



Lipoproteins and apolipoproteins in the young and familial risk of coronary atherosclerosis

Cuno S.P.M. Uiterwaal^a, Jacqueline C.M. Witteman^a, Willy-Anne H.J. van Stiphout^a, Xeno H. Krauss^b, Anthony M. de Bruijn^a, Albert Hofman^a, Diederick E. Grobbee^{a,*}

^aDepartment of Epidemiology & Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

^bDepartment of Cardiology, Zuiderziekenhuis, Rotterdam, The Netherlands

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Abstract

The aim of this study was to assess the predictive value of lipoproteins and apolipoproteins at a young age for the development of coronary artery disease at middle and older ages. Because children of coronary artery disease patients are at high risk themselves we compared lipoprotein and apolipoprotein levels between the offspring of parents with and without coronary artery disease. We selected a group of male patients ($n = 90$), who had severe coronary atherosclerosis at angiography, and a reference group of male controls ($n = 62$), who had no coronary atherosclerosis at angiography. Lipoprotein and apolipoprotein levels were determined in 115 sons and 73 daughters of the patients with severe coronary atherosclerosis. These were compared to levels in 68 sons and 47 daughters of controls. Additionally, lipoprotein and apolipoprotein levels were compared between patients and controls as well as between their spouses. In sons of patients, lower levels of HDL₃ cholesterol (-0.07 mmol/l, standard error of the mean (SEM) 0.03, $P < 0.05$) and apolipoprotein A2 (-5.1 mg/dl (SEM, 1.4), $P < 0.001$) were found compared to sons of controls. Similar differences were observed in daughters of such patients without, however, achieving statistical significance. No significant differences between the groups of offspring were found for total cholesterol, LDL cholesterol, HDL and HDL₂ cholesterol, triglycerides and apolipoproteins A-I and B. Patients had higher levels of total (group difference 0.6 mmol/l (SEM, 0.18), $P < 0.001$) and LDL cholesterol (0.6 mmol/l (SEM, 0.17), $P < 0.001$), triglycerides (0.6 mmol/l (SEM, 0.16), $P < 0.001$) and apolipoprotein B (21.2 mg/dl (SEM, 5.1), $P < 0.001$), and lower HDL cholesterol (0.1 mmol/l (SEM, 0.04), $P < 0.05$) than controls. Spouses of patients had higher levels of triglycerides (0.23 mmol/l (SEM, 0.11), $P < 0.05$). Our findings add to the growing evidence that predictors for atherosclerotic disease can be detected relatively early in life. It is concluded that reduced levels of HDL₃ cholesterol and apolipoprotein A2 may be early risk indicators for coronary atherosclerosis later in life.

Keywords: Apolipoproteins; Family; Coronary

* Corresponding author. Tel.: +31 10 408 7489; fax: +31 10 436 5933.

1. Introduction

Coronary heart disease as well as its risk factors tend to aggregate in families [1–4]. Recent prospective studies have shown that a parental history of myocardial infarction is an independent risk factor for coronary artery disease in offspring [5,6]. It follows from this that children of patients with coronary heart disease are at increased risk of developing the disease at middle or older age. Early risk factors for the life-long process of atherosclerosis may therefore be identified by relating disease in parents and risk factors in their offspring. Atherosclerotic lesions that developed early in life have been shown to be related to cholesterol levels and other risk factors [7–10]. Although total serum cholesterol levels measured in adolescent men have been shown to be associated with the occurrence of manifest cardiovascular disease later in life [11], less is known about the role of lipoprotein and apolipoprotein levels in early life as risk factors for atherosclerosis later in life. The majority of family studies related risk factors in offspring to parental (history of) myocardial infarction and seem to indicate that specifically apolipoproteins B and A1 are important indicators for risk of myocardial infarction later in life [12–15].

In the present study, we examined the association between offspring risk factors and parental atherosclerosis, as assessed by angiography. We therefore studied lipoprotein and apolipoprotein levels in 188 children of male patients who suffered from severe clinically manifest and angiographically proven coronary atherosclerosis which were compared to levels measured in 115 children of male controls who did not have coronary atherosclerosis at diagnostic coronary angiography.

