Metabolism
Clinical and Experimental

VOL 45, NO 7 JULY 1996

The Effect of Physical Activity on Serum Total and Low-Density Lipoprotein Cholesterol Concentrations Varies With Apolipoprotein E Phenotype in Male Children and Young Adults: The Cardiovascular Risk in Young Finns Study

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Apolipoprotein E (apo E) determines serum total (TC) and low-density lipoprotein (LDL-C) cholesterol concentrations and is thus associated with coronary heart disease (CHD) risk. We studied if the effect of physical activity (PA) on serum TC and LDL-C concentrations varies with apo E phenotype in a population-based sample of children and young adults with regular PA. The study cohort consisted of subjects aged 9, 12, 15, 18, 21, and 24 years in 1986 (N = 1,498) participating in a large multicenter study of cardiovascular risk factors in children and young adults. Serum lipid concentrations were determined enzymatically, and apo E phenotypes by isoelectric focusing and immunoblotting. The composition of the diet was determined by a 48-hour recall method, and a PA index was calculated on the basis of frequency, intensity, and duration of activity assessed by a questionnaire. LDL-C ($P = .0082$), TC ($P = .014$), and the high-density lipoprotein cholesterol (HDL-C)/TC ratio ($P = .0004$) responses to exercise varied with apo E phenotype. The effect of PA on LDL-C, TC, or HDL/TC was not found in apo E phenotype E4/4. A moderate inverse effect of PA on TC and LDL-C and a positive effect on HDL/TC was found in subjects with E4/3 and E3/3 phenotypes. Similar but stronger associations were found between these variables within the group of E3/2 males. The effect of PA on serum lipid levels was strongest within the phenotype E3/2. These associations were not explained by dietary habits. Apo E phenotype partly determines the effect of PA on serum TC and LDL-C in Finnish male children and young adults with regular PA.

ATHEROSCLEROSIS is a slowly progressing process that may originate in childhood. Fatty streaks and intimal lipid accumulations occur in coronary arteries in children, and these lesions often progress to fibrous plaques.[1] Serum lipid concentrations have been linked to early arterial lesions in the aorta and coronary arteries.[2,3] Serum total cholesterol (TC) concentrations in young adults predict premature coronary heart disease (CHD) in middle age.[4] An atherogenic lipid profile is defined as a pattern of elevated serum cholesterol and triglyceride (TG) levels with an elevation of dense low-density lipoprotein (LDL) particles and a reduction of high-density lipoprotein cholesterol (HDL-C).[5-7] Plasma lipid and lipoprotein concentrations are determined by genetic and environmental factors such as diet and physical activity (PA).[8-11] Apolipoprotein E (apo E) determines serum TC and LDL cholesterol (LDL-C) concentrations and contributes to CHD risk.[12,13] Apo E is a ligand for lipoprotein receptors.[14,15] Physiologically, its most important function is to mediate specific uptake of plasma very–low-density lipoproteins, chylomicron remnants, and intermediate-density lipoprotein (IDL) by the liver.[14,15] Three major apo E isoforms, E2, E3, and E4, exist in plasma.[16] These isoforms are coded by three codominant alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, resulting in six major apo E phenotypes: E2/2, E3/2, E4/2, E3/3, E4/3, and E4/4.[16,17]

Apo E4 isoform is associated with high serum TC and LDL-C concentrations in most[18,19] but not all[20] populations. The genetic disposition of apo E phenotype on atherosclerosis can already be seen in 15- to 30-year-old subjects,

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Submitted April 30, 1994; accepted January 29, 1996.

Supported by grants from The Yrjö Jahnsson Foundation and in part by a fellowship from the Finnish Ministry of Education (S.T.) and a fellowship from the Emil Aaltonen Foundation (T.L.). The Cardiovascular Risk in Young Finns study was supported by the Sigrid Juselius Foundation, the Medical Research Council of Finland, and the Juho Vainio Foundation.

