COPD and environmental risk factors other than smoking

8. Childhood infection

Author : P N Lee
Date : 12th November 2007

1. Papers identified

Using the procedures described in "COPD and risk factors other than smoking. 1. Identifying Relevant Papers," 40 papers were identified as relevant.

2. The papers

Given the long history of the evidence here, I felt it useful to summarize the information presented in the papers selected in chronological order. This is done below, in the form of a paragraph, usually quite short, relating to each reference.

Oswald et al (1953)[1] compared patients in London with chronic bronchitis with "comparable controls". 26.3% of cases, as against 6.3% of controls, lost time at school from respiratory infections.

In a study of UK postmen, Reid and Fairbairn (1958)[2] compared those invalided out with bronchitis and those still in service as regards attacks of bronchitis at various ages. At age 15-24, both the attack rate (122 vs 13 attacks per man-years) and the average duration of attacks (12.8 vs 2.8 days) was much higher in the bronchitics. These results were later referred to by Reid (1969)[3] in a talk entitled "The beginnings of bronchitis."

Six years later, Leeder (1975)[4] presented a review on the "Role of infection in the cause and course of chronic bronchitis and emphysema". This paper floated the idea that chronic bronchitis may arise "because repeated respiratory tract infections cause permanent damage to the airways and lead to the chronic disease", but clearly did not consider that the evidence presented represented any form of proof. He, and also Reid earlier, referred to evidence that within cohorts of British men born in 1921, 1931, 1941 and

1951, those with high childhood mortality risks from respiratory diseases had higher mortality rates from respiratory disease later in life.

In 1977, Burrows et al[5] presented results of a cross-sectional study in Tucson. There was a very strong relationship of childhood respiratory trouble to current COPD and a variety of respiratory symptoms, which was evident in never, ex- and current smokers. Further evidence from this study was presented in other papers in the same year.[6,7]

In 1983, Samet et al[8] published a review paper on "the relationship between respiratory illness in childhood and chronic airflow obstruction in adulthood". The summary states that "Relevant epidemiologic studies, however, have provided conflicting results, and many are flawed by recall bias" and notes that "A complete test of the hypothesis would require follow-up of study subjects from birth to adulthood with monitoring of respiratory infections and pulmonary function". Apart from the studies noted above,[1,2,5] Samet et al refer to a study by Harnett and Mair[9] who followed up adults who had been identified 30 years previously as prone to "catarrh" or subject to "recurrent bronchitis", finding no significant difference in respiratory symptoms or lung function from a control group. However, this study was very small. Samet et al also refer to a study by Fletcher et al[10] which reported a significant relationship of smoking-adjusted FEV_1 (but not FEV_1 slope over an 8 year follow-up) with a history of childhood bronchitis, childhood pneumonia or pleurisy.

In a general review of the epidemiology of COPD in 1984, Higgins[11] included a short section on "Infections of the respiratory tract". She cited the 1979 US Surgeon General Report[12] for the statement that "Several studies have shown that childhood respiratory illnesses may be associated with reduced lung function at older ages."

Two years later, in the British Medical Journal, Barker and Osmond[13] reported the results of ecological analyses based on mortality data for England and

Wales by region and time. Results of two types of analysis were presented, both of which led the authors to the conclusion that childhood respiratory infection is a very strong determinant of risk of chronic bronchitis in adult life. The first was a regional correlation, showing that areas of England and Wales which in 1921-5 had high infant mortality rates from bronchitis and pneumonia (and hence presumably high infection rates in those who survived), also tended in 1968-78 to have high death rates from chronic bronchitis. The second was an Osmond and Gardner analysis of death rates from chronic bronchitis and emphysema and from lung cancer, which showed that for both sexes both diseases had a similar pattern of risk by birth cohort (which they attributed to smoking), but a very different pattern of risk by period of death with no obvious trend for lung cancer but a sharp decline for bronchitis (which they attributed to reduced childhood infection and to the advent of antibiotics). At the time I felt that these analyses were of considerable interest, though the interpretation of the findings was not as straightforward as the authors indicated. For full details of my views, the interested reader is referred to Review 346 and to a letter I published in the BMJ.[14] Later analyses by my group[15] of the time trend data showed clearly that there was, in England and Wales, a steeply declining trend in mortality from COPD which clearly could not be explained by trends in smoking habits, or the introduction of the Clean Air Act in 1956, and may relate to a decrease in childhood infection.

