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ORIGINAL ARTICLE

Effects of early intake of fruit or vegetables in relation to later asthma and allergic sensitization in school-age children

Frode NJÅ[1], Wenche NYSTAD[2], Karin C. LØDRUP CARLSEN[3], Øystein HETLEVIK[4] & Kai-Håkon CARLSEN[5]

[1]*Geilomo Children's Hospital for Asthma and Allergy, Geilo and Sandvika, Norway,* [2]*Section of Epidemiology, Department of Population Health Sciences, National Institute of Public Health, Oslo, Norway,* [3]*Department of Paediatrics, Section of Allergology and Pulmonology, Woman–Child Division, Ullevål University Hospital, Oslo, Norway,* [4]*Community GP, Odda, Norway and* [5]*Voksentoppen Research Institute and Children's National Hospital of Asthma, Allergy and Chronic Lung Diseases, University of Oslo, Oslo, Norway*

Abstract

Aim: To assess the associations between nutrition supplements in infancy and later asthma and allergy in school-age children, and to explore the impact of environmental factors in early life. *Methods:* Five hundred and two children underwent clinical examination, skin prick test and a second parentally completed questionnaire within 2 y of a cross-sectional questionnaire-based study, including 4585 primary school children (6–16 y old) in 1994 from urban Oslo (37%), the mountainous area of Hallingdal (42%), and the industrial, coastal area of Odda (21%). The children were selected from the 1994 survey on the basis of reported diagnosed asthma ($n=166$), wheeze in the last 12 mo ($n=155$) and no asthma/no wheeze ($n=181$). Questions were related to nutrition and environmental exposure in early life. Possible associations between allergic sensitization or asthma at school age and exposures were estimated by logistic regression analysis, adjusting for potential confounders. *Results:* Daily intake of fresh fruit or vegetables, but not extra vitamins or cod liver oil supplements, in infancy decreased the risk of asthma (adjusted odds ratio (aOR) 0.57 (95% confidence interval (CI): 0.37–0.88). Early supplements of cod liver oil and extra vitamins were associated with increased allergic sensitization (aOR 1.78 (95% CI: 1.03–3.07) and 1.71 (95% CI: 1.01–2.88), respectively). A significantly higher prevalence of allergic sensitization was found in children living in Hallingdal compared to Odda, while the latter children, on the other hand, had the highest prevalence of house dust mite allergy ($p=0.001$ vs Hallingdal and $p=0.04$ vs Oslo).

Conclusion: The present study suggests that the early introduction of daily fresh fruit or vegetables may decrease the risk of asthma after 1 y of life, whereas allergic sensitization at school age seemed to increase with extra vitamin and cod liver oil supplements during infancy. Living area influenced allergic sensitization, with differences between coastal and inland areas.

Key Words: *Asthma, allergy, environmental exposure, fresh fruit, vitamin supplements*

Introduction

Potential risk factors for asthma and allergy may be classified as either host or environmental factors. Host factors such as gender, race, and genetic predisposition to atopy and airway hyperresponsiveness are definitive or can often be measured relatively easily. Environmental factors that influence susceptible individuals to develop disease are, however, often complex, rendering measurements of exposure difficult.

Nutrition, both in early life and later, is debated as a possible factor that may influence asthma and allergy development and probably modulate further disease development.

Potential risk factors for asthma are sensitization to indoor and outdoor allergens, second-hand smoke (SHS), moisture-damaged houses and air pollution, respiratory tract infections, socio-economic status, family size, diet and drugs, and obesity [1]. It is claimed

Correspondence: F. Njå, Malmskrivervn. 27, NO-1337 Sandvika, Norway. Fax: +47 67 56 43 59. E-mail: fnja@online.no

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that sensitization to indoor allergens is most strongly associated with asthma [2]. However, allergen exposure varies according to geographical locations and variation in climate. Several of the factors mentioned above are also considered to influence the risk of allergic sensitization. These are air pollution [3], respiratory tract infections [4] and family size [5], whereas others, such as for example SHS, are debated in this respect [6,7], and some may even protect against allergy, such as nutritional supplements [8,9]. The "hygiene hypothesis" is proposed to be partly involved in the rise of allergic diseases, with bacterial deprivation as a proposed risk factor [10].

