[84, 85, 88, 90-92]

These mechanisms contribute to destruction of lung tissue and elastin leading to emphysema. This cycle of further inflammation and tissue damage is self-perpetuating. Results are seen as chronic bronchitis due to significant mucus production leading to airway remodelling and obstruction of the small airways, and emphysema with destruction of the lung parenchyma, reduction in the elasticity of the lung tissue, and closure or collapse of the small airways.[30, 63, 89-93] The associated decreasing lung function is seen as an increase in the rate of age-related decline.[60, 84, 93, 94]

The damage caused to the lungs by chronic exposure to cigarette smoke has been likened to an increased rate of biological ageing, where impaired defence and repair systems result in a rate of cellular damage beyond that which normally occurs with chronological ageing.[93, 95] Smoking has also been found to contribute significantly to premature ageing of the skin[93, 96-98] and similar damage at the cellular level may be the mechanism involved in other diseases such as cancers and atherosclerosis.[95] As well as being the major cause of COPD, smoking is recognised as causing cancer in many

different sites including the bladder, the cervix, the oesophagus, the kidney, the larynx, the oral cavity and pharynx, the pancreas and the lungs, and causing acute myeloid leukaemia.[90, 99] Smoking also causes other potentially fatal diseases including ischaemic heart disease, abdominal aortic aneurysm, stroke, and pneumonia.[80, 82, 99, 100]

Several large studies have shown that the rate of decline of lung function returns to that of never-smokers following smoking cessation and this is demonstrated to be more beneficial when quitting occurs earlier rather than later.[76, 101-104] Risk of other smoking-related illnesses also falls after smoking cessation.[105]

Spirometry in smoking cessation counselling

The best method of reducing the risk of developing COPD, or to slow down the progression of the disease, is to stop smoking.[106]

In describing the normal course of disease progression in airflow obstruction, Fletcher and Peto showed decline in lung function is greater in smokers who are susceptible to the toxins in cigarette smoke (evidenced by greater rates of decline of FEV_1) than in non-susceptible smokers[94], and that the rate of decline for susceptible smokers who stop smoking reverts to that of never-smokers. This project followed working men in London for approximately eight years. A more contemporary concept is to classify patients with obstruction into different phenotypes based on whether they are fast or slow decliners. Fletcher and Peto suggested that FEV_1 could be used as a screening tool to detect susceptible smokers in middle-age, and that the identification of a FEV_1 that is lower than expected could help to persuade smokers to quit by showing evidence of lung damage caused by smoking.[94]

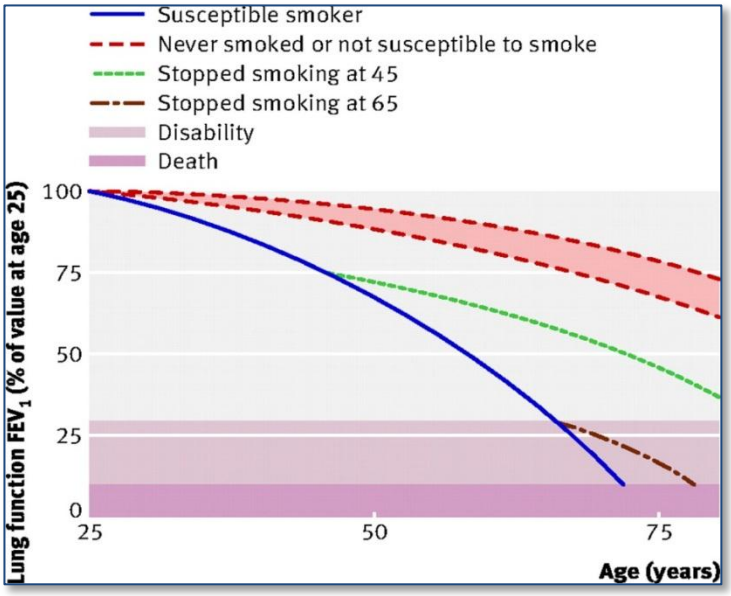

Figure 5: Fletcher and Peto graph
Adapted from the original by Fletcher and Peto showing the 'normal' age-related decline of lung function (FEV_1) in healthy never-smokers (or those not susceptible to cigarette smoke) and the steeper rate of decline seen in susceptible smokers. A return to the normal rate of decline is seen in those smokers who quit early (at 45 years) and those who quit later (65 years). Used with permission from BMJ.

The Framingham Offspring study showed that the graph of expected decline in lung function created by Fletcher & Peto[94] could be extended to females.[102] Two other recent research projects indicate that the rate of decline in FEV_1 in the early stages of the disease could be greater than previously thought while at the same time being slower in the later stages of disease. However these results come from subgroup analyses that were originally unplanned.[107]

Researchers continued to investigate methods of using spirometry to promote smoking cessation and reduce the prevalence of diseases caused by cigarette smoking. In 1974, a respiratory questionnaire was combined with spirometry feedback at an urban emphysema screening centre in USA. The significance of respiratory symptoms was explained together with information about spirometry results; "lung age" was included in their test results.[108, 109] Follow-up of over 1,600 people occurred 18 to 36

months after being screened, a quit rate of 20% was reported. There was no control group and there is insufficient information to determine the methods used, including the population being studied, the equipment used, how lung age was communicated, or the method of follow-up. Having noted that smokers had lower pulmonary function than non-smokers, the authors stated that the

> *"…experience suggested the value of using an estimated lung age based on ventilatory function as a psychological tool to confront the smokers with the apparent premature aging of their lungs".*[109]

'Premature ageing' was used to explain the effect of damage caused to the lungs by cigarette smoking where lung function at a particular age was lower than expected, or was equivalent to what would be expected for a healthy never-smoker at a later stage in life.

Similarly, Australian research published in 1979 also compared the mean chronological age of smokers to average predicted ages given the mean lung function observed in different categories of smoker who smoked greater than 10 cigarettes per day.[110] Lung function was significantly lower in cigarette smokers than in non-smokers, with greater decline in lung function with age. The authors demonstrated this in FEV_1, FVC and FEV_1/FVC (expressed as %); also that lung function declined at a greater rate in heavier rather than lighter smokers. They concluded that showing the decline in lung function related to chronological age may be useful in convincing smokers of the harmful effects of smoking.

Morris and Temple published the concept of lung age six years later, in 1985.[109] They manipulated previously published predictive equations for several spirometric parameters[111] and re-solved them for age (Table 1). In doing this Age becomes the dependent variable, and Height and the observed values (e.g. FEV_1, FVC, FEV_1/FVC) become the independent variables (predictors).[109] Higher lung age estimates reflect poorer lung function, where the lungs seem to have 'aged' beyond the person's actual age. Linking a person's observed lung function to the age where these results would be considered to be normal produced a more easily understood method of communicating spirometry results to smokers that illustrated the deterioration in lung function caused by smoking.[109]

Males	FEV_1 =	0.092*H– 0.032*Age -1.260.
	Lung age =	2.870*H – 31.25*Observed FEV_1 -39.375
Females	FEV_1 =	0.089*H– 0.025*Age – 1.932
	Lung age =	3.560*H – 40.000*Observed FEV_1 – 77.280

Table 1: Morris and Temple lung age equations
Predictive equations for FEV_1 for males and females, from 1971[111], and the corresponding lung age equation.[109] In the lung age equation, predicted FEV_1 is substituted with the observed FEV_1 for that person. H = height (inches). FEV_1 = Forced expiratory volume in first second.

Morris and Temple investigated components of the FVC manoeuvre (FVC, FEV_1, $FEF_{25-75\%}$ (litres/second) and $FEF_{200-1200}$ (litres/second)), that had previously been used to develop predictive equations.[111] They compared the Standard Error (SE) for each test (or combination of tests) to determine which gave the most reliable result for estimating lung age. They determined that FEV_1 was the most appropriate by having the smallest SE. They then applied all the lung age equations to an independent dataset whose subjects had been previously classified normal/abnormal based on

responses in a respiratory health questionnaire, and on results of pulmonary function tests. Again, lung age based on FEV_1 produced results with the least number of outliers. Results showed that lung age approximated chronological or actual age for previously determined normal results, while lung age estimates were greater than chronological age for abnormal results. It was hypothesised that providing results of spirometry as lung age to smokers during smoking cessation counselling may provide the impetus for them to quit their smoking habit. [109]

Researchers have continued to attempt to find a way of increasing smoking cessation rates by communicating spirometry results to smokers. Study design has varied, and results have been mixed.

Research where spirometry was part of the intervention

Where spirometry was part of the intervention in RCTs, early studies from Australia in a general practice setting[112], and from the USA (in a health promotion setting for Veterans[113]) reported much higher quit rates in the group receiving the intervention than the control groups. The Australian study did not give details of method of communication of spirometry results[112], while the American study compared subject results to expected values for a non-smoker.[113]

Another study, from Norway[114], provided feedback by letter instead of face to face with physician or health counsellor. The personalised feedback included linking previous answers regarding smoking and asbestos exposures with FEV_1 results (no details were given of how spirometry results were communicated) with information

about increased risk with exposure to asbestos, low FEV_1, or both. Results were similar to the previous two studies but with less difference observed between groups.

In 1999, a further study from America gave spirometry results as %predicted, using reference values by Crapo.[115] Researchers found no difference between the intervention/control groups, however this trial gave different levels of advice in both groups depending on motivational stage.[116]

In 2006 a Swedish study investigated whether annual spirometry for three years would improve quit rates. This was combined with brief smoking cessation advice (delivered by a nurse) and a physician letter that detailed results and any changes from previous tests. Smokers with COPD had significantly higher quit rates than those with normal lung function after three years. In those with normal lung function, smoking cessation rates were not increased with repeated spirometry. [117]

In 2009, Kotz et al from the Netherlands, used confrontational counselling using spirometry results together with nortriptyline, a tricyclic antidepressant sometimes used to assist smoking cessation, but the study was underpowered to show any significant difference in sustained quit rates after one year.[118]

Research where spirometry results were communicated using lung age

A detailed look at research where lung age was the method used to communicate spirometry results in the intervention group is not definitive as the number of trials is not large. Some papers report pilot studies which involve small numbers and therefore lack power.[119-121] Others report complex trials comparing several different interventions of which only one was spirometry.[118, 122-124] Difficulties in recruiting and

retaining participants can also result in trials being underpowered.[118] The results remain inconclusive.

Italian RCT, Segnan, 1991

An Italian RCT in a general practice setting[122] compared

(1) minimal intervention (usual care) with

(2) repeated counselling only,

(3) repeated counselling plus nicotine gum, and

(4) repeated counselling with spirometry results presented as lung age.

Quit rates in all arms of the study that used repeated counselling were higher than the minimal intervention group although none reached statistical significance. The research team experienced multiple problems: fewer participants than anticipated meant the study was underpowered, poor adherence to study protocol by the GPs resulted in contamination between groups, and there was low compliance where less than half of those in spirometry group actually had spirometry. Within the spirometry group, those who actually had spirometry had a higher cessation rate than non-compliers.

American Senior High School or Community College settings, Prokhorov et al, 1996-2008

Several studies in American Senior High School or Community College settings, including two pilot studies, have shown inconclusive results.

(1) An early pilot study[120] in a Senior High School had 26 students perform spirometry. The mean age was 17.2 years. 95.5% of subjects had FEV_1>80%

predicted regardless of smoking status, although current smokers experienced more respiratory symptoms than did non-smokers.

(2) A pilot Randomised Controlled Trial (RCT)[121] compared a control group with an intervention group which completed a respiratory symptoms questionnaire and performed spirometry. Both groups received a brochure about smoking including the chemical content of cigarettes, diseases related to smoking including mortality statistics, short term risks, and a description of lung age and how it is measured. Spirometry results were expressed as lung age; these were combined with feedback on reported respiratory symptoms. The research team found no significant difference in worry and desire to quit between the control and intervention groups. Increasing lung age resulted in participants being less interested, and saying they had not expended full effort in the breathing manoeuvres required for successful spirometry. The mean chronological age of these participants was 20.5 years. A selection bias could have occurred as payment was made to the 124 volunteer subjects for their participation.

(3) The "Look at Your Health" project[123] trialled computer-assisted smoking cessation counselling in community college students which gave personalised feedback on health risks and readiness to alter smoking behaviour. The cluster RCT involved 426 students in 15 pair-matched campuses. The standard care group received brief counselling, were provided with a self-help manual and were strongly advised to quit. The intervention group received a motivational counselling intervention and feedback about lung function, with spirometry results provided as LA. There was a higher quit rate in the intervention group at

ten month follow-up: reported cotinine-validated quit rates of those who completed the program – 16.6% (experimental group), 10.1% (usual care group), $p = 0.07$. When recalculated as intention to treat, where all who didn't complete the program were assumed to be continuing smokers, the quit rates fell to 11.4% (intervention) and 8.2% (usual care). This sample had a mean age of 22.8 years.

Possible problems in these projects may have arisen in using the Morris lung age equations as 20-45% of the sample were not Caucasian. Also, the age of many of the subjects in these studies may have been outside the range of the reference equation informing the lung age equations (20-84 years).[111] The age of the subjects could also mean that the cumulative effects of smoking may not have been evident although others have found that cigarette smoking has a deleterious effect on levels of lung function and on the airways in both adolescent males and females despite low cumulative levels of smoking.[125, 126] The other factor in these studies is that the lungs of such young participants are still growing.

Polish population studies, 2003, 2006

Two similar papers describe projects that followed-up subjects 12 months after large voluntary national spirometry screening programs that included brief smoking cessation counselling delivered by a physician in high-risk Polish populations.[127, 128] Although these have no control groups, the reported quit rates are higher than what is normally seen in 'usual care situations'. In both these screening programs, FEV_1%predicted was superimposed on a simplified Fletcher and Peto graph, showing the relationship between the actual result and the predicted value for age, and the

subsequent expected decline if smoking continued. In those with normal spirometry, advice focussed on risk of developing COPD, lung cancer, coronary artery disease and harmful effects of smoke to family members. Smoking status was validated by exhaled carbon monoxide.

(1) In 2003 Gorecka et al reported a quit rate of 9.3%, and that subjects with airflow limitation (AL) were more likely to have quit than those with normal lung function and that those with more severe AL had higher quit rates.[127]

(2) Of almost 4,500 current smoking adults who were invited for follow-up after screening in 2000-2001, 13.4% had quit at 12 months (assuming those not attending follow-up appointments were all current smokers). Again, those with AL were more likely to have quit than those with normal lung function.[128]

Get PHIT (Pro-active Health Intervention for Tobacco-users) RCT, McLure, 2010

All subjects enrolled in the Get PHIT (Pro-active Health Intervention for Tobacco-users) RCT were advised to quit, given self-help materials, and access to free phone-counselling program. The control group also received personalised feedback regarding diet, physical activity and BMI. The intervention group received personally tailored feedback on self-reported symptoms, and smoking-related medical conditions that included carbon monoxide levels and results of their spirometry test using the Fletcher and Peto graph. If FEV_1were <80% predicted, lung age was used to communicate results. Quit rates for people with impaired lung function were significantly greater than those with normal lung function at 6 months (p=0.05) but not at 12 months (p=0.26). Smoking status was not biochemically confirmed.[124]

Step2Quit trial, Parkes, 2008

The most positive result to date in any project where lung age was used to communicate spirometry results is from the Step2Quit trial.[129] This RCT, conducted in a primary care setting in the UK, tested lung age as the intervention rather than spirometry. All recruited subjects underwent spirometry and were told that their lung function would be measured 12 months later to determine whether there had been any deterioration. Randomisation to either control or intervention group was blinded, and determined by computer generated random numbers. Intervention and control groups were both advised of their results by personalised letter, approximately four weeks after testing, were advised to quit, and offered referral to smoking cessation counselling. The intervention group received their spirometry results as lung age which was illustrated using a modified Fletcher and Peto graph (see Figure 5, page 23). If their lung age was lower than chronological age they were told their results were normal. Those in the control group had spirometry results communicated as the raw value of FEV_1 with no further explanation. At follow-up 12 months later, smoking status in self-reported quitters was confirmed by exhaled carbon monoxide as well as by salivary cotinine. All analyses were performed on the intention to treat basis, where those for whom contact was lost were classified as continuing to smoke. Of the 561 subjects who participated, the verified quit rate was 6.4% in the control group, and 13.6% in the intervention group (p=0.005). Both groups also showed reduced average consumption (self-reported).[129, 130] Higher smoking cessation rates were seen in patients with both increased and normal Lung Age.

In a pulmonary function laboratory

Lung age has been investigated most recently in another pilot study, in a pulmonary function laboratory situation.[119] The control group received a printed information sheet on community-based smoking cessation resources after their pulmonary function test. The intervention group received motivational interviewing lasting approximately 15 minutes if their FEV_1 was <80% predicted, with LA used to illustrate the dangers of smoking. They also received a follow-up letter from the investigating physician. At one month the difference between quit attempts in the intervention group (n=32) was not statistically significant to the number of quit attempts in the control group (n=24, p=0.59). When stratified by high versus normal lung age there were twice as many reported quit attempts in those with high lung age in the intervention group (n=39) as those with high lung age in the control group (n=17, p=.089). Lung age was not communicated to the control group.

Qualitative study, Parker, 2008.

The lung age concept has also been investigated qualitatively in a focus group setting of primary care patients who had been diagnosed with or at risk of COPD.[131] This group found the concept to be easily understood, and felt that they would be motivated to quit smoking if their doctor told them their lung age was greater than their actual age.

Lung age research in ethnicities other than Caucasians

Japanese researchers have also investigated lung age in a series of papers specific to those of Japanese ethnicity. Specific lung age equations for Japan were developed by re-solving the Japanese Respiratory Society's FEV_1 predictive equation for age.[132] Lung age was then estimated using both a conventional spirometer and a FEV_1/FEV_6 meter

in 768 subjects in hospital settings[132], and evaluated in the context of post-operative complications in lung cancer patients[133], and in obese males.[134] Their results show that lung age in Japanese subjects is greater in current smokers than in both ex- and non-smokers, and this is also the case in healthy current smokers.[132, 134] Researchers from Tokyo have recently suggested a method to interpret lung age results which takes the wide range of normal values into account.[135] This group have also determined that FEV_1 is the most appropriate parameter for estimating lung age.[135]

Conclusion

Different phenotypes for COPD are recognised which can be classified as those with a fast or slow rate of decline of lung function. This is similar to terminology coined by Fletcher and Peto in 1977, where those with fast rates of decline were described as "susceptible to cigarette smoke" and those with slow rates of decline were "not susceptible".[94] Hutchinson hypothesised that reduced VC was a predictor of mortality[8] and low FEV_1 has also been associated with mortality.[136-138] It is likely that predicted mortality is related to fast decliners and it is therefore possible that lung age could be a surrogate measure to identify fast decliners.

However, on reviewing the lung age literature a major concern is that the Morris and Temple lung age equations from 1985[109] are based on data collected in the mid to late 1960s.[111] Despite recommendations from the leading associations of respiratory medicine and respiratory science (ATS/ERS) that predictive equations should be updated approximately every ten years, lung age equations for Caucasians have not been updated. They rely on predictive equations that are over 40 years old, yet they

are expected to be applicable in today's populations. This led to the hypothesis that the use of lung age equations based on data gathered over 40 years ago may have a negative impact on the results of research using lung age. Improving the estimation of Lung Age to provide more accurate feedback to smokers is more likely to have a positive effect on their motivation to quit.

Research Question

Can new lung age equations be constructed using recently collected data?[139] Will these be more valid than the Morris and Temple equations in current day samples?

Chapter 3: Exploring the need to update lung age equations

Primary Care Respiratory Journal (2010); 19(3): 242-247

Background

In 2007, a pilot study was conducted to determine preliminary Australian predictive equations for the Impulse Oscillometry System (IOS) parameters – respiratory impedance Z5, respiratory resistance R5 to R35 and respiratory reactance X5 to X35 (Masterscreen IOS®, Carefusion, Yorba Linda, California).[139] Lung function was also measured by spirometry using the same instrument. Subsequently, spirometric predictive equations were also developed. These allowed comparison with existing Australian spirometry predictive equations that were published in 1995[140] to determine if the sample could be considered normal. This pilot study has provided the only published IOS predictive equations for Australian Caucasian adults.

Comparisons using dummy subjects illustrated differences between the German equations for the above IOS parameters, and the preliminary Australian equations. The spirometry predictive equations from this pilot were found to be similar to the earlier equations, which gave the Australian preliminary equations for IOS added validity.

The main limitation to this study was the small sample size (n=126). The fact that it was age & sex stratified gave it strength in that the equations are equally applicable for older adults as for younger adults. The sample was structured to have approximately 10 males and 10 females in each 10-year age bracket, from 25-74 years. This pilot study paper was submitted for the award of MPH by the first author. It is still

generating international interest and is provided as background information in Appendix 1.