Britten et al (1987)[16] reported results from a cohort of UK men and women born in 1946. In both men and women, lower peak flow and higher respiratory morbidity at age 36 were independently associated not only with current indices of poor social circumstance and cigarette smoking but also with poor home environment at age 2 years and lower respiratory tract illness before age 10. The authors considered that the findings provided additional evidence for a causal relation between childhood respiratory experience and adult respiratory disease.

Burrows et al (1988)[17] presented further analyses of FEV_1 from the Tucson Epidemiological Study of Airways Obstructive Disease. In non-asthmatic subjects aged 40-74, the authors note that "a history of respiratory trouble

before 16 yr of age continues to appear to increase susceptibility to smoking effects …", but "as in previous studies, the possible bias of preferential recall of childhood illnesses by impaired subjects limits interpretations of this association."

Yamagu et al (1988)[18] reported results of a cross-sectional study in Beijing in men and women aged 40+ in three areas. Multiple regression analyses showed that the prevalence of obstructive lung disease was highest in the rural area, and was significantly increased in relation to age, cigarette smoking, low SES and positive history of respiratory diseases.

Paoletti et al (1989)[19] reported results of a cross-sectional study in Italy, comparing subjects with or without childhood respiratory infections before age 12. Subjects with childhood infections had the highest prevalence of respiratory symptoms and diseases and the lowest lung function values, regardless of smoking habit.

Barker et al (1991)[20] described the results of follow-up of 5718 men in Hertfordshire, England born in 1911-1930 whose birth weights, weights at 1 year, and childhood illnesses were recorded at the time by health visitors. Bronchitis or pneumonia in infancy was associated with a significant 0.17 litre reduction in adult FEV_1 and with an increased odds ratio of respiratory symptoms in adult life independently of smoking, social class and birth weight. No association was found between FEV_1 and lower respiratory tract infection between the ages of 1 and 5 years. Deaths from COPD were determined but analyses in relation to childhood illnesses were not reported, presumably due to lack of power.

In the same year, Martyn[21], from David Barker's group in Southampton, published a book chapter entitled "Childhood infection and adult disease". The section relating to chronic lung disease summarizes the Barker and Osmond findings[13]and presents arguments why the results do suggest a causal effect of infections in childhood.

Mann et al (1992)[22] presented analyses based on a UK population born in 1946, and followed ever since, with additional information obtained from the parents and firstborn offspring of the subjects. In the population itself, lower respiratory tract problems at age 36 were best predicted by poor home environment, parental bronchitis, atmospheric pollution, childhood lower respiratory illness and later smoking.

Ding et al (1992)[23] studied 90 cases in Beijing admitted to hospital for acute lower respiratory tract infection before 7 year olds who were followed up for 24-31 years. Their siblings without such infection during childhood were the controls. The prevalence of CB in the infection group (12.2%) was significantly higher than in the control group (2.2%), with smoking and infection noted to have synergistic effects. (Based on an English abstract of an untranslated Chinese paper.)

Shaheen et al (1994)[24], also from David Barker's group, related respiratory illness documented in the first 2 years of life to the lung function of 618 men and women with a mean age of 70 years living in Derbyshire. Pneumonia before age 2 was associated with a significantly reduced FEV_1 in men and a non-significantly reduced FEV_1 in women after adjustment for smoking and asthma. Bronchitis, measles and whooping cough were not associated with diminished adult lung function.

