European Heart Journal (1998) **19,** 395–401

High incidence of dyslipidaemia in the offspring of Greek men with premature coronary artery disease

L. S. Rallidis, N. H. Papageorgakis*, A. A. Megalou*, N. J. Exadactylos†, G. K. Tsitouris† and E. G. Papasteriadis

*Department of Cardiology, General Hospital of Nikea, Piraeus; †Department of Cardiology and *Biochemistry Laboratory, Evangelismos Hospital, Athens, Greece*

Aim The present study aimed to assess the incidence and type of lipid disorders in the offspring of young Greek coronary patients.

Methods One hundred and ninety-three children and youngsters were divided into two groups. Group A consisted of 104 children whose fathers had sustained a myocardial infarction before the age of 55 years. Eighty-nine young subjects matched for age, gender, dietary and smoking habits without a familial history of coronary artery disease served as controls (group B). Total cholesterol, triglycerides, high density lipoprotein cholesterol, low density lipoprotein cholesterol and lipoprotein(a) were measured in the children and the affected fathers.

Results Fifty-three percent of the offspring of young coronary patients had elevated total cholesterol or elevated triglycerides or decreased high density lipoprotein cholesterol or a combination, while the 80·4% of the affected fathers had lipid disorders. The distribution of lipid disorders in the children bore a striking resemblance to those seen in their affected fathers and there was a significant correlation between offspring–father total cholesterol, low density lipoprotein cholesterol and lipoprotein(a). When excess lipoprotein(a) was added to the lipid disorders the incidence of dyslipidaemia in the offspring of the affected individuals was increased to 63·5%.

Conclusions Dyslipidaemia is very common in the offspring of Greek men with premature coronary artery disease; this occurrence emphasizes the need always to evaluate the lipid profile in these children. The detection of dyslipidaemia necessitates the early institution of preventive measures with the expectation that the incidence of cardiovascular disease will decrease later in life.
(Eur Heart J 1998; 19: 395–401)

Key Words: Family history, lipoprotein(a), offspring, premature coronary artery disease, total cholesterol.

Introduction

Multiple studies have demonstrated that atherosclerosis has its silent beginning during childhood[1,2]. Fatty streaks are the earliest grossly visible arterial lesions of the atherosclerotic process. Autopsy studies have suggested that fatty streaks are the precursors of mature atherosclerotic lesions[3]. Coronary artery disease, particularly when it presents early in adult life, has been observed to have a familial tendency. This clustering of coronary artery disease is partly explained by the familial aggregation of the traditional risk factors (hyperlipidaemia, hypertension and diabetes mellitus)[4], while unknown or new factors such as fibrinogen[5–7] and plasminogen activator inhibitor-1[8] may also contribute. With the development of risk factor modification methods in adults, has emerged the possibility of preventing or delaying the coronary artery disease when appropriate measures are applied early in life.

In our study, we assessed the incidence and type of lipid disorders in the offspring of men with premature coronary artery disease and explored the correlation with the lipid levels of their fathers.

Methods

Study population

We studied 193 children and youngsters. Group A consisted of 104 children (6–25 years old) whose fathers had sustained a myocardial infarction under the age of 55 years ('cases'). These children were recruited in a consecutive manner from male patients who had been admitted to our Cardiology Department over the period

Revision submitted 31 August 1997, and accepted 5 September 1997.

Correspondence: Loukianos Rallidis, MD, 74 Thermopylon, Argyroupolis 16451, Athens, Greece.

0195-668X/98/030395+07 $18.00/0 hj970770

Table 1 Characteristics of the young subjects with (group A) and without (group B) a history of premature paternal myocardial infarction

	Group A (n = 104)	Group B (n = 89)	*P* value
Variables in offspring			
Age (years)	16·7 ± 6	17·3 ± 6·5	ns
Boys/girls	54/50	44/45	ns
Body mass index (kg . m^{-2})	22·3 ± 4·2	21·9 ± 3·8	ns
Systolic blood pressure (mmHg)	104 ± 13	105 ± 14	ns
Diastolic blood pressure (mmHg)	73 ± 9	72 ± 10	ns
Smoking habit (%)	17	18	ns
Oral contraceptive use	1	1	ns

