Association between early life history of respiratory disease and morbidity and mortality in adulthood

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► Supplementary tables 1 and 2 are published online only at http://thorax.bmj.com/content/vol63/issue5

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Received 4 July 2007
Accepted 19 November 2007

ABSTRACT

Background: Early life exposure to respiratory diseases is associated with lung impairment in adulthood. The objective of this study was to investigate morbidity, and respiratory and other cause specific mortality, among people who reported a medical history of bronchitis, pneumonia and asthma early in life.

Methods: We studied an historical cohort of male students who attended Glasgow University between 1948 and 1968 and for whom long term follow-up and cause specific mortality were available (9544 students, 1553 deaths). A medical history of respiratory diseases, including bronchitis, pneumonia and asthma, along with other disease risk factors and socioeconomic conditions, were collected during university health examinations. A subsample responded to a postal follow-up in adulthood (n = 4044), which included respiratory and other chronic disease questions.

Results: A medical history of a respiratory disease (bronchitis, pneumonia and asthma) in early life was associated with a 57% greater risk of overall respiratory disease mortality in adulthood and a more than twofold increase in chronic obstructive pulmonary disease mortality (fully adjusted hazard ratio (HR) 2.37; 95% CI 1.16, 4.83). In addition, students reporting a history of bronchitis had a 38% higher risk of cardiovascular disease mortality (95% CI 1.06, 1.80). Respiratory disease in early life was also associated with a higher risk in adulthood of chronic phlegm, dyspnoea and doctor's diagnosis of asthma, bronchitis and emphysema (adjusted odds ratios ranging from 1.40 to 6.95 for these outcomes).

Conclusion: An early life history of respiratory diseases is associated with higher mortality and morbidity risk in adulthood in men, the associations being seen particularly for respiratory related and cardiovascular deaths among those with a history of bronchitis. All early life respiratory diseases appeared to be negatively associated with later adult respiratory health.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in industrialised societies.[1] Ecological and individual data studies in adults and children have all pointed to early life origins of COPD.[2 3] Furthermore, individuals with early life lung impairment are also at higher risk of cardiovascular disease (CVD), although the mechanisms that relate these conditions are unclear.[4]

Studies investigating early life associations with disease in adults are often based on recall of their past childhood illnesses with the potential for recall bias of exposures among adults suffering from respiratory diseases in adulthood.[3] Reports from parents on illnesses in their offspring are also often misclassified.[3] Follow-up studies of children have examined whether lung function in adulthood is related to early life exposures but few have sufficient long term follow-up to investigate whether and how these affect the pattern of adult disease risk.[2] Observational studies of historical cohorts can evaluate these hypotheses and report long term follow-up of cause specific disease risk. Although residual confounding due to the limitations of historically collected data can limit inferences based on these data, evaluating the specificity of associations between exposures and different causes of death can nevertheless help to identify potential confounders.

The objective of this study was to investigate whether individuals with a history of bronchitis, pneumonia or asthma in early life have a higher mortality and/or morbidity risk in adulthood in a historical cohort of male students who attended Glasgow University between 1948 and 1968. We additionally investigated whether a higher haematocrit among people with impaired lung function could explain a potential association between respiratory disease and CVD mortality.

METHODS

Detailed information on the Glasgow Alumni Cohort is available elsewhere.[5] Briefly, between 1948 and 1968, students in Glasgow University were invited to attend a health examination carried out by physicians. All data were recorded using a standard questionnaire. Information on socio-demographic characteristics, health behaviours and past medical history, including bronchitis, asthma, pneumonia and childhood diseases, were obtained. Data collected during the physical examination included measurements of height, weight, blood pressure and haemoglobin levels. A total of 11756 men, representing about 50% of the complete male student population, participated in the study. Since 1998, 84.5% (n = 9932) of the male cohort has been successfully traced through the National Health Service Central Register, which provides continuous updates on the date and cause of death for members of the cohort. Only men are included in this report because of the small number of women attending university at that time and the low number of female deaths. Students aged more than 30 years at the time of examination (n = 382) and those with an unknown date of censoring (n = 6) were excluded from these analyses, which comprised a total of 9544 students.

Between 2001 and 2002, members of the cohort who were still alive (n = 8410) were contacted through a postal questionnaire that sought to determine additional childhood and adulthood information. About 50% of the male cohort

(n = 4044) responded to this follow-up. The authors obtained ethics approval for the follow-up study and informed consent from participants.