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0026-0495/96/4507-0001$03.00/0

whose surface area of atherosclerotic lesions, together with serum cholesterol, increases according to phenotypes E3/2 < E3/3 < E4/3.[21]

Previous intervention studies have shown that an increase in PA decreases body weight, percentage of body fat, serum TC, LDL-C, apo B, TG, and insulin concentrations and increases serum HDL-C and apo A-I concentrations. These studies have been mostly based on aerobic exercise such as running or bicycling,[9,22-27] but resistance training also has effects on the serum lipid profile.[28,29] In addition, similar associations between PA and CHD risk factors have been found in epidemiological studies in children and young adults with regular PA.[30,31]

The aim of the present study was to evaluate the effect of PA on serum TC and LDL-C concentrations in different apo E phenotype in a young Finnish population.

SUBJECTS AND METHODS

Study Population

The Cardiovascular Risk in Young Finns Study is a multicenter study on atherosclerosis precursors in Finnish children and young adults. The initial cohort included 3,596 children and young adults aged 3, 6, 9, 12, 15, and 18 years who were chosen from the national population register according to their unique personal identification number. The first cross-sectional survey was conducted in 1980. Follow-up studies were performed in 1983 and 1986. Details of the subject selection and study design have been presented elsewhere.[32,33] The present report includes results for 713 males and 785 females who participated in the study in 1986 (Table 1) for whom determinations of apo E phenotype were available. The study protocol was approved by the ethics committees of each of five participating universities (medical schools of Helsinki, Kuopio, Oulu, Tampere, and Turku).

Anthropometric Examinations

At the physical examination, height was measured by a Seca anthropometer and weight by a Seca weighing scale (Vogel & Halke, Hamburg, Germany). Subscapular skinfolds were measured from the nondominating side using a Harpenden skinfold caliper. Body mass index ([BMI] kilograms per square meter) was calculated.[34]

PA and Dietary Habits

Participation in leisure-time PA was assessed with a questionnaire. Participants were asked about the frequency and intensity of participation in PA outside school hours. An index for leisure-time PA was calculated from the product of intensity times estimated duration times monthly frequency.[35,36] For intensity, we used coefficient values of 4 (never sweating and becoming breathless) corresponding to light aerobic activity, 6 (some sweating and becoming breathless) corresponding to moderate aerobic activity, and 10 (heavy sweating and becoming breathless) corresponding to intense aerobic activity. The coefficient values, 4, 6, and 10, for different levels of intensity were chosen to estimate the metabolic cost of each intensity level. The values were estimated from existing tables.[35-37] A mean value of 30 minutes for duration (coefficient 0.5) was used in the case of PA other than supervised exercise. In the case of supervised exercise (participation in a sports club session), a mean value of 45 minutes for duration (coefficient 0.75) was used. A coefficient value of 0 for duration was used in case of no leisure-time PA. Coefficient values for monthly frequency of activity were 0.5 (< once per month), 1 (once per month), 2.5 (two to three times per month), 4.3 (once per week), 17 (two to six times per week), and 30 (once per day). The range of the index was 0 to 225. The distribution of the PA index was skewed to the right in both sexes, ie, high index levels were less frequent than low levels (data not shown).

Dietary interviews of every second consecutive subject were conducted by trained interviewers using the 48-hour recall method.[38,39]

Table 1. Apo E Phenotype Distribution

Apo E Phenotype	Male	Female
E2/2	3*	2*
E3/2	35	45
E3/3	432	467
E4/2	14*	14*
E4/3	226	244
E4/4	20	29
Total	730	801

*Excluded.