1992–1994 with an acute myocardial infarction. There was no maternal history of coronary artery disease in these children. Children with a family history of diabetes mellitus or hypertension were excluded. Also, patients whose children were under the age of 6 years did not participate. One hundred and fifty-six men under the age of 55 years presented to our Department with acute myocardial infarction, of whom 31 were excluded due to coexisting diabetes mellitus or hypertension. Twenty-four patients who were unmarried or had no children or whose children were under the age of 6 years were not recruited. From the remaining 101 patients, 78 (mean age 46 ± 6 years) agreed to the participation of their children in our study. After discharge, the patients were examined over a 4-month period. Two patients died in the early post-infarction period and 25 did not attend the follow-up appointment. In the remaining 51 patients, lipid levels were measured at 4 months when it was expected that acute-phase changes in lipids due to myocardial infarction would have resolved completely.

Eighty-nine young subjects (6–24 years old) without a familial history of coronary artery disease (parents and grandparents), diabetes mellitus or hypertension served as controls (group B). These were recruited from a primary and technical school in Athens. The mean age of their fathers was 50 ± 7 years. A detailed history was taken from all the young subjects concerning smoking and dietary habits and use of oral contraceptives for girls. Blood pressure was measured with a mercury sphygmomanometer. The body mass index was defined as weight/height^2 (kg . m^{-2}).

Biochemical analyses

After a 12 h fast, venous blood was drawn between 0730 and 0900 h. Serum for lipid measurements was prepared from additive-free blood samples by centrifugation for 10 min at 3000 ***g***. Serum was transferred in aliquots to plastic tubes and stored at 4 °C until assay within 48 h. Total cholesterol and triglycerides were measured by an enzymatic method in a Technicon RA-1000 analyser. High density lipoprotein cholesterol was assayed by dextran sulphate-magnesium precipitation. Low density lipoprotein cholesterol was calculated according to the Friedeland–Fredrickson formula: low density lipoprotein cholesterol = total cholesterol − (triglycerides/5 + high density lipoprotein cholesterol). Lipoprotein(a) was measured in a Behring 100 nephelometer by a nephelometric method. The within-assay coefficient of variation for total cholesterol, triglycerides and high density lipoprotein cholesterol was 2%, 3·1% and 2·2%, respectively. The intra-assay coefficient of variation for lipoprotein(a) was 4·7%.

Statistical methods

Values are expressed as mean ± SD. Logarithmic transformation was made on lipoprotein(a) in order to normalize its highly skewed distribution. Differences between means were compared with an unpaired Student's t-test and differences in proportions with the chi-square statistic. Simple linear regression analysis was applied to examine the relationship between two variables. A *P* value <0·05 was considered significant.

Results

Table 1 shows the characteristics of the subjects studied. The two groups did not differ significantly with respect to age, sex, body mass index, systolic and diastolic blood pressure, cigarette smoking and oral contraceptive use for girls.

The results of lipid measurements are shown in Table 2. Mean levels of total cholesterol, low density lipoprotein cholesterol, lipoprotein(a), total cholesterol/high density lipoprotein cholesterol and low density lipoprotein cholesterol/high density lipoprotein cholesterol were higher in the children of the affected individuals compared to the controls. This difference was maintained in the subgroup of boys (Fig. 1, top panel) but was abolished for the ratios of total cholesterol/high density lipoprotein cholesterol and low density lipoprotein cholesterol/high density lipoprotein cholesterol in the subgroup of girls (Fig. 1, bottom panel).

Table 2 Lipid values in offspring of young coronary men (group A) and controls (group B)

	Group A (n = 104)	Group B (n = 89)	*P* value
TC (mg . dl^{-1})	197·4 ± 50	174·9 ± 30·1	0·0005
Triglycerides (mg . dl^{-1})	77·4 ± 41	69·9 ± 32·8	ns
HDL-C (mg . dl^{-1})	52·1 ± 13·1	53 ± 11·7	ns
LDL-C (mg . dl^{-1})	129·8 ± 49·3	108·6 ± 28·2	0·0003
Lipoprotein(a) (mg . dl^{-1})*	22·5 ± 2·6	14·1 ± 2·1	0·0002
TC/HDL-C	4 ± 1·56	3·48 ± 1·03	0·006
LDL-C/HDL-C	2·68 ± 1·39	2·18 ± 0·89	0·004

HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, TC = total cholesterol.
*Geometric mean.

