

ORIGINAL PAPER

Serum cholesterol level in infancy is inversely associated with subsequent allergy in children and adolescents. A 20-year follow-up study

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Clinical and Experimental Allergy

Summary

Background Previous studies suggest an association between an altered lipoprotein profile and atopy. The association has been hypothesized to be due to alterations in the dietary fat intake, a factor possibly contributing to the increase of allergic diseases in industrialized countries.

Objective We aimed at assessing whether there is an association between the serum lipid levels in infancy and subsequent development of allergic symptoms in childhood and adolescence.

Methods A cohort of 200 unselected newborns was prospectively followed up from birth to age 20 years (from 1981 to 2002) with repeated measurements of total cholesterol from birth and throughout the first year of life. The subjects were re-examined at the ages of 5, 11 and 20 years, with assessment of the occurrence of allergic symptoms, skin prick testing (SPT) and measurement of total IgE and of the total, high- and low-density lipoprotein cholesterol.

Results Children and adolescents with allergic symptoms, SPT positivity and an elevated IgE had lower total cholesterol levels in infancy and childhood than the non-atopic subjects. The difference was not detectable in cord blood, but became significant from age 2 months onward.

Conclusion The inverse association between the cholesterol level in infancy and subsequent manifestations of atopy seems not to be due to atopy-related dietary alterations, because it was already present in early infancy, when virtually all the infants were on a similar diet, i.e. on exclusive breastfeeding.

Keywords adolescence, allergy, children, cholesterol, low-density lipoprotein

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Introduction

The frequency of atopic manifestations, i.e. of allergic rhinoconjunctivitis, atopic eczema, allergic asthma and IgE-reactivity, has increased over the past decades [1–3]. The few available previous studies on serum cholesterol and atopy indicate that a low level of serum cholesterol is associated with the occurrence of atopic diseases [4–6]. This has been suggested to be due to increased consumption of n-6 polyunsaturated fatty acids and decreased consumption of saturated fatty acids [6]. Parallel to the increase of atopic manifestations, the consumption of saturated fat and n-3 polyunsaturated fatty acids has decreased and that of n-6 polyunsaturated fatty acids has increased in industrialized countries, and these alterations in dietary fat intake are considered as

possible contributing causes of the increase in allergic diseases [7–9].

We chose to investigate the relationship of serum lipids and atopic manifestations in a prospective cohort of unselected newborns followed up from birth to age 20 years. This study is unique in design, because all the participants received exclusive breastfeeding as their early feeding regimen, and exclusive breastfeeding was maintained as long as it was nutritionally sufficient for the infant [10]. Serum cholesterol measurements were performed repeatedly during the first year of life, and even on cord blood. Therefore, we were able to compare the occurrence of atopic manifestations in childhood and adolescence, and cholesterol levels in early infancy, when virtually all the participants were on a similar diet, i.e. on human milk feeding.

Methods

Subjects

This investigation is part of a nutritional follow-up study of 200 unselected newborns and their mothers, which was initiated in 1981 [10]. Healthy, non-smoking mothers with an uncomplicated pregnancy and delivery and a full-term healthy infant with birth weight appropriate for gestational age were invited to participate. The mothers were encouraged to breastfeed exclusively for as long as possible. During the exclusive breastfeeding, the infants received human milk without any supplementary formula or solid foods; only water and routine vitamins were allowed. The infants and the mothers were seen frequently during the first year of life [10]; consequently, the duration of exclusive breastfeeding was reliably recorded. The number of infants on strictly exclusive breastfeeding was 167 at 2 months, 116 at 6 months, 36 at 9 months and seven at 12 months of age. When exclusive breastfeeding became insufficient for the infant, the infant was gradually weaned to a cow's-milk-based formula (Tutteli®; Valio, Helsinki, Finland) and after 3 months of age to solid foods. In accordance to a national recommendation, all the infants received vitamin A (1000 IU/day) and vitamin D (400 IU/day) supplementation (Vitol®, Orion, Espoo, Finland) from birth through the second year of life.

