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High lipid levels and coronary disease in women in Göteborg—outcome and secular trends: a prospective 19 year follow-up in the BEDA* study

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Aims To provide contemporary data on the effect of high cholesterol and high triglycerides on the risk of coronary heart disease (CHD) and mortality in Swedish women and to describe secular trends with respect to serum lipids, body mass index (BMI) and smoking in the source population.
Methods We followed 1372 women aged 39–64 years and without prior cardiovascular disease from 1980 to 1999 through record-linkage with the Swedish hospital discharge and cause-specific death registers. Risk factor measurements were done at baseline. Every fifth year between 1980 and 1995 coronary risk factors were assessed in independent samples of the source population.
Results In multivariate analyses, a 1 mmol increase in cholesterol was associated with a 51% increased risk of myocardial infarction (MI) and/or revascularisation (MI; $p<0.0001$) and a 30% increased risk of being hospitalised for CHD ($p<0.0004$). Women with cholesterol, 7–7.9 mmol/l, had a threefold risk of MI (HR 3.44 (1.63–7.23)) and hazard ratios in the highest cholesterol category, ≥8 mmol/l, was 4.49 (1.92–10.50) as compared to women with cholesterol below 6 mmol/l. A 1 mmol increase in triglycerides was associated with a 49% increased risk of MI ($p=0.002$) and a 45% increased risk of being hospitalised for CHD ($p=0.001$) after adjustment for major coronary risk factors. A moderate increase in triglycerides, 1.0–1.5 mmol/l, conferred no significant increase in risk of coronary events as compared to below 1.0 mmol/l. Women with high triglycerides, 1.5–1.9 mmol/l, had a doubled risk of MI (HR 2.55 (1.20–5.42)) and hazard ratios in the highest triglyceride category, ≥2.0 mmol/l, was 3.35 (1.48–7.60). Both high cholesterol and high triglycerides predicted mortality but the magnitude was smaller than for coronary events. During the study period the proportion of women with low cholesterol profile, below 6.0 mmol/l, increased on average from 49 to 68% and the proportion of women with low triglyceride levels, below 1.0 mmol/l, decreased from 59 to 36% in the source population. A modest increase in BMI was noted.
Conclusions Both high fasting cholesterol and high fasting triglycerides strongly predicted coronary events in middle-aged Swedish women. The favourable decline in cholesterol levels and smoking rates during the study period was offset by a marked increase in triglyceride levels. The findings suggest that interventional strategies

* BEDA is not an acronym but the archetypal Göteburg woman, tough, sharp-witted, and with a generous heart.

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directed to correct abnormalities in the triglyceride metabolism may be specifically warranted in women.

Introduction

Coronary heart disease (CHD) is a major cause of mortality, morbidity and disability in women. It adversely affects women health-related quality of life and it imposes a significant burden on health care resources. The scope of these impacts is significant when considering the duration of disease and the frequency of symptoms.

Due to an aging population the absolute number of deaths due to cardiovascular disease is increasing in women despite an overall reduction in mortality.[1] There are also studies showing that the development with respect to decreasing trends in incidence and mortality from CHD have been less favourable in women than in men. This could, partly, be related to emerging trends in coronary risk factors, like obesity and triglyceride levels[2,3] implying that metabolic factors could be of particular importance for the development of CHD in women. In line with such arguments are findings in several studies showing that metabolic aberrations like triglycerides, diabetes and HDL cholesterol seem to have a greater impact on CHD risk in women than in men.[4,5]

Hypercholesterolemia and hypertriglyceridemia are generally accepted as strong risk factors for CHD. However, there have been relatively few long-term follow-up studies that examined the impact of cholesterol and triglycerides on CHD risk in middle-aged women as compared to the extensive research conducted in men. In addition, studies in women have varied considerably in terms of age characteristics, definition of end-points, geographical locations, length of follow-up, and time-periods covered.[6,7]

In prospective studies from the 1960s, particularly in those from Scandinavia, a high triglyceride profile was consistently found to be associated with an increased risk of incident coronary events and mortality while no association was reported with cholesterol.[8–11] We observed a similar pattern in a case control study conducted in the 1980s with findings that high triglycerides and low apolipoprotein AI but not total cholesterol was independently associated with myocardial infarction (MI) in women below 55 years as compared to random controls.[12] Contrary to these findings, recent follow-up studies from Scandinavia have reported a strong association of cholesterol with CHD incidence and mortality in middle-aged women[13,14] while the association of triglycerides and CHD has been inconsistent.[15,13]

The aim of this study was to estimate effects of high lipid values on the risk of CHD and mortality in Swedish women and to describe secular trends with respect to serum lipids, body mass index (BMI) and smoking in the source population.