Table 3 shows the type and incidence of dyslipidaemia in the offspring of young coronary patients and their fathers. Dyslipidaemia was classified into single lipid disorders such as high total cholesterol, high triglycerides, decreased high density lipoprotein cholesterol or into a combination of two or three lipid abnormalities. These categories were mutually exclusive.

Cut-off points of abnormal lipid levels for the children were defined for total cholesterol and triglyceride levels above the 90th percentile (total cholesterol >198 mg . dl^{-1}, triglycerides >119 mg . dl^{-1}) and for high density lipoprotein cholesterol levels below the 10th percentile (<39 mg . dl^{-1}) of the control group. For the fathers 'abnormal' lipid levels were considered as follows: total cholesterol >220 mg . dl^{-1}, triglycerides >200 mg . dl^{-1} and high density lipoprotein cholesterol <35 mg . dl^{-1}.

When excess lipoprotein(a) (>51 mg . dl^{-1}, the 90th percentile of the control group) was taken into account, 11 (10·6%) children with a history of premature coronary artery disease had as single lipid disorder the high lipoprotein(a) raising the total incidence of dyslipidaemia to 63·5%.

When we explored the relationship of lipids between the children and their affected fathers there was significant positive correlation with total cholesterol, low density lipoprotein cholesterol and lipoprotein(a) (Fig. 2).

Discussion

Coronary artery disease is multifactorial and caused by the interaction of genetic and environmental factors. The genetic component is believed to be more predominant than the environmental when coronary atherosclerosis presents early in life. In addition, premature coronary artery disease tends to run in families. Although the familial clustering of coronary artery disease is not entirely explained by the familial aggregation of the traditional coronary risk factors[4], hyperlipidaemia contributes largely.

The sampling of the young subjects in our study was such as to enhance the genetic origin of the documented lipid disorders. None of their fathers was diabetic or hypertensive. It is well documented that both these conditions have an important genetic component[9,10] and if present they affect the lipid profile. Furthermore, the children of the two studied groups had comparable dietary or smoking habits, were matched for body mass index and were living in the same urban area.

In our study, total cholesterol, low density lipoprotein cholesterol and lipoprotein(a) were higher in the cases compared to controls and this difference remained when the children were divided into single sex groups.

The relationship between cholesterol and coronary artery disease has been supported by many epidemiological studies[11,12]. However, the relationship between cholesterol to clinical disease cannot be evaluated easily in children because clinically significant coronary artery disease does not occur in children except in those with homozygous familial hypercholesterolaemia. The early appearance of coronary artery disease in this disorder demonstrates that young arteries are not resistant to the atherogenic effect of high cholesterol[13]. There is compelling evidence that fatty streaks progress through transitional lesions to advanced forms of atherosclerosis. Analysis from the Bogalusa Heart Study[14] has shown that ante-mortem levels of total cholesterol and low density lipoprotein cholesterol were associated with coronary artery fatty streaks at autopsy in 150 persons aged 6 to 30 years. The importance of early detection of hypercholesterolaemia lies in the possibility of delaying or arresting the progression of early atherosclerotic lesions by lowering elevated cholesterol.

Although there are no prospective studies demonstrating the beneficial effect of long-term lipid lowering policy in dyslipidaemic children, regression studies in adults after lowering cholesterol[15,16] allows the belief that similar effects will be expected in children.

Lipoprotein(a) is a low density lipoprotein particle that has been modified by the binding of a unique glycoprotein called apolipoprotein(a) to apolipoprotein

