

The Environment and Childhood Asthma (ECA) Study in Oslo: ECA-1 and ECA-2

Lødrup Carlsen KC. The Environment and Childhood Asthma (ECA) Study in Oslo: ECA-1 and ECA-2.
Pediatr Allergy Immunol 2002; 13 (Suppl. 15): 29–31.
© 2002 Blackwell Munksgaard

An observed increase in asthma admissions in Oslo during the 1980s prompted a prospective birth cohort study to ask the following question: was air pollution (outdoor and indoor) (in a broad sense) associated with asthma development in young children? During 12 months from 1 January 1992, 3,754 children (birth weight ≥ 2000 g) in Oslo were enrolled at birth into the Environment and Childhood Asthma (ECA) study and followed to 2 years of age (ECA-part I). Cord blood, a detailed questionnaire (family and pregnancy history of disease, environmental exposures, socio-economic status) completed by the mother and lung function measurements ($n = 803$) were collated at birth. Detailed questionnaires completed every 6 months for 2 years included the child's disease history, feeding habits and environmental exposures. A nested case-control study comprised 306 children with confirmed minimum two episodes of bronchial obstruction (rBO) and 306 controls (without lower respiratory tract disease) with clinical investigations (including tidal breathing lung function, beta-2 responsiveness and allergy assessment) and environmental exposure assessments (indoor and outdoor). Home dampness and low ventilation, as well as maternal smoking in pregnancy, but not outdoor air pollution increased the risk of rBO. Lung function at birth was decreased among newborns whose mother smoked during pregnancy. To understand better the early risk factors for asthma and allergy development, a follow-up study started (in 2001; ECA-part II) of all cases and controls, and those with lung function measured at birth (total 1,230 invited) (9–10 years of age). This involved clinical investigation, allergy assessments, lung function, airway hyper responsiveness measures, exhaled nitric oxide and immunological as well as allergen exposure investigations.

Karin C. Lødrup Carlsen

Department of Paediatrics, Division of Woman and Child Health, Ullevål, University Hospital, Oslo, Norway

Key words: allergy; asthma; child; environment; lung function; risk factors

Karin C. Lødrup Carlsen, MD, PhD, Department of Paediatrics, Division of Woman and Child Health, Ullevål University Hospital, University of Oslo, N-0407 Oslo, Norway
Tel.: +47 22 11 87 65
Fax: +47 22 11 86 63
E-mail: karinloedrup.carlsen@ullevaal.no

An increase in the number of hospital admissions as a result of asthma was observed throughout the 1980s in Oslo (1), raising the obvious question: why? Environmental factors were targets for suspicion at the time, and therefore we wanted to investigate possible predisposing and causative factors for asthma development, including the role of pollution. At this time, lung function measurements had become available for very young, non-sedated children (2,3). However, a large study was required to answer the hypothesis of environmental underlying causes of the suspect increase in asthma prevalence, assessing a wide range of possible contributing factors. With the new possibility of performing lung function measurements at birth in a large epidemiological set-

ting, with clinical investigations during follow-up, the Environment and Childhood Asthma (ECA) study was conceived.

The aim of the study was to determine any association (detectable) between environmental factors and the development of early childhood asthma.

The first part of the ECA study (ECA-1) was a prospective birth cohort study with a nested case-control design, running from January 1992 to September 1995, initiated by Professor Kai-Håkon Carlsen (Voksentoppen Centre) and Professor Leiv Bakketeig (National Institute of Public Health). The study was a collaboration between the Department of Paediatrics at Ullevål Hospital and the section of Epidemiology at the National Institute of Public Health, with environmental

assays performed at the section of Environmental Medicine in the same institution. Three research fellows have presented their doctoral theses from the ECA study: Karin C. Lødrup Carlsen (1995), Per Nafstad (1997), and Leif Øie (1999) (4–6).

Study design (ECA-1)

A total of 3,754 healthy newborn children were recruited at the delivery wards of the two main Oslo hospitals (Aker Hospital and Ullevål Hospital) between 1 January 1992 and 15 March 1993. Inclusion criteria were: birth weight of minimum 2,000 g; no immediate plans to move out of Norway; no serious illness which might impair respiration; no extra oxygen or assisted ventilation at 6 h of life; and sufficient language comprehension by the parents to be able to complete questionnaires (7). Cord blood was collected from all children whenever possible. At Ullevål Hospital, the 'lung function cohort' comprised 803 neonates (from the total cohort) with lung function measured [tidal flow-volume (TFV) loops and passive respiratory mechanics] at a mean age of 2.7 days, between January and November 1992 (7). Two previous (pilot) studies from our group had demonstrated that lung function had stabilized sufficiently by the second day of life (3) in awake subjects (2) to justify measurements at this time. The 'nested case control' population consisted of 306 defined children who had experienced at least two episodes (or one period for >4 weeks) of bronchial obstruction (BO) (predefined criteria) (8) before their second birthday (9). The 306 controls were the children born closest in time to a defined case, who upon inclusion (as well as by the second birthday) had not exhibited symptoms or signs of BO.