Methods

The Göteborg BEDA study of cardiovascular disease in women started in 1980. A random sample (n=1746) of the female population in Göteborg born between 1915 and 1941 (n=69,569 in 1979) were invited to a screening examination. Women of younger ages were oversampled such that twice as many women below the age of 55 years were invited to the screening examination as compared to those above this age. Of those invited, 1413 women (81%) were investigated between November 1979 and February 1981. None of the women were pregnant. Five were excluded because of prior AMI (3), coronary by-pass (1), or hospitalisation for angina (1) before screening. Women with self-reported angina pectoris but no previous infarction-suspect attack were included in the analysis.

Data on smoking habits, physical activity, education, menopausal state and diabetes were collected by a postal questionnaire that was sent to all subjects along with an invitation to the study. Smoking habits were defined as never smokers, former smoker of more than 1 month duration, smoking 1–14 cigarettes per day, or 15 cigarettes per day, or more. Physical activity in leisure time was coded according to a four-graded scale, with 1 representing sedentary activity, 2 moderate activities such as walking, or light gardening during at least 4 h per week, and 3–4 representing regular, strenuous, or very strenuous activity;[16,17] the latter two categories were collapsed into one as there were few women in category 4. Additional questionnaires were filled in at screening. Women with at least 6 months since their last menstrual period were defined as post-menopausal. Education was coded into: (1) compulsory education only, (2) secondary education, and (3) college or university education. Alcohol use was quantified using a quantity-frequency questionnaire separately for beer, wine and spirits. One glass of beer, or of wine, or a

measure of 4–8 cl of spirits were considered as one drink. Alcohol intake was converted into an approximate number of drinks per week and coded into: (1) no or less than weekly intake of alcohol, (2) 1–7 drinks/week, and (3) >7 drinks/week.

Screening examinations were performed in the morning. Weight and height were measured, and BMI calculated as weight (kg) divided by height in metres squared. Approximated quartiles of the BMI distribution were formed with cut-off limits of <22, 22–24, 24–27, and >27 m/kg^2. Blood pressure was measured to the nearest 2 mmHg after 5 min rest with the subject seated. Serum cholesterol concentration (from a sample taken after fasting for at least 12 h) was determined according to Cramér and Isaksson[18] and triglycerides according to Carlsson and Wadström.[19] Of the 1408 women without prior hospitalisation for cardiovascular disease, 36 had missing values for lipids, and were excluded from multivariate analyses, which, consequently, are based on the 1372 remaining women. Levels of cardiovascular risk factors in 1985, 1990 and 1995 were assessed in random samples of the source population within the framework of the WHO MONICA Project.[2]

Follow-up procedures

All women in the study were followed until 31 December 1999. The Swedish national register on deaths due to specific causes from the years 1980 to 1999 and the Swedish hospital discharge register were matched against a computer file of the women in the study, after approval of the review board of the Göteborg University Ethics Committee. In 1987, there was a change from the eighth to ninth revision of the International Classification of Disease, and in 1997 from the 9th to the 10th.

MI was defined as a discharge or death with an ICD code of 410 or I21 as the principal or underlying diagnosis. Coronary revascularisation was defined as discharge with any operation code of '3066', '3067', '3127', '3080', 'FNA', 'FNC', or 'FNG', along with a diagnosis of CHD. Any CHD was defined as a discharge or death with an ICD code of 410, 411, or 413 (ICD-8 and ICD-9), 120 or I21 (ICD-10) as the principal diagnosis. There were 56 MIs, 27 revascularisations (11 in women with no preceding MI) and altogether 114 cases with a discharge or death with any coronary disease. A separate category of women with either discharge or death with MI or coronary revascularisation was created, comprising 67 women.