Of the 200 infants, 84 (42%) had a family history of allergy, defined as the presence of at least one first-grade relative with allergic symptoms [11]. Two of the 200 infants were lost to follow-up during the first year. Of the remaining 198 children, 163 (82%) were re-assessed at 5 years, 150 (76%) at 11 years and 164 (83%) at 20 years of age with skin prick testing (SPT), a clinical examination and parental (at ages 5 and 11 years) and personal (at age 20 years) structured interviews by a physician unaware of the early feeding history and serum lipid levels.

Definitions of allergic symptoms

Atopic dermatitis was defined as a chronic or relapsing itchy dermatitis with a characteristic morphology and distribution [12]. Atopic dermatitis was recorded if present at a follow-up examination, or if it had been diagnosed by a physician and there was a history of relapsing eczema with typical features and localization during the preceding year.

Allergic rhinoconjunctivitis was defined as recurrent non-infectious rhinitis at pollen seasons or on aeroallergen exposure, and/or itching and watery discharge of the eyes at pollen seasons or on aeroallergen exposure.

Recurrent wheezing was recorded if the subject had a diagnosis of bronchial asthma, or two or more separate episodes of respiratory distress and wheezing.

Symptoms of food hypersensitivity were defined as a repeated history of itching or swelling of the lips, the oral mucosa or the throat, urticarial eruption or severe vomiting after ingestion of a specific food. At age 20 years, symptoms of food hypersensitivity were no longer taken into account. The prevalences of allergic symptoms at ages of 5, 11 and 20 years as well as the demographic data have been published previously [11].

Serum total cholesterol, high-density lipoprotein and low-density lipoprotein

Serum total cholesterol was determined in cord blood at birth ($n = 193$), at the ages of 2 months ($n = 192$), 4 months ($n = 192$), 6 months ($n = 190$), 9 months ($n = 188$) and 12 months ($n = 196$) and at the ages of 5 years ($n = 160$), 11 years ($n = 150$) and 20 years ($n = 162$). Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were determined at the ages of 5, 11 and 20 years. After centrifugation of the blood, the cells and the serum were separated, and the serum samples were stored at +4 °C until analysed. All the cholesterol analyses were performed within 24 h of blood sampling. Serum total cholesterol was determined with an AutoAnalyzer [13]. The lipoprotein cholesterol concentration was measured by an enzymatic method [14]. Cholesterol was quantified from the infranant, and HDL cholesterol was determined after heparin-manganese precipitation of apo B-containing particles [15]. The difference between the total cholesterol and HDL cholesterol values in the infranant gives the LDL cholesterol value. The serum cholesterol and lipoprotein levels during the first year of life and the tracking of serum cholesterol and lipoproteins from birth to age 11 years in this cohort have been published previously [16, 17].

Serum total immunoglobulin E

Serum total IgE was determined by the Pharmacia UniCAP total IgE system (Pharmacia Diagnostics, Uppsala, Sweden) at the ages of 5 years ($n = 161$), 11 years ($n = 126$) and 20 years ($n = 162$). Total IgE at age 5 years was determined in sera collected in 1986 and stored at -20 °C until analysed in 2004. The cut-off for an elevated total IgE was set to 130 kU/L at the ages of 11 and 20 years, and to 48 kU/L at age 5 years [18].

Skin prick testing

We performed SPTs at the ages of 5 years ($n = 160$), 11 years ($n = 149$) and 20 years ($n = 164$) with standardized allergen extracts (ALK, Copenhagen, Denmark) of birch, alder, timothy, Kentucky blue, mugwort, cat, dog, *Dermaphagoides pteronyssinus*, cow's milk, egg and codfish; histamine hydrochloride (10 mg/mL) and a diluent control

were included. A positive SPT was defined as at least one test reaction with a mean diameter equal to or greater than half the diameter of the histamine weal [19].

