

Risk Factors for Coronary Heart Disease in Middle-Aged Men in Crete in 1982

CHRIST ARAVANIS*, RONALD P MENSINK**, ADRIAN CORCONDILAS†, PAUL IOANIDIS‡,
EDITH J M FESKENS** AND MARTIJN B KATAN**

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Risk factors for coronary heart disease were studied in healthy middle-aged Cretan men in order to compare them with the middle-aged men of a previous generation studied in 1960 as the Cretan cohort of the Seven Countries Study (1960). In the present cohort mean values for total cholesterol were 5.48 mmol/L, for HDL-cholesterol 1.26 mmol/L, for triglycerides 1.41 mmol/L, for systolic blood pressure 128 mmHg, and for diastolic blood pressure 77 mmHg. Serum cholesterol was higher and blood pressure slightly lower than the values observed in 1960. However, it is uncertain whether these changes were real or caused by changes in methodology. The mean body mass index has increased from 22.6 in 1960 to 26.9 kg/m² in 1982, due to an increase in fatness. The percentage of smokers had increased from 57.4% to 74.1%. Upon multiple regression analysis the body mass index, the subscapular to triceps skinfold ratio and smoking were negatively and independently related with HDL-cholesterol. Body mass index correlated positively with serum triglycerides.

Although the incidence of coronary heart disease is still low in Crete, it is concluded that there is nothing in the risk profile of these middle-aged men to suggest that they are at a low risk for coronary heart disease.

Of all cohorts studied in the Seven Countries Study the incidence of coronary heart disease (CHD) was the lowest in the Cretans.¹ The remarkably low incidence of CHD in this, as well as in the other Greek and the Italian cohorts forms a compelling argument for considering the Mediterranean diet and lifestyle protective against CHD. However, over the past 25 years the way of life in the Mediterranean countries, including diet and physical activity, have undergone profound changes. It appeared of interest to document these changes and to try and explain those observed. Here we report risk factors for coronary heart disease, including HDL-cholesterol, for a recently studied cohort of middle-aged Cretan men. A comparison is made with the Cretan cohort from the Seven Countries Study. In addition, relationships within the present cohort of serum lipids and blood pressure with age, body mass index, the subscapular to triceps skinfold ratio and smoking habits are discussed.

METHODS

The study area consisted of three small villages—Ano Archanes, Patsides and Scalani—, and of Kato Archanes, a rural municipality encompassing a somewhat larger area than the other three. All are located in the same area as that for the Seven Countries Study, about 30 km south east of Iraklion (Crete). With the help of the local authorities a roster was established of all men aged between 40 and 59 years. In the three smaller villages all men were invited, but in Kato Archanes only a random sample of five out of every nine were invited as the total number was higher than could be managed by the team. Every effort was made to develop good relationships with the subjects, their families and the local authorities and doctors. The clinician's schedule allowed time for medical advice when this was sought by subjects or their family members. The response of the population to the appeal was prompt, coverage perfect and the help from authorities, doctors and the people excellent. In the end all 401 eligible men entered the study.

The study protocol conformed to that followed in the Seven Countries Study.² Data on habitual physical activity, smoking habits, and a medical history were obtained. Also, a physical examination was carried out. Systolic and diastolic blood pressure were measured twice with a mercury sphygmomanometer, with the subject lying down. These two measurements were subsequently averaged.

* Medical Center of Athens, 47 Vasilis Sophias Ave, 106 76 Athens, Greece.

** Department of Human Nutrition, Agricultural University, Wageningen, The Netherlands.

† Metaxas' Diagnostic and Therapeutic Center, Piraeus, Greece.

‡ Evangelismos' Hospital, 45-47 Ypsilandou Street, 115 21 Athens, Greece.

Reprint requests: Ronald P. Mensink, Department of Human Nutrition, Agricultural University, PO Box 8129, 6700 EV Wageningen, The Netherlands.

Body weight without clothes was measured to the nearest kg, and height without shoes to the nearest cm. Body mass index was calculated as weight/height² (kg/m²). Triceps and subscapular skinfold thicknesses were measured and then summated. The ratio of the subscapular to triceps skinfold thickness, as an index of centrally versus peripherally deposited body fat, was calculated. In a random subsample of men a fasting blood sample was analysed for serum total and HDL-cholesterol, and serum triglycerides at the Department of Biochemistry, University of Athens, Greece. Serum lipids were analysed in duplicate using test kits and procedures of Boehringer Mannheim. Total cholesterol was determined by the acetic anhydride method (cat no 124 931) calibrated with Boehringer Preciset cholesterol solutions (cat no 15 730). HDL-cholesterol was determined after precipitation of apolipoprotein-B containing lipoproteins with Mg-phosphotungstate (cat no 543 004). Accuracy was checked by analysis of commercial control sera. For all serum lipids deviations found were less than 3% of the target values.

