

**THE SIGNIFICANCE OF
RESPIRATORY IMPAIRMENT
FOR PUBLIC HEALTH IN
SCOTLAND**

**Report of a symposium held at the University of
Glasgow
on 17th February 2011**

SUMMARY



This symposium was held to review the public health significance of what is known about the epidemiology of respiratory impairment, based largely on Scottish studies, but also drawing on expert and generalist knowledge.

Respiratory impairment, as measured by forced expiratory volume (FEV1) was first described in the Renfrew and Paisley (Midspan) general population study as the most important determinant of premature mortality, after cigarette smoking, and the most important determinant of premature mortality in lifelong non-smokers. This observation holds true in the more recent findings of the MRC West of Scotland Twenty-07 Study and serial Scottish Health Surveys.

The epidemiology and importance of respiratory impairment is that it is associated with mortality from most causes, extending far beyond its associations with respiratory disease and providing a substantial additional explanation of poor health in Scotland in general and Glasgow in particular.

It is possible that these observations account for part of the “Glasgow and Scottish Effects” which have been described, mostly on the basis of ecological data, as the component of high mortality rates in Glasgow and Scotland which are not explained by conventional risk factors.

The natural history of lung function comprises an initial period of growth, reaching a peak in early adulthood and followed by a period of decline with age, which may be fast or slow depending on the respiratory hazards encountered. It seems likely that the initial period of growth is not specific to the lung, but is part of general body growth and development.

Despite the strength and consistency of the epidemiological signal, it is not clear what actions can be taken to maximise respiratory function or to prevent or slow subsequent decline. More research is needed, especially in non-smokers.

The clinical implications are also unclear, although it is possible that spirometry could substitute for measures of either serum cholesterol or post-code deprivation in estimations of cardiovascular risk.

A crucial but unresolved question is whether lung function in Scotland is improving over time. Continued public health monitoring of respiratory function is needed to answer this question.

GUEST EXPERTS

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Imperial College London

Professor David Strachan
St George's Hospital and Medical School, London

Professor Jorgen Vestbo
Universities of Manchester and Copenhagen

Professor John Frank
MRC Scottish Collaborating Centre for Public Health Research and Policy

Professor Cairns Smith,
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PRESENTERS

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Dr Carole Hart
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BACKGROUND

The first major Midspan paper on respiratory impairment was published in the British Medical Journal in 1996 (1).

- *Increased death rates from all causes, ischaemic heart disease, all cancers, lung cancer, stroke, respiratory disease and other causes have been found among healthy middle aged men and women with reduced (including moderately reduced) forced expiratory volume in one second (FEV1).*
- *These increased risks, with the exception of the cancers, are apparent for life-long non-smokers*
- *FEV1 is second in importance to cigarette smoking as a predictor of subsequent all cause mortality and is as important as cholesterol in predicting mortality from ischaemic heart disease*

In an accompanying editorial, David Strachan wrote (2),

What are the public health implications? Diminished lung function may be a cumulative indicator of environmental influences on mortality or may have direct effects on survival after myocardial infarction or stroke. Forced expiratory volume is influenced both by lung development in childhood and by destructive insults to the lung tissues during adult life. At its peak in early adult life, it is related to both prenatal and postnatal growth, and thus may be a better integrated measure of developmental influences on survival than adult height. Arguably, taking a long term public health perspective, FEV should be considered as a potentially modifiable risk factor, its association with premature mortality indicating a plausible mechanism for causal relations between family circumstances in childhood and the chances of surviving through middle age”.

More recently, Burney and Hooper, concluded their report of a cohort study of 7489 Americans (3),

Survival in asymptomatic adults without chronic respiratory diagnoses or persistent respiratory symptoms is associated with FVC and not with airways obstruction, as measured by the FEV1/FVC ratio. The relation of FEV1 to survival is indeed strong, but secondary to the association of FEV1 to FVC.

WHAT DOES RESPIRATORY IMPAIRMENT PREDICT?

Findings from the Midspan Studies – Graham Watt

This paper is based on a published review of Midspan publications on aspects of respiratory epidemiology (4)

Between 1972 and 1976, Victor Hawthorne led the baseline study of over 7000 men and 8000 women, comprising almost 80% of the general populations of Renfrew and Paisley. It was unusual for a large, prospective epidemiological study to be based in such a population, with high levels of socio-economic deprivation and all cause mortality rates, and for a study at that time, to include so many women.

The baseline study showed high levels of cigarette smoking in men and women. More men than women had given up smoking. There were high levels of COPD, as measured by the MRC questionnaire, but these were not as high as levels of breathlessness, defined as being out of breath while walking on the flat with someone of one's own age. A recurring observation of the studies has been that this measure of COPD captured only a small proportion of people with respiratory impairment.

The symptom levels were high, compared with levels recorded in other studies carried out at the same time, including the Whitehall Study of Civil Servants (which used identical methods – Geoffrey Rose having piloted the Whitehall Study methods in the west of Scotland), the Tecumseh Community Health study in Michigan and the WHO Collaborative Study (another Midspan study based on a west of Scotland occupational cohort), and probably reflected several things, including the generally shorter stature of Midspan participants, and their exposure in a depressed and poor area to numerous hazards to respiratory health.

There were strong social gradients not only in smoking in men, and in women, but also in the proportion who had given up smoking. There were the usual expected steep gradients, with COPD and breathlessness being particularly high in social class 5.

Even in people who had never smoked, there were significant background levels of COPD and breathlessness, suggesting other hazards to respiratory health in this population.

After 25 years, respiratory causes of death were the 4th commonest cause of death in men and in women. 61% of men had died and 9% of these had died of

respiratory causes, of which about a half were due to COPD. Fewer women had died but the pattern of respiratory deaths was similar.

