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Do childhood respiratory infections continue to influence adult respiratory morbidity?

S.C. Dharmage*, B. Erbas*, D. Jarvis[#], M. Wjst[¶], C. Raherison[+], D. Norbäck[§], J. Heinrich[¶], J. Sunyer[ƒ,,##] and C. Svanes[¶¶]**

ABSTRACT: The aim of the present study was to examine the influence of childhood respiratory infections on adult respiratory health.

In 1992–1994, the European Community Respiratory Health Survey recruited community based samples of 20–44-yr-old people from 48 centres in 22 countries. Study participants completed questionnaires and underwent lung function testing. On average, 8.9 yrs later, 29 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.

In total, 9,175 patients participated in both studies, of whom 10.9% reported serious respiratory infections (SRI) before 5 yrs of age and 2.8% reported hospitalisation for lung disease (HLD) before 2 yrs if age. SRI was associated with current wheeze (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.7–2.2), asthma (OR 2.5, 95% CI 2.2–3.1), and lower forced expiratory volume in one second (FEV_1; 89 mL; 95% CI 54–126), forced vital capacity (FVC; 49 mL; 95% CI 8–90) and FEV_1/FVC ratio (-1.2%; 95% CI -1.8– -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 a decline in lung function. Similar findings were observed for HDL. These associations were significantly consistent across centres. SRI was associated with lower FEV_1 when excluding ever asthmatics and current wheezers. The impact of early infections was significantly larger in subjects exposed to maternal or active smoking.

The impact of childhood respiratory infections on the respiratory system may not only last into adulthood but also influence development and persistence of adult respiratory morbidity.

KEYWORDS: Adult asthma, adult lung function, childhood respiratory infections

The impact of severe childhood respiratory infections on childhood asthma and lung function has been 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 the first 2–3 yrs of age have been identified as predictors of childhood asthma [2–7], poor lung function [4, 8] and impaired lung growth [4]. Some studies have found that the association between early respiratory infections and childhood respiratory morbidity is stronger among males [4, 8], while in the current study it was found to be stronger among females [9]. Only a 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.* [15] showed that pneumonia before age 2 yrs is related to lower forced expiratory volume in one second (FEV_1) in elderly males. Furthermore, severe childhood respiratory infections have been related to asthma commencing at any time in life [16]. To

AFFILIATIONS
*The University of Melbourne, Melbourne, Australia.
[#]Imperial College, London, UK.
[¶]Helmholtz Zentrum München, Neuherberg, Germany.
[+]University of Bordeaux 2, Bordeaux, France.
[§]Uppsala University, Uppsala, Sweden.
[ƒ]Centre for Environmental Research and
**Institut Municipal d'Investigació Médica, Barcelona, and
[##]CIBER Epidemiologia y Salud Pública, Spain.
[¶¶]The University of Bergen, Bergen, Norway.

CORRESPONDENCE
S.C. Dharmage
Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, The University of Melbourne, Level 1, 723 Swanston Street, Carlton, VIC 3052
Australia
Fax: 61 93495815
E-mail: s.dharmage@unimelb.edu.au

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date, no studies have examined the longitudinal change of lung function and respiratory symptoms of this high-risk group of adults.

In the present study, data of an 8.9 yr follow-up of a cohort of adults from 28 European centres of the European Community Respiratory Health Survey (ECRHS) was analysed 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 has been published in the *European Respiratory Journal* [17]. Briefly, between 1991–1993, 48 study centres in 22 countries participated in the first round of ECRHS 1 [18], which comprised of two stages. Each participating centre selected a random sample of subjects aged 20–44 yrs from an area defined by pre-existing administrative boundaries with a population of $\geqslant$150,000. Where possible an up to date sampling frame was used to randomly select a minimum of 1,500 males and 1,500 females. These study subjects were posted a screening questionnaire in ECRHS 1 stage 1. Subsequently, 38 centres invited a random 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 sociodemographic 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 immunoglobulin (Ig)E. On average 8.9 yrs (interquartile range 8.3–9.5 yrs) after the initial investigation, 29 centres re-investigated the participants of the laboratory study using similar methods (ECRHS 2) [19]. The present study included all the centres 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 ever having asthma, current wheeze, lower lung function measurements and changes in asthma status and lung function measurements between ECRHS 1 and ECRHS 2. 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 ECRHS 1. Persistent wheeze in the longitudinal analysis was defined if participants answered yes to this question in both ECRHS 1 and ECRHS 2. 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 ECRHS 2 but not in ECRHS 1. FEV_1, forced vital capacity (FVC) and the FEV_1/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: 1) in ECRHS 1 ''Did you have a serious respiratory infection (SRI) before 5 yrs of age?'' and 2) for ECRHS 2 ''Were you hospitalised before 2 yrs of age for lung disease?''