Sixty men suffering from cardiovascular, hepatic, renal, gallbladder, or thyroid disease or diabetes mellitus as diagnosed at the physical examination or by history, and nine men in whom the presence or absence of one of these diseases could not be ascertained were excluded from the statistical analyses. Thus, data from 332 men were used.

Statistical Analysis

Pearson correlation coefficients were first computed to examine the relationships between variables. For this purpose serum triglycerides and systolic and diastolic blood pressure were transformed into their natural logarithm to reduce skewness and kurtosis. Multiple linear regression was carried out with serum lipids, the HDL to total cholesterol ratio, and the diastolic and systolic blood pressure as dependent variables. Independent variables were body mass index, the subscapular to triceps ratio, present smoking (0=no or ex, 1=yes) and physical activity (0=light or moderate, 1=heavy). As the number of ex-smokers was small, the ex-smokers were counted with the non-smokers. Also, the men involved in light physical activity were added to the category with moderate physical activity. Presence of interaction was assessed by adding cross-products terms to the regression equation. Analysis of residuals was performed to check the validity of the regression model. A p-value of <0.05 was considered as statistically significant.

RESULTS

Table 1 lists the physical characteristics of the study

TABLE 1 Characteristics of a sample of middle-aged men living in rural villages on the Greek island of Crete in 1982

Characteristics	N	Mean	SD	Range
Age (years)	332	49.6	5.7	40 - 59
Weight (kg)	331	77.1	12.6	51 - 120
Height (cm)	332	169.0	6.1	152 - 190
Body mass index (kg/m ²)	331	26.9	3.7	18.7 - 39.1
Triceps skinfold thickness (mm)	332	6.9	3.0	3 - 22
Subscapular skinfold thickness (mm)	332	14.7	6.9	4 - 47
Subscapular to triceps skinfold ratio	332	2.2	0.8	1.0 - 5.4
Total serum cholesterol (mmol/L)	239	5.48	0.93	3.23 - 8.42
HDL-cholesterol (mmol/L)	244	1.26	0.24	0.62 - 1.91
HDL- to total cholesterol ratio	239	0.24	0.06	0.09 - 0.52
Serum triglycerides (mmol/L)	240	1.42	0.65	0.45 - 3.44
Systolic blood pressure (mmHg)	332	127.6	15.8	90 - 185
Diastolic blood pressure (mmHg)	332	76.6	10.9	50 - 122

population, and serum lipid values of a subsample. Table 2 shows the smoking habits and physical activity. The large majority of the men were smokers, and more than 80% of the men claimed to be very active, mostly in agricultural labour.

In view of the striking increase in body fatness in these men compared with those of a generation ago (Table 6), further analyses focussed on various measures of fatness as explanatory variables for serum lipids and blood pressure. In Table 3 the men are divided into categories using tertiles of body mass index and of the subscapular to triceps skinfold ratio. Although these two variables were correlated ($p=0.37$, $p<0.001$), it can be seen that they do not measure exactly the same characteristic, because an appreciable number of men fell into different categories for body mass index and skinfold ratio. It may be assumed that the skinfold ratio partly reflects the distribution of fat

TABLE 2 Smoking habits and physical activity of a sample of middle-aged men living in rural villages on the Greek island of Crete in 1982

	No	%
Smoker		
- Yes	245	74.0
- No	70	21.1
- Ex	16	4.8
Physical activity		
- Light	4	1.2
- Moderate	41	12.5
- Heavy	284	86.3

TABLE 3 Correspondence between tertile distributions of the body mass index and of the ratio of the subscapular to triceps skinfold thickness in middle-aged rural Cretan men. The linear product-moment correlation between the two measures was 0.37 ($n=331$, $p<0.001$)

Body mass index	Subscapular to triceps skinfold ratio			
	Low (<1.77)	Middle (1.77 - 2.33)	High (>2.33)	All
Low (<25.3 kg/m ²)	16.9%	13.0%	3.0%	32.9%
Middle (25.3 - 28.7 kg/m ²)	10.9%	12.1%	10.6%	33.5%
High (>28.7 kg/m ²)	5.4%	9.4%	18.7%	33.1%
All	33.2%	34.4%	32.3%	100.0%

over the body, with a high ratio reflecting an accumulation of fat on the trunk instead of on the extremities.