Variable description

Every student was asked about his past medical history. Among other diseases, the physician recorded whether the student had had bronchitis, asthma, pneumonia, hay fever, eczema and/or urticaria and a number of childhood infections, including mumps, measles, rubella, chickenpox, whooping cough, scarlet fever, diphtheria and jaundice. These were ticked in the questionnaire if the student reported ever having had them. The number of childhood infections was summed and this was coded as an ordinal variable from 0 to 8. Socioeconomic position at university was assigned by coding father's occupation into social class, a five point scale from I (highest social class) to V (lowest social class), using the Registrar General's classification.[6 7] Age (years), number of siblings, whether the student was first born, height (cm), body mass index (BMI) (kg/m^2), systolic and diastolic blood pressure (mm Hg) and smoking (none versus moderate or heavy) were considered as potential confounders. Haemoglobin levels were also measured using two techniques throughout the study period (Haldane and Sahli methods) and these were analysed separately. We used the first non-missing haemoglobin value for each student (some students had haemoglobin levels measured at subsequent medical examinations). For the analysis, age specific (in years) z scores of haemoglobin levels were calculated.

Among former students who participated in the postal follow-up in 2001–2002, the following adult characteristics were obtained through a self-response questionnaire: height (cm), BMI (kg/m^2), leg length (cm), adult socioeconomic position based on the main occupation held (I to V), smoking (never versus former or current), physical activity (no exercise versus exercise long enough to work up a sweat or a rapid heart beat at least once a week), doctor's diagnosis of CVD (angina, stroke or heart attack), high cholesterol, high blood pressure, asthma, bronchitis or emphysema, cancer (lung, bowel/colon, prostate or other) and diabetes. All disease variables were coded as present or absent. The MRC Respiratory Questionnaire was used to define chronic phlegm (''Do you usually bring up phlegm in the morning on most days for as much as 3 months in winter?'') and dyspnoea, which were both coded as present or absent.[8] In addition, respondents reported their birth weight.

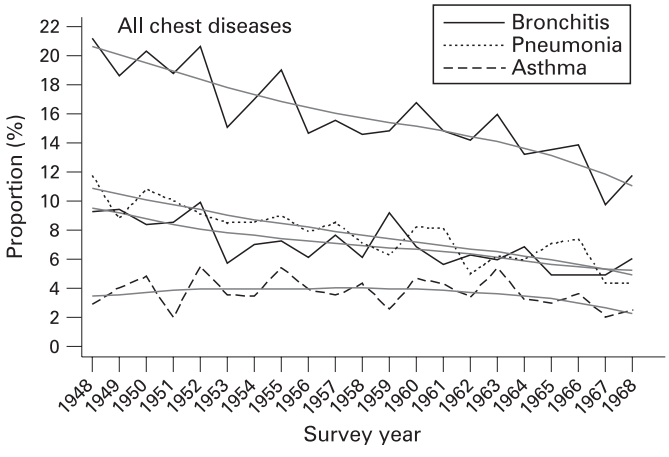

Figure 1 Proportion of students reporting a medical history of bronchitis, pneumonia and asthma at university. Glasgow Alumni Cohort, 1948–1968.

Cause specific mortality

Date for death for all causes was recorded. ICD9 and ICD10 codes were used to group cause specific mortality: respiratory disease (ICD9: 460–519; ICD10: J40–J47); COPD mortality included bronchitis and emphysema (ICD9: 490–492; ICD10: J40–J44); CVD (ICD9: 390–459; ICD10: I00–I99, G45); coronary heart disease (CHD) (ICD9: 410–414, 429.2; ICD10: I20–I25, I51.6); stroke, excluding subarachnoid haemorrhage (ICD9: 431–438; ICD10: I61–I69, G45); all cancer (ICD9: 140–208; ICD10: C00–C97); lung cancer (ICD9: 162; ICD10: C34); prostate cancer (ICD9: 185; ICD10: C61); colon cancer (ICD9:153; ICD10: C18); and external causes of death, including accidents, suicide and violence (ICD9: 800–999, E800–E999; ICD10: S00–T98, V01–Y89).

Statistical analysis

Descriptive characteristics are presented as age and year of survey (if specified) adjusted through multivariable regression analysis. A smoothed trend in the proportion of students with a medical history of bronchitis, pneumonia or asthma was obtained by calculating a locally weighted regression (lowess function in Stata) with a bandwidth of 0.8.

