Serum Lipid Profiles Poorly Correlate With *Chlamydia pneumoniae*, *Helicobacter pylori*, and Cytomegalovirus Seropositivity in Prospectively Followed-Up Healthy Children

Iina Volanen, Olli T. Raitakari, Raija Vainionpää, Martti Arffman, Johanna Aarnisalo, Susanna Anglé, Katriina Kallio, Olli Simell

**Objective**—Chronic *Chlamydia pneumoniae* (*Cpn*), *Helicobacter pylori* (*Hp*), and herpes virus infections have been associated with atherogenic serum lipid profile and an excess of cardiovascular events in adults. Because mechanisms leading to atherosclerosis are active since early childhood, we examined whether *Cpn*, *Hp*, or cytomegalovirus (CMV) seropositivity relates to serum lipid, lipoprotein, or apolipoprotein concentrations in children. We also looked for factors increasing probability of *Cpn* seropositivity in children.

**Methods and Results**—*Cpn*-specific IgG and IgA, as well as *Hp*-specific and CMV-specific IgG antibodies were assessed by enzyme immunoassay in 199 apparently healthy children, followed-up from 7 to 11 years of age. Serum lipid profiles were studied at the ages of 7, 9, and 11 years using standard methods. Neither seroconversion to *Cpn* IgG or IgA antibody positivity nor persistent seropositivity for *Cpn*, *Hp*, or CMV was associated with proatherogenic serum lipid values. Children with siblings were more likely to possess *Cpn* antibodies than children without siblings (IgG: OR, 5.24; 95% CI, 1.63 to 16.82; IgA: OR, 3.32; 95% CI, 1.15 to 9.57).

**Conclusions**—These data suggest that contrary to the observations in adults, *Cpn*, *Hp*, and CMV seropositivity in otherwise healthy children is not associated with disturbances in serum lipid profile. (Arterioscler Thromb Vasc Biol. 2005; 25:827-832.)

**Key Words:** atherosclerosis ■ *Chlamydia pneumoniae* ■ cytomegalovirus ■ *Helicobacter pylori* ■ lipids

Advanced age,1 male gender,1 low socioeconomic status,2 household crowding,2 living in less developed countries,3 winter season,4 and smoking5 are examples of the factors that predict exposure to *Chlamydia pneumoniae* (*Cpn*), an intracellular Gram-negative bacterium commonly causing respiratory tract infections. Coronary artery disease (CAD) and *Cpn* infections share predisposing factors, such as old age and smoking, that increase the risk of CAD and chronic *Cpn* infection,6 known to associate with ischemic heart disease and acute myocardial infarction.7,8

A prominent hypothesis has been that the increased CAD risk in connection with a chronic *Cpn* infection might be mediated by the induction of a proatherogenic lipoprotein profile as the acute phase response to an infection, targeted primarily to protect the host from further injury, is accompanied by changes in the lipid metabolism similar to those proposed to promote atherogenesis. These changes comprise, in particular, raised concentration of triglycerides9 and decreased concentration of high-density lipoprotein (HDL) cholesterol.10 In fact, lipid profiles in adults with persisting *Cpn* seropositivity without respiratory tract symptoms resembled those seen during acute infections.11 Interestingly, *Helicobacter pylori* (*Hp*), another Gram-negative bacterium causing chronic infection of the gastric mucosa, and cytomegalovirus (CMV), a herpes virus, in adults have been associated with CAD,12,13 as well as with disturbances in lipid and lipoprotein metabolism.14–16 These observations further suggest that alteration of lipid metabolism by chronic bacterial and viral infections might contribute to the development of atherosclerosis.