Respiratory causes of death, however, underestimate the importance of respiratory impairment in this population. David Hole's 1996 paper showed that for equal increments of FEV1, from 65% to 115% of expected values, there was a steady decline in coronary mortality in men and in women. The same pattern was seen for stroke, respiratory disease and for deaths from all causes.

Relative hazard ratios, comparing mortality in the lowest and highest quintiles of FEV1 confirmed this general pattern of increased mortality associated with respiratory impairment, not only from respiratory and cardiovascular causes, but also in men, in women and in life long non-smokers. The pattern also held true when focusing on IHD and respiratory deaths in people who were free of symptoms of IHD and respiratory disease at baseline, and also after excluding deaths within five years of the baseline study.

Population attributable risks for all cause and IHD mortality were higher for reduced FEV1 than for any other measurable risk factor, including blood pressure and serum cholesterol, and was second only to cigarette smoking in terms of overall effect, in men and women.

COPD is too narrow a focus to capture the epidemiological consequences of respiratory impairment. As Jorgen Vestbo wrote in a pre-circulated paper (4),

*COPD will never be fully understood
if it is constantly viewed simply as COPD.*

Over 23 years of follow up, 79% of participants had at least one acute hospital admission, the average being 4.6 admissions. Respiratory diagnoses were the 9th most common principal discharge diagnosis. In terms of respiratory impairment, however, having a FEV1 in the lowest quartile of the population distribution was associated with a 27% increase in the likelihood of hospital admission, a 50% increase in the chance of a serious admission and a 98% increase in the chance of hospital admission with a fatal outcome.

The inclusion of so many men and women from one area meant that many were married or cohabiting, which allowed comparison of cohabitees, where neither had ever smoked, defined as controls; passive smokers, defined as lifelong non-smokers exposed to a co-habiting smoker; and active smokers, living in households where both cohabitees smoked. The observed associations of passive smoking with respiratory symptoms, angina and mortality rates

provided evidence of the harm that comes from living with someone who smokes cigarettes.

The population included just over 4000 married couples, which made it possible to identify and track down the numbers and whereabouts of their adult offspring. For the Midspan Family Study it proved possible to contact and study over 1000 sons and nearly 1300 daughters aged 30-59, from nearly 1500 families. The offspring are of special interest because, unusually for a family study, they had reached adulthood and there had been time for predispositions to be expressed.

Comparing age-standardised prevalences at age 45-54, the prevalence of smokers halved in both sons and daughters. There was also a substantial increase in the proportions of sons and daughters in non-manual occupations.

Hay fever was three times, and asthma twice as common in sons as in fathers, and in daughters compared with mothers. Other respiratory symptoms have declined in prevalence – wheeze, chronic sputum production and breathlessness.

The increases in hay fever, a marker of atopy, and asthma occurred similarly in non-smoking and smoking families. The decreases in respiratory symptoms were most marked in smoking families, suggesting that other factors, for example, increases in height and improvements in air quality, may have been responsible for this change.

In sons who smoked and who did not have asthma, a parental history of COPD death reduced FEV1 by 235 ml, but this increased to 319 ml for parental COPD deaths under 70, and to 478 ml for deaths under 70 with COPD as the first cause of death. Given that the annual decline in FEV1, after it peaks in early adulthood, is about 30 ml per year, a strong family history of parental death from COPD is associated, in sons who smoke, with the equivalent of about 16 years decline in lung function.

The numbers affected by such a family history are small. More generally, in the 25% of sons and daughters who smoked, the effect of their mother having smoked 10 cigarettes per day was to increase offspring's risk of COPD by 79%. In terms of reduced FEV1, the effect of a mother smoking 10 cigarettes per day on FEV1 in sons and daughters was numerically equivalent to 10 years of personal smoking. Maternal smoking casts a long shadow, therefore, on the health of offspring, which is a cause for concern in parts of the world where maternal smoking is becoming more common.

In summary, this study with large numbers, its representative nature, inclusion of women, 25 years follow up and extension to the next generation, has provided a wealth of findings on the importance of respiratory function as a

determinant of population health. The picture which emerges is broader, and more important, than that based on studies of respiratory symptoms and respiratory causes of death.

Offspring can escape much of their early environment, but parental smoking has long term effects. There are fascinating differences between families and between offspring within families, which call out for further investigation.

Do these findings matter now, given that participants in the Renfrew and Paisley Study went to school before World War 2, and were born and brought up before the Clean Air Act, when what visible air pollution did to the outsides of houses, it also did to the insides of lungs? Patterns of cigarette smoking have also changed. However, the combination of poor early nutrition, air pollution and cigarette smoking is still topical in China, the largest country in the world. Perhaps for that population, the Midspan findings describe what the future will entail.

New findings from the Midspan Family Study : Carole Hart

2338 adult offspring of married couples who participated in the Renfrew/Paisley Study, took part in a baseline study in 1996, when offspring were aged 30-59 years. 2257 (97%) provided a measurement of FEV1.

These offspring were born between 1936 and 1966. By the end of 2009, 55 sons and 45 daughters had died.

Percent predicted FEV1 was defined as the observed level divided by the level predicted, on the basis of a linear regression equation incorporating height and age in healthy never smokers without asthma. Gender did not have an independent effect, so data for sons and daughters were combined.

The small number of events meant that relative mortality rates were compared between tertiles of the distribution of percent predicted FEV1. 52 deaths occurred in the lowest tertile, 31 in the middle tertile and 17 in the highest tertile.

Relative mortality rates increased by 45% per standard deviation decline in percent predicted FEV1, adjusting for age, and by 39%, adjusting for all risk factors.