Table 2. Selected Anthropometric and Biochemical Parameters in the Study Cohort

Parameter	Males (n = 785)	Females (n = 713)	*P*
Age	15.9 ± 4.8	16.2 ± 4.8	
PA index*	3.4 ± 1.4	3.2 ± 1.3	.0055
BMI (kg/m²)	20.3 ± 3.5	20.0 ± 3.3	.0115
Subscapular thickness (mm)	9.2 ± 5.3	12.1 ± 6.2	.0001
TC (mmol/L)	4.65 ± 0.89	4.94 ± 0.97	.0001
LDL-C (mmol/L)	2.87 ± 0.83	3.06 ± 0.89	.0001
HDL-C (mmol/L)	1.39 ± 0.26	1.49 ± 0.26	.0001
HDL/TC ratio	0.31 ± 0.07	0.31 ± 0.06	.3554
TG (mmol/L)	0.86 ± 0.46	0.87 ± 0.34	.1178
Apo B (g/L)	0.86 ± 0.23	0.92 ± 0.25	.0017
Apo A-I (g/L)	1.43 ± 0.21	1.54 ± 0.23	.0001
Fat content of daily energy intake (%)	39.7 ± 6.3	37.3 ± 6.3	.0001
Total intake of cholesterol (mg/d)	481 ± 336	340 ± 214	.0001
Intake of saturated fatty acids (g/1,000 kcal energy)	21.7 ± 5.4	20.4 ± 5.3	.0002

NOTE. *P* values for differences in the means were calculated in an analysis of covariance adjusted for age, and refer to the mean difference between groups.

*Logarithm.

Blood Sampling and Storage

Venous blood samples were drawn from an antecubital vein into tubes containing EDTA, with the subject recumbent after an overnight fast. Plasma samples were stored at −20°C for up to 20 months until phenotyped. For assays of serum lipid, blood was allowed to clot at room temperature for 60 minutes before separation of serum. Sera were stored at −25°C a maximum of 14 months until analyzed.

Apo E Phenotyping

Phenotype analysis (Table 1) was performed using slight modifications of the original method of Mentzel and Utermann.[40] We used delipidated plasma, isoelectric focusing, cysteamine treatment, and immunoblotting. The method is described in detail by Lehtimäki et al.[41]

Lipid and Apolipoprotein Analyses

Lipid analyses were performed in duplicate at the laboratory of the Research and Development Unit, Social Insurance Institution,

Turku, Finland. This laboratory continuously checks cholesterol determinations with the World Health Organization reference laboratory in Prague, The Czech Republic. Serum TC (CHOD-PAP; Boehringer, Mannheim, Germany) and TG (Boehringer) were determined by standard enzymatic methods. Serum HDL-C level was measured from the serum supernatant after precipitation of very-low-density lipoprotein and LDL with dextran sulfate (DS-500,000) and $MgCl_2$.[42] LDL-C concentrations were calculated by the Friedewald formula.[43] Apo A-I and apo B were determined by immunoturbidometry.[44] Details of the methods have been presented elsewhere.[44] Intraassay coefficients of variation for the determinations of TC, HDL-C, and TG were 1.6%, 1.7%, and 2.6%, respectively. Interassay coefficients of variation were 2.2% for TC, 3.8% for HDL-C, and 4.4% for TG.

Statistical Methods

Serum TG and PA index values were log-transformed for statistical computations because of skewed distributions. We calculated indicator variables (0/1) for apo E phenotypes E3/2, E3/3, E4/3, and E4/4. Phenotypes E2/2 (n = 5) and E4/2 (n = 28) were excluded from the analyses due to the small number of cases.

Differences in selected lipid and anthropometric variables between the sexes are presented as the mean ± SD, and *P* values for differences in these means were calculated in an analysis of covariance adjusted for age. The PA × apo E phenotype interaction was tested by linear regression analyses. Dependent variables were LDL-C, TC, HDL-C, HDL/TC ratio, and TG. The independent variables included main effects for PA (PA index) and apo E phenotype (indicator variables), and a PA × apo E phenotype interaction term (interaction between phenotypes E4/4 and E3/2).

Pearson correlation coefficients were calculated between dietary variables and the PA index, and *P* values for these associations were calculated in regression analyses adjusted for sex.

Analyses were performed using version 6.04 of the Statistical Analysis System (SAS) scientific software for microcomputers (SAS Institute, Cary, NC).

