EPIDEMIOLOGY

Serum cholesterol and acute myocardial infarction: a case-control study from the GISSI-2 trial

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Abstract

***Objective*—To examine the role of serum cholesterol in acute myocardial infarction in a population of patients with no history of coronary heart disease and to establish the nature of this association, the degree of risk, and the possible interaction between serum cholesterol and other major risk factors for acute myocardial infarction.**

***Design*—Case-control study.**

***Setting*—90 hospitals in northern, central, and southern Italy.**

***Patients*—916 consecutive cases of newly diagnosed acute myocardial infarction and 1106 hospital controls admitted to hospital with acute conditions not related to known or suspected risk factors for coronary heart disease.**

***Data collection*—Data were collected with a structured questionnaire and blood samples were taken by venepuncture as soon as possible after admission to hospital from cases and controls. Blood cholesterol concentrations were available for 614 cases and 792 controls.**

***Results*—After adjustment by logistic regression for sex, age, education, geographical area, smoking status, body mass index, history of diabetes and hypertension, and family history of coronary heart disease the estimated relative risks of acute myocardial infarction for quintiles of serum cholesterol (from lowest to highest) were 2·3 (95% confidence interval (CI) 1·6 to 3·4), 3·1 (95% CI 2·1 to 4·6), 4·1 (95% CI 2·8 to 6·0), and 5·2 (95% CI 3·5 to 7·7). The estimated relative risk across selected covariates increased from the lowest to the highest quintile of serum cholesterol particularly for men, patients under 55 years of age, and smokers. When the possible interaction of known risk factors with serum cholesterol was examined, smoking habits, diabetes, and hypertension had approximately multiplicative effects on relative risk.**

***Conclusions*—This study indicates that serum cholesterol was an independent risk factor for acute myocardial infarction. This association was linear, with no threshold level. Moreover, there was a multiplicative effect between cholesterol and other major risk factors on the relative risk of acute myocardial infarction.**

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Epidemiologists and clinicians continue to debate which interventions aimed at reducing the most common risk factors in coronary heart disease are most effective in primary prevention.[1–6] Epidemiological studies have established a positive association between blood cholesterol concentrations and coronary heart disease. According to the classic "lipid hypothesis" there is a strong correlation between high concentrations of serum cholesterol and development of atherosclerosis and subsequently the occurrence of clinical manifestations of coronary heart disease.[7–10]

Some policy statements for clinical guidelines suggest that there are threshold concentrations of serum cholesterol below which the risk of coronary heart disease is lower.[11–14] A large observational population study (Multiple Risk Factors Intervention Trial, MRFIT), however, suggested that the risk of coronary heart disease is strong, and increases linearly with serum cholesterol concentration.[15]

The incidence of and mortality from coronary heart disease and acute myocardial infarction in each country varies with the mean serum cholesterol concentration for that country.[16–18] In populations with higher mean concentrations (such as those in North Europe and North America) coronary heart disease is responsible for more than half of all deaths.[19–22] In other countries, such as Japan, some Mediterranean regions, and most developing countries, lower mean serum cholesterol concentrations are associated with a lower incidence of and mortality from coronary heart disease.[23–26] Moreover, within some countries risk profiles for coronary heart disease and particularly for acute myocardial infarction are different in areas where lifestyle habits (diet, physical activity, behaviour pattern) are different.[27–30] This may be true of Italy.

We have examined the relation between cholesterol and acute myocardial infarction in patients without a history of coronary heart disease. The present large case-control study was designed to control for several other major risk factors for coronary heart disease.

Patients and methods

This case-control study was conducted between September 1988 and June 1989 within the hospital network of the GISSI-2 study (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto), a randomised controlled clinical trial including 12 490 cases of acute myocardial infarction that was designed to assess the risk/benefit profile of streptokinase and alteplase (and of their possible association with heparin) in the treatment of acute myocardial infarction.[31]

Ninety hospitals, in northern, central, and southern Italy that took part in the GISSI-2 trial were enrolled in this case-control study.