Statistical methods

The current analysis only included the subjects of the random samples who participated in both ECRHS 1 and ECRHS 2.

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-reported asthma were considered as outcome variables in the analysis. In addition, continuous measures of lung function, FEV_1, FVC and the FEV_1/FVC ratio were defined as the outcome variables. The primary exposure variables were SRI aged $<$5 yrs and hospitalisation for lung disease (HLD) aged$<$2 yrs. Confounding effects related to age, sex and social class were adjusted for in all the models and in addition height was included in models on lung function outcome measures. Moreover, 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 generalised linear mixed effects model with a binomial distribution and logit link function for binary response variables was considered.

As a first step, crude base models (age and height adjusted for lung function outcomes) were developed with each exposure variable. Confounders were then included and those that made a significant contribution to the final parsimonious models were retained. 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% confidence interval (CI). To examine whether SRI or HLD was associated with a long-term decline in lung function the difference between FEV_1 at ECRHS 1 and ECRHS 2 was computed as the outcome. A similar measure was used for FVC and the FEV_1/FVC ratio. 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 with 95% CI. Data were stratified by sex, 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 <0.05 was considered to be statistically significant.

RESULTS

In total, 9,175 individuals participated in both studies, of which 884 (9.6%) reported SRI aged $<$5 yrs and 224 (2.4%) reported HLD aged $<$2 yrs. Overall, 150 (17%) of the respondents who reported a SRI aged $<$5 yrs also reported hospitalisation for lung disease aged $<$2 yrs. Only 64 (1%) of the respondents

who reported not having had an SRI aged <5 yrs reported HLD aged <2 yrs.

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 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 at <5 yrs of age, number of older siblings and personal smoking were not associated with any of the indicators of childhood respiratory infections.

Mixed effects models were developed to evaluate the association between indicators of childhood SRI and lung function measurements (table 3). In a crude (age and height) adjusted mixed effects regression, SRI aged <5 yrs 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 aged <2 yrs showed similar findings to SRI aged <5 yrs. In both a crude and adjusted analyses of FEV_1 and FVC, HLD aged <2 yrs was a significant predictor of lower lung function. However, the evidence for an association between HLD aged <2 yrs and FEV_1/ FVC ratio was modest. Neither SRI aged <5 yrs nor HLD aged <2 yrs were significantly associated with changes in FEV_1, FVC or the FEV_1/FVC ratio over 8.9 yrs.

People who were exposed to maternal smoking and had a HLD aged <2 yrs, had lower FVC compared with 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 4 displays crude and adjusted estimates of exposures to SRI aged <5 yrs and HLD aged <2 yrs separately, from a mixed effects regression models for asthma and wheeze. SRI aged <5 yrs 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 aged <2 yrs was associated with self-reported asthma, current wheeze and persistent wheeze. There was some evidence that SRI aged <5 yrs and HLD aged <2 yrs were associated with new current wheeze and HLD aged <2 yrs was associated with new self-reported asthma.

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

To examine the temporality of the association, the analysis on the association between SRI and HLD on asthma, wheeze and lung function was repeated after excluding those who developed asthma before 5 yrs of age (see online supplementary material table 3b and table 4b). In total, 20% of the 1,247 participants who have previously had or have asthma, reported their first attack of asthma before <5 yrs of age. The results were consistent between the analyses.

