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DO CHILDHOOD RESPIRATORY INFECTIONS CONTINUE TO INFLUENCE ADULT RESPIRATORY MORBIDITY?

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Impact of the study: The impact of severe childhood respiratory infections on childhood respiratory morbidity is clear but their long term implications are still controversial. This analysis of European Community Respiratory Health Survey data provides *evidence that the effects of severe childhood respiratory infections may not only persist into adulthood but also influence development and persistence of adult respiratory morbidity*.

Key words: childhood respiratory infections, adult lung function and asthma

ABSTRACT

Objective: To examine the influence of childhood respiratory infections on adult respiratory health. **Methods:** In 1992-94, European Community Respiratory Health Survey recruited community based samples of 20-44 year old people from 48 centers in 22 countries. Study participants completed questionnaires and underwent lung function testing. On average, 8.9 years later, 28 centres re-investigated their samples using similar methods. Mixed effects models comprising an estimate for the random variation between centres were used to evaluate the relevant associations. **Results:** 9,175 participated in both studies, of which 10.9% reported serious respiratory infections before 5 years (SRI) and 2.8% reported hospitalisation for lung disease before 2 years (HDL). SRI was associated with current wheeze (OR=1.9; 95% CI=1.7-2.2), asthma (OR=2.5 95% CI 2.2-3.1), and lower FEV_1 (89ml 95% CI 54-126), lower FVC (49ml 95% CI 8-90), and FEV_1/FVC ratio (-1.2% 95% CI -1.8 to –0.6). Childhood respiratory infections were also associated with new asthma (OR 1.5 95% CI 1.03-2.0]), new wheeze (OR=1.5 95% CI 1.0-2.4), and persistent wheeze (OR 2.2 95% CI 1.4-3.6) but not with decline in lung function. Similar findings were observed for HDL. These associations were consistent across centers ($p_{heterogeneity} > 0.05$). SRI was associated with lower FEV_1 when excluding ever asthmatics and current wheezers. The impact of early infections was larger in subjects exposed to maternal ($p_{interaction}=0.09$) or active ($p_{interaction}=0.02$) smoking. **Conclusions:** The impact of childhood respiratory infections on respiratory system may not only last into adulthood but also influence development and persistence of adult respiratory morbidity. (Word count 230)

INTRODUCTION

The impact of severe childhood respiratory infections on childhood asthma and lung function is established. However, their implications on adult respiratory morbidity are still uncertain. This is mainly related to the scarcity of longitudinal studies investigating these associations beyond childhood.

A recent review suggests the host response rather than the infecting organism of childhood respiratory infections is the best predictor of consequences on respiratory health(1). Having recurrent chest illness, viral bronchiolitis, lower respiratory infections and doctor treated airway disease during first 2-3 years of age have been identified as predictors of childhood asthma (2-7), poor lung function(4, 8) and impaired lung growth (4). Some have found the association between early respiratory infections and childhood respiratory morbidity is stronger among boys(4, 8) while we found it was stronger among women (9). Only few studies have examined respiratory repercussions of early childhood respiratory infections in adults. These have found viral bronchiolitis during infancy and childhood pneumonia to be associated with respiratory symptoms and lower lung function in young adults (5, 10-14). Shaheen et al. showed that pneumonia before age two is related to lower FEV_1 in elderly men (15) Furthermore, severe childhood respiratory infections have been related to asthma commencing at any time in life (16). To date, none have examined the longitudinal change of lung function and respiratory symptoms of this high risk group of adults.

In this study, we analysed data of an 8.9-year follow-up of a cohort of adults from 28 European centers of the European Community Respiratory Health Survey (ECRHS) to

determine whether severe childhood respiratory infections predict prevalence, incidence and persistence of asthma, level of lung function and change in lung function in young adults.

