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# THE EPIDEMIOLOGY OF RESPIRATORY IMPAIRMENT AND DISEASE IN TWO GENERATIONS OF THE RENFREW AND PAISLEY (MIDSPAN) STUDY

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## ABSTRACT

Measures of respiratory symptoms and function have been studied in two successive generations over a 25 year period, based on a larger original cohort of 15,411 men and women aged 45-64 and a subsequent family study comprising 2298 adult sons and daughters aged 30-59 from 1477 families. Poor respiratory health is a dominant feature of the original cohort, in association with high rates of socio-economic deprivation and mortality rates from all causes. Measures of chronic obstructive pulmonary disease (COPD), such as the MRC chronic bronchitis questionnaire, hospital admissions and death certification, underestimate the contribution of measured respiratory impairment to poor health and premature mortality. Cigarette smoking within families is a predictor of future ill health in family members, as shown by the associations between passive smoking and cardiorespiratory health in cohabiting adults and between maternal smoking and reduced FEV1 in adult offspring. The prevalences of chronic sputum production and cigarette smoking have fallen between the generations, while the prevalences of hay fever and atopic asthma increased. These trends and the aggregation of respiratory impairment within families provide many opportunities for further investigation.

## INTRODUCTION

The Renfrew and Paisley (MIDSPAN) Study is one the longest-running prospective population studies in the world and spans two generations of adults living in west central Scotland. Poor cardio-respiratory health has been a dominant feature of the study population and has given rise to many important and original observations. This paper provides a brief overview of the study and a review and commentary on the main respiratory findings.

## **METHODS**

### **Study populations**

The original study cohort recruited 7058 men and 8353 women aged 45-64, between 1972 and 1976, comprising 80% of the general population in this age group in the two towns of Renfrew and Paisley. The towns are adjacent to the south-west border of the city of Glasgow, within the large, post-industrial, Clydeside population, which is characterised by high levels of socio-economic deprivation and premature mortality.

The original cohort included 4064 married couples, who were contacted in 1995 either directly or via death certificate informants, to seek information on the number, dates of birth and current addresses of all natural offspring. Addresses were available for 3445 couples, of whom 2841 replied, providing the names and addresses of 4829 offspring aged 30-59, from 2365 couples with children. 3202 offspring from 1767 couples lived locally and formed the eligible population for a second study. In 1996, 1040 male and 1298 female offspring from 1477 families participated (the response rate for individuals was 73% and for families was 84%).

### **Measurements**

Both studies included comprehensive questionnaires and physical measurements, for which the methods have been described previously (1-3). Data common to both studies include assessments of cigarette smoking, responses to the MRC bronchitis and Rose chest pain questionnaires, and measurements of blood pressure, cholesterol, body mass index and electrocardiography. A large number of other variables were measured in blood

samples taken from offspring (4). Stored DNA is available for 2225 offspring and 556 surviving parents. Reported and recorded birthweights are available for 1714 and 678 offspring respectively.

Forced expiratory volume in one second (FEV1) was measured in the original cohort (5) using a Garthur Vitalograph (best of two expirations with the subject standing) and in the offspring study using a Fleisch pneumotachograph and American Thoracic Society (ATS) standards to define spirogram acceptability (6). The spirometer's calibration was checked before every session. To improve spirometric quality, technicians were given performance feedback. A total of 2294 subjects attempted spirometry of whom 2195 (96%) provided at least two ATS acceptable curves. Between-visit coefficients of variation for FEV1 and FVC were 3%.

Predicted values of FEV1 were obtained separately in each generation from linear regressions on age and height in healthy men and women who had never smoked and who did not have asthma (2,5,7).

### **Follow-up**

All participants have been followed up for all cause and disease-specific mortality, cancer incidence and hospital admissions. Deaths reported in this manuscript have been coded to ICD9.

## RESULTS

### **Baseline findings in the original cohort**

Over 80% of men in every age group had smoked at some stage of their lives. 25% were ex-smokers when studied in 1972-76, 54% women had smoked, but only 7% had stopped by the time of the study (1).

The age-related prevalence of chronic bronchitis, defined according to the MRC questionnaire, rose from 3.6% in men aged 45-49 to 8.9% in men aged 60-64. Compared with the figures for chronic bronchitis, more than twice as many men were breathless on effort while walking with people of their own age on level ground. Overall, 13.6% of men reported breathlessness and 5.9% reported symptoms of chronic bronchitis (1).