To examine the recall bias, those with self-reported asthma or current wheeze in 1992 were excluded and repeated the analysis on the association between SRI, HLD and lung function in 1992 (see online supplementary material 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

TABLE 1 Distribution of childhood respiratory infections and asthma outcomes by country

Country	SRI aged <5 yrs	HLD aged <2 yrs	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
Netherlands	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

SRI: serious respiratory infection; HLD: hospitalisation for lung disease. #: included who did not report the relevant outcome in European Community Respiratory Health Survey (ECRHS) 1 but reported in ECRHS 2.

TABLE 2 Distribution of relevant characteristics of participants by childhood respiratory infections

	SRI aged <5 yrs			HLD aged <2 yrs		
	Yes	No	p-value	Yes	No	p-value
Age yrs	35±0.2	34±0.1	0.02	33±0.4	34±0.1	0.06
Male	44	48	0.02	44	48	0.2
Social class 1 and 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 siblings	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 aged <5 yrs	44	43	0.8	49	46	0.4
Atopy	35	33	0.2	33	42	0.005
Personal smoking			0.2			0.4
Never	45	42		45	42	
Past	21	23		21	21	
Current	44	45		44	47	
Pack-yrs of smoking						
Pack-yrs in ECRHS 1	1.5 (0–12)	1.2 (0–11)	0.1	2.0 (0–11)	1.2 (0–11)	0.4
Pack-yrs in ECRHS 2	1.9 (0–16)	1.5 (0–15)	0.4	2.5 (0–15)	1.5 (0–15)	0.4

Data are presented as mean±SD, % or median (interquartile range), unless otherwise stated. SRI: serious respiratory infections; HLD: hospitalisation for lung disease; ECRHS: European Community Respiratory Health Survey.

centres ($p_{heterogeneity}$ >0.05; see online supplementary material figs 1 and 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 yrs of follow-up. Severe childhood respiratory infections were also associated with a lower level of adult lung function, but were not related to lung function decline. The findings were consistent between centres with a 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.

The first 3–4 yrs of life is a time characterised by multiplication of alveoli and growth of the bronchi [20]. The present 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 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, the current 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 by JOHNSTON *et al.* [13] showing that childhood pneumonia was related to poor lung function in adults with no history of wheeze.

Maternal smoking was higher among those with childhood respiratory infections. The impact of HLD aged <2 yrs on FVC was greater among those whose mothers smoked. Similarly, SRI aged <5 yrs 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 the development of new asthma and wheeze over the 8-yr follow-up in the present study.

Early viral respiratory infections have been suggested to lead to allergic sensitisation by 3 yrs of age and therefore to the development of asthma [21]. Some studies suggest that atopy prone children may develop more prominent symptoms with infections, which present as serious respiratory infection [3]. A 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 yrs of age was observed. Similarly, allergic sensitisation in children aged >7 yrs [4, 5, 7, 10] or young adults [4, 5, 7, 10] was related neither to childhood lower respiratory infections [4, 5, 7, 10] nor to doctor treated airway disease [4, 5, 7, 10].

TABLE 3 Association between serious respiratory infection (SRI) aged <5 yrs, hospitalisation for lung disease (HLD) at <2 yrs of age and lung function measurements in 1992: mixed effects regression model

	Mean of the outcome	Difference in the outcome	95% CI	p-value
FEV_1 mL				
SRI aged <5 yrs				
Yes	3600			
No	3750			
Crude#		-99±19	-137– -61	<0.001
Adjusted¶		-89±18	-126– -54	<0.001
HLD aged <2 yrs				
Yes	3620			
No	3740			
Crude#		-145±35	-214– -76	<0.001
Adjusted¶		-144±33	-211– -78	<0.001
FVC mL				
SRI aged <5 yrs				
Yes	4460			
No	4570			
Crude#		-57±0.022	-101– -14	0.01
Adjusted¶		-49±0.021	-90– -8	0.02
HLD aged <2 yrs				
Yes	4450			
No	4570			
Crude#		-137±40	-216– -58	0.001
Adjusted¶		-145±38	-220– -70	<0.001
FEV_1/FVC %				
SRI aged <5 yrs				
Yes	80.98			
No	82.42			
Crude#		-1.185±0.240	-1.656– -0.714	<0.001
Adjusted¶		-1.191±0.309	-1.798– -0.586	<0.001
HLD aged <2 yrs				
Yes	81.39			
No	82.31			
Crude#		-0.857±0.437	-1.715–0.0002	0.05
Adjusted¶		-0.709±0.451	-1.593–0.175	0.12

Data are expressed as coefficient±SE, unless otherwise stated. CI: confidence interval; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity. #: controlling for age and height; ¶: controlling for age, height, sex, maternal smoking, maternal asthma, social class and random effects for centre.