Statistical methods

Incidence rates were based on the number of person-years calculated from date of first examination until first event of the studied non-fatal end-points or death or end of study period, December 31, 1999. We used SAS statistical package (Version 8e). In the cross-sectional analyses, multilinear regression tests were used for age adjustment. In the prospective part of study, age-adjusted proportional hazards analyses were used to calculate hazard ratios. Adjustments were done for age (years). In the multivariable adjusted analyses, smoking was entered as never, former or current smoking, menopause and diabetes were coded as 1 for yes and 0 for no, systolic blood pressure, and BMI were entered as continuous variables as were serum cholesterol and serum triglycerides unless stated otherwise. Leisure time physical activity was entered as sedentary (level 1) versus non-sedentary (levels 2–3). With respect to education secondary and college/university were compared with compulsory education only. For alcohol, 1–7 drinks per week was considered as the reference.

Results

Fasting serum cholesterol and triglycerides were categorised with focus on high lipid levels and also with the aim of forming clinically meaningful cut-off limits. At the baseline examination every fifth women had either cholesterol of 7 mmol/l or above (22%) or triglycerides of 1.5 mmol/l or above (17%) and 8% presented with the combination (Table 1).

The relation of fasting cholesterol and triglycerides and major cardiovascular risk factors were in the directions expected (Table 1). There were strong positive associations of cholesterol and triglycerides with age, blood pressure and BMI as well as strong inverse associations with educational level. In addition, women in the higher triglyceride categories were more likely to be smokers, have diabetes, consume more alcohol and be less active. Cholesterol and triglycerides were strongly related. Post-menopausal women were more likely to have high cholesterol levels also after correction for age.

During 19 years of follow-up we documented 67 incident MIs and/or revascularisations (MI), 114 hospitalisations for CHD and 164 deaths. The age-adjusted risk for subsequent coronary outcomes and mortality according to non-lipid risk factors are given in Table 2. High BMI, systolic blood pressure, smoking and diabetes predicted CHD incidence and moderate leisure time physical activity was associated with a protective effect. In general, the

Table 1 Age-adjusted baseline variables according to serum lipids in women examined in 1979–1981

		Age (years)	Post-meno-pausal (%)	Ever use of HRT (%)	Serum cholesterol (mmol/l)	Serum triglyceride (mmol/l)	Body mass index (kg/m^2)	Systolic blood pressure (mmHg)	Current smokers (%)	Diabetes (%)	Compulsory education only (%)	Drinking alcohol less than weekly (%)	More than 7 drinks/ week (%)	Mainly sedentary leisure time activity (%)
Serum cholesterol, mmol/L														
<6.0	666	46.5	40	11	5.22	0.94	24.1	133	35	2	60	64	8	21
6.0–6.9	400	50.2	44	11	6.48	1.18	25.0	137	38	1	69	62	9	28
7–7.9	216	53.6	47	14	7.41	1.31	24.7	137	43	3	70	69	9	26
≥8.0	90	55.1	67	23	8.74	1.62	25.4	142	36	0	72	68	17	20
p		<0.0001	0.003	0.24	–	<0.0001	0.0002	<0.0001	0.09	0.69	0.001	0.47	0.13	0.077
Serum trigylceride, mmol/L														
<1.0	806	47.4	42	10	5.89	0.76	23.6	133	30	1	58	59	9	19
1.0–1.4	339	51.3	47	13	6.32	1.26	25.2	135	44	2	69	67	8	28
1.5–1.9	145	52.2	48	18	6.75	1.77	26.6	143	46	0	73	71	5	33
≥2.0	82	53.8	46	12	7.05	2.81	27.4	143	47	8	81	63	15	48
p		<0.0001	0.42	0.52	<0.0001	–	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.002	0.60	<0.0001
Combined lipids[a]														
Low	504	45.9	40		5.23	0.75	23.4	132	31	1	57	60	8	18
Intermediate	760	50.6	46		6.53	1.20	25.0	136	39	2	68	64	9	27
High	108	55.3	52		7.88	2.22	26.6	143	53	4	81	77	9	26
		<0.0001	0.024		–	–	<0.0001	<0.0001	<0.0001	0.009	<0.0001	0.046	0.98	<0.0001

[a]Low=serum cholesterol <6 and serum triglyceride <1mmol/l; high=serum cholesterol ≥7 and serum triglyceride ≥1.5mmol/l; intermediate=all other.