There were 916 patients (801 men and 115 women, median age 57, range 24–74) under 75 years of age consecutively admitted to hospital for a confirmed episode of acute myocardial infarction, without a history of ischaemic heart disease who conformed with the GISSI-2 criteria.[31]

The controls were patients under 75 years of age admitted to the same hospitals as the cases. They had acute conditions not related to known or potential risk factors for acute myocardial infarction. Patients with history of ischaemic heart disease or admitted for cardio-cerebrovascular, neoplastic, or any other chronic diseases were excluded from the control group. The control group consisted of 1106 patients (976 men and 130 women median age 57 years, range 23–74) with similar distributions of sex age, and hospital admission. They had been admitted with injuries (mostly fractures and sprains (40%); with non-traumatic orthopaedic disorders (mostly low back pain and intervertebral disc disorders) (15%); for surgery (including plastic surgery (25%); and with other illnesses such as acute infections or skin, ear, nose, and throat disorders (20%).

A cardiologist at each hospital selected patients and collected, by a structured questionnaire, data on personal and sociodemographic characteristics, lifestyle habits (such as smoking, consumption of alcohol and of coffee and other beverages containing methylxanthine, physical activity, and presence of a network of social relationships), medical history of selected diseases, family history of cardiovascular diseases, and, for women, gynaecological and obstetric data. The presence of diabetes, hypertension, and hyperlipidaemia was recorded if the patient was being treated or had a clinical record of the condition. All interviewers were trained and checked for reliability and consistency. The reproducibility, and hence the reliability, of different sections of the questionnaire varied. It was low for social networks but satisfactory ($t > 0{\cdot}8$) for sociodemographic factors, smoking, medical history, and family history of cardiovascular diseases.

Blood samples were taken from cases and controls by venepuncture as soon as possible after admission to hospital. Fasting total serum cholesterol concentrations were measured by the standard method available in Italian hospital laboratories. Serum cholesterol concentrations were reported for 614 cases (542 men and 72 women) aged 24–74 years (median age 56·5 years) and for 792 controls (705 men and 87 women) aged 23 to 74 years (median age 56·3). Those patients who were excluded from the study because fasting total serum cholesterol was not available, resembled those who were included.

Statistical analysis

We computed the odds ratios, as estimators of relative risks (RR) of acute myocardial infarction, with their 95% confidence intervals (CI) by the Mantel-Haenszel procedure[32] for quintiles of the distribution of serum cholesterol. The significance of the linear trends in risk was assessed by the χ^2 test described by Mantel.[32] Further, the potential reciprocal confounding effects of sex, age, years of education, geographic area (north, central, and southern Italy), cigarette smoking (never, ex, current), body mass index (Quetelet's index (QI = kg/m^2)), history of diabetes and hypertension, and family history of coronary heart disease were controlled for by unconditional multiple logistic regression.[33–34]

On the basis of multivariate RR estimates, attributable risk (AR) was computed by the method of Bruzzi *et al*,[35] which provides a

Table 1 Distribution of 614 cases of acute myocardial infarction and 792 controls according to socioeconomic and clinical variables

	Cases		*Controls*	
Variables	*n*	*%*	*n*	*%*
Sex:				
Male	542	88·3	705	89·0
Female	72	11·7	87	11·0
Age (yr):				
<45	76	12·4	118	14·9
45–54	160	26·1	194	24·5
55–64	231	37·6	289	36·5
65–74	147	23·9	191	24·1
Years of education:				
⩽7	329	54·0	543	69·3
7–11	174	28·6	157	20·0
⩾12	106	17·4	84	10·7
Geographical area:				
North	206	34·4	266	34·2
Central	127	21·2	181	23·3
South	265	44·3	311	42·5
Smoking habits				
Never smokers	98	16·0	227	28·9
Ex smokers	94	15·3	168	21·3
Current smokers				
<20	133	21·7	156	19·9
⩾20	289	47·0	235	29·9
Coffee consumption (cups/day):				
0–1	165	26·9	355	44·8
2–4	350	57·0	387	48·9
⩾5	99	16·1	50	6·3
Body mass index (BMI)*:				
<25	206	33·6	350	44·2
25–30	322	52·4	358	45·2
>30	86	14·0	84	10·6
Hypertension:				
No	438	71·3	655	82·7
Yes	176	28·7	137	17·3
Diabetes mellitus:				
No	542	88·3	729	92·0
Yes	72	11·7	63	8·0
Family history:				
AMI in at least 1 relative	138	22·5	79	10·0
AMI in at least 2 relatives	23	3·7	12	1·5

* Quetelet's index: weight in kg/height in metres.^{2} Small discrepancies in the totals are explained by lack of some information in a few patients.