Reactive oxygen species have been implicated as a causative of airway inflammation, and reduced levels of antioxidant vitamins are found in the serum of children with bronchial asthma [11] and in the induced sputum of adult asthmatics [12]. Low intake of fruit rich in vitamin C in children has been associated with respiratory symptoms such as cough and wheeze [13]. We therefore hypothesized that early introduction of fresh fruit or vegetables might protect against asthma and allergic sensitization later in childhood.

The main aim of the present study was to investigate whether nutritional factors in the first year of life influenced the risk of asthma and allergic sensitization in school-age children, and secondary aims were to assess the role of exposure to local environmental factors.

Patients and methods

The present study is based upon a cross-sectional survey performed in 1994 of 4585 schoolchildren, aged 6–16 y, living in urban Oslo, a mountainous area in Hallingdal, and the industrial, coastal area of Odda, using the questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC) [14]. Recruitment to the study in Oslo consisted of all children in a random sample of school classes ($n=2577$), whereas all school children in Hallingdal ($n=1177$) and Odda ($n=831$) participated. A second questionnaire was sent to all children who had answered and returned the first questionnaire (the ISAAC questionnaire). This follow-up questionnaire, completed by the parents or guardians, was directed towards family history of atopic diseases, indoor environmental factors, prenatal exposure to SHS, breastfeeding and consumption of fresh fruit or vegetables, and extra vitamins and the use of cod liver oil supplements.

Based on the first questionnaire, three groups of children were further contacted for clinical examinations. The inclusion criteria were: (a) parentally reported doctor-diagnosed asthma—wheeze last 12 mo or no wheeze or asthma symptoms for the asthma group, wheeze group and control group, respectively; (b) willingness to participate in the present follow-up study; (c) attending 1st to 9th grade (6–16 y of age) in 1994–1995. Exclusion criteria: children with uncompleted follow-up questionnaires were excluded.

The present study, with clinical examinations and skin prick test, was performed within 1 to 2 y following the original 1994 survey [14]. In the asthma and wheeze groups, all children from Hallingdal and Odda participated, whereas children from Oslo were randomly selected to the two groups, if eligible. The sampling probability in the asthma group and in the wheeze group in Oslo was 0.66 and 0.58, respectively. The control group comprised randomly selected children from all areas in whom no wheeze or no asthma was reported. The sampling probability for controls was 0.04, 0.11 and 0.10 in Oslo, Hallingdal and Odda, respectively. The geographical distribution of the three groups is shown in Table I. The asthma group consisted of 209 children initially invited for further

Table I. Demographic data and results of skin prick test (SPT) in the study population.

	Oslo	Hallingdal	Odda	*p*
Area distribution ($n=502$)	186	210	106	
Age, mean (SD)[a]	12.4 (2.7)	13.1 (2.6)⋆	12.3 (2.4)	0.008 vs Odda, 0.002 vs Oslo
Gender; male (%)	51	45	53	n.s.
Asthma/wheeze/control group ($n=502$)	66/56/64	68/67/75	32/32/42	
Body mass index (SD)	18.5 (2.5)⋆	20.3 (3.3)	20.2 (4.1)	$p<0.001$
Positive SPT, *n* (%)	72 (39)	101 (48)⋆	34 (32)	0.007 vs Odda
HDM positive SPT, *n* (%)	8 (4.3)	4 (1.9)	11 (10.4)⋆	0.001 vs Hallingdal, 0.04 vs Oslo
Mould positive SPT, *n* (%)	4 (2.2)	3 (1.4)	0	
Pollen[b] positive SPT, *n* (%)	62 (33.3)	85 (40.5)⋆	26 (24.5)	0.005 vs Odda
Pet[c] positive SPT, *n* (%)	42 (22.6)	67 (31.9)⋆	23 (21.7)	0.038 vs Oslo
Food[d] positive SPT, *n* (%)	8 (4.3)	2 (1.0)	2 (1.9)	

[a] Age at the time of clinical examination.
[b] Pollen includes birch, timothy and mugwort.
[c] Pet includes dog and cat.
[d] Food: egg and cow's milk.
⋆ indicates statistical significance.

investigations, of whom 196 responded and 166 (79%) were eligible with complete data. The corresponding numbers of children in the wheeze group and control group were 186/166/155 (83%) and 248/209/181 (73%), respectively.

Clinical tests included skin prick test (SPT) performed out of the pollen season in all participating children, of whom 502 (88%) were eligible with completed questionnaires and thus enrolled into the present study.