2. Subjects and methods

From 1987 to 1992, two groups of male patients were selected from the coronary angiography databases of the cardiology departments of the Zuiderziekenhuis in Rotterdam (1987–1991), the Academic Hospital Dijkzigt in Rotterdam

(1988–1989), the Refaja Ziekenhuis in Dordrecht (1990–1991), and the Antonius Hospital in Nieuwegein (1992), the Netherlands. The index group had severe coronary atherosclerosis, defined as more than 70% stenosis in at least three major coronary vessels at angiography (patients). A reference group had no or only minor angiographic lesions, defined as 20% stenosis or less in all coronary vessels (controls). Additional criteria for both groups of men were: (1) age between 45 and 65 years, (2) blood pressure not exceeding 160/100 mmhg, (3) absence of liver disease, diabetes mellitus, thyroid disease, and renal disease, (4) coronary angiography within 2 years preceding examination, (5) first consultation of a physician for cardiac complaints within 5 years preceding examination for this study. Eligible subjects were sent a letter in which they, their children and spouse were invited to participate in the study. Spouses of patients and controls were included in the study to enable distinction between a paternal-offspring and a maternal-offspring origin of offspring group differences in lipid profiles. The average time elapsed since catheterisation to the present examination was 12.6 ± 6.0 months (mean \pm S.D.) for patients and 13.6 ± 6.4 months for controls.

2.1. Measurements

The patients, spouse, sons and daughters were asked to come to the hospital at 09:00 h after fasting for at least 12 h. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a random zero sphygmomanometer (Hawksley). Fasting serum blood samples were drawn by antecubital venipuncture for measurement of triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL cholesterol), high density lipoprotein cholesterol (HDL cholesterol), its subfractions HDL₂ cholesterol and HDL₃ cholesterol, apolipoprotein A1, apolipoprotein A2, and apolipoprotein B. Height and weight were measured without shoes and heavy clothing. The Quetelet-index was calculated as weight (kg) divided by squared height (m²).

The patients and controls answered a questionnaire about the number of first degree relatives

who had suffered from myocardial infarctions and the use of medication at the time of examination (medication was taken to the hospital). Parents and children answered a questionnaire referring to a 1-month period prior to the examination, with questions on use of medication, habitual alcohol intake, coffee intake, and smoking habits. In addition, spouses and daughters were asked about the use of oral contraceptives, menstrual cycle and pregnancies. Sons and daughters were also asked about changes in lifestyle (physical activity, smoking behaviour, and fat intake) since their fathers had first been examined by a physician for cardiac complaints. In the first 50 families selected for this study all members were invited for baseline measurements only. In these families the response rate was 92%. In the next 102 families, the sons (80 sons of patients and 57 sons of controls) were invited to come to the hospital on a separate day because of their simultaneous involvement in another study for which the criteria and conditions were similar to those in the present study. The sons as well as the daughters from these 102 families underwent the same measurements under the same conditions as the offspring of the first 50 families. The protocol of the extended study required sons from these 102 families to stay in the hospital for 12 h, and the response rate was lower (65%) in this group of sons.

2.2. Laboratory analysis

Serum total cholesterol was measured with an automated enzymatic method, using the Boehringer Mannheim (FRG) CHOD-PAP reagent kit [16]. HDL and LDL cholesterol were measured by the same method after precipitation. For HDL cholesterol, the phosphotungstate method according to Burstein et al. [17] was used with a minor modification as described by Grove [18]. For LDL cholesterol, precipitation was carried out with polyvinylsulphate (Boehringer Mannheim, FRG). Throughout the entire study period the results of both total cholesterol and HDL cholesterol were within limits of the quality control programme of the WHO Regional Lipid Reference Centre (Prague, Czechoslovakia). Apolipoproteins A1 and B were assayed by an automated immunoturbidimetric method (Kone Diagnostics, Espoo, Finland). Apolipoprotein A2 was determined by radial immunodiffusion against specific antiserum (Boehringer Mannheim, FRG) according to Cheung and Albers, with slight modifications [19]. All automated analyses were carried out on the Kone Specific Analyzer (Kone Instruments, Espoo, Finland) using frozen (-20°C) serum samples. HDL₂ and HDL₃ cholesterol subfractions in serum were assayed as described by Gidez et al. [20] with slight modifications.