16.4% of women were breathless when walking with people of their own age on level ground, compared with 4.1% who had symptoms of chronic bronchitis. The youngest women had higher levels of breathlessness on effort compared with men (15.7% v 8.8%). The oldest men aged 60-64 had higher levels of chronic bronchitis than women at this age (8.9% v 4.4%). Otherwise, there only small gender differences in these variables. The prevalences of chronic bronchitis and breathlessness both showed strong social class gradients.

The prevalences of chronic bronchitis and other symptoms of respiratory impairment were higher than in other populations studied at the same time, including the Whitehall Study of Civil Servants, the Tecumseh Community Health Study and the WHO Collaborative Study of employed men (8). Prevalence rates in Renfrew were also higher than the prevalences observed some ten years later in rural and more affluent urban settings in Scotland (Scottish Heart Health Study, unpublished data).

FEV1 fell with age and showed strong social class gradients in men and women (1).

### **Follow-up of original cohort**

Dividing men and women separately into fifths of the distributions of observed/predicted FEV1, relative hazard ratios for mortality after 15 years were highest in the bottom quintile, not only for respiratory causes of death, but also for every other major category of death, including ischaemic heart disease, lung cancer, stroke and other causes (5). This pattern of observation persisted after excluding deaths within the first five years of follow-up, and was also found in life-long non-smokers.

Reduced FEV1 was second only to cigarette smoking (in terms of percentage population attributable risk for all cause mortality in men and women), ranking substantially higher than blood pressure, social class and cholesterol. In this study, FEV1 was the most important physical measurement for predicting premature death (4)

### **Hospital use**

Between 1972 and 1995, 79% of the cohort experienced at least one acute hospital stay, with an average of 4.6 episodes per person and a mean length of stay per episode of 11.9 days (reducing from 13.8 days in 1975 to 5.6 days in 1995). Follow-up of hospital admission data showed that disease of the respiratory system provided the principal diagnosis for 5.1% of hospital admissions. Individuals in the lowest quartile of FEV1 measurement were 27% more likely to be admitted than those in the top quartile, 50% more likely to have



a "serious" admission and 98% more likely to have a hospital admission resulting in death (9)

### **Death certificates**

In the 25 years following the initial study, 4267 men (61%) and 3746 women (45%) died (Table 1). Respiratory deaths ranked fourth in men (9.3%) after coronary heart disease, cancer and stroke, and fourth in women (8.4%) after cancer, coronary heart disease and stroke. COPD deaths comprised 49% of 397 respiratory deaths in men and 43% of 315 respiratory deaths in women.

### **Passive smoking**

The high response rates in the original study meant that there was often more than one participant per household (10). Passive smoking could be studied, therefore, on the basis of a lifelong non-smoking index case and whether the cohabitee had ever smoked or never smoked. Symptoms of breathlessness and excess sputum production were increased in passive smokers, although these findings did not reach statistical significance. Forced expiratory volume in one second, adjusted for covariates was significantly lower in passive smokers than in controls. All cause mortality was also higher in passive smokers, as were all causes of death related to smoking and mortality from lung cancer and ischaemic heart disease. A dose-response relationship was found, based on the amount of cigarettes smoked by the co-habitee.

### **Inter-generational trends**

Comparing age standardised prevalences of respiratory illness, smoking and social class at age 45-54 years, the percentage of current smokers fell between 1972-6 and 1996 from 55% in fathers to 26% in sons, and from 52% in mothers to 24% in daughters (3). The percentage with chronic sputum production fell from 24% in fathers to 14% in sons and from 13% in mothers to 7% in daughters. The

proportion of participants in non-manual occupations rose from 32% in fathers to 55% in sons, and from 47% in mothers to 77% in daughters.

In never smokers, age and sex standardised prevalences of asthma and hay fever were 3.0% and 5.8% respectively in 1972-6, rising to 8.2% and 19.9% in 1996. In ever smokers, the corresponding values were 1.6% and 5.4% in 1972-6 and 5.3% and 15.5% in 1996. In both generations, the prevalence of asthma was higher in those who reported hay fever (atopic asthma). In never smokers, reports of wheeze not labelled as asthma were about 10 times more common in 1972-76 than in 1996. With a broader definition of asthma (asthma and/or wheeze) to minimise diagnostic bias, the overall prevalence of asthma changed little. However, diagnostic bias mainly affected non-atopic asthma. Atopic asthma increased more than twofold (prevalence ratio 2.52) whereas the prevalence of non-atopic asthma did not change (1.00).