METHODS

Study subjects and data collection methods

The full protocol of the ECRHS (17) can be found at www.ecrhs.org. Briefly, between 1991-93, 48 study centers in 22 countries participated in the first round of European Community Respiratory Health Survey (ECRHS 1)(17) (www.ecrhs.org), which comprised of two stages. Each participating center selected a random sample of subjects 20-44 years old from an area defined by preexisting administrative boundaries with a population at least 150,000. Where possible an up to date sampling frame was used to randomly select a minimum of 1500 men and 1500 women. These study subjects were mailed a screening questionnaire in ECRHS 1 Stage 1. Subsequently 38 centres invited a random sample and a symptomatic sample of postal survey participants of ECRHS 1 Stage 1 to take part in clinical investigations (ECRHS 1 stage 2). Subjects responded to a detailed a questionnaire including socio-demographic details, respiratory symptoms during the preceding 12 months, allergic symptoms and family history. They also performed baseline spirometry and underwent bronchial challenge with methacholine, and provided a blood sample for measurement of IgE. On average 8.9 years (inter-quartile range 8.3 to 9.5 years) later, 29 centres re-investigated the participants of the laboratory study using similar methods (ECRHS 2)(18). The present study included all the centers that participated in both surveys when examining

outcomes related to the questionnaire survey but excluded two centres when examining lung function tests. One of these did not conduct lung function tests and the other had methodological issues with the measurements of lung function.

Definitions of respiratory morbidity outcomes

Adult respiratory morbidity was defined as having ever had asthma, current wheeze, lower lung function measurements and change in asthma status and lung function measurements between ECRHS1 and ECRHS2. Participants were classified as having "current wheeze" in the cross sectional analysis if they answered yes to the question: "Have you had wheezing or whistling at any time during the last 12 months?" in the ECRHS1. "Persistent wheeze" in the longitudinal analysis was defined if they answered yes to this question in both ECRHS1 and ECRHS2. Participants were classified as having had self reported asthma in the cross sectional analysis if they answered yes to the question "Have you ever had asthma?" and new self reported asthma in the longitudinal analysis if they answered yes to this question in ECRHS2 but not in ECRHS1. Forced Expiratory Volume, Forced Vital Capacity (FVC) and the FEV1/FVC ratio were also used to assess the lung function outcomes.

Definitions of childhood infections

Exposure to childhood infections was defined using the following two questions

- ECRHS1: "Did you have a serious respiratory infection before 5 years of age?" (SRI)

- ECRHS 2: “Were you hospitalized before two years of age for lung disease?”(HLD)

Statistical Methods

The current analysis included only the subjects of the random samples who participated in both ECRHS1 and ECRHS2.

Binary measures of asthma and current wheeze (i.e. wheeze during last 12 months); self reported asthma, persistent wheeze, new current wheeze and new self report asthma were considered as outcome variables in the analysis. In addition, continuous measures of lung function; FEV_1, FVC and the ratio of FEV_1 to FVC were defined as the outcome variables. The primary exposure variables were SRI < 5 years and HLD < 2 years. Confounding effects related to age gender and social class were adjusted for in all the models and in addition height was included in models on lung function outcome measures. In addition, variables consistently associated with the exposures at $p<0.2$ were included as confounders in all the models.

Mixed effects models were used to evaluate the association between exposure and outcome variables. A linear mixed effects model was used for the lung function models and a generalized linear mixed effects model with a binomial distribution and logit link function for binary response variables was considered.

As a first step we developed crude base models (age and height adjusted for lung function outcomes) with each exposure variable. We then included confounders and retained those that made a significant contribution to the final parsimonious models. Parameter estimates from the lung function models may be interpreted as a change in

lung function with a change in each exposure variable and corresponding 95%CI. To examine whether SRI or HLD was associated with a long term decline in lung function we computed the difference between FEV_1 at ECRHS1 and ECRHS2 as the outcome. A similar measure was used for FVC and ratio of FEV to FVC. To determine whether each of the models were correctly specified the Hausman specification test was performed. Results from the binary outcome models are presented as odds ratios (OR) with 95%CI.Data were stratified by gender, current smoking, maternal smoking and maternal asthma and then tested for interactions.