Table 1
Characteristics of patients, controls and their spouses

	Patients (n = 90)	Controls (n = 62)	Spouses of patients (n = 91)	Spouses of controls (n = 61)
Age (years)	56.4 ± 7.6	52.2 ± 8.1**	52.5 ± 9.4	49.2 ± 7.9*
Height (cm)	175.6 ± 6.0	178.6 ± 7.9*	166.3 ± 6.1	166.2 ± 6.4
Weight (kg)	78.5 ± 8.7	79.8 ± 11.0	72.4 ± 12.5	71.4 ± 10.3
Quetelet-index (kg/m ²)	25.4 ± 2.2	25.0 ± 2.9	26.2 ± 4.5	25.9 ± 3.9
SBP (mmHg)	127.2 ± 12.8	127.5 ± 16.9	127.0 ± 16.7	125.3 ± 14.8
DBP (mmHg)	84.1 ± 11.1	82.1 ± 10.3	83.6 ± 11.1	81.0 ± 8.3
Current smoking (%)	18.9	21.0	18.7	36.1*
Alcohol intake (g/day)	13.8 ± 13.6	14.1 ± 11.4	6.4 ± 7.7	6.7 ± 8.0
Coffee drinking (%)	98.9	93.5	97.8	98.4

Values are means ± S.D., unless stated otherwise; SBP, systolic blood pressure; DBP, diastolic blood pressure.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for differences between patients and controls and their spouses.

Table 2
Characteristics of sons and daughters of patients and controls

	Sons of patients (n = 115)	Sons of controls (n = 68)	Daughters of patients (n = 73)	Daughters of controls (n = 47)
Age (years)	25.5 ± 6.4	22.5 ± 5.6**	25.4 ± 8.3	21.4 ± 7.7**
Height (cm)	180.8 ± 9.7	181.3 ± 11.3	167.0 ± 7.5	167.6 ± 9.9
Weight (kg)	75.8 ± 12.9	73.8 ± 13.3	63.7 ± 11.5	60.1 ± 14.0
Quetelet-index (kg/m ²)	23.0 ± 2.9	22.3 ± 3.1	22.9 ± 4.0	21.2 ± 3.8*
SBP (mmHg)	122.9 ± 13.4	118.2 ± 14.5*	113.5 ± 14.5	116.0 ± 11.2
DBP (mmHg)	79.4 ± 10.1	73.9 ± 12.7**	74.3 ± 11.0	72.5 ± 8.4
Current smoking (%)	33.9	29.4	37.0	19.1*
Alcohol intake (g/day)	11.6 ± 12.9	9.3 ± 9.6	4.8 ± 6.0	5.6 ± 6.4
Coffee drinking (%)	82.6	73.5	75.3	51.1**
Post menarche (%)	—	—	92.8	84.1
Pregnant at examination (%)	—	—	2.9	7.1
Use of oral contraceptives (%)	—	—	43.5	45.2

Values are means ± S.D., unless stated otherwise; SBP, systolic blood pressure; DBP, diastolic blood pressure.
P* < 0.05; *P* < 0.01; ****P* < 0.001 for differences between sons and daughters of patients and controls.

HDL₂ and HDL₃ cholesterol subfractions were separated using stepwise precipitation of apolipoprotein B containing lipoproteins with heparin/Mn²⁺ in two steps and HDL₂ with dextran-sulphate.

2.3. Statistical methods

Mean values and standard deviations were calculated for all characteristics of the patients and controls, and their spouses, sons and daughters, separately. Mean group differences in baseline characteristics were tested with the *t*-test or Mann–Whitney *U*-test when appropriate, and the χ^2 -test for proportional data. All further analyses were adjusted for age. Adjusted mean values for lipoproteins levels in parents and offspring were obtained using linear regression analysis with the (apo)lipoprotein level as the dependent and a group indicator and age as the independent variables. Because of the dependency of measurements between brothers and between sisters within families, group differences between lipoprotein values in the offspring were analyzed using a repeated measures analysis of variance where patients and controls were considered the sampling units (BMDP, 1990). In this analysis,

lipoprotein values in sons and daughters were considered repeated measures within families. In the repeated measures analysis mean lipoprotein levels were adjusted for age, as well as for a combination of age, height, weight, systolic blood pressure, diastolic blood pressure, smoking, alcohol intake and in daughters, the use of oral contraceptives. The associations between (apo)lipoprotein levels in family members were assessed by linear regression analysis of patients and controls, their spouses, and the first sons or daughters taking part in the study.

3. Results

Table 1 shows the characteristics of the patients and the controls, as well as their spouses. Only the group differences in smoking in spouses remained statistically significant after adjustment for age.