We recently demonstrated that a sizeable proportion of 7- to 8-year-old children have persistently elevated *Cpn* IgG and IgA antibody values,17 supporting the contention that chronic *Cpn* infections might exist already in early childhood. In this study, we examined whether *Cpn*, *Hp*, or CMV seropositivity is associated with proatherogenic serum lipid values in prospectively followed-up 7- to 11-year-old healthy children, as has been documented in adults. Because of some contradictory findings in studies addressing the relationship between *Cpn* seropositivity and socioeconomic and lifestyle...
variables, we also evaluated associations between Cpn antibodies and the low-saturated-fat, low-cholesterol dietary intervention of the STRIP study,\textsuperscript{18} child’s apolipoprotein E (apoE) phenotype, socioeconomic status, parental smoking, and the season during which the serum sample was drawn.

**Methods**

**Study Design and Subjects**

The design and protocol of the ongoing STRIP study (Special Turku Coronary Risk Factor Intervention Project for Children) have been described in detail.\textsuperscript{18} Briefly, 1054 voluntary families with 1062 6-month-old infants were recruited in 1990 through 1992 and randomized to an intervention group (n=540) to receive detailed individualized dietary and lifestyle counseling aiming at minimizing intervention children’s exposure to known environmental atherosclerosis risk factors, or to a control group (n=522). The well-being, growth, dietary intake, and serum lipid and lipoprotein concentrations of the children were monitored during regular visits of the families to the STRIP counseling team at 6- to 12-month intervals. Since 5 years of age, the venous blood samples were drawn after an overnight fast. The samples were kept frozen at −70°C until the analysis. The study protocol was approved by the local ethics committee. Parental informed consent was obtained in each case.

As part of the STRIP trial, Cpn, Hp, and CMV antibodies were measured between the ages of 7 and 11 years in a random, time-restricted sample of 199 consecutive STRIP children (110 boys) born in 1989 to 1990. Equal numbers of the children belonged to the STRIP intervention group (n=99) and the STRIP control group (n=100). The children showed no apparent respiratory or gastrointestinal symptoms at the time of the blood draws.

**Antibody Assays**

Enzyme immunoassay (EIA) technique was used to determine Cpn-specific IgG and IgA antibodies (IgG-EIA and IgA-EIA; Ani Labsystems, Helsinki, Finland) and anti-CMV IgG antibodies (an in-house EIA test) at the ages of 7, 8, 9, 10, and 11 years, and anti-Hp IgG antibodies (an in-house EIA test) at the ages of 7, 9, 10, and 11 years. CMV antigen was prepared and CMV EIA test performed as described.\textsuperscript{18,20} Anti-Hp antibodies were measured by an in-house EIA technique using sonicated Hp (ATCC 12301) in phosphate-buffer saline as an antigen, alkaline phosphate-conjugated antihuman IgG (DAKO code D03336) as a conjugate, and p-nitrophenylphosphate di-Na-salt (Reagenia 153006) as a color substrate. Seropositivity was assigned according to the specifications of each product as follows: Cpn seropositivity was expressed as enzyme immunoassays using an IgG value of >45 enzyme immunoassays and an IgA value of >12 enzyme immunoassays as cutoff points, as recommended by the manufacturer; a positive CMV result was defined as an absorbance 3-times higher than the absorbance of the negative control sample and being at least 0.15; for anti-Hp antibodies, IgG antibody titers of ≥300 were regarded as positive.

**Serum Lipids**

Serum cholesterol, HDL cholesterol, apolipoprotein A-1 (apoA-1), apoB, serum lipoprotein(a) (Lp[a]) values at the ages of 9 and 11 years and serum triglyceride values at the ages of 7, 9, and 11 years, and apoE phenotype were determined as described.\textsuperscript{18,21–23} Low-density lipoprotein (LDL) cholesterol concentrations were calculated.\textsuperscript{24}

**Background Data**

Background data were collected during the STRIP visits and by means of questionnaires mailed to the parents in the autumn of 1999. Demographic data included data on education of parents and socioeconomic status of families. The season of the blood draw, the family size (number of children in the family) at each age category, and parents' smoking habits, enquired yearly during the family’s STRIP visits, were also used as background data. All study children were nonsmokers. At the age of 11 years, the study physician determined each child’s pubertal stage according to the Tanner staging (testicle size, breast development, and pubic hair). The children were classified as either prepubertal or pubertal, because none of them had completed puberty.