Relative all cause mortality ratios, adjusted for confounding variables, were 2.22 in the lowest tertile, 1.70 in the middle tertile and 1.0 in the highest tertile.

Equivalent figures of cancer mortality were 2.21, 1.75 and 1.0. Lung cancer accounted for most of this gradient.

Although the numbers of events were small, similar gradients were found for coronary heart disease, respiratory and other causes of mortality.

In conclusion, respiratory impairment as measured by percent predicted FEV1 continues to predict mortality in the second Midspan generation.

New findings from the Scottish Health Surveys: Linsay Gray

Random samples of the Scottish population were surveyed in 1995, 1998 and 2003, with survey data being linked subsequently to Scottish Morbidity Records for hospital admissions, cancer registrations and deaths in Scotland (5).

The surveys took place in two stages, beginning with an interview, which was followed by a nurse home visit to carry out a range of biological measurements. In total, 92% of participants agreed to record linkage.

In the sample of 17,147 with respiratory measurements and complete covariates of interest, the average age was 47, with most participants born since 1950. There was little difference in FEV1 across the cohorts.

Quintiles of the distribution of percent predicted FEV1 were identified as for the Midspan studies. Men and women with values below 81% and 82%, respectively, comprised the lowest quintile and were considered to have respiratory impairment.

Respiratory impairment was associated with increased relative risks of all cause, respiratory, CVD and cancer mortality.

In view of the recent paper by Burney and Hooper (3), the analyses were repeated, accounting for FVC.

Absolute FVC had some effect on the relationship between FEV1 and all cause mortality in men, and attenuated the association in women.

The Relative Index of Inequality (RII), comparing the relative risks of extreme ends of distributions, was used to compare the importance of FEV1 for mortality, relative to other risk factors.

Predicted FEV1 was the 5th most important risk factor in men (after BP reduction medication, diabetes, social class and cigarette smoking), while FVC was the second most important risk factor in women (after diabetes).

In conclusion, FEV1 remains predictive of mortality, even in the most recently born cohorts. FEV1 remains a key predictor of mortality, especially among women. FVC may be even more important for women.

New findings from the MRC 20-07 Study: Michaela Benzeval

This preliminary analysis looked at the relationship between change in FEV and subsequent mortality. Few studies have looked at this, but all have found that decline in FEV had an added effect on mortality in addition to the effect of the initial FEV.

This presentation was based on two of the three 20-07 cohorts, born around 1932 and 1952, which were first surveyed in 1987 and were then followed up for 20 years (6). Each cohort had five waves of data collection, carried out at 5 year intervals. The sampling strategy included both regional and enhanced locality samples.

The cohort born in 1932, which aged from 55 to 75 during the study period, included 1551 men and women at the outset, of whom 663 took part in the fifth and final survey, by which time 425 people had died.

The cohort born in 1952, which aged from 35 to 55 during the study period, included 1444 men and women at the outset, of whom 999 took part in the fifth and final survey, by which time 76 people had died.

The study included over 10,000 person contacts, of which 4% did not include a FEV measurement. Another 6% were excluded for not providing a satisfactory measurement. Maximum recorded values were used for the analysis

The change in the spirometer used to measure lung function from the third wave onwards precluded analysis of trends in FEV1 over time, but still allows comparison of FEV ranking over time, despite the use of different measurement methods.

Mean recorded FEV and percent predicted FEV declined over time. Starting levels of % predicted FEV, and decline in levels of % predicted FEV were both associated with increased all cause mortality and self reported CHD morbidity.

In the older cohort, the hazard ratio for increased mortality associated with a 20% reduction in FEV at baseline was 1.43, reducing to 1.31 after full adjustment for other variables. The opposite pattern was seen in the younger cohort, but with smaller numbers of deaths.

For a 20% decline in FEV in the older cohort, the hazard ratios were larger than for a 20% lower FEV at baseline. A similar pattern was seen in the younger cohort.

Discussion points

It was suggested that some of the analyses be repeated, omitting lung function measures taken near the end of life, in order to avoid the possibility of reverse causation.

Concern was expressed that in controlling for the usual factors of age, gender and height, important information may be lost concerning the role of height in determining lung function.

Concern was also expressed about the possibility of measurement drift over time using microspirometers. It is also more difficult to assess the satisfactory nature of performance, given that microspirometers provide no visual display of performance.

Comparing measurements across cohorts using different instruments is difficult. Even when different instruments are calibrated to the same standard, say a 1 litre volume, there may still be systematic differences in measurement across the range of lung volumes being recorded. Restricting analyses to percentage of predicted FEV1, and comparisons of rankings over time, may help overcome some of the difficulties of combining such data from different sources

Such evidence as there is, however, suggests that performance in lung function tests is improving over time.

In general, with the exception of the Midspan family study, lung function tests have been included in most population surveys as one of many measurements, with no particular interest in the problems of measuring lung function. The resulting data may be relatively crude, therefore, and while useful for epidemiological analyses of groups, may fall short of providing precise characterisation of individuals.

AETIOLOGICAL QUESTIONS

Is poor lung function a cause or consequence of asthma? Paul Johnson

People with asthma have impaired lung function but it is not known whether the lung function deficits are a cause or a consequence of their asthma. Genes affecting lung function have been identified in largely non-asthmatic populations. These genes do not affect asthma. Either poor lung function is not a heritable cause of asthma, or it is, but different genetic variants affect lung function in asthmatics and non-asthmatics.

Only one study has found heterogeneity in familial aggregation between asthmatics and non-asthmatics, but this finding has not been replicated (7). Before abandoning research that targets lung function as a way to influence asthma, it is important to know whether lung function is inherited in a similar way in individuals with and without asthma.