Discussion relating to Paper One

Following publication of the IOS pilot study, a further search of the literature regarding predictive equations for spirometry identified the Step2quit RCT[129] which provided a stimulus to investigate spirometry predictive equations further, especially in relation to the concept of lung age. To investigate the behaviour of LA equations in a contemporary sample, the 1985 Morris & Temple lung age equations[109] were initially applied to the Port Lincoln sample described above, and produced rather low lung age estimates across the whole sample (data not shown). At the same time, the background to the Morris & Temple lung age equations was explored by looking into the spirometric equations that informed the concept[111] including the sample used, and the method used to determine starting point of the test. Morris et al had used the method developed by Kory et al (published in 1961)[141], which involved measuring the

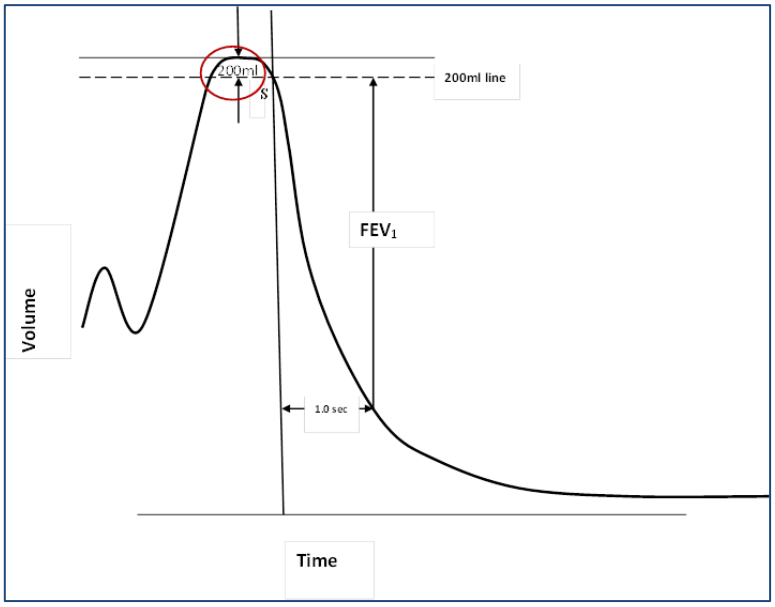

Figure 6: The Kory method of determining time zero
Adapted from Kory et al, 1961. Am J Med, 30:243-58

FEV_1 from when the forced expiratory curve crossed the 200ml line of the spirograph (Figure 6). This was not commonly used[142], and appears to underestimate FEV_1 by up to 179mls[143, 144] compared with the back extrapolation technique currently recommended by ATS/ERS (Figure 7).[41]

Figure 7: Back-extrapolation method of determining the new time zero
Adapted from Miller et al. 2005. Eur Respir J, 26:319-338

To investigate the performance of the Morris LA equations further, LA equations using the spirometry equation for FEV_1 from the Port Lincoln pilot study were created. LA estimates using both LA equations were determined for current smokers and healthy never smokers in an independent dataset. The mean LAs were compared using Student's t-test as described in the paper that follows.

The most important message of this analysis is that in this sample, the Morris & Temple equation indicated a seemingly protective effect of smoking, by giving a mean lung age for current smokers that was almost 13 years below chronological age. This goes against all knowledge of the damage to the lungs caused by smoking, and could adversely affect any quit smoking message if used in smoking cessation counselling.

This result strongly suggests that the Morris equations are not suitable for use in contemporary populations.

This paper generated international debate, as included in the Appendices

- Editorial by renowned spirometry experts appeared in the same edition of the PCRJ[145] – Appendix 2

- Letters to the Editor, both about this article, as well as responding to the editorial comment

    - The letter to the editor regarding my paper, from Dr J Hansen (California USA) and includes the authors' response to this[146] - Appendix 3

    - Hansen also wrote a response to the editorial[147] – Appendix 4

    - Parkes and Greenhaulgh wrote a response to the editorial[148] – Appendix 5

- other evidence of international interest was found in citations:

    - Respiratory Care Year in Review 2010: Part 1. Asthma, COPD, Pulmonary Function Testing, Ventilator-Associated Pneumonia[149]
    - La notion d'âge pulmonaire peut-elle aider à arrêter le tabac? [Does the concept of lung age help smokers to quit smoking?] 2011[150]
    - Novel regression equations predicting lung age from varied spirometric parameters, 2012[151]

These Australian LA equations have been used to inform LA estimates in the Primary Care Respiratory Toolkit, a resource for health care professionals on the Australian Lung Foundation website.[152] – Appendix 6

Results of this study were presented as an oral paper at the Australian and New Zealand Society of Respiratory Science (ANZSRS) Annual Scientific Meeting, Darwin 2009.[153]

Statement of Authorship

Title of Paper	Exploring the need to update lung age equations
Publication Status	⦿ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	Newbury W, Newbury J, Briggs N, Crockett A. (2010) Exploring the need to update lung age equations. Primary Care Respiratory Journal, 19(3): 242-247.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Wendy Newbury		
Contribution to the Paper	Literature search, data collection, data interpretation, writing of manuscript, acted as corresponding author		
Signature		Date	30/4/13.

Name of Co-Author	Jonathan Newbury		
Contribution to the Paper	Helped in data interpretation and manuscript evaluation		
Signature		Date	13-6-13

Name of Co-Author	Nancy Briggs		
Contribution to the Paper	Helped with data analysis and evaluation of manuscript		
Signature		Date	30/Apr/2013

Name of Co-Author	Alan Crockett		
Contribution to the Paper	Supervised development of project, assisted in data interpretation, helped evaluate and edit manuscript.		
Signature		Date	30/4/13

Newbury, W., Newbury, J., Briggs, N. & Crockett, A. (2010) Exploring the need to update lung age equations.
Primary Care Respiratory Journal, v. 19(3), pp. 242-247

Chapter 4: Newer equations better predict lung age in smokers: a retrospective analysis using a cohort of randomly selected participants.

Primary Care Respiratory Journal (2012); 21(1): 78-84

Introduction

This chapter describes the second phase to this body of work. Having considered the limitations of the previous paper a larger dataset was sourced for the next comparisons. The North West Adelaide Health Study (NWAHS) Stage 2 dataset comprised 3206 randomly selected male and female community dwelling adults who attended the study clinic; data were collected from 2004 to 2006.[154] Those who had results for pre-bronchodilator spirometry, with a smoking status of "never smoker" or "current smoker" (CS), and who were aged between 25 and 75 years at the time of the clinic visit were selected for inclusion. The never smokers with a self-reported doctor diagnosis of asthma, chronic bronchitis or emphysema were then excluded, giving a subgroup of never smokers in apparently good respiratory health (HNS, n=980)

Paper One had described what was possible evidence of the cohort and/or period effects. (See Chapter 6, page 90 for a full discussion of the period and cohort effects). The second phase of research aimed to test this further by developing four other LA equations from predictive equations for FEV_1 where data was gathered between those of Morris and Temple[111] (late 1960s) and the newer 'Newbury' equations[139] (2007). These selected equations span 40 years of data collection. The final set of six equations comprised:

- Two equations from USA
    - Morris & Temple[109]: USA; based on data collected in late 1960s[111]
    - Hankinson et al[46]: USA; data collected 1988-94 (3rd National Health and Nutrition Examination Survey, (NHANES III))
- Two equations from Europe/UK
    - Quanjer et al[59]: equations still in common use in the UK and Europe – summary equations compiled from different published studies conducted between 1950s-80s (European Community for Steel and Coal (ECSC))
    - Falaschetti et al[155]: data collected 1995-96 (Health Survey for England) provide later equations from UK
- Two equations from Australia
    - Gore et al[140]: data collected 1990 (Pilot Survey of the Fitness of Australians, Australia) provided equations from a larger sample from Australia
    - Newbury et al[156]: based on pilot study data gathered in 2007.[139]

The results from the analyses presented in this paper support the likelihood that cohort and period effects exist and that these contribute to the large differences in predicted values using these equations. This is evident in the older equation from Europe (ECSC, Quanjer[59]) producing similar values to those of Morris[111] from the same

era, while the three equations whose data were collected during the late 1980s to early 1990s (Falaschetti[155], Gore[140], Hankinson[46]) were also similar to each other. Similarly, the equations produced by the Port Lincoln pilot study[139] (the most recently collected data) produce the highest values; this is consistent with the above premise, however the limitations that apply to pilot studies must be remembered – especially those related to small numbers, and volunteer samples.

This paper was published in the Primary Care Respiratory Journal[157], and also had a linked Editorial.[158] This has been included in Appendix 7.

Statement of Authorship

Title of Paper	Newer equations better predict lung age in smokers: a retrospective analysis using a cohort of randomly selected participants
Publication Status	⦿ Published, ○ Accepted for Publication, ○ Submitted for Publication, ○ Publication style
Publication Details	Newbury W, Lorimer M, Crockett A. (2012) Newer equations better predict lung age in smokers: a retrospective analysis using a cohort of randomly selected participants. Primary Care Respiratory Journal, 21(1) 78-84.

Author Contributions

By signing the Statement of Authorship, each author certifies that their stated contribution to the publication is accurate and that permission is granted for the publication to be included in the candidate's thesis.

Name of Principal Author (Candidate)	Wendy Newbury		
Contribution to the Paper	Conception and design of the project, analysis of data, interpretation of results, writing of manuscript.		
Signature		Date	30/4/13

Name of Co-Author	Michelle Lorimer		
Contribution to the Paper	Assisted with analysis of data, interpretation of results and editing and reviewing of manuscript.		
Signature		Date	30/4/13

Name of Co-Author	Alan Crockett		
Contribution to the Paper	Assisted with conception and design of project, interpretation of results, and reviewing of manuscript.		
Signature		Date	30/4/13

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Newbury, W., Lorimer, M. & Crockett, A. (2012) Newer equations better predict lung age in smokers: a retrospective analysis using a cohort of randomly selected participants.
Primary Care Respiratory Journal, v. 21(1), pp. 78-84

Chapter 5: Investigating Delta Lung Age in independent datasets

Introduction

In 2010 an alternative LA equation was published in the European Respiratory Journal. This equation calculates the difference (in years) between estimated LA and the chronological age – Delta Lung Age (ΔLA).[159] This communicates the same message that cigarette smoking damages the lungs but in a different format:

- ΔLA – the difference between your chronological age and your lung age based on your current lung function is 20 years.

- LA – even though you are only 40 years old, your lung function is the same as a 60 year old's.

There are several aspects that make this LA equation different to the others. LA equations have traditionally been based on observed FEV_1[109, 156], however the ΔLA equation was based on FEV_1/FVC ratio.[159] It was derived from a predictive equation for FEV_1/FVC previously developed using the NHANES III dataset[160] and was designed as a single equation to be suitable for the three main ethnicities in the USA, namely American Caucasians, African-Americans, and Mexican-Americans. This single equation was also designed to be applicable to both males and females. Traditionally, predictive equations for lung function tests including spirometry are both sex- and ethnicity-specific.

The authors claimed that this equation was superior to both the Morris LA equation[109] and the Newbury LA equation[156] as it best predicted a LA that matched chronological

age in healthy never smokers (HNS).[146, 147, 159] On close investigation, it became apparent that these comparisons were not carried out using independent datasets, but in the same dataset used to generate the ΔLA equation. A predictive equation will always give a good result when used with the same data from which it was derived. The ΔLA equation has not been validated using an independent dataset therefore it was felt that a further comparison was warranted.

This chapter describes the next phase of the lung age research, the aim of which was to compare Hansen's ΔLA equation with several LA equations based on FEV_1, using independent datasets comprised of Caucasian subjects. For added strength and uniqueness, three independent datasets were used.

The null hypothesis was that LA estimates using the ΔLA equations would be no different in terms of intercept and slope to those using LA equations based on FEV_1 alone.

Methods

Four LA equations were selected for this comparison: the original Morris LA equation[109], the Newbury LA equation[156], the ΔLA equations[159], and finally the LA equation based on Hankinson's predictive equation (for Caucasians) for FEV_1 from 1999[46] which had been part of the earlier comparison of lung age equations (Chapter 4 of this thesis).[157] As the Hankinson equation was also developed using NHANES III data this allowed a comparison of two equations from the same dataset. Three of the selected equations were based on FEV_1 alone (Morris, Hankinson, Newbury) while the ΔLA equation was based on the FEV_1/FVC ratio. Another difference was that the

Morris, Newbury and Hansen predictive equations were derived using linear regression techniques, whilst the Hankinson equation was quadratic in form. As the Hansen equation calculated ΔLA, this was converted to LA for easier comparison, by adding ΔLA to chronological age. These four LA equations were then applied to three independent datasets.

Ex-smokers were excluded from all datasets, as were subjects outside the ages of 25-74 years. Subjects younger than 25 years were excluded as it has been well documented that lungs continue to mature until early adulthood.[59, 161] HNS and current smokers (CS) were defined in each dataset. HNS were defined as having no existing diagnosis of respiratory disease such as asthma, chronic bronchitis or emphysema. Ethnicities other than Caucasian were excluded where this was known. Subjects without valid FVC results according to the ATS/ERS 2005 criteria[41] were excluded in all three datasets.

Datasets

Three Australian datasets were selected to provide a wide range of subjects, and to increase generalisability. They included an urban dataset of community based adults, the North West Adelaide Health Study Stage 2 dataset (NWAHS, n=3566), a rural dataset of community based adults, the Whyalla Intergenerational Study of Health (WISH, n=701) and a workplace dataset from Adelaide, South Australia (the Metropolitan Fire Service (MFS), n=553).

The NWAHS Stage 2 dataset is from a longitudinal study of a randomly selected sample of the population aged over 18 years, from the northern and western suburbs of

Adelaide, South Australia.[154, 162] The sample numbered 1505 after exclusion criteria were applied. Data had been collected using the EasyOne® Spirometer (nnd Medizintechnik AG, Zurich, Switzerland).

WISH is a population sample recruited by random selection of residential households within the regional city confines of Whyalla, an industrial city in South Australia.[163] Data had also been collected using the EasyOne® Spirometer. As the Quality Control Grade (QC Grade – an indication of the quality and reproducibility of the result) was available in this dataset, subjects with a QC Grade of D (tests not reproducible) or F (no acceptable test) were excluded. This sample numbered 257 after all exclusion criteria were applied.

The MFS workplace dataset had 553 subjects (Males 539). In this dataset, females were excluded due to relatively small numbers (n=14). After applying the exclusion criteria, the sample numbered 340. Spirometry data had been collected using the Masterscreen Impulse Oscillometry System® instrument (Carefusion, Hoechberg, Germany).

Statistical analysis

A lung age estimate was calculated using each of the four lung age equations for each subject, based on their height and observed FEV_1 or FEV_1/FVC ratio. In order to account for these repeated measures for each subject a linear mixed effects model was used, with an unstructured covariance structure to account for the variability in lung age equations.[164] This approach is similar to a regression analysis, and has Lung Age as the dependent variable, and Sex-Smoking Status (a variable which combined

both the Sex and Smoking Status categorical variables, for ease of interpretation), Equation Group (a newly created variable with an indicator for each of the four equations defined by first author i.e. Hankinson, Hansen, Morris or Newbury), and Chronological Age included as independent variables. The initial model included all independent variables as main effects, all two-way interactions and the three-way interaction; the final model equation was determined by backward elimination. Separate analyses for each dataset were performed in SAS version 9.3® and statistical significance was set at $p<0.01$ to make allowance for multiple comparisons.

Approval to use each of these datasets was granted by the respective research groups who owned the data. As this project used de-identified data, the University of Adelaide's Human Research Ethics Committee ruled that no further ethics approval was required.

Results

The datasets that were used for these comparisons were initially explored for descriptive purposes (see Table 2). In the two community-based datasets (NWAHS and WISH), the mean age of CS was 3-6 years lower than that of HNS for males and females. The males of the MFS dataset were taller than their counterparts in the community based datasets, and had a higher mean FEV_1 and FVC although the mean FEV_1/FVC ratio was lower. This probably reflects the very high level of physical fitness required for members of the MFS workforce. Similar situations have been described in the earlier 1991 ATS guidelines on Lung Function Testing.[37]

Dataset	Sex	Smoking Status	Age (range)	Height	FEV_1	FVC	FEV_1/FVC
NWAHS	Male	HNS (n=426)	50.5 (25-74)	176.1 (7.29)	3.55(0.72)	4.37(0.87)	81.44(5.92)
		CS (n=268)	47.7 (25-74)	176.2 (6.85)	3.33(0.79)	4.25(0.88)	77.87(8.52)
	Female	HNS (n=566)	53.6 (25-74)	161.4 (6.80)	2.47(0.53)	2.98(0.62)	82.82(5.11)
		CS (n=245)	46.9 (26-74)	162.5 (6.18)	2.50(0.64)	3.13(0.69)	79.72(8.68)
WISH	Male	HNS (n=52)	50.1 (26-73)	176.6 (7.4)	3.61(0.69)	4.6(0.93)	78.2(5.73)
		CS (n=58)	45.7 (25-70)	176.0 (7.1)	3.24(0.91)	4.3(0.97)	73.9(10.62)
	Female	HNS (n=94)	49.8 (25-74)	163.2 (5.4)	2.66(0.58)	3.33(0.63)	79.8(5.54)
		CS (n=53)	43.7 (26-73)	162.7 (5.8)	2.59(0.70)	3.4(0.79)	75.6(7.43)
MFS	Male	HNS (n=290)	42.7 (25-60)	180.6 (6.5)	4.51(0.67)	5.9(0.83)	75.8(5.5)
		CS (n=50)	42.8 (28-60)	180.2 (6.3)	4.28(0.71)	5.84(0.80)	73.3(7.29)

Table 2: Descriptive statistics of all three datasets used for comparisons

Descriptive statistics by sex and smoking status, showing mean (range) for Age in years, and mean (SD) for Height (cm); FEV_1 and FVC in Litres; FEV_1/FVC expressed as %. SD: Standard Deviation. NWAHS – North West Adelaide Health Study; WISH – Whyalla Intergenerational Study of Health; MFS – Metropolitan Fire Service. HNS – Healthy never smokers; CS – current smokers

Mean LA estimates for all three datasets, and each equation group (Hankinson, Hansen, Morris, Newbury), appear in Table 3. Mean LA is greater for CS than for HNS as actual age increases in each equation group which may be due to the accumulative effect of smoking. This occurs in all datasets.

Dataset	Sex	Smoking Status	Equation Group			
			Hankinson	Hansen	Morris	Newbury
NWAHS	Male	HNS	57.7 (-24.2 to 105.9)	41.1 (-22.6 to 135.2)	48.6 (-11.5 to 109.8)	68.6 (8.6 to 133.1)
		CS	64.2 (10.9 to 121.1)	51.9 (3.2 to 197.2)	55.8 (8.7 to 134.9)	76.4 (27.2 to 160.8)
	Female	HNS	60.4 (-1.91 to 96.8)	45.3 (-9.35 to 127.3)	49.9 (-7.8 to 98.7)	60.7 (16.2 to 99.6)
		CS	59.6 (-0.5-113.6)	52.2 (1.3-226.0)	50.2 (7.3-128.6)	61.2 (27.0 to123.1)
WISH	Male	HNS	56.6 (0.0 to 91.6)	49.5 (14.0 to 91.4)	47.4 (3.5 to 87.3)	67.5 (21.7 to 111.0)
		CS	65.6 (-1.2 to 122.6)	62.8 (6.3 to 207.9)	58.1 (6.8 to 133.7)	78.9 (22.2 to 162.4)
	Female	HNS	53.9 (-0.4 to 89.1)	51.52 (10.6 to 97.8)	44.9 (2.5 to 86.0)	57.0(22.1 to 90.7)
		CS	57.6 (24.2 to 102.3)	62.3(13.7 to 144.2)	47.2 (2.1 to 107.8)	58.8(24.1 to 107.1)
MFS	Male	HNS	34.5 (-32.3 to 81.9)	47.8 (6.4 to 109.2)	23.8 (-20.0 to 74.7)	43.5 (-0.9 to 97.1)
		CS	41.6 (-14.9 to 93.5)	55.9 (21.8 to 128.7)	30.5 (-5.9 to 93.5)	50.5 (11.8 to 114.7)

Table 3: Mean lung age (range) for each equation group

Equation groups are defined by name of first author. Lung Age in years; HNS - Healthy Never Smokers; CS - Current Smokers; NWAHS – North West Adelaide Health Study; WISH – Whyalla Intergenerational Study of Health; MFS – Metropolitan Fire Service.

