Associations of serum lipid concentrations and obesity with mortality in women: 20 year follow up of participants in prospective population study in Gothenburg, Sweden

Calle Bengtsson, Cecilia Björkelund, Leif Lapidus, Lauren Lissner

Abstract

***Objective*—To examine association of different measures of serum lipid concentration and obesity with mortality in women.**

***Design*—Prospective observational study initiated in 1968-9, follow up examination after 12 years, and follow up study based on death certificates after 20 years.**

***Setting*—Gothenburg, Sweden.**

***Subjects*—1462 randomly selected women aged 38-60 at start of study.**

***Main outcome measures*—Total mortality and death from myocardial infarction as predicted by serum cholesterol and triglyceride concentrations, body mass index, and ratio of circumference of waist to circumference of hips.**

***Results*—170 women died during follow up, 26 from myocardial infarction. Serum triglyceride concentration and waist:hip ratio were significantly associated with both end points (relative risk of total mortality for highest quarter of triglyceride concentration *v* lower three quarters 1·86 (95% confidence interval 1·30 to 2·67); relative risk for waist:hip ratio 1·67 (1·18 to 2·36)). These associations remained after adjustment for background variables. Serum cholesterol concentration and body mass index were initially associated with death from myocardial infarction, but association was lost after adjustment for background variables. Serum triglyceride concentration and waist:hip ratio were independently predictive of both end points (logistic regression coefficient for total mortality for triglyceride 0·514 (SE 0·150), p=0·0006; coefficient for waist:hip ratio 7·130 (1·92), p=0·0002) whereas the other two risk factors were not (coefficient for total mortality for cholesterol concentration −0·102 (0·079), p=0·20; coefficient for body mass index −0·051 (0·027), p=0·05).**

***Conclusions*—Lipid risk profile appears to be different in men and women given that serum triglyceride concentration was an independent risk factor for mortality while serum cholesterol concentration was not. Consistent with previous observations in men, localisation of adipose tissue was more important than obesity per se as risk factor in women.**

Departments of Primary Health Care and Medicine, University of Gothenburg, Gothenburg, Sweden
Calle Bengtsson, *professor*
Cecilia Björkelund, *clinical lecturer*
Leif Lapidus, *associate professor*
Lauren Lissner, *associate professor*

Correspondence to:
Professor C Bengtsson, Department of Primary Health Care, Vasa Hospital, S-411 33 Gothenburg, Sweden.

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Introduction

It is generally assumed that people who are obese or hypercholesterolaemic are at greater risk of death from cardiovascular disease. Epidemiological studies, however, have not consistently supported this assumption. Some studies have suggested that the localisation rather than the degree of obesity is a risk factor for cardiovascular disease in women.[1-3] Similarly, high triglyceride concentrations may pose a greater threat than hypercholesterolaemia in women.[4-9] Because some of these studies did not investigate the independent contributions of these four risk factors in the prediction of mortality and cardiovascular disease, we have re-examined this issue.

A cohort of women has been studied in Gothenburg, Sweden, since 1968 and has now been followed up for 20 years. We have related baseline risk factors to death from myocardial infarction and total mortality during follow up.

Subjects and methods

SUBJECTS

In 1968-9, 1462 women in Gothenburg, Sweden, who were aged 38, 46, 50, 54, or 60 were recruited to the study.[10] The systematic sampling based on date of birth and the high rate of participation (90·1%) ensured that the recruits were a representative cross section of women from the community in the age groups studied. The cohort was re-examined in 1974-5[11] and in 1980-1.[12] In 1980-1, 1154 women attended the examination and another 197 women were contacted by telephone or postal interview so that 1351 women gave information about history of myocardial infarction and stroke. Of those recruited in 1968-9, 1383 were known to be still alive in 1980-1 and vital status was ascertained in 1458 of them.[12]