### **Effect on offspring FEV1 of parental death from COPD**

Analysis of FEV1 values for male offspring who smoked, and with a parent who had died of COPD, showed striking reductions in FEV1 compared to controls (Table 2). In cases with COPD mentioned anywhere on the death certificate, the average reduction in FEV1 in offspring was 235 ml. In cases with COPD mentioned as the underlying cause of death, the decrement was 255 ml. Confining these analyses to parental deaths under 70 gave decrements of 319 ml with any mention of COPD on the death certificate and 478 ml with COPD mentioned as the underlying cause of death.

### **Familial aggregation of FEV1**

Strict comparison and interpretation of trends in spirometric data between the two studies is not possible, because of the different measurement methods

employed. It is possible, however, to rank individuals within generation-specific distributions and to observe the nature and extent of familial aggregation of FEV1.

The prevalence of high FEV1 (a value in the top quintile) was highest (41%) in the adult offspring of parents who both had high FEV1, while the prevalence of low FEV1 (a value in the bottom quintile) was highest (37%) in the offspring of parents who both had low FEV1 (Figure 1). However, there are exceptions. 6% of the adult offspring of parents with high FEV1 had low personal values of FEV1, while 7% of the adult offspring of parents who both had low FEV1 had high personal values of FEV1. Such observations, and investigation and comparison of offspring from the different categories may help to explain why respiratory impairment runs in some families but not others, and why some individuals appear to “escape” the phenotype shared by their parents.

### **Early origins of adult disease**

An early analysis based on data from the two generations, showed an inverse relationship between maternal smoking and FEV1 in adults (11). Because FEV1 and FVC are strongly correlated, it was unclear whether the association in question reflected a link with lung volume, airflow limitation, or both. This analysis was extended, therefore, to investigate whether maternal and personal smoking synergise to increase airflow limitation (7). Residual FEV1 was estimated as an expression of FEV1 variation that was not associated with FVC. Irrespective of personal smoking, maternal smoking was inversely associated with FEV1 and FVC, and also FEV1/FVC, forced mid-expiratory flow rates and residual FEV1 in current smokers but not in never or former smokers. The clinical relevance of these findings was assessed in ever smokers without asthma: 10 cigarettes per day of maternal cigarette smoking increased prevalent COPD in offspring by 1.7

(95% confidence interval 1.2 – 2.5) after adjustment for covariates. Within families, the effect of a mother smoking 10 cigarettes per day over twenty years previously, has the same effect on airflow limitation in offspring as 10 years of personal smoking. Maternal smoking impairs lung volume irrespective of personal smoking and appears to synergise with personal smoking to increase airflow limitation and COPD.

### **FEV1 and cardiovascular risk status**

In cross-sectional analyses of the offspring generation, taller men and women had more favourable cardiovascular profiles than shorter people (12). Leg length was the component of adult height most strongly associated with cardiovascular risk. Genetic influences did not seem to underlie the height-CHD associations. However, FEV1 was more strongly associated than height with the cardiovascular risk factors examined, suggesting that it may be a better biomarker for the factors underlying associations between pre-adult exposures and adult cardiovascular disease. The findings provide indirect evidence that measures of lung development and pre-pubertal growth act as biomarkers for childhood exposures that may modify an individual's risk of developing CHD.

Current work is proceeding to assess the effect of new risk factors in explaining familial aggregation and disease risk. For example, the strength of the association between C-reactive protein (CRP) and cardiovascular disease is sufficiently consistent that a recent joint American Heart Association/Center for Disease Control statement produced guidelines for its potential incorporation into future risk factor stratification (13). In the MIDSPAN offspring, we have shown an association between CRP levels and area-based definitions of socio-economic deprivation, which is independent of known confounding factors such as age, sex, smoking status and obesity (14). It is possible that socio-economic deprivation, as

assessed by place of residence is associated with an aggregation of features which results in an increase in low-grade background systemic inflammation, indicated by an increase in the plasma concentration of CRP which is not explained by associations with smoking and body mass index.