Follow-up study (total cohort)

Questionnaires were distributed every 6 months (the first time at the maternity ward) to obtain data, including: family history of atopic diseases; socio-economic factors; health of the mother during pregnancy; smoking history (during pregnancy as well as later for any family member); pets in the home; day care of the child; health of the child (respiratory, allergic, skin as well as general diseases); vaccinations; exposure to traffic; etc.

Follow-up and clinical investigations: Case-control study

Upon inclusion (as soon as possible after the second BO if <20 months of age) of most cases and some controls (mostly postponed until 2 years of age owing to the time limitation), as well as at

2 years of age, the children were invited to undertake: clinical examination; parental interview of child's diseases and environment; baseline and TFV reversibility (after salbutamol) measurements (when possible); skin-prick testing (at 2 years of age); immunoglobulin (Ig)E, IgA, IgM, serum-eosinophil cationic protein (s-ECP) analyses; and analysis of specific IgE, if a positive skin-prick test was obtained.

Environmental investigation

Environmental investigations were performed in 215 case-control pairs (10) as soon as possible after a case was defined. The environmental investigations consisted of dust sampling of various allergens from the living room, bedroom, as well as house-dust mites from the mattress and pillows of the child's bed (additionally stored for further analyses, as appropriate), description of the child's home (building characteristics, etc.), personal carried NO-analyser during 14 days, and measured and estimated area pollutant for specified periods of time (10–12).

Results

The major findings of the ECA-1 study published to date are summarized in Table 1. However, the clinical data from the 2-year follow-up are currently being analysed and will soon be available for publication.

The present report describes the number of investigations available from the ECA-1 study among the 1,233 children who will be invited to participate in the follow-up study (ECA-2), commencing enrolment during the summer of 2001. These children comprise the lung-function cohort (n = 803), as well as the 285/306 cases and 286/306

Table 1. Major findings, to date, of the Environment and Childhood Asthma-1 (ECA-1) study

1. No significant association between NO₂ and development of OAD during the first 2 years of life (12)
2. Lung function at birth (tidal flow-volume and passive respiratory mechanics) was significantly reduced (dose-response) in children exposed to tobacco smoke products *in utero* (13)
3. Risk factors at birth for OAD by 2 years of age: Reduced lung function at birth (tPTEF/tE) and maternal smoking during pregnancy (14)
4. Environmental risk factors for OAD by 2 years of age: Visible moisture damage in the home, possible association with amount of 'plastisers' (10,11,15)
5. Strong correlation between s-ECP and the degree of reversibility to salbutamol (by TFV loops) in infants (cases and controls) (8)
6. Increased s-ECP among healthy children (controls) exposed for passive tobacco smoke (16)

OAD, obstructive airways disease; s-ECP, serum eosinophil cationic protein; TFV, tidal flow volume; tPTEF/tE, ratio of time to reach peak expiratory flow to total expiratory time.

controls who attended one (163 and 242, respectively) or two (142 and 67, respectively) clinical follow-up visits.

Cord blood (CB) IgE was available for 968 children (79%) [619 (78%) of whom were from the lung-function cohort], 227 (80%) cases, and 231 (81%) controls.

Baseline TFV loops were successfully obtained for 162 (61%) cases at 2 years of age (90 of whom also provided TFV-loop data upon inclusion) and 69 at birth (13 also upon inclusion). The corresponding numbers for controls were 154 (59%) (54 also upon inclusion), and 81 at birth (six also upon inclusion). Consequently, 1,227 baseline measurements of lung function were available for analyses, 574 obtained after birth (TFV measurements) and an additional 663 (TFV and/or passive respiratory mechanics) at birth. Whereas only one baseline TFV measurement was available in 92 cases and 109 controls, 146 subjects (85 cases) had at least two baseline measurements, whereas 13 cases and six controls had baseline TFV measurements for three investigation time-points. Approximately two-thirds of all 2-year visits were performed by two (of five) investigators, both with substantial experience in TFV measurements. Successful baseline TFV measurements were obtained in 67% and repeated measurements after salbutamol inhalation (reversibility test) in 52% of the 2-year-old children assessed by these two investigators.