In 1988-9 (20 years after the initial study) we obtained updated information from the Swedish National Death Registry and, for surviving subjects, from the Swedish Person and Address Registry. By comparing these registers, we identified 1450 of the initial 1462 participants. We obtained copies of death certificates for all the deaths in this group and identified deaths from myocardial infarction as those in which the death certificate gave myocardial infarction as the principal cause of death. A postmortem examination was carried out in 68% of a subsample of 59 of these deaths, which is in accordance with the necropsy rate reported from Gothenburg.[13]

CLINICAL EXAMINATION

In the initial study of 1968-9 blood samples were taken from the subjects after they had fasted overnight[4] for measurement of total serum cholesterol concentration[14] and serum triglyceride concentration.[15] The women were weighed to the nearest 0·1 kg with a balance scale while they were wearing only briefs. Their height (without shoes) was measured to the nearest 0·5 cm, and their body mass index was calculated (weight (kg)/(height (m))^2). A steel tape measure was used to measure the women's waist circumference, midway between the lower rib margin and the iliac crest, and hip circumference at the widest point between the iliac crest and buttock. The circumferences were measured in a standing position and to the nearest 1 mm. The waist circumference was divided by the hip circumference to give a ratio. All the anthropometric measurements were performed by one observer. Information about smoking habits was obtained by means of a standardised interview.

STATISTICAL METHODS

Risk ratios and their confidence limits were calculated with the Mantel-Haenszel extension of the χ^2 test.[16] The relative risks of mortality from myocardial

TABLE I—*Numbers (percentages) of 1462 women recruited in Gothenburg in 1968-9 who were included at each follow up and their cumulative mortality*

Year of birth	At 12 year follow up (1980-1)	At 20 year follow up (1988-9)	Cumulative mortality: All causes	Cumulative mortality: From myocardial infarction
1930 (n=372)	308 (83)	366 (98)	18 (5)	2
1922 (n=431)	332 (77)	428 (99)	28 (6)	2
1918 (n=398)	325 (82)	395 (99)	53 (13)	5
1914 (n=180)	140 (78)	180 (100)	37 (21)	13
1908 (n=81)	49 (61)	81 (100)	34 (42)	4
Total (n=1462)	1154 (79)	1450 (99)	170 (12)	26

infarction and of overall mortality were studied in relation to serum lipid concentrations and indicators of obesity as recorded in the initial population study. For the primary variable being analysed the risk to women in the highest quarter of that variable was compared with that to women in the lower three quarters. As an important confounder associated with most of the independent and dependent variables studied, age was considered in all our calculations. In calculations of adjusted relative risks in multivariate analysis, background risk factors were defined as high (above the median) or low (below the median value). A multiple logistic regression analysis was used to test the independence of the risk factors studied. p Values below 0·05 were considered to be significant.

TABLE II—*Initial characteristics of 1462 women recruited in Gothenburg in 1968-9 by age. Values are means (SD)*

Age (years)	
Serum cholesterol concentration (mmol/l)	
38 (n=365)	6·3 (0·91)
46 (n=426)	6·8 (1·40)
50 (n=396)	7·2 (1·09)
54 (n=178)	7·4 (1·08)
60 (n=81)	7·3 (0·91)
Serum triglyceride concentration (mmol/l)	
38 (n=365)	1·10 (0·44)
46 (n=427)	1·20 (0·66)
50 (n=396)	1·26 (0·58)
54 (n=178)	1·39 (0·69)
60 (n=81)	1·34 (0·62)
Body mass index (kg/m²)	
38 (n=366)	23·39 (3·85)
46 (n=428)	25·53 (3·43)
50 (n=396)	24·75 (3·82)
54 (n=180)	24·93 (4·24)
60 (n=81)	25·15 (3·61)
Waist:hip ratio	
38 (n=347)	0·725 (0·498)
46 (n=410)	0·733 (0·492)
50 (n=376)	0·749 (0·051)
54 (n=180)	0·754 (0·552)
60 (n=81)	0·776 (0·590)

Results

Table I shows the number of participants at different times during follow up and the number of deaths, and table II shows the initial characteristics of the women with respect to the risk factors studied. Altogether 170 of the 1450 women followed up for 20 years had died, 75 in the first 12 years of follow up and 95 in the final eight years, and 26 women had died of myocardial infarction.