Cox proportional hazards models, with age as the time scale, were used to estimate the risk of overall and cause specific mortality associated with a medical history of bronchitis, asthma and pneumonia in early life, adjusting for potential confounders. The assumption of proportional hazards was graphically investigated with log–log plots and formally tested with the Schoenfeld test. If the assumption was violated because of a confounder variable, the analysis was carried out stratifying for this variable. In stratified analysis, in the context of Cox analysis, the baseline hazards are allowed to differ across the stratifying variable but the coefficient of the exposure variable is the same across strata. The main disadvantage of a stratified model is that the effect of the stratifying variable is not estimated, but its effects are controlled for without assuming proportional hazards. This was the case for smoking and CVD and CHD mortality. The assumption of proportionality was violated for respiratory disease and COPD mortality associated with a history of asthma because of a different risk in deaths occurring at a young age. Thus only those dying after the age of 50 years were considered for this specific cause of death; in this group, the proportionality assumption held. Continuous variables were centred at their mean value. Participants with missing information on confounders, such as smoking status, height, BMI and systolic blood pressure at university (n = 556), were excluded. Additional analysis adjusting for haemoglobin level—a measure of haematocrit level—was carried out to assess the hypothesis that higher haematocrit among people with impaired lung function could explain a potential association between respiratory diseases and CVD mortality.

Logistic regression analyses were carried out to quantify the association between a medical history of respiratory disease in early life and adult symptoms of chronic phlegm, dyspnoea and doctor's diagnosis of several chronic diseases among the subsample that responded to the adult postal questionnaire. Those who did not report their smoking status in adulthood (n = 28) were excluded from this analysis.

To control for potential residual confounding caused by smoking, these analyses were repeated among never smokers,

Table 1 Age and survey year adjusted early life descriptive characteristics of former students (full sample) by presence or absence of respiratory disease in early life

	Bronchitis/pneumonia/asthma				
	Yes		No		p Value
Age* (y) (n, median)	1550	19.7	7994	19.5	0.14†
⩾3 siblings (n (%))	1549	20.6	7991	21.5	0.44
Firstborn (n (%))	1528	58.0	7899	54.1	0.005
Manual father's occupation (n (%))	1494	7.3	7685	7.3	0.67
Height (cm) (n, mean)	1541	174.9	7956	174.8	0.40
Body mass index (kg/m^2) (n, mean)	1539	21.4	7951	21.6	0.01
Systolic blood pressure (mm Hg) (n, mean)	1542	130.6	7944	130.7	0.07
Diastolic blood pressure (mm Hg) (n, mean)	1540	77.6	7925	77.0	0.31
Smoking (n (%))	1478	8.6	7587	8.5	0.77
Alcohol consumption (n (%))	1329	53.4	6913	54.6	0.09
Hay fever (n (%))	1550	12.0	7994	5.3	<0.001
Eczema and/or urticaria (n (%))	1550	7.7	7994	2.7	<0.001
No of childhood infectious diseases‡ (n, mean)	1550	3.06	7994	2.87	<0.001

Glasgow Alumni Cohort, 1948–1968.
*Not adjusted for age.
†Wilcoxon rank sum test.
‡Childhood infectious diseases included mumps, measles, rubella, chickenpox, whooping cough, scarlet fever, diphtheria and jaundice.

defined as those participants who reported being non-smokers at university and also stated being never smokers in adulthood. In addition, Cox analyses were carried out separately for two periods, before and after 1960, to evaluate the influence of a potential misclassification of history of asthma on the results, as the reported history of asthma was decreasing in the Glasgow cohort after 1960 but reports from the literature were pointing to an increase in the prevalence of asthma in the population during this time period.[9]

RESULTS

The proportion of students with a medical history of bronchitis and pneumonia decreased throughout the study period whereas the proportion of those reporting asthma remained fairly constant until the beginning of the 1960s when it also declined (fig 1). Students with a medical history of bronchitis, pneumonia or asthma were more likely to be the firstborn, were slightly thinner and were more likely to have a history of hay fever, eczema and/or urticaria, and reported a higher mean number of childhood infectious diseases (table 1) compared with those who did not have a history of these respiratory ailments. Descriptive characteristics for each respiratory disease category were similar with the exception of moderate or heavy smoking which was more frequent among those who reported a past history of bronchitis. Hay fever and eczema/urticaria were more common among those who reported bronchitis or asthma but not among those who reported a past history of pneumonia.