In the asthma group, 134/166 (81%) reported symptoms within the last 12 mo. At the time of the clinical investigations, the children in Hallingdal were 1 y older (mean) than in Oslo and Odda, whereas mean body mass index (BMI, defined as height/weight^2) was lower in Oslo than in the other regions ($p < 0.001$) (Table I). Gender, parental asthma, and/or rhinoconjunctivitis and/or atopic dermatitis did not differ between the groups.

The regional medical ethics committee approved the present study, and signed, informed consent was obtained from the child and his/her parents or guardians prior to inclusion in the sample population.

Outcome variable

The diagnosis of asthma was applied as reported by the parents or guardians in the first survey as a positive response to the question "Has the child been treated by a doctor or admitted to hospital for asthma?" (Odda and Hallingdal) or as a positive answer to the question "Does the child still have asthma?" (Oslo). Regarding the analysis of early intake of fresh fruit or vegetables, vitamin supplements and cod liver oil, children whose parents reported asthma during the first year of life were excluded ($n = 17$).

Skin prick test (SPT) was performed according to the Nordic guidelines (15), using the following nine allergens: house dust mite (HDM) (*Dermatophagoides pteronyssinus*), mould (*Cladosporium herbarum*), animal dander (dog and cat), birch pollen, timothy pollen, mugwort pollen, cow's milk and hen's egg (Soluprick, ALK, Copenhagen, Denmark). A histamine dihydrochloride solution (10 mg/ml) was used as a positive control, and the allergen diluent as a negative control. Weal size was measured after 15 min, and the histamine-induced weal recorded as half the sum of the largest plus the perpendicular diameter. A weal size corresponding to the histamine weal size was considered to be 3+; weals of half of that size were given the value 2+. A subject was considered sensitized if at least one allergen was $\geqslant 2+$.

The SPT results are shown by area in Table I.

Exposures

Intake of fresh fruit or vegetables was reported in the second questionnaire as daily, 4–6 times/wk, 1–3 times/wk and less than once per week. In the analyses, daily intake was analysed versus intake less often than daily. Consumption was divided into checkboxes representing different age categories: 0–11 mo, 1–2 y, 3–4 y, 5–6 y and at school age. Neither the exact month of life when the intake started during the first year of life nor further quantification of the intake was reported. In the main analysis, the exposure 0–11 mo was used, but in a subanalysis the interval 1–2 y was also applied. Breastfeeding was reported by months; the mean period was 8.9 mo, and 95.2% of the mothers breastfed for at least 3 mo. Extra vitamin and cod liver oil supplements were reported in relation to the same age groups, and the exposure 0–11 mo applied.

Indoor environmental exposures, such as exposure to SHS (maternal indoor smoking), allergens (keeping dogs or cats), moisture damage and window pane condensation were also reported in relation to age, and exposure during the age category 0–11 mo was applied in the analysis. Possible pollution related to outdoor exposures was categorically reported and included in analyses as the area of living: Oslo representing urban living, Odda a small, industrial, coastal town, and Hallingdal a non-polluted, high-altitude environment. The variables are shown in Table II, as reported in the first year of life.

Other variables

Parental atopy was defined as positive if at least one of the parents reported asthma, rhinoconjunctivitis and/or atopic dermatitis. Parent education was categorized in three steps according to the total number of school years' attendance including primary school to university level. Second-hand smoking was defined as maternal smoking, either during pregnancy or during the first year of life.

Statistics

The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS release 10.1 for Windows; SPSS Inc., Chicago, Illinois, USA). Demographic data are given as mean with standard deviation (SD). The χ^2 test was used for frequency tables, the Mann-Whitney U-test for comparison between groups and the Student's *t*-test for comparing continuous variables. Statistical significance was defined as $p < 0.05$. Multiple logistic regression analysis was applied to estimate the associations between the exposures and outcomes (allergic sensitization and asthma), adjusting for possible confounders. The results are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Missing data for early intake of daily fresh fruit or vegetable ($n = 46$, 9.2%) were given an extra value and used as categorical variables in the logistic regression analysis. Missing data for moisture damage and window pane

Table II. Summary of variables by area.