Table 2 Outcome according to non-lipid risk factors in women examined in 1980 and followed until 1999

	Number of women (% of total)	AMI or revascularisaton		Any hospitalisation for coronary heart disease		Mortality	
		Per 1000 observation years (*n*)	Age-adjusted HR	Per 1000 observation years (*n*)	Age-adjusted HR	Per 1000 observation years (*n*)	Age-adjusted HR
Postmenopausal							
No	770	1.2 (17)	1.00	2.7 (39)	1.00	3.5 (51)	1.00
Yes	602	4.7 (50)	1.77 (0.82–3.80)	7.1 (75)	1.12 (0.64–1.96)	10.4 (113)	1.10 (0.69–1.78)
Bodymass index, kg * m^{-2}							
<22	372	1.0 (7)	1.00	2.5 (17)	1.00	5.0 (35)	1.00
22–24	343	2.3 (15)	1.92 (0.78–4.72)	3.9 (25)	1.34 (0.72–2.50)	4.8 (31)	0.77 (0.48–1.26)
24–27	352	3.0 (19)	2.33 (0.97–5.56)	5.8 (37)	1.93 (1.08–3.43)	7.7 (50)	1.20 (0.78–1.85)
>27	304	4.8 (26)	3.27 (1.40–7.64)	6.5 (35)	1.90 (1.05–3.43)	8.6 (48)	1.13 (0.72–1.77)
Systolic blood pressure:							
<130	571	0.8 (9)	1.00	2.0 (22)	1.00	3.8 (41)	1.00
130–144	403	3.1 (23)	2.79 (1.27–6.11)	5.2 (38)	1.99 (1.17–3.41)	5.7 (43)	1.09 (0.70–1.69)
146–158	207	4.1 (15)	2.89 (1.22–6.87)	6.1 (22)	1.91 (1.03–3.56)	11.3 (42)	1.63 (1.03–2.58)
≥160	191	5.9 (20)	3.80 (1.64–8.82)	9.6 (32)	2.81 (1.56–5.06)	10.9 (38)	1.38 (0.85–2.24)
Smoking habits							
Never smoker	707	1.8 (24)	1.00	3.8 (50)	1.00	4.6 (61)	1.00
Former smoker	179	2.4 (8)	1.53 (0.69–3.42)	4.2 (14)	1.26 (0.69–2.27)	5.6 (19)	1.44 (0.86–2.42)
Smoking 1–14 cigarettes/day	318	4.4 (25)	2.70 (1.54–4.74)	5.7 (32)	1.64 (1.05–2.56)	10.1 (58)	2.40 (1.68–3.45)
Smoking >14 cigarettes/day	167	3.4 (10)	3.17 (1.48–6.76)	6.1 (18)	2.50 (1.44–4.35)	8.6 (26)	3.09 (1.93–4.96)
Diabetes							
No	1350	2.5 (62)	1.00	4.4 (108)	1.00	6.2 (156)	1.00
Yes	22	15.3 (5)	5.14 (2.06–12.84)	18.7 (6)	4.00 (1.75–9.13)	22.8 (8)	2.78 (1.36–5.67)
Education							
Compulsory only	867	3.3 (52)	1.00	5.4 (85)	1.00	7.1 (114)	1.00
Secondary	328	2.1 (13)	0.74 (0.40–1.35)	4.0 (24)	0.82 (0.52–1.30)	5.4 (33)	0.87 (0.59–1.29)
College or university	177	0.6 (2)	0.29 (0.07–1.21)	1.5 (5)	0.41 (0.17–1.02)	5.1 (17)	1.18 (0.70–1.99)
Alchol consumption							
Little or none	872	3.1 (49)	1.27 (0.72–2.23)	4.9 (78)	1.10 (0.72–1.68)	7.1 (115)	1.38 (0.94–2.02)
1–7/week	381	2.2 (16)	1.00	4.1 (29)	1.00	4.8 (35)	1.00
>7/week	117	0.9 (2)	0.56 (0.13–2.45)	2.9 (6)	0.87 (0.36–2.09)	6.5 (14)	1.85 (0.99–3.46)
Leisure time physical activity							
Sedentary	325	4.2 (24)	1.00	6.8 (39)	1.00	9.6 (56)	1.00
Moderate	941	2.1 (37)	0.50 (0.30–0.83)	3.7 (65)	0.53 (0.35–0.78)	5.6 (99)	0.56 (0.40–0.78)
Active	105	3.0 (6)	0.82 (0.34–2.01)	5.1 (10)	0.80 (0.40–1.61)	4.0 (8)	0.46 (0.22–0.97)
Use of hormone replacement therapy ever							
No	1203	2.5 (56)	1.00	4.2 (92)	1.00	6.3	1.00
Yes	169	3.5 (11)	0.94 (0.49–1.80)	7.1 (22)	1.19 (0.74–1.91)	7.3	0.81 (0.52–1.26)

