ORIGINAL ARTICLE

Serum lipid and apolipoprotein profiles in newborns and six-year-old children: The Tallinn Young Family Study

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Abstract
Seventy children aged 6 years (34 boys, 36 girls) were studied for cardiovascular risk factors. Among the children 40 had also been investigated at birth. The aim of the study was to determine changes in serum lipoprotein parameters from birth up to preschool age and to assess the role of some relevant factors that might affect the process. An obvious association was found between serum apolipoprotein (apo) B levels, the apoB/apoA-I ratio and lipoprotein(a) (Lp(a)) levels at birth and at 6 years of age ($r = 0.43; p < 0.05, r = 0.73; p < 0.0001$ and $r = 0.81; p < 0.0001$, respectively). Thirty percent of children who were in the top quartile by apoB or total cholesterol levels and 66.7% of those in this quartile by apoB/apoA-I ratio at birth remained in the top quartiles also in the follow-up study. The significantly higher apoB/apoA-I ratio in newborns and the apoB/apoA-I and apoB values in the 6-year-old children were observed in the carrier apoE4 isof orm as compared to E3 homozygotes. A significant influence of apoE polymorphism on serum apoB/apoA-I ratio and apoB level in preschool children was confirmed by ANOVA one-way analysis of variance. In a multiple regression analysis from all the studied factors, the independent determinants of apoB level in preschool age were apoE phenotype, gestational age and Apgar score in the first minute of life. Thus, tracking of serum Lp(a), apoB, apoB/apoA-I ratio and total cholesterol levels from birth up to 6 years of age was demonstrated. The association between apoE polymorphism and serum lipoprotein parameters became more obvious after the first 6 years of life.

Key Words: Apolipoproteins, apolipoprotein E polymorphism, children, lipids, lipoprotein(a), newborn, tracking
Introduction

Atherosclerosis begins in childhood and early adulthood [1–5]. Serum lipid levels measured in children and young adults are associated with atherosclerotic changes [6,7] and predict coronary heart disease (CHD) as well as mortality due to cardiovascular diseases in middle age [8]. It is therefore important to identify CHD risk factors as early as possible. In the past few years several studies have been assessed with the goal of tracking serum lipid levels. The main epidemiological studies [9–12] have shown that children with elevated total cholesterol (TC) or low-density lipoprotein cholesterol (LDLC) levels tend to maintain high levels throughout childhood and into adult life. Tracking of serum lipid and lipoprotein levels has been well documented in older children and adolescents [13–18] but little is known about trends during the first years of life from birth [6,19,20]. Many studies [21–23] but not all [24,25] have indicated that high plasma lipoprotein(a) (Lp(a)) levels are associated with higher risk of coronary heart disease. Plasma Lp(a) level is under strict genetic control and thus about 90% of the concentration is genetically determined [26]. In cord sera from neonates with a positive family history of CHD, Lp(a) levels were higher than those in neonates with a negative CHD history [27,28]. It was suggested that Lp(a) is a marker of risk for CHD from birth.

Apolipoprotein (apo) E, a component of plasma chylomicrons, chylomicron remnants, very low-density lipoproteins and high-density lipoproteins (HDLs), has three main isoforms E2, E3 and E4 [29]. The apoE phenotype is associated with TC and LDLC levels in blood serum [30,31]. As apoE polymorphism strongly affects the tracking of serum cholesterol, the usefulness of cholesterol screening in predicting future cholesterol has to be evaluated, taking into consideration the apoE phenotype [31].

The aim of the study was to determine gains in serum lipid and apolipoprotein levels from birth up to 6 years of age and to assess the role of some relevant factors affecting the process.

Material and methods

Subjects and study design

A cohort of 6-year-old children was studied for cardiovascular risk factors. Forty of the children were investigated for the first time at birth within the framework of the Tallinn Young Family Study [32,33]. A total of 70 children (34 boys, 36 girls) were included in the study.

A sample of couples married in Tallinn during January 1994–December 1995 and their newborn babies were studied for cardiovascular risk factors. A total of 230 men, 366 women of fertile age and 267 babies were investigated. Cord blood analyses were performed in 151 babies, and these families were asked to take part in the second study. For different reasons (refusal to participate, change of address, divorces, no response to repeated calls), only 70 from these families participated in the second study carried out between June 2000 and April 2002.

