0031-3998/93/3405-0670$03.00/0
PEDIATRIC RESEARCH

Vol. 34, No. 5, 1993
Printed in U.S.A.

High Lipoprotein(a) in Children from Kindreds with Parental Premature Myocardial Infarction

ALONSO MARQUEZ, SOAIRA MENDOZA, HUGO CARRASCO, TRACEY HAMER, AND CHARLES J. GLUECK

University of the Andes, Merida, Venezuela, and the Cholesterol Center, Jewish Hospital of Cincinnati, Cincinnati, Ohio 45229

ABSTRACT. In 98 children from 98 kindreds, 49 with and 49 without parental premature myocardial infarction (age ≤45 y), our specific aim was to determine whether, and to what degree, lipoprotein(a) [Lp(a)] and other atherogenic lipids and lipoproteins might be overexpressed in children from premature infarction kindreds. Median Lp(a) (270 mg/L) in case boys was nearly twice that in control boys (140 mg/L) ($p \leq 0.001$). In a logistic regression model including age, Quetelet index (relative ponderosity), Lp(a), apo A1, apo B, triglyceride, and pubertal status, the 24 case boys had higher Lp(a) ($p = 0.03$), higher triglyceride ($p = 0.036$), and marginally lower apo A1 ($p = 0.06$) than the 26 control boys. Median Lp(a) in case girls (200 mg/L) was much higher than in control girls (150 mg/L) ($p \leq 0.01$). In a logistic regression model including age, Quetelet index, Lp(a), apo A1, apo B, triglyceride, and menarchal status, Lp(a) was higher ($p = 0.02$), apo B was marginally higher ($p = 0.07$), and apo A1 was lower ($p = 0.008$) in 25 case girls than in 23 control girls. Reflecting familial clustering of major lipid-lipoprotein risk factors for coronary heart disease, children from kindreds with premature parental myocardial infarction were distinguished from children from control kindreds by high Lp(a) and also had higher apo B and triglyceride and lower apo A1 levels. (*Pediatr Res* 34: 670–674, 1993)

Abbreviations

Lp(a), lipoprotein (a)
CHD, coronary heart disease

Lp(a) is a cholesterol-carrying lipoprotein composed of the major structural protein of LDL (apo B 100) linked by a disulfide bridge to apo(a), a glycoprotein with considerable homology to plasminogen (1, 2). Lp(a) is an independently atherogenic lipoprotein, and may be thrombogenic (1, 2). As recently reported from the Bogalusa Heart Study (3), Caucasian children (8–17 y of age) from kindreds with parental premature myocardial infarction had higher levels of Lp(a) (224 mg/L) than those without parental myocardial infarction (170 mg/L, $p < 0.01$). Moreover, the prevalence of parental myocardial infarction was higher in parents of children whose Lp(a) was defined as "high" (>250 mg/L) than in those whose Lp(a) levels were ≤250 mg/L (9.5 *versus* 5.4%, $p < 0.01$) (3). Similar findings have been reported by Kostner *et al.* (4) and Hoefler *et al.* (5). In the study by Hoefler *et al.* (5), children from kindreds with parental myocardial infarction were much more likely to have Lp(a) levels >250 mg/L (32%) than controls (13.4%).

Multiple previous studies of progeny of parents with premature myocardial infarction have revealed lower HDL cholesterol, lower apo A1/apo B ratios, and higher LDL cholesterol in pediatric case subjects compared with pediatric controls (6–12). Because the origin of atherosclerosis is in childhood (13, 14), and because lipid and lipoprotein risk factors (VLDL, LDL, and HDL cholesterol) and smoking are related to both fatty streaks and raised lesions in the abdominal aorta in children and in young men (13, 14), diagnosis and therapy of pediatric risk factors (15) for adult cardiovascular disease are very important.

Our specific aim in the current study of 49 progeny of parents with premature myocardial infarction and 49 control children (no parental premature infarction) was to assess coronary artery disease risk factors in children, with a particular focus on serum Lp(a).

MATERIALS AND METHODS

Cases and controls. The study was carried out in 98 Mestizo (mixed South American Indian-Spanish) schoolchildren in Merida, Venezuela, a college, resort, and regional administrative center, population 74 000, high in the foothills of the Andes mountains. The relative ethnic contributions of Indian or Spanish ancestors to the Mestizo children could not be determined by historical or family records. The ethnic background of the Mestizo children in the Andean foothills is one of generations of variegated Indian-Spanish mixtures.