In a separate analysis we found that after adjusting for potential confounders, there was a negative association between birthweight and CRP, whereby a 1kg increase in birth weight is associated with a 10.7% decrease in CRP (15). We have also observed an inverse relationship between levels of CRP and raw FEV1, with more than a doubling of CRP levels between the highest and lowest quartiles of FEV1 (unpublished data).

## DISCUSSION

The Renfrew and Paisley general population study is one of the longest running prospective studies of cardiorespiratory risk and disease, and is unusual in several respects, including its setting in a population with very high levels of socio-economic deprivation and premature mortality, its initial 80% coverage of this population and the inclusion of similar proportions of men and women. The setting in a single locality, combined with relatively low population mobility, has also enabled follow up studies, including a major study of adult offspring, using similar measurement methods.

The baseline established high levels of respiratory symptoms, in association with known risk factors and hazards such as cigarette smoking, short stature and poor housing and air quality.

A major finding of the study has been the importance of respiratory impairment, as measured by FEV1 and other measures of lung function, comparing observed with predicted, in determining future risk of hospital admissions and mortality, not only for respiratory diagnoses, but also all other major causes of hospital admission and death. The observation of this pattern in life-long non-smokers and in people who were free of respiratory symptoms at baseline, and after exclusion of deaths within the first five years of follow-up, all point to a general effect of respiratory impairment on population health, that is not fully captured by focusing on respiratory symptoms and diagnoses.

The pervasive effect of respiratory impairment on mortality is confirmed by the observation that the population attributable risks for all cause and for CHD mortality were higher for reduced FEV1 than for any other measurable risk factor, including blood pressure and cholesterol, and was second only to cigarette smoking in terms of overall effect.

The study shows that smoking in the home environment is harmful to other family members, not only via the cumulative effects of passive smoking on cardiorespiratory symptoms and disease, but also the long term effects on respiratory function in adult offspring.

An important feature of the MIDSPAN Family study is that the adult offspring are old enough to demonstrate expression of their predisposition and susceptibility to adverse behaviours and environments. Thus, a family history of premature parental death from COPD is seen to be associated with a substantial reduction in FEV1 in adult offspring who smoke, while a history of maternal smoking is associated with both an increased prevalence of COPD and reduction of FEV1 in adult offspring.

In general, symptoms of COPD are less prevalent in adult offspring than in the parent generation, particularly in families who smoke, suggesting improvements not only in general health, in association with increased stature and upward social mobility, but also in exposure to other respiratory hazards.

At the same time, the study shows a tripling of the prevalence of atopy, based on the changing prevalence of hay fever, and a doubling of the prevalence of asthma, in both smokers and non-smokers.

Levels of FEV1 are seen to aggregate in families, at both ends of the population distribution, but there are fascinating exceptions to the general rule, with "high" offspring of "low" parents and vice versa, which call out for further investigation and explanation.

The study confirms that FEV1, with height, may be a useful biomarker of future susceptibility to cardiovascular risk and disease, representing the combined and cumulative effects of early influences on growth and development. The observed, separate, associations between C-reactive protein levels and socio-economic deprivation, birth weight and FEV1 raise the possibility of an inflammatory basis to this early disease predisposition.

Although respiratory impairment is clearly important as a predictor of premature mortality and poor health, it is less clear whether any interventions, other than smoking cessation, can be employed to improve future outcomes. Until such measures become available, population monitoring of respiratory function may nevertheless have a useful role to play, in providing a general measure of current and future population health.