Viegi et al (1994)[25] present further results from the Italian cross-sectional study described by Paoletti et al.[19] In these multivariate analyses, childhood respiratory infections were not independently related to chronic cough or phlegm, wheeze or dyspnoea, were positively related to asthma symptoms (but only in women), and were not related to abnormalities in lung function.

Shaheen et al (1995)[26] summarizes results from the Southampton group's studies in Hertfordshire[20] and in Derbyshire[24] considered above, concluding that the results "support a causal relationship between LRTI [lower

respiratory tract infection] in early life and subsequent COPD." Shaheen et al (1997)[27] is similar.

Silverman and Speizer (1996)[28] is a general overview paper on "Risk factors for the development of chronic obstructive pulmonary disease". The Section on "respiratory infections" covers both adult and childhood infections, summarizing some of the evidence considered above. They note that in adults acute respiratory illnesses typically are not associated with permanent loss of lung function, but "more compelling evidence links childhood respiratory illnesses to slower growth and lower maximal attained level of pulmonary function, but the definite association of childhood infection to the development of COPD remains to be proved."

Shaheen et al (1998)[29] presented results from a follow-up study in 1986 of 1070 children born in St Andrew's from 1921 to 1935 for whom information on birth weight and respiratory illnesses up to age 14 was available. Pneumonia before age 2 was associated with a significant reduction in FEV_1 and FVC after controlling for age, sex, smoking, height, and other illnesses before two years. Similar reductions were seen in men and women. Bronchitis before two years was associated with smaller deficits in FEV_1 and FVC. The authors consider that the deficits in lung function associated with pneumonia and bronchitis in the first two years of life "are consistent with a causal relation".

Johnston et al (1998)[30] describe follow-up of another British birth cohort, this time born in 1958. A history of pneumonia by age seven years was associated with a significant reduction in FEV_1 (by 102 ml) and in FVC (by 173 ml) at age 34 or 35, after adjustment for sex, age and smoking. A history of whooping cough was associated with smaller deficits, significant only for FVC. The authors note that "it remains unclear whether pneumonia causes the deficit in lung function or whether pneumonia is more common among children who have poor lung function before the disease".

Berglund et al[31] carried out a cross-sectional study in an elderly nonsmoking population in California in which a multiple logistic regression analysis included a self-reported history of childhood respiratory illness (FF 2.15, 95% CI 1.38-3.20) among the significant risk factors for obstruction on pulmonary function tests.

A review paper by Hogg in 1999[32] notes that "many epidemiological studies have implicated childhood respiratory infections as an independent risk factor for the subsequent development of persistent asthma and chronic obstructive pulmonary disease (COPD)". The possible role of viruses is discussed, but epidemiological data are not considered. Studies of the molecular mechanisms of viral infections of the airways are advocated.

Another review paper, mainly considering possible mechanisms, is by Martinez (1999)[33]. He concludes that "several lines of evidence suggest that susceptibility for both asthma and COPD may be at least in part determined very early in life, or during fetal life".

Yet another review paper (Sethi, 2000[34]) considers "bacterial infection and the pathogenesis of COPD". The long-term follow-up studies of the Southampton group[20,24,29,30] are discussed. Sethi notes that "Although the association between childhood lower respiratory tract infection and impaired lung function in adulthood is now well established, there is ongoing debate as to whether this association reflects a cause-effect relationship in which the infectious process damages a vulnerable lung undergoing rapid postnatal growth and maturation". He states that "there are several unanswered questions regarding bacterial infection in COPD that can be exciting areas of investigation".

Further results from the Italian cross-sectional study were presented by Viegi in 2000[35]. Three endpoints of COPD were considered, based on differing lung function criteria. In multiple regression analyses childhood respiratory

infections were a significant risk factor in four of the six analyses (3 criteria x 2 sexes) with odds ratios typically about 1.6.