The 49 Mestizo case children (24 boys, 25 girls) came from kindreds where a parent had sustained premature myocardial infarction (at ≤45 y of age). Parental premature myocardial infarction was systematically documented by clinical, electrocardiographic, myocardial enzymatic, and coronary arteriographic studies. All 49 parents with premature myocardial infarction had greater than 50% occlusion of at least two coronary arteries on coronary angiography.

The Mestizo control group (26 boys, 23 girls) came from kindreds where the parents had not experienced premature coronary artery disease, had no clinical symptoms related to coronary artery disease, and had no familial history of premature coronary artery disease. The control children were selected from the same schools as the case subjects, and were further selected to match the case subjects' socioeconomic status.

Lipid, lipoprotein, and apolipoprotein determinations. After a 12-h fast, blood was obtained for a measurement of total cholesterol, triglyceride, HDL and LDL cholesterol by enzymatic reactions from Boehringer Mannheim (Indianapolis, IN) analyzed with the Abbott Dichromatic ABA-100 (Abbott Laboratories, N. Chicago, IL). Apo A1 and apo B were quantitated by electroimmunoassay (16).

Serum Lp(a) was measured by enzyme immunoassay, using a

Received March 29, 1993; accepted June 14, 1993.
Correspondence and reprint requests: Charles J. Glueck, M.D., Cholesterol Center, Jewish Hospital, 3200 Burnet Ave., Cincinnati, OH 45229.
Supported in part by Grant M-392-91, Merida Venezuela, M-402, and by Grants 732 and 2-728 from the Jewish Hospital Medical Research Council, Jewish Hospital of Cincinnati.

monoclonal anti-Lp(a) antibody (17). We have shown that the Terumo enzyme immunoassay (17) is interchangeable with an ELISA (Imubind) method (18). In paired aliquots in 210 patients, the intraclass correlation was significant ($r = 0.91$, $p < 0.0001$) and the lower limit of the 95% confidence interval of the intraclass correlation ($r = 0.89$) was significant (*i.e.* >0.75) (18). For the Terumo method, the within-day coefficient of variation was 1.47%, and for the Imubind method, it was 3.4% (18). Between-day coefficients of variation were 4.7% for the Terumo method and 3.0% for the Imubind method (18).

Study protocol. This study followed a protocol approved by the Institutional Review Committee of the University of the Andes and was carried out with signed informed consent.

When case and control schoolchildren were studied in the outpatient center of the University of Andes, in addition to lipid, lipoprotein, and apolipoprotein measurements (as above), their age, weight, height, pubertal and menarchal status, and systolic and diastolic blood pressures were recorded. In both case subjects and controls, a 7-d diet record was obtained. Using energy and nutrient tables for Venezuelan populations (19), a semiquantitative estimation of group nutritional patterns was obtained, with data available for total calories, protein, saturated and polyunsaturated fat, carbohydrates, and cholesterol intake.

Statistical methods. Because most of the lipid, lipoprotein, and apolipoprotein data were not normally distributed, Wilcoxon nonparametric tests of difference were used to compare groups (20) (Table 1). Although the ages of case subjects and controls did not differ ($p > 0.1$), male case subjects were (on average) 1 y older and female case subjects were 2 y older (Table 1). To assess for the possible effects of age and age-associated higher Quetelet indices, we also covariance-adjusted the data in Table 1 for age and Quetelet index, and then compared the adjusted least square means (20).

Logistic regression (20) (Table 2) was used with group as the dependent variable, and explanatory variables included Quetelet index, age, Lp(a), apo A1, apo B, triglyceride, menarchal state (for girls), and pubertal state (for boys).

Differences in nutrient intakes (g/1000 cal of energy intake, percent of calories) between groups were compared by *t* tests (20) because the data were normally distributed.