A LA value that is lower than chronological age reflects a higher than mean predicted value for FEV_1 (or FEV_1/FVC ratio). Negative LA estimates (e.g. Table 3: NWAHS Males HNS: Hankinson -24.2 years, Hansen -22.6 years, Morris -11.5 years) are biologically impossible, but reflect how the equation deals with the high end of the range of FEV_1 (or FEV_1/FVC ratio) measurements. Negative LA values tend to occur in HNS, using the equations that are based on earlier data (Morris, Hankinson, Hansen), and this is likely to be due at least in part, to cohort and/or period effects. However, the main purpose of LA is for use in CS where this is less likely to occur.

As seen in Table 3, the ΔLA (Hansen) equation gives widely varied and extremely high LA estimates in all datasets, more so in CS than in HNS, although this is not necessarily

reflected in the mean values. This was explored by developing the boxplots of the LA Residuals (the difference between the predicted and the observed values) for each of the equation groups in each of the NWAHS subgroups (Figure 8). In the HNS in this dataset, the Hansen equation group has the greatest range in females, while in males the range with the Hansen equation was similar to the spread with the Morris equations although the Hansen equation had a more positive tendency than did the Morris equations. In CS, the range seen in the Hansen equation group in both females and males is far greater than the other equation groups.

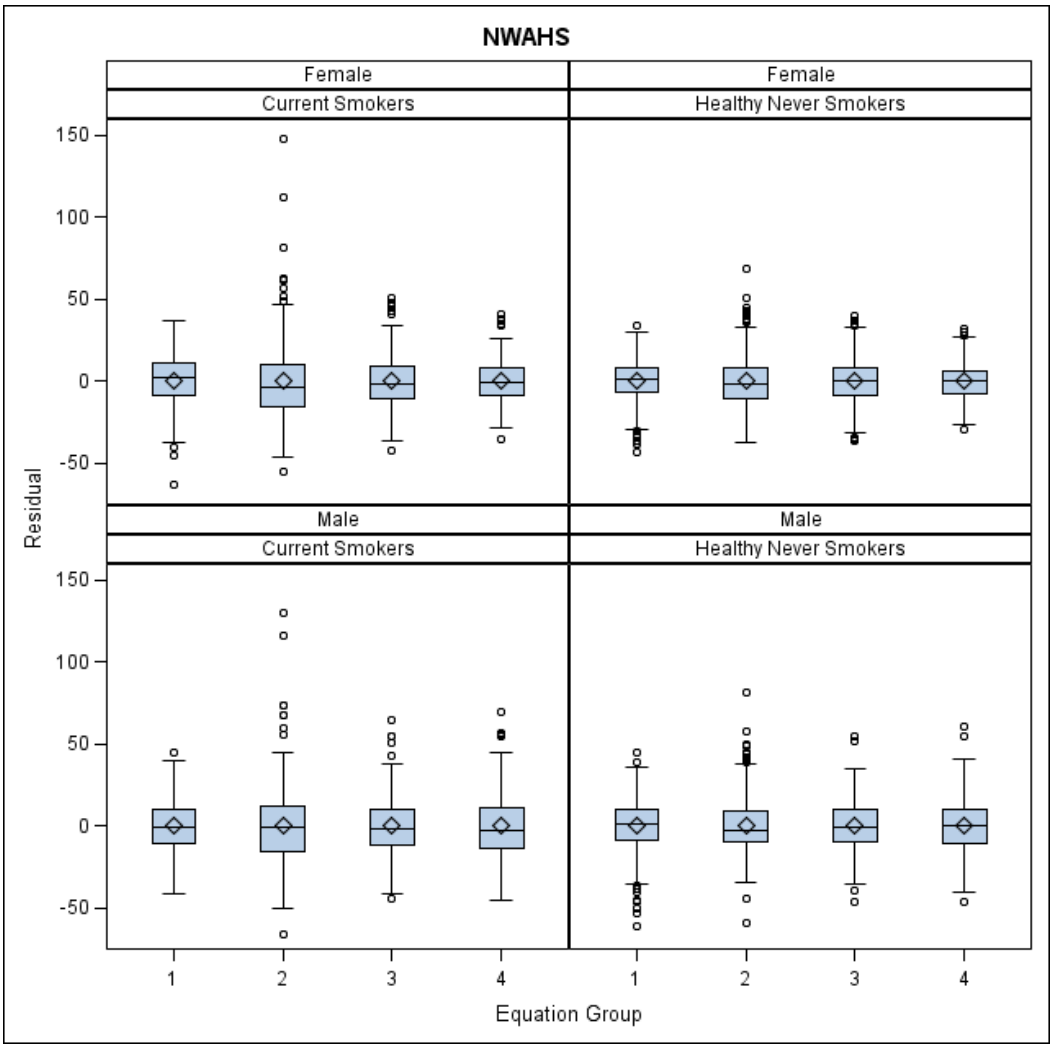

Figure 8: Boxplots of residuals: NWAHS
Equation Groups – 1: Hankinson; 2: Hansen; 3: Morris; 4: Newbury
The top and bottom of the boxes indicate the interquartile range (IQR). The line inside the box indicates the median value, while the marker inside the box indicates the mean value. The whiskers that extend from each box indicate the range of values that are outside the interquartile range - ≤1.5*IQR. The circles beyond the ends of the whiskers are considered to be outliers.

In the WISH dataset, the Hansen equation gives the widest spread for HNS in females but not in males (Figure 9). In CS, the range is again greatest for the Hansen equation.

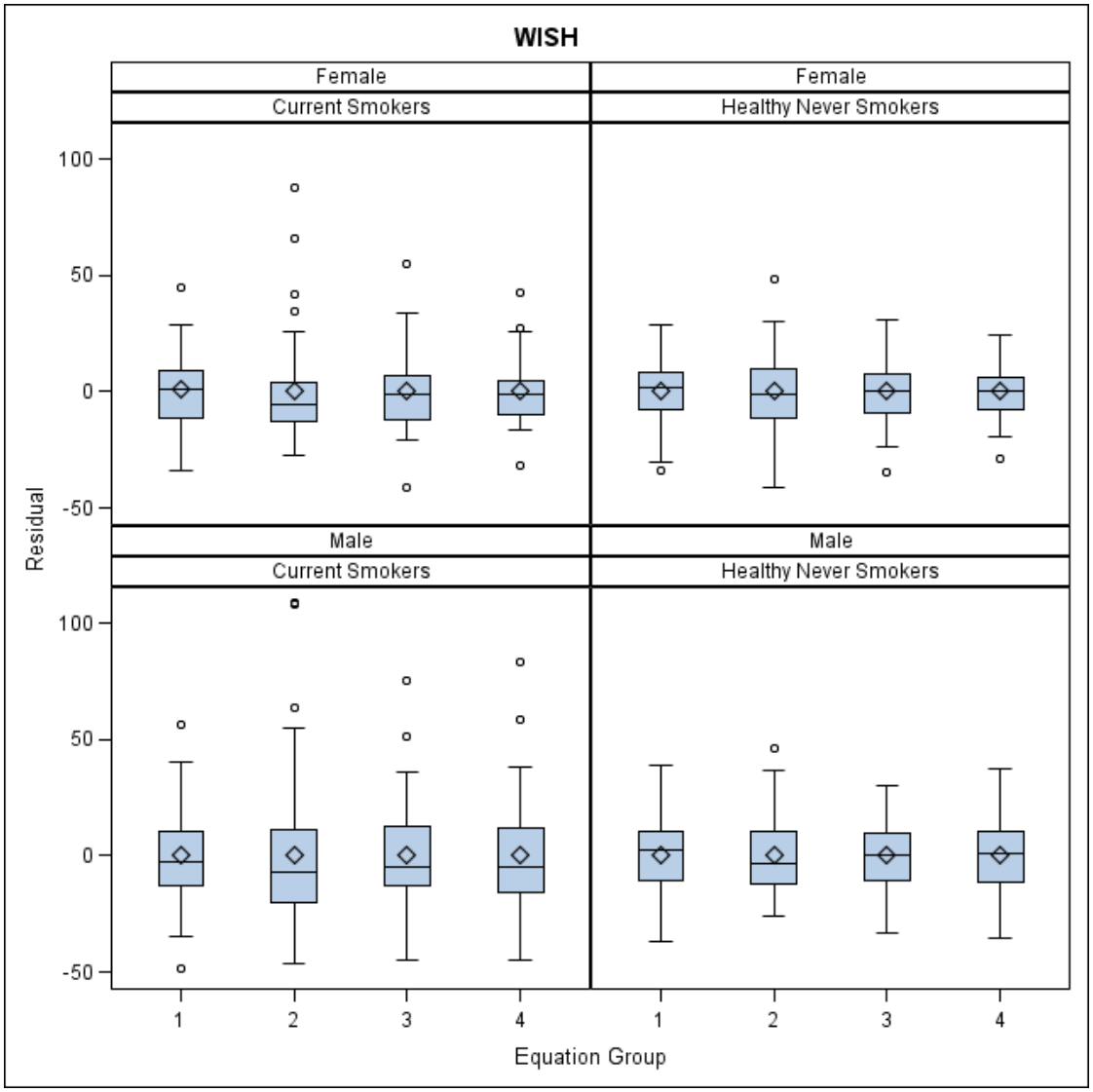

Figure 9: Boxplots of residuals – WISH.
Equation Groups – 1: Hankinson; 2: Hansen; 3: Morris; 4: Newbury
See note to Figure 8 for explanation of symbols.

The results of the linear mixed effects model indicated that the three-way interaction between Equation Group, Sex-Smoking Status (or just Smoking Status in MFS) and Age was statistically significant in each dataset (NWAHS: $p < 0.0001$; WISH: $p < 0.0001$; MFS:

p <0.0001). Therefore separate regression equations, with separate slopes and intercepts, were defined from the data for each combination of Equation Group (Hankinson, Hansen, Morris, Newbury) and Sex-Smoking Status (Male HNS, Male CS, Female HNS, Female CS). The main effect of Equation Group, and the main effect of Sex-Smoking Status, and the interactions of these define the intercept of the predictive models; the terms that include age define the slope. All regression equations for each dataset are provided in Table 4. It should be noted these are not predictive equations used for estimating the LA in individuals, but rather they describe the regression lines fitted from the scatter of data for each LA equation in each smoking subgroup (male CS, male HNS, female CS, and female HNS) from each dataset. The regression equations in Table 4 take the following form:

LA = Constant (reflecting the intercept) + coefficient*Age (defining the slope of the regression line).

Dataset	Sex	Equation Group	Current Smokers	Healthy Never Smokers
NWAHS	Male	Hankinson	LA = 13.08 + 1.07*A	LA = 15.75 + 0.83*A
		Hansen	LA = -12.50 + 1.35*A	LA = 2.04 + 0.78*A
		Morris	LA = -3.74 + 1.25*A	LA = 3.59 + 0.90*A
		Newbury	LA = 14.39 + 1.30*A	LA = 23.30 + 0.91*A
	Female	Hankinson	LA = -4.57 + 1.34*A	LA = 5.89 + 0.99*A
		Hansen	LA = -10.13 + 1.33*A	LA = 5.47 + 0.74*A
		Morris	LA = -16.35 + 1.42*A	LA = -3.07 + 0.99*A
		Newbury	LA = 9.46 + 1.10*A	LA = 20.02 + 0.76*A
WISH	Male	Hankinson	LA = 7.91 + 1.26*A	LA = 13.31 + 0.86*A
		Hansen	LA = -7.15 + 1.53*A	LA = 29.29 + 0.40*A
		Morris	LA = -9.55 + 1.48*A	LA = 0.06 + 0.94*A
		Newbury	LA = 8.22 + 1.54*A	LA = 20.78 + 0.93*A
	Female	Hankinson	LA = -2.37 + 1.33*A	LA = -5.18 + 1.18*A
		Hansen	LA = 10.43 + 1.18*A	LA = 0.76 + 1.02*A
		Morris	LA = -17.15 + 1.47*A	LA = -11.19+ 1.12*A
		Newbury	LA = 8.24 + 1.15*A	LA = 13.21 + 0.88*A
MFS	Male	Hankinson	LA = -27.69 + 1.55*A	LA = -21.42 + 1.24*A
		Hansen	LA = -9.02 + 1.51*A	LA = 12.02 + 0.84*A
		Morris	LA = -29.97 + 1.41*A	LA = -19.54 + 1.01*A
		Newbury	LA = -14.60 + 1.52*A	LA = -0.73 + 1.03*A

Table 4: Regression equations for Lung Age for each dataset
Separate equations are provided for each equation group and sex-smoking status.
LA = Lung Age; A = Age in years. NWAHS – North West Adelaide Health Study; WISH – Whyalla Intergenerational Study of Health; MFS – Metropolitan Fire Service.

To determine which equation fits chronological age best in HNS, both slope and intercept are taken into account. In HNS a slope coefficient of 1 reflects the ideal situation, with an increase of one year in LA for each year of chronological age. The Morris and the Newbury equations consistently had slope coefficients closest to 1 in the male HNS subgroups of each of these three datasets. In the NWAHS females, the slope of the Morris and the Hankinson equations were both closest to 1. The ΔLA equation had a slope coefficient that was less than the other equations in most HNS subgroups. This gives a flatter slope than would be expected, and is particularly marked in WISH males. The ΔLA equation had the slope coefficient closest to 1 only for female HNS in the WISH dataset.

There were no discernible patterns detected in intercept differences between the Hansen results and the other equations.

Results of the linear mixed effects model using the NWAHS dataset are presented graphically in Figure 10 (males) and Figure 11 (females). Differences that are probably attributable to the cohort and/or period effects can be seen in the higher intercepts of the newer equations that are based on FEV_1 alone (Hankinson is greater than Morris, Newbury is greater than Hankinson and Morris.) The Hansen equation appears to under-predict LA compared to chronological age in HNS across the 25-74 year age range in both males and females in this dataset.

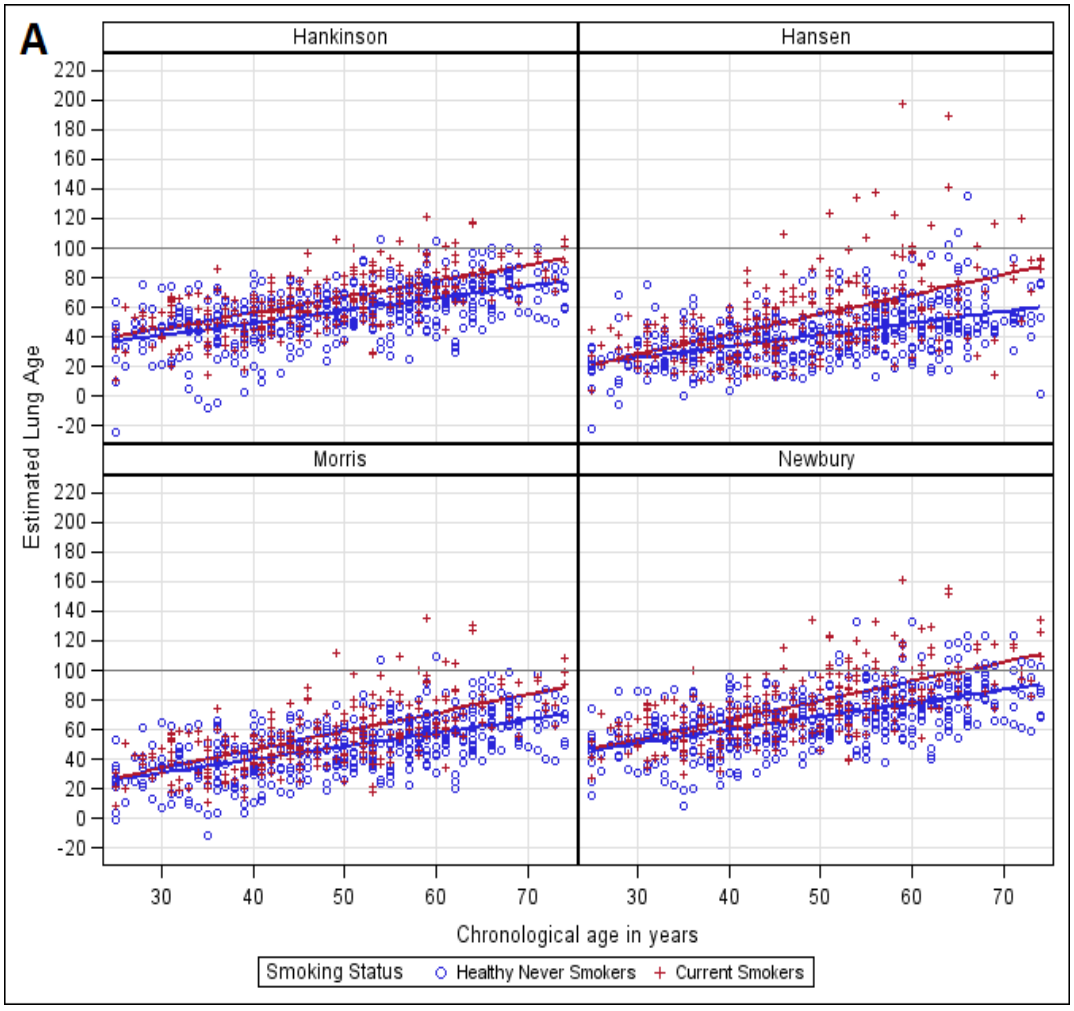

Figure 10: Scatterplots with regression lines – NWAHS Males.
Regression lines are overlaid on the scatterplots of lung age versus chronological age, with equation groups classified by first author. (Healthy never smokers: blue; current smokers: red). In CS: when the all equations were compared to Hansen, statistically different intercepts were seen in Hankinson ($p<0.0001$), in Newbury ($p<0.0001$), but not in Morris ($p=0.69$). The differences in slope only reached significance against Hankinson ($p=0.003$).

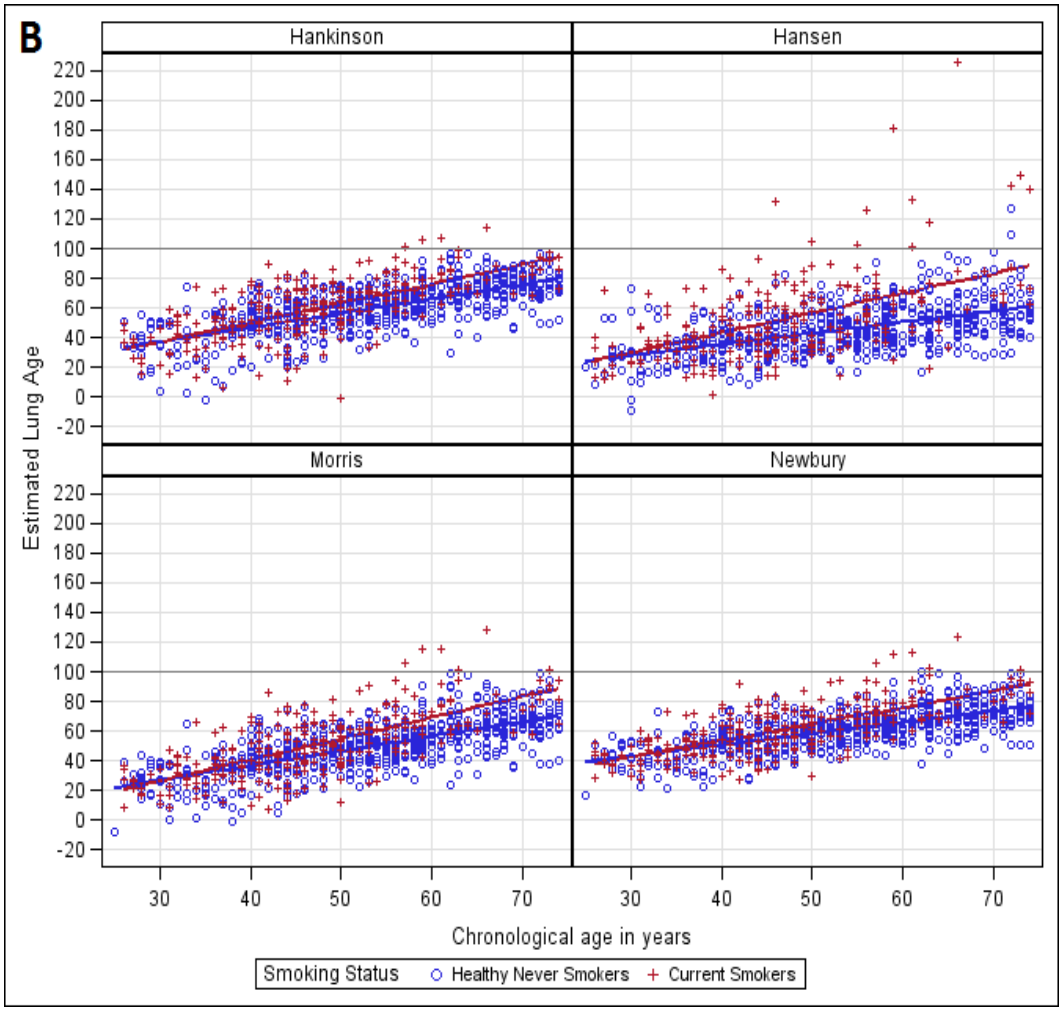

Figure 11: Scatterplots with regression lines – NWAHS females.
Regression lines are overlaid on the scatterplots of lung age versus chronological age, with equation groups classified by first author. (Healthy never smokers: blue; current smokers: red). In CS: significant differences in intercept were only seen when the Hansen equation was compared with Newbury ($p<0.0001$); differences in slope did not reach statistical significance against any of the 3 equations (Hankinson $p=0.88$; Morris $p=0.37$; Newbury $p=0.018$).