RESULTS

The relations of apo E phenotype and PA on serum lipids in a population-based sample of 1,498 subjects (713 males and 785 females) aged 9 to 24 years with regular PA were studied. Subject characteristics are shown in Table 2. Males were physically more active than females, on average, although median values for PA did not differ between sexes. Males were leaner and had lower levels of TC, LDL-C, HDL-C, apo B, and apo A-I, but no difference was found in the HDL/TC ratio or TG between the sexes. The

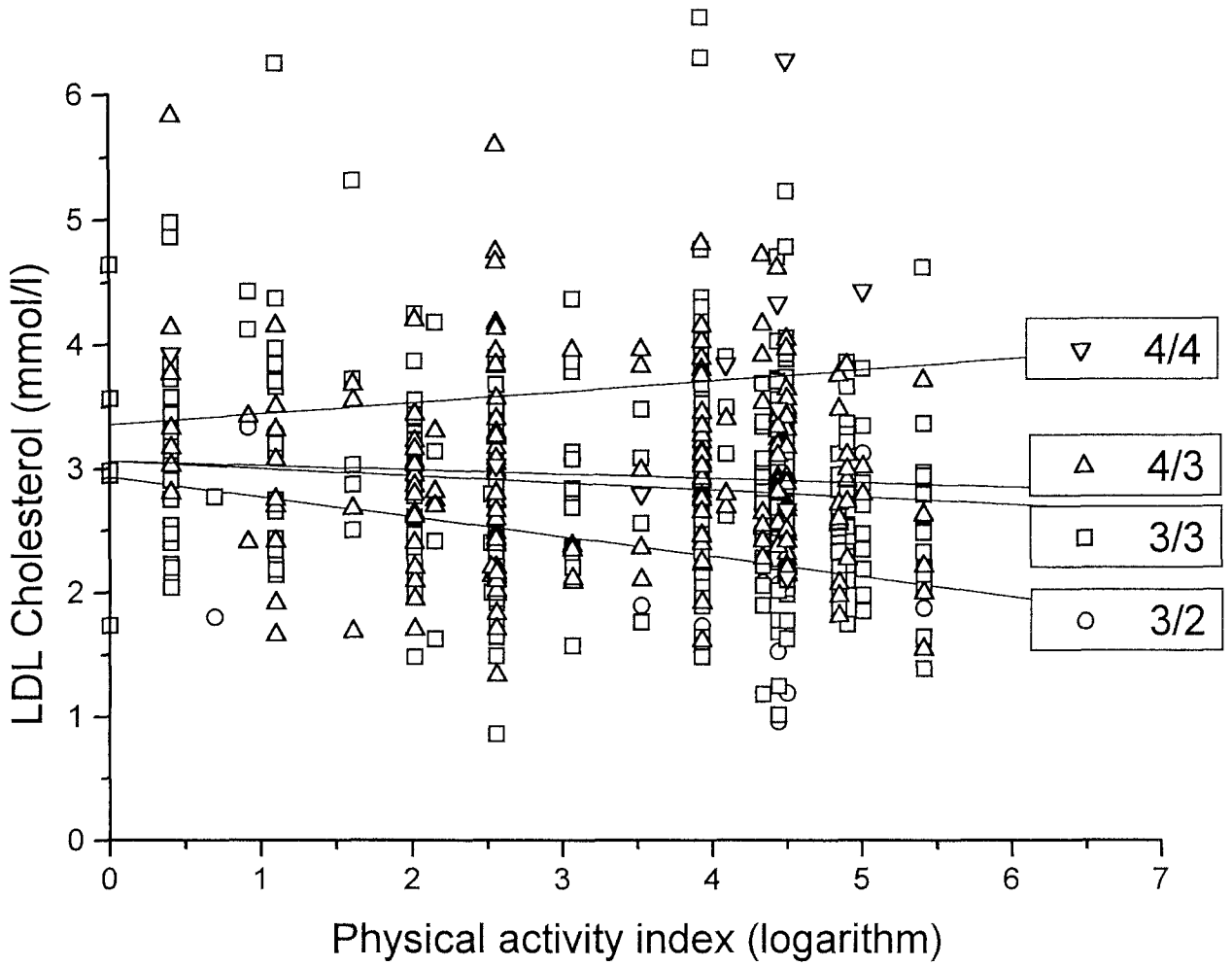

Fig 1. Relationship between serum LDL-C and PA in different apo E phenotypes in 9- to 24-year-old Finnish males. Lines denote linear regression curves. The apo E × PA interaction was statistically significant (*P* = .0082). Linear regression equations are as follows: apo E4/4, LDL-C = 3.36 + 0.086 · PAI; apo E4/3, LDL-C = 3.06 − 0.037 · PAI; apo E3/3, LDL-C = 3.06 − 0.060 · PAI; apo E3/2, LDL-C = 2.94 − 0.16 · PAI.

median value of 51 for the PA index in both males and females corresponded approximately to 1.2 hours of running every week.

Associations between serum lipids and exercise were different in males and females. Significant ($P < .05$) PA × sex interactions were found in TC, LDL-C, and the HDL/TC ratio. In males, PA was associated inversely with body mass index (BMI) ($P = .0001$), subscapular thickness ($P < .0001$), TC ($P = .025$), LDL-C ($P = .012$), TG ($P = .0002$), and apo B ($P = .0041$) and positively with HDL-C ($P = .0043$) and the HDL/TC ratio ($P = .0002$). In females, exercise was inversely associated with BMI ($P = .0009$), subscapular thickness ($P < .0001$), and serum TG ($P < .0004$).