Univariate Pearson correlation coefficients of body mass index and the subscapular to triceps ratio with various serum lipid parameters and blood pressure values are given in Table 4. Both the body mass index and the subscapular to triceps ratio correlated negatively with HDL-cholesterol, and positively with triglycerides and with systolic and diastolic blood pressure. We performed a multiple regression analysis to estimate the separate effects of both anthropometric variables on CHD risk factors. Also, smoking, age and physical activity were added to the model. Physical activity as assessed in this study was not associated with any of the dependent variables, and it was therefore omitted from the model. Table 5 shows the results of multiple regression analysis. None of the independent variables contributed significantly to explanation of differences in serum cholesterol. Body mass index, the subscapular to triceps ratio and smoking were negatively and independently related to HDL-cholesterol. Body mass index correlated positively with triglycerides. Both age and body mass index were positively related to systolic and diastolic blood pressure. In addition, the subscapular to triceps ratio was positively correlated with systolic blood pressure

TABLE 4 Univariate Pearson correlation coefficients (r) of body mass index (BMI) and of the subscapular to triceps skinfold thickness ratio (subs/tric) with total serum and HDL-cholesterol, serum triglycerides and systolic and diastolic blood pressure

	BMI		Subs/tric	
	N	r	N	r
Total cholesterol	238	0.10	239	0.10
HDL-cholesterol	243	-0.19**	244	-0.21***
Triglycerides	239	0.26***	240	0.16*
Systolic blood pressure	331	0.27***	332	0.18***
Diastolic blood pressure	331	0.27**	332	0.16**

*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

TABLE 5 Multiple regression coefficients of the relations of age, body mass index (BMI), subscapular to triceps skinfold ratio (subs/tric) and smoking with serum total and HDL-cholesterol (mmol/L), serum triglycerides (mmol/L) and blood pressure (mmHg). The regression coefficient represents the predicted change in the dependent variable when the independent variable changes one unit

Independent variable	Dependent variable				
	Cholesterol (mmol/L)	HDL cholesterol (mmol/L)	Triglycerides (mmol/L)	Blood pressure Systolic (mmHg)	Diastolic (mmHg)
Constant	4.6906	1.5401	-0.0469	57.34	36.16
Age (years)	0.0004	0.0037	-0.0015	0.76***	0.26*
BMI (kg/m ²)	0.0188	-0.0098*	0.0468***	0.99***	0.81***
Subs/tric	0.1044	-0.0576**	0.0685	2.56*	1.28
Smoking†	0.0582	-0.1000**	0.1779	0.41	4.18**
R ² (%)	1.7	10.3	9.5	14.7	11.8
N	237	242	238	330	330

*, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

† (0=no or ex, 1=yes)

and smoking with diastolic blood pressure. No interactions between the independent variables was observed.

DISCUSSION

Of all the cohorts of middle-aged men studied by Keys *et al* in their monumental study, the Cretan cohort showed the lowest incidence of coronary heart disease in the subsequent 10 years.¹ The present study describes a smaller but similar group of men living in the same area one generation later. Surprisingly, none of the reported risk factors suggests that they are at low risk for coronary heart disease. A comparison of the present cohort with their predecessors of 1960 shows that certain things have changed profoundly on Crete. Tables 6 and 7 present the values for the two generations side by side. The most striking change is the increase in body fatness. The mean body mass index is much higher for the present cohort than for the 1960-cohort. As differences in height are small, but differences in sum of skinfolds are large, it is obvious that there is an increase in total body fat. According to the classification of Garrow,³ 49.9% of the men in the present cohort are moderately overweight (body mass index 25–29.9 kg/m²) and 20.2% severely overweight (body mass index >30.0 kg/m²), a tenfold increase over the 1.9% of the men in the 1960-cohort who were severely overweight.¹ Median values for triceps skinfolds remained virtually unchanged. Therefore the increase in the sum of the triceps and subscapular skinfolds must be due to an increase in thickness of the layer of fat on the trunk.