RESULTS

Differences between case subjects and controls for lipids, lipoproteins, and Lp(a). As summarized in Table 1, there was a consistent pattern of significant ($p \leq 0.05$) differences between case subjects and controls (within sex) as follows: *1*) HDL cholesterol and apo A1 were lower in case subjects than in control children; *2*) apo B was higher in case subjects than in control children; *3*) the ratio of apo A1 divided by apo B was lower in case subjects than in control children; *4*) the ratio of HDL divided by LDL cholesterol was lower in case subjects than in control children; and *5*) Lp(a) was higher in case subjects than in controls.

This pattern of differences between case subjects and controls by Wilcoxon tests (Table 1) was replicated, with levels of significance essentially unchanged, after covariance adjusting for age and Quetelet index (data not shown).

Male case subjects had much higher median Lp(a) (270 mg/L) than male controls (140 mg/L, $p = 0.001$) (Table 1). Similarly, female case subjects had much higher Lp(a) than female controls (200 *versus* 150 mg/L, $p = 0.003$) (Table 1). The Lp(a) distribu-

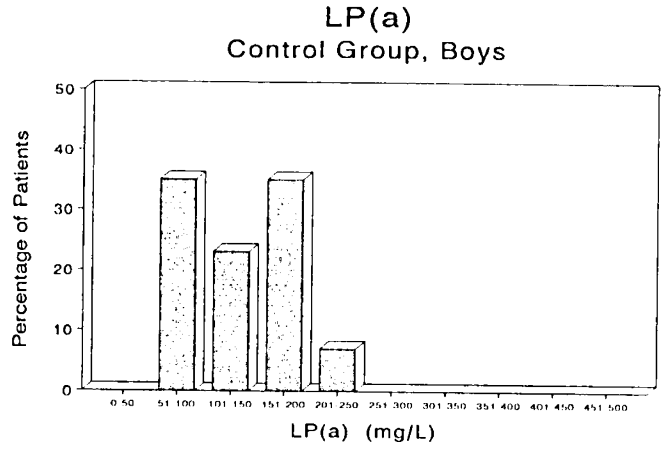
Table 1. *Clinical characteristics, lipids, lipoproteins, and apolipoproteins in progeny of parents with premature myocardial infarction and in controls**

	Boys						Girls					
	Cases ($n = 24$)			Controls ($n = 26$)			Cases ($n = 25$)			Controls ($n = 23$)		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
Age (yr)	11	13	6	10	11	4.2	13	14	6	11	11	5
Weight (kg)	39	38	21	33	31	13	42	41	18	39	36	17
Height (cm)	139	148	35	137	141	25	140	150	23	141	147	23
SBP (mm Hg)	105	100	14	102	100	15	102	100	11	98	100	8.7
DBP (mm Hg)	63	60	8	62	60	7	64	60	7.6	61	60	7
Quetelet index ($kg/cm^2 \times 1000$)	1.85	1.81	0.31	1.67	1.64†	0.26	2.1	1.9	0.52	1.9	1.8	0.33
Waist/hip ratio (U)	0.92	0.92	0.05	0.9	0.92	0.11	0.87	0.87	0.09	0.86	0.86	0.1
TC (mmol/L)	4.69	4.18	1.71	4.10	4.00	1.1	4.85	4.78	1.15	4.40	4.60	0.83
TG (mmol/L)	1.17	1.11	0.44	0.95	0.94	0.36	1.29	1.20	0.57	1.13	1.10	0.39
HDLC (mmol/L)	0.95	0.93	0.18	1.33	1.32‡	0.27	1.14	1.09	0.33	1.31	1.29§	26
LDLC (mmol/L)	3.23	2.75	1.61	2.53	2.37	0.82	3.1	2.92	1.01	2.55	2.43	0.84
HDLC/TC (U)	0.21	0.21	0.06	0.32	0.31‡	0.04	0.2	0.26	0.08	0.3	0.28	0.07
HDLC/LDLC (U)	0.35	0.33	0.17	0.59	0.55†	0.25	0.41	0.4	0.19	0.58	0.52§	0.27
Apo A1 (mg/L)	830	840	170	990	1000†	160	850	840	190	1010	950†	170
Apo B (mg/L)	630	610	130	530	540†	110	680	660	200	530	540†	80
Apo A1/apoB (U)	1.37	1.44	0.39	1.93	1.88‡	0.41	1.35	1.54	0.45	1.95	1.85†	0.41
Lp(a) (mg/L)	290	270	103	150	140‡	47	270	200	140	160	150†	60

* SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDLC, HDL cholesterol; LDLC, LDL cholesterol.
† $p \leq 0.01$.
‡ $p \leq 0.001$.
§ $p \leq 0.05$.