Venous fasting blood samples from 6-year-old children and cord blood of newborns were collected for biochemical analyses. The cord blood consisted of a mixture of arterial and venous blood obtained after delivery by milking the portion proximal to the placenta. Only timely (37–42 weeks) born neonates without congenital anomalies were included in the study.
In the 6-year-old children, weight and height were measured and body mass index (BMI), i.e. weight (kg) divided by the square of the height (m²), was calculated. Systolic and diastolic blood pressures (Korotkoff phases I and V) were also measured.

Nutrition patterns of the 6-year-old children were assessed using a semiquantitative food frequency questionnaire completed with the aid of the mothers during an interview. The frequency and the portion size of main foodstuffs were registered. The intake of carbohydrates, food fibres and cholesterol (mg/day) from eggs, dairy, meat and fish products were calculated using food composition tables [34,35].

The status of vitally important organ systems in newborns was evaluated using the Apgar method of scoring in the first and fifth minutes after birth, as previously described [32,33]. A total score of 10 indicates that an infant is in the best possible condition. A healthy newborn usually scores between 7 and 10.

Parents were asked to complete a questionnaire, which included their own and child’s lifestyle variables as well as details about their medical history.

Lipid and lipoprotein analyses

Serum was separated by centrifugation (10 min, 1500 g) and stored at -20°C in three separate aliquots. Sera were thawed only once. Total serum cholesterol (TC), HDL-C and triglycerides (TGs) were determined enzymatically, using commercial reagents (HUMAN, Wiesbaden, Germany). Serum HDL-C concentration was measured after precipitation of non-HDL lipoproteins with dextran sulphate/magnesium chloride [36]. Lipid analyses were performed in the Laboratory of Biochemistry of Tallinn Diagnostic Centre using an analyser “Dynamic” (KONE Instruments OY, Espoo, Finland). The quality control system for the assay used in our laboratory was the Labquality Control System (Helsinki, Finland). Serum LDL-C concentration was calculated according to the Friedewald equation [37].

Concentrations of serum Lp(a) were determined at the National Public Health Institute, Helsinki, using an immunoradiometric assay as already described [24,38]. Quality control of the Lp(a) assay in the present study was followed as previously described [24,38]. ApoB was quantified by Laurell’s rocket electrophoresis [39] using references of Orion Diagnostica (Espoo, Finland). The method was intercalibrated with the immunoturbidimetric assay used in the National Public Health Institute, Helsinki [39].

ApoE phenotype was determined by isoelectric focusing of delipidated serum samples followed by Western blotting and immunodetection [40]. Purified rabbit anti-human apoE antisera was used as the first antibody and peroxidase-conjugated goat anti-rabbit IgG (DAKO) as the second antibody. For statistical analyses, apoE phenotypes were grouped into three classes: the carriers of the E2 isoform (E2/2 and E2/3), E2+ class; the E3/3-subjects; the carriers of E4 isoform (E3/4 and E4/4), E4+ class. Individuals with the E2/4 phenotype were excluded from the analysis, being carriers of alleles with an inverse effect on lipid metabolism.

The study was approved by the Tallinn Medical Ethics Committee and all families gave their informed consent to participate in the study.

Statistical methods

All statistical analyses were done using the programs STATISTICA, STATGRAPHICS, MedCalc 5 [41]. Mean values, medians and standard deviations were calculated. Spearman’s rank correlation coefficients were used to evaluate associations between
Lp(a) and other lipoproteins, and Pearson's linear correlation analysis was used in other cases. Student's t-test was used to make comparisons between certain groups. Multiple linear regression analysis was used to clear out independent correlates of lipoprotein parameters. A one-way ANOVA test was performed to analyse the effect of apoE phenotype on serum lipoprotein parameters.

Results

Serum mean lipid and lipoprotein values at birth and 6 years later are listed in Table I. The values increased from birth to 6 years of age. Correlations of serum lipoprotein values at birth with the same parameters six years later were calculated. The correlation was significant for Lp(a) (r=0.81; p<0.0001), apoB/apoA-I ratio (r=0.73; p<0.0001) and apoB levels (r=0.43; p<0.05).