Meta-analyses according to Dersimonian and Laird (19) were used to investigate potential heterogeneity between countries in the associations between childhood infections and subsequent adult respiratory morbidity.

All statistical tests were two tailed and a p value below 0.05 was considered to be statistically significant. All analyses were performed using Stata Release 8 (StataCorp. Stata Statistical Software: Release 7. College Station (TX): Stata Corporation).

RESULTS

9,175 individuals participated in both studies, of which 884 (9.6%) reported SRI <5 years of age and 224 (2.4%) reported HLD <2 years of age. 17% (n=150) of the respondents who reported a SRI <5 years of age also reported hospitalization for lung disease <2 years of age. Only 1% (64) of the respondents who reported not having had a SRI <5 years of age reported HLD <2 years of age.

Table 1 illustrates the distribution of indicators of severe childhood respiratory infections and disease outcomes of interest by country of study. There was a substantial

variation in the distribution of severe childhood respiratory infections and different asthma outcomes across countries.

Table 1: Distribution of childhood respiratory infections and asthma outcomes by country

Country (n)	SRI <5 years (%)	HLD <2 years (%)	Current wheeze %	Self reported asthma %	New* current wheeze	New* self reported asthma
Australia	14.91	10.45	35.20	16.36	13.74	4.95
Estonia	14.67	9.34	23.94	2.32	8.12	0.40
Switzerland	13.65	2.94	14.63	8.50	11.79	5.25
Norway	11.76	2.54	22.48	8.22	17.53	6.59
Germany	11.21	2.71	15.42	3.90	11.42	5.82
Iceland	11.09	3.70	17.83	6.09	14.02	6.48
Sweden	10.46	3.21	25.29	7.98	10.96	6.01
Italy	10.04	1.73	11.56	8.65	8.28	3.37
Belgium	9.73	2.04	19.91	4.08	9.20	2.30
UK	9.05	1.70	28.43	11.27	18.75	7.21
Netherland	7.48	1.32	15.13	3.95	7.75	8.22
USA	6.60	2.04	22.84	9.69	16.45	7.34
France	6.59	1.36	18.75	13.01	8.64	4.37
Spain	6.50	2.10	21.66	3.83	15.66	4.51

*New included who did not report the relevant outcome in ECRHS 1 but reported in ECRHS2

Table 2 describes the relevant participants' characteristics by indicators of severe childhood respiratory infections. Maternal smoking and maternal asthma were associated with both indicators of childhood respiratory infections. Reported history of bedroom sharing or nursery/school attendance< age 5 years, number of older siblings and personal smoking were not associated with any of the indicators of childhood respiratory infections.

Table 2: Distribution of relevant characteristics of participants by childhood respiratory infections

	SRI<5 years			HLD< 2 years		
	Yes	No	p	Yes	No	p value
Age mean (SD)	35 (0.2)	34(0.1)	0.02	33(0.4)	34 (0.1)	0.06
Gender:male %	44%	48%	0.02	44%	48%	0.2
Social class 1 & 2 %	34%	31%	0.07	31%	32%	0.6
Maternal smoking %	26%	24%	0.08	31%	24%	<0.01
Paternal smoking %	63%	65%	0.1	63%	65%	0.3
Maternal asthma %	10%	8%	<0.01	11%	7%	0.01
Paternal asthma %	9%	7%	<0.01	8%	7%	0.5
Number of older sibs (median& range)	1(0-9)	1(0-15)	0.5	1(0-6)	1 (0-15)	0.4
Shared the bedroom with any older children (%)	47%	46%	0.4	46%	43%	0.4
Attended nursery, preschool or school <5 years (%)	44%	43%	0.8	49%	46%	0.4
Atopy %	35%	33%	0.2	33%	42%	0.005
Personal smoking %						
Never	45%	42%	0.2	45%	42%	0.4
Past	21%	23%		21%	21%	
Current	44%	45%		44%	47%	
Pack years of smoking (median& range)						
Pack years in ECRHS 1	1.5(0-12)	1.2(0-11)	0.1	2.0(0-11)	1.2(0-11)	0.4
Pack years in ECRHS 2	1.9 (0-16)	1.5 (0-15)	0.4	2.5 (0-15)	1.5 (0-15)	0.4