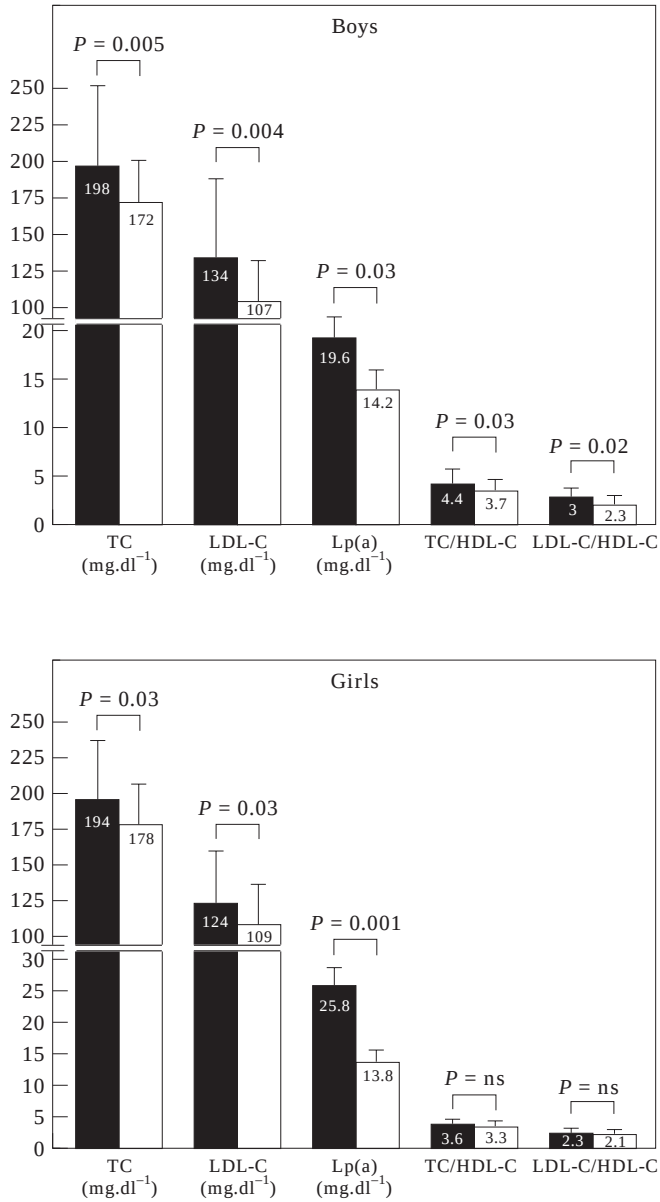

Figure 1 **Comparison of total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), lipoprotein(a) [Lp(a)], TC/high density lipoprotein cholesterol (HDL-C) and LDL-C/HDL-C in subgroups of boys (top panel) and girls (bottom panel) with (■) and without (□) a history of premature paternal myocardial infarction. The bars represent mean ± SD. Lipoprotein(a) mean is geometric mean.**

B. Apolipoprotein(a) is strikingly similar to plasminogen and in vitro studies have ascribed thrombogenic properties to lipoprotein(a)[17,18]. Clinical studies have shown a link between premature coronary artery disease and increased levels of lipoprotein(a)[19,20]. Racial differences in serum lipoprotein(a) distribution relative to parental myocardial infarction were studied in 2438 children between 8 and 17 years of age[21]. White children with parental myocardial infarction had increased levels of lipoprotein(a) compared to those without parental myocardial infarction (22·4 vs 17·1 mg . dl^{-1}).

Lipoprotein(a) is the only major lipid risk factor which remains remarkably constant in an individual. In addition, lipoprotein(a) shows a strong heritability. This strong genetic component was also indicated in our study by the positive association found between the lipoprotein(a) levels of the children and their fathers. Srinivasan *et al.*[21] have postulated that serum lipoprotein(a) levels could be substituted for the knowledge

Table 3 Types and incidence of dyslipidaemia in the affected fathers (n=51) and their offspring (n=75). Also, incidence of dyslipidaemia in all children (n=104) with a history of premature coronary artery disease

Category	Fathers (n=51)		Offspring (n=75)*		All children (n=104)†	
	n	% Total	n	% Total	n	% Total
↑TC	21	41·2	24	32	31	29·8
↑TG	0	0	3	4	4	3·8
↓HDL-C	6	11·8	5	6·7	8	7·7
↑TC+↑TG	5	9·8	3	4	6	5·8
↑TC+↓HDL-C	4	7·8	1	1·3	1	1
↑TG+↓HDL-C	1	2	0·0	0·0	1	1
↑TC+↑TG+↓HDL-C	4	7·8	2	2·7	4	3·8
Total abnormalities	41	80·4	38	50·7	55	52·9

*Children whose fathers lipids were determined. †All children with a history of premature paternal myocardial infarction. HDL-C=high density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides.

of parental history of premature coronary artery disease in distinguishing patients from controls[22]. This will be particularly useful in identifying children at risk when parents are still quite young.