Cerveri et al (2001)[36] reported results from a cross-sectional study in almost 18,000 subjects aged 20-44 in 35 centres in 16 countries (the European Community Respiratory Health Survey = ECRHS). Respiratory symptoms and pulmonary function were related to various risk factors including a self-reported serious respiratory infection before the age of 5 years. The prevalence of chronic bronchitis was not independently related to such infection in either sex. No analyses were presented relating infection to FEV_1, and the discussion does not refer to childhood infection at all.

Bakke (2003)[37] is a general review paper on "Factors affecting growth of FEV_1". In the section on lower respiratory tract infection, "population studies of children and adults with retrospective ascertainment of LTRI" are not reviewed as being "obviously subject to recall bias". As regards "population studies of adults with independent ascertainment of LTRI" reference is made to three studies cited above[20,29,30], Bakke concludes that "it seems clear that LTRI in childhood is related to lower lung function as an adult. However, it remains to be clarified weather (sic) the childhood pneumonia causes the observed deficit in lung function or the pneumonia occurs more frequently in children with a lower pre-morbid lung function".

Lange et al (2003)[38] reported results from the Copenhagen City Heart Study starting in 1976-1978. Multiple logistic regression included chest infections in childhood as a significant predictor of chronic bronchitis, with an odds ratio of 2.1 (95% CI 1.602.9).

De Marco et al (2004)[39] presented further results from the large ECRHS survey. In multiple regression analysis, respiratory infections in childhood were noted to be significantly and homogeneously associated with both GOLD stage 0 (at risk) and GOLD stages I+ (COPD). After adjustment for smoking,

ETS exposure, occupational exposure, SES, sex and country, the relative risk for stage I+ was estimated as 1.62 (1.24-2.12).

Marossy et al (2007)[40] used the 1958 British Birth Cohort to examine the relationship between childhood chest illness and change in FEV_1 or in FVC between age 35 and 45. Analyses were conducted separately for pneumonia, whooping cough, wheeze by age 7 years or wheeze onset by age 8 to 16 years, but no significant associations were seen. The authors conclude that "childhood chest illness does not adversely affect the rate of decline of lung function in mid-adult life". Referring back to the study of Johnston et al[30] they state that "Because it has been shown that childhood pneumonia is associated with reduced ventilatory function in the fourth decade of life, it is likely that the disease causes a reduction in the maximal attained lung function rather than an accelerated decline during adulthood or that premorbid lung function is a predisposing factor for childhood pneumonia.

3. Overall comments

It is clearly very difficult to collect together convincing evidence that the incidence of COPD, which typically occurs at age 60 or older, is causally affected by infections occurring some 50 years earlier, in childhood. However, it is a possibility that remains of interest, as it is a major interest of a number of review papers cited above[4,8,21,26,27,32-34]. Generally, these reviews conclude that the evidence is suggestive, but not conclusive.

There are a number of cross-sectional studies which generally report an association between infection in childhood and either presence of chronic bronchitis or COPD or reduced lung function[1,5-7,10,17-19,25,31,35,36] though in some studies significant relationships were not seen for all endpoints studied. One problem of studies of this type is recall bias, with people suffering from COPD, or symptoms related to it, being likely to be more ready to remember past infections.

Another approach is using ecological studies, and here the study of Barker and Osmond[13] reported that areas in England which had a high rate of mortality from childhood respiratory infection clearly tended years later also to have high rates of mortality from COPD. However, it is well known that drawing inferences from such studies is a dangerous procedure.

In principle, the best evidence comes from studies in which details of childhood infections were recorded at the time they occurred and linked to subsequent onset of COPD. There are a number of studies of this type, many conducted in the United Kingdom, where the hypothesis seems of particular interest. These can be divided into four groups:

(i) Studies of UK postmen[2,3]. Here, though a strong relationship was seen, the earliest age group for which infections were reported is 15-24, so the relevance to childhood infection is not direct.

(ii) Studies of British birth cohorts[16,22,30,40]. These are limited by the study group only being quite young (typically 35-45) at the time of the publication, so do not relate to COPD mortality.