Table 2 Age adjusted descriptive characteristics of former students who responded to the adulthood postal questionnaire, by presence or absence of respiratory disease in early life

	Bronchitis/pneumonia/asthma				
	Yes		No		p Value
Age* (y) (n, median)	564	65.8	3125	64.0	0.001†
Birth weight (g) (n, mean)	255	3530.7	1461	3517.8	0.77
Height (cm) (n, mean)	608	176.9	3381	176.4	0.09
Body mass index (kg/m^2) (n, mean)	595	25.4	3328	25.5	0.31
Leg length (cm) (n, mean)	592	75.7	3320	75.9	0.58
Adult social class I (n (%))	504	52.7	2649	52.5	0.94
Former or current smoker (n (%))	613	57.8	3403	55.5	0.29
Exercise ⩾1/week	608	68.5	3394	65.3	0.13
MRC Respiratory Questionnaire					
Chronic phlegm (n (%))	611	11.9	3392	7.6	<0.001
Dyspnoea (n (%))	576	17.2	3193	12.7	0.003
Doctor's diagnosis					
Cardiovascular disease (n (%))	584	16.4	3291	15.5	0.54
High cholesterol (n (%))	581	21.8	3283	24.9	0.23
High blood pressure (n (%))	613	32.9	3359	31.0	0.35
Asthma (n (%))	584	26.8	3255	5.0	<0.001
Bronchitis or emphysema (n (%))	580	27.6	3255	6.8	<0.001
Cancer (n (%))	566	7.9	3196	6.8	0.35
Diabetes (n (%))	608	4.2	3376	5.0	0.35

Glasgow Alumni Cohort, 2001–2002.
*Not adjusted for age.
†Wilcoxon rank sum test.

Table 3 Hazard ratio (HR) and 95% confidence interval (CI) for association between past history of respiratory diseases in early life and cause specific mortality*

	Deaths (n)	Bronchitis (HR (95% CI))	Pneumonia (HR (95% CI))	Asthma (HR (95% CI))	Any respiratory disease (HR (95% CI))
All causes	1553	1.07 (0.89, 1.28)	1.10 (0.93, 1.31)	0.91 (0.69, 1.20)	1.09 (0.96, 1.24)
Model 2†		1.05 (0.88, 1.26)	1.11 (0.93, 1.31)	0.91 (0.69, 1.21)	1.08 (0.95, 1.23)
Model 3‡		1.05 (0.87, 1.26)	1.11 (0.93, 1.31)	0.89 (0.67, 1.19)	
Respiratory	89	1.31 (0.66, 2.62)	2.27 (1.32, 3.90)	1.99 (0.87, 4.56)	1.66 (1.03, 2.67)
Model 2†		1.25 (0.63, 2.49)	2.19 (1.27, 3.77)	1.87 (0.81, 4.28)	1.57 (0.98, 2.54)
Model 3‡		1.07 (0.53, 2.18)	2.11 (1.22, 3.66)	1.65 (0.71, 3.87)	
COPD	30	1.76 (0.61, 5.05)	2.54 (1.04, 6.22)	3.16 (0.95, 10.46)	2.66 (1.31, 5.41)
Model 2†		1.59 (0.55, 4.57)	2.33 (0.95, 5.72)	2.81 (0.84, 9.37)	2.37 (1.16, 4.83)
Model 3‡		1.11 (0.37, 3.36)	2.06 (0.83, 5.16)	2.56 (0.74, 8.80)	
CVD	600	1.36 (1.05, 1.77)	0.95 (0.71, 1.26)	0.87 (0.55, 1.38)	1.14 (0.93, 1.40)
Model 2§		1.37 (1.05, 1.78)	0.97 (0.73, 1.30)	0.89 (0.56, 1.41)	1.15 (0.94, 1.41)
Model 3¶		1.38 (1.06, 1.80)	0.95 (0.71, 1.27)	0.84 (0.53, 1.33)	
CHD	399	1.25 (0.89, 1.74)	1.07 (0.76, 1.50)	0.95 (0.56, 1.63)	1.16 (0.90, 1.48)
Model 2§		1.25 (0.90, 1.75)	1.10 (0.78, 1.54)	0.98 (0.58, 1.67)	1.17 (0.91, 1.49)
Model 3¶		1.24 (0.88, 1.74)	1.08 (0.77, 1.52)	0.94 (0.55, 1.61)	
Stroke	110	1.70 (0.97, 2.98)	0.59 (0.26, 1.35)	1.05 (0.39, 2.85)	1.12 (0.70, 1.81)
Model 2†		1.68 (0.96, 2.95)	0.59 (0.26, 1.35)	1.04 (0.38, 2.82)	1.11 (0.69, 1.79)
Model 3‡		1.77 (1.00, 3.13)	0.56 (0.24, 1.27)	0.96 (0.35, 2.65)	
All cancer	550	0.76 (0.54, 1.08)	1.11 (0.83, 1.47)	0.64 (0.37, 1.11)	0.98 (0.79, 1.23)
Model 2†		0.75 (0.53, 1.07)	1.09 (0.82, 1.46)	0.64 (0.37, 1.11)	0.97 (0.77, 1.21)
Model 3‡		0.77 (0.54, 1.09)	1.13 (0.85, 1.51)	0.66 (0.38, 1.16)	