**Statistical Methods**

Serum lipid, lipoprotein, and apolipoprotein concentrations were first compared between the Cpn IgG and IgA seropositive and seronegative children separately at the ages of 7, 9, and 11 years. We then studied the effect of persistent Cpn and CMV IgG, and Cpn IgA antibody positivity on the serum lipid values at the age of 11 years. We considered those children persistently Cpn-positive if serum samples were positive for IgG or IgA antibody measurements in at least the last 3 age categories during the follow-up (9 to 11 years), whereas a child was considered having a latent CMV infection ever since IgG seroconversion. Those children whose Cpn IgG and IgA antibodies were below the cutoffs or who had not CMV-seroconverted during the follow-up (7 to 11 years) were considered controls in this analysis. Paired t test was used in all aforementioned comparisons without covariates.

We have previously shown that at least up to the age of 7 years, the repeatedly given dietary counseling in the STRIP study markedly lowered the serum total and LDL cholesterol concentrations in the boys.\textsuperscript{25} In the present study, therefore, the examined association between Cpn or CMV antibodies and lipid values was adjusted for the STRIP study group (intervention versus control group), as well as gender, height, weight, the family size, and, at the age of 11 years, pubertal status. To adjust for these potential confounders, analysis of covariance was performed to test associations between antibodies and lipids. General linear models were used to assess the potential interaction, and thereby confounding effect, of gender with Cpn or CMV antibodies in serum lipid concentrations. Furthermore, general linear models with adjustment for age were used to look at changes in serum total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride concentrations in children who seroconverted from Cpn IgG or IgA seronegativity to Cpn seropositivity during the 4-year follow-up period.

Because only 5 children possessed anti-Hp IgG antibodies over the follow-up, lipid comparisons between these subjects and children without Hp antibodies were performed at the age of 11 years and by paired t test only. Because of the skewed distribution of serum triglyceride and Lp(a) values, the values of these 2 variables were log-transformed for the statistical analyses. The results are shown as means with 95% confidence intervals (CIs) for the mean values.

To study the effects on child’s Cpn seropositivity of the child’s apoE phenotype, the family size, parents’ smoking habits, total income of the family, years of parental education, and season of the blood draw, each variable was classified into 2 categories. Generalized estimation equations-estimated odds ratios (ORs) with 95% CIs were calculated from generalized linear models with repeated measures for this categorical data, and also for the STRIP study group, to determine the influence of the variables on probability of the child to be seropositive for Cpn IgG or IgA.

The differences were considered significant at P<0.05. The SAS release 8.2 program package (SAS Institute, Cary, NC) was used in all statistical analyses.

**Results**

**Cpn and CMV Antibody Prevalences**

The prevalences of Cpn and CMV antibody positivity of the study children are presented in Table 1. For both pathogens, the prevalences are given for the values exceeding the cutoff limits for IgG and, for Cpn, also for IgA. In addition, to further describe the Cpn antibody status of the children, the proportions of the children exceeding the cutoff limits for both Cpn IgG and IgA seropositivity are presented.

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Cpn IgG and IgA antibody prevalences both peaked at the age of 8 years, with 35% of the children then possessing IgG
antibodies and 29% possessing IgA antibodies. After that age, the percentage of IgG seropositive children remained rather stable, whereas IgA antibody positivity gradually decreased during the follow-up period. Between the ages of 7 and 11 years, only 3 children seroconverted from CMV IgG negativity to IgG positivity.

To test the stability of the Cpn antibody positivity during the 4-year follow-up, generalized estimation equation-estimated ORs with 95% CIs for IgG and IgA seropositivity at the ages of 9, 10, and 11 years, depending on seropositivity at the age of 7 years, were calculated. For both IgG and IgA, Cpn seropositivity at the age of 7 years was associated with an ≈5-fold risk of being seropositive also at the ages of 9, 10, and 11 years, with the ORs over time of 5.01 (95% CI, 2.45 to 10.25) for IgG and 4.77 (95% CI, 2.13 to 10.67) for IgA, respectively.