Table 2 Distribution of 614 cases of acute myocardial infarction and 792 controls according to quintiles of serum cholesterol

Quintiles (mg/dl)	Cases		Controls	
	n	%	*n*	%
<171	66	10·7	228	28·8
171–195	109	17·8	173	21·8
196–219	130	21·2	155	19·6
220–249	146	23·8	126	15·9
⩾250	163	26·5	110	13·9

Table 3 Relative risks (and 95% confidence intervals) of acute myocardial infarction according to quintiles of serum cholesterol

Quintiles (mg/dl)	Relative risk	
	MLRa	*MLRb*
<171	1	1
171–195	2·2 (1·5 to 3·2)	2·3 (1·6 to 3·4)
196–219	2·9 (2·0 to 4·2)	3·1 (2·1 to 4·6)
220–249	4·2 (2·9 to 6·0)	4·1 (2·8 to 6·0)
⩾250	5·4 (3·7 to 7·8)	5·2 (3·5 to 7·7)
$\chi^2$1 trend	98·07*	78·66*

(a) Estimates adjusted for sex, age, and geographic area. (b) Multiple logistic regression includes terms for sex, age, years of education, geographic area, cigarette smoking, body mass index, history of diabetes and hypertension, and family history of CHD.
* $p < 0·001$.

summary attributable risk for multiple factors after allowance for confounding. The method requires information on only the joint distribution of the risk factors among cases and on the adjusted RR associated with each factor. Provided that unbiased RR estimates are obtained and that the cases can be assumed to be representative of all cases in the population in terms of exposure distribution, this method can be applied to data from hospital based case-control studies. Whenever risk factors are not mutually exclusive, their combined attributable risk will differ from the simple sum of the attributable risks for each factor.[35]

Results

Cases and controls had similar age, sex, and geographical distributions (table 1). Cases of acute myocardial infarction tended to be more educated than controls and a higher proportion were smokers and coffee drinkers. Cases were more frequently obese, with a Quetelet's index (QI) over 25. Similarly, diabetes (11·7% of cases of acute myocardial infarction and 8·0% of controls), hypertension (28·7% of cases of acute myocardial infarction and 17·3% of controls), and positive family history of coronary heart disease (26·2% of cases of acute myocardial infarction and 11·5% of controls) were more common in the acute myocardial infarction group.

Table 2 shows the distribution of cases and controls according to quintiles of serum cholesterol. There were more cases in the higher cholesterol quintiles. In fact, only 11% of the cases compared with 29% of the controls had serum cholesterol below 171 mg/dl (mmol/l 4·43) and 71·5% of the cases of acute myocardial infarction had concentrations above 196 mg/dl (5·07 mmol/l) compared with 49·4% of controls.

The relative risk of acute myocardial infarction increased from 2·3 (95% CI 1·6 to 3·4) in the second quintile to 3·1 (95% CI 2·1 to 4·6) in the third, to 4·1 (95% CI 2·8 to 6·0) in the fourth, and to 5·2 (95% CI 3·5 to 7·7) in the group with highest values (table 3).

Table 4 shows the relative risks of acute myocardial infarction and the estimates of the χ^2 for linear trend test according to quintiles of serum cholesterol in separate strata of selected covariates. With all the variables that were taken into account there was an increasing relative risk and a significant linear trend with increasing concentrations of serum cholesterol. In men the estimated risk was 2·2 in the lowest quintile and 3·2, 4·3, 4·9 for subsequent quintiles, with a statistically significant linear trend in risk. The risk of acute myocardial infarction in the highest quintile was more than ninefold that of the lowest one for subjects under 55 years of age, with a significant linear trend (χ^2 trend = 57·86). In the older age group the increase in risk was three times that of the lowest quintile, with a significant linear trend (χ^2 trend = 26·13). The association of serum cholesterol with acute myocardial infarction was also consistent among strata of smoking.

For some variables, the association between serum cholesterol and acute myocardial infarction was apparently stronger in the high risk strata (that is, among smokers, heavy coffee drinkers, and overweight subjects). The risk estimates were particularly high in very obese patients: in the two highest quintiles of serum cholesterol the RR was increased 20-fold.