No significant sex differences were found in lipid levels by apo E phenotypes. Apo E phenotype was associated with TC ($P < .0001$), LDL-C ($P < .0001$), the HDL/TC ratio ($P < .0001$), and apo B ($P < .0001$). No such associations were found in HDL-C ($P = .29$), TG ($P = .33$), and apo A-I ($P = .82$).

PA was not significantly associated with TC or LDL-C in females, and therefore we present results for the males only. LDL-C, TC, and HDL/TC ratio associations to exercise varied with apo E phenotype. PA × apo E phenotype interactions were statistically significant in LDL-C ($P = .0082$), TC ($P = .014$), and the HDL/TC ratio ($P = .0004$). No such interactions were found in the HDL-C ($P = .77$), TG ($P = .56$), apo B ($P = .24$), or apo A-I ($P = .63$) response to exercise. The effect of PA on LDL-C, TC, or the HDL/LDL ratio was not found in apo E phenotype E4/4. A moderate inverse effect of PA on TC and LDL-C (Fig 1) and a positive effect on the HDL/TC ratio (Fig 2) were found in the phenotypes E4/3 and E3/3, and a similar but stronger association was found between these variables within phenotype E3/2 in males.

PA was correlated positively with daily total energy intake per kilogram body weight ($r = .13$, $P = .013$) and inversely with the proportion of fat in the daily energy intake ($r = -.19$, $P < .0001$) and the amount of saturated fatty acids per 1,000 kcat energy ($r = -.21$, $P < .0001$; Table 3). No correlation was found between PA and daily total intake of cholesterol per kilogram body weight ($r = .020$, $P = .39$).

DISCUSSION

There are no differences in serum TC and LDL-C between apo E phenotypes in newborns,[45] but these phenotype differences are evident in 3-year-old children.[41] Therefore, differences formed after birth may be due to environmental factors, ie, diet or different PA levels operating early in life. Our results agree with the idea that differences in