	Oslo	Hallingdal	Odda	*p*
Daily fruit/vegetables supplements 0–11 mo, *n* (%)	95 (51)	111 (53)	54 (51)	n.s
Vitamin supplements 0–11 mo, *n* (%)	145 (78)	150 (71)	77 (73)	n.s.
Cod liver oil supplements 0–11 mo, *n* (%)	27 (12)	46 (22)	30 (28)*	0.02 vs Oslo
Breastfed (ever), %	93.5	91.4	95.2	n.s.
Smoking during pregnancy, *n* (%)	52 (28)	62 (30)	46 (43.4)*	0.008 vs Oslo, 0.013 vs Hallingdal
Smoking indoors 0–11 mo, *n* (%)	41 (22)	56 (27)	39 (37)*	0.007 vs Oslo
Condense on window panes 0–11 mo, *n* (%)	27 (15)	37 (18)	27 (26)	n.s.
Moisture damage 0–11 mo, *n* (%)	11 (6)	14 (7)	12 (11)	n.s.
Cat indoors 0–11 mo, *n* (%)	11 (6)	33 (16)*	8 (8)	0.002 vs Oslo, 0.042 vs Odda
Dog indoors 0–11 mo, *n* (%)	18 (10)	43 (21)*	9 (9)	<0.001 vs Odda and Oslo
Parental atopy, *n* (%)	106 (57)	108 (51)	56 (33)	n.s.

* indicates statistical significance.

condensation ($n=406$ (80.9%) and 356 (70.9%), respectively) were given the value 0 together with the negative answer to the questionnaire. In the final multiple logistic regression, including all variables, 11 children were missing. Introducing the covariates one by one altered the influence upon the main outcomes only minimally; therefore, the multiple analysis model was applied with all variables included.

Results

Daily consumption of fresh fruit or vegetables during the first year of life was negatively associated with asthma (aOR 0.57, 95% CI: 0.37–0.88). Breastfeeding, extra vitamins or cod liver oil supplement in the first year of life did not decrease the risk of asthma (Figure 1), neither did less than daily intake of fresh fruit or vegetables nor daily intake during the second year of life (data not shown). Allergic sensitization was not influenced by the early intake of daily fresh fruit or vegetables, but tended to be positively associated with the early intake (0–11 mo) of extra vitamins and cod liver oil, with aORs of 1.71 (95% CI: 1.01–2.88) and 1.71 (95% CI: 1.03–3.07), respectively (Figure 2). The influence of the environmental factors analysed in the same logistic regression model are shown in Figures 1 and 2.

Subanalysis comparing the risk of asthma and wheeze by early nutritional factors categorized by allergic sensitization shows that the influence of early intake of fresh fruit or vegetables tended to be weakened in the wheeze group (Table III).

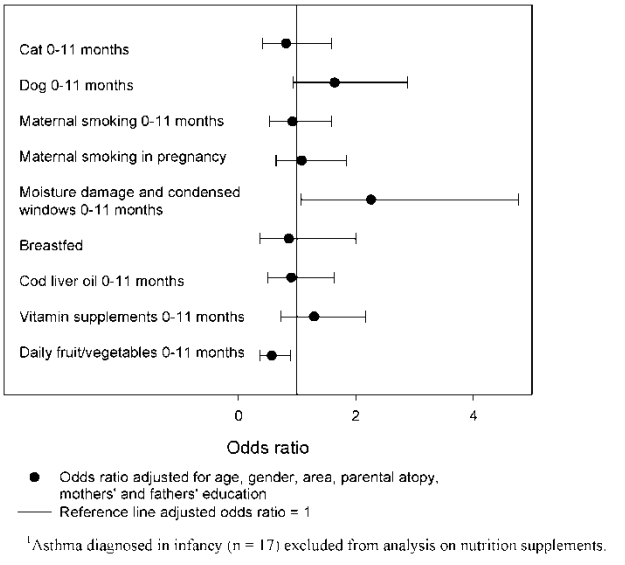

Figure 1. Association between early life exposure and asthma[1] in school-age children shown by adjusted odds ratios with 95% confidence intervals.