In our study, 53% of the offspring of young coronary patients had a lipid disorder. The most frequent disorder was the isolated elevation of total cholesterol observed in 30% of the offspring. The next most frequent abnormality was isolated low high density lipoprotein cholesterol (7·7%). From the combination of lipid disorders, hypercholesterolaemia+hypertriglyceridaemia was the most commonly seen in 5·8% of the children. When excess lipoprotein(a) was added to the lipoprotein disorders the incidence of dyslipidaemia was increased to 63·5%. Lee *et al.*[23] who studied 173 progeny from 63 families in which the father had angiographically diagnosed coronary artery disease by 50 years of age, found dyslipidaemia in 51% of the progeny. However, there was a different distribution in the type of lipid disorders, with isolated low high density lipoprotein cholesterol being the most frequent disorder present in 17% of children, followed by increased low density lipoprotein cholesterol in 12% of progeny. Lipoprotein(a) had not been determined in this study.

It is worth noting the relatively high mean total cholesterol levels (175 mg . dl^{-1}) in the control group compared to the mean levels of American children (160 mg . dl^{-1})[24], which mainly reflects the change in the dietary habits in the Greek population. The Mediterranean diet of the early 1970s, which was related to low mortality from coronary artery disease[25], has been replaced by a 'westernized' type of diet. This change has contributed to the general increase in the rate of coronary events among Greeks over the past 25 years[26]. It would appear from the above that there is a need to apply dietary recommendations, such as low saturated fat and cholesterol (NCEP recommendations[27]), not only to high risk dyslipidaemic children but also generally to the young, with the aim of maintaining cholesterol levels to less than 150 mg . dl^{-1}[10].

We found a striking resemblance in the type and distribution of dyslipidaemia between the affected fathers and their children. The higher incidence of dyslipidaemia in the affected fathers was probably due to the impact of some environmental factors, such as smoking, which is more frequent in this age group. Furthermore, the sampling was biased towards patients with more severe lipid disorders, since all selected fathers had already developed coronary artery disease. This resemblance, in association with the positive father–offspring correlation of total cholesterol, low density lipoprotein cholesterol and lipoprotein(a) further shows the heritability of lipid disorders. Genest *et al.*[28] also examined the parent–offspring correlation of lipids in 102 families with coronary artery disease under the age of 60 years. The strongest correlation was found with lipoprotein(a) and they concluded that lipoprotein(a) has probably the strongest genetic determinant. In our study, total cholesterol had the most significant correlation. From the distribution of total cholesterol values in the father–offspring correlation, it was evident that the strength of correlation was partly influenced by a subgroup of individuals with high total cholesterol levels. This subgroup was composed mainly of subjects with known familial disorders, such as familial hypercholesterolaemia. However, even after the removal of the children with relatively high levels of total cholesterol (>280 mg . dl^{-1}), the correlation of father–offspring total cholesterol preserved its significance.

In conclusion, our results show that lipid disorders are very common in the offspring of young Greek coronary patients and account largely for their familial predisposition for coronary artery disease. Therefore, all these children should be screened for dyslipidaemia, and dietary measures should be applied as a first step approach. The beneficial effect of lowering cholesterol in adults supports the expectation that similar measures in children will decrease the incidence of heart disease in adult life. The strong genetic component of lipoprotein(a) in association with its atherogenic potential