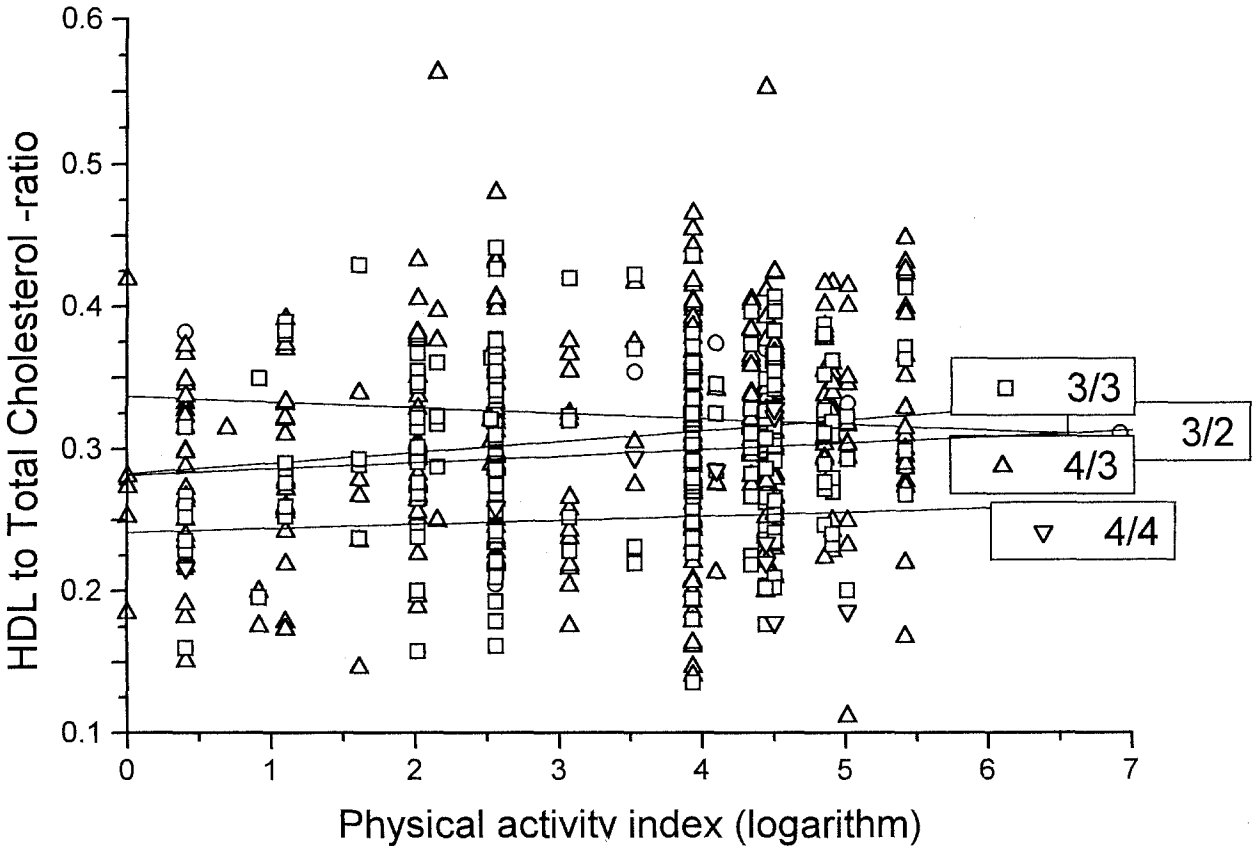

Fig 2. Relationship between the serum HDL/TC ratio and PA in different apo E phenotypes in 9- to 24-year-old Finnish males. Lines denote linear regression curves. The apo E × PA interaction was statistically significant ($P = .0004$). Linear regression equations are as follows: apo E4/4, HDL/TC = 0.24 + 0.0030 · PAI; apo E4/3, HDL/TC = 0.28 + 0.0077 · PAI; apo E3/3, HDL/TC = 0.28 + 0.0047 · PAI; apo E3/2, HDL/TC = 0.34 − 0.0038 · PAI.

Table 3. Correlations Between PA Index and Dietary Variables

Variable	Males	Females	*P*
Total energy intake (kcal/d/kg)	.13	.031	.013
Total fat intake (g/d/kg)	−.052	−.004	.44
Proportion of fat in daily energy intake (%)	−.19	−.097	.0001
Saturated fat intake			
g/1,000 kcal energy	−.21	−.054	.0001
g/d/kg	−.002	.003	.99
Total cholesterol intake (mg/d/kg)	.020	.043	.39

NOTE. *P* values were calculated in an ANOVA and analysis of covariance, and refer to the pooled correlation.

apo E phenotypes are due to external factors. On the other hand, our results suggest that the associations between PA and serum lipids are influenced by apo E phenotype in Finnish children and adolescents with regular PA. LDL-C, TC, and HDL/TC ratio associations with exercise varied with apo E phenotype. The effect of PA on serum lipids was not found in apo E phenotype E4/4. A moderate inverse effect of PA on TC and LDL-C and a positive effect on the HDL/TC ratio were found in phenotypes E4/3 and E3/3, and even stronger associations were found between these variables within phenotype E3/2 in males.