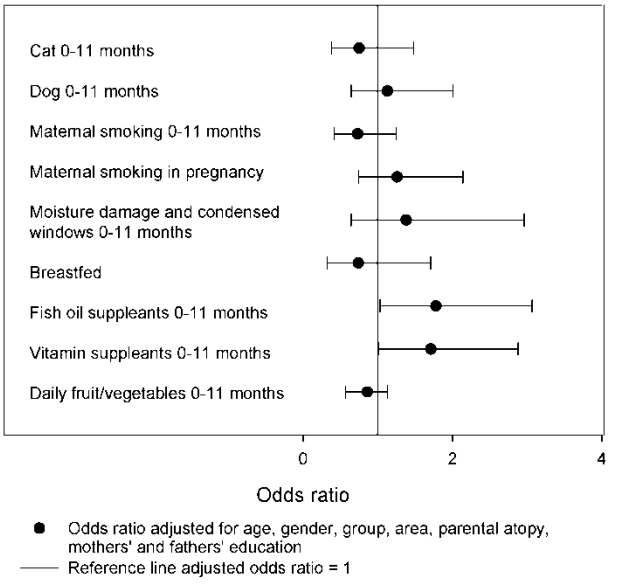

Figure 2. Association between early life exposures and positive skin prick test in school-age children shown by adjusted odds ratios with 95% confidence intervals.

Table III. Multiple logistic regression analysis[a] showing associations between children with asthma[b] and wheeze as outcome, categorized by allergic sensitization, and exposure of breastfeeding, supplements of vitamins, cod liver oil and fresh fruit or vegetables 0–11 mo.

			Asthmatic children ($n=149$)		Wheeze children ($n=155$)	
			SPT negative ($n=61$)	SPT positive ($n=88$)	SPT negative ($n=91$)	SPT positive ($n=64$)
Exposures		n	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Breastfed	no	28	1	1	1	1
	yes	466	0.34 (0.10–1.27)	2.04 (0.55–7.60)	0.23 (0.05–1.09)	0.88 (0.17–4.54)
Vitamins	no	129	1	1	1	1
	yes	372	1.68 (0.73–3.88)	0.88 (0.36–2.11)	1.03 (0.50–2.11)	0.27 (0.07–1.08)
Cod liver oil	no	398	1	1	1	1
	yes	103	1.17 (0.44–3.11)	0.70 (0.30–1.65)	1.30 (0.54–2.18)	0.36 (0.11–1.24)
Fresh fruit or	no	196	1	1	1	1
vegetables daily	yes	260	0.50 (0.26–0.97)*	0.56 (0.29–1.07)	0.67 (0.34–1.32)	1.04 (0.40–2.71)

[a] Adjusted for age, gender, area, parental education, parental atopy, exposure to dog and cat, and mothers' smoking 0–11 mo and during pregnancy.
[b] Children diagnosed with asthma the first year of life excluded.
* indicates statistical significance.

The prevalence of lifetime asthma was 9.4, 5.4 and 8.5% in Oslo, Odda and Hallingdal, respectively (previously published [14]). The outdoor environmental exposure estimates in infancy, expressed as area of living, demonstrated no associations to later asthma, whereas children living in Hallingdal were significantly more often sensitized than children living in Odda ($p=0.007$).

In Odda, 21.9% of asthmatic children were sensitized to HDM, while HDM sensitization occurred only in 10.6% and 4.4% of the asthmatic children in Oslo and Hallingdal, respectively ($p=0.027$). In Hallingdal, the wheeze group had significantly more pet and pollen sensitization than the children from Odda and Oslo (Table IV).

Parental atopy was the only variable that significantly increased the risk for both allergic sensitization and asthma, with aORs of 1.94 (95% CI: 1.28–2.94) and 1.80 (95% CI: 1.19–2.71), respectively.

Female gender tended to be negatively associated with allergic sensitization (aOR 0.64, 95% CI: 0.43–0.96) and asthma (aOR 0.68, 95% CI: 0.46–1.02).

The children from Oslo had lower BMI than both the children from Odda and Hallingdal ($p>0.001$). There was no correlation between BMI and asthma or allergic sensitization.

Discussion

The present study suggests that daily consumption of fresh fruit or vegetables in infancy was significantly associated with less asthma in school-age children and that early intake of extra vitamin or cod liver oil supplements may increase the risk of later allergic sensitization. Living in a high-altitude, non-industrial, rural area was associated with increased prevalence of allergic sensitization.

Our finding that daily consumption of fresh fruit or vegetables decreased the risk of later asthma is in accordance with recently published studies demonstrating that regularly consumption of dietary vitamin C resulted in less wheeze and persistent cough [13,16], and less shortness of breath with wheeze, less severe wheeze and less nocturnal cough in young school children [13]. Further, reduced levels of vitamin C have been found in the serum of asthmatic children [11] and in the induced sputum of adult asthmatics [12]. Reduced lung function (FEV1) has been found in both children and adults with low dietary vitamin C

Table IV. Allergic sensitization by per cent shown for area and the diagnostic groups.