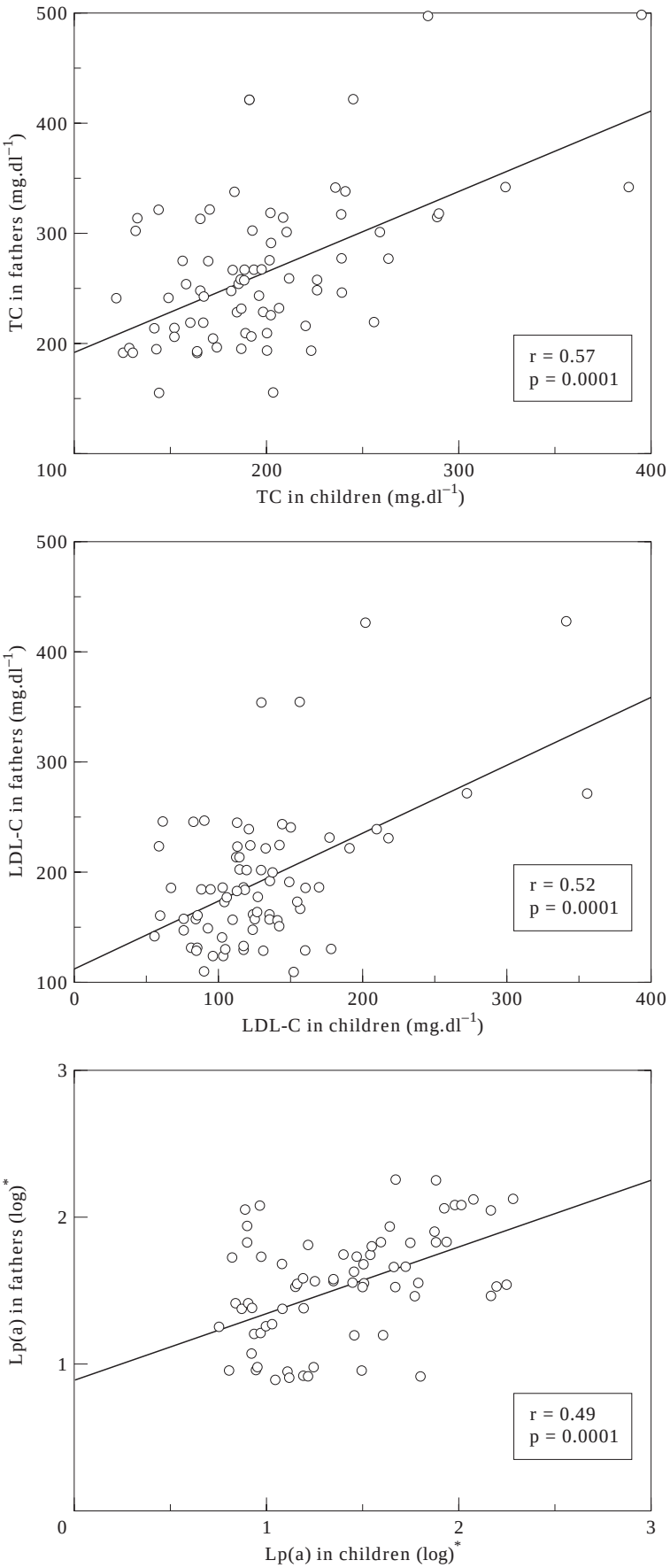

Figure 2 **Correlation of total cholesterol (TC) (top panel), low density lipoprotein cholesterol (LDL-C) (middle panel) and lipoprotein(a) [Lp(a)] (bottom panel) between the affected fathers (n = 51) and their children (n = 75). *log = logarithmic transformation.**

favours its determination in children with a family history of premature coronary artery disease.

References

[1] Holman RL, McGill Jr HC, Strong JP, Geer JC. The natural history of atherosclerosis. The early aortic lesions as seen in the middle of 20th century. Am J Pathol 1958; 34: 209–35.

[2] Enos WF, Holmes RH, Beyer J. Coronary disease among United States soldiers killed in action in Korea: Preliminary report. JAMA 1953; 152: 1090–3.

[3] Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis 1989; 9 (Suppl I): I19–I32.

[4] Kate LP, Boman H, Daiger SP, Motulsky AG. Familial aggregation of coronary heart disease and its relation to known genetic risk factors. Am J Cardiol 1982; 50: 945–53.

[5] Rallidis LS, Papageorgakis NH, Megalou AA, Anagnostou ED, Chatzidimitriou GI, Tsitouris GK. Fibrinogen in the offspring of men with premature coronary artery disease. Eur Heart J 1995; 16: 1814–8.

[6] Sanchez-Bayle M, Cocho P, Baeza J, Vila S. Fibrinogen as a cardiovascular risk factor in Spanish children and adolescents. Am Heart J 1993; 126: 322–6.