Results of the analysis using the WISH dataset of rural community-dwelling adults are shown graphically in Figures 12 and 13.

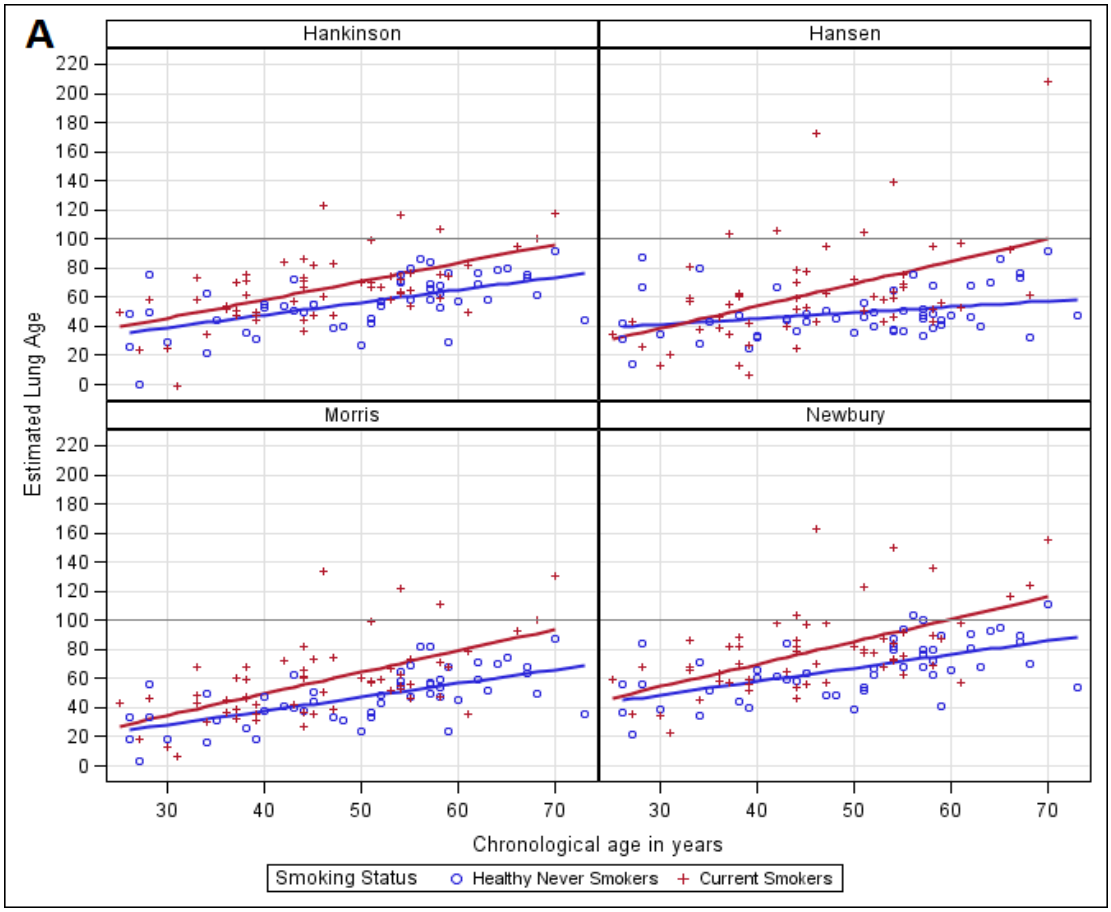

Figure 12: Scatterplots with overlaid regression lines – WISH Males
Regression lines are overlaid on the scatterplots of lung age versus chronological age, with equation groups classified by first author. (Healthy never smokers: blue; current smokers: red).
In CS: when Hansen equation was compared with the other equations, neither intercept nor slope were found to be significantly different. Hankinson differences: p=0.87 (intercept), p=0.61 (slope). Morris differences: p=0.05 (intercept), p=0.18 (slope); Newbury differences: p=0.66 (intercept), p=0.09 (slope).

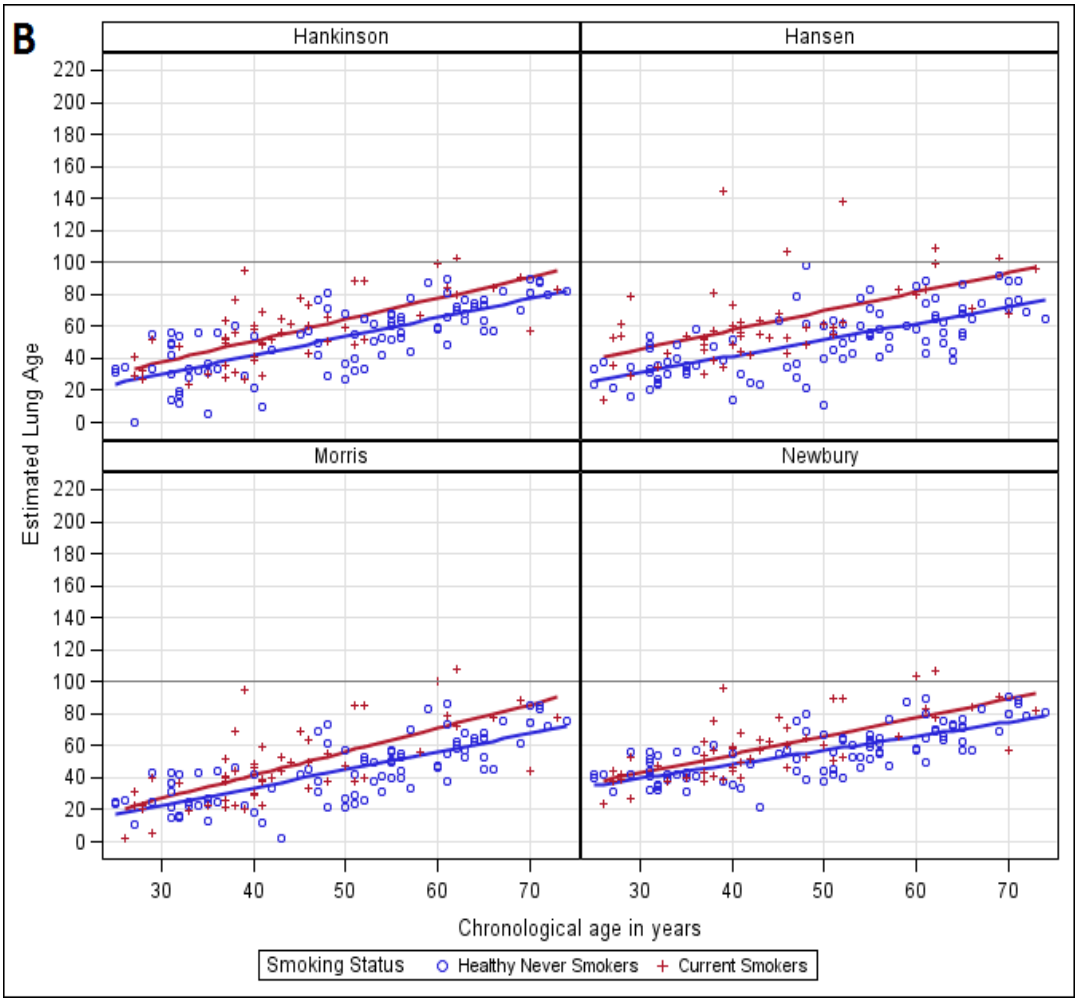

Figure 13: Scatterplots with overlaid regression lines – WISH females
Regression lines are overlaid on the scatterplots of lung age versus chronological age, with equation groups classified by first author. (Healthy never smokers: blue; current smokers: red). In CS: when Hansen equation was compared with the other equations, intercept differences were statistically significant against Morris ($p<0.0001$) but not Hankinson ($p=0.018$) or Newbury ($p=0.26$). Differences in slope were significant against Morris ($p=0.0009$) but not Hankinson ($p=0.03$) or Newbury ($p=0.26$).

The MFS dataset results are seen in Figure 14. The Hansen equation again produces a greater range than the Newbury or the Morris equation in CS, although this is not as marked as in the community based samples. This could be due to a healthy worker effect.

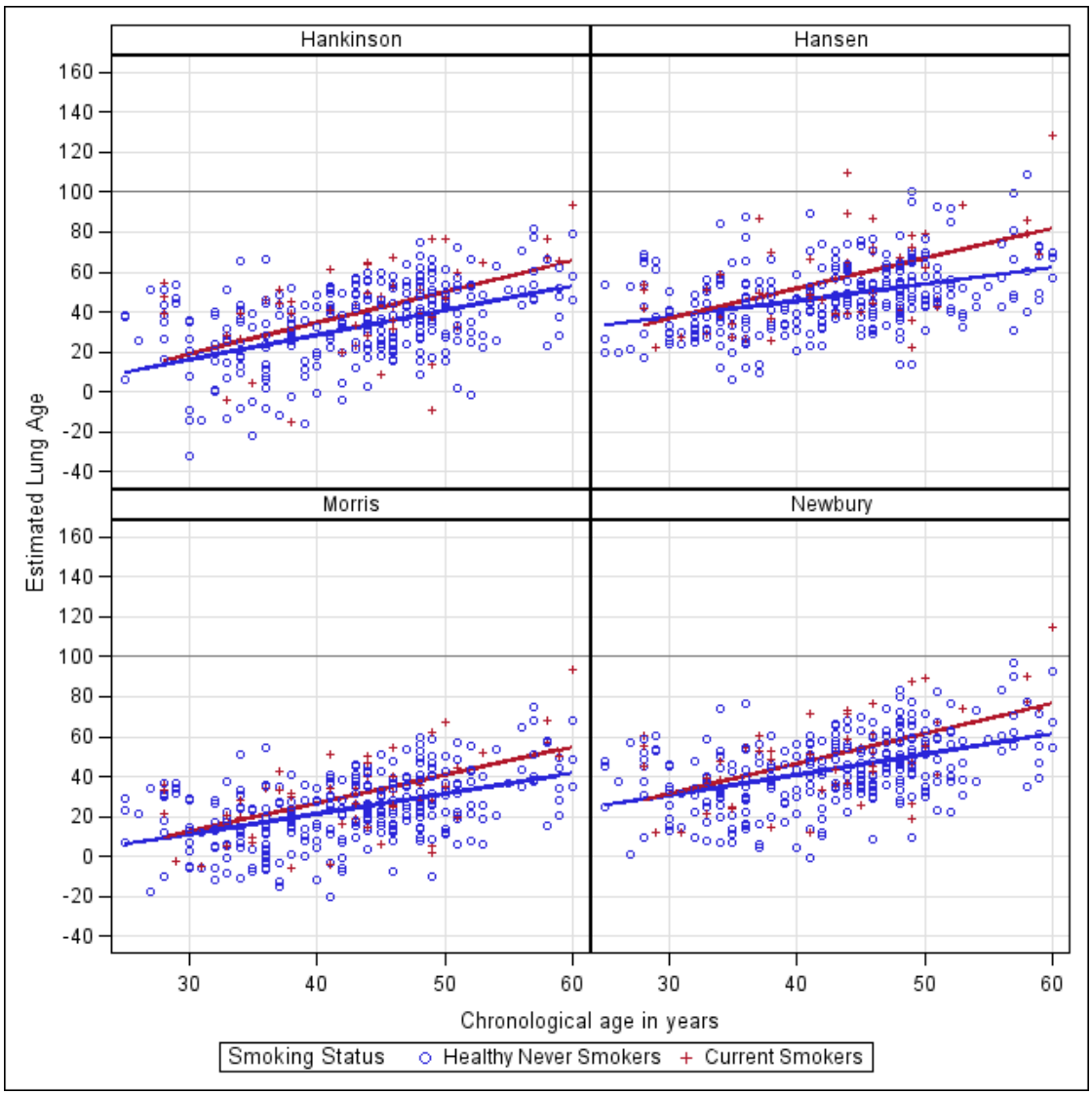

Figure 14: Scatterplots with overlaid regression lines – MFS (Males only)
Regression lines are overlaid on the scatterplots of lung age versus chronological age, with equation groups classified by first author. (Healthy never smokers: blue; current smokers: red).
In CS: when Hansen equation was compared with the other equations, neither intercept nor slope were significantly different in any equation. Hankinson p=0.13 (intercept), p=0.90 (slope); Morris p=0.04 (intercept), p=0.66 (slope); Newbury p=0.59 (intercept), p=0.99 (slope).

Discussion

Four different lung age equations have been evaluated using independent Australian datasets. These results show that ΔLA does not give LA estimates that are consistently statistically significantly different to those based on FEV_1 in both HNS and CS in these datasets. It can therefore be deduced that the null hypothesis has not been disproven. Taken together with the bizarre LA estimates that ΔLA gives for some individuals, there is no advantage to be gained in using ΔLA in current smokers.

The ΔLA equation was developed as a single equation for males and females of multiple ethnicities – Caucasian, African-American, and Mexican-American as represented in the NHANES III dataset. As people of Hispanic ethnicity are shorter than their Caucasian counterparts[165] and are over-represented in this sample compared with the general population, this may produce a bias in this equation. With very low numbers of African-Americans and Mexicans in the Australian population, the external validity of the ΔLA equation in our setting is doubtful. Given that differences in lung volumes between ethnicities are likely to be related to height, this may contribute to the differences seen in this comparison, as the other LA equations (Morris, Hankinson, Newbury) were defined separately for males and females, of Caucasian ethnicity. Others however have found that the FEV_1/FVC ratio is virtually independent of ethnicity.[58]

The authors of the ΔLA equations state that the ratio of FEV_1/FVC has "much less variability than absolute measures of other spirometric volumes or flows"[147] and suggest that this is why LA using their equation best matches chronological age in HNS in their comparisons[146, 147, 159], however it is possible that the use of a ratio of two

measures masks the variability of both measures.[166 (p36)] A more likely explanation is that the close match achieved by Hansen et al resulted from flawed methodology when the same dataset was used to both generate the equations and to validate their utility. The Hankinson LA equations (also derived from the same NHANES III dataset, but developed specifically for males or females of Caucasian ethnicity) behave in a similar fashion to the other equations based on FEV_1 (Morris, Newbury). Therefore, the differences seen with the ΔLA equation are probably due to either the use of the FEV_1/FVC ratio, or to the sample from which it was derived.

Interpretation based on the CS subgroups in each dataset is important as this is the target group in the general population. The most striking difference between all equation groups is seen in both datasets of randomly selected subjects, where the Hansen ΔLA equation has the largest range in LA estimates. The extreme values for LA generated by the Hansen ΔLA equation seen in some individuals have affected the slope of the regression line for the CS groups in each dataset, resulting in a larger difference between CS and HNS than that seen in the other equation groups (see Figures 10-14).

The subjects with highest LA estimates in the Hankinson, Morris and Newbury equation groups are not always the same as those with the highest LA estimates in the Hansen equation group. As the same subjects/results have been used to give the four LA estimates in each dataset, and all things pertaining to the measurement at the time of recording the result are also the same (e.g. spirometer, guidelines used, interaction between subject and technician) it is likely these differences occur because of the

difference in the structure of the LA equations, i.e. the use of the FEV_1/FVC ratio rather than FEV_1 alone.

Strengths and Limitations

A considerable strength of this research is the use of several independent datasets, both urban and rural, two of which were composed of randomly selected community-dwelling adults. This makes the results of this research more generalisable to the wider Australian communities.

A further strength is the use of a linear mixed effects model which uses each individual's result in the analysis and therefore gives more robust results than analyses which report the mean and standard deviation.

Two of the datasets used for these comparisons had collected their spirometry data using the EasyOne® spirometer, while the third had used the spirometry function on the laboratory-standard Masterscreen IOS®. The EasyOne® spirometer has been found to be accurate and suitable for use in primary care settings[167], however other researchers suggest results obtained with office spirometers (including the EasyOne®) may not be interchangeable with results from laboratory standard devices, in particular regarding the reproducibility of FVC.[168, 169] This may offer some explanation as to the different results seen in the analyses using the MFS and the community-based datasets. The study that informed the Newbury LA equations[139] used the same equipment as the MFS dataset (Masterscreen IOS®) and the field workers for these two projects had both been trained by the same person (AC). This may also help to explain the goodness of fit between the Newbury LA equations and the MFS data.

Regarding the original datasets which informed the LA equations that were compared in this project, the Port Lincoln data was sourced in a rural town with no heavy industry; and the sample was age and sex stratified. This resulted in predictive equations that were equally relevant across the age range (25-74 years).[139] In contrast both the Morris sample[111] and the NHANES III sample had considerably fewer older adults than younger which may have added bias to their prediction equations. A limitation to using the Hankinson LA equations was that these were unable to estimate LA in some subjects in all three datasets, due to the quadratic form of the equation (as previously mentioned in Chapter 4).The MFS dataset also has some limitations: it is a workplace dataset with many subjects being much fitter than the average person and analysis using this dataset was limited to males.

Interpretation of findings in relation to previously published work

Hansen et al derived the ΔLA equations[159] using FEV_1/FVC from the NHANES III dataset but compared them with the Morris LA equations using the same dataset. Not surprisingly they concluded that the ΔLA equations were a better fit than the Morris equations. A further comparison with both the Morris[109] and the Newbury[156] equations drew the same conclusion[146] but again this used the NHANES III dataset. The project described in this chapter has compared the FEV_1/FVC ΔLA equation with three other LA equations based on FEV_1 alone, using several independent datasets. This is the first comparison involving the ΔLA equation to do so in datasets comprised of Caucasian subjects.

A recent conference abstract reported results from a longitudinal follow-up study in Japan of patients attending a preventive medical centre for an annual health check.[170]

This analysis showed that locally derived LA equations[132] were a better match for annual rate of change than the Morris or the Hansen LA equations in a never-smoked Japanese population, however the two equations from USA had less variation around the regression line in HNS than the Japanese equation. The results seem to differ from those presented in this chapter, but comparisons are difficult due to different study designs and samples, and limited information being available in this abstract.

Conclusion

The results from these comparisons provide the first indication of how the ΔLA equations behave in independent datasets of Caucasian subjects, and highlight the need to use independent datasets when comparing or validating predictive equations. If the original dataset is used to validate equations derived from it then this will lead to erroneous interpretation as, by definition, predictive equations will fit the sample from which they were derived.

The results reported in this chapter indicate that there is no advantage to be gained in using the ΔLA equation over LA equations based on FEV_1 alone. However there is a need to develop current predictive equations for lung function that are relevant to the Australian population. LA equations based on up-to-date data can then be investigated to determine their effect on smoking cessation in the smoking population.

Chapter 6: Discussion

Main results

This thesis has generated a number of original contributions to the body of knowledge regarding the estimates of lung age, and has demonstrated that it is possible to estimate LA by converting other spirometric predictive equations for FEV_1 to the LA format. This gives further options to use LA in smoking cessation research/counselling that may be more relevant/appropriate to particular populations than the original equation published in 1985.

Three linked studies, using independent datasets, have shown that the older predictive equations give lower predicted values for FEV_1 than do newer equations. These differences remain evident in the corresponding LA estimates. This concurs with both the cohort effect where lung function appears to have increased due to increased growth across successive birth cohorts and with the period effect where the accuracy of measurement of lung function has increased due to the advances in equipment and methods at the time of measurement.

While the first study used a workplace dataset for comparisons, the second and third studies both used independent datasets of randomly selected community dwelling adults for further comparisons. The differences between LA estimates between the Morris and the other LA equations based on FEV_1 are consistent in all three studies. The match between mean Newbury LA and mean chronological age that had been seen in the male HNS of the workplace dataset was not replicated in the HNS in the community-based datasets. The third study reported that there is no advantage in using the ΔLA equation to estimate LA.