RELATIVE RISKS

Table III shows the age adjusted relative risks for all deaths and for death from myocardial infarction associated with each quarter of the four risk factors. The lowest quarter was used as the reference with a relative risk of one. Increased relative risks in the highest quarter were more pronounced for serum triglyceride concentration and the ratio of waist circumference to hip circumference than for serum cholesterol concentration and body mass index. For all deaths, the relative risk increased for each successive quarter of waist:hip ratio and serum triglyceride concentration. For death from myocardial infarction, a smooth dose-response pattern was seen only for the waist:hip ratio. The risks for women in the highest quarter of each risk factor were compared with those of women in the lower three quarters (table III). For all deaths and death from myocardial infarction, significantly increased relative risks were observed for serum triglyceride concentrations and waist:hip ratios. For serum cholesterol concentration and body mass index, significant associations were observed with respect to death from myocardial infarction only.

Table IV shows the relative risks for the highest quarter compared with the lower three quarters after adjustment was made for an additional background risk factor (above or below its median value) as well as for age. Serum triglyceride concentration was the covariate for serum cholesterol concentration, and cholesterol was the covariate for triglyceride. Body mass index and waist:hip ratio were covariates for each other. The relative risks remained significantly elevated for serum triglyceride concentration and waist:hip ratio with respect to all deaths and to death from myocardial infarction. No significant associations remained for serum cholesterol concentration or body mass index.

TABLE III—*Age adjusted risks of all deaths and death from myocardial infarction for quarters of each variable relative to risk for lowest quarter*

	Relative risk of each quarter: 1st	2nd	3rd	4th	Relative risk (95% confidence interval) 4th quarter *v* 1st-3rd quarters
All deaths					
Serum cholesterol concentration	1	1·67	1·08	1·62	1·36 (0·93 to 1·98)
Serum triglyceride concentration	1	1·10	1·43	2·22	1·86 (1·30 to 2·67)***
Body mass index (kg/m²)	1	0·89	0·73	1·13	1·38 (0·97 to 1·97)
Waist:hip ratio	1	1·07	1·60	2·03	1·67 (1·18 to 2·36)**
Death from myocardial infarction					
Serum cholesterol concentration	1	1·56	1·04	3·80	2·44 (1·07 to 5·55)*
Serum triglyceride concentration	1	2·35	1·46	7·41	4·01 (1·80 to 8·91)***
Body mass index (kg/m²)	1	0·79	1·18	2·23	2·26 (1·05 to 4·86)*
Waist:hip ratio	1	2·01	3·01	7·25	3·62 (1·74 to 7·53)***

*p<0·05, **p<0·01, ***p<0·001.

TABLE IV—*Relative risks (95% confidence intervals) of all deaths and death from myocardial infarction for highest quarter of each primary variable against lower three quarters after adjustment for age and a background variable*

Primary variable	Background variables	
All deaths		
Serum cholesterol concentration	Triglyceride concentration	1·19 (0·81 to 1·75)
Serum triglyceride concentration	Cholesterol concentration	1·90 (1·31 to 2·76)***
Body mass index	Waist:hip ratio	1·18 (0·81 to 1·71)
Waist:hip ratio	Body mass index	1·77 (1·22 to 2·57)**
Death from myocardial infarction		
Serum cholesterol concentration	Triglyceride concentration	2·00 (0·86 to 4·67)
Serum triglyceride concentration	Cholesterol concentration	3·70 (1·67 to 8·19)**
Body mass index	Waist:hip ratio	1·69 (0·75 to 3·82)
Waist:hip ratio	Body mass index	3·70 (1·55 to 8·84)**