[7] Bara L, Nicaud V, Tiret L, Cambien F, Samama MM. Expression of a paternal history of premature myocardial infarction on fibrinogen, factor VIIC and PAI-1 in European offspring — The EARS Study. Thromb Haemost 1994; 71: 434–40.

[8] Rallidis LS, Megalou AA, Papageorgakis NH, Trikas AG, Chatzidimitriou, GI, Tsitouris GK. Plasminogen activator inhibitor 1 is elevated in the children of men with premature myocardial infarction. Thromb Haemost 1996; 76: 417–21.

[9] Ferrari P, Weidmann P, Shaw S, Giachino D. Altered insulin sensitivity, hyperinsulinemia and dyslipidaemia in individual with a hypertensive parent. Am J Med 1991; 91: 589–96.

[10] Kwiterovich PO. Prevention of coronary artery disease starting in childhood: what risk factors should be identified and treated? Cor Art Dis 1993; 4: 611–30.

[11] Stamler J, Wentworth D, Neaton JD (for the MRFIT Research Group). Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Intervention Trial (MRFIT). JAMA 1986; 256: 2823–8.

[12] Castelli WP, Garrison RJ, Wilson PWF, Abbot RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA 1986; 256: 2835–8.

[13] Allen JM, Thompson GR, Myant NB, Steiner R, Oakley CM. Cardiovascular complications of homozygous familial hypercholesterolaemia. Br Heart J 1980; 44: 361–8.

[14] Tracy RE, Newman WP, Wattigney WA, Berenson GS. Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa Heart Study. Am J Med Sci 1995; 310 (Suppl 1): 37–41.

[15] Watts GF, Lewis B, Brunt JNH *et al.* Effects on coronary artery disease of lipid-lowering diet, or diet cholestyramine in the St. Thomas' Atherosclerosis Regression Study (STARS). Lancet 1992; 339: 563–9.

[16] Buchwald H, Varco RL, Matts JP *et al.* Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolaemia. N Engl J Med 1990; 323: 946–55.

[17] Mbewu AD, Durrington PN. Lipoprotein(a): structure, properties and possible involvement in thrombogenesis and atherogenesis. Atherosclerosis 1990; 85: 1–14.

[18] Miles LA, Fless GM, Levin EG, Scanu AM, Plow EF. A potential basis for the thrombotic risks associated with lipoprotein (a). Nature 1989; 339: 301–3.

[19] Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto Jr AM. Association of levels of lipoprotein Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. Circulation 1986; 74: 758–65.

[20] Hoefler G, Harnoncourt F, Paschke E, Mirtl W, Pfeiffer KH, Kostner GM. Lipoprotein Lp(a): a risk factor for myocardial infarction. Arteriosclerosis 1988; 8: 398–401.

[21] Srinivasan SR, Dahlen GH, Jarpa RA, Webber LS, Berenson GS. Racial (black-white) differences in serum lipoprotein (a) distribution and its relation to parental myocardial infarction in children. Circulation 1991; 84: 160–7.

[22] Durrington PN, Hunt L, Ishola M, Arrol S, Bhatnagar D. Apolipoproteins (a), AI, and B and parental history in men with early onset ischaemic heart disease. Lancet 1988; 1: 1070–3.

[23] Lee J, Lauer RM, Clarke WR. Lipoproteins in the progeny of young men with coronary artery disease: Children with increased risk. Pediatrics 1986; 78: 330–7.

[24] Tamir I, Heiss G, Glueck CJ, Christensen B, Kwiterovich P, Rifkind BM. Lipid and lipoprotein distributions in white children ages 6–19 yr. The Lipid Research Clinics Program Prevalence Study. J Chron Dis 1981; 34: 27–39.

[25] Keys A. Coronary heart disease in seven countries. Circulation 1970; 41 (Suppl 1): 1–211.

[26] Kafatos A, Kouroumalis I, Vlachonikolis I, Theodorou C, Labadarios D. Coronary-heart-disease risk-factor status of the Cretan urban population in the 1980s. Am J Clin Nutr 1991; 54: 591–8.

[27] National Cholesterol Education Program (NCEP). Report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics 1992; 89 (Suppl): 525–84.

[28] Genest JJ, Martin-Munley SS, McNamara JR *et al.* Familial lipoprotein disorders in patients with premature coronary artery disease. Circulation 1992; 85: 2025–33.