Table 2 gives the characteristics for sons and daughters of patients and controls. After adjustment for age only the group differences in diastolic blood pressure in sons remained statistically significant.

In Table 3, the mean (apo)lipoprotein levels are given for patients and controls and their spouses.

Table 3
Lipoprotein and apolipoprotein levels in patients and controls and their spouses

	Patients (<i>n</i> = 90)	Controls (<i>n</i> = 62)	Spouses of patients (<i>n</i> = 91)	Spouses of controls (<i>n</i> = 61)
TC (mmol/l)	6.9 (0.11)	6.3 (0.14)***	6.6 (0.2)	6.6 (0.18)
LDL-C (mmol/l)	5.1 (0.11)	4.5 (0.13)***	4.6 (0.15)	4.8 (0.19)
HDL-C (mmol/l)	1.1 (0.03)	1.2 (0.04)*	1.4 (0.03)	1.3 (0.03)
HDL ₂ -C (mmol/l)	0.2 (0.01)	0.2 (0.02)	0.4 (0.03)	0.3 (0.02)
HDL ₃ -C (mmol/l)	0.9 (0.02)	0.9 (0.02)	1.1 (0.03)	1.0 (0.02)
TG (mmol/l)	2.09 (0.09)	1.50 (0.12)***	1.48 (0.08)	1.25 (0.06)*
Apo A1 (mg/dl)	133.5 (2.5)	135.6 (3.8)	155.0 (3.5)	145.2 (3.8)
Apo A2 (mg/dl)	45.3 (0.8)	46.6 (0.8)	47.3 (0.7)	47.1 (0.9)
Apo B (mg/dl)	131.4 (3.3)	110.2 (3.7)***	111.0 (3.6)	106.0 (3.5)

Values are means (SEM), adjusted for age; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; Apo, apolipoprotein.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for differences between patients and controls and their respective family members.

As expected, there were considerable differences with regard to lipids and apolipoproteins between the patients and controls. Further adjustment for other risk factors did not materially change these results (data not shown). In the spouses the only difference was a higher triglyceride level in the spouses of patients and a higher apolipoprotein A1 after adjustment for other risk factors.

Table 4 shows the mean age adjusted lipoprotein and apolipoprotein values for the sons and differences between the two groups of sons for lipoprotein and apolipoprotein levels, as analyzed with repeated measures analysis of variance. Sons of patients on average had adverse lipoprotein and apolipoprotein levels compared with sons and daughters of controls with significantly lower levels of HDL₃ cholesterol and of apolipoprotein A2.

Table 5 shows lipoprotein and apolipoprotein levels for daughters of patients and controls with lower HDL₃ cholesterol and apolipoprotein A2 levels in daughters of patients, but only reached borderline statistical significance. An additional repeated measures analysis in which all families were excluded if either one or both parents and one or more offspring had total cholesterol levels exceeding 300 mg/dl, yielded similar results. Exclusion of families in which one of the parents had a total cholesterol level exceeding 300 mg/dl still gave similar results with significantly lower levels of HDL₃ cholesterol and apolipoprotein A2 in

sons of patients.

Fig. 1 gives the associations for total cholesterol and apolipoprotein A1 among family members. Statistically significant associations were found for total cholesterol except between fathers and spouses and sons and daughters. For LDL cholesterol and apolipoprotein B similar associations were observed. The strongest associations were found for apolipoprotein A1. Between fathers and mothers associations were observed for HDL₃ cholesterol ($b = 0.25$, 95% CI 0.12, 0.39) and apolipoprotein A1 ($b = 0.43$, 95% CI 0.32, 0.55). Much weaker or no associations between family members were observed for the other lipoproteins.

We assessed the effects of possible changes in lifestyle, possibly advised to patients, which may have been passed on to the children. There were no differences between the two groups of sons with regard to changes in reported smoking behaviour, alcohol intake and fat intake after their fathers had been first examined for cardiac complaints. However, 39% of daughters of patients reported to have diminished their fat intake, as opposed to 17% of daughters of controls (Yates corrected χ^2 5.1, $P = 0.02$). Life-style advise given to patients may be assumed to have more influence on offspring living at home than offspring living separately from their parents. Therefore, an additional analysis was performed in the offspring living separately from their parents, which showed lower levels of HDL₃ cholesterol

Table 4
Differences in lipoprotein and apolipoprotein levels in the sons of patients and controls