(iii) Studies by the Barker group in Southampton who followed up populations in Hertfordshire[20], Derbyshire[24] or St Andrew's[29] in which information on infections had been recorded in childhood. While these studies were consistent in demonstrating that pneumonia in early life was a predictor of subsequent reductions in lung function, after adjustment for smoking habits, there were too few deaths from COPD in those with pneumonia in early life to study mortality.

(iv) Some other studies where populations with childhood infections had been followed up over a long period. One of these[9], which found no association with early life "catarrh" or "recurrent bronchitis" was quite small. Another[23], also quite small, in China, did find an association with acute lower respiratory tract infection in childhood.

This evidence, taken as a whole, is interesting and strongly suggestive, but still inconclusive. Possibilities of confounding seem to remain, and there are no data on the specific type of bacterium or virus involved.

4. References

1. Oswald NC, Harold JT, Martin WJ. Clinical pattern of chronic bronchitis. *Lancet* 1953;**265**:639-43.

2. Reid DD, Fairbairn AS. The natural history of chronic bronchitis. *Lancet* 1958;**1**:1147-52.

3. Reid DD. The beginnings of bronchitis. *Proceedings of the Royal Society of Medicine* 1969;**62**:311-6.

4. Leeder SR. Role of infection in the cause and course of chronic bronchitis and emphysema. *J Infect Dis* 1975;**131**:731-42.

5. Burrows B, Knudson RJ, Lebowitz MD. The relationship of childhood respiratory illness to adult obstructive airway disease. *Am Rev Respir Dis* 1977;**115**:751-60.

6. Burrows B, Lebowitz MD, Knudson RJ. Epidemiologic evidence that childhood problems predispose to airways disease in the adult (an association between adult and pediatric respiratory disorders). *Pediatr Res* 1977;**11**:218-20.

7. Lebowitz MD, Burrows B. Quantitative relationships between cigarette smoking and chronic productive cough. *Int J Epidemiol* 1977;**6**:107-13.

8. Samet JM, Tager IB, Speizer FE. The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. *Am Rev Respir Dis* 1983;**127**:508-23.

9. Harnett RWF, Mair A. Chronic bronchitis and the catarrhal child. *Scott Med J* 1963;**8**:184.

10. Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema. An eight-year study of early chronic obstructive lung disease in working men in London*. New York, Toronto: Oxford University Press; 1976.

11. Higgins M. Epidemiology of COPD: state of art. *Chest* 1984;**85(suppl 6)**:3-8S.

12. US Surgeon General. *Smoking and health. A report of the Surgeon General*. Rockville, Maryland: US Department of Health, Education, and Welfare; Public Health Service; 1979. DHEW Publication No. (PHS) 79-50066. http://www.cdc.gov/tobacco/sgr/index.htm

13. Barker DJP, Osmond C. Childhood respiratory infection and adult chronic bronchitis in England and Wales. *Br Med J* 1986;**293**:1271-5.

14. Lee PN. Childhood respiratory infection and adult chronic bronchitis in England and Wales [Letter]. *Br Med J* 1987;**294**:118.

15. Lee PN, Fry JS, Forey BA. Trends in lung cancer, chronic obstructive lung disease, and emphysema death rates for England and Wales 1941-85 and their relation to trends in cigarette smoking. *Thorax* 1990;**45**:657-65.

16. Britten N, Davies JMC, Colley JRT. Early respiratory experience and subsequent cough and peak expiratory flow rate in 36 year old men and women. *Br Med J* 1987;**294**:1317-20.

17. Burrows B, Knudson RJ, Cline MG, Lebowitz MD. A reexamination of risk factors for ventilatory impairment. *Am Rev Respir Dis* 1988;**138**:829-36.

18. Yamaguchi S, Kano K, Shimojo N, Sano K, Xu XP, Watanabe H, *et al*. Risk factors in chronic obstructive pulmonary malfunction and "chronic bronchitis" symptoms in Beijing district: a joint study between Japan and China. *J Epidemiol Community Health* 1988;**43**:1-6.

19. Paoletti P, Prediletto R, Carrozzi L, Viegi G, Di Pede F, Carmignani G, *et al*. Effects of childhood and adolescence-adulthood respiratory infections in a general population. *Eur Respir J* 1989;**2**:428-36.

20. Barker DJP, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 1991;**303**:671-5.

21. Martyn CN. Childhood infection and adult disease. *Ciba Found Symp* 1991;**156**:93-108.

22. Mann SL, Wadsworth MEJ, Colley JRT. Accumulation of factors influencing respiratory illness in members of a national birth cohort and their offspring. *J Epidemiol Community Health* 1992;**46**:286-92.

23. Ding D-J, MORE. (Follow up study of the effect of acute lower respiratory tract infection during childhood on chronic bronchitis in adults). *Zhonghua Jie He He Hu Xi Za Zhi* 1992;**15**:341-3, 379.

24. Shaheen SO, Barker DJP, Shiell AW, Crocker FJ, Weild GA, Holgate ST. The relationship between pneumonia in early childhood and impaired lung function in late adult life. *Am J Respir Crit Care Med* 1994;**149**:616-9.

25. Viegi G, Carrozzi L, Di Pede F, Baldacci S, Pedreschi M, Modena P, *et al*. Risk factors for chronic obstructive pulmonary disease in a north Italian rural area. *Eur J Epidemiol* 1994;**10**:725-31.

26. Shaheen SO, Barker DJP, Holgate ST. Do lower respiratory tract infections in early childhood cause chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 1995;**151**:1649-52.

27. Shaheen S. The beginnings of chronic airflow obstruction. *Br Med Bull* 1997;**53**:58-70.

28. Silverman EK, Speizer FE. Risk factors for the development of chronic obstructive pulmonary disease. *Med Clin North Am* 1996;**80**:501-22.

29. Shaheen SO, Sterne JAC, Tucker JS, Florey CdV. Birth weight, childhood lower respiratory tract infection, and adult lung function. *Thorax* 1998;**53**:549-53.

30. Johnston IDA, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998;**338**:581-7.

31. Berglund DJ, Abbey DE, Lebowitz MD, Knutsen SF, McDonnell WF. Respiratory symptoms and pulmonary function in an elderly nonsmoking population. *Chest* 1999;**115**:49-59.

32. Hogg JC. Childhood viral infection and the pathogenesis of asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med* 1999;**160**:S26-S28.

33. Martinez FD. Role of respiratory infection in onset of asthma and chronic obstructive pulmonary disease. *Clin Exp Allergy* 1999;**29 Suppl 2**:53-8.

34. Sethi S. Bacterial infection and the pathogenesis of COPD. *Chest* 2000;**117**:286S-91S.

35. Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci S, Carrozzi L, *et al*. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. *Chest* 2000;**117**:339S-45S.

36. Cerveri I, Accordini S, Verlato G, Corsico A, Zoia MC, Casali L, *et al*. Variations in the prevalence across countries of chronic bronchitis and smoking habits in young adults. *Eur Respir J* 2001;**18**:85-92.

37. Bakke PS. Factors affecting growth of FEV_1. *Monaldi Arch Chest Dis* 2003;**59**:103-7.

38. Lange P, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. *Age Ageing* 2003;**32**:636-42.

39. de Marco R, Accordini S, Cerveri I, Corsico A, Sunyer J, Neukirch F, *et al*. An international survey of chronic obstructive pulmonary disease in young adults according to GOLD stages. *Thorax* 2004;**59**:120-5.

40. Marossy AE, Strachan DP, Rudnicka AR, Anderson HR. Childhood chest illness and the rate of decline of adult lung function between ages 35 and 45 years. *Am J Respir Crit Care Med* 2007;**175**:355-9.