Another way to assess tracking is to determine the proportion of children who are persistently in the highest quartile. Of the children who had Lp(a) levels and an apoB/apoA-I ratio exceeding the 75th percentile at the baseline examination, 80% and 67%, respectively, had levels in the highest quartile after the follow-up period. Thirty percent of children who were in the top quartile by apoB and TC values in the initial study remained in the top quartiles also in the follow-up study.

Most of the children studied (62.7%) had the apoE3/3 phenotype. Carriers of the E2 isoform (phenotypes 2/2+2/3) and the E4 isoform (phenotypes 4/2+4/3) amounted to 14.9% and 22.4% of children, respectively. Phenotype E4/4 was not detected. There were no significant differences in serum lipid levels in cord blood in relation to apoE polymorphism, but the ratio of apolipoproteins, apoB/apoA-I, was significantly higher in apoE4 subjects than in subjects with E3/3 phenotypes (0.31 ± 0.1 and 0.24 ± 0.05, respectively; p<0.05).

The effect of apoE phenotype on serum lipid and apolipoprotein values in 6-year-old children is summarized in Table II. TC, LDLc and apoB values tended to increase according to apoE phenotype groups in the order E2+, <E3/3, <E4+. In children with apoE4 isoform, the mean apoB level was significantly higher as compared to apoE3 homozygotes (Table II). The ratio of apoB/apoA-I was significantly higher in apoE4+ subjects versus apoE2+ carriers and apoE3/3 homozygotes. A significant influence of apoE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Newborns n=40</th>
<th>6-year-old children, n=70</th>
<th>Changes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/l</td>
<td>1.87 ± 0.6</td>
<td>4.22 ± 0.9</td>
<td>+125.7</td>
</tr>
<tr>
<td>HDLC, mmol/l</td>
<td>0.6 ± 0.19</td>
<td>1.02 ± 0.25</td>
<td>+70.0</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>0.47 ± 0.2</td>
<td>0.69 ± 0.24</td>
<td>+22.4</td>
</tr>
<tr>
<td>LDLc, mmol/l</td>
<td>0.98 ± 0.4</td>
<td>2.9 ± 0.87</td>
<td>+196.0</td>
</tr>
<tr>
<td>ApoA-I, g/l</td>
<td>0.92 ± 0.15</td>
<td>1.31 ± 0.14</td>
<td>+42.4</td>
</tr>
<tr>
<td>ApoB, g/l</td>
<td>0.23 ± 0.06</td>
<td>0.82 ± 0.16</td>
<td>+263.5</td>
</tr>
<tr>
<td>ApoB/apoA-I</td>
<td>0.25 ± 0.08</td>
<td>0.63 ± 0.12</td>
<td>+152.0</td>
</tr>
<tr>
<td>HDLC%</td>
<td>34.1 ± 7.5</td>
<td>24.8 ± 6.83</td>
<td>-27.4</td>
</tr>
<tr>
<td>Lipoprotein(a), g/l</td>
<td>0.04 ± 0.03</td>
<td>0.24 ± 0.32</td>
<td>+510.0</td>
</tr>
<tr>
<td>Median, g/l</td>
<td>0.025</td>
<td>0.09</td>
<td>+260.0</td>
</tr>
</tbody>
</table>