In the Midspan family study, 14% of families had at least one family member who had “ever had asthma”.

The heritability of adjusted lung function was moderate at 30% for FEV1 and 32% for FVC. Heritability of FEV1 was significantly lower in asthma families (19%) than in non-asthma families (34%)

There was no parent of origin effect in asthma families. This observed low heritability of FEV1 in asthma families appears driven by a low mother-son correlation.

Evidence of a parent of origin effect would have encouraged further enquiry of whether poor lung function is a cause or consequence of asthma. These findings provide tentative evidence that the inheritance of FEV1 is different in asthma families, but in an unexpected way, that could be due to chance and which requires corroboration.

Discussion points

In the Midspan family study, there were two types of offspring who did not participate – those who had moved away and who were not approached, and those who still lived locally but who chose not to take part.

Caution is needed in identifying “asthmatic and non-asthmatic families”, because of the confounding effect of smoking and the several asthmatic phenotypes.

Although bronchodilation helps to sort out asthmatic phenotypes, this is often not practicable in population studies.

Less than 1% of variation in lung function is explained by the latest genetic studies.

What are the determinants of respiratory impairment and are they reversible?

Mark Upton

Understanding these questions is made more complicated by the natural history of the rise, plateau and fall of lung function and the difficulty of looking either backwards or forwards from cross sectional or short term data. Ideally we would study many of these questions with a birth cohort, in which causes would precede effects.

What is it about lung function that predicts mortality? What aspects of lung physiology are important? To answer these questions, we need to focus most on never smokers.

Some clues are available from studies of the epidemiology of respiratory symptoms. In the Busselton study, there was no association between wheeze, adjusted for all other factors, and mortality, while there was an association with breathlessness (8).

Breathlessness due to lung causes has much more to do with lung volume than with expiratory airflow. Wheeze is much more strongly related to expiratory airflow. When the effects of breathlessness and wheeze on lung function are mutually adjusted for each other, breathlessness is related to FVC, while wheeze is related to FEV1 and FEV1/FVC but not to FVC.

In lifelong never smokers in the Whitehall study, all cause mortality was related to both FEV1 and to FVC (9). As the association with FEV1 was slightly stronger, subsequent analyses focused on FEV1. The Copenhagen Study showed similar findings (10).

In the ARIC study, excluding people with respiratory symptoms, and adjusting for smoking, FVC was more strongly associated with all cause mortality than was FEV1 (3).

Of course FEV1 depends on FVC, as a measure of lung volume, but also on flow. In Midspan offspring, the correlation of FEV1 and FVC holds at about 0.9 in never, former and current smokers, dropping a little in current smokers. The consistent strength of the relationship, even in asthmatics, helps explain the apparent interchangeability of FEV1 and FVC in epidemiological analyses.

In the Midspan family study we paid a great deal of attention to the quality control of spirometry, providing participants with visual feedback on their performance, which made it easier to maintain effort for at least 6 seconds.

Research nurses were also given regular feedback on the quality of the data they had collected, which improved the acceptability and reproducibility of measurements.

Vital capacity can be measured directly (either as slow vital capacity or inspiratory vital capacity), but in practice it is usually estimated with a forced expiratory manoeuvre. Although the Framingham Study included measurements of vital capacity, their relationship with mortality has never been published.

It is possible that we introduce additional confounding variables by using a forced expiratory manoeuvre to estimate vital capacity.

At high lung volumes, increases in intrapleural pressure lead to increases in expiratory airflow, but at middle and low lung volumes, there is little effect. The practical consequence is that when carrying out forced expiration from a position of maximum inspiration, expiratory flow is influenced significantly by the amount of effort that is put into the task. Women in particular seem not to make a maximal effort at the start of forced expiration. When participants are excluded from analysis on the basis of their not being able to produce reproducible manoeuvres (up to 12% in some studies), important population data may be lost. By providing technician support and visual feedback on their performance to participants, it was possible to reduce substantially the number of exclusions for this reason.

Older people find it harder to blow hard, as do people with limiting long term illnesses and people with lower socio-economic status. Very thin people also find it hard to blow for 6 seconds.

In the Framingham study, grip strength correlated with lung function (11). There are at least two ways in which grip strength might contribute to the link between FVC and mortality, via connections with either expiratory or inspiratory muscle strength.

Vital capacity is the difference between total lung capacity and residual volume. It's not known what effect either TLC or RV have on mortality. Vital capacity declines with age because of an age-related increase in residual volume. Total lung capacity does not change with age. Although the increase in residual volume is driven partly by age-related loss of lung elastic recoil, this cannot be the explanation for the effect of vital capacity on mortality in the ARIC study, because loss of elasticity also drives age-related decrements in FEV1/FVC ratio, yet FEV1/FVC does not predict all cause mortality

TLC is set by the balance between inspiratory muscle strength and the recoil of the lungs. Residual volume is the result of the balance between expiratory muscle strength and the recoil of the chest wall.

Muscle strength determines not only whether we can perform a test, but also the starting level of lung volume from which forced expiration starts. In boys, RV as a proportion of TLC goes down in adolescence, as a result of their increased muscle strength. Strength development in childhood may be an important determinant, therefore, of the relationship we are trying to study between FVC and mortality.

In historical studies by John Hutchinson, every additional inch of height was associated with 8 additional cubic inches of lung capacity at a given temperature (12). Age had little effect before the age of 50.

Similar associations between height and vital capacity have been observed in current international studies and in the Midspan offspring study, although the strength of the association has increased since the mid-19th century.

Birth cohorts show relationships between birth weight and adult FVC.

Secular increases in height are driven mainly by increases in leg length.

Leg length, rather than sitting height, is the component of height that is most associated with mortality.