Table 2. *CHD risk factors differentiating case subjects from controls (logistic regression)*

	Explanatory variable	Parameter estimate	χ^2	p
Boys: Case subjects/controls	Lp(a)	0.45	4.63	0.031
	Triglyceride	0.06	4.39	0.036
	Apo A1	−0.08	3.53	0.060
	Model: Case subject/control = Quetelet index + age + Lp(a) + apo A1 + Apo B + triglyceride + pubertal status			
Girls: Case subjects/controls	Apo A1	−0.11	6.97	0.008
	Lp(a)	0.14	5.41	0.02
	Apo B	0.13	3.27	0.07
	Model: Case subject/control = Quetelet index + age + Lp(a) + apo A1 + apo B + triglyceride + menarchal status			



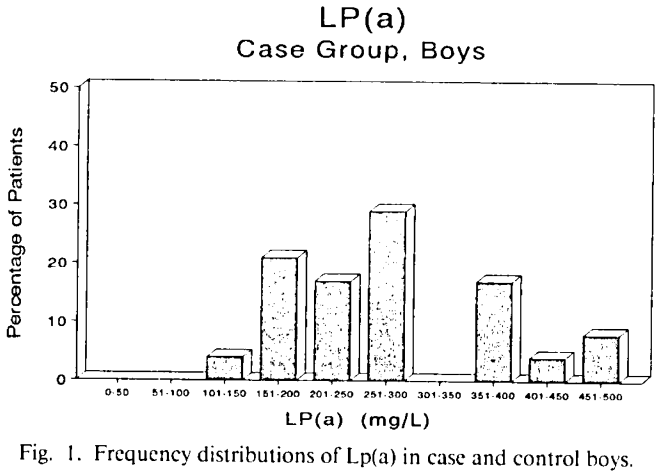
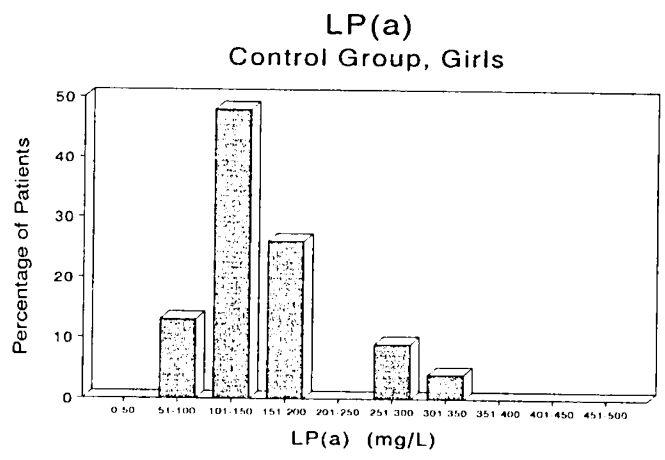


Fig. 1. Frequency distributions of Lp(a) in case and control boys.



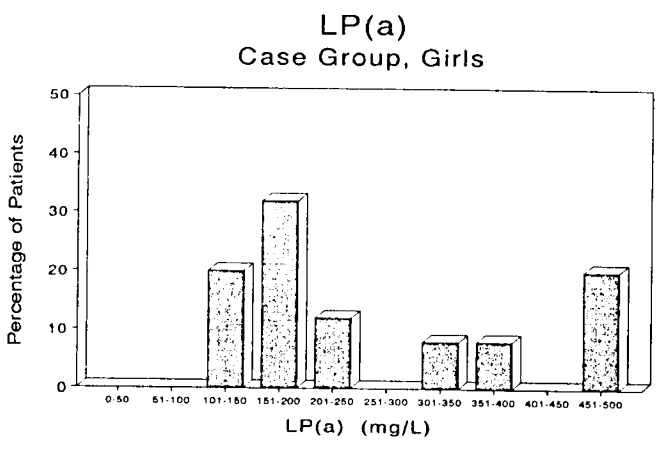


Fig. 2. Frequency distributions of Lp(a) in case and control girls.

tion in case subjects was sharply skewed toward higher values than in controls (Figs. 1 and 2).