Abbreviations: M=mean; TC=total cholesterol; HDLC=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol.
Table II. Serum lipoprotein values (M±SD) according to apoE phenotype groups in 6-year-old children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>E2+ (n=9)</th>
<th>E3/3 (n=40)</th>
<th>E4+ (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mmol/l</td>
<td>3.97±0.63</td>
<td>4.11±1.0</td>
<td>4.43±0.74</td>
</tr>
<tr>
<td>HDLc, mmol/l</td>
<td>1.10±0.32</td>
<td>0.99±0.24</td>
<td>1.01±0.25</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>0.68±0.19</td>
<td>0.66±0.26</td>
<td>0.74±0.21</td>
</tr>
<tr>
<td>LDLc, mmol/l</td>
<td>2.56±0.63</td>
<td>2.82±0.91</td>
<td>3.08±0.86</td>
</tr>
<tr>
<td>ApoA-I, g/l</td>
<td>1.37±0.13</td>
<td>1.32±0.14</td>
<td>1.27±0.14</td>
</tr>
<tr>
<td>ApoB, g/l</td>
<td>0.73±0.12</td>
<td>0.84±0.07</td>
<td>0.90±0.08</td>
</tr>
<tr>
<td>ApoB/apoA-I</td>
<td>0.54±0.11</td>
<td>0.64±0.10**</td>
<td>0.72±0.11</td>
</tr>
<tr>
<td>HDLc%</td>
<td>28.09±7.62</td>
<td>24.84±6.13</td>
<td>23.59±8.01</td>
</tr>
<tr>
<td>TC/HDLc</td>
<td>3.85±1.26</td>
<td>4.27±1.08</td>
<td>4.65±1.41</td>
</tr>
<tr>
<td>Lipoprotein (a), g/l</td>
<td>0.13±0.14</td>
<td>0.26±0.39</td>
<td>0.30±0.28</td>
</tr>
</tbody>
</table>

Abbreviations: M=mean; TC=total cholesterol; HDLc=high-density lipoprotein cholesterol; LDLc=low-density lipoprotein cholesterol.

*p<0.001 = comparison between E3/3 and E4+ groups in apoB level and comparison between E2+ and E4+ groups in apoB/apoA-I ratio.

**p<0.05 = comparison between E3/3 and E4+ groups in apoB/apoA-I ratio.

phenotype on serum apoB level and apoB/apoA-I ratio at 6 years of age was revealed by ANOVA one-way analyses of variance (p=0.038 and p=0.001, respectively). No significant differences between the apoE phenotype groups were revealed in TG, HDLc and apoA-I levels.

In 6-year-old children multiple regression analyses were performed to determine environmental and clinical factors independently associated with lipoprotein parameters. In the models the serum lipid and apolipoprotein data were dependent variables, while gestational age, birthweight, Apgar score at birth, height at the age of 1 and 6 years, blood pressure, breastfeeding duration, dietary cholesterol intake, parents' smoking habits and apoE phenotype class were independent variables. The significant independent determinants of serum lipoprotein parameters are presented in Table III. Serum TC and LDLc levels were found to be independently negatively correlated with the gestational age of the child and positively with the father's smoking habits. Serum apoB level was independently positively associated with apoE phenotype class and negatively with gestational age, as well as Apgar score (Table III).

To test the effect of apoE polymorphism on the build-up of lipoprotein levels during the first 6 years of life, differences in LDLc, apoB and apoB/apoA-I ratio between newborns and 6-year-old children were analysed by apoE phenotype groups (Table IV). The increase

Table III. Factors independently and significantly correlated with serum atherogenic lipoprotein fractions in 6-year-old children assessed by multiple linear regression analysis.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent positive and negative correlates</th>
<th>Coefficient of determination, %</th>
<th>F ratio</th>
<th>p-value of the model</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>Gestational age (−), fathers' smoking (+)</td>
<td>36.39</td>
<td>10.58</td>
<td>0.001</td>
</tr>
<tr>
<td>LDLc</td>
<td>Gestational age (−), fathers' smoking (+)</td>
<td>36.97</td>
<td>11.73</td>
<td>0.001</td>
</tr>
<tr>
<td>ApoB</td>
<td>Gestational age (−), apoE class (+), Apgar score in first min of life (−)</td>
<td>33.37</td>
<td>9.35</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: TC=total cholesterol; LDLc=low-density lipoprotein cholesterol.
Table IV. Comparison of serum LDLc, apoB/apoA-I ratio and apoB level (M±SD) in newborns and 6-year-old children by apoE phenotype groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>ApoE2+</th>
<th>ApoE3/3</th>
<th>ApoE4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDLc, mmol/l</td>
<td>Newborns</td>
<td>1.0±0.16</td>
<td>1.0±0.44</td>
<td>0.94±0.4</td>
</tr>
<tr>
<td>n=28</td>
<td>n=4</td>
<td>n=17</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td>6-year-old</td>
<td></td>
<td>2.56±0.63</td>
<td>2.82±0.91</td>
<td>3.1±0.86</td>
</tr>
<tr>
<td>children</td>
<td>n=62</td>
<td>n=9</td>
<td>n=40</td>
<td>n=13</td>
</tr>
<tr>
<td>Changes, (%)</td>
<td>Newborns</td>
<td>+1.33(148.5)</td>
<td>+1.52(182.0)</td>
<td>+2.14(227.7)</td>
</tr>
<tr>
<td>n=34</td>
<td>n=4</td>
<td>n=22</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td>6-year-old</td>
<td></td>
<td>0.73±0.12</td>
<td>0.84±0.07</td>
<td>0.90±0.08</td>
</tr>
<tr>
<td>children</td>
<td>n=62</td>
<td>n=9</td>
<td>n=40</td>
<td>n=13</td>
</tr>
<tr>
<td>Changes, (%)</td>
<td>ApoB/apoA-I</td>
<td>+0.50(217.6)</td>
<td>+0.62(283.2)</td>
<td>+0.65(254.9)</td>
</tr>
<tr>
<td>Newborns</td>
<td>n=34</td>
<td>n=4</td>
<td>n=22</td>
<td>n=8</td>
</tr>
<tr>
<td>6-year-old</td>
<td></td>
<td>0.54±0.11</td>
<td>0.64±0.10</td>
<td>0.72±0.11</td>
</tr>
<tr>
<td>children</td>
<td>n=62</td>
<td>n=9</td>
<td>n=40</td>
<td>n=13</td>
</tr>
<tr>
<td>Changes, (%)</td>
<td></td>
<td>+0.30(125.0)</td>
<td>+0.40(166.6)</td>
<td>+0.41(132.2)</td>
</tr>
</tbody>
</table>