### Cpn, CMV, and Hp Seropositivity and Serum Lipids

Because gender produced no confounding effects on analysis of the correlation between Cpn or CMV seropositivity and serum lipid values of the children, we combined the 2 sexes for all later lipid analyses.

In the cross-sectional analyses at the ages of 7, 9, and 11 years, no differences in serum total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, apoaI-1, or apob concentrations were observed between Cpn IgG or IgA seropositive and seronegative children. Similarly, neither IgG nor IgA seropositivity was related to Lp(a) values at the ages of 9 and 11 years. After adjustment for the STRIP study group (intervention versus control), gender, height, weight, family size, and, at the age of 11 years, the pubertal stage, IgG and IgA antibodies, and the serum lipid profiles continued to show poor association. As an example, the mean serum total cholesterol concentration at the age of 11 years was 4.43 mmol/L (95% CI, 4.19 to 4.66) in the IgG-positive children and 4.47 mmol/L (95% CI, 4.34 to 4.59) in the IgG-negative children (adjusted \( P=0.94 \)). Similarly, there were no significant differences in mean serum total cholesterol concentrations between IgA-positive and IgA-negative 11-year-old children (4.57 [95% CI, 4.25 to 4.89] versus 4.44 mmol/L [95% CI, 4.32 to 4.56], respectively; adjusted \( P=0.40 \)).

Neither persistent IgG nor IgA seropositivity for Cpn, comprising those children having antibodies against Cpn in at least 3 consecutive age categories of the 5 measured, affected serum lipid, lipoprotein, or apolipoprotein concentrations at the age of 11 years in the prospectively followed-up study children (Table 2). The difference in both crude and adjusted means for the serum lipid concentrations remained insignificant between children with persistent IgG or IgA seropositivity and children with antibody values below the cutoff limits during the entire follow-up.

Between the ages of 7 and 9 years, 18 children seroconverted from Cpn IgG negativity to IgG positivity and 17 children from Cpn IgA negativity to IgA positivity. Later, the number of seroconversions decreased. Six children IgG-seroconverted between 9 and 10 years and 1 between 10 and 11 years; 3 children IgA-seroconverted between 9 and 10 years and 1 between 10 and 11 years. For all lipid parameters measured, no significant changes were observed in the values before and after the Cpn IgG or IgA seroconversions.

Eighty-three children (42%) had CMV infection. At the age of 11 years, the CMV IgG-negative and CMV IgG-positive children showed no significant differences in serum total cholesterol (mean 4.43 versus 4.50 mmol/L; \( P=0.52 \)), LDL cholesterol (mean 2.77 versus 2.82 mmol/L; \( P=0.61 \)), HDL cholesterol (mean 1.27 versus 1.30 mmol/L; \( P=0.51 \)), triglyceride (mean 0.77 versus 0.76 mmol/L; \( P=0.89 \)), apoaI-1 (mean 1.38 versus 1.40 g/L; \( P=0.55 \)), apob (mean 0.83 versus 0.84 g/L; \( P=0.72 \)), or Lp(a) (mean 67.49 versus 87.97 mg/mL; \( P=0.15 \)) values. The studied associations remained insignificant after adjustment for the STRIP study group, gender, height, weight, family size, and pubertal stage.

Regarding comparisons of Hp-seropositive and Hp-seronegative children at age 11 years, all mean serum lipid and lipoprotein values except for total cholesterol were closely similar in the 5 Hp IgG-positive children and the Hp

<table>
<thead>
<tr>
<th>Antibody Status</th>
<th>Number (% of Cpn Antibody-Positive Children</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG &gt;45 EIU</td>
<td></td>
<td>7 (n=172)</td>
</tr>
<tr>
<td>IgA &gt;12 EIU</td>
<td></td>
<td>45 (26.2)</td>
</tr>
<tr>
<td>IgG &gt;45 EIU and IgA &gt;12 EIU</td>
<td></td>
<td>33 (19.2)</td>
</tr>
<tr>
<td>IgG present</td>
<td></td>
<td>21 (12.2)</td>
</tr>
</tbody>
</table>

*The percentage is less than in the 9-year-old children because of a few missing serum samples from formerly CMV-positive children.