All three studies confirmed that LA estimates are higher in current smokers (CS) than in never smokers without previously diagnosed lung disease (HNS) as chronological age increases. This is evident across all equation groups in all independent datasets and reflects the poorer lung function in the CS groups. However, there is still an overlap seen between CS and HNS that is due to the wide spread of results around the mean. Smoking is not the sole cause of poor lung function, however smoking is recognised as being the major cause of reduced lung function in western societies and is known to have a negative influence on the maximum level attained, the length of the plateau in early adulthood, and the rate of age-related decline of lung function.[49, 53] It is not only personal smoking habits which affect these in the individual – pre-natal and early childhood exposure to cigarette smoke can impact negatively on a child's lung development; workplace and social exposures will also contribute. Many of these exposures are interwoven with other aspects of socioeconomic status including level of education, type of employment, physical activity, poor diet and long term exposure to air pollution.[53] People of lower socioeconomic status are also more likely to be smokers.[171]

Cohort and Period Effects

The differences seen across the six selected equation groups are linked to the populations used to generate the predictive equations as well as factors relevant to the year of data collection.[172] The confusion in the literature over what is a cohort effect and what is a period effect deserves to be clarified.

Cohort Effect

The cohort effect is a term used to describe intrinsic differences seen between generations which are related to early life experiences and exposures from an earlier period that are not present in later generations. Improved nutrition and lifestyles, with better access to improved medical care including vaccinations and antibiotics, changes in level of air pollution can all contribute.[172-174] Cohort effects are seen in cross-sectional data, and relate to the year of birth or age at enrolment.[172, 173, 175]

Height and weight have generally been increasing in adults in many parts of the world since mid-19th Century. Together with the rate of physical development and maturing in children, this phenomenon is also termed 'secular trend' or 'secular change' and is recognised as being affected by an interaction between nutrition and illness.[176] Increased height is linked to greater chest size which over generations results in larger lung volumes. The cohort effect has been quantified to be approximately 5ml/year in a 24-year longitudinal study[174], and over a period of 25 years this would be approximately 125mls.[173, 174]

Period effect

The period effect relates to the year of survey and can also influence results, although this is more likely to occur with longitudinal data.[175] Contributing factors include advances in instruments, the associated software used, changes in guidelines, etc.[173, 175] These are extrinsic factors that influence the actual measurement at the time of testing rather than the person's actual lung volume as would appear to occur with the cohort effect. Some papers refer to war, famine, epidemics and natural disasters[172] as well as differences in air pollution, types of cigarettes and percentage of population

smoking, vaccinations etc. as period effects[174] however these possibly better fit the description of cohort effect referred to above as they would affect a person's actual lung volume.

A learned effect where subsequent results are higher than at the initial test is also considered to be a period effect.[175] This is due to the prior learning of the technique leading to better performance of the manoeuvre at the later visits. As this relates more to the repeated measures in longitudinal studies than to cross-sectional studies, it is not considered to be relevant to the current analyses.

There were approximately 20-25 years between collection of the data that informed the Morris et al predictive equations[111] and the data that informed the Hankinson et al[46], the Falaschetti et al[155], and the Gore et al[140] predictive equations, and a further 10-15 years to when the Port Lincoln data were collected.[139] Period effects including advances in equipment and changes in techniques across a shorter timeframe (covering 1973-78 and 1985-90) have been estimated to show an increase of 250ml in men, and 219ml in women[173, 174] but in the period between Morris and the present day, 40 years, the expected difference would be much greater.

Instruments over this period of time have evolved from water-sealed volume-displacement spirometers requiring manual calculation of results, to fully computerised flow sensing instruments. Computerisation and advances in sensor technology has meant greater instrument accuracy, with the software used for analysis becoming so complex that results are now based on many samples per second. Increased computer power means results are now available instantly, and in many

cases includes feedback on the quality of the test. These factors combine to result in measurements made today being more accurate than those made 40 years ago.

Appendix 8 shows how FEV_1 has increased over 40 years, using the predictive equations that have been compared in Study Two. Others however report no evidence of a cohort effect (secular trend) in data covering 30 years.[177]

Cohort and period effects in relation to LA research

In the first study, the mean LA using the Newbury equation was very similar to the mean chronological age of HNS in the MFS dataset. This fits with both the cohort and the period effects as explained above, as the data collection for the MFS and the PL samples occurred in the same year with the same instrument used for data collection.

The differences between the equation groups seen in the second study are also consistent with the cohort and period effects. Because the predictive equations selected for comparisons included an older set and a more recent one from each region, this analysis was able to show similar differences in the different countries/regions:

- for UK/Europe, the Quanjer equation's predicted FEV_1 (collected 1960-80) was lower than that predicted by Falaschetti (collected 1995-96);
- the same is seen in the USA equations, the Morris equation's predicted FEV_1 (collected pre-1971) was lower than that predicted by Hankinson (collected 1988-94);

- in Australia, the Gore equation's predicted FEV_1 (collected 1991-92) was lower than that predicted by the Newbury equation (collected 2007).

When the equations from the same era are examined (e.g. Gore, Hankinson, and Falaschetti), the predicted FEV_1 for males is very similar until after the age of 50 where the Hankinson and Falaschetti values decrease at a greater rate than the Gore values, this is probably due to the quadratic form of these two equations. The predicted values for females do not follow the same pattern as closely, with the Hankinson values falling less steeply than the Falaschetti or the Gore values. Again, this can be seen in the table in Appendix 8.

The cohort effect suggests that the results of these three studies might be explained at least in part by the increasing heights across generations, as increased height leads to higher lung volumes. The mean heights for each sample (Morris, Hankinson, Falaschetti, Gore, Newbury) are, however, remarkably similar as can be seen in Table 1 in the Study Two publication on page 64. (As the range only was provided for the summary equations of Quanjer et al, it is not possible to determine the mean height.) This provides a strong argument for these differences being due to period effects such as advances in technology, or changes in guidelines.

The three studies in this thesis use cross-sectional data, all of which had been collected at the same time (2006-08). Comparisons also involved predictive equations developed over a period of time that spans 40 years. It is extremely likely that both the cohort and the period effects will have influenced results.

Inconsistencies between comparisons

While the Newbury LA estimates closely matched the chronological age of HNS of the MFS dataset, this was not the case in the later comparisons using the community-based datasets. There are some possible explanations for this.

Sample differences of original equations

One possibility is related to the differences in the samples used to generate the original predictive equations, prior to the mathematical re-solving to produce the LA equations. The Morris sample[111] was discussed in Study One[156], and was thought to not be representative of a current day population. The Quanjer sample from the same era, was not a sample as such as these were summary equations from different published equations; information on the actual subjects is limited.[178] The samples whose data informs the predictive equations (Morris[111], Quanjer[178], Hankinson[46], Falaschetti[155], Gore[140], Newbury[139]) have been examined further particularly in relation to the age distribution and the equipment used, and details appear in Appendix 9.

Form of equation

The LA equations that were linear in form were found to be more reliable in estimating LA than were the equations that were quadratic in form. The Hankinson and the Falaschetti LA equations were not always able to determine a LA estimate for each case due to their complex quadratic form.

The greater range seen in LA estimates that was seen in these datasets using the ΔLA equation when compared with LA equations based on FEV_1 alone has been discussed

in detail in Chapter 5. This greater range makes this form of LA equation less reliable than those based on FEV_1 alone.

Lung Age in Smoking cessation

Counselling:

Current Australian guidelines for health professionals for supporting smoking cessation recommend counselling combined with pharmacotherapy for nicotine dependent smokers.[179] Nicotine is the addictive component found in cigarette smoke. When inhaled, absorption into the bloodstream occurs quickly and it is rapidly transported to the brain where it acts on the reward pathways which are normally associated with the feelings of pleasure.[179, 180] Some medications can increase success of smoking cessation attempts. All pharmacological interventions appear to have some risk and side effects, including the possibility of severe psychiatric and cardiovascular adverse events.[181-184]

Smoking cessation counselling can involve: brief motivational advice, referral to intensive treatment programs such as the Quit program, individual or group counselling and be face-to-face or by telephone. Counselling can be individually tailored and include relevant feedback such as spirometry results[185]; LA can be used to communicate these results. As LA is a drug-free intervention, it is free of drug product side effects.

Paradigms of smoking cessation counselling

The Transtheoretical model of change describes an individual's movement backwards and forwards through 5-6 stages of preparedness to quit at any one time (pre-

contemplation, contemplation, preparation, action, maintenance or relapse, termination).[186-188] The action stage is when a quit attempt is made. This model has influenced smoking cessation advice for approximately 30 years, with different smoking cessation advice offered depending on the stage to which a smoker belongs at the time, however there appears to be little evidence that stage-based interventions are successful in altering smoking behaviour.[189]

An alternative model has been suggested[190, 191] where tailored interventions increase motivational tension and contain triggers that prompt quit attempts –the 3 T's model (tension, trigger, treatment).[64,65,192] Triggers that inspire a quit attempt can increase the likelihood of success. Such triggers can include pregnancy, or an adverse health event related to smoking (e.g. heart attack). Communicating individualised biomarkers of the risk of future harm may also increase motivational tension. These can include lung function tests by spirometry with results expressed as lung age estimates.

Lung age, as an intervention used in conjunction with smoking cessation counselling, can fit into both paradigms. It can provide the trigger for smokers to quit in the 3T's model, or it can be used to assist smokers to move through different stages of change, ultimately to making a quit attempt. The desired outcome in both instances is for the smoker to successfully quit smoking.

Subjective age versus chronological age

Discrepancies are known to exist between chronological age (measured in years, and counted from a person's date of birth) and subjective age (the age a person would like to be, or be thought to be – again measured in years, but not linked to the birth date).

Research indicates that young people prefer to be thought of as being a little older/more 'grown-up' than they actually are. This could possibly be part of the explanation as to why young people take up smoking – to appear to be older than they are. Older adults (middle-aged and older) however often have a subjective age that is lower than their chronological age, more so in women than in men.[193] A younger subjective age was found to be related to a fear of ageing linked in particular to both physical and sexual decline.[193]

The cellular damage caused by the accumulation of toxins in cigarette smoke that is seen in the lungs of smokers can also be seen in premature ageing of the skin.[95, 194] Biological ageing beyond chronological age occurs in a dose-related manner where greater facial wrinkling is seen in those who have smoked for longer lengths of time, and with greater numbers of cigarettes smoked.[96, 97, 195]

There are therefore similarities in the concepts of chronological age/subjective age and the fear of ageing, and chronological age/biological age where smokers' lungs could be described as 'prematurely aged' as a result of damage caused by repeated exposure to cigarette smoke. This supports the concept of communicating lung age to smokers, and may be the psychological mechanism that could provide the trigger for smokers to commence the quit smoking process.

In relation to other research

Japanese lung age

As well as the Japanese LA equation derived by re-solving of the FEV_1 equation[132] which is of similar form to the Morris LA equation, novel Japanese LA equations

produced by regression of multiple spirometric parameters have been developed recently.[151] Spirometric parameters of 8000 healthy never smokers (25-87 years), who attended a general health screening examination in south west Japan in 2009-10, were used to inform the new Spirometry Derived LA equations (SDL-age). Predictors in these equations, determined by multiple linear regression, for males were Height, FEV_1, FEV_1/FVC, and Forced Expiratory Flow at 50% of the forced exhalation (FEF_{50}); and for females were Height, FEV_1, FEV_1/FVC, Peak Expiratory Flow (PEF) and FEF_{50}. The equations were validated using a group of 6400 subjects who attended the same clinic during 2008-09, and were then tested on a group of 446 never-smoking subjects, screened between April 2008 and March 2009 whose FEV_1/FVC ratio was below the LLN. Results indicate that the SDL-age equations detected differences in worsening stages of airflow limitation based on FEV_1%predicted. This interesting line of research deserves further investigation in other ethnicities.

Hansen ΔLA

Originally, it was thought that it was the ΔLA equation was more likely to suit the US population better than the Australian population, however the FEV_1/FVC ratio has been shown to be virtually independent of ethnicity.[58] The Hansen equation was also developed to be suitable for both males and females, despite females having greater FEV_1/FVC than males. It may be this factor rather than the effect of ethnicity that has contributed to the differences in the third study.

The graph used by Hansen to illustrate that the ΔLA equation matched HNS in the NHANES III sample better than did the Morris or the Newbury equations[146] actually mirrors the period/cohort effects as discussed in this thesis: the oldest equation

(Morris) predicts lowest, the Newbury equation predicts highest, and the intermediate equation (Hansen) predicts between the two (See Appendix 3 for this letter to the editor).

Editorial comment to Papers One and Two

Editorials by respected authorities on spirometry for both the first and second publications are provided in Appendix 2[71] and 7.[158] Both editorials were critical of the concept of LA, but at the same time brought legitimate issues into the debate about LA. Both declare it does not take account of the scatter of results around the mean. Indeed, this is inherently linked to the wide range of normal in all spirometry parameters as predictive equations cannot take into account all the influences on lung function such as body build, fitness levels etc.[145] A Japanese research team has recently suggested a method of taking the range of normal (based on 95% confidence intervals) into account when estimating lung age.[135] They suggest that when FEV_1 falls between the upper level of normal (ULN) and the LLN then LA is consistent with the chronological age; if FEV_1 is below the LLN then LA is considered to be older than the age at the LLN for that value. This warrants further investigation in the Australian population.

While both editorials also suggest that the tracking of lung function in individuals each decade would enable detection of accelerated decline, this practice is probably beyond the ability of most health systems/governments to provide due to logistics (availability of resources such as well-staffed respiratory laboratories) and the financial cost of providing such a service, and in reality is not likely to occur.

Other issues raised include it being plausible to associate smoking with harm done to the lungs only when FEV_1 and FEV_1/FVC fall below the LLN in people with a history of 20 or more years of smoking.[145] With the damage to the lungs from cigarette smoking being cumulative it would be better to detect any increased rate of decline at an earlier stage. This could possibly be done by case-finding in primary care rather than by proper screening processes.[196, 197] Both editorials maintain that predictive equations need to fit the population by having a representative and reliable reference population and Cooper goes further to say that a single LA equation for the global population is not rational.[145, 158] This echoes the message in the second paper of this thesis (Chapter 4).

Collated equations

Global Lung Initiative (GLI) – a new type of predictive equation

A very recent development in the international debate on predictive equations has been the combining of existing data from around the world which has resulted in the release of all-age predictive equations meant to be suitable globally.[58, 198] This project used complex statistical methods to determine normal values for several spirometry variables for people of Caucasian ethnicity in the first instance, who are aged from 3-95 years of age. The development of essentially one 'equation' to cover this age range addresses the main problem when moving from adolescent to adult equations, when there were often discrepancies at the intersecting ages.

There are some concerns though with this approach. It appears that the largest datasets came from only a few countries – the USA (NHANES III, Multi-Ethnic Study of

Atherosclerosis), Switzerland or England (HSE). It also would appear that the collated data are already 20-40 years old.[177, 199] Given that the ATS/ERS guidelines suggest reference values be updated every 10 years[42], the use of these equations for adults may be no better than using the NHANES III equations, for example, that are now over 20 years old. The age distribution in the collated sample is also of concern and is strongly skewed to the right, as there are many more subjects aged 8-10 years old than any other age and this may impact on the equations.

Of the data relating to Caucasian ethnicity, the Australian data appears to account for approximately 1.2% of the total sample (n=982 out of 80140, before exclusion due to missing data or outliers).[58] Such a small sample would have minimal (if any) impact on final results. A further concern is that by making these equations more generalisable for global use they are likely to be less specific to the Australian population. The current ATS/ERS guidelines still call on equations to be selected on the basis of being applicable to the community being studied.[37, 42] As Australia is geographically isolated, and not as densely populated as USA or Europe (with associated lower levels of airborne pollution) the best way to get relevant equations may be to generate them locally.

The suitability of these international equations for healthy Caucasian subjects from Australia and New Zealand, is currently being researched with initial results suggesting a reasonable fit despite detecting statistically significant differences.[199] The all-age equations are still under investigation in Australia and New Zealand.[200, 201]

These issues clearly need further investigation. Quanjer et al suggest that there was no evidence found of 'secular trends' in the data collected from Caucasian subjects over the last 30 years.[177] This however is contrary to the findings in the three studies investigating lung age that have been reported in this thesis.

Limitations

Of the three independent datasets that were used for these comparisons unfortunately none are ideal. It is likely that some of these differences between these samples have contributed to the differences in the results seen between datasets.

- The MFS is a workplace dataset where exposures to smoke and fumes are possible in normal day to day workplace situations. Protective respirators are available for use, but may not have been used regularly in the past. However, the effects of these exposures might be counterbalanced by the fact that many of the subjects are extremely fit and have been described as occupational athletes.

- The NWAHS is randomly selected sample of an urban area which covers the north and west regions of Adelaide. This area contains approximately half of Adelaide's population, and one quarter of the state's population[162] and is likely to be affected by industrial and vehicular pollution (due to the location of industrial areas and major roads). This region of Adelaide has areas of significant industry including but not limited to large cement works, paint manufacturing, ship building and ship maintenance.

- Even though WISH is a rural dataset (Whyalla has a remoteness classification of 3: outer regional Australia[202]), Whyalla is the third largest city in South Australia (SA). This industrial city has revolved around mining, processing and export of iron ore, steel manufacturing (since 1930), and ship building (late 1930's to 1978). There has been concern in recent years over the respiratory health of Whyalla's residents due in part to concerns over dust pollution from the movement of iron ore through the city[203], and Whyalla has been found to have statistically significant higher rates of COPD and lung cancer than in Port Lincoln and other comparison towns.[204]

A further limitation is that the Newbury LA equations, while developed using the most recently collected data, have come from pilot study data. Despite the sample being evenly age- and sex-stratified, and results being similar to the previously developed Gore equations[140], it still remains that this was a pilot study sample of limited numbers.

The population-based samples which were used for these comparisons, NWAHS and WISH, had higher prevalence of obese subjects in the HNS and CS subgroups than occurred in the general Australian population at the time, the MFS sample and the Port Lincoln sample whose results informed the newest LA equation.[156] This may have influenced the results in the studies using these datasets.

Recommendations

There are several recommendations and ideas for further research that come from this body of work.

1. LA equations should be developed specifically for different regions/ethnicities using a population-relevant FEV_1 predictive equation derived from recently collected data. Using old LA equations based on old data for contemporary populations will effectively dilute the message of the extent that smoking harms lung function.

2. As LA equations of quadratic form have been shown to be unable to estimate LA for some subjects, further investigation into quadratic LA equations is needed.

3. Further investigation needs to occur of taking into account the upper and lower limits of normal as described by Yamaguchi et al.[135] Even if LA is not greater than chronological age it is important to convey the danger of continued smoking and not to convey a possible 'protective effect' of smoking.

4. Newly-determined predictive equations for spirometry that are relevant across Australia are needed. Ideally, such a project should be multi-centred, involve a random urban and rural sample of healthy never smokers and cover the range of different ethnicities that now make up the Australian population. There is a real need to derive up to date predictive equations for indigenous Australians. While this ideal project would not be inexpensive to do, the benefits would be significant.

5. Establish whether lung age using Australian LA equations is useful in quit smoking counselling, by firstly running a pilot study to determine effect and to assist with sample size calculation, followed by a RCT.
    - Hypothesis: spirometry results communicated as lung age associated with smoking cessation counselling will lead to improved quit rates compared with the control.
    - Setting: multi-centred, primary care.
    - Control group: spirometry with smoking cessation brochure
    - Intervention group: 10 minute counselling session, spirometry communicated as LA, smoking cessation brochure
    - Follow-up after 12 months; smoking status verified by exhaled carbon monoxide, salivary cotinine.
6. Disadvantaged groups: Smoking prevalence is higher in people of lower socio-economic status.[205] Certain subgroups of the population such as Indigenous people, those with poor mental health, and also prisoners are also more likely to be current smokers.[205] As in the general population, smoking cessation would benefit these people with improvements in health outcomes as well as financial benefits.[206] For those with mental illness, smoking cessation may lead to lower doses of medication being needed.[206] As lung age is an easily-understood method of explaining spirometry results, it may prove successful as an intervention in these groups and future research projects could investigate this.

Chapter 7: Summary

This body of research has shown that the differences seen between predictive equations for spirometric parameters are consistent with the period and cohort effects. These are most evident between the oldest and the most recent equations regardless of country of origin but are also seen between older and more recent equations generated in the same country/region (UK/Europe; USA; Australia) 15-30 years apart.

Results of the comparison of LA equations and the ΔLA equation based on the FEV_1/FVC ratio showed that there was no advantage to using the ΔLA equation.

Lung age generated by the Morris equation is available in several types of spirometer used in primary care, however this can estimate values for lung age that are 20 years lower than that of the newer LA equations. This may lessen the impact of the message in smoking cessation counselling, and may have contributed to the overall inconclusive results seen in studies using LA as an intervention.