Abbreviations: M=mean; LDLc=low-density lipoprotein cholesterol.

in LDLc level was 1.5-fold higher in carriers of the E4 isoform when compared with that in the E2 group (227.7% versus 148.5%).

In a pairwise analysis, the difference between apoB levels and apoB/apoA-I values in the two studies was smaller among apoE2 isoform carriers compared with that in carriers of the E4 isoform (p=0.030 and p=0.002, respectively). Furthermore, in apoE2+ children, the difference in LDLc between the initial and final study was lower than that in apoE4+ children (p=0.060).

Discussion

The present study shows significant positive correlations between serum Lp(a), apoB/apoA-I ratio and and apoB levels at birth and the same parameters 6 years later. We found that 80% of children with an initial Lp(a), 67% with an initial apoB/apoA-I ratio and 30% with an initial apoB level above the 75th percentile remained in that quartile during the follow-up study. It was demonstrated that in the first months of life Lp(a) levels increased 2-fold compared with birth, reaching full genetic expression in the first year of life [42,43]. Thereafter, Lp(a) levels show only very minor changes during life, i.e. levels in adulthood are similar to those in childhood [44-46]. As for apoB, previous studies have shown the higher (0.57-0.59) correlation coefficient for apoB in year 1 versus year 4 [47].

In the present study serum TC, HDLC, TG and LDLc levels at birth did not correlate with these indices 6 years later. It was demonstrated by other researchers that tracking of the phenomenon is age-dependent. TC level at birth was not predictive of levels at the age of 6 months [48], but there was a significant correlation between TC levels at the age of 6 months and 7 years [9]. The level of tracking becomes higher from 2 years of age [49]. The tracking coefficient for serum lipids was greater if the child was older at the initial measurement [19,50,15]. In a cohort of 10 to 14-year-old children, more than 70% that were in the top quintile of TC, LDLc and apoB in an initial investigation remained in the top quintile 5 years later [51].
We found that only 30% of children with an initial TC level above the 75th percentile remained in that quartile at the follow-up study. Similar results were shown earlier: 40% of the children who were above the 75th percentile at 12 months remained over the 75th percentile at the age of 5 years [5]. Thus, in general, our results are in accordance with previous investigations.

In a Finnish study in which lipoproteins were measured in the first year of life and at the age of 5 years, the effect of nutrition on the level of tracking of lipids was examined. There was a higher level of tracking for lipoproteins from 6 or 9 months versus 5 years of age in exclusively breast-fed babies than for those on formula and solid foods [5]. It is concluded that tracking of serum lipids emerges in early childhood and that this pattern is susceptible to nutritional influences during the first years of life [5,52]. Thus, dietary pattern is usually related to blood lipid parameters, but this was not revealed in our study. It seems that for demonstrating these associations in preschool children, more precise dietary survey methods such as the 24-h recall interview with food models [53] should be applied.