CMV indicates cytomegalovirus; Cpn, Chlamydia pneumoniae; EIU, enzyme immunonunit.
IgG-negative children. For instance, the mean HDL cholesterol concentrations of the 2 groups of children were 1.22 mmol/L (95% CI, 0.95 to 1.49) and 1.29 mmol/L (95% CI, 1.24 to 1.33), respectively. However, the mean total cholesterol concentration was significantly lower in the Hp IgG-positive children (3.78 mmol/L; 95% CI, 3.35 to 4.21) than in the IgG-negative children (4.48 mmol/L; 95% CI, 4.37 to 4.59; P=0.040).

Other Measures and Cpn Seropositivity

Cpn IgG and IgA antibodies were more common in children who had siblings than in those who did not (IgG: OR, 5.24; 95% CI, 1.63 to 16.82; IgA: OR, 3.32; 95% CI, 1.15 to 9.57) (Table 3). Cpn seropositivity showed no significant correlation with the STRIP study group, child’s apoE4-positivity, parental smoking, household income, years of parental education, or season when the serum sample was drawn.

Discussion

This study, conducted in apparently healthy children, showed that Cpn, Hp, or CMV seropositivity in childhood is not associated with proatherogenic alterations in serum lipid, lipoprotein, or apolipoprotein values. Our findings suggest

<table>
<thead>
<tr>
<th>Table 2. Serum Lipid, Lipoprotein, and Apolipoprotein Concentrations at Age 11 Years in Children With Persistent Chlamydia pneumoniae IgG or IgA Antibodies and in Children Without Antibodies Against Cpn During the Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
</tr>
<tr>
<td>(n=75–76¶)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
</tr>
<tr>
<td>Triglycerides, mmol/L*</td>
</tr>
<tr>
<td>apoA-1, g/L</td>
</tr>
<tr>
<td>apoB, g/L</td>
</tr>
<tr>
<td>Lp(a), mg/L*</td>
</tr>
<tr>
<td>Values are means with 95% confidence intervals (CIs) in parentheses. *After logarithmic transformation. †Analysis of covariance for group means after adjustment for the STRIP study group, gender, height, weight, pubertal stage (pubertal vs prepubertal), and family size. ¶Seronegative=neither IgG nor IgA antibodies during the follow-up (7–11 years). §Persistent seropositivity=IgG or IgA antibodies at least at 9, 10, and 11 years of age. ¶Number of children varies because of missing lipid values.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. The Influence of Socioeconomic Variables, Parental Smoking, the STRIP Study Group, and the apoE Phenotype of the Child, and the Season of the Blood Draw on Predicting Chlamydia pneumoniae IgG or IgA Seropositivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intervention vs control group of the STRIP study</td>
</tr>
<tr>
<td>apoE4-negative vs apoE4-positive‡</td>
</tr>
<tr>
<td>Siblings vs no siblings</td>
</tr>
<tr>
<td>Parents not smoking vs one or both of the parents smoking</td>
</tr>
<tr>
<td>Total income of the family per year, below vs above 47 000€</td>
</tr>
<tr>
<td>Total years of the mother’s education, below vs above median</td>
</tr>
<tr>
<td>Total years of the father’s education, below vs above median</td>
</tr>
<tr>
<td>Season of the blood draw, not winter vs winter§</td>
</tr>
<tr>
<td>*IgG value &gt;45 EU and IgA value &gt;12 EU as cutoff points. †Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from repeated generalized linear models for categorical data to determine the probability of being seropositive. The OR is the ratio of the odds in the first group vs in the last group mentioned. ‡Children with phenotype E2/4, E3/4, or E4/4. §Month of the blood draw November, December, or January.</td>
</tr>
</tbody>
</table>
that infections caused by these microbes do not promote atherosclerosis by disturbing the lipid metabolism, at least at this early age.