Sixteen percent of the adult Australian population are daily smokers.[207] Although this continues to decrease due to strong public health messages over many years there is still scope for further options in smoking cessation counselling that may help those who have been reluctant to quit or have ignored population-wide messages. LA is one such option that is easily implemented in primary care, and may prompt an attempt to quit smoking, but up-to-date equations based on FEV_1 should be used. A RCT with LA as the intervention is proposed.

Chapter 8: Appendices

Appendix 1: A pilot study to evaluate Australian predictive equations for the Impulse Oscillometry System

Newbury, W, Crockett, A, Newbury, J. 2008. Respirology, vol 13, page 1070-75.

Background paper only (previously submitted for Master of Public Health).

Newbury, W., Crockett, A. & Newbury, J. (2008) A pilot study to evaluate Australian predictive equations for the impulse oscillometry system.
Respirology, v. 13(7), pp. 1070-1075

Appendix 2: Should we use 'lung age?'

Editorial: Primary Care Respiratory Journal, Volume 19(3): 197-99

Quanjer, P.H. & Enright, P.L. (2010) Should we use lung age?.
Primary Care Respiratory Journal, v. 19(3), pp. 197-199

Appendix 3: Measuring the lung age of smokers.

Primary Care Respiratory Journal. 2010, 19(3): 286-87

Letter to the editor, with Authors' Reply

Hansen, J. (2010) Measuring the lung age of smokers.
Primary Care Respiratory Journal, v. 19(3), pp. 286-287

Appendix 4: Lung age is a useful concept and calculation

Letter to the Editor, Primary Care Respiratory Journal, 2010, 19(4): 400-401

Hansen, J. (2010) Lung age is a useful concept and calculation.
Primary Care Respiratory Journal, v. 19(4), pp. 400-401

Appendix 5: Paradoxes of spirometry results, and smoking cessation

Letter to the Editor, Primary Care Respiratory Journal, 2010, 19(3):295-96

A part of the debate regarding Lung Age, following publication of the article: “Exploring the need to update lung age equations”.

Parkes, G. & Greenhalgh, T. (2010) Paradoxes of spirometry results, and smoking cessation. *Primary Care Respiratory Journal, v. 19(3), pp. 295-296*

Appendix 6: Lung Age Estimator, Primary Care Respiratory Toolkit

URL: http://lungfoundation.com.au/professional-resources/1692-2/general-practice/primary-care-respiratory-toolkit/

Date accessed: 18th April 2013

The Primary Care Respiratory Toolkit is found on the Australian Lung Foundation website and includes a Lung Age Estimator that is based on the Newbury LA equations.[152] A qualitative evaluation of the resource performed by the Discipline of General Practice at the University of Adelaide reports that:

> *"The generated chart was strongly praised as a useful tool to enhance the patient consultation, encouraging better patient understanding, demonstrating changes over time and potentially motivating improved patient behaviour."* [208]

NOTE:
This appendix is included on pages 130-132 of the print copy of the thesis held in the University of Adelaide Library.

Appendix 7: Dawning of a new lung age?

Editorial, Primary Care Respiratory Journal; 2012, 21(1):15-16.

Cooper, B. (2012) Dawning of a new lung age?.
Primary Care respiratory Journal, v. 21(1), pp. 15-16

Appendix 8: Changes in Predicted FEV_1 across 40 years according to different predictive equations

Tables of Predicted FEV_1 showing increases for both males and females across a 40 year time frame, using the predictive equations used for comparisons in Paper Two.

Predicted FEV_1 for females (Height 168cm), across age range 25-75						
age	Morris	Quanjer	Falaschetti	Hankinson	Gore	Newbury
25	3.27	3.41	3.49	3.47	3.57	3.87
30	3.15	3.29	3.42	3.39	3.44	3.71
35	3.02	3.16	3.33	3.31	3.30	3.55
40	2.90	3.04	3.22	3.22	3.17	3.40
45	2.77	2.91	3.08	3.12	3.04	3.24
50	2.65	2.79	2.93	3.01	2.91	3.08
55	2.52	2.66	2.77	2.89	2.77	2.93
60	2.40	2.54	2.59	2.76	2.64	2.77
65	2.27	2.41	2.41	2.62	2.51	2.62
70	2.15	2.29	2.22	2.47	2.38	2.46
75	2.02	2.16	2.04	2.32	2.25	2.30

Table 5: Differences in predicted FEV_1 (females) in equations spanning 40 years

Predicted FEV_1 for males (Height 178cm), across age range 25-75						
age	Morris	Quanjer	Falaschetti	Hankinson	Gore	Newbury
25	4.33	4.44	4.60	4.59	4.67	4.93
30	4.17	4.29	4.50	4.47	4.52	4.79
35	4.01	4.15	4.38	4.35	4.38	4.64
40	3.85	4.00	4.24	4.22	4.24	4.49
45	3.69	3.86	4.09	4.09	4.10	4.34
50	3.53	3.71	3.93	3.94	3.95	4.19
55	3.37	3.57	3.73	3.78	3.81	4.04
60	3.21	3.42	3.53	3.62	3.67	3.90
65	3.05	3.28	3.33	3.45	3.53	3.75
70	2.89	3.13	3.12	3.27	3.39	3.60
75	2.73	2.99	2.91	3.08	3.24	3.45

Table 6: Differences in predicted FEV_1 (males) in equations spanning 40 years

Appendix 9: Age distributions of samples.

The age distributions of the samples used to generate the predictive equations used in these comparisons have also been explored.

Morris et al, 1971: Spirometric Standards for Healthy Nonsmoking Adults.[111]

The method of recruitment for this study was not described, and almost 80% of the sample were members of two church groups. The setting was a rural area, of low altitude, to the south of Portland, Oregon, USA. The sample would not be considered to be representative of a 'normal' population by today's standards as discussed in Paper One[156], although participants had been screened by questionnaire prior to testing for smoking history, respiratory symptoms or diagnoses, and workplace pollution. The age distribution of the sample used by Morris, Koski and Johnson for their 1971 predictive equations[111] was heavily skewed to the right with a majority of younger subjects. The equipment used was a water-sealed Stead-Wells spirometer.

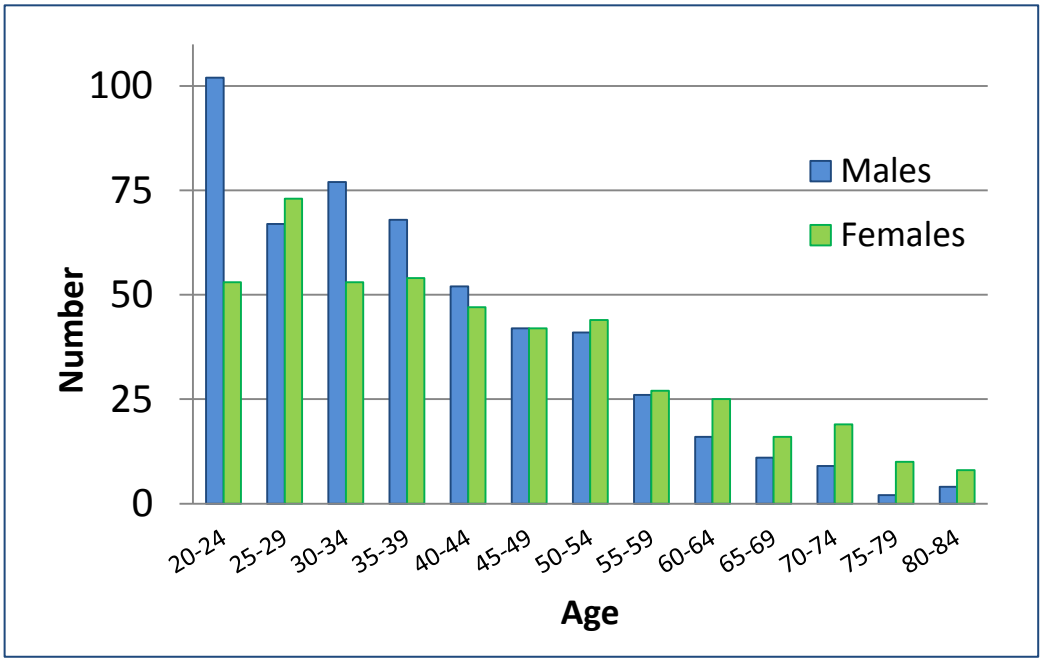

Figure 15: Age distribution of the Morris sample
The Morris sample is strongly skewed to the right, more so in males than in females.

Quanjer et al, (ECSC) 1993: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests. European Community for Steel and Coal.[59]

The age distributions of the samples that contributed to the summary equations were not provided although the age range for the summary equations is given as 18-70 years of age.

NHANES III

The third National Health and Nutrition Examination Survey (NHANES III) was conducted between 1988 and 1994.[209] The sample came from households across 81 counties across the USA, and was structured to comprise greater proportions of children (aged 2 months to 5 years) and older adults (aged over 60 years). Also, African-American and Mexican-American subjects each comprised 30% of the sample despite comprising only 12 and 5% of the population respectively.[209] The equipment used was a modified Ohio Medical dry rolling seal spirometer. All participants were remunerated.

Hankinson et al, 1999: Spirometric Reference Values from a Sample of the General U.S. Population.[46]

Of the 20627 subjects who performed spirometry, only 7429 asymptomatic lifelong non-smoking subjects were used to develop the reference values published in 1999. Of the Caucasians aged over 21 years, 476 were males, and 926 were females. The age distributions in this NHANES III sample of adult Caucasian males are also skewed to the

right, (less so in adult females). These are shown in Figure 16. All males, particularly older males, are under-represented.

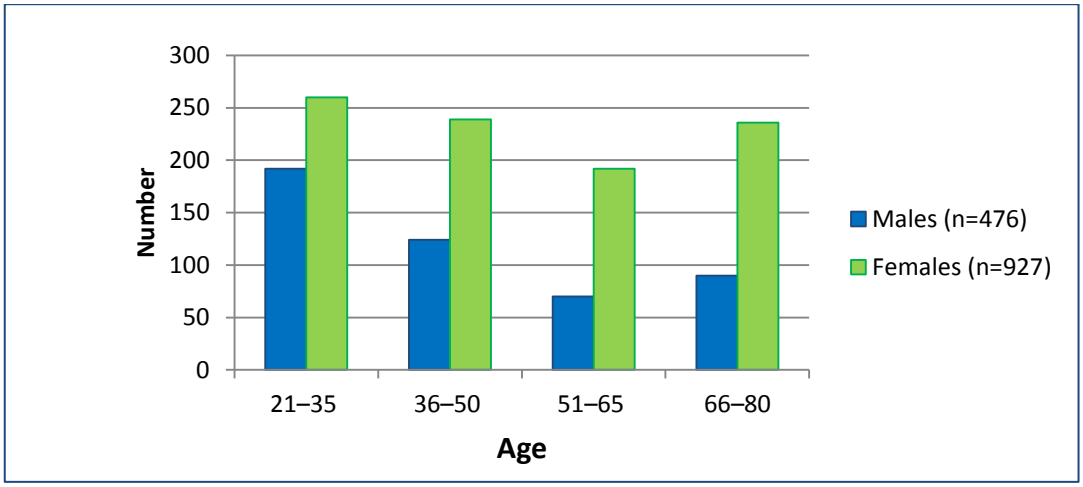

Figure 16: Age distribution of the Hankinson sample (Caucasians), from NHANES III

Hansen et al, 2010: Calculating Gambling Odds and Lung Ages for Smokers.[159] Hansen's ΔLA equation is based on his earlier work using the NHANES III dataset that had defined a single equation for $\%FEV_1/FVC$ using never-smoking males and females of Caucasian, African-American and Mexican-American ethnicity (n=5907).[160] The age-distribution of the NHANES III sample defined by Hansen[159] is also strongly skewed to the right in all but female Caucasian Americans. In this sample, males (particularly older males) are again under-represented; as are older females.

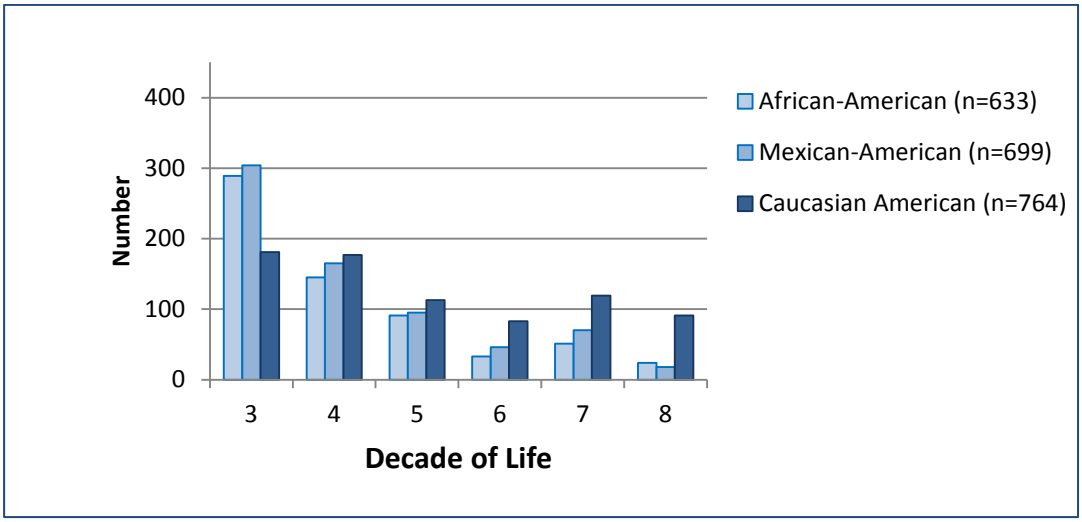

Figure 17: Age distribution of Hansen's Male sample; NHANES III

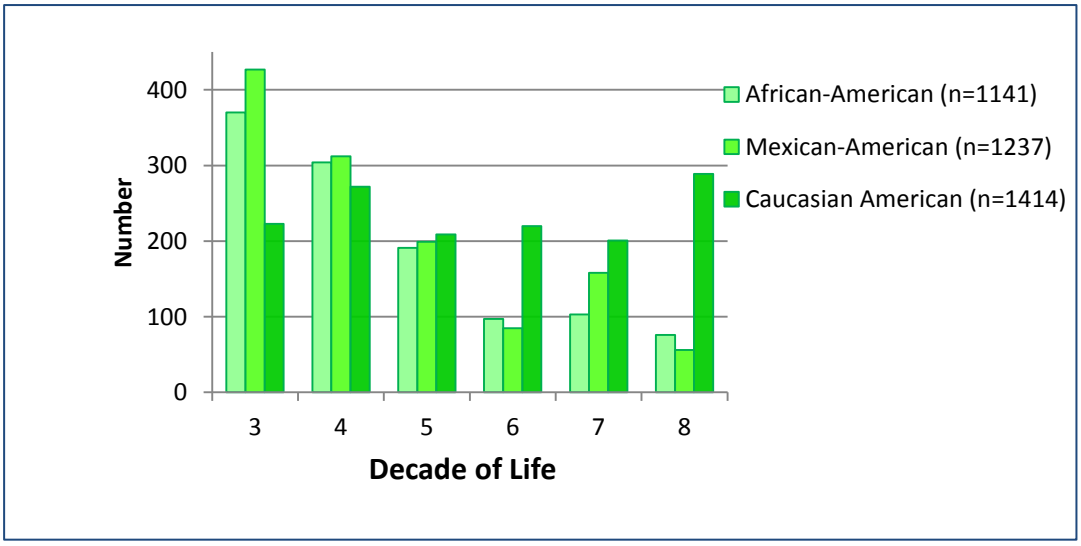

Figure 18: Age distribution of Hansen's female sample; NHANES III

Falaschetti et al, 2004: Prediction equations for normal and low lung function from the Health Survey for England.[155]

Data were collected 1995-96 on a portable Vitalograph Escort spirometer with a Fleisch pneumotachograph. The sample was a stratified random sample structured to

be sociodemographically representative of the English population. The age distribution of this healthy non-smoking sample was also skewed to the right. The equation for adult males includes those aged ≥25, and is strongly skewed to the right. The equation for adult females includes all ≥16 years.

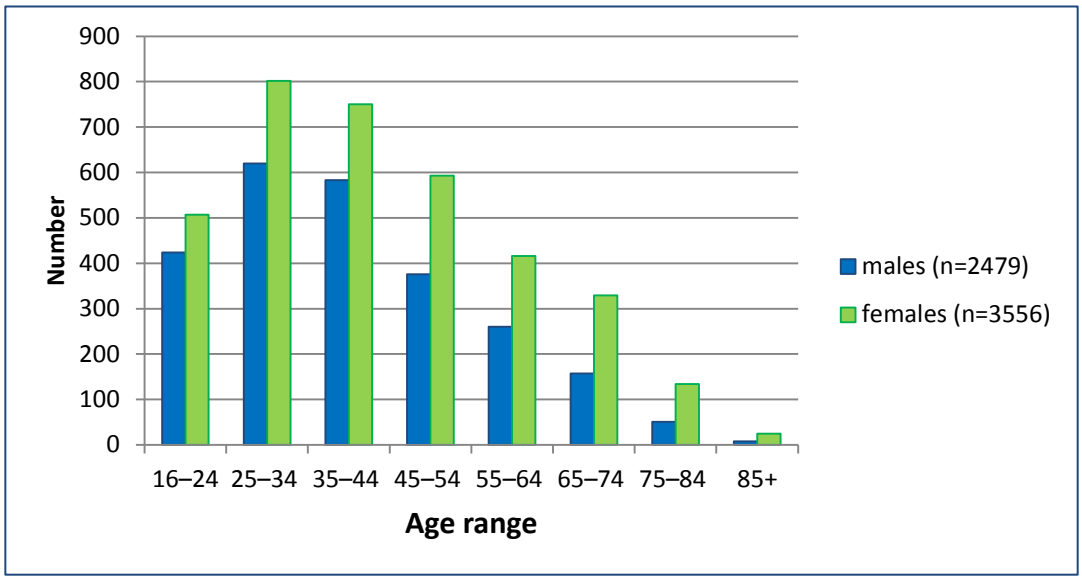

Figure 19: Age distribution of the Falaschetti sample

Gore et al: 1995. Spirometric standards for healthy adult lifetime nonsmokers in Australia.[140]

This was a sub-study of the 1990 Pilot Survey of the Fitness of Australians, whose 2,298 subjects had been randomly selected from the adult population of metropolitan Adelaide, South Australia. A subgroup of 1,302 subjects underwent spirometry testing with a Cybermedic pneumotachograph spirometer. Selection of only the asymptomatic lifetime nonsmokers gave a sample size of 414.

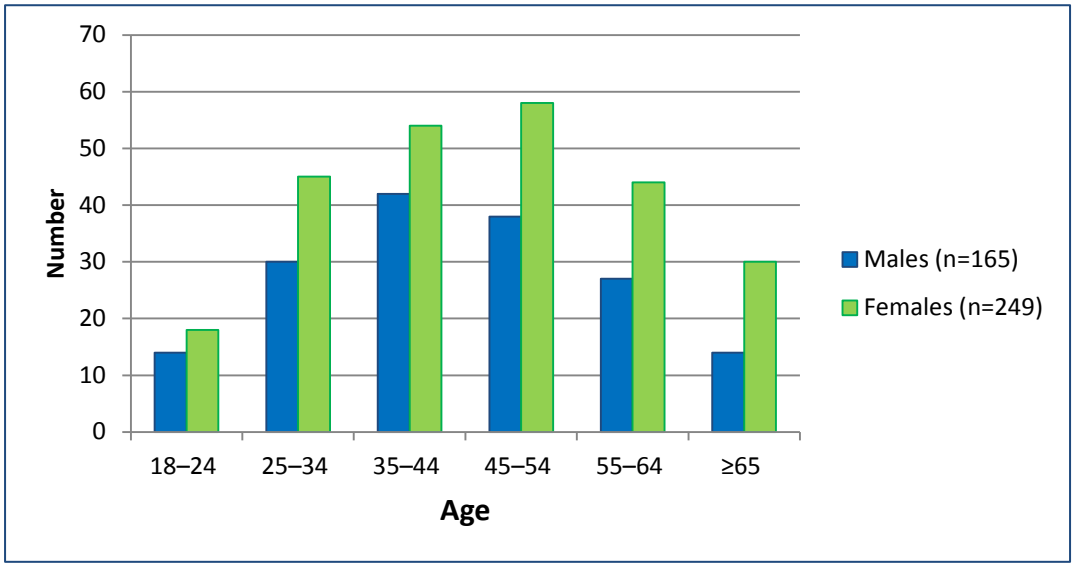

Figure 20: Age distribution of the Gore et al sample
Males and females are normally distributed; males were proportionally under-represented.