Mixed effects models were developed to evaluate the association between indicators of childhood RI and lung function measurements (Table 3A). In a crude (age and height) adjusted mixed effects regression SRI < 5 years was significantly associated with lower FEV_1, FVC and FEV_1/FVC ratio and this remained a significant predictor of all three measures even after controlling for other confounding variables. Mixed effects regression models for HLD < 2 years showed similar findings to SRI < 5 years. In both a crude and adjusted analyses of FEV_1 and FVC, HLD < 2 years was a significant predictor of lower lung function. However, the evidence for an association between HLD <2 years and FEV1/ FVC ratio was modest. Neither SRI < 5 years nor HLD < 2 years were significantly associated with change in FEV1, FVC or ratio of FEV1 to FVC over 8.9 years.

Table 3A Association between severe respiratory infections before 5 years (SRI), hospitalisation for lung disease before 2 years (HLD) and lung function measurements: mixed effects regression model.

	Mean of the outcome	Difference in the outcome: Coefficient (standard error)	95% CI	P Value
FEV_1 – 1992				
SRI <5 years				
Yes	3.60 l			
No	3.75 l			
Crude[a]		-99 ml (19)	-137 to -61	<0.001
Adjusted[b]		-89 ml (18)	-126 to -54	<0.001
HLD < 2 years				
Yes	3.62 l			
No	3.74 l			
Crude[a]		-145 ml (35)	-214 to -76	<0.001
Adjusted[b]		-144 ml (33)	-211 to -78	<0.001
FVC – 1992				
SRI <5 years				
Yes	4.46 l			
No	4.57 l			
SRI <5 years				
Crude[a]		-57 ml (0.022)	-101 to -14	0.01
Adjusted[b]		-49 ml (0.021)	-90 to -8	0.02
HLD < 2 years				
Yes	4.45 l			
No	4.57 l			
Crude[a]		-137 ml (40)	-216 to -58	0.001
Adjusted[b]		-145 ml (38)	-220 to -70	<0.001
FEV_1/FVC – 1992				
SRI <5 years				
Yes	80.98%			
No	82.42%			
SRI <5 years				
Crude[a]		-1.185% (0.240)	-1.656 to -0.714	<0.001
Adjusted[b]		-1.191% (0.309)	-1.798 to -0.586	<0.001
HLD < 2 years				
Yes	81.39%			
No	82.31%			
Crude[a]		-0.857% (0.437)	-1.715 to 0.0002	0.05
Adjusted[b]		-0.709% (0.451)	-1.593 to 0.175	0.12

[a]controlling for age, height l: litre ml: mille litre

[b]controlling for age, height, sex, maternal smoking, maternal asthma, social class and random effects for centre.

People who were exposed to maternal smoking and had a HLD < 2 years had lower FVC compared to those who were not exposed to maternal smoking and had a HLD. Although the inclusion of an interaction term was of borderline significance (p=0.09) the mixed effects model explained 70% of the variation in FVC.

Table 4A displays crude and adjusted estimates of exposures SRI < 5 years and HLD < 2years separately, from a mixed effects regression models for asthma and wheeze. SRI < 5 years was significantly associated with an increased risk of self reported asthma, new self reported asthma, current wheeze and persistent wheeze. Similarly, there was strong evidence that HLD < 2 years was associated with self reported asthma, current wheeze and persistent wheeze. There was some evidence that SRI < 5 years and HLD < 2 years were associated with new current wheeze and HLD < 2 years was associated with new self reported asthma.