Group	Asthma			Wheeze			Control			*p*
Area	Oslo	Hallingdal	Odda	Oslo	Hallingdal	Odda	Oslo	Hallingdal	Odda	
Pollen[a]	47.0	47.1	28.1	30.4	49.3*	21.9	21.9	25.3	26.2	0.007 vs Odda
Pets[b]	43.9	47.1	37.5	12.5	37.3*	9.4	9.4	13.3	16.7	0.002 vs Oslo,
										0.004 vs Odda
HDM	10.6	4.4	21.9*	1.8	1.5	3.1	0	0	7.1	0.007 vs Hallingdal

[a] Pollen includes birch, timothy and mugwort.
[b] Pets include dog and cat.
HDM: house dust mite.
* indicates significant difference.

consumption [17,18]. However, we are not aware of any study demonstrating that daily consumption of fresh fruit or vegetables as a source of dietary vitamin C in the first year of life decreased the risk of asthma in school age. Neither intake less frequent than daily nor during the second year of life demonstrated any protective effect against the development of asthma. The antioxidant effect of fresh fruits and vegetables may be especially important during a critical time period during the first year of life.

Extra vitamin supplements were not associated with later asthma development. This is in accordance with other observations that it is the dietary form of vitamin C and not specifically vitamin C supplement that exerts the protective effect upon asthma development [19]. Surprisingly, extra vitamin supplements were, however, associated with increased risk of allergic sensitization. This might possibly be explained by additives in these formulas [20,21].

Although a lack of unsaturated fish oils has been suggested to promote the Th2 T-cell system, with a subsequent increased risk of atopic development [9,22], we could not demonstrate any such effect. Rather, we found an increase in allergic sensitization and no influence upon asthma. Some studies have, however, found a negative effect on respiratory health in children with low consumption of fish [16].

The role of early exposure to indoor furry pets is debated. In the present study, keeping an indoor furry pet during early life had no significant influence upon the risk of developing asthma or skin sensitization during school age, when adjusting for potential confounders. Although pet-keeping in several studies was associated with increased asthma or allergy development [23,24], others have demonstrated the protective effects upon allergic sensitization of cat-keeping [25]. One study showed that the effect of pet-keeping upon the child's risk of wheeze by 5 y depended upon parental history of allergy (26). It should be kept in mind that pet-keeping in Norway is not comparable to living on farms, as has been reported in Austrian studies, where livestock share housing with humans. Thus, the possible protective effects of exposure to bacterial flora reported to be associated with farming may not be applicable in our society [27,28].

Moisture damage combined with signs of indoor increased humidity with window pane condensation, but not maternal smoking, in early life was found to significantly increase the risk of asthma, but not atopy. These findings are generally in accordance with current opinion [29], whereas the lack of a significant effect of SHS on asthma was less in line with the majority of publications [30,31]. The high incidence of missing responses to the question of increased humidity and moisture damage in the questionnaire makes these estimates uncertain, but it is assumed that the majority belonged to the unexposed group.

Sensitivity to HDM was more frequently found in the western coastal area of Odda compared to inland areas. Similar findings have been reported from Sweden [32] as well as other continents [33]. The effect is likely to be related to the humid climate of the south-west coast of Norway, favouring the living conditions for mites as well as other possible differences in local allergens, climate and environmental exposures.

Regional differences were also observed in relation to pets in the present study. The higher prevalence of pet sensitivity in Hallingdal compared to Oslo may possibly reflect that pet-keeping is more common in rural areas than cities. This is in contrast to the findings of Bråbäck and co-workers, who reported that cat allergy as well as total furry pet allergy were more common in urban schoolchildren [34]. Pollen sensitization was found more often in the children from Hallingdal than Odda. A high prevalence of pollen sensitization is also found in other high-altitude areas [35], but it is reported to be higher in cities than surrounding rural areas [34].