Differences in total serum cholesterol values should be interpreted with some caution, as these can have been influenced by a shift in laboratory methods. For

TABLE 6 Median values for height, sum of subscapular and triceps skinfold thicknesses, body mass index, total serum cholesterol and blood pressure for middle-aged Cretan men in 1960¹ and in 1982 (present study), by five-year age groups

	Age	1960		1982		Difference
		N	Median	N	Median	
Height (cm)	40-44	158	166	74	170	+4
	45-49	199	166	93	171	+5
	50-54	172	166	85	168	+2
	55-59	146	165	79	167	+2
Triceps skinfold (mm)	40-44	160	6	75	6	0
	45-49	202	5	93	6	+1
	50-54	175	6	85	7	+1
	55-59	148	5	79	6	+1
Sum of skinfolds (mm)	40-44	160	14	75	20	+6
	45-49	202	14	93	21	+7
	50-54	175	15	85	22	+7
	55-59	148	14	79	19	+5
BMI (kg/m ²) ⁺	40-59	675	22.6	332	26.9	+4.3
Total serum cholesterol (mmol/L)	40-44	152	5.12	56	5.40	+0.28
	45-49	190	5.14	68	5.56	+0.42
	50-54	167	5.43	62	5.56	+0.13
	55-59	143	5.37	53	5.61	+0.24
Systolic blood pressure (mmHg)	40-44	158	131	75	125	-6
	45-49	201	132	93	120	-12
	50-54	173	135	85	125	-10
	55-59	146	138	79	130	-8
Diastolic blood pressure (mmHg)	40-44	158	80	75	75	-5
	45-49	201	80	93	75	-5
	50-54	173	81	85	75	-6
	55-59	146	83	79	80	-3

+ mean value

all age groups the median total serum cholesterol value was higher in the 1982-cohort than in the 1960-cohort. However, in spite of their fatness the present cohort as yet does not have higher serum total cholesterol or lower HDL-cholesterol values than their counterparts in other Western countries.⁴⁻⁷ This might be attributed to the diet of these rural Cretan men, who consume large amounts of olive oil (Aravanis *et al*, unpublished

TABLE 7 Distribution of smoking habits for the Cretan cohort from the Seven Countries Study (1960)¹ and the present Cretan cohort (1982)

Age (years)		Smoker					
		1960-cohort			1982-cohort		
		Yes	No	Ex	Yes	No	Ex
		%					
40-44		61.9	20.0	18.1	74.7	17.3	8.0
45-49		56.0	26.7	17.3	74.2	22.6	3.2
50-54		56.3	24.4	19.3	72.9	24.7	2.4
55-59		55.4	23.0	21.6	74.4	19.2	6.4

results). Table 7 shows that the percentage of smokers has increased. This might reflect the increase in wealth, combined with the lack of education in Crete regarding the health consequences of this habit.

The apparent decrease in blood pressure in comparison with the previous cohort is surprising, because the increase in body fatness should have led to the opposite.^{5,8} Blood pressure measurements are difficult to standardize, especially over a long period, and it is not unlikely that the observed fall in blood pressure is a methodological artefact.

Multiple regression analysis suggested that the body mass index and the body fat localization as estimated by the subscapular to triceps ratio have independent and additive effects on HDL-cholesterol. This agrees with the results from the San Antonio Heart Study, reported by Haffner *et al*.⁹ Thus, the body mass index and the subscapular to triceps ratio each appear to be measuring something different (see also Table 3). While the body mass index is a general index of adiposity, the subscapular to triceps ratio is a measure of subcutaneous fat distribution. Low values indicate relatively large amounts of peripherally deposited fat, while high values indicate relatively large amounts of centrally deposited fat. The importance of body fat distribution and its relation to disease is a recurrent theme in recent studies, all showing that upper body obesity, as indicated by a high waist to hip circumference ratio, is more often associated with metabolic disorders than lower body obesity.^{10,11} However, the division into upper and lower body obesity is not equivalent to the division into centrally and peripherally deposited subcutaneous fat;¹² the subscapular to triceps skinfold thickness ratio refers to the distribution of subcutaneous fat deposits, while the waist to hip circumference ratio also includes intra-abdominal fat deposits. It has been suggested that these fat deposits have different metabolic characteristics,¹³ and are therefore possibly associated with different metabolic disorders.

The results of this study thus suggest that in addition to the known effects of a high body mass index and smoking on risk factors for coronary heart disease, a high subscapular to triceps skinfold ratio has an independent and unfavourable effect on HDL-cholesterol.

Mortality from ischaemic heart disease for men aged 35 to 74 has risen in Greece from 117 per 100 000 per year in 1961 to 181 in 1984 (age-adjusted to European Standard Population; data courtesy of Drs H Kesteloot and J V Joossens, Leuven). The rise was completed by 1978, and since then, values have been stable. In spite of this marked increase, Greece is still one of the

countries with the lowest mortality from IHD in the world.¹⁴ However, it will be interesting to see if the present cohort will enjoy the same relative immunity from coronary heart disease as previous generations, considering their unfavourable risk factor status.

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