Glasgow University cohort 1948–1968
*All models adjusted for year of survey.
†Adjusted for height, body mass index, systolic blood pressure and smoking status.
‡Adjusted for all early life respiratory diseases, height, body mass index, systolic blood pressure and smoking status.
§Adjusted for height, body mass index and systolic blood pressure; stratified for smoking status.
¶Adjusted for all early life respiratory diseases, height, body mass index and systolic blood pressure; stratified for smoking status.
CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

In the subsample that replied to the adult self-reported questionnaire, those individuals who had reported a medical history of bronchitis, pneumonia or asthma at university were slightly older than those without such a medical history (table 2). A higher proportion of them reported chronic phlegm and dyspnoea, or had been given a doctor's diagnosis of asthma and bronchitis and/or emphysema. Among former students who reported asthma in early life, 71.7% reported a doctor's diagnosis of asthma whereas among those who did not have asthma in early life 5.8% reported a doctor's diagnosis of asthma ($p<0.001$). There were no differences in the proportion of other chronic diseases or risk factors such as CVD, hypertension, high cholesterol, diabetes or cancer. These characteristics were similar when each respiratory disease was analysed separately (results not shown).

During the study follow-up there were 1553 deaths (17.3%): 6.3% respiratory disease deaths, 38.6% CVD deaths, 35.4% cancer deaths, 5.3% due to external causes and 14.4% due to other causes. Overall, a history of past respiratory disease was not associated with higher all-cause mortality (table 3). There was strong evidence that a past history of pneumonia was associated with a doubling of the risk of respiratory mortality and of COPD (bronchitis, emphysema) mortality. A past history of asthma was also associated with 2.6-fold higher COPD mortality risk, but this association did not reach statistical significance at the 0.05 level. Students with a past history of bronchitis had a 38% higher risk (adjusted hazard ratio (HR) 1.38; 95% confidence interval (CI) 1.06, 1.80) of CVD mortality, which was mostly caused by death from stroke (adjusted HR 1.77; 95% CI 1.00, 3.13). This association remained the same after adjusting for haemoglobin level, a correlate of haematocrit (results not shown). A history of bronchitis, pneumonia or asthma was not associated with external causes of death, overall cancer mortality or with lung or colon cancer mortality (see supplementary table 1 online). There was evidence that students reporting pneumonia had a higher risk of prostate cancer mortality (adjusted HR 2.23; 95% CI 1.13, 4.41).

A history of bronchitis in early life was moderately associated with chronic phlegm, dyspnoea and a doctor's diagnosis of asthma, and was very strongly associated with a doctor's diagnosis of bronchitis and emphysema in adulthood (table 4). An early life history of asthma was moderately associated with later dyspnoea, and a doctor's diagnosis of bronchitis and emphysema and was very strongly associated with a doctor's diagnosis of asthma (OR 33.38; 95% CI 22.48, 49.58). These results were similar, or even stronger, among never smokers (see supplementary table 2 online).

DISCUSSION

A medical history of respiratory disease (bronchitis, pneumonia or asthma) early in life was associated with a 57% higher risk of overall respiratory disease mortality in adulthood and a more than twofold increase in mortality due to COPD among this cohort of male former students attending Glasgow University from 1948 to 1968. In addition, students reporting bronchitis in early life had a 38% higher risk of CVD mortality. Respiratory disease in early life was also related to a later higher risk of chronic phlegm, dyspnoea, doctor's diagnosis of asthma, bronchitis and emphysema. These associations remained similar or increased among never smokers and were also similar when comparing surveys carried out before or after 1960, to evaluate misclassification of asthma.