During the acute stage of infections, serum triglyceride concentration clearly increases, whereas HDL cholesterol, apoA-I, apoB, and LDL cholesterol concentrations decrease, and concentration of total cholesterol is modified by infections in an inconsistent manner. Interestingly, whereas serum LDL cholesterol concentration declines because of infection, the proportion of small, dense LDL particles (subclass pattern B), considered to be more atherogenic than larger LDL, increases. Little data exist regarding the relationship between Cpn, Hp, or CMV seropositivity and serum lipid profile in healthy children, despite the early acquisition of these pathogens. In adults, however, several cross-sectional studies have shown an association between Cpn, Hp, and CMV IgG antibody titers, and clearly atherogenic lipid profiles. In addition, in connection with CMV seropositivity, the Lp(a) values have been markedly elevated. However, the findings of the present study complement the observation by Hoffmeister et al in adults by showing that Cpn and CMV seropositivity at the ages of 7, 9, and 11 years poorly associates with serum lipids. Furthermore, marked increases neither in serum Cpn IgG nor IgA resulted in altered lipid values. No atherogenic changes were found in serum lipids at the age of 11 years in children with Hp IgG antibodies compared with children without Hp antibodies during the follow-up. However, because of the small number of subjects with Hp IgG antibodies, these results should be interpreted cautiously.

Like Hp, which causes chronic gastric infection and CMV, which establishes a latent lifetime infection, Cpn bacterium is also able to persist in the host. Such chronic infection is considered to be most reliably marked by persistent Cpn IgA seropositivity, because IgA class Cpn antibodies have a half-life of only ~1 week. In men, serological markers of a chronic Cpn infection have shown a significant association with increased triglyceride and decreased HDL cholesterol concentrations, changes that are also present during the acute phase of a Cpn infection. In rodents, during the acute stage of bacterial infection, these alterations in HDL cholesterol and triglyceride concentrations, promoting atherogenesis, have been attributed to the action of lipopolysaccharide (LPS), which is a prominent endotoxin and a typical constituent of the cell wall of Gram-negative bacteria. LPS administration activates the production of several cytokines, including the tumor necrosis factor (TNF)-α, which increases plasma cholesterol and triglyceride concentrations in animals. Continuous production of inflammatory cytokines by cells chronically infected with Cpn or Hp, both being Gram-negative bacteria, may therefore contribute to the development of the observed changes, typically predisposing to CAD, in serum lipid pattern. Furthermore, CMV and Cpn as intracellular pathogens might serve as a source of persistent local infection within the atherosclerotic plaque. However, in the present study in healthy children, neither persistently elevated Cpn IgA nor persistently elevated Cpn, Hp or CMV IgG antibody concentrations were associated with abnormalities in serum lipids at the age of 11 years. Thus, it appears that the possible aggravating effects of persistent infection on atherogenesis are mainly mediated through other mechanisms than altered serum lipid profile at least before adulthood. One possibility is that a longer period of exposure to the pathogens is needed, or that in adults increased serum lipid values for years along with potential atheromas might enhance subject’s susceptibility to chronic infection. This hypothesis is compatible with the observation that viable Cpn, as well as CMV and Hp DNA, have been found in atherosclerotic lesions but seldom in vessel walls without evident atherosclerosis. The hypothesis is further strengthened by the finding that in mice, hypercholesterolemia has been required for the Cpn to exacerbate the development of atherosclerotic lesions in aorta.

In summary, our data suggest that Cpn, Hp, and CMV seropositivity in otherwise healthy children correlates poorly with serum lipid values. Thus, it seems that these infections do not promote atherosclerosis in childhood by acting through changes in the lipid profile. However, other pathways may already link infections and atherosclerosis during the early years of life.

**Acknowledgments**

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**References**


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