Missing data for body mass index in one woman, for smoking in one, for alcohol in two and for physical activity in one woman.

associations with MI were stronger than for the end-point hospitalisations for CHD. Postmenopausal state and use of hormone replacement therapy were not associated with CHD incidence after correction for age. Smoking and diabetes predicted all cause mortality while moderate and high physical activity asserted a protective effect.

The incidence rate of MI rose from 0.9 per 1000 person-years among women with cholesterol below 6.0 mmol/l to 9.3 per 1000 person-years among those with cholesterol above or equal to 8.0 mmol/l (Table 3). After correction for non-lipid risk factors the risk was significantly increased in women with cholesterol 7–7.9 mmol/l (HR 4.03 (1.96–8.31)) and women with cholesterol equal to or above 8 mmol/l had an almost sixfold increased risk (HR 5.75(2.51–13.15)) as compared to women with cholesterol below 6 mmol/l. Adjustment for coronary risk factors including triglycerides attenuated the risk estimates, but only modestly and the risk remained significantly increased for women with high cholesterol (≥7 mmol/l). When cholesterol was tested as a continuous variable a 1 mmol increase was associated with a 51% increased risk of MI (HR 1.51 (1.26–1.81)).

There was a similarly significant association between fasting triglycerides and the incidence of MI (Table 3). The hazard ratios corrected for non-lipid variables were increased for all triglyceride categories (1.0–1.4, 1.5–1.9, ≥2 mmol/l) and were 2.13 (1.08–4.22), 2.55 (1.20–5.45) and 5.57 (2.54–12.22), respectively, as compared to below 1 mmol/l. Inclusion of cholesterol in the multivariable adjustment attenuated the risk estimates and particularly in the highest triglyceride category. Still, women with triglycerides equal to or above 2 mmol/l had a threefold increased risk (HR 3.35 (1.48–7.60)). The risk estimates were materially unchanged when usage of hormone replacement treatment was added in the model (data not shown). The adjusted risk of MI per millimolar increase of triglycerides was 1.49 (1.15–1.92).

Of the total number of women suffering MI during follow-up, 34% occurred among the small proportion of the population with both high cholesterol (≥7 mmol/l) and high triglyceride levels (≥1.5 mmol/l) at baseline as compared to 10% among the women with low lipids defined as both cholesterol below 6 mmol/l and triglycerides below 1 mmol/l (HR 7.86 (3.11–19.88)). The largest number of events (55%) occurred in women with intermediately elevated lipids.

Hospitalisations for CHD increased with increasing lipid levels and the relationship was similar to what we observed for MI but less strong (Table 4). Women with cholesterol 7–7.9 mmol/l had a threefold increase in risk (HR 3.01 (1.78–5.11)) as did women with cholesterol equal to or above 8 mmol/l (HR 3.16 (1.65–6.08)) compared to below 6 mmol/l after adjustment for non-lipid coronary risk factors. In women with triglycerides 1.0–1.5 mmol/l the HR was 2.60 (1.50–4.51) after adjustment for multiple non-lipid risk factors and women with triglycerides ≥2 mmol/l had a HR of 3.25 (1.75–6.05) compared to women below <1 mmol/l. The risks were modestly attenuated after inclusion of both lipids in the multivariable adjustment. The hazard ratio of being hospitalised for CHD per unit increase of cholesterol and triglycerides was 1.37 (1.19–1.57) and 1.58 (1.29–1.94), respectively.

Both cholesterol and triglycerides predicted all cause mortality (Table 5). The risk increased significantly across categories of cholesterol (p for trend 0.0003) and triglycerides (p for trend <0.0001) but the magnitude was less steep than for coronary events.

Changes in lipid levels in the source population between 1980 and 1995 are shown in Table 6. Cholesterol declined significantly in all age groups and the proportion of women with cholesterol levels below 6.0 mmol/l, increased, on average, from 49 to 68%. In contrast, the proportion of women with serum triglycerides below 1 mmol/l decreased from 59 to 36%. Mean age-adjusted values of serum triglycerides increased from 1.13 to 1.34 mmol/l during the study period (p<0.0001) mainly in women below 54 years. In all age groups the proportion of smokers decreased, on average from 35 to 27%. Mean age-adjusted BMI increased from 24.6 to 25.2 (p=0.003) with a significant increase observed only in the age group of 55–64 years.