Table 4A: Association between serious respiratory infection (SRI) < 5 years, hospitalisation for lung disease (HLD) < 2 years and indicators of asthma: mixed effects regression model.

		N (% with the outcome)	Odds Ratio	95% CI	P Value
Self report asthma					
SRI <5 years	Yes	259 (22.70)			
	No	882 (77.30)			
Crude			2.61	2.22 to 3.07	<0.001
Adjusted[a]			2.53	2.14 to 3.00	<0.001
HLD < 2 years	Yes	87 (7.04)			
	No	1,149 (92.96)			
Crude			3.58	2.72 to 4.72	<0.001
Adjusted[a]			3.51	2.63 to 4.67	<0.001
New self report asthma					
SRI <5 years	Yes	62 (13.51)			
	No	397 (86.49)			
Crude			1.47	1.11 to 1.95	0.007
Adjusted[a]			1.48	1.03 to 1.85	0.03
HLD < 2 years	Yes	16 (3.29)			
	No	470 (96.71)			
Crude			1.58	0.93 to 2.68	0.09
Adjusted[a]			1.60	0.94 to 2.73	0.08
Current Wheeze					
SRI <5 years	Yes	410 (16.86)			
	No	2,022 (83.14)			
Crude			1.92	1.67 to 2.21	<0.001
Adjusted[a]			1.91	1.65 to 2.20	<0.001
HLD < 2 years	Yes	115 (4.41)			
	No	2,494 (95.59)			
Crude			1.98	1.53 to 2.55	<0.001
Adjusted[a]			1.95	1.49 to 2.54	<0.001
Persistent Wheeze					
SRI <5 years	Yes	270 (18.24)			
	No	1,210 (81.76)			
Crude			1.34	1.06 to 1.69	0.01
Adjusted[a]			1.31	1.02 to 1.66	0.03
HLD < 2 years	Yes	87 (5.39)			
	No	1,527 (94.61)			
Crude			2.11	1.35 to 3.28	0.001
Adjusted[a]			2.24	1.40 to 3.57	0.001
New Current Wheeze					
SRI <5 years	Yes	95 (10.97)			
	No	771 (89.03)			
Crude			1.21	0.96 to 1.53	0.11
Adjusted[a]			1.23	0.97 to 1.57	0.09
HLD < 2 years	Yes	28 (3.01)			
	No	903 (96.99)			
Crude			1.46	0.96 to 2.23	0.08
Adjusted[a]			1.53	0.99 to 2.36	0.05

[a]controlling for age, sex, maternal smoking, maternal asthma, social class and random effects for centre.

People who currently smoke and had a SRI<5 years were at a higher risk of having new self reported asthma in the follow-up ($p<0.001$) compared to those who do not smoke and had a SRI<5 years. The interaction term was significant ($p=0.02$).

To examine the temporality of the association, we repeated the analysis on the association between SRI and HLD on asthma, wheeze and lung function after excluding those who developed asthma before age 5 (Online repository Table 3B and Table 4B). 20% of the 1,247 who have had asthma and provided the age at first attack of asthma reported to have their first attack of asthma <5 years. The results were consistent between the analyses.

To examine the recall bias, we excluded those with self reported asthma or current wheeze in 1992 and repeated the analysis on the association between SRI, HLD and lung function in 1992 (Online repository Table 3C). Results were consistent between the two analyses.

The meta-analysis demonstrated that the associations between SRI and HLD, and respiratory outcomes were consistent across centers ($p_{heterogeneity} >0.05$) (Online repository: Figure 1 and Figure 2).

DISCUSSION

Adults reporting severe childhood respiratory infections had more asthma and wheeze, continued to wheeze, and developed more new asthma and wheeze in adult life than controls during 9 years of follow-up. Severe childhood respiratory infections were also associated with lower level of adult lung function, but were not related to lung function decline. The findings were consistent between centers with different prevalence of

childhood infections, and an association with lung function was also present when excluding all subjects with asthma and current wheeze. Childhood respiratory infections were a stronger predictor for adult respiratory morbidity among subjects exposed to maternal or active smoking.