Table 4 Odds ratio (OR) and 95% confidence interval (CI) for association of past history of bronchitis, pneumonia, asthma in early life and adult self-reported outcomes and symptoms

	Total	Bronchitis (OR (95% CI))	Pneumonia (OR (95% CI))	Asthma (OR (95% CI))	Any respiratory disease (OR (95% CI))
Chronic phlegm*	3982	2.12 (1.51, 2.99)	1.13 (0.74, 1.71)	1.61 (0.96, 2.67)	1.64 (1.25, 2.16)
Model 2†		2.08 (1.48, 2.93)	1.11 (0.73, 1.68)	1.58 (0.95, 2.64)	1.63 (1.23, 2.15)
Model 3‡		1.60 (1.06, 2.43)	1.05 (0.65, 1.69)	1.32 (0.72, 2.43)	
Dyspnoea*	3750	1.48 (1.07, 2.06)	1.17 (0.83, 1.65)	1.72 (1.11, 2.66)	1.42 (1.11, 1.82)
Model 2†		1.45 (1.05, 2.02)	1.15 (0.81, 1.63)	1.68 (1.08, 2.61)	1.40 (1.10, 1.79)
Model 3‡		1.36 (0.97, 1.91)	1.06 (0.74, 1.51)	1.54 (0.98, 2.42)	
Asthma*	3823	4.19 (3.08, 5.68)	2.26 (1.60, 3.18)	39.86 (27.06, 58.71)	6.95 (5.46, 8.86)
Model 2†		4.18 (3.08, 5.68)	2.25 (1.60, 3.18)	39.84 (27.05, 58.69)	6.95 (5.46, 8.86)
Model 3‡		2.62 (1.79, 3.82)	1.36 (0.89, 2.08)	33.38 (22.48, 49.58)	
Bronchitis or emphysema*	3819	8.38 (6.37, 11.01)	1.62 (1.14, 2.30)	7.74 (5.43, 11.05)	5.25 (4.18, 6.60)
Model 2†		8.25 (6.26, 10.87)	1.59 (1.12, 2.26)	7.74 (5.41, 11.08)	5.22 (4.15, 6.56)
Model 3‡		7.07 (5.29, 9.45)	0.92 (0.62, 1.39)	5.59 (3.76, 8.30)	
CVD*	3858	1.09 (0.78, 1.52)	1.05 (0.75, 1.47)	0.96 (0.59, 1.54)	1.10 (0.86, 1.40)
Model 2†		1.06 (0.76, 1.49)	1.04 (0.74, 1.45)	0.94 (0.58, 1.51)	1.08 (0.85, 1.38)
Model 3‡		1.07 (0.76, 1.51)	1.03 (0.74, 1.45)	0.92 (0.56, 1.50)	
Cancer*	3743	1.03 (0.64, 1.67)	1.31 (0.85, 2.03)	0.58 (0.25, 1.34)	1.19 (0.86, 1.67)
Model 2†		1.03 (0.64, 1.67)	1.31 (0.85, 2.03)	0.58 (0.25, 1.34)	1.20 (0.86, 1.67)
Model 3‡		1.05 (0.64, 1.71)	1.35 (0.87, 2.11)	0.55 (0.24, 1.28)	

Glasgow Alumni Cohort, 2001–2002.
*Age adjusted.
†Adjusted for adult smoking.
‡Adjusted for all early life respiratory diseases and adult smoking.

Respiratory disease mortality

COPD is an important contributor to adult mortality and several studies suggest that early life respiratory diseases, including infections, lead to or contribute to the development of adult COPD.[2 3] Ecological studies reported high adult mortality from bronchitis and emphysema in geographical areas that had experienced high infant mortality from bronchitis and pneumonia in the past,[10] and showed that exposure to airborne infectious diseases during the first year of life was associated with higher mortality risk at ages 55–80 years.[11 12]

Individual data studies, from either children or adults, generally support the hypothesis that lung abnormalities persist from early to adult life.[2] A follow-up of the 1946 birth cohort, a prospective study in the UK, found that individuals with one or more respiratory infections before the age of 2 years had a higher prevalence of chronic cough at the age of 25 years.[13] The effect seemed particularly important in infections occurring in early infancy when the lungs are developing. Bronchitis, pneumonia and whooping cough before the age of 5 years were associated with reduced forced expiratory volume in 1 s in adulthood.[14] A follow-up of the 1958 British birth cohort found that pneumonia and whooping cough by the age of 7 years were associated with reduced ventilatory function in young adulthood.[15] The mechanism explaining reduced lung function among those who suffered pneumonia infection in childhood is most likely through failure to attain full potential lung function rather than lung function loss in adulthood.