Newbury et al, 2008: A pilot study to evaluate Australian predictive equations for the impulse oscillometry system.[139]

This pilot study sample was designed to be evenly age- and sex stratified. Participants were volunteers, from in and around Port Lincoln on the lower Eyre Peninsula, South Australia. Smoking status was determined, and if participants had smoked >10 cigarettes per day for more than 5 years, they were excluded. This study used a Masterscreen IOS, with a Lily-type heated pneumotachograph.

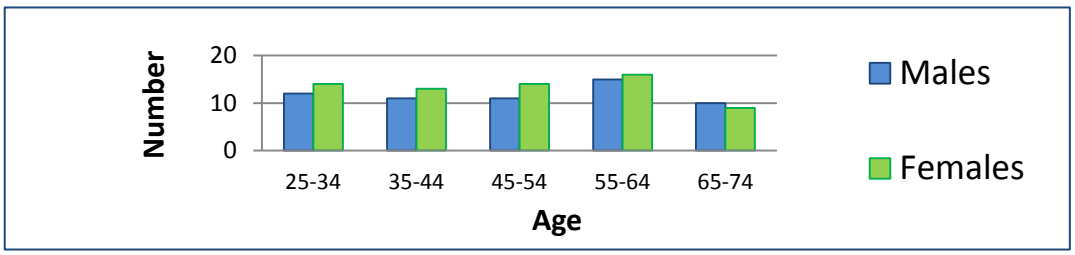

Figure 21: Age distribution of the Newbury sample
Approximately equal numbers of males and females, with similar numbers in each decade.

Chapter 9: Bibliography

1. Gibson G. Spirometry: then and now. Breathe. 2005;1(3):207.
2. Spriggs E. The history of spirometry. Br J Dis Chest. 1978;72:165-80.
3. Kentish E. An account of a pulmometer, by which may be known the power and capacity of the lungs to receive the atmospheric air. An Account of Baths, and of a Madeira-House, at Bristol. London: Longman, Hurst, Rees, Orme, & Browne; 1814. p. 81-117.
4. Meiklejohn A, Thackrah C. The life, work and times of Charles Turner Thackrah, surgeon and apothecary of Leeds (1795-1833) *with* The effects of arts, trades, and professions, and of civic states and habits of living, on health and logevity: with suggestions for the removal of many of the agents which produce disease, and shorten the duration of life. 1957 ed. London: E & S Livingstone Ltd; 1857. Available from:
5. Hutchinson J. Society of Arts. Pneumatic apparatus for valuing the respiratory powers. Lancet. 1844;43(1085):390-1. DOI: 10.1016/s0140-6736(02)71692-9.
6. Hutchinson J. Lecture on vital statistics, embracing an account of a new instrument for detecting the presence of disease in the system. Lancet. 1844;43(1091):567-70. DOI: 10.1016/s0140-6736(02)73338-2.
7. Hutchinson J. Lecture on vital statistics, embracing an account of a new instrument for detecting the presence of disease in the system. Concluded from p570. Lancet. 1844;43(1092):594-7. DOI: 10.1016/s0140-6736(02)34335-6.
8. Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Medico-Chirurgical Transactions. 1846;29:137-252.
9. Petty T. John Hutchinson's mysterious machine revisited. Chest. 2002;121:219S-23S. DOI: 10.1378/chest.121.5_suppl.219S.
10. Braun L. Spirometry, measurement, and race in the nineteenth century. J Hist Med Allied Sci. 2005;60(2):135-69. DOI: 10.1093/jhmas/jri021.
11. Warren P. The history of diagnostic technology for diseases of the lungs. CMAJ. 1999;161:1161-3.
12. Warren P, Warren F. Window on the breast: 19th century English developments in pulmonary diagnosis. Lancet. 1997;349:798-801. DOI: 10.1016/S0140-6736(96)10510-9.

13. Kellogg RH. Laws of Physics Pertaining to Gas Exchange. Comprehensive Physiology: John Wiley & Sons, Inc.; 2011. p. 13-31.
14. Bishop P. A bibliography of John Hutchinson. Med Hist. 1977;21:384-96.
15. Speizer F. John Hutchinson, 1811-1861. The first respiratory disease epidemiologist. Epidemiology. 2011;22:e1-e9. DOI: 10.1097/EDE.0b013e318209dedc.
16. Beigel H. On spirometry. Lancet. 1864;83(2111):180-81. DOI: 10.1016/S0140-6736(02)59317-X.
17. Beigel H. On spirometry. Lancet. 1864;83(2109):119-20. DOI: 10.1016/S0140-6736(02)59265-5.
18. Salter H. Lectures on dyspnoea. Lecture III (Concluded). Lancet. 1865 28 October 1865;86(2200):475-78. DOI: 10.1016/S0140-6736(02)58417-8.
19. Balfour T. Contribution to the study of spirometry. Medico-Chirurgical Transactions. 1860;43:263-69.
20. Bain W. On a portable spirometer. Br Med J. 1870;1(475):129. DOI: 10.1136/bmj.1.475.129.
21. Calverley P, Wedzicha J. Chronic obstructive pulmonary disease past, present and future. Thorax. 2007;62:1026-27. DOI: 10.1136/thx.2007.092635.
22. Yernault J. The birth and development of the forced expiratory manoeuvre: a tribute to Robert Tiffeneau (1910-1961). Eur Respir J. 1997;10:2704-10. DOI: 10.1183/09031936.97.10122704.
23. Gaensler E. Analysis of the ventilatory defect by timed capacity measurements. Am Rev Tuberc. 1951;64:256-78.
24. Ayers W, Abraham S, Ward S, Weihrer A, Rosner S, Caceres C. Description of a computer program for analysis of the forced expiratory spirogram. II Validation. Comput Biomed Res. 1968;2:220-28.
25. Banks D, Wang M, McCabe L, Billie M, Hankinson J. Improvement in lung function measurements using a flow spirometer that emphasizes computer assessment of test quality. J Occup Environ Med. 1996;38(3):279-83.
26. Hoffer E, Kanarek D, Kazemi H, Barnett G. Computer interpretation of ventilatory studies. Comput Biomed Res. 1973;6:347-54.
27. Krumpe P, Weigt G, Martinez N, Marcum R, Cummiskey J. Computerized rapid analysis of pulmonary function test: use of a least mean squares correlation for interpretation of data. Comput Biol Med. 1982;12(4):295-307.

28. Morris J. Spirometry in the evaluation of pulmonary function. West J Med. 1976;125:110-18.
29. Enright P, Skloot G, Cox-Ganser J, Udasin I, Herbert R. Quality of spirometry performed by 13,599 participants in the World Trade Center worker and volunteer medical screening program. Respir Care. 2010;55(3):303-09.
30. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Revised 2011): Global Initiative for Chronic Obstructive Lung Disease, Inc; 2011.
31. Van Schayck CP, D'Urzo A, Invernizzi G, Roman M, Stallberg B, Urbina C. Early detection of chronic obstructive pulmonary disease (COPD): the role of spirometry as a diagnostic tool in primary care. Prim Care Respir J. 2003;12:90-3.
32. Standardization of definitions and symbols in respiratory physiology. Fed Proc. 1950;9(3):602-5.
33. Gandevia B, Hugh-Jones P. Terminology for measurements of ventilatory capacity. A report to the Thoracic Society. Thorax. 1957;12:290-93.
34. American College of Chest Physicians. Clinical Spirometry - Recommendations of the Section on Pulmonary Function Testing Committee on Pulmonary Physiology. Chest. 1963;43:214-19. DOI: 10.1378/chest.43.2.214.
35. American Thoracic Society. ATS Statement - Snowbird workshop on standardization of spirometry. Am Rev Respir Dis. 1979;119(5):831-8.
36. American Thoracic Society. Standardization of spirometry - 1987 update. Am Rev Respir Dis. 1987;136(5):1285-98.
37. American Thoracic Society. Lung Function Testing: Selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991;144:1202-18.
38. American Thoracic Society. Standardization of spirometry - 1994 update. Am J Respir Crit Care Med. 1995;152(3):1107-36.
39. Guidelines for the measurement of respiratory function. Recommendations of the British Thoracic Society and the Association of Respiratory Technicians and Physiologists. Respir Med. 1994;88:165-94.
40. Miller M, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Resp J. 2005;26:153-61. DOI: 10.1183/09031936.05.00034505.

41. Miller M, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Resp J. 2005;26(2):319-38. DOI: 10.1183/09031936.05.00034805.
42. Pellegrino R, Viegi G, Brusasco V, Crapo R, Burgos F, Casaburi R, et al. Interpretive strategies for lung function tests. Eur Resp J. 2005;26:948-68. DOI: 10.1183/09031936.05.00035205.
43. Levy M, Quanjer P, Booker R, Cooper B, Holmes S, Small I. Diagnostic spirometry in primary care. Proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations. Prim Care Respir J. 2009;18(3):130-47. DOI: 10.4104/pcrj.2009.00054.
44. Crapo R. The role of reference values in interpreting lung function tests. Eur Respir J. 2004;24:341-42. DOI: 10.1183/09031936.04.00063804.
45. Arnett J. Vital capacity of the lungs: changes occurring in health and disease. J Clin Invest. 1935;14(5):543-49. DOI: 10.1172/JCI100704.
46. Hankinson J, Odencrantz J, Fedan K. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999;159(1):179-87.
47. Ip M. Lung function testing in health and disease: Issues pertaining to Asia-Pacific populations. Respirology. 2011;16:190-97. DOI: 10.1111/j.1440-1843.2010.01850.x.
48. Becklake M. Concepts of normality applied to the measurement of lung function. Am J Med. 1986;80:1158-64.
49. Kerstjens H, Rijcken B, Schouten J, Postma D. Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax. 1997;52:820-27. DOI: 10.1136/thx.52.9.820.
50. Postma D, Brusselle G, Bush A, Holloway J. I have taken my umbrella, so of course it does not rain. Thorax. 2012;67:88-9. DOI: 10.1136/thoraxjnl-2011-200758.
51. Weiss S. Lung function and airway disease. Nat Genet. 2010;42(1):14-6. DOI: 10.1038/ng0110-14.
52. Van Sickle D, Magzamen S, Mullahy J. Understanding socioeconomoic and racial differences in adult lung function. Am J Respir Crit Care Med. 2011;184:521-27. DOI: 10.1164/rccm.201012-2095OC.
53. Soto-Martinez M, Sly P. What goes around, comes around: childhood influences on later lung health?: Relationship between environmental exposures in children and adult lung disease: The case for outdoor exposures. Chron Respir Dis. 2010;7:173-86. DOI: 10.1177/1479972309345929.

54. McFadden E, Luben R, Wareham N, Bingham S, Khaw K. How far can we explain the social class differential in respiratory function? A cross-sectional population study of 21,991 men and women from EPIC-Norfolk. Eur J Epidemiol. 2009;24:193-201. DOI: 10.1007/s10654-009-9326-y.
55. Miller A, Thornton J. The interpretation of spirometric measurements in epidemiologic surveys. Environ Res. 1980;23(2):444-68. DOI: 10.1016/0013-9351(80)90078-X
56. Marks G. Are reference equations for spirometry an appropriate criterion for diagnosing disease and predicting prognosis? Thorax. 2012;67:85-7. DOI: 10.1136/thoraxjnl-2011-200584.
57. Quanjer P, Brazzale D, Boros P, Pretto J. Implications of adopting the Global Lungs 2012 all-age reference equations for spirometry. Eur Respir J. 2013;ePub ahead of print. DOI: 10.1183/09031936.00195512.
58. Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Culver B, et al. Multi-ethnic reference values for spirometry for the 3-95 year age range: the Global Lung Function 2012 equations. Eur Resp J. 2012;40 (6):1324-43. DOI: 10.1183/09031936.00080312.
59. Quanjer P, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Resp J. 1993;6:Suppl 16, 5-40.
60. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. Lancet. 2012;379:13141-51. DOI: 10.1016/S0140-6736(11)60968-9.
61. Miller M. Chronic obstructive pulmonary disease and '150 years of blowing'. Hosp Med. 1998;59:719-22.
62. Warren C. The nature and causes of chronic obstructive pulmonary disease: A historical perspective. Can Respir J. 2009;16:13-20.
63. Barnes P. New concepts in Chronic Obstructive Pulmonary Disease. Annu Rev Med. 2003;54:113-29. DOI: 10.1146/annurev.med.54.101601.152209.
64. American Thoracic Society, European Respiratory Society. Standards for the diagnosis and management of patients with COPD: American Thoracic Society and European Respiratory Society; 2004.
65. McKenzie D, Abramson M, Crockett A, Dabscheck E, Glasgow N, Jenkins S, McDonald C, et al. The COPDX Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease V2.30: The Australian Lung Foundation, and The Thoracic Society of Australia & New Zealand; 2011.

66. Townsend M. Conflicting definitions of airways obstruction: drawing the line between normal and abnormal. Chest. 2007;131:335-6. DOI: 10.1378/chest.06-2736.
67. Hoesein F, Zanen P, Lammers J-W. Lower limit of normal or FEV1/FVC <0.70 in diagnosing COPD: an evidence-based review. Respir Med. 2011;105:907-15. DOI: 10.1016/j.rmed.2011.01.008.
68. Mannino D, Buist A, Vollmer W. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? Thorax. 2007;62:237-41. DOI: 10.1136/thx.2006.068379.
69. King James I. A counter-blaste to tobacco. 1604 [7/10/2011]. Available from: http://extra.shu.ac.uk/emls/iemls/resour/mirrors/rbear/james1.html
70. Doll R. Uncovering the effects of smoking: historical perspective. Stat Methods Med Res. 1998;7:87-117. DOI: 10.1177/096228029800700202.
71. Witschi H. Profiles in toxicology. A short history of lung cancer. Toxicol Sci. 2001;64(1):4-6. DOI: 10.1093/toxsci/64.1.4.
72. White C. Research on smoking and lung cancer: a landmark in the history of chronic disease epidemiology. Yale J Biol Med. 1990;63(1):29-46.
73. Doll R, Hill AB. A study of the aetiology of carcinoma of the lung. Br Med J. 1952;2(4797):1271-86. DOI: 10.1136/bmj.2.4797.1271.
74. Wynder E, Graham E. Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. A study of six hundred and eighty-four proved cases. JAMA. 1985;253:2986-94.
75. Doll R, Hill AB. The mortality of doctors in relation to their smoking habits. Br Med J. 1954;1:1451. DOI: 10.1136/bmj.1.4877.1451.
76. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. Br Med J. 2004 June 2004;328:1519-28. DOI: 10.1136/bmj.38142.554479.AE.
77. Geiss O, Kotzias D. Tobacco, Cigarettes and Cigarette Smoke. An overview. Luxembourg: Directorate-General Joint Research Centre, Institute for Health and Consumer Protection, Centre JR; 2007. EUR 22783 EN.
78. Rabinoff M, Caskey N, Rissling A, Park C. Pharmacological and chemical effects of cigarette additives. American Journal of Public Health. 2007;97:1981-91.
79. Tonnesen P, Carrozzi L, Fagerstrom K, Gratziou C, Jimenez-Ruiz C, Nardini S, et al. Smoking cessation in patients with respiratory disease: a high priority, integral

component of therapy. Eur Resp J. [ERS taskforce]. 2007;29:390-417. DOI: 10.1183/09031936.00060806.

80. Musk A, de Klerk N. History of tobacco and health. Respirology. 2003;8:286-90.
81. Burns D. Cigarettes and cigarette smoking. Clin Chest Med. 1991;12:631-42.
82. Bernhard D, Moser C, Backovic A, Wick G. Cigarette smoke - an aging accelerator? Exp Gerontol. 2007;42:160-65. DOI: 10.1016/j.exger.2006.09.016.
83. Gudis D, Cohen N. Cilia dysfunction. Otolaryngol Clin North Am. 2010;43:461-72. DOI: 10.1016/j.otc.2010.02.007.
84. Hogg J. Lung structure and function in COPD. Int J Tubercul Lung Dis. 2008;12:467-79.
85. Soltani A, Sohal S, Reid D, Wood Baker R, Walters E. Airway remodeling in chronic obstructive pulmonary disease (COPD), a review. Annals of Respiratory Medicine. 2011.
86. Tamashiro E, Xiong G, Anselmo-Lima W, Kreindler J, Palmer J, Cohen N. Cigarette smoke expousre impairs respiratory epithelial ciliogenesis. Am J Rhinol Allergy. 2009;23:117-22. DOI: 10.2500/ajra.2009.23.3280.
87. Fahy J, Dickey B. Airway mucus function and dysfunction. N Engl J Med. 2010;363:2233-47. DOI: 10.1056/NEJMra0910061.
88. Barnes P, Shapiro S, Pauwels R. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003;22:672-88. DOI: 10.1183/09031936.03.00040703.
89. Hogg J. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet. 2004;364:709-21. DOI: 10.1016/S0140-6736(04)16900-6.
90. U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
91. Barnes P. Mediators of Chronic Obstructive Pulmonary Disease. Pharmacol Rev. 2004;56:515-48. DOI: 10.1124/pr.56.4.2.
92. Churg A, Zhou S, Wright J. Matrix metalloproteinases in COPD. Eur Respir J. 2012;39:197-209. DOI: 10.1183/09031936.00121611.
93. MacNee W. Accelerated lung aging: a novel pathogenic mechanism of chronic obstructive pulmonary disease (COPD). Biochem Soc Trans. 2009;37:819-23. DOI: 10.1042/BST0370819.

94. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1:1645-48. DOI: 10.1136/bmj.1.6077.1645.

95. Adams J, White M. Biological ageing. Eur J Public Health. 2004;14:331-34. DOI: 10.1093/eurpub/14.3.331.

96. Dupati A, Helfrich Y. Effect of cigarette smoking on skin aging. Expert Rev Dermatol. 2009;4:371-78.

97. Morita A. Tobacco smoke causes premature skin aging. J Dermatol Sci. 2007;48:169-75. DOI: 10.1016/j.jdermsci.2007.06.015.

98. Leung W-C, Harvey I. Is skin ageing in the elderly caused by sun exposure or smoking? Br J Dermatol. 2002;147:1187-91. DOI: 0.1046/j.1365-2133.2002.04991.x.

99. U.S. Department of Health and Human Services. The Health Consequences of Smoking: a Report of the Surgeon General. Atlanta, GA: U.S Department of Health and Human SErvices, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004.

100. Wald N, Hackshaw A. Cigarette smoking: an epidemiological overview. British Med Bull. 1996;52:3-11.

101. Anthonisen N, Connett J, Murray R. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002;166:675-79. DOI: 10.1164/rccm.2112096.

102. Kohansal R, Martinez-Camblor P, Agusti A, Buist A, Mannino D, Soriano J. The natural history of chronic airflow obstruction revisited. An analysis of the Framingham Offspring Cohort. Am J Respir Crit Care Med. 2009;180:3-10. DOI: 10.1164/rccm.200901-0047OC

103. Peat J, Woolcock A, Cullen K. Decline of lung function and development of chronic airflow limitation: a longitudinal study of non-smokers and smokers in Busselton, Western Australia. Thorax. 1990;45:32-7. DOI: 10.1136/thx.45.1.32.

104. Scanlon P, Connett J, Waller L, Altose M, Bailey W, Buist A, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med. 2000;161(381-90). DOI: 10.1164/ajrccm.161.2.9901044.

105. U.S. Department of Health and Human Services. The health benefits of smoking cessation: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1990. DHHS Publication No. (CDC) 90-8416.