**p<0·01, ***p<0·001.

TABLE V—*Age adjusted relative risks (95% confidence intervals) of total mortality for highest quarter of each primary variable against lowest quarter after stratification at median value of secondary variable*

Primary and secondary variables		p Value*
Serum cholesterol concentration:		
Low triglyceride concentration†	1·38 (0·61 to 3·12)	0·91
High triglyceride concentration‡	1·66 (0·81 to 3·40)	0·71
Serum triglyceride concentration:		
Low cholesterol concentration†	2·99 (1·48 to 6·04)	<0·001
High cholesterol concentration‡	1·65 (0·79 to 3·45)	0·008
Body mass index:		
Low waist:hip ratio†	1·00 (0·45 to 2·24)	0·14
High waist:hip ratio‡	0·88 (0·49 to 1·58)	0·63
Waist:hip ratio		
Low body mass index†	1·39 (0·68 to 2·84)	0·009
High body mass index‡	6·97 (2·45 to 19·81)	<0·001

*According to logistic regression analysis of continuous variables.
†Below median value; ‡above median value.

We also calculated relative risks of all deaths for the four variables after stratification at the median value of the covariates (table V). The risks for women in the highest quarter of serum triglyceride concentration relative to the lowest quarter were significantly increased in both the high and low cholesterol concentration groups according to logistic regression analysis of continuous variables (table V). Similarly the relative risks for high waist:hip ratio were significantly increased in groups with high and low body mass index. The risks for serum cholesterol concentration and body mass index were not significant. The limited number of end points available in these analyses renders such conclusions tentative, and the number of deaths from myocardial infarction was considered too low to carry out similar stratified analyses.

PREDICTIVE VALUE OF RISK FACTORS

A multiple logistic regression analysis was conducted in which the independent predictive value of the four risk factors were studied as continuous variables in relation to all deaths and death from myocardial infarction (table VI). For total mortality the strongest independent risk factors were serum triglyceride concentration (p=0·0006) and waist:hip

TABLE VI—*Multiple logistic regression analysis of age adjusted associations between values of risk factors recorded at start of study and mortality after 20 years of follow up*

Variable	All deaths			Death from myocardial infarction		
	Logistic regression coefficient	SE	p Value	Logistic regression coefficient	SE	p Value
Serum cholesterol concentration	-0·102*	0·079	0·20	-0·091*	0·142	0·52
Serum triglyceride concentration	0·514	0·150	0·0006	0·656	0·260	0·01
Body mass index	-0·051*	0·027	0·05	0·050	0·053	0·35
Waist:hip ratio	7·130	1·92	0·0002	8·903	3·968	0·02

*Negative coefficients indicate inverse relation.

ratio (p=0·0002). Increased body mass index was marginally associated with reduced risk of mortality (p=0·05). Serum cholesterol level was not a significant independent risk factor (p=0·20). With respect to death from myocardial infarction, serum triglyceride concentration and waist:hip ratio were significant risk factors (p=0·01 and p=0·02 respectively), while neither serum cholesterol concentration nor body mass index displayed significant predictive value.

To further examine the independent contributions of the four risk factors studied with respect to total mortality, the above analysis was repeated after stratifying the sample into two groups of 562 smokers and 811 non-smokers. Serum triglyceride concentration and waist:hip ratio were associated with increased risk of total mortality in both smokers (p=0·05 and 0·02 respectively) and non-smokers (p=0·004 and 0·001 respectively). These associations were independent of body mass index and serum cholesterol levels, which remained non-significant in both groups.