Cholesterol absorption efficiency from the intestine increases in the order of E2 (E3 or E4) < E3/3 < E4 (E3 or E4),[46] and these differences in absorption may, in part, explain differences in the LDL-C response to exercise in different apo E phenotypes. That is, subjects with E4/4 may absorb cholesterol from the intestine effectively enough to override the possible metabolic effect of PA on LDL-C. Also, the LDL apo B catabolic rate from plasma decreases in the order of E2 > E3/3 > E4.[46] The enzymes for TG hydrolysis such as lipoprotein lipase show increased activity during exercise.[47,48] There is no difference in lipoprotein lipase activity by apo E phenotypes.[12] With increasing LPL activity, more IDLs are available due to breakdown of TG-rich lipoproteins. Subjects with E4/4 seem to convert IDL to LDL effectively,[49,50] but the LDL catabolic rate from plasma is lower than in the other apo E phenotypes.[51] This implicates downregulation of LDL receptor activity as one possible mechanism behind the association of apo E polymorphisms and PA with serum cholesterol concentrations. Thus, both increased intestinal absorption of cholesterol and decreased LDL removal from plasma are possible explanations for the finding that the effect of PA is not found in subjects with the E4/4 phenotype. To our knowledge, there are no previous studies suggesting this kind of interaction between genetic factors—apo E phenotypes—and PA on serum cholesterol levels.

An increased demand of carbohydrates and fatty acids as energy substrates follows an increase in PA. Therefore, we analyzed whether our results were influenced by a possibly increased intake of dietary fat and cholesterol in subjects with increased PA. PA was correlated positively with daily total energy intake per kilogram body weight, but inversely with the proportion of fat of the daily energy intake and amount of saturated fatty acids per 1,000 kcal energy. As a result, no correlation was found between PA and daily total intake of cholesterol per kilogram body weight. The PA × apo E phenotype interaction on LDL-C variables was not explained by differences in intake of dietary cholesterol with increased PA.

The frequency, intensity, and duration of physical training are the basic elements of PA.[35] The definition of PA in the present study was based on an index calculated from these variables. The association between obesity variables and PA in the present study indicates that our PA index is a valid measure of leisure time PA. Also, PA evaluation with a questionnaire in children and adolescents has been considered acceptable.[52] Also, apo E phenotype was associated with LDL-C, TC, the HDL/TC ratio, and apo B in agreement with previous studies.[13]

The benefits of PA were evident among young males with respect to many CHD risk factors, ie, obesity, TC, LDL-C, apo B, HDL-C, and TG in males. Our results on these relationships in males are in agreement with previous studies.[30,31,53-57] However, the benefits of PA among females were seen in obesity variables and serum TG levels only. Therefore, it may be that there is a sex difference in the lipid response to exercise. Females were also somewhat less physically active than males especially in terms of intensity in the present study, which may partly explain the sex difference. The absolute level of PA may have been too low to induce changes in serum lipids in females. In addition, endogenous hormones influence lipid and apolipoprotein concentrations, which may also explain the sex difference.

In conclusion, our results suggest that differences in serum TC and LDL-C between subjects with different apo E phenotypes are influenced by the level of PA in Finnish male children and young adults. In the Finnish population, where the frequency of the apo E4 isoform is high,[41] this physiological PA-gene interaction may, to some extent, modify the expression of hypercholesterolemia and subsequently affect the high CHD incidence. However, the association between PA and LDL-C in apo E phenotype 4/4 is no excuse for physical inactivity, since no inverse association was found between PA and the HDL/TC ratio.

ACKNOWLEDGMENT

We thank Niina Railo for technical assistance.

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