Severe impairment of respiratory function in adulthood leads to greater mortality.[16] The increased mortality among adult asthmatics is due to deaths classified as bronchitis, emphysema and asthma[17] but the real overlap between these three diagnoses remains controversial.[2] Adult lung impairment is the result of both compromised lung development in childhood and the rate of decline of lung function throughout adulthood.[2] Thus early life respiratory diseases are likely to determine, or contribute to, greater adult mortality risk. There are, however, few studies that have collected concurrent information on childhood or early adulthood chest illnesses and which can also provide mortality risk, because of the long follow-up needed. It did not appear, from our results, that a particular early life respiratory illness was responsible for the higher adult respiratory mortality risk, suggesting that lung damage may occur with any of these exposures.

CVD mortality

Lung function in adulthood is associated with mortality due to CVD in several studies.[16 18 19] Some[20 21] but not all[22] have reported specifically higher risks of non-fatal and fatal stroke. Schanen *et al* found asthma to be an independent risk factor for incident stroke but not CHD,[23] results that were not replicated in our study in which only bronchitis was specifically associated with higher CVD and stroke mortality (not incidence). However, a history of bronchitis in early life was not associated with a doctor's diagnosis of CVD in adulthood.

One of the possible mechanisms for an increased CVD risk is exposure to infectious agents.[24] Chronic bronchitis[25] and *Chlamydia pneumonia*[26] have been related to atherogenic processes. Acute infection in childhood was associated with impaired endothelium dependent vasodilation in the ALSPAC birth cohort.[27] In the current study, we did not find a greater risk of CVD or stroke mortality among students who reported pneumonia in early life, although some of the risk associated with bronchitis may have been due to an underlying infection.

Another hypothesis proposes that higher haematocrit among people with impaired lung function explains a higher CVD mortality, although the results appear complex[28] and might be due to residual or unmeasured confounders. In our study, we did not find evidence supporting this hypothesis.

Residual confounding

Residual confounding, particularly as a result of socioeconomic conditions and smoking, could partly explain the higher respiratory and CVD mortality risk. To investigate this possibility, additional survival analyses were carried out

adjusting for father's occupational class but the associations either did not change or, for some diseases, were even strengthened (results not shown). We could not adjust for adult socioeconomic conditions but this cohort of university students is relatively socially homogenous and most have held social class occupations I or II in adulthood. Thus the likelihood of residual confounding as a result of poor socioeconomic circumstances in adulthood is likely to be small given the social characteristics of this sample.

Similarly, we could not adjust the survival analysis for adult smoking history. Students with a past history of bronchitis were more often smokers at university whereas the prevalence of smoking among those who had asthma was lower, as people with asthma tend not to smoke because of worsening of their symptoms.[29] There were no differences in smoking pattern among the subsample that responded to the adult questionnaire. In addition, as stated in the introduction, evaluating the specificity of the association between exposures and different causes of death allowed us to explore issues of residual confounding. If the association found between history of bronchitis and CVD were a result of smoking, we would have expected to find a higher mortality risk due to lung cancer among those exposed to bronchitis, since the association between tobacco and lung cancer is much stronger than that between tobacco and CVD; however, there was no evidence of an association with lung cancer, indicating that bronchitis acts through non-smoking related mechanisms. Moreover, the results were the same when the analyses were restricted to individuals who had been non-smokers at university.

The association between history of respiratory disease and symptoms and doctor's diagnosis of respiratory diseases in adulthood was not explained by residual confounding due to smoking as these associations remained present among never smokers.

Other considerations

A history of pneumonia was associated with a higher risk of prostate cancer mortality. This result is likely to be a chance finding unless it is replicated in other studies where similar information might be available. In addition, the number of deaths due to prostate cancer was small.