In adolescence, it appears to be sitting height that drives the development of lung size.

Discussion points

Can FVC performance be improved by training? If yes, is this a short term effect or does it confer long term health benefits?

Swimmers inspire very quickly and can increase their inspiratory muscle strength by training. It is not know whether swimmers have better life expectancy. Nor bagpipers.

It was felt that the ATS guidelines for excluding FVC measurements are too rigid. The ability to maintain expiration for 6 seconds should not determine whether measurements are acceptable. Reaching a plateau is more important than lasting for 6 seconds.

Only an observant and experienced technician can tell whether full inspiration has been achieved.

It was noted that Afro-Americans have poorer lung function than white Americans, but it is not clear why.

It was suggested that sitting height may be a useful proxy for chest size.

In the Midspan Family Study, the associations of FEV1 with leg length were slightly weaker than their relation with trunk length (13)

CLINICAL AND PUBLIC HEALTH QUESTIONS

What does FEV1 add to CVD risk prediction?

Kenny Lawson

This worked example followed the SIGN guidelines for identifying people without CVD but with modifiable risk factors for CVD at an early stage when preventive measures are likely to be most effective.

Just over 10,000 asymptomatic Midspan patients were assessed for CVD risk using the ASSIGN risk scoring tool, which takes account of current age, gender, socio-economic status (based on postcode, using the Scottish Index of Multiple Deprivation), family history, diabetes, cigarettes smoked per day, systolic blood pressure, HDL and total cholesterol, giving a ten year risk score for a CVD event (14). Risks above 20% are considered to be high risk, meriting preventive measures.

Can we estimate the importance of % predicted FEV1 as an additional risk factor, not only statistically, but also clinically?

Using the linked Midspan-SMR data set, outcome data comprised SMR1 data for all CVD hospital admissions, with deaths recorded from GROS. 14% of participants had a CVD event in the ten years after screening.

Average % FEV1 predicted was 92% for men and 95% for women.

Missing data included family history and HDL cholesterol. These analyses proceeded without these variables.

In females, for every percentage increase in FEV1, there is a 1% protective effective in the reduction of CVD risk (p,0.01). In males, the protective effect is less at 0.5%, and on the border of statistical significance.

For example, in non-smoking women of 45 years with average risk factors, the effect of including FEV1 at 80% of the predicted level is to increase CVD risk from 7 to 8% - not a large difference.

In older men living in the most deprived areas, however, the effect of including FEV1 at 50% of the predicted level increases CVD risk from 41 to 47%%. This impact is greater, but in an individual who is already at very high risk relative to the threshold for intervention.

It appears, therefore, that while the added effect of predicted FEV1 is statistically significant, the clinical implications for individual patients are less clear.

Are there nevertheless some “tipping points” which make the inclusion of FEV1 data important for some patients, in terms of their being classified at high CVD risk?

For illustration, the analysis used the risk factor combinations that define orthodox 10 year risk tables (e.g. JBS, EUROSCORE). We then calculated the ASSIGN 10 year risk score with and without predicted FEV1 as a risk factor. The inclusion of predicted FEV1 can shift individuals from intermediate to high risk categories, but usually on the basis of large percentage predicted FEV1 reductions of 50% and 30%, irrespective of socio-economic status.

A key observation is that in people who are already at high risk on the basis of other CVD risk factors, including socio-economic status, reduced predicted FEV1 has little additional effect on CVD risk.

In Midspan only 4% of the population have FEV1 values below 50% predicted. At the 30% level, the proportion is about 1%.

Redoing these analyses with FEV and FVC instead of FEV1, the results were significant for women but not for men.

Discussion points

Can FEV1 help in parts of the country where postcodes are a poor guide to socio-economic status, because of the ecological fallacy? That remains a research question.

Similarly, could knowledge of FEV1 help to restrict the need for universal cholesterol testing, given that spirometry is relatively cheap to carry out?

It was pointed out that the dominant effect of increasing age on CVD risk is that other risk factors become less important in older people, when large numbers are categorised at high CVD risk on grounds of age alone. Kenny Lawson and Andy Briggs are developing a method to remove the dominant effect of age by estimating CVD risk and life expectancy, based upon modifiable risk factors. This will also provide an opportunity to estimate the potential benefits from changes to modifiable risk factors

It was pointed out that any additions to CVD screening should be assessed in terms of the accepted screening criteria including sensitivity and specificity of test and the availability of effective treatments.

This analysis using Midspan provides reason for follow-up work. The analysis could be repeated using the linked SHeS-SMR which includes all ASSIGN variables and FEV1. Using a recent representative cohort could also allow estimation of the percentage of the population who may be reclassified at high CVD risk.

**Public health monitoring:
review of Scottish Health Survey data**

Alastair Leyland

Scottish Health Surveys were conducted in 1995, 1998, 2003 and 2008, when FEV1 was measured during nurse interviews, which leads to reduced numbers in later surveys (6). Analyses of inequalities by social class are based on 8583 men and 10318 women, drawing from all four surveys but with the largest numbers from the first two surveys. For practical reasons, analyses of social patterns within these data are based on either individual social class or education, as the change from Carstairs score to SIMD as the area-based deprivation measure of choice meant that comparable measures were not available at all time points.

There was no trend of FEV1 over time in men aged 15-24. There are however trends of increasing lung volume in older age groups up to age 74, which is good news. The trends may be associated with secular trends in height, but this is unlikely to be the sole explanation. In women there were significant increases in FEV1 over time in every age group up to age 84.