Discussion

Our study shows that increased serum triglyceride concentration and abdominal adiposity are associated with a sharply increased risk of both total mortality and death from myocardial infarction whereas an increased serum cholesterol concentration and increased general adiposity—expressed as body mass index—are much weaker risk factors. We stress our results concerning serum lipids as there has been much interest worldwide in elevated serum cholesterol concentration as a risk factor for cardiovascular disease. High serum cholesterol concentration is generally appreciated to be a risk factor in men, and determination of serum cholesterol concentration has been incorporated in many screening programmes. However, little attention has been given to the possibility that the risk profiles associated with serum lipids may be quite different in women. There is increasing evidence that increased serum triglyceride values are more predictive in the screening of women. One study comparing women in Gothenburg who had myocardial infarction with participants in our population study showed a strong association between serum triglyceride concentration and myocardial infarction but not between serum cholesterol concentration and myocardial infarction.[4] This observation was confirmed prospectively in our 12 year follow up study[5]: serum triglyceride concentration was significantly and independently correlated with the incidence of myocardial infarction, stroke, and overall death whereas serum cholesterol concentration was not predictive of any of these end points. Similar results have been observed in other studies (such as another cross sectional study in Gothenburg,[6] the Stockholm prospective study,[7] and the Framingham study[8 9]) while we are not aware of any study showing the opposite.

In many studies overall obesity—often expressed as an elevated body mass index—has not been significantly related to myocardial infarction[17 18] or only in very large samples.[19] Our results show that the localisation of the adipose tissue is more important than the total amount of it. We found that an increased ratio of waist circumference to hip circumference was a significant risk factor for mortality from myocardial infarction and total mortality independent of body mass index whereas body mass index itself was not a significant independent risk factor. These results are consistent with those reported after our 12 year follow up.[1]

With respect to total mortality, we conducted several stratified tests in an attempt to identify particular groups at risk. The effect of elevated serum triglyceride concentrations was similar irrespective of whether serum cholesterol levels were low or high. The waist:hip ratio had a significant effect in combination with low and high body mass index. The effects of triglyceride concentration and waist:hip ratio were also present in both smokers and non-smokers. We hope that larger studies will be able to further address this question with special attention to mortality from myocardial infarction.

It is clear that the small number of end points may limit the statistical power for examination of several risk factors. However, our analysis suggests that serum triglyceride concentration and waist:hip ratio are strong independent risk factors for all deaths and death from myocardial infarction. The results from this study of women are of interest because they are based on a representative population sample, there was a high initial participation rate, and information could be obtained from 99% of the initial participants after 20 years.

Clinical implications

- It is often assumed that the risk factors associated with cardiovascular disease are the same in women as in men
- In particular, all types of obesity and hypercholesterolaemia are assumed to increase cardiovascular risk
- This 20 year study of Swedish women, however, showed that increased serum triglyceride concentration and abdominal adiposity were associated with sharply increased risks of death from myocardial infarction and from all causes
- In contrast, increased serum cholesterol concentration and body mass index (an indicator of general adiposity) were much weaker risk factors
- The different strengths of these risk factors should be taken into account when considering risk in women

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Association of restriction fragment length polymorphism in alcohol dehydrogenase 2 gene with alcohol induced liver damage

D I N Sherman, R J Ward, M Warren-Perry, Roger Williams, T J Peters

Abstract

***Objective*—To investigate the role of genetically determined differences in the enzymes of alcohol metabolism in susceptibility to liver damage from misusing alcohol.**

***Design*—Use of pADH36 probe to study PVU II restriction length fragment polymorphism in alcohol dehydrogenase 2 gene in white alcohol misusers and controls.**

***Setting*—Teaching hospital referral centres for liver disease and alcohol misuse.**

***Subjects*—45 white alcohol misusers (38 with alcoholic liver disease) and 23 healthy controls.**

***Main outcome measures*—Alcohol misuse, the presence and severity of alcoholic liver disease, alcohol dependency, and family history of alcohol misuse.**