Coronary heart disease risk factors as independent significant determinants between case and control children. By logistic regression in boys, case subjects had higher Lp(a) ($p = 0.03$), higher triglyceride ($p = 0.036$), and marginally lower apo A1 ($p = 0.06$) (Table 2). By logistic regression in girls, case subjects had higher Lp(a) ($p = 0.02$), marginally higher apo B ($p = 0.07$), and lower apo A1 ($p = 0.008$) (Table 2).

Nutrient intake. As displayed in Figure 3, the percentages of calories from protein, fat, saturated fat, polyunsaturated fat, and carbohydrate did not differ ($p > 0.1$) when comparing case subjects with controls.

Mean (SEM) total caloric intake/d was higher in case subjects (1615 ± 437) than in controls (1313 ± 474) ($p \leq 0.01$). Mean (SEM) intake of protein (g/1000 cal/d) in controls (41.8 ± 1.36) and case subjects (43.5 ± 0.87) did not differ ($p > 0.1$, Fig. 4), nor did intake of total fat in controls (31.4 ± 1.46) and case subjects (33.9 ± 1.44). Controls ingested more carbohydrate (149.3 ± 4.37 g/1000 cal/d) than case subjects (131 ± 3.89) ($p = 0.002$) and less cholesterol (149.8 ± 4.7 mg/1000 cal/d) than case subjects (176.5 ± 6.7) ($p = 0.002$) (Fig. 4).

DISCUSSION

Given the heritability of the major CHD risk factors, total, HDL, and LDL cholesterol, apo A1, apo B, and Lp(a) (1–12,

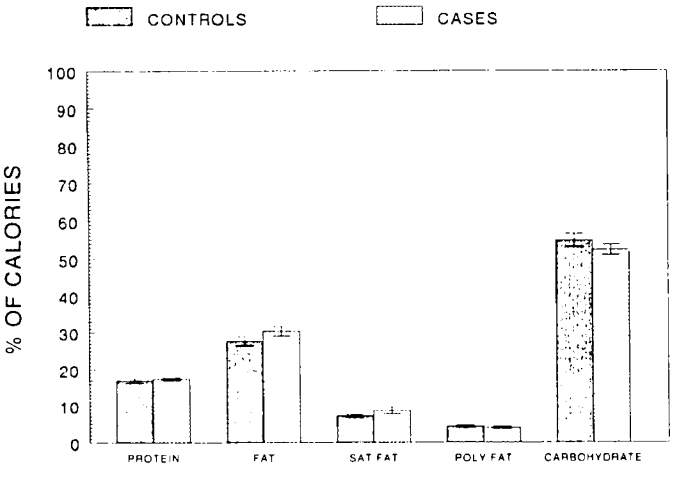


Fig. 3. Mean (SEM) percent of calories from protein, fat, saturated fat, polyunsaturated fat, and carbohydrate in case subjects *vs* controls.

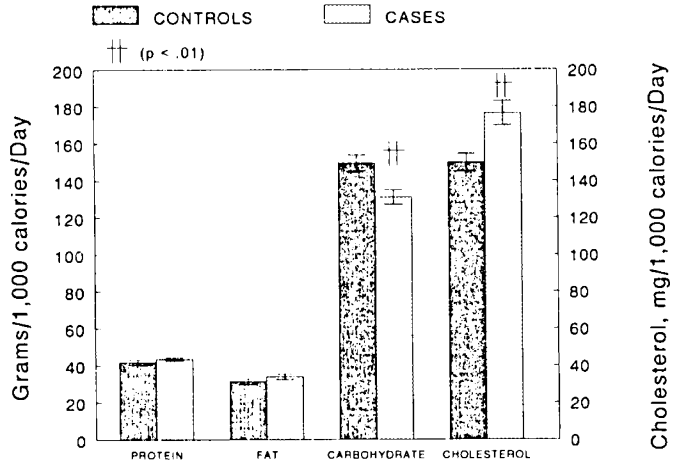


Fig. 4. Mean (SEM) dietary protein, fat, and carbohydrate (g/1000 cal/d) and dietary cholesterol (mg/1000 cal/d) in case subjects *vs* controls.