106. Siafakas N, Vermeire P, Pride N, Paoletti P, Gibson J, Howard P, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J. 1995;8:1398-420. DOI: 10.1183/09031936.95.08081398.
107. Decramer M, Cooper C. Treatment of COPD: the sooner the better? Thorax. 2010;65:837-41. DOI: 10.1136/thx.2009.133355.
108. Morris J, Sturman W. Spirometry and Respiratory Questionnaire: value for screening and smoking cessation (abstract). Am Rev Respir Dis. 1974;109:702.
109. Morris J, Temple W. Spirometric "lung age" estimation for motivating smoking cessation. Prev Med. [Short report]. 1985;14(5):655-62.
110. Gibson J, Gallagher H, Johansen A, Webster I. Lung function in an Australian population: 2. Spirometric performance and cigarette-smoking habits. Med J Aust. 1979 Apr 21;1(8):354-58.
111. Morris J, Koski A, Johnson L. Spirometric standards for healthy nonsmoking adults. Am Rev Respir Dis. 1971;103(1):57-67.
112. Richmond R, Webster I. A smoking cessation programme for use in general practice. Med J Aust. 1985;142:190-94.
113. Risser N, Belcher D. Adding spirometry, carbon monoxide, and pulmonary symptom results to smoking cessation counseling: A randomized trial. J Gen Intern Med. 1990;5:16-22.
114. Humerfelt S, Eide G, Kvale G, Aaro L, Gulsvik A. Effectiveness of postal smoking cessation advice: a randomized controlled trial in young men with reduced FEV1 and asbestos exposure. Eur Respir J. 1998;11:284-90. DOI: 10.1183/09031936.98.11020284.
115. Crapo R, Morris A, Grardner R. Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis. 1981;123:659-64.
116. Sippel J, Osborne M, Bjornson W, Goldberg B, Buist A. Smoking cessation in primary care clinics. J Gen Intern Med. 1999;14:670-76. DOI: 10.1046/j.1525-1497.1999.11088.x.
117. Stratelis G, Molstad S, Jakobsson P, Zetterstrom O. The impact of repeated spirometry and smoking cessation advice on smokers with mild COPD. Scand J Prim Health Care. 2006. DOI: 10.1080/02813430600819751.
118. Kotz D, Wesseling G, Huibers MJH, van Schayck OCP. Efficacy of confronting smokers with airflow limitation for smoking cessation. Eur Resp J. 2009;33(4):754-62. DOI: 10.1183/09031936.00116308

119. Kaminsky D, Marcy T, Dorwaldt A, Pinckney R, DeSarno M, Solomon L, et al. Motivating smokers in the hospital pulmonary function laboratory to quit smoking by use of the lung age concept. Nicotine Tob Res. 2011;13 (11):1161-66. DOI: 10.1093/ntr/ntr096

120. Prokhorov A, Emmons K, Pallonen U, Tsoh J. Respiratory response to cigarette smoking among adolescent smokers: a pilot study. Prev Med. 1996;25:633-40. DOI: 10.1006/pmed.1996.0099.

121. Lipkus I, Prokhorov A. The effects of providing lung age and respiratory symptoms feedback on community college smokers' perceived smoking-related health risks, worries and desire to quit. Addict Behav. 2007;32(3):516-32. DOI: 10.1016/j.addbeh.2006.05.018.

122. Segnan N, Ponti A, Battista R, Senore C, Rosso S, Shapiro S, et al. A randomized trial of smoking cessation interventions in general practice in Italy. Cancer Causes Control. 1991;2(4):239-46.

123. Prokhorov A, Yost T, Mullin-Jones M, de Moor C, Fort K, Marani S, et al. "Look At Your Health": Outcomes associated with a computer-assisted smoking cessation counseling intervention for community college students. Addict Behav. 2008;33:757-71. DOI: 10.1016/j.addbeh.2007.12.005.

124. McClure J, Ludman E, Grothaus L, Pabiniak C, Richards J. Impact of spirometry feedback and brief motivational counseling on long-term smoking outcomes: A comparison of smokers with and without lung impairment. Patient Educ Couns. 2010;80:280-3. DOI: 10.1016/j.pec.2009.11.002.

125. Gold D, Wang X, Wypij D, Speizer F, Ware J, Dockery D. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med. 1996;335(13):931-7. DOI: 10.1056/NEJM199609263351304.

126. Van Miert E, Sardella A, Bernard A. Biomarkers of early respiratory effects in smoking adolescents. Eur Respir J. 2011;38:1287-93. DOI: 10.1183/09031936.00000911.

127. Gorecka D, Bednarek M, Nowinski A, Puscinska E, Goljan-Geremek A, Zielinski J. Diagnosis of airflow limitation combined with smoking cessation advice increases stop-smoking rate. Chest. 2003;123:1916-23. DOI: 10.1378/chest.123.6.1916.

128. Bednarek M, Gorecka D, Wielgomas J, Czajkowska-Malinowska M, Regula J, Mieszko-Filipczyk G, et al. Smokers with airway obstruction are more likely to quit smoking. Thorax. 2006;61(10):869-73. DOI: 10.1136/thx.2006.059071

129. Parkes G, Greenhalgh T, Griffin M, Dent R. Effect on smoking quit rate of telling patients their lung age: the Step2Quit randomised controlled trial. Br Med J. 2008;336(7644):598-600. DOI: 10.1136/bmj.39503.582396.25

130. Parkes G. Effect on smoking quit rate of telling patients their lung age. A randomised controlled trial [Dissertation]. London: University College London; 2009.

131. Parker D, Goldman R, Eaton C. A qualitative study of individuals at risk for or who have chronic obstructive pulmonary disease: What do they understand about their disease? Lung. 2008;186(5):313-16. DOI: 10.1007/s00408-008-9091-9.

132. Toda R, Hoshino T, Kawayama T, Imaoka H, Sakazaki Y, Tsuda T, et al. Validation of "Lung Age" measured by spirometry and handy electronic FEV_1/FEV_6 meter in pulmonary diseases. Intern Med. 2009;48(7):513-21. DOI: 10.2169/internalmedicine.48.1781.

133. Haruki T, Nakamura H, Taniguchi Y, Miwa K, Adachi Y, Fujioka S. 'Lung age' predicts post-operative complications and survival in lung cancer patients. Respirology. 2010;15:495-500. DOI: 10.1111/j.1440-1843.2010.01708.x.

134. Mitsumune T, Senoh E, Nishikawa H, Dachi M, Kajii E. The effect of obesity and smoking status on lung age in Japanese men. Respirology. 2009;14(5):757-60. DOI: 10.1111/j.1440-1843.2009.01541.x.

135. Yamaguchi K, Onizawa S, Tsuji T, Aoshiba K, Nagai A. How to evaluate “Spirometric” lung age – What method is approvable? Respir Physiol Neurobiol. 2011;178(2):349-51. DOI: 10.1016/j.resp.2011.06.012.

136. Bang K, Gergen P, Kramer R, Cohen B. The effect of pulmonary impairment on all-cause mortality in a national cohort. Chest. 1993;103:536-40.

137. Schunemann H, Dorn J, Grant B, Winkelstein W, Trevisan M. Pulmonary function is a long-term predictor of mortality in the general population. 29-year follow-up of the Buffalo Health Study. Chest. 2000;118:656-64.

138. Ryan G, Knuiman M, Divitini M, James A, Musk AW, Bartholomew H. Decline in lung function and mortality: the Busselton Health Study. J Epidemiol Community Health. 1999;53:230-34. DOI: 10.1136/jech.53.4.230.

139. Newbury W, Crockett A, Newbury J. A pilot study to evaluate Australian predictive equations for the Impulse Oscillometry System. Respirology. 2008;13(7):1070-75. DOI: 10.1111/j.1440-1843.2008.01375.x.

140. Gore C, Crockett A, Pederson D, Booth M, Bauman A, Owen N. Spirometric standards for healthy adult lifetime nonsmokers in Australia. Eur Resp J. 1995 May 1, 1995;8(5):773-82. DOI: 10.1183/09031936.95.08050773.

141. Kory R, Callahan R, Boren H, Syner J. The Veterans Administration-Army cooperative study of pulmonary function. 1. Clinical spirometry in normal men. Am J Med. 1961;30:243-58. DOI: 10.1016/0002-9343(61)90096-1.

142. Lebowitz M, Holberg C. Comparisons of spirometric reference values and the proportions of abnormal subjects among males smokers and those symptomatic in a community population. Am Rev Respir Dis. 1990;141(6):1491-96. DOI: 10.1164/ajrccm/141.6.1491.

143. Smith A, Gaensler E. Timing of forced expiratory volume in one second. Am Rev Respir Dis. 1975;112:882-85.

144. Sood A, Dawson B, Henkle J, Hopkins-Price P, Qualls C. Effect of change of reference standard to NHANES III on interpretation of spirometric 'abnormality'. Int J Chronic Obstruct Pulmon Dis. 2007;2(3):361-67. DOI: 10.2147/COPD.S.

145. Quanjer P, Enright P. Should we use 'lung age'? Prim Care Respir J. 2010;19(4):197-99. DOI: 10.4104/pcrj.2010.00045.

146. Hansen J. Measuring the lung age of smokers. Prim Care Respir J. 2010;19(3):286-87. DOI: 10.4104/pcrj.2010.00048.

147. Hansen J. Lung age is a useful concept and calculation. Prim Care Respir J. 2010;19(4):400-1. DOI: 10.4104/pcrj.2010.00074.

148. Parkes G, Greenhalgh T. Paradoxes of spirometry results, and smoking cessation. Prim Care Respir J. 2010;19(3):295-96. DOI: 10.4104/pcrj.2010.00056.

149. Rubin B, Dhand R, Ruppel G, Branson R, Hess D. Respiratory Care Year in Review 2010: Part 1. Asthma, COPD, Pulmonary Function Testing, Ventilator-Associated Pneumonia. Respir Care. 2010;56(4):488-502. DOI: doi: 10.4187/respcare.01286.

150. Housset B. La notion d'âge pulmonaire peut-elle aider à arrêter le tabac? [Does the concept of lung age help smokers to quit smoking?]. Rev Prat. 2011;61:600-1.

151. Yamaguchi K, Omori H, Onoue A, Katoh T, Ogata Y, Kawashima H, et al. Novel regression equations predicting lung age from varied spirometric papameters. Respir Physiol Neurobiol. 2012;183:108-14. DOI: 10.1016/j.resp.2012.06.025.

152. Primary Care Respiratory Toolkit. Australian Lung Foundation; 2011 [16 April, 2013]. Available from: http://lungfoundation.com.au/professional-resources/1692-2/general-practice/primary-care-respiratory-toolkit/

153. Newbury W, Crockett A, Newbury J. Australian predictive equations for the Impulse Oscillometry System. Respirology. [Abstract]. 2008;13(Suppl 2):A67.

154. Grant J, Taylor A, Ruffin R, Wilson D, Phillips P, Adams R, et al. Cohort Profile: The North West Adelaide Health Study (NWAHS). Int J Epidemiol. 2009 Dec;38(6):1497-86. DOI: 10.1093/je/dyn262.

155. Falaschetti E, Laiho J, Primatesta P, Purdon S. Prediction equations for normal and low lung function from the Health Survey for England. Eur Resp J. 2004;23:456-63. DOI: 10.1183/09031936.04.00055204.

156. Newbury W, Newbury J, Crockett A. Exploring the need to update lung age equations. Prim Care Respir J. 2010;19(3):242-47. DOI: 10.4104/pcrj.2010.00029.

157. Newbury W, Lorimer M, Crockett A. Newer equations better predict lung age in smokers: a retrospective analysis using a cohort of randomly selected participants. Prim Care Respir J. 2012;21(1):78-84. DOI: 10.4104/pcrj.2011.00094.

158. Cooper B. Dawning of a new lung age? Prim Care Respir J. 2012;21(1):15-6. DOI: 10.4104/pcrj.2012.00021.

159. Hansen J, Sun X-G, Wasserman K. Calculating gambling odds and lung ages for smokers. Eur Resp J. 2010;35(4):776-80. DOI: 10.1183/09031936.00107709.

160. Hansen J, Sun X-G, Wasserman K. Ethnic- and sex-free formulae for detection of airway obstruction. Am J Respir Crit Care Med. 2006;174(5):493-98. DOI: 10.1164/rccm.200604-517OC.

161. Janssens J, Pache J, Nicold L. Physiological changes in respiratory function associated with ageing. Eur Respir J. 1999;13:197-205.

162. Grant J, Chittleborough C, Taylor A, dal Grande E, Wilson D, Phillips P, et al. The North West Adelaide Health Study: detailed methods and baseline segmentation of a cohort for selected chronic diseases. Epidemiol Perspect Innov. 2006 12 April 2006;3(4). DOI: 10/1186/1742-5573-3-4.

163. Haren M, Misan G, Grant J, Buckley J, Howe P, Taylor A, et al. Proximal correlates of metabolic phenotypes during 'at-risk' and 'case' stages of the metabolic disease continuum. Nutr Diabetes. 2012;2(1):e24. DOI: 10.1038/nutd.2011.20.

164. Laird N, Ware J. Random-Effects models for longitudinal data. Biometrics. 1982;38(4):963-74.

165. Ogden C, Fryar C, Carrol M, Flegal K. Mean body weight, height, and body mass index, United States 1960-2002. Advance data from vital and health statistics; no 347. Hyattsville, Maryland: National Center for Health Statistics; 2004.

166. Dytham C. Choosing and Using Statistics: A Biologist's Guide. 3rd ed: John Wiley & Sons; 2011. Available from: http://sunsetridgemsbiology.wikispaces.com/file/view/Choosing+and+Using+Statistics.pdf.

167. Walters J, Wood-Baker R, Walls J, Johns D. Stability of the EasyOne ultrasonic spirometer for use in general practice. Respirology. 2006;11:306-10. DOI: 10.1111/j.1440-1843.2006.00842.x.

168. Barr R, Stemple K, Mesia-Vela S, Basner R, Derk S, Henneberger P, et al. Reproducibility and validity of a handheld spirometer. Respir Care. 2008;53(4):433-41.

169. Liistro G, Vanwelde C, Vincken W, Vandevoorde J, Verleden G, Buffels J, et al. Technical and functional assessment of 10 office spirometers. A multicenter comparative study. Chest. 2006;130:657-65. DOI: 10.1378/chest.130.3.657.

170. Sato S, Muro S, Takahashi T, Hirai T, Mishima M, Sato A. Annual changes of "lung age". Validation of lung age equation by 5-year follow up study in Japan. Am J Respir Crit Care Med. [conference abstract]. 2012;185:2012:A5881.

171. Frith P, Cafarella P, Duffy J. Chronic obstructive pulmonary disease (COPD) is a major personal and public health burden in Australia. Aust NZ J Pub Health. 2008;32(2):139-41. DOI: 10/1111/j.1753-6405.2008.00190.x.

172. Lebowitz M. Age, period and cohort effects. Am J Respir Crit Care Med. 1996;154(6):S273-S7. DOI: 10.1164/ajrccm/154.6_Pt_2.S273.

173. Sharma G, Goodwin J. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging. 2006;1(3):253-60. DOI: 10.2147/CIA.S.

174. Xu X, Laird N, Dockery D, Schouten J, Rijcken B, Weiss S. Age, period and cohort effects on pulmonary function in a 24-year longitudinal study. Am J Epidemiol. 1995;141(6):554-66.

175. Ware J, Dockery D, Louis T, Xu X, Ferris B, Speizer F. Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. Am J Epidemiol. 1990;132(4):685-700.

176. Cole T. The secular trend in human physical growth: a biological view. Econ Hum Biol. 2003;1:161-68. DOI: 10.1016/S1570-677X(02)00033-3.

177. Quanjer P, Stocks J, Cole T, Hall G, Stanojevic S. Influence of secular trends and sample size on reference equations for lung function tests. Eur Resp J. 2011;37:658-64. DOI: 10.1183/09031936.00110010.

178. Quanjer P. Standardization of lung function tests. Bull Eur Physiopathol Respir. 1983;19(Suppl 5):1-95.
179. Zwar N, Richmond R, Borland R, Peters M, Litt J, Bell J, et al. Supporting smoking cessation: a guide for health professionals. Melbourne: The Royal Australian College of General Practitioners; 2011.
180. Tobacco Addiction: National Institute on Drug Abuse; 2012. 12-4342.
181. Singh S, Loke Y, Spangler J, Furberg C. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. CMAJ. 2011;183(12):1359-66. DOI: 10.1503/cmaj.110218.
182. Harrison-Woolrych M. Varenicline for smoking cessation. What can we learn from the story so far? Br Med J. 2012;345:e7547. DOI: 10/1136/bmj.e7547.
183. Harrison-Woolrych M, Ashton J. Psychiatric adverse events associated with varenicline: an intensive postmarketing prospective cohort study in New Zealand. Drug Saf. 2011;34:763-72. DOI: 10.2164/11594450-000000000-00000.
184. Hughes J, Stead L, Lancaster T. Antidepressants for smoking cessation. Cochrane Database of Systematic Reviews. 2007. DOI: 10.1002/14651858.CD000031.pub3.
185. Tashkin D, Murray R. Smoking cessation in chronic obstructive pulmonary disease. Respir Med. 2009;103(7):963-74. DOI: 10.1016/j.rmed.2009.02.013.
186. Prochaska J, DiClemente C. Stages and processes of self-change of smoking: toward an integrative model of change. J Consult Clin Psychol. 1983;51(3):390-95.
187. Prochaska J, Velicer W. The Transtheoretical Model of Health Behavior Change. Am J Health Promot. 1997;12(1):38-48.
188. Perz C, DiClemente C, Carbonari J. Doing the right thing at the right time? The interaction of stages and processes of change in successful smoking cessation. Health Psychol. 1996;15(6):462-68.
189. Riemsma R, Pattenden J, Bridle C, Sowden A, Mather L, Watt I, et al. Systematic review of the effectiveness of stage based interventions to promote smoking cessation. Br Med J. 2003;326:1175. DOI: 10.1136/bmj.326.7400.1175.
190. Sutton S. Back to the drawing board? A review of applications of the transtheoretical model of substance use. Addiction. 2001;96:175-86. DOI: 10.1080/09652140020017049.
191. West R. Time for a change: putting the Transtheoretical (Stages of Change) Model to rest. Addiction. 2005;100:1036-39. DOI: 10.1111/j.1360-0443.2005.01139.x.

192. West R, Sohal T. "Catastrophic" pathways to smoking cessation: findings from national survey. Br Med J. 2006;332:458-60. DOI: 10.1136/bmj.38723.573866.

193. Montepare J, Lachman M. "You're only as old as you feel": Self-preceptions of age, fears of aging, and life satisfaction from adolescence to old age. Psychol Aging. 1989;4:73-8.

194. Maciewicz R, Warburton D, Rennard S. Can increased understanding of the role of lung development and aging drive new advances in chronic obstructive pulmonary disease? Proc Am Thorac Soc. 2009;6:614-17. DOI: 10.1513/pats.200908-094RM.

195. Kennedy C, Bastiaens M, Bajdik C, Willemze R, Westendorp R, Bouwes Bavinck J. Effect of smoking and sun on the aging skin. J Invest Dermatol. 2003;120:548-54.

196. Price D, Crockett A, Arne M, Garbe B, Jones R, Kaplan A, et al. Spirometry in primary care case-identification, diagnosis and managment of COPD. Prim Care Respir J. 2009;18(3):216-23. DOI: 10.4104/pcrj.2009.00055.

197. Jordan R, Lam K, Cheng K, Miller M, Marsh J, Ayres J, et al. Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach. Thorax. 2010;65:492-98. DOI: 10.1136/thx.2009.129395.

198. Stanojevic S, Wade A, Stocks J, Hankinson J, Coates A, Pan H, et al. Reference ranges for spirometry across all ages. A new approach. Am J Respir Crit Care Med. 2008;177:253-60. DOI: 10.1164/rccm.200708-12480C.

199. Thompson B, Stanojevic S, Abramson M, Beasley R, Coates A, Dent A, et al. The all-age spirometry reference ranges reflect contemporary Australasian spirometry. Respirology. 2011;16:912-17. DOI: 10.1111/j.1440-1843.2011.01970.x.

200. Brazzale D, Hall G, Pretto J, editors. The effect of adopting the new GLI reference equations on the interpretation of spirometry. ANZSRS Annual Scientific Meeting; 2013; Darwin: Respirology.

201. Fingleton J, Williams M, Charles T, Beasley R, editors. Choice of reference range markedly changes estimates of population disease prevalence and severity. TSANZ Annual Scientific Meeting; 2013; Darwin: Respirology.

202. Australian Bureau of Statistics. Australian Standard Geographic Classification Remoteness Structure. Australian Bureau of Statistics; [updated 1 February 2013]. Available from: http://www.abs.gov.au/websitedbs/d3310114.nsf/home/remoteness+structure

203. Rivett K. Ambient air monitoring at Whyalla, South Australia. Monitoring campaign 2004-06: Air and Noise Branch, South Australian Environment Protection Authority.; 2007. ISBN 978-1-921125-50-8.

204. South Australia Department of Health. Whyalla Health Impact Study Report: Department of Health; 2007. Available from: http://www.health.sa.gov.au/pehs/whyalla/071203-Whyalla-report.pdf.

205. Scollo M, Winstanley M. Tobacco in Australia: Facts and issues. 4th ed. Melbourne: Cancer Council Victoria; 2012. Available from: Available from www.TobaccoInAustralia.org.au

206. Campion J, Checinski K, Nurse J. Review of smoking cessation treatments for people with mental illness. Advances in psychiatric treatment. 2008;14:208-16. DOI: 10.1192/apt.bp.107.003483.

207. Profiles of Health, Australia, 2011-2013. Canberra: Australian Bureau of Statistics; 2012. 29/10/2012 4338.0.

208. Aylward P, Crockett A. Qualitative evaluation of the 'Primary Care Respiratory Toolkit': Interviews with General Practitioners and Practice Nurses from GP practices in South Australia. : Australian Lung Foundation; 2011.

209. Plan and operation of the third National Health and Nutrition Examination Survey, 1988-94.: National Center for Health Statistics; 1994.