	Sons of patients (n = 115)	Sons of controls (n = 68)	Adjusted for	Difference	P-value
TC (mmol/l)	5.4 (0.11)	5.0 (0.10)	Age	0.11 (0.15)	0.46
			Age, risk factors ^a	0.0005 (0.16)	0.99
LDL-C (mmol/l)	3.7 (0.11)	3.3 (0.10)	Age	0.14 (0.15)	0.36
			Age, risk factors	0.09 (0.16)	0.57
HDL-C (mmol/l)	1.2 (0.02)	1.2 (0.03)	Age	-0.04 (0.05)	0.43
			Age, risk factors	-0.07 (0.05)	0.12
HDL ₂ -C (mmol/l)	0.2 (0.01)	0.2 (0.02)	Age	0.02 (0.03)	0.35
			Age, risk factors	0.005 (0.03)	0.86
HDL ₃ -C (mmol/l)	0.9 (0.02)	1.0 (0.02)	Age	-0.07 (0.03)	0.048
			Age, risk factors	-0.09 (0.04)	0.007
TG (mmol/l)	1.16 (0.06)	1.13 (0.07)	Age	-0.03 (0.10)	0.78
			Age, risk factors	-0.11 (0.10)	0.27
Apo A1 (mg/dl)	126.6 (2.5)	123.8 (2.8)	Age	3.1 (4.8)	0.52
			Age, risk factors	-2.8 (4.5)	0.54
Apo A2 (mg/dl)	44.1 (0.6)	47.5 (1.3)	Age	-5.1 (1.4)	0.0003
			Age, risk factors	-4.4 (1.3)	0.0007
Apo B (mg/dl)	89.4 (2.5)	83.9 (2.5)	Age	2.1 (3.6)	0.57
			Age, risk factors	-0.6 (3.7)	0.87
Apo A1/Apo B	1.6 (0.04)	1.5 (0.06)	Age	0.07 (0.08)	0.39
			Age, risk factors	0.007 (0.08)	0.92

Values are means (SEM), adjusted for age and mean differences (values sons patients - values sons controls) as calculated with repeated measures analysis of variance; p-values compare sons of patients with sons of controls; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; Apo, apolipoprotein.

^aAdjusted for risk factors: height, weight, systolic blood pressure, diastolic blood pressure, smoking, alcohol intake.

(difference -0.07 mmol/l (SEM, 0.04), $P = 0.07$) and apolipoprotein A2 (-5.5 mg/dl (SEM, 0.5), $P = 0.0003$) in sons of patients. Similar results were observed in daughters of patients who had lower levels of HDL₃ cholesterol (-0.12 mmol/l (SEM, 0.05), $P = 0.02$) and apolipoprotein A2 (-4.5 mg/dl (SEM, 1.9), $P = 0.02$).

4. Discussion

In this study, sons of patients with coronary atherosclerosis had lower HDL₃ cholesterol and apolipoprotein A2 levels compared to sons of controls. Daughters of patients tended to also have lower levels of HDL₃ cholesterol and apolipoprotein A2, but these differences reached only borderline significance. No differences were found for other lipoproteins and apolipoproteins measured.

Before interpreting these findings some methodologic aspects of the study need to be discussed. The angiographical selection of patients and controls enabled us to maximize the atherosclerotic contrast between these groups, as reflected in differences in lipoprotein and apolipoprotein levels. An important advantage of studying risk factors in offspring in relation to disease in parents is that the risk factors are measured well before the manifestations of atherosclerosis. A further advantage is that although there may be differences between the patients and controls with regard to lifestyle and medication, important differences, particularly with respect to medication, will not be present in the offspring. Although a higher proportion of daughters of patients reported to have changed fat intake since their father's first examination for cardiac complaints, perhaps explaining group differences, this was not accompanied by a change in other aspects of lifestyle, in

Table 5
Differences in lipoprotein and apolipoprotein levels in the daughters of patients and controls