Statistical analyses

The cholesterol concentrations were log-transformed before statistical calculations. The results of the ANOVA for repeated measurements were significant at the level of $P < 0.05$. A two-tail unpaired Student's t -test was used for evaluating the significance of the differences between the population means. A $P < 0.05$ was considered to be statistically significant. Logistic regression analyses were performed in order to control for the effect of potential covariates. The factors taken into account as potential covariates were gender, duration of exclusive breastfeeding (< 6 or ≥ 6 months), smoking in the household during the infant's first year of life and a family history of allergy. In addition, smoking at age 20 years was included for the outcomes at age 20 years.

Ethical considerations

The Ethical Review Board of the Hospital for Children and Adolescents and the Ethical Review Board for Internal Medicine of Helsinki University Hospital approved the study. Written informed consent was obtained from the parents at the beginning of the study, and from the participants of the 20-year re-examination.

Results

Cholesterol concentrations during the first year of life and subsequent allergic symptoms

Cholesterol concentrations in cord blood did not differ significantly in subjects with and without subsequent allergic symptoms, SPT positivity or elevated total IgE at the ages of 5, 11 and 20 years (Figs 1 and 2). As published previously, 14 (7%) children of this cohort had clinical signs suggestive of atopy during the first year of life [20]. These children had lower cholesterol concentrations throughout infancy as compared with the symptom-free infants.

Allergic symptoms at 5 years of age are inversely associated with cholesterol concentrations in infancy and childhood

The 40 children with allergic symptoms at 5 years of age had lower cholesterol concentrations in infancy and at age years of 5 than the symptom-free children (Tables 1 and 2). The difference was significant at ages 2, 4 and 6 months, and at 5 years ($P = 0.01$, 0.04 , 0.01 and 0.04 , respectively). At age 2 months, nearly all the infants were

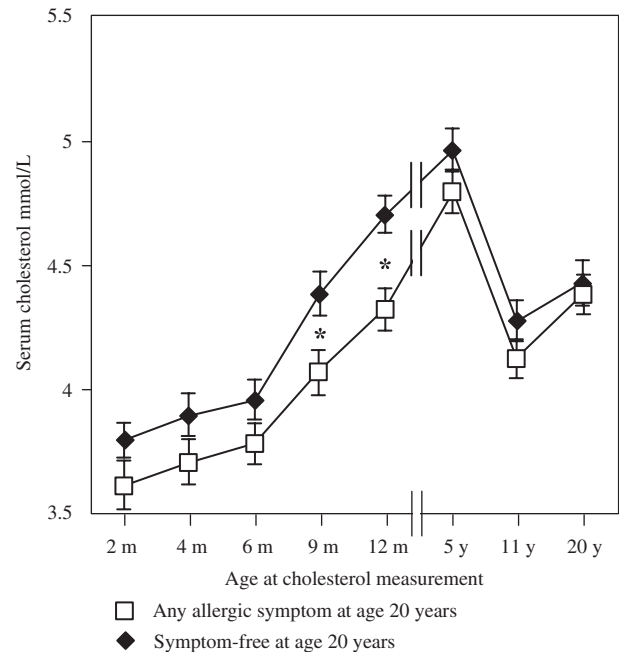


Fig. 1. Serum total cholesterol ($\pm$ SEM) in subjects with and without allergic symptoms at age 20 years. M, months, y, years. Significant differences marked with an asterisk.