21), it was not surprising in our study that progeny of parents with premature myocardial infarction had lower HDL cholesterol, lower apo A1, lower apo A1/apo B ratios, higher LDL cholesterol, and higher Lp(a) than children from families without premature myocardial infarction. Although case children ingested more dietary cholesterol than controls, case subjects and controls did not differ in regard to total fat intake per 1000 cal/d and had comparable percentages of calories from total fat, saturated fat, and polyunsaturated fat.

In our study, in both boys and girls from families with premature myocardial infarction, Lp(a) was an independent significant determinant of case subjects *versus* controls, congruent with the report of the Bogalusa Heart Study (3), and with studies by Kostner *et al.* (4) and Hoefler *et al.* (5).

Although case subjects were not significantly older than controls ($p > 0.10$), male and female case subjects were (on average) 1 and 2 y older, respectively, than controls. Older children might have relatively lower total and HDL cholesterol levels than younger children because of the effects of puberty (22, 23). Older children might also have a higher Quetelet index than younger children (24). Thus, differences in total, HDL, and LDL cholesterol and apo B between case subjects and controls may be slightly underestimated and differences in Quetelet index overestimated in this study. However, case-control differences for the measured lipid, lipoprotein, and apolipoprotein variables were not affected by covariance adjusting for age and Quetelet index. Moreover, both age and Quetelet index were included in the logistic regression models and were not significant discriminants between case subjects and controls.

The complex contributions of puberty (22, 23), age, and Quetelet index (24) to distributions of lipids, lipoproteins, and apolipoproteins in both case and control children probably accounted to a large degree for the nonnormality of the distributions. Lp(a) is almost never normally distributed (1–5) and appears to be independent of pubertal status, Quetelet index, age, and type of nutritional intake, with levels predominantly genetically determined (1–5, 25).

Given the heritability of Lp(a) and its association with premature CHD (3–5, 25–27), it is not surprising, in this and in previous studies (3–5), that progeny of parents with premature myocardial infarction are much more likely to have high levels of Lp(a) than control children. Uniformly effective therapeutic interventions for Lp(a) are not yet available for either adults or children (1). However, because Lp(a) is synergistic with other CHD risk factors (particularly LDL cholesterol) (1, 2), identification of children from families with premature myocardial infarction who have high Lp(a) and who have other major risk factors for CHD, should, in our opinion, intensify the level of intervention (15) against treatable CHD risk factors. Moreover, when and if safe and effective therapeutic interventions to lower Lp(a) are available, and if it can be shown in adults that lowering Lp(a) independently reduces CHD risk, then these interventions can be expeditiously applied to children with previously diagnosed high Lp(a) and strong family histories of premature CHD.