To analyse the effect of interactions, relative risks were computed for cholesterol when other major risk factors for acute myocardial infarction were present (table 5). In those with a cholesterol concentration higher than 200 mg/dl (5·18 mmol/l) who were current smokers the relative risk was 7·6 (95% CI 3·8 to 15·3). For those smokers with a fasting serum cholesterol of >200 mg/dl (5·18 mmol/l) and with history of diabetes mellitus the relative risk was 4·3 (95% CI 2·5 to 7·5). For patients with high serum cholesterol concentrations and history of hypertension the relative risk was 5·0 (95% CI 3·4 to 7·3).

Discussion

This case-control study confirms and further quantifies a positive association between serum cholesterol concentration and risk of acute myocardial infarction in a Western population with a low mean serum cholesterol concentration. Even a moderately high serum cholesterol concentration increased the risk of acute myocardial infarction developing. These results provide convincing evidence that there is no threshold effect. This association was linear and was not materially changed when allowance was made for

Table 4 Estimated relative risk (95% confidence intervals) of acute myocardial infarction according to quintiles of serum cholesterol (mg/dl) in separated strata of selected covariates

Variables	*<171*	*171–195*	*196–219*	*220–249*	*≥250*	*Cases*	*χ^2 trend*
Sex							
Male	1	2·2 (1·5 to 3·3)	3·2 (2·1 to 4·7)	4·3 (2·9 to 6·5)	4·9 (3·2 to 7·4)	542	70·37*
Female	1	4·3 (1·1 to 16·4)	2·9 (0·9 to 10·9)	2·5 (0·6 to 10·6)	8·6 (2·2 to 33·1)	72	7·16†
Age (y)							
<55	1	2·2 (1·0 to 4·6)	4·5 (2·2 to 9·0)	8·1 (3·9 to 16·5)	9·5 (4·7 to 19·3)	236	57·86*
≥55	1	2·4 (1·5 to 3·8)	2·5 (1·6 to 4·1)	2·7 (1·7 to 4·4)	3·7 (2·3 to 6·0)	378	26·13*
Years of education							
<7	1	3·1 (1·9 to 5·1)	3·4 (2·1 to 5·5)	3·8 (2·3 to 6·2)	5·5 (3·3 to 9·2)	329	41·23*
7–11	1	1·2 (0·5 to 2·6)	1·9 (0·8 to 4·2)	2·9 (1·3 to 6·3)	3·0 (1·3 to 6·7)	174	11·87*
≥12	1	2·1 (0·7 to 6·8)	5·1 (1·7 to 15·4)	14·0 (4·2 to 46·4)	12·0 (3·7 to 38·7)	106	29·47*
Geographical area:							
North	1	2·7 (1·3 to 5·8)	4·0 (1·9 to 8·6)	5·8 (2·8 to 12·1)	6·6 (3·1 to 13·8)	206	31·36*
Central	1	2·6 (1·1 to 6·4)	2·5 (1·1 to 5·7)	2·0 (0·9 to 4·5)	3·9 (1·7 to 8·9)	127	6·95†
South	1	2·2 (1·2 to 3·7)	2·9 (1·7 to 5·1)	5·2 (2·9 to 9·4)	5·0 (2·7 to 9·1)	265	39·25*
Smoking habits:							
Never smokers	1	3·2 (1·2 to 8·7)	4·8 (1·8 to 12·7)	6·1 (2·3 to 17·9)	7·8 (2·9 to 21·1)	98	19·46*
Ex smokers	1	0·9 (0·4 to 2·2)	1·8 (0·7 to 4·5)	2·0 (0·8 to 5·1)	2·2 (0·8 to 5·6)	94	5·09‡
<20	1	1·3 (0·5 to 3·1)	2·1 (0·9 to 5·1)	2·9 (1·2 to 7·0)	4·4 (1·7 to 11·4)	133	12·59*
≥20	1	3·6 (1·9 to 6·6)	3·8 (2·1 to 7·0)	5·8 (3·1 to 10·7)	6·2 (3·4 to 11·6)	289	38·12*
Coffee consumption (cups/day):							
0–1	1	2·6 (1·3 to 5·1)	2·4 (1·2 to 4·8)	4·0 (2·0 to 7·9)	4·5 (2·2 to 9·3)	165	19·90*
2–4	1	2·0 (1·2 to 3·4)	3·4 (2·0 to 5·7)	4·1 (2·4 to 7·0)	4·9 (2·9 to 8·2)	350	43·40*
≥5	1	2·3 (0·6 to 9·4)	4·4 (0·9 to 21·1)	3·3 (0·8 to 13·4)	5·6 (1·4 to 22·8)	99	5·55‡
Body mass index (kg/m²)							
<25	1	1·7 (1·0 to 3·0)	2·2 (1·2 to 4·1)	2·5 (1·3 to 4·7)	6·3 (3·2 to 12·5)	209	28·65*
25–30	1	2·6 (1·4 to 4·7)	3·4 (2·0 to 6·0)	4·4 (2·5 to 7·9)	4·1 (2·3 to 7·1)	322	27·32*
>30	1	7·2 (1·7 to 30·3)	9·9 (2·4 to 40·0)	22·0 (5·2 to 93·5)	26·3 (6·4 to 109·0)	86	27·12*
Hypertension:							
Yes	1	1·6 (0·7 to 3·7)	1·8 (0·8 to 4·1)	2·6 (1·1 to 6·0)	3·0 (1·3 to 6·7)	176	8·31†
No	1	0·4 (0·3 to 1·5)	1·5 (1·0 to 2·3)	1·9 (1·3 to 2·9)	2·1 (1·4 to 3·3)	438	36·05*
Diabetes:							
Yes	1	9·6 (2·3 to 40·0)	11·3 (2·6 to 49·1)	15·1 (2·6 to 88·0)	6·6 (1·5 to 29·5)	72	4·18‡
No	1	0·5 (0·3 to 0·8)	1·5 (1·0 to 2·2)	2·0 (1·4 to 2·9)	2·5 (1·7 to 3·7)	542	47·45*
Positive family history							
AMI in at least 1 relative	1	3·0 (1·0 to 8·6)	2·5 (0·9 to 6·9)	3·7 (1·3 to 10·3)	2·9 (1·1 to 7·7)	79	3·81