Recall bias is a potential problem in all questionnaire-based epidemiological studies. In the present study, the parents were asked for food supplements and environmental factors in infancy many years later, with a subsequent risk for both overestimates and underestimates. The parents of asthmatic children might be expected to report more intake of fresh fruits, vegetables, vitamins and cod liver oil, while underreporting of SHS is possible, due to the negative focus of tobacco exposure. However, it is likely that indoor dampness may be more often reported in families with children suffering from respiratory problems. Neither the exact age when the food supplements started during infancy nor the quantities were reported, rendering the results less accurate. Another weakness of the present study is the age span of 10 y among the children; the youngest children being closer to the actual risk factors than the older children. Parental education may also influence dietary habits and reporting quality. However, since this was adjusted for without changes in estimates, this is unlikely to influence our results. The influence on allergic sensitization by the intake of extra vitamins and cod liver oil might be a random chance finding due to the relative small sample size, thus we cannot draw any firm conclusions based upon the present study. However, we can suggest a potential association with less asthma among the children ingesting more fresh fruit or vegetables in infancy, and this finding needs to be explored further in larger prospective studies.

The most important factor regarding specific allergic sensitization and asthma development, in addition to parental atopy, is local environmental exposure. In the comparable populations from the three study areas

with the same degree of parental atopy, the lowest prevalence of allergic sensitization was found in the polluted industrial area, and the highest prevalence in the less-polluted, high-altitude area, suggesting that local environmental factors may be of importance as triggering factors for allergic sensitization. These findings are in accordance with the result of a Swedish study comparing allergic sensitization between the north and south regions (36).

Conclusions

The early introduction of daily fresh fruit or vegetables may decrease the risk of asthma development. Environmental exposure probably influences allergic sensitization, with differences between urban, mountainous and industrialized areas.

References

[1] Gobal strategy for asthma management and prevention. 2nd ed. Washington, DC: National Institutes of Health; 2002.

[2] Platts-Mills TA, Vervloet D, Thomas WR, Aalberse RC, Chapman MD. Indoor allergens and asthma: report of the Third International Workshop. J Allergy Clin Immunol 1997;100:S2–24.

[3] Takafuji S, Nakagawa T. Air pollution and allergy. J Investig Allergol Clin Immunol 2000;10:5–10.

[4] Schauer U, Hoffjan S, Bittscheidt J, Kochling A, Hemmis S, Bongartz S, et al. RSV bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. Eur Respir J 2002;20:1277–83.

[5] Jarvis D, Chinn S, Luczynska C, Burney P. The association of family size with atopy and atopic disease. Clin Exp Allergy 1997;27:240–5.

[6] Strachan DP, Cook DG. Health effects of passive smoking. 5. Parental smoking and allergic sensitisation in children. Thorax 1998;53:117–23.

[7] Hjern A, Hedberg A, Haglund B, Rosen M. Does tobacco smoke prevent atopic disorders? A study of two generations of Swedish residents. Clin Exp Allergy 2001;31:908–14.

[8] Laiho K, Ouwehand A, Salminen S, Isolauri E. Inventing probiotic functional foods for patients with allergic disease. Ann Allergy Asthma Immunol 2002;89 Suppl 1:75–82.

[9] Nafstad P, Nystad W, Magnus P, Jaakkola JJ. Asthma and allergic rhinitis at 4 years of age in relation to fish consumption in infancy. J Asthma 2003;40:343–8.

[10] Strannegard O, Strannegard IL. The causes of the increasing prevalence of allergy: is atopy a microbial deprivation disorder? Allergy 2001;56:91–102.

[11] Kalayci O, Besler T, Kilinc K, Sekerel BE, Saraclar Y. Serum levels of antioxidant vitamins [alpha tocopherol, beta carotene, and ascorbic acid] in children with bronchial asthma. Turk J Pediatr 2000;42:17–21.

[12] Kongerud J, Crissman K, Hatch G, Alexis N. Ascorbic acid is decreased in induced sputum of mild asthmatics. Inhal Toxicol 2003;15:101–9.

[13] Forastiere F, Pistelli R, Sestini P, Fortes C, Renzoni E, Rusconi F, et al. Consumption of fresh fruit rich in vitamin C and wheezing symptoms in children. SIDRIA Collaborative Group, Italy [Italian Studies on Respiratory Disorders in Children and the Environment]. Thorax 2000;55:283–8.

[14] Nystad W, Magnus P, Røksund O, Svidal B, Hetlevik Ø. The prevalence of respiratory symptoms and asthma among school children in three different areas of Norway. Pediatr Allergy Immunol 1997;8:35–40.

[15] Aas K, Belin L. Standardization of diagnostic work in allergy. First report from the standardization committee of the Northern Society of Allergology 1971. Acta Allergol 1972;27:439–68.