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## REFERENCES

1. Hawthorne VM Watt GCM Hart CL Hole DJ Smith GD Gillis CR Cardiorespiratory disease in men and women in urban Scotland. Baseline characteristics of the Renfrew/Paisley (MIDSPAN) study population. *Scottish Medical Journal* 1995;40:102-107
2. Watt GCM Hart CL Hole DJ Smith GD Gillis CR Hawthorne VM. Risk factors for cardiorespiratory and all cause mortality in men and women in urban Scotland : 15 year follow up *Scottish Medical Journal* 1995;40:108-112
3. Upton MN, McConnachie A, McSharry C, Hart CL, Davey Smith G, Gillis CR, Watt GCM. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *Br Med J* 2000;321:88-92.
4. (See <http://www.gla.ac.uk/faculties/medicine/midspan>)
5. Hole DJ, Watt GCM, Davey Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function in men and women : findings from the Renfrew and Paisley prospective population study. *Br Med J* 1996; 313:711-5.
6. Upton MN, Ferrell CM, Bidwell C, McConnachie A, Goodfellow J, Davey Smith G, Watt GCM. Improving the quality of spirometry in an epidemiological study. *Public Health* 2000;114:353-360.
7. Upton M N, Davey Smith G, McConnachie A, Hart C L, Watt G C M. Maternal and personal cigarette smoking synergize to increase airflow limitation in adults. *Am J Respir Crit Care Med* 2004;169:479-487.
8. Ebi-Kryston KL, Hawthorne VM, Rose G, Shipley MJ, Gillis CR, Hole DJ, Carmen W, Eshleman S, Higgins MW. Breathlessness, chronic bronchitis and reduced pulmonary function as predictors of cardiovascular disease mortality among men in England, Scotland and the United States. *Int J Epidemiol* 1989;18 (1):84-88.
9. Hanlon P Walsh D Whyte BW Scott SN Lightbody P Gilhooly MLM. Hospital use by an ageing cohort : an investigation into the association between biological, behavioural and social risk markers and

subsequent hospital utilisation. *Journal of Public Health Medicine* 1998;20:467-76

10. Hole DJ Gillis CR Chopra C Hawthorne VH. Passive smoking and cardiorespiratory health in a general population in the west of Scotland. *BMJ* 1989;299:423-7
11. Upton MN, Watt GCM, Davey Smith G, McConnachie A, Hart CL. Permanent effects of maternal smoking on offsprings' lung function. Research letter. *Lancet* 1998;352:453.
12. Gunnell D, Whitley E, Upton MN, McConnachie A, Davey Smith G, Watt GCM. Associations of height, leg length, and lung function with cardiovascular risk factors in the Midspan Family Study. *J Epidemiol Community Health* 2003;57:141-146.
13. Pearson TA Mensah GA Alexander RW Anderson JL Cannon RO Criqui M Fadl YY Fortmann SP Hong Y Myers GL Rifai N Smith SC Taubert K Tracy RP Vinicor F, Centers for Disease Control and Prevention. Markers of inflammation and cardiovascular disease : applications to clinical and public health practice : A statement from the Centers for Disease Control and Prevention and the Am Heart Association. *Circulation* 2003;107:499-511.
14. O'Reilly DSTJ Upton MN Caslake MJ Robertson M Norrie J McConnachie A Watt GCM Packard CJ. Plasma C-reactive protein concentration demonstrates a direct relationship between systemic inflammation and social deprivation. Submitted for publication.
15. Sattar N, McConnachie A, O'Reilly D, Upton M N, Greer I A, Davey Smith G, Watt G. Inverse association between birth weight and C-reactive protein concentrations in the Midspan Family Study. *Arterioscler Thromb Vasc Biol.* 2004;24:583-587.

**TABLE 1**

**Ranking of causes of death after 25 years of follow up of 7058 men and 8353 women aged 45-64 in the Renfrew and Paisley (MIDSPAN) Study**

	<b>Men</b>	<b>Women</b>
1.	Coronary heart disease (36%)	Cancer (30%)
2.	Cancer (30%)	Coronary heart disease (28%)
3.	Stroke (10%)	Stroke (15%)
4.	Respiratory (9%)	Respiratory (8%)
5.	Other (7%)	Other (9%)
6.	Other CVD (6%)	Other CVD (7%)
7.	Digestive (2%)	Digestive (3%)

TABLE 2

Decrements of FEV1 in male offspring who smoke, associated with various definitions of COPD death in a parent

Family history	Effect on FEV1 (95% CI)
COPD anywhere on the death certificate	-235 ml (-64 to -407 ml) p=0.007
COPD as first cause of death	-255 ml (+36 to -546) p=0.086
COPD anywhere on death certificate Death < 70 years	-319 ml (-2 to -636) p=0.049
COPD as first cause of death, Death < 70 years	-478 ml (-12 to -943) p=0.044

Adjusted for age, maternal smoking, pack years of personal smoking, parental social class, parental housing tenure, personal social class, personal housing tenure.

FIGURE 1

Familial aggregation of FEV