The main strengths of this study are its prospective nature with concurrent measurement of early life respiratory diseases, thus reducing bias as a result of adulthood recall of childhood illnesses. The long term follow-up has allowed us to evaluate specific causes of death. One of the main limitations of this study is the lack of detailed information on how the health examination was conducted at university. The little overlap between the different respiratory diseases, few students having reported more than one, suggests that care was taken to differentiate between the three diseases. Students with a history of asthma more often reported other allergic conditions, such as hay fever, eczema and/or urticaria, as would be expected, whereas those who had pneumonia did not. Most likely, bronchitis and asthma may have been difficult to tease apart, as suggested by the higher prevalence of other allergic conditions among participants reporting bronchitis. If this were the case, it could also explain the decreasing prevalence of asthma after the 1960s in this cohort, a time when it is thought to be increasing in the general population.[9] However, the results did not change when health examinations were analysed separately before and after 1960.

Under-ascertainment of early life respiratory illness remains an issue in our study as students were asked to recall symptoms from their past. However, this recall is likely to be less biased than when symptoms are recalled in later adulthood because of the shorter time between childhood and the student questionnaire and because students recalled their past symptoms without knowledge of their future adult morbidity or mortality risk. Although loss to follow-up could potentially bias our results, only if the direction of the association among those who are lost to follow-up were in the opposite direction (ie, lower respiratory disease risk among those reporting early life respiratory symptoms) would the conclusions of this work change.

Finally, since we performed a substantial number of statistical tests, some of the results with p values lower than 0.05 may have arisen by chance alone. We have pointed out the results from our study that are replicated in the literature and those where no previous reporting has occurred (eg, pneumonia and prostate cancer).

In summary, a medical history of bronchitis, pneumonia or asthma in early life is associated with a higher mortality risk due to respiratory deaths and strongly associated with higher respiratory disease morbidity in adulthood. A history of bronchitis was also associated with higher CVD risk.

Funding: The authors acknowledge the financial support of the Stroke Association; Chest, Heart and Stroke Scotland; the National Health Service Research and Development Cardiovascular Disease Programme; and the World Cancer Research Fund to carry out the Glasgow University Alumni cohort study. BG is funded by a UK Medical Research Council Fellowship in Health of the Public. PMcC is funded by a career scientist award from the Research and Development Office for Health and Personal Social Services in Northern Ireland. MJ from The Centre for Public Health Research (Massey University, Wellington, New Zealand) is supported by a Programme Grant from the Health Research Council of New Zealand. GDS holds a Robert Wood Johnson Foundation Investigators Award in Health Policy Research. The authors' work was independent of the funding sources.

Competing interests: None.

Ethics approval: yes.

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Lung alert

Pharmacogenetic basis for severe asthma exacerbations

Activation of CD23, a low affinity IgE receptor, results in downregulation of IgE-mediated immune responses. CD23 is encoded for by the Fc fragment of IgE low affinity II receptor (FCER2) gene. IgE levels may increase in children with asthma treated with inhaled corticosteroids, and this may be explained by a decrease in FCER2 expression by corticosteroids. Also, elevated IgE levels are associated with an increased risk of severe exacerbations of asthma. This study investigates whether single nucleotide polymorphisms (SNPs) in FCER2 are associated with increased severe exacerbations in patients with asthma on inhaled corticosteroids.

Three hundred and eleven children randomised to inhaled budesonide and followed up over a period of 4 years as part of the Childhood Asthma Management Program were included in the study. SNPs were identified from resequencing FCER2 genomic fragments. The primary outcome was ''severe exacerbations'', which comprised either an emergency department visit or hospitalisation for asthma. Associations between FCER2 status and 4-year log IgE levels and severe exacerbations were analysed. Subsequent confirmatory analyses of the main effects of a novel common SNP, T2206C, were analysed in white and African American subgroups. Baseline IgE levels were associated with severe exacerbations. Variations in SNPs, including T2206C, were significantly associated with increased IgE levels. The SNPs associated with increased IgE were associated with an increased risk of severe exacerbations. There was a markedly increased tendency for severe exacerbations in both white and African American subjects homozygous for the mutant T2206C allele. This association was not seen in subjects not on inhaled corticosteroids.

This interesting study suggests a possible pharmacogenetic predictor of severe exacerbations in asthma. However, the specific nature of the subject group prevents generalisation.

► Tantisira KG, Silverman ES, Mariani TJ, *et al*. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. *J Allergy Clin Immunol* 2007;**120**:1285–91

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