Apolipoprotein E polymorphism is a genetic determinant of plasma lipid levels and of CHD risk. In several populations the e2 allele is associated with low plasma TC, LDLC and apoB levels, whereas the e4 allele is related to high plasma TC, LDLC and apoB levels in adults [8] as well as in children [52,54]. Our study demonstrates the association of apoE polymorphism with serum apoB level and the apoB/apoA-I ratio among 6-year-old children. Mean serum apoB/apoA-I ratio and apoB level at the age of 6 years in carriers of the E4 isoform were significantly higher than these values among apoE2+ children (p < 0.001). The LDLC mean level was marginally higher in apoE4+ subjects than that in apoE2+ subjects. In newborns, only the apoB/apoA-I ratio was associated with apoE phenotype. Thus, our results are in accordance with the standpoint on the apo e4 allele being associated with high levels, and the e2 allele with low levels of TC, LDLC and apoB [55,56]. As previously indicated [57], subjects homozygous for apoE2 absorbed intestinal cholesterol less efficiently than those homozygous for apoE3, while apoE4 homozygotes absorbed the highest fraction of intestinal cholesterol. Furthermore, persons with apoE4 isoform had a faster clearance of dietary fat than those with other isoforms. The presence of an influence of apoE phenotype on serum TC and LDLC was demonstrated in 3-year-old children [15], but not in newborns [15,58]. Steinmetz et al. [52] demonstrated an association of apoE4 with apoB levels in umbilical cord blood. In our study, despite the lack of statistical association between apoE phenotype and TC or LDLC concentrations in preschool age children, the mean serum TC and LDLC showed a clear trend towards increase in order of classes E2+, E3/3, E4+. We agree with other investigators that, because of the low levels of atherogenic lipid fractions and low number of subjects, it is not easy to demonstrate statistically significant relationships between apoE polymorphism and lipids in newborns [59]. Thus, it seems that the apoE phenotype has a certain effect on serum TC and LDLC during the first years of life and that environmental factors such as dietary pattern can exaggerate this effect.

Comparing the build-up of LDLC level from birth up to the age of 6 years by apoE phenotype groups, the increase was 1.5-fold greater among carriers of the E4 isoform than in the E2 group. Similar changes have also been described in several other studies [58,60,61]. The Bogalusa Heart Study demonstrated that apoE polymorphism significantly influenced the longitudinal (16 years) change in LDLC, whereas the e2 allele lowered the adulthood cholesterol level to a greater extent than the childhood level (61). Their earlier reports [30] and other studies [54,62] found no such effect on longitudinal changes of lipoproteins. These earlier studies [30] were too short in duration (5–6 years) to detect any
appreciable longitudinal changes. At the same time, it was indicated that the $c2$ allele induces a lowering of apoB and the $c4$ allele generates a marked increase in apoB during the first year of life [58]. It has been suggested that the apoE locus not only influences the levels and longitudinal changes of lipoprotein levels but also modulates the association between lifestyle-related factors and lipoproteins [61].

Thus, in the present study the main independent determinants of apoB level in 6-year-old children were the apoE phenotype, gestational age and Apgar score in the first minute of life. The result is in accordance with the view that the apoE phenotype can modulate the association of other factors with lipoproteins. At the same time, the data confirm the hypothesis of the foetal/infant origin of atherosclerotic cardiovascular diseases [63]. Our findings indicate that a slight association between apoE polymorphism and serum lipoprotein parameters already exists at birth and the effect becomes stronger during the first six years of life.

Acknowledgements

This work was supported by grants 2641 and 4061 of the Estonian Science Foundation. We express our gratitude to Professor Ulrike Beisiegel, Universitäts-Krankenhaus Eppendorf, Hamburg, Germany, for her personal involvement in the management of the apoE polymorphism studies in Estonia. We also thank Sirkka Metiäinen, Virva Korhonen, Sari Nuutinen and Anu Kull for excellent technical assistance, and Sergei Malygin for statistical help.

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