Estimates from multiple logistic regression models including terms for sex, age, years of education, geographic area, cigarette smoking, body mass index, history of diabetes and hypertension, and family history of CHD (whenever appropriate). * $p < 0·001$, † $p < 0·01$, ‡ $p<0·05$.

Table 5 Relative risks (and 95% confidence intervals) for interaction between serum cholesterol and other selected risk factors for acute myocardial infarction

	Relative risk (MLRa)	
Variables	*<200 mg/dl*	*≥200 mg/dl*
Smoking habits:		
Never smokers	1	2·5 (1·4 to 4·2)
Ex smokers	1·5 (0·8 to 2·9)	3·2 (1·8 to 5·7)
Current smokers	2·8 (1·7 to 4·6)	7·6 (3·8 to 15·3)
Diabetes:		
No	1	2·6 (2·0 to 3·4)
Yes	2·2 (1·2 to 3·9)	4·3 (2·5 to 7·5)
Hypertension:		
No	1	2·6 (2·0 to 3·4)
Yes	2·1 (1·3 to 3·3)	5·0 (3·4 to 7·3)

(a) Multiple logistic regression includes terms for sex, age, years of education, geographic area, cigarette smoking, body mass index, history of diabetes and hypertension, and family history of CHD.

several risk factors. There was a positive linear trend within each stratum for every covariate that we examined.

Several risk factors for acute myocardial infarction have been repeatedly and strongly correlated in various observational studies:[36–40] in addition to total serum cholesterol these were cigarette smoking, obesity, raised blood pressure, and diabetes mellitus. The mechanism of the effect of cholesterol on the risk of acute myocardial infarction is likely to be independent of those of smoking, diabetes, and hypertension. In fact, particularly for smoking, the combined risk estimated for exposure to the two factors was consistent with the multiplicative effect of interaction on the relative risk.

A major strength of this study lies in the accuracy of the criteria for diagnosis of acute myocardial infarction and in the exclusion

from the analysis of the subjects in whom a history of coronary heart disease could have led to modifications in lifestyle habits.

A possible weakness of this study is the exclusion of fatal cases of acute myocardial infarction. We analysed data from only the patients with acute myocardial infarction who lived long enough to be interviewed. None the less, the association between serum cholesterol concentration and acute myocardial infarction was seen in other studies[14 41–42] both for fatal and non-fatal acute myocardial infarction.