REFERENCES

1. Glueck CJ, Glueck HI, Tracy T, Speirs J, McCray C, Stroop D 1993 Relationships between lipoprotein(a), lipids, apolipoproteins, basal and stimulated fibrinolytic regulators, and D-Dimer. Metabolism 42:236–246
2. Scanu AM 1992 Lp(a): a link between thrombosis and atherosclerosis. Eur J Epidemiol 8(suppl 1):76–78
3. Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS 1991 Racial (black-white) differences in serum lipoprotein(a) distribution and its relation to parental myocardial infarction in children. Bogalusa Heart Study. Circulation 84:160–167
4. Kostner GM, Czinner A, Pfeiffer KH, Bihari-Varga M 1991 Lipoprotein(a) concentrations as risk indicators for atherosclerosis. Arch Dis Child 66:1054–1056
5. Hoefler G, Harnoncourt F, Paschke E, Mirtl W, Pfeiffer KH, Kostner GM 1988 Lipoprotein Lp(a). A risk factor for myocardial infarction. Arteriosclerosis 8:398–401
6. Widhalm K, Koch S, Pakosta R, Schurz M, Brendinger M 1992 Serum lipids, lipoproteins and apolipoproteins in children with and without familial history of premature coronary heart disease. J Am Coll Nutr 11(suppl):32S–35S
7. Glueck CJ, Fallat RW, Tsang R, Buncher CR 1974 Hyperlipemia in progeny of parents with myocardial infarction before age of 50. Am J Dis Child 127:70–75
8. Pometta D, Micheli H, Raymond C, Oberhaensli I, Svenram A 1980 Decreased HDL cholesterol in prepubertal and pubertal children of CHD patients. Atherosclerosis 36:101–109
9. DeBaecker G, Hulstaert F, DeMunck K, Rosseneu M, van Parijs L, Dramaix M 1986 Serum lipids and apoproteins in students whose parents suffered prematurely from myocardial infarction. Am Heart J 112:478–484
10. Perova N, Aingorn H, Metelskaya V, Dorofeeva T, Belonkonj N 1988 Plasma lipid and apoprotein levels in children hereditarily predisposed to coronary heart disease. Acta Paediatr Scand 77:559–562
11. Freedman DS, Srinivasan SR, Shear CL, Webber LS, Berenson GS 1986 The relation of apolipoproteins A1 and B in children to parental myocardial infarction. N Engl J Med 315:721–726
12. Lee J, Lauer RM, Clarke WR 1986 Lipoproteins in the progeny of young men with coronary artery disease: children with increased risk. Pediatrics 78:330–337
13. Newman III WP, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, Williamson GD, Webber LS, Berenson GS 1986 Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis: the Bogalusa Heart Study. N Engl J Med 314:138–144
14. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group 1990 Relationship of atherosclerosis in young men to serum lipoprotein cholesterol concentrations and smoking. JAMA 264:3018–3024
15. NCEP 1991 Report of the expert panel on blood cholesterol levels in children and adolescents. US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD
16. Laurell CB 1966 Quantitative estimation of protein by electrophoresis in agarose gel containing antibodies. Ann Biochem 15:45–52
17. Silberman S, Armentrout M, Vella FA, Saha AL 1990 Macra Lp(a) for

quantitation of human lipoprotein(a) by enzymes. Clin Chem 36:961
18. Glueck CJ, McCray C, Stroop D, Tracy T, Speirs J 1992 Measurement of Lp(a): comparison of Terumo and Imubind methods. Clin Res 40:414A(abstr)
19. Mendoza S, Contreras G, Ineichen E, Fernandez M, Nucete H, Morrison JA, Gartside P, Glueck CJ 1980 Lipids and lipoproteins in 1298 Venezuelan and 472 American school children: within and cross-cultural comparisons. Pediatr Res 14:272–277
20. Snedecor GW, Cochran WG 1980 Statistical methods, 7th Ed. Iowa State University Press, Ames, IA
21. Glueck CJ, Laskarzewski P, Rao DC, Morrison JA 1985 Familial aggregations of coronary risk factors. In: Connor W, Bristow D (eds) Coronary Heart Disease. Lippincott, Philadelphia, pp 173–193
22. Morrison JA, Laskarzewski PM, Rauh JL, Brookman R, Mellies M, Frazer M, Khoury P, deGroot I, Kelly K, Glueck CJ 1979 Lipids, lipoproteins, and sexual maturation during adolescence: the Princeton maturation study. Metabolism 28:641–649
23. Morrison JA, DeGroot I, Edwards BK, Kelly KA, Mellies MJ, Khoury P, Glueck CJ 1978 Lipids and lipoproteins in 927 school children, ages 6–18 years. Pediatrics 62:990–995
24. Laskarzewski PM, Morrison JA, Mellies MJ, Kelly K, Gartside PS, Khoury P, Glueck CJ 1980 Relationships of measurements of body mass to plasma lipoproteins in school children and adults. Am J Epidemiol 111:395–407
25. Sandhofer C, Saha N, Kark J, Rees A, Jaross W, Dieplinger H, Hoppichler F, Boerwinkle E, Utermann G 1992 Apo(a) isoforms predict risk for coronary heart disease. A study in six populations. Arteriosclerosis Thrombosis 12:1214–1226
26. Armstrong VW, Cremer P, Eberle E, Manke A, Schulze F, Wieland H, Kreuzer H, Seidel D 1986 The association between serum Lp(a) concentration and angiographically assessed coronary arteriosclerosis. Atherosclerosis 62:249–257
27. Wang XL, Wilcken DE, Dudman NP 1992 Early expression of the apolipoprotein(a) gene: relationships between infants and their parents' serum apolipoprotein(a) levels. Pediatrics 89:401–406