Discussion

In this population-based study in middle-aged Swedish women, followed for 19 years, we found that high fasting cholesterol and high fasting triglycerides were strongly associated with an increased risk of MI and/or revascularisations, hospitalisations for CHD and total mortality. The associations were independent of age, menopausal state, systolic blood pressure, BMI, diabetes, alcohol use, physical activity, education and any lipids.

Hypercholesterolemia is generally accepted as one of the strongest risk factors for CHD. In an analysis of 13 studies conducted during the 1950s to early 1970s in women below 65 years the crude relative risk pooled across studies for fatal CHD was 2.44 among those with cholesterol levels of

Table 3 Myocardial infarction and/or coronary revascularisation according to serum cholesterol and serum triglyceride levels in women examined in 1979–1981 and followed until 1999

	Number of women (% of total)	Observation years	Cases (*n*)	Per 1000 observation years	Hazard ratio adjusted for age	Multivariable adjusted[a] hazard ratio	Multivariable adjusted[a] hazard ratio, including both lipids
Serum cholesterol, mmol/L							
<6.0	666 (49)	12,646	12	0.9	1.00	1.00	1.00
6.0–6.9	400 (29)	7356	16	2.2	1.80 (0.84–3.85)	1.52 (0.70–3.26)	1.38 (0.64–2.99)
7–7.9	216 (16)	3730	25	6.7	4.58 (2.21–9.49)	4.03 (1.96–8.31)	3.44 (1.63–7.23)
≥8.0	90 (7)	1513	14	9.3	5.78 (2.54–13.14)	5.75 (2.51–13.15)	4.49 (1.92–10.50)
Per mmol increase					1.58 (1.34–1.87)	1.57 (1.33–1.87)	1.51 (1.26–1.81)
p for trend					<0.0001	<0.0001	<0.0001
Serum triglyceride, mmol/L							
<1.0	806 (59)	15,334	16	1.0	1.00	1.00	1.00
1.0–1.4	339 (25)	6087	20	3.3	2.41 (1.23–4.71)	2.13 (1.08–4.22)	1.81 (0.91–3.58)
1.5–1.9	145 (11)	2496	16	6.4	4.39 (2.15–8.98)	3.30 (1.55–7.03)	2.55 (1.20–5.42)
≥2.0	82 (6)	1329	15	11.3	7.37 (3.53–15.38)	5.57 (2.54–12.22)	3.35 (1.48–7.60)
Per mmol increase					1.86 (1.55–2.22)	1.65 (1.30–2.10)	1.49 (1.15–1.92)
p for trend					<0.0001	<0.0001	0.002
Combined lipids[b]							
Low	504 (37)	9672	7	0.7	1.00	1.00	–
Intermediate	760 (55)	13,835	37	2.7	2.70 (1.18–6.17)	2.19 (0.95–5.07)	–
High	108 (8)	1754	23	13.1	10.72 (4.35–26.43)	7.86 (3.11–19.88)	–

[a] Adjusted for age, menopause, smoking, diabetes, physical activity, systolic blood pressure, body mass index, alcohol consumption and education.
[b] Low=serum cholesterol <6 and serum triglyceride <1mmol/l; high=serum cholesterol ≥7 and serum triglyceride ≥1.5mmol/l; intermediate=all other.

Table 4 All hospitalisations for coronary heart disease by serum cholesterol and serum triglyceride levels in women examined in 1979–1981 and followed until 1999