Analyses of inequality were based on the slope index of inequality, describing a regression line for the trend over time using the entire data set, and interpretable as a comparison of the extremes. Men aged 25-34 are the only age group in which there appears to be a decrease in inequality. For the first three surveys there was clear inequality with lower social classes having lower FEV1 by about 0.5 litres in men. In the most recent survey, however, the numbers are small and difficult to interpret on their own. In all other age-sex groups, there is no consistent pattern of changing inequalities.

In women there is a suggestion of decreasing inequality in women 15-24 and widening inequality in women aged 65-74.

When education is used instead of social class, a similar pattern is seen.

On average the social differences come to about 0.4 litres for men and women, whether based on social class or education.

The above figures are based on crude FEV1 data and do not take account of differences due to height.

Analyses based on predicted FEV1 show a strong decline with age in men and women. Age has a stronger effect than height. Survey year also had a small effect suggesting that lung function is increasing over time, independently of height, at a slow rate.

Trends in inequality again suggest diminishing inequality in men aged 25-34 but no consistent change in other age groups.

For women, the patterns are similar, clustering around a 10% reduction in predicted FEV1 in the most disadvantaged groups and showing decreasing inequality in the youngest age group.

Using education as an indicator there is again decreasing inequality in men aged 25-34, increasing inequality in men aged 35-44 and no significant trends in women in any of the age groups.

In summary, decreases in inequalities were found by social class and education in men aged 25-34, an increase in inequality was found by education for men aged 35-44 and a decrease in inequalities by social class for women aged 15-24.

The magnitude of the differences were about 7% and 9% for social class in men and women respectively. For education, the differences were 9 and 10% respectively.

The 0.45 litre difference in FEV across the social spectrum in men is equivalent to 10.5 cm in height or 12 year's decline in lung function, while the difference of 0.40 litre in women is equivalent to 11.5 cm in height or 14 year's decline in lung function.

Related analyses of linked SHS data suggest that an increase in FEV1 of 1 litre is associated with a decrease of 70% in subsequent mortality in men and a 80% reduction in mortality in women.

Alternatively, the observed differences of 0.45 litre and 0.40 litre in men and women are associated with hazard ratios of 0.6 and 0.5 respectively.

Differential patterns of smoking explain 20-25% of inequalities in FEV1, which is equivalent to the effect of height. Weight, physical activity and respiratory illness have little impact on inequalities (data for 1998-2008 only). Parental social class explains a further 20% of inequalities (data for 2003-08 only). Second hand smoke exposure and urban/rural residence had no impact on inequalities.

In conclusion, there are trends of increasing FEV1 for men 25-64 and women aged 15 and over. There is a general pattern of inequalities at all ages, which

appear to be decreasing in men aged 25-34 (for FEV1 or FVC, based on social class or education) while remaining unchanged at other ages and in women. The observed inequalities are equivalent to about 11 cm in height, or 12-14 years in age, and are associated with reduced hazards of mortality of 40% in men and 50% in women. Smoking and parental social class contribute to these inequalities but leave about 50% of the variation unexplained.

Discussion points

The secular changes over time are small, and much less than the differences observed between cohorts.

Scepticism was expressed concerning the observed trends in the youngest age groups, given the low response rates, and the likely differences between respondents and non-respondents. Weighting techniques are unlikely to correct for this.

The observed associations of lung function and their equivalence to years of decline in lung function appear to help explain a substantial part of the social patterning of the difference between chronological and physiological age.

The decrease in inequality in men aged 25-34 is counter-intuitive with population trends in mortality. While the SHS data may be true for participants in the SHS, they may not reflect wider society and the main causes of death in this age group. It was observed that the sort of people who die of drink, drugs and violence in this age group may not be the sort of people who take part in health surveys.

It is possible that the inequalities in FEV1 observed in the youngest age groups are due to differential growth and development within social groups.

Are there trends in time for FEV1 or FVC in healthy never smokers?

As predicted FEV1 is increasing over time in some groups. this cannot be explained by trends in height.

GENERAL DISCUSSION

For **Jorgen Vestbo**, lung function tests are not just for public health monitoring. They may also be useful in clinical practice, especially in recognising undiagnosed asthma and/or COPD, for example in younger people. In clinical practice, a problem is the lack of longitudinal data. A predicted FEV of 83% is not too bad, unless a previous measurement was 120%. However, in order to characterise individuals, clinicians need high quality data, usually made by experienced technicians. Imprecise data which are good enough for

epidemiology are unlikely to be good enough for clinical practice. The “best of 3” approach is insufficient. He preferred FEV1 to FVC, as FEV1 relates more to clinical work.

For **David Strachan** the interest of the topic was not only whether risk prediction could be improved in individuals, or the place of lung function tests in public health monitoring, but also whether there may be clues to the constitutional determinants of health and shortened life expectancy. An impressive fact is that the early epidemiological findings have stood the test of time and are still important. There are unresolved issues about the importance of FEV1 and FVC, and also sitting height and leg length. A key determinant of good health, however, is body size. Bigger people live longer. Chest size is probably a surrogate for the size of internal organs and their reliance, or ability to sustain insults. Strength is also important, not only in expiration but also inspiration. Grip strength may be an indirect indicator of such strength. Chest recoil is another important part of the equation. In terms of outcome, does lung function predict incident disease or case-fatality? Does this make a difference to individual risk prediction, in terms of the shifts in the numbers of people categorised at high or middling risk with and without lung function data? On the population health issue, body size is the outcome of many early life determinants. Of particular interest are the determinants of lung function in life long never smokers.