Blood samples were obtained by venepuncture in 241 (129 also upon inclusion) cases and 247 (59, respectively) controls, for analyses of haemoglobin, differential leucocyte count, IgE, IgM, IgG (with subclasses) and IgA, and s-ECP, as well as serum myeloperoxidase.

ECA follow-up study in Oslo: ECA-2

The main outcome variable in the ECA-1 study was recurrent or chronic BO by 2 years of age. With the present knowledge that the majority of children with wheeze during the first 3 years of life will not have later asthma, the ECA-1 outcome is clearly not sufficient to answer any hypotheses in relation to childhood asthma. Therefore, the initial analyses must be repeated when the children have reached school age and recategorized into asthma or not asthma. Only then can the main question regarding environmental factors in relation to hereditary and constitutional factors be addressed adequately. Consequently, the follow-up study of the (clinical cohorts) of the ECA study (ECA-2) in the Oslo study is commencing at present, and is expected to be completed by 2003. We hope that further follow-up studies of this

population will be possible at regular intervals throughout childhood, well into the participants' adult life.

References

1. JONASSON G, LODRUP CARLSEN KC, LEEGAARD J, CARLSEN KH, MOWINCKEL P, HALVORSEN KS. Trends in hospital admissions for childhood asthma in Oslo, Norway, 1980–95. *Allergy* 2000; 55: 232–9.
2. LODRUP KC, MOWINCKEL P, CARLSEN KH. Lung function measurements in awake compared to sleeping newborn infants. *Pediatr Pulmonol* 1992; 12: 99–104.
3. LODRUP-CARLSEN KC, CARLSEN KH. Lung function in awake healthy infants: The first five days of life. *Eur Respir J* 1993; 6: 1496–500.
4. LODRUP-CARLSEN KC. Lung function by tidal breathing in awake neonates, infants and young children. Doctoral thesis, Oslo: University of Oslo, 1995.
5. NAFSTAD P. Tobacco smoke exposure in early life. Assessment of exposure and health effects. Oslo: Section of Epidemiology, Department of Population Health Sciences, National Institute of Public Health, 1997.
6. ØIE L. The role of indoor building characteristics as exposure indicators and risk factor for development of bronchial obstruction in early childhood. Trondheim: Institutt for klima-og kuldeteknikk, Norges Teknisk-Naturvitenskapelige Universitet, 1998.
7. LODRUP CARLSEN KC, MAGNUS P, CARLSEN KH. Lung function by tidal breathing in awake healthy newborn infants. *Eur Respir J* 1994; 7: 1660–8.
8. LODRUP CARLSEN KC, HALVORSEN R, AHLSTEDT S, CARLSEN KH. Eosinophil cationic protein and tidal volume loops in children 0–2 years of age. *Eur Respir J* 1995; 8: 1148–54.
9. NAFSTAD P, KONGERUD J, BOTTEN G, HAGEN JA, JAAKKOLA JJ. The role of passive smoking in the development of bronchial obstruction during the first 2 years of life. *Epidemiology* 1997; 8: 293–7.
10. ØIE L, NAFSTAD P, BOTTEN G, MAGNUS P, JAAKKOLA JK. Ventilation in homes and bronchial obstruction in young children. *Epidemiology* 1999; 10: 294–9.
11. NAFSTAD P, ØIE L, MEHL R, et al. Residential dampness problems and symptoms and signs of bronchial obstruction in young Norwegian children. *Am J Respir Crit Care Med* 1998; 157: 410–4.
12. MAGNUS P, NAFSTAD P, ØIE L, et al. Exposure to nitrogen dioxide and the occurrence of bronchial obstruction in children below 2 years. *Int J Epidemiol* 1998; 27: 995–9.
13. LODRUP CARLSEN KC, JAAKKOLA JJ, NAFSTAD P, CARLSEN KH. *In utero* exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997; 10: 1774–9.
14. LODRUP CARLSEN KC, CARLSEN KH, NAFSTAD P, BAKKETEIG L. Perinatal risk factors for recurrent wheeze in early life. *Pediatr Allergy Immunol* 1999; 10: 89–95.
15. JAAKKOLA JJ, ØIE L, NAFSTAD P, BOTTEN G, SAMUELSEN SO, MAGNUS P. Interior surface materials in the home and the development of bronchial obstruction in young children in Oslo, Norway. *Am J Public Health* 1999; 89: 188–92.
16. LODRUP CARLSEN KC, HALVORSEN R, CARLSEN KH. Serum inflammatory markers and effects of age and tobacco smoke exposure in young non-asthmatic children. *Acta Paediatr* 1998; 87: 559–64.