	Daughters of patients (n = 47)	Daughters of controls (n = 73)	Adjusted for	Difference	P-value
TC (mmol/l)	5.6 (0.14)	5.0 (0.15)	Age	0.19 (0.24)	0.43
			Age, risk factors ^a	0.28 (0.25)	0.27
LDL-C (mmol/l)	3.6 (0.14)	3.1 (0.15)	Age	0.16 (0.26)	0.55
			Age, risk factors	0.24 (0.25)	0.34
HDL-C (mmol/l)	1.5 (0.04)	1.5 (0.04)	Age	−0.005 (0.06)	0.87
			Age, risk factors	−0.04 (0.05)	0.44
HDL ₂ -C (mmol/l)	0.4 (0.03)	0.4 (0.03)	Age	0.05 (0.04)	0.10
			Age, risk factors	0.06 (0.04)	0.09
HDL ₃ -C (mmol/l)	1.1 (0.02)	1.1 (0.03)	Age	−0.05 (0.04)	0.27
			Age, risk factors	−0.07 (0.04)	0.14
TG (mmol/l)	1.14 (6.0)	1.04 (8.0)	Age	0.09 (0.12)	0.46
			Age, risk factors	0.13 (0.11)	0.24
Apo A1 (mg/dl)	159.6 (3.7)	151.6 (4.3)	Age	10.6 (6.4)	0.10
			Age, risk factors	11.9 (6.5)	0.07
Apo A2 (mg/dl)	46.6 (1.0)	48.0 (1.0)	Age	−2.7 (1.6)	0.11
			Age, risk factors	−2.1 (1.6)	0.21
Apo B (mg/dl)	86.9 (2.6)	77.8 (3.6)	Age	5.7 (5.2)	0.29
			Age, risk factors	8.1 (4.8)	0.09
Apo A1/Apo B	1.9 (0.07)	2.1 (0.09)	Age	−0.05 (0.13)	0.73
			Age, risk factors	−0.08 (0.12)	0.45

Values are means (SEM), adjusted for age and mean differences (values daughters patients − values daughters controls) as calculated with repeated measures analysis of variance; P-values compare daughters of patients with daughters of controls; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; Apo, apolipoprotein.

^aAdjusted for risk factors: height, weight, systolic blood pressure, diastolic blood pressure, smoking, alcohol intake, and use of oral contraceptives.

particular smoking. Furthermore, as it is not likely that changes to healthier lifestyles affect lipoprotein levels unfavourably, such changes, if present, will result in an underestimation of the true differences. Support for the absence of important effects of lifestyle changes was found in the demonstration of the same differences in offspring living separately from their parents who are probably less affected by lifestyle advice given to the patients, as the total groups of offspring. A possible explanation for smaller differences between the groups of daughters is that the transmission of risk of atherosclerosis or the transmission of risk factors is more pronounced from fathers to sons than from fathers to daughters. This might have been different if female coronary artery disease patients and female controls had been sampled.

Our findings are generally in agreement with those in other studies [21] in that the offspring of patients suffering from coronary artery disease have less favourable lipid profiles. However, studies have indicated that particularly apolipoprotein A1, apolipoprotein B, and their ratio as measured in offspring of CAD patients are more strongly related to risk of cardiovascular disease than other (apo)lipoproteins [13–15,22]. In the present study, apolipoprotein A1 was somewhat higher in offspring of patients. In agreement with earlier studies were the higher apolipoprotein B levels in offspring of patients, although differences were not statistically significant. In contrast to earlier studies, we found HDL₃ cholesterol and apolipoprotein A2 levels to be lower in offspring of patients. Differences in results may be explained by the fact that in the majority of the earlier