For **Peter Burney**, the meeting had covered a huge agenda and many issues which merit further research and discussion. Precise questions are essential. For example, whether smokers are included or excluded raises a host of different research questions. In the ARIC study published in Thorax, a main aim was to establish population norms, addressing the issue of ethnicity. African Americans have lower lung function than white Americans, and associated higher mortality, but when known risk factors, such as height and smoking are taken into account, the ethnic differences disappear. In the US, it is controversial to suggest that race is a proxy for social class. On the FVC v FEV1 issue, these are so inter-related that it is difficult to disentangle their relative importance. More important is FVC versus the FEV1/FVC ratio. Another issue is the tendency in research studies to exclude individuals with unsatisfactory performance in lung function tests. These may include many people with important morbidity. At the moment, the priority is to understand the epidemiology and aetiology, and then the practical value of this information. How can FVC be changed? If compulsory swimming improved FVC, would that deliver the hoped for benefits in terms of interrupting the causal pathway? Unfortunately, the causal pathways are not well understood. More research is needed on that issue. At present, almost all the criteria required to justify screening of lung function are not met. So although it may be of interest and use for clinicians to have access to such information there is at present no strong argument for the data to be collected on a population basis.

The increasing fragmentation and discontinuity of care makes it more difficult to imagine such long term monitoring of all patients in a practice.

In view of the apparent equivalence of FEV1 and FVC, why has there been so much focus on FEV1? No clear answer emerged, except perhaps that investigators find FVC a more difficult measurement to make. The main uncertainty is whether people have taken a full inspiration prior to a forced expiratory manoeuvre.

Graham Watt asked whether “it was all about growth” with lung function simply the only test of an internal organ system which can be carried out non-invasively and relatively easily in large numbers of young people. Determinants of growth and subsequent decline might apply to several body systems. A practical consequence is that unless deficits in FVC and FEV1 are specific, it seems unlikely that treatments directed at lung function could reverse the associated morbidity and mortality.

As an epidemiologist, **Cairns Smith** expressed fascination with a risk factor that seemed to be consistent in explaining everything. However, information on mechanisms is lacking. Possibly lung function is a confounding variable, but if it is “measuring something else”, it does so very well. He drew a comparison with the epidemiology of smoking behaviour, in which smokers tend to be lumped together, despite many different patterns of smoking behaviour and consumption. Better understanding of the process of decline in lung function and rate would be helpful. At present, decline can only be identified in retrospect. Indoor air pollution is also an important and neglected environmental context in which lung function could be investigated. As a public health physician, he was concerned not to screen for conditions for which there is no effective intervention. Most events occur in people who are not at high risk, so population measures should also be considered.

It was said that statins have been shown to improve survival in patients with COPD. However, it is not known whether lung function helps to predict response.

John Frank drew attention to similar models of growth and decline, such as bone mass. What are the determinants that can be influenced via primary prevention, to increase the peak and to reduce decline. These causal factors are unlikely to be the same. Might a prolonged period of breast feeding help to reach higher peaks of lung function? Does steroid therapy in premature babies lead to poorer lung function in survivors. Should swimming be compulsory? He observed that regular swimmers are “built” in a different way from non-swimmers. What population monitoring system would let us know what we had achieved? If the age of peaks of lung function have a wide variance, cross-sectional measures will miss important information. Repeat measures are needed to understand trajectories and establish norms. The SHS, with its annual

surveys, is a step in the right direction. A better approach, however, would be to add lung function data to existing Scottish early life cohorts, such as GUS (Growing Up in Scotland, comprising two cohorts).

A crucial unanswered question is whether lung function in Scotland is improving over time. The evidence from the Twenty-07 and Scottish Health Studies is inconclusive, and confounded by changes in measurement methodology, possible improvements in performance of the tests and uncertainty concerning the representativeness of serial population samples. In the Scottish Health Survey data there are upwards trends in FEV1 which may be associated with secular trends in height (which implies that the trend is in actual FEV1 rather than height-adjusted FEV1).

David Strachan commented that when his colleagues compared the 1946 and 1958 British birth cohorts, each measured at age 43-45 years, they initially found quite a substantial improvement in both FEV1 and FVC over that 12-year birth interval, adjusting for sex, height and a range of other covariates. But after testing in detail the performance of the different spirometers, they concluded that the residual cohort difference could be explained away by technical artefacts (15)

It is possible that the wide ranging effect of respiratory impairment on premature mortality from many causes of death may account for part of the “Glasgow and Scottish Effects” which have been described, mostly on the basis of ecological data, as the component of high mortality rates in Glasgow and Scotland which are not explained by conventional risk factors (16).

It was said that gas exchange and lung function are largely separate issues. Restricted gas exchange is much more a clinical issue and is not an issue at the levels of respiratory impairment which generally occur in population studies.

Asthma was again raised as a possible confounding issue, especially in studies of younger people where it is under-diagnosed. Without bronchodilation, it is impossible to be sure who has asthma and who hasn't. Asthma is much more likely to be under-diagnosed in people under 45.

In the Copenhagen Study, 40% of smokers developed COPD compared with 8% of never smokers (17). Although COPD in smokers is usually attributed to smoking, that is clearly not the complete story. Lung function measurements could help to tease out the different types of trajectory.

It was agreed that the Chinese population seems set to repeat the epidemiology which has been observed in western populations over the last 30-40 years.

Should screened individuals with respiratory impairment be entered into rehabilitation studies? There is evidence that patients with mild COPD take less exercise, which may also influence susceptibility to coronary heart disease.

Reference was made to the Heart Protection Study in showing the importance of treating CVD risk rather than cholesterol levels per se (18). Might this justify risk scores including FEV1, even though there is no intervention to alter FEV1 directly? (i.e. in the same way that family history is included as a risk factor)

Has Pharma been influential in determining the focus on FEV1 rather than FVC? It was said that in most studies, the effects of FEV1 and FVC are similar.