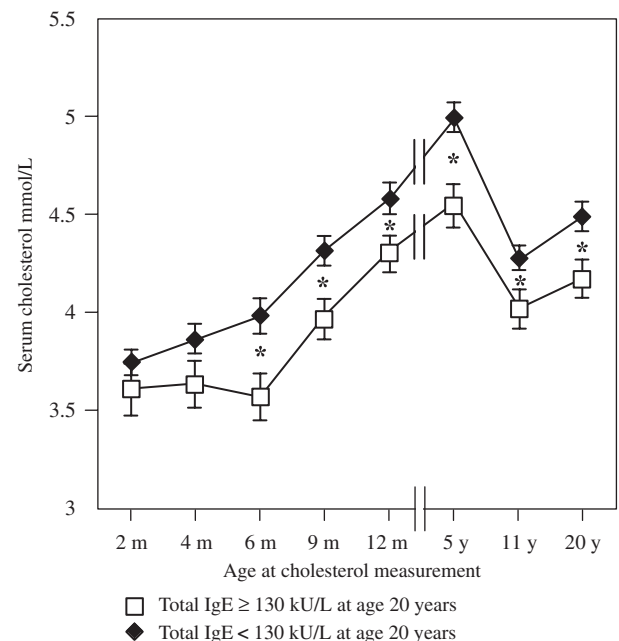


Fig. 2. Serum total cholesterol ($\pm$ SEM) in subjects with an elevated and a normal total IgE at age 20 years. M, months, y, years. Significant differences marked with an asterisk.

on a similar diet, i.e. 94% of them were being breastfed, so the finding was not dependent on differences in the diet.

Most of the children with allergic symptoms at age 5 years had atopic dermatitis or symptoms of food

Table 1. Mean serum total cholesterol (mmol/L, $\pm$ SD) in infancy and the prevalence of allergic symptoms at age 5 years

Age	2 months	4 months	6 months	9 months	12 months
<i>Outcome</i>					
Symptom-free ($n = 123$)	3.77 (± 0.78)	3.82 (± 0.87)	3.98 (± 0.84)	4.35 (± 0.84)	4.54 (± 0.77)
Atopic dermatitis ($n = 28$)	3.38 (± 0.64)	3.49 (± 0.69)	3.62 (± 0.86)	4.10 (± 0.71)	4.31 (± 0.67)
<i>P</i> *	0.02	0.08	0.02	0.09	0.40
Food hypersensitivity ($n = 19$)	3.27 (± 0.88)	3.61 (± 0.70)	3.57 (± 0.84)	4.21 (± 0.75)	4.28 (± 0.63)
<i>P</i> *	0.01	0.20	0.01	0.28	0.39
All rhinoconjunctivitis ($n = 7$)	3.63 (± 0.75)	3.31 (± 0.42)	3.08 (± 0.97)	3.71 (± 0.60)	4.17 (± 0.59)
<i>P</i> *	0.63	0.15	0.01	0.07	0.39
Recurrent wheezing ($n = 5$)	3.00 (± 1.13)	3.14 (± 0.31)	3.24 (± 1.07)	4.32 (± 1.10)	4.26 (± 0.90)
<i>P</i> *	0.02	0.09	0.04	0.94	0.43
Any allergic symptom ($n = 40$)	3.40 (± 0.78)	3.52 (± 0.43)	3.60 (± 0.77)	4.24 (± 0.81)	4.36 (± 0.68)
<i>P</i> *	0.01	0.04	0.01	0.26	0.49

**P*-values calculated for the difference between the mean cholesterol levels of the symptomatic and the symptom-free children and adjusted for gender, exclusive breastfeeding for ≥ 6 months, family history of allergy, and smoking in the household during the infant's first year.

Table 2. Mean serum total, HDL and LDL cholesterol (mmol/L, $\pm$ SD) and allergic symptoms at age 5 years

	Total cholesterol	HDL	LDL
<i>Outcome</i>			
Symptom-free ($n = 123$)	4.95 (± 0.74)	1.49 (± 0.27)	3.20 (± 0.68)
Atopic dermatitis ($n = 28$)	4.53 (± 0.70)	1.52 (± 0.40)	2.78 (± 0.57)
<i>P</i> *	0.009	0.68	0.003
Food hypersensitivity ($n = 19$)	4.61 (± 0.69)	1.51 (± 0.39)	2.86 (± 0.55)
<i>P</i> *	0.06	0.79	0.03
Recurrent wheezing ($n = 5$)	4.54 (± 0.26)	1.79 (± 0.29)	2.59 (± 0.44)
<i>P</i> *	0.23	0.017	0.04
Any allergic symptom ($n = 40$)	4.67 (± 0.66)	1.57 (± 0.38)	2.86 (± 0.57)
<i>P</i> *	0.04	0.18	0.004

**P*-values calculated for the difference between the mean cholesterol levels of the symptomatic and the symptom-free children.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

hypersensitivity or a combination of these. The children with atopic dermatitis had lower cholesterol concentrations at the ages of 2 and 6 months ($P = 0.02$) and 5 years ($P = 0.01$, Tables 1 and 2) than the symptom-free children. Children with an elevated total IgE (≥ 48 kU/L) had lower cholesterol concentrations in infancy than the children with total IgE below 48 kU/L; however, the differences were not statistically significant.