***Results*—A two allele polymorphism (A and B) was identified. In control subjects the allele frequencies were 85% for A and 15% for B compared with 37% and 63% respectively in alcohol misusers ($p < 0{\cdot}001$). B allele was significantly associated with severe liver damage ($p < 0{\cdot}05$) as well as alcohol dependency and family history of alcohol misuse compared with controls.**

***Conclusion*—Inherited variation in enzymes of ethanol metabolism may contribute to the pathogenesis of alcohol induced liver damage. This supports the presence of a genetic component in alcohol misuse.**

Department of Clinical Biochemistry and Institute of Liver Studies, King's College School of Medicine and Dentistry, London SE5 9PJ
D I N Sherman, *clinical research fellow*
R J Ward, *honorary lecturer*
M Warren-Perry, *research assistant*
Roger Williams, *director*
T J Peters, *professor of clinical biochemistry*

Correspondence and requests for reprints to: Dr D I N Sherman, Institute of Liver Studies, King's College School of Medicine and Dentistry, London SE5 9PJ

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Introduction

Although 10-15% of the population are classified as chronic alcohol misusers,[1] the incidence of alcohol related diseases varies considerably among people with comparable levels of intake. Alcoholic fatty liver is found in 90-100% of chronic misusers but only 10-20% subsequently develop cirrhosis.[2] A genetic effect in alcoholism was first suggested by studies of children of alcoholic parents adopted into non-alcoholic families,[3] and studies of concordance in twins have shown some genetic predisposition to alcohol induced cirrhosis.[4] Multiple environmental and genetic factors clearly influence drinking behaviour and the development of alcoholism,[5] and the inherited component in alcohol induced liver damage is almost certainly derived from several genes.

Genes influencing ethanol metabolism are likely to be the most important candidate genes for alcoholic liver disease. Studies in twins have shown that genetic factors account for most of the repeatable variation in ethanol metabolism between individuals.[6] In addition, dependent alcoholics undergoing detoxification show alterations in ethanol metabolism compared with misusers without signs of dependency or control subjects.[7] Acetaldehyde, the highly toxic product of ethanol metabolism, is thought to play an important part in alcohol induced liver damage and may also contribute to the pathogenesis of alcohol dependency.[8,9] It is therefore likely that alcohol dehydrogenase, which accounts for over 90% of ethanol metabolism in the liver and determines the rate of acetaldehyde formation, is implicated in genetic susceptibility to alcoholic liver disease.

Alcohol dehydrogenase shows considerable polymorphism. It has more than 20 different isoenzymes with greatly differing kinetic properties in vitro.[10,11] The enzyme is encoded by three gene loci, ADH_1, ADH_2, and ADH_3, which lie adjacent to each other on chromosome 4. Polymorphism is present only at the ADH_2 and ADH_3 loci.[12] We investigated the association between a genetic marker—a two-allele restriction fragment length polymorphism in the gene ADH_2—with historical features of alcoholic liver disease and clinical features of alcohol dependency in a white population.

Materials and methods

We studied 45 alcoholic patients and 23 non-alcoholic control subjects, all of whom were white. The patients were referrals to teaching hospital liver disease and alcohol misuse units, whereas the control subjects were research or laboratory staff recruited on a voluntary basis (table I). Although the average age of the controls was younger (mean 36 *v* 52 years), most of the alcohol misusers had established drinking habits by their mid-30s. All of the controls drank less than an average of 24 g of ethanol daily. All patients had consumed at least 80 g of ethanol daily (mean 146 (SE 9·8) g/day) for a minimum of two (mean 13·6 (1·8) years) and had come to medical attention because of the direct consequences of their alcohol misuse. Twenty one of the 45 patients showed clinical features of, and satisfied questionnaire criteria for, alcohol dependency and 19 had a family history of alcoholism, with at least one affected first degree relative.

Thirteen patients were referred for either detoxification or treatment of alcohol misuse, and 32 for treatment of acute alcoholic hepatitis or complications of cirrhosis (bleeding oesophageal varices, ascites, or