The current study has many methodological strengths. The large sample size provided sufficient power to investigate rare events such as HLD and SRI. 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 a different prevalence 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 adults reporting on childhood pets twice 9 yrs apart

TABLE 4 Association between serious respiratory infection (SRI) aged <5 yrs, hospitalisation for lung disease (HLD) at <2 yrs of age and indicators of asthma: mixed effects regression model

	Subjects	OR	95% CI	p-value
Self-reported asthma				
SRI aged <5 yrs				
Yes	259 (22.70)			
No	882 (77.30)			
Crude		2.61	2.22–3.07	<0.001
Adjusted#		2.53	2.14–3.00	<0.001
HLD aged <2 yrs				
Yes	87 (7.04)			
No	1149 (92.96)			
Crude		3.58	2.72–4.72	<0.001
Adjusted#		3.51	2.63–4.67	<0.001
New self-reported asthma				
SRI aged <5 yrs				
Yes	62 (13.51)			
No	397 (86.49)			
Crude		1.47	1.11–1.95	0.007
Adjusted#		1.48	1.03–1.85	0.03
HLD aged <2 yrs				
Yes	16 (3.29)			
No	470 (96.71)			
Crude		1.58	0.93–2.68	0.09
Adjusted#		1.60	0.94–2.73	0.08
Current wheeze				
SRI aged <5 yrs				
Yes	410 (16.86)			
No	2022 (83.14)			
Crude		1.92	1.67–2.21	<0.001
Adjusted#		1.91	1.65–2.20	<0.001
HLD aged <2 yrs				
Yes	115 (4.41)			
No	2494 (95.59)			
Crude		1.98	1.53–2.55	<0.001
Adjusted#		1.95	1.49–2.54	<0.001
Persistent wheeze				
SRI aged <5 yrs				
Yes	270 (18.24)			
No	1210 (81.76)			
Crude		1.34	1.06–1.69	0.01
Adjusted#		1.31	1.02–1.66	0.03
HLD aged <2 yrs				
Yes	87 (5.39)			
No	1527 (94.61)			
Crude		2.11	1.35–3.28	0.001
Adjusted#		2.24	1.40–3.57	0.001
New current wheeze				
SRI aged <5 yrs				
Yes	95 (10.97)			
No	771 (89.03)			
Crude		1.21	0.96–1.53	0.11
Adjusted#		1.23	0.97–1.57	0.09
HLD aged <2 yrs				
Yes	28 (3.01)			
No	903 (96.99)			
Crude		1.46	0.96–2.23	0.08
Adjusted#		1.53	0.99–2.36	0.05

Data are presented as n (% with the outcome), unless otherwise stated. OR: odds ratio; CI: confidence interval. #: controlling for age, sex, maternal smoking, maternal asthma, social class and random effects for centre.

showed a high reliability in adults reporting on a childhood event; however, some degree of nondifferential misclassification was present [22]. The fact that almost all subjects reporting HLD in ECRHS 2 had reported serious childhood infections 9 yrs earlier in ECRHS 1 suggest that the reporting is relatively reliable. Conversely, concerning childhood infections, asthmatics may recall early infections more accurately, thus causing differential misclassification and a spurious association between childhood infections and the indicators of asthma. However, the present 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. Furthermore, recall error when assessing childhood infections (SRI) in ECRHS 1 is unlikely to have affected reporting of subsequent onset of asthma or wheeze 9 yrs later. Thus, it seems unlikely that the observed associations between childhood respiratory infections and measures of respiratory morbidity are entirely explained by recall bias.

The current 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 the present study highlight the importance of primary prevention of childhood respiratory infections through immunisations. Given that the adverse impact of serious childhood respiratory infections was aggravated by maternal and personal smoking, the current authors 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 a better insight into the nature and mechanism of the on going alteration in airway function related to childhood respiratory infections.

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