The LDL cholesterol concentration at age 5 years was significantly lower in the children with allergic symptoms than in the symptom-free children (Table 2). The HDL cholesterol concentration was similar in allergic and non-allergic children, with the exception of the five children with recurrent wheezing, who had a higher mean HDL cholesterol than the symptom-free children.

Total immunoglobulin E at age 11 years is inversely associated with cholesterol concentrations in infancy and childhood

Children with an elevated total IgE (≥ 130 kU/L, $n = 31$) had consistently lower total cholesterol concentrations throughout infancy and childhood than those with total IgE below 130 kU/L, and there was a significant difference in the cholesterol concentrations at ages 2, 4, 6 and 12 months ($P = 0.04$, 0.01, 0.05 and 0.01, respectively) and at 5 years ($P = 0.05$). These associations remained significant after adjusting for potential covariates. However, allergic symptoms at age 11 years were not associated with alterations in total, LDL or HDL cholesterol at that age.

Atopic manifestations at age 20 years are inversely associated with cholesterol concentrations in infancy, childhood and adolescence

The 85 subjects with allergic symptoms at 20 years of age had lower cholesterol concentrations throughout repeated measurements in infancy and childhood as compared with the symptom-free subjects (Fig. 1). The differences in cholesterol concentrations at ages 9 and 12 months ($P = 0.01$ and 0.002, respectively) were significant after adjusting for potential covariates (Table 3). Furthermore, subjects who were SPT positive at age 20 years had lower cholesterol concentrations in infancy, childhood and adolescence as compared with the SPT-negative subjects. The difference was significant at ages 4 and 12 months, and 5 years (Table 3).

Total IgE ≥ 130 kU/L at age 20 years ($n = 42$) was associated with decreased cholesterol concentrations throughout infancy, childhood and adolescence (Fig. 2). The associations between IgE ≥ 130 kU/L and cholesterol at ages 6 and 9 months, and 5, 11 and 20 years were significant after adjusting for potential covariates (Table 3).

Table 3. The association of serum cholesterol concentrations and subsequent atopic manifestations at age 20 years as adjusted for potential covariates*

	OR (95% CI)	P
Cholesterol at age 4 months		
Skin prick test positivity at age 20 years	0.62 (0.39–0.96)	0.04
Cholesterol at age 6 months		
IgE $\geq$ 130 kU/L at age 20 years	0.49 (0.28–0.84)	0.01
Cholesterol at age 9 months		
Any allergic symptom at age 20 years	0.57 (0.36–0.91)	0.02
Atopic dermatitis at age 20 years	0.36 (0.18–0.73)	0.01
IgE $\geq$ 130 kU/L at age 20 years	0.55 (0.31–0.95)	0.03
Cholesterol at age 12 months		
Any allergic symptom at age 20 years	0.46 (0.29–0.76)	0.002
Allergic rhinoconjunctivitis at age 20 years	0.41 (0.23–0.73)	0.002
Skin prick test positivity at age 20 years	0.54 (0.33–0.90)	0.02
Cholesterol at age 5 years		
Skin prick test positivity at age 20 years	0.59 (0.34–1.01)	0.05
IgE $\geq$ 130 kU/L at age 20 years	0.41 (0.21–0.77)	0.01
Cholesterol at age 11 years		
Any allergic symptom at age 20 years	0.47 (0.25–0.88)	0.02
Allergic rhinoconjunctivitis at age 20 years	0.43 (0.21–0.89)	0.02
IgE $\geq$ 130 kU/L at age 20 years	0.40 (0.18–0.90)	0.03
Cholesterol at age 20 years		
IgE $\geq$ 130 kU/L at age 20 years	0.56 (0.33–0.96)	0.04
LDL cholesterol at age 5 years		
Allergic rhinoconjunctivitis at age 20 years	0.50 (0.25–0.97)	0.04
IgE $\geq$ 130 kU/L at age 20 years	0.32 (0.15–0.68)	0.003
LDL cholesterol at age 11 years		
Recurrent wheezing at age 20 years	0.25 (0.07–0.87)	0.03
Allergic rhinoconjunctivitis at age 20 years	0.40 (0.18–0.86)	0.02
IgE $\geq$ 130 kU/L at age 20 years	0.37 (0.16–0.84)	0.02
LDL cholesterol at age 20 years		
IgE $\geq$ 130 kU/L at age 20 years	0.48 (0.26–0.89)	0.02