The TORCH study is the only COPD intervention study with mortality as an outcome, with only 1500 patients in each arm (19). Very few outcome data are available. The effectiveness of statins is based on observational studies.

CONCLUSIONS AND RECOMMENDATIONS

The symposium was held to review the public health significance of what is known about the epidemiology of respiratory impairment, based largely on Scottish studies, but also drawing on expert and generalist knowledge.

The meeting confirmed the significance of respiratory impairment, as measured by FEV1 or by FVC, as a major predictor of disease-specific and all cause mortality in men and women, including never smokers, based on data from several Scottish cohorts.

Public health importance of lung function

The epidemiology and importance of respiratory impairment is that it affects mortality from most causes, extending far beyond its associations with respiratory disease and providing a substantial additional explanation of poor health in Scotland in general and Glasgow in particular.

It is possible that these observations account for part of the “Glasgow and Scottish Effects” which have been described, mostly on the basis of ecological data, as the component of high mortality rates in Glasgow and Scotland which are not explained by conventional risk factors.

Natural history

The natural history of lung function comprises an initial period of growth, reaching a peak in early adulthood and followed by a period of decline with age, which may be fast or slow depending on the respiratory hazards encountered. It seems likely that the initial period of growth is not specific to the lung, but is part of general body growth and development.

Despite the strength and consistency of the epidemiological signal, it is not clear what actions can be taken to maximise respiratory function or to prevent or slow subsequent decline. More research is needed, especially in non-smokers.

If the epidemiological findings concerning respiratory impairment are part of a more general phenomenon, whereby impaired body growth is associated with premature mortality, it would seem unlikely that interventions focused on the lung could substantially reverse these wider effects.

A separate issue concerns the epidemiology of airways obstruction, as measured by FEV1/FVC, including its reversible (asthmatic) and non-reversible forms. Over the course of the listed studies, atopy, hay fever and asthma have all increased in prevalence, while symptoms of COPD have declined. The symposium noted that the genetic determinants of asthma are not the same as those associated with lung function.

From an aetiological point of view, there is great interest in both the antenatal and postnatal determinants of the development of lung function in never smokers, as well as the determinants of the onset and rate of subsequent lung function decline. New or modified existing research cohorts are needed to address these questions.

What to measure ?

As measurements, FEV1 and FVC are very closely related, and are largely interchangeable in studies of non-respiratory mortality. The convention has been to use FEV1, but there is some suggestion that FVC is a better explanatory measure. However, with FVC data, there is often uncertainty as to whether the measurement has followed a full inspiration and whether expiration reached a plateau.

The convention has been to correct measurements of FEV1 to a predicted measure based on normal values observed in someone of similar age, sex and height, who has never smoked and who has no respiratory symptoms. It is possible that the correction for height loses important aetiological information, given that greater body size is itself associated with better health and longevity.

Clinical implications

It is not clear whether measurements of lung function have clinical utility. While longitudinal data are desirable in indicating whether a current measurement has been stable or dynamic over time, there is currently no sound reason why such longitudinal data should be collected except in research studies. Most of the criteria required for screening have not been met.

There is currently no clinical intervention, other than smoking cessation, which has been shown to improve lung function, or to slow the process of decline.

Measurements of FEV1 add predictive value to cardiovascular disease risk scores, but usually in people who are already at high risk with risk scores in excess of intervention thresholds. Further analyses may identify subgroups of people in which FEV1 data may have important positive or negative predictive value.

Further analyses could also determine whether FEV1 measurements might substitute for post code assessments of socio-economic deprivation, potentially removing this source of ecological fallacy from CVD risk estimation.

Public health monitoring

A crucial but unresolved question is whether lung function in Scotland is improving over time. Recent improvements in life expectancy in Scotland, as in most countries, could be due to changes in “constitution” or “resilience”, for which lung function could be an indicator, possibly reflecting influences across the life course. On the other hand, if lung function has not changed over successive generations, another explanation must be driving improvements in life expectancy.

There is a need for continued public health monitoring of lung function in Scotland by the Scottish Health Survey, to establish whether, in whom and why lung function is improving.

Research questions

There is also a need for further research to describe and explain the epidemiology of respiratory impairment, especially in non-smokers, with a view to identifying and evaluating measures to improve public health.

- Most Scottish studies have focused on FEV1 rather than *Forced Vitality Capacity*. There is evidence that FVC may be more important. Re-analyses of Scottish studies should address this issue, especially in never smokers.
- Existing datasets could be used to assess to what extent respiratory impairment is associated with *disease incidence and/or case-fatality*.
- Data from serial Scottish Health Surveys (SHeS) should be used to describe the *social patterning of lung function* in Scotland.

- Existing data could also be used to explore the *inter-relationship of height and lung function*. For example, two people might have the same % predicted FEV1, while one is short and the other tall. In general, it is better to be tall. Is it better to be tall with some respiratory impairment (<100% of predicted) or short with no respiratory impairment?
- Analyses of linked SHeS/SMR/GROS data should explore the *inter-changeability of measurements of lung function, serum cholesterol and postcode deprivation* (SIMD) in the prediction of cardiovascular risk. This work should also identify situations in which lung function measurements make a substantial difference to CVD risk.
- Existing Scottish *longitudinal studies of health in childhood and adolescence* (Growing up in Scotland) should include serial measures of lung function as these cohorts get older. Is breastfeeding associated with better long term lung growth? What is known about the determinants and timing of peak lung function?
- Studies could assess the importance of *muscular strength*, for example, as measured by grip strength, as a determinant of inspiratory and expiratory performance. Is the relatively increased inspiratory capacity acquired by swimmers associated with health benefits in later life?

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ANNEX A

LIST OF RELEVANT MIDSPAN PUBLICATIONS

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