The choice of hospital controls could be criticised as not being representative of the general population and as introducing selection bias. We carefully considered patients admitted to the same hospitals as the cases. They had various acute diseases not related to known or potential risk factors for acute myocardial infarction so that they were typical of the same population as the cases. The distribution in each hospital of age, sex and geographic area was similar for cases and controls. A further advantage of using hospital controls is that the quality of information is the same as for the cases, because both groups had been ill and admitted to hospital. Case-control studies provide accurate information on the role of recent exposure because they avoid the interval between data collection and the occurrence of acute myocardial infarction, which might dilute the strength of relation.

The measurement of total serum cholesterol rather than various lipoproteins could be regarded as a limitation of this study. Nevertheless the observation of a strong and consistent relation with such an overall measure as total cholesterol is of specific interest, because it indicates that even one simple measurement is a strong predictor of subsequent myocardial infarction. Among the other strengths of the study was the fact that blood samples were taken as quickly as possible after the admission to hospital of cases and controls. This procedure was applied in each category of patients and did not influence the accuracy of measurement. The lipid and cholesterol state of the patients can be assessed accurately in the first 48 hours after an acute myocardial infarction.[43] Also the single serum cholesterol measurement on which analyses were based does not represent a methodological problem because the random error to which a single measurement is subject could at most produce a systematic underestimation of the real association between the usual cholesterol concentration and disease.[44]

In Italy mean cholesterol concentration and the risk of acute myocardial infarction are lower than in most Northern European and American populations and higher than in Asian and in developing countries. In our study mean total serum cholesterol was 223·4 (SD 46·6) (5·8 mmol/l) in the cases and 198·8 (SD 49·2) (5·2 mmol/l) in the controls. Populations with lower concentrations of cholesterol also have lower rates of coronary heart disease. The population with the highest concentration of serum cholesterol (East Finland, median total serum cholesterol = 6·6 mmol/l) has a death rate from coronary heart disease 15 times that of the population with the lowest serum cholesterol (Japan, median total serum cholesterol = 4·1 mmol/l).[45]

The continuous linear association that we found is consistent with the results of the Multiple Risk Factor Intervention Trial study (MRFIT), which showed a linear relation between serum cholesterol concentration and coronary heart disease. Moreover, the linear increment in coronary heart disease rates for a given increment in serum cholesterol was larger at higher concentrations of serum cholesterol. This linear trend was apparent for serum cholesterol concentrations that were lower than those generally considered as safe in Western populations.[21]

The different sex and age risk profiles for acute myocardial infarction in our study accord with data from many other epidemiological studies.[45] In the Donolo-Tel Aviv Prospective Coronary Artery Disease Study[46] the incidence of definite coronary events increased from 6% in men with total cholesterol concentrations below 200 mg/dl (5·18 mmol/l) to 25% in men with concentrations above 264 mg/dl (6·84 mmol/l). The corresponding figures in women were 3% and 10%. Gender and age do influence the extent to which total cholesterol and other risk factors can be linked to rates of coronary heart disease. Data from the Framingham study showed that the coronary heart disease rates among women with total cholesterol above 6·9 mmol/l are lower than among men with values in the normal range.[47] In this study the relation between serum cholesterol and myocardial infarction was stronger at younger ages, though the association was also present in the elderly.

The Framingham Study showed that in subjects aged $\geqslant 60$ the relative risk of coronary heart disease was reduced by decreasing serum cholesterol concentrations.[41 48–49] In contrast, 12 years of follow-up data from the Honolulu Heart Program showed no decrease in the relative risk of coronary heart disease between the first and the fourth quartiles of total serum cholesterol when fatal and non-fatal events were compared in men aged 52–59 and 65–74.[50]

In terms of attributable risks, our study suggests that 58% of first episodes of acute myocardial infarction in this population could have been avoided by reducing serum cholesterol below 196 mg/dl (5·07 mmol/l) and that 45% would have been avoided by decreasing the serum cholesterol of patients in each quintile to the respective lower quintile.

In conclusion, these results confirm that serum cholesterol is an important risk factor for acute myocardial infarction and that preventive measures are needed.

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Notes