*Multivariate logistic regression. Independent variables used in the model: Gender, exclusive breastfeeding for $\geq$ 6 months, family history of allergy, smoking in the household during the infant's first year and smoking status of the subject at age 20 years.

OR, Odds ratio; CI, confidence interval.

Subjects with IgE $\geq$ 130 kU/L had a lower LDL cholesterol concentration at 5, 11 and 20 years of age ($P=0.001$, 0.02 and 0.02, respectively) as compared with subjects with IgE below 130 kU/L. Furthermore, low LDL cholesterol at age 11 years was associated with subsequent allergic rhinoconjunctivitis ($P=0.02$) and recurrent wheezing ($P=0.03$) at age 20 years (Table 3).

Discussion

We report that children and adolescents with clinical and laboratory manifestations of atopy had lower cholesterol concentrations throughout infancy, childhood and adolescence as compared with non-allergic subjects. Interestingly, this difference was not detectable in cord blood, but already became significant at age 2 months, when vir-

tually all the infants were on a similar diet, i.e. on human milk feeding.

This prospective 20-year follow-up study involved an unselected cohort of healthy infants and mothers, all of whom were encouraged to maintain strictly exclusive breastfeeding as long as it was nutritionally sufficient for the infant. Consequently, 94% of the infants were breastfed for at least the first 2 months [11]. Breastfeeding results in lower cholesterol levels in adulthood as compared with early weaning and bottle-feeding [21], and it has been associated with a reduced LDL/HDL ratio later in life [22] as well as with an allergy-protective effect [23]. In our study, exclusive breastfeeding prolonged for 9 months or more was associated with increased atopic dermatitis and food hypersensitivity at age 5 years and with increased food hypersensitivity at age 11 years in children with a family history of allergy [11]. However, the inverse associations of total and LDL cholesterol levels, and atopic manifestations remained significant after adjusting for the duration of exclusive breastfeeding. Adjusting for the total duration of breastfeeding instead of exclusive breastfeeding did not alter the results.

We have recently reported from this cohort an inverse association of the plasma retinol level at age 2 months and subsequent atopic manifestations [24]. However, there was no statistically significant correlation between the serum cholesterol and the plasma retinol levels at age 2 months (Spearman's rank test, $P=0.17$, $\rho=0.1$).

Previous observations of an altered lipoprotein profile and atopy are based on cross-sectional studies. Joki et al. [4] found that young children with food allergy have lower total cholesterol than healthy children, and 26–45% of the children with food allergy also had a low HDL cholesterol concentration. The authors speculated that the restricted diet of the children with food allergy contributed to the low cholesterol concentrations. Shenoi et al. [5] reported significantly lower total and HDL cholesterol levels in children with respiratory allergy, i.e. asthma or allergic rhinitis than in the non-atopic controls. Schäfer et al. [6] studied adults aged 27–78 years in a case-control study and found a positive association between the HDL cholesterol level and the frequency of allergic rhinoconjunctivitis and atopic eczema. In addition, they found a negative association between total and LDL cholesterol levels and the frequency of allergic rhinoconjunctivitis and allergic sensitization, but these were no longer significant after adjustment for covariates.