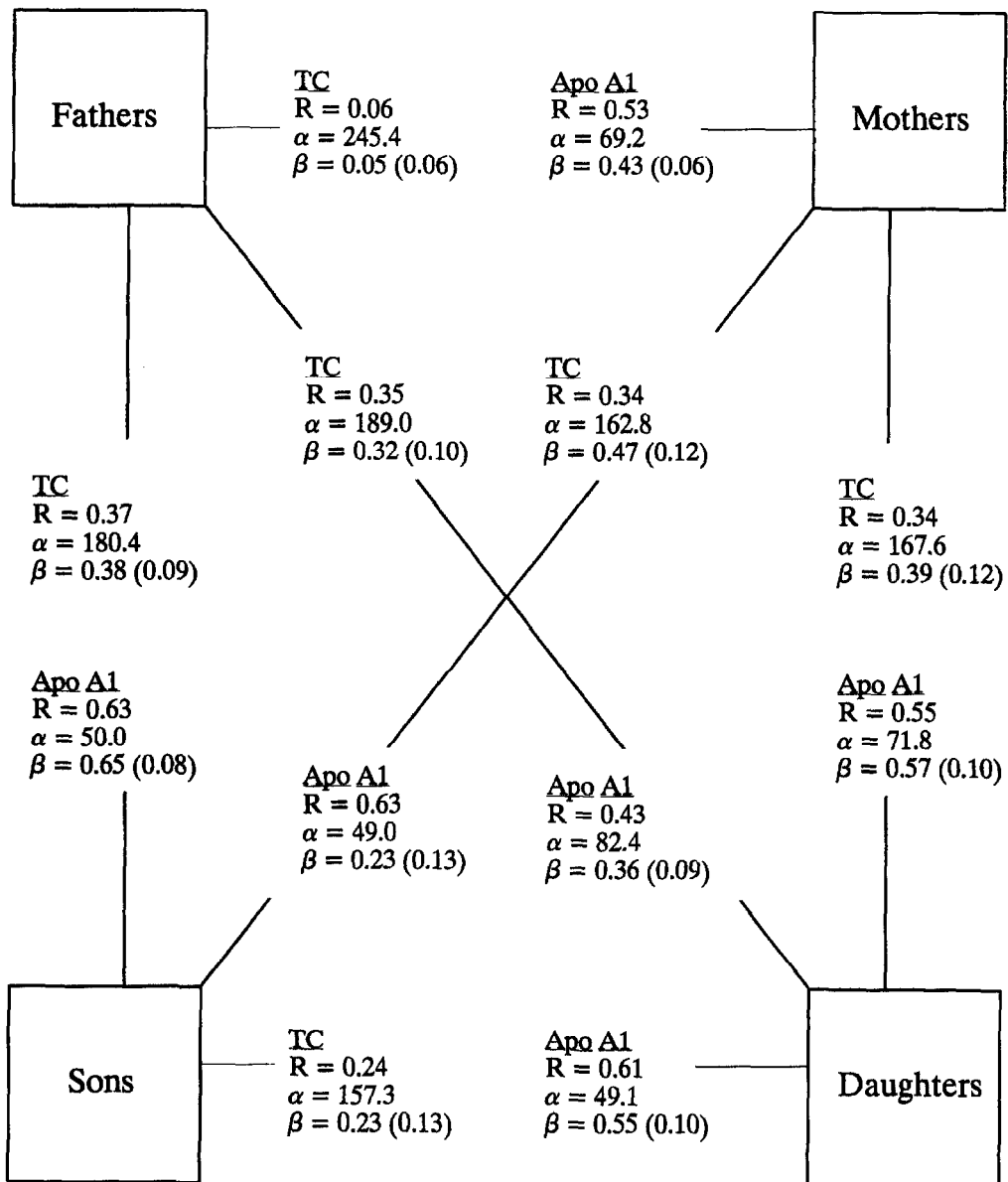


Fig. 1. TC, total cholesterol; Apo A1, apolipoprotein A1; R, correlation coefficient; linear regression: α , intercept; β , regression coefficient (standard error of the mean).

studies, offspring risk factors were studied in relation to myocardial infarction in the parents [13–15], while the results from the present study probably pertain more specifically to atherosclerosis. Another explanation may be that in the present study the offspring were older than in other studies [13,22].

An inverse relation between HDL cholesterol and risk of ischemic heart disease is well established [23–26]. HDL cholesterol levels aggregate in families of patients with myocardial infarction [27,28], and HDL cholesterol subfractions and apolipoproteins A1 and A2 have been reported to be strongly and independently associated with risk

of myocardial infarction [29,30]. Our results are in line with these studies and suggest that HDL cholesterol, its subfractions and related apolipoproteins play a role in atherogenesis early in life. The specific role of HDL subfractions HDL₂ and HDL₃ in the inverse relation with ischemic heart disease still has to be elucidated, although HDL₃ is thought to be the most important factor in this respect. In the present study total HDL cholesterol levels are somewhat lower in sons of patients and not materially different between the two groups of daughters, and HDL₂ cholesterol tends to be higher in both the sons and in daughters of patients, which is suggestive of a shift from HDL₃ to HDL₂ cholesterol.

In summary, we have found lower levels of HDL₃ cholesterol and apolipoprotein A2 in the offspring, particularly sons, of coronary artery disease patients. Our findings add to the growing evidence that predictors for atherosclerotic disease can be detected relatively early in life. The results suggest that reduced levels of HDL₃ cholesterol and apolipoprotein A2 may be early risk indicators for coronary atherosclerosis later in life.

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