	Number of women (% of total)	Observation years	Cases (*n*)	Per 1000 observation years	Hazard ratio adjusted for age	Multivariable adjusted[a] hazard ratio	Multivariable adjusted[a] hazard ratio, including both lipids
Serum cholesterol, mmol/L							
<6.0	666 (49)	12,580	27	2.1	1.00	1.00	1.00
6.0–6.9	400 (29)	7295	33	4.5	1.71 (1.02–2.87)	1.55 (0.92–2.60)	1.41 (0.83–2.39)
7–7.9	216 (16)	3685	37	10.0	3.24 (1.90–5.50)	3.01 (1.78–5.11)	2.63 (1.53–4.52)
≥8.0	90 (7)	1509	17	11.3	3.33 (1.75–6.35)	3.16 (1.65–6.08)	2.50 (1.28–7.90)
Per mmol increase					1.40 (1.22–1.61)	1.37 (1.19–1.57)	1.30 (1.13–1.50)
p for trend					<0.0001	<0.0001	0.0004
Serum triglyceride, mmol/L							
<1.0	806 (59)	15,250	39	2.6	1.00	1.00	1.00
1.0–1.4	339 (25)	6005	31	5.2	1.60 (0.99–2.60)	1.52 (0.93–2.49)	1.37 (0.83–2.24)
1.5–1.9	145 (10)	2484	26	10.5	3.13 (1.88–5.23)	2.60 (1.50–4.51)	2.17 (1.25–3.78)
≥2.0	82 (6)	1330	18	13.5	3.82 (2.13–6.84)	3.25 (1.75–6.05)	2.26 (1.17–4.38)
Per mmol increase					1.79 (1.51–2.12)	1.58 (1.29–1.94)	1.45 (1.16–1.80)
p for trend					<0.0001	<0.0001	0.001
Combined lipids[b]							
Low	504 (37)	9631	18	1.9	1.00	1.00	–
Intermediate	760 (55)	13,695	68	5.0	2.02 (1.18–3.46)	1.75 (1.01–3.02)	–
High	108 (8)	1743	28	16.1	5.48 (2.90–10.39)	4.42 (2.28–8.57)	–

[a] Adjusted for age, menopause, smoking, diabetes, physical activity, systolic blood pressure, body mass index, alcohol consumption and education.
[b] Low=serum cholesterol <6 and serum triglyceride <1mmol/l; high=serum cholesterol ≥7 and serum triglyceride ≥1.5mmol/l; intermediate=all other.

Table 5 Mortality from all causes by serum cholesterol and serum triglyceride levels in women examined in 1979–1981 and followed until 1999

	Number of women (% of total)	Observation years	Deaths (*n*)	Per 1000 observation years	Hazard ratio adjusted for age	Multivariable adjusted[a]hazard ratio	Multivariable adjusted[a] hazard ratio, including both lipids
Serum cholesterol, mmol/L							
<6.0	666	12,690	45	3.5	1.00	1.00	1.00
6.0–6.9	400	7437	47	6.3	1.34 (0.88–2.03)	1.33 (0.87–2.02)	1.22 (0.80–1.87)
7–7.9	216	3818	50	13.1	2.17 (1.41–3.33)	2.04 (1.32–3.15)	1.77 (1.13–2.78)
≥8.0	90	1614	22	13.6	1.95 (1.13–3.37)	1.98 (1.14–3.46)	1.53 (0.86–2.73)
Per mmol increase					1.27 (1.12–1.42)	1.25 (1.11–1.40)	1.18 (1.04–1.34)
p for trend					<0.0001	0.0003	0.011
Serum triglyceride, mmol/L							
<1.0	806	15,395	57	3.7	1.00	1.00	1.00
1.0–1.4	339	6150	52	8.5	1.70 (1.15–2.50)	1.69 (1.14–2.52)	1.59 (1.06–2.37)
1.5–1.9	145	2598	27	10.4	1.85 (1.15–2.98)	1.71 (1.03–2.84)	1.49 (0.89–2.50)
≥2.0	82	1415	28	19.8	3.35 (2.09–5.36)	2.79 (1.67–4.68)	2.20 (1.26–3.82)
Per mmol increase					1.60 (1.39–1.84)	1.49 (1.25–1.77)	1.40 (1.16–1.68)
p for trend					<0.0001	<0.0001	0.0004
Combined lipids[b]							
Low	504	9697	26	2.7	1.00	1.00	–
Intermediate	760	13,985	104	7.4	1.91 (1.22–2.98)	1.80 (1.14–2.85)	–
High	108	1877	34	18.1	3.35 (1.93–5.81)	2.83 (1.59–5.03)	–

[a]Adjusted for age, menopause, smoking, diabetes, physical activity, systolic blood pressure, body mass index, alcohol consumption and education.
[b]Low=serum cholesterol <6 and serum triglyceride <1mmol/l; high=serum cholesterol ≥7 and serum triglyceride ≥1.5mmol/l; intermediate=all other.

Table 6 Lipids, body