We found the LDL cholesterol levels to be decreased in allergic subjects and in those with an elevated IgE, whereas HDL cholesterol levels were similar in allergic and non-allergic subjects. Hence, we conclude that the decreased total cholesterol in allergic subjects was due to a decreased LDL cholesterol level. A relatively low total and LDL cholesterol level may modulate the immune response. Children with high LDL cholesterol have higher blood

T lymphocyte CD3, CD4 and CD8 subset counts than those with normal LDL cholesterol [25]. In the present study, the lipoprotein cholesterol concentrations were measured at ages 5, 11 and 20 years. In future studies, it might be interesting to assess the possible association of the LDL and HDL cholesterol levels during the first year of life, and the subsequent development of atopic symptoms.

According to the previous literature, there is no established cut-off level of total IgE that can reliably distinguish atopic from non-atopic individuals. This is due to the considerable overlap between the total IgE levels in atopic and non-atopic individuals [26, 27]. In our study, in order to use an elevated total IgE as one of the outcomes, we set the cut-offs for IgE so that they represent a clearly elevated total IgE, i.e. to 130 kU/L at the ages of 11 and 20 years, and to 48 kU/L at the age of 5 years [19]. When the cut-off for an elevated total IgE at age 20 years was decreased to 110 kU/L, the reference value for adults used by the laboratory of our hospital, the results remained unaltered.

An increased intake of n-6 polyunsaturated fatty acids and a decreased intake of n-3 fatty acids have been suggested to have contributed to the increase of atopic diseases in industrialized countries [7]. Indeed, several studies demonstrate an altered dietary and serum polyunsaturated fatty acid composition with higher levels of n-6 fatty acids in atopic subjects [28, 29]. A high intake of saturated fatty acids increases serum cholesterol [30], whereas linoleic acid, the major dietary n-6 polyunsaturated fatty acid, has an opposite effect [31]. Therefore, if the increased intake of n-6 fatty acids is causative for atopic diseases, total cholesterol may be expected to be inversely correlated with manifestations of atopy [6]. However, the unique set-up of our study enabled the important observation that the cholesterol levels of subjects with subsequent atopic manifestations were significantly lower already in early infancy, at a time when most of the infants were still on exclusive breastfeeding. Therefore, our results suggest that the differences in cholesterol levels between atopic and non-atopic subjects are not explained by differences in diet.

In our study, the fatty acid composition of breast milk during exclusive breastfeeding or the dietary intake of polyunsaturated fatty acids later in childhood was not monitored. Breast milk fatty acid composition may be associated with the development of atopic symptoms in the infant [32, 33]. In a Swedish study, breast milk from allergic mothers was shown to contain low levels of n-3 and n-6 polyunsaturated fatty acids, and a high arachidonic acid (n-6): eicosapentaenoic acid (n-3) ratio in breast milk was related to the development of allergic symptoms in the infant [34]. Conflicting results were reported from an Australian study, in which breast milk fatty acid profile was found to be independent of maternal atopy, and high levels of n-3 fatty acids in breast

milk were associated with increased risk of atopy in the infant [35].

Cholesterol is rich in lipid rafts, specialized plasma membrane domains with signal transduction potential [36]. These domains have been implicated in regulating mast cell activation [37, 38]. *In vitro*, cholesterol depletion has been shown to enhance high-affinity IgE receptor-mediated mast cell degranulation and cytokine production [39, 40].

We found that the inverse association between cholesterol concentration and subsequent development of allergic symptoms, SPT positivity and an elevated IgE was present as early as at 2 months of age. This suggests that a decreased cholesterol level may contribute to the early steps in the pathogenesis of allergic sensitization. Once the atopic constitution is established, the association of atopic manifestations and serum lipid levels may be less significant. This hypothesis is supported by the observations that a low serum cholesterol level is associated with food allergy and respiratory allergy in children, but the association is not significant in adults [4–6].

Conclusion

The serum total cholesterol level in infancy and childhood is inversely associated with subsequent atopic manifestations, i.e. allergic symptoms, SPT positivity and an elevated total IgE in childhood and adolescence.

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