[16] Antova T, Pattenden S, Nikiforov B, Leonardi GS, Boeva B, Fletcher T, et al. Nutrition and respiratory health in children in six Central and Eastern European countries. Thorax 2003;58:231–6.

[17] Cook DG, Carey IM, Whincup PH, Papacosta O, Chirico S, Bruckdorfer KR, et al. Effect of fresh fruit consumption on lung function and wheeze in children. Thorax 1997;52:628–33.

[18] Strachan DP, Cox BD, Erzinclioglu SW, Walters DE, Whichelow MJ. Ventilatory function and winter fresh fruit consumption in a random sample of British adults. Thorax 1991;46:624–9.

[19] Miedema I, Feskens EJ, Heederik D, Kromhout D. Dietary determinants of long-term incidence of chronic nonspecific lung diseases. The Zutphen Study. Am J Epidemiol 1993;138:37–45.

[20] de Montis G, Truong M, Toussaint B, Berman D, Toudoire C. [Peanut sensitization and oily solution vitamin preparations]. Arch Pediatr 1995;2:25–8.

[21] Kull I, Hallner E, Lilja G, Ohman-Johansson AC, Oman H, Wickman M. Peanut oil in vitamin A and D preparations: reactions to skin test and manifestation of symptoms. Pediatr Allergy Immunol 1999;10:21–6.

[22] Kankaanpaa P, Sutas Y, Salminen S, Lichtenstein A, Isolauri E. Dietary fatty acids and allergy. Ann Med 1999;31:282–7.

[23] Melen E, Wickman M, Nordvall SL, Hage-Hamsten M, Lindfors A. Influence of early and current environmental exposure factors on sensitization and outcome of asthma in preschool children. Allergy 2001;56:646–52.

[24] Rugtveit J. Environmental factors in the first months of life and the possible relationship to later development of hypersensitivity. Allergy 1990;45:154–6.

[25] Hesselmar B, Aberg N, Aberg B, Eriksson B, Björksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999;29:611–7.

[26] Celedon JC, Litonjua AA, Ryan L, Platts-Mills T, Weiss ST, Gold DR. Exposure to cat allergen, maternal history of asthma, and wheezing in first 5 years of life. Lancet 2002;360:781–2.

[27] Braun-Fahrländer C, Leal GMG. Prevalence of hay fever and allergic sensitisation in farmer's children and their peers living in the same rural community. Clin Exp Allergy 1999;29:28–34.

[28] von Mutius E, Braun-Fahrlander C, Schierl R, Riedler J, Ehlermann S, Maisch S, et al. Exposure to endotoxin or other bacterial components might protect against the development of atopy. Clin Exp Allergy 2000;30:1230–4.

[29] Bornehag CG, Blomquist G, Gyntelberg F, Jarvholm B, Malmberg P, Nordvall L, et al. Dampness in buildings and health. Nordic interdisciplinary review of the scientific evidence on associations between exposure to "dampness" in buildings and health effects [NORDDAMP]. Indoor Air 2001;11: 72–86.

[30] Gergen PJ, Fowler JA, Maurer KR, Davis WW, Overpeck MD. The burden of environmental tobacco smoke exposure on the respiratory health of children 2 months through 5 years of age in the United States: Third National Health and Nutrition Examination Survey, 1988 to 1994. Pediatrics 1998;101:E8.

[31] Joad JP. Smoking and pediatric respiratory health. Clin Chest Med 2000;21:37–viii.

[32] Warner AM, Björksten B, Munir AK, Moller C, Schou C, Kjellman NI. Childhood asthma and exposure to indoor allergens: low mite levels are associated with sensitivity. Pediatr Allergy Immunol 1996;7:61–7.

[33] Peat JK, Toelle BG, Gray EJ, Haby MM, Belousova E, Mellis CM, et al. Prevalence and severity of childhood asthma and

allergic sensitisation in seven climatic regions of New South Wales [see comments]. Med J Aust 1995;163:22–6.

[34] Bråbäck L, Kälvesten L. Urban living as a risk factor for atopic sensitization in Swedish schoolchildren. Pediatr Allergy Immunol 1991;2:14–9.

[35] Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills, et al. Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath. Am J Respir Crit Care Med 1995;151:1388–92.

[36] Hesselmar B, Aberg B, Eriksson B, Aberg N. Allergic rhino-conjunctivitis, eczema, and sensitization in two areas with differing climates. Pediatr Allergy Immunol 2001;12: 208–15.