First 3-4 years of life is a time characterised by multiplication of alveoli and growth of the bronchi (20). Our findings suggest that serious respiratory infections during this critical period of lung development may cause permanent changes making lung function suboptimal, which may be carried over to the adult life. This is in accordance with literature showing that young adults with a past history of bronchiolitis or pneumonia had lower lung function and more respiratory symptoms than those without such a history (5, 10, 11, 13, 14). It could be argued that having early respiratory infections is a marker of asthma (7). However, our subgroup analysis on lung function restricted to those who never had asthma produced similar results to the main analysis contradicting this argument. This agrees with the study of Johnston et al showing that childhood pneumonia was related to poor lung function in adults with no history of wheeze (13).

Maternal smoking was higher among those with childhood respiratory infections. The impact of HLD<2 years on FVC was greater among those whose mothers smoked. Similarly, SRI< 5 years was a significant predictor of new self reported asthma only among current smokers. These findings may suggest that further environmental insults to the lungs are likely to compound the damage already caused by respiratory infections. Such compounding effects may explain the associations between respiratory infections and impaired lung function growth in children (8), asthma starting at any time in life

(16) and development of new asthma and wheeze over the eight year follow-up in our study.

Early viral respiratory infections have been suggested to lead to allergic sensitization by three years of age and therefore to the development of asthma (21). Some suggest that atopy prone children may develop more prominent symptoms with infections, which present as serious respiratory infection (3). We observed higher prevalence of atopy defined using specific IgE levels among those who had been hospitalised for lung disease but not among those who had a serious respiratory infection before 5 years of age. Similarly, allergic sensitization in children over 7 years of age (4, 5, 7, 10) or young adults (4, 5, 7, 10) was neither related to childhood lower respiratory infections (4, 5, 7, 10) nor to doctor treated airway disease (4, 5, 7, 10).

This study has many methodological strengths. The large sample size provided sufficient power to investigate rare events such as hospitalization for lung disease and serious respiratory infections. Objective measures of respiratory morbidity were collected via lung function testing. Results can be generalised widely as the study was conducted across many countries, and the fact that the findings were consistent across centres with different prevalences of SRI and HLD strengthen the conclusion that there is an underlying biological effect.

The main limitation of the study is related to the retrospective collection of information on childhood respiratory infections. A study of adult reporting of childhood pets twice 9 years apart, showed high reliability in adult reporting of a childhood event, however, some degree of non-differential misclassification was present (22). The fact that almost

all subjects reporting hospitalisation for lung disease in ECRHS II had reported serious childhood infections 9 years earlier in ECRHS I suggest that the reporting is relatively reliable. Concerning childhood infections, on the other hand, asthmatics may recall early infections more accurately, thus causing differential misclassification and a spurious association between childhood infections and the indicators of asthma. However, our results on the association between childhood infections and adult lung function were reproduced in the analysis restricted to subjects without any history of asthma and current wheeze. Further, recall error when assessing childhood infections (SRI) in ECRHS I is unlikely to have affected reporting of subsequent onset of asthma or wheeze nine years later. Thus, it seems unlikely that the observed associations between childhood respiratory infections and measures of respiratory morbidity are entirely explained by recall bias.

Our findings have important clinical practice, public health and research implications. Clinicians as well as adults with a past history of serious childhood respiratory infections should be made aware of the possible increased risk of chronic respiratory health problems. Findings of this study highlight the importance of primary prevention of childhood respiratory infections through immunizations. Given that the adverse impact of serious childhood respiratory infections was aggravated by maternal and personal smoking, we suggest that every effort should be made to discourage parental and personal smoking among those with such a history. Further studies are required to gain better insight into the nature and mechanism of the on going alteration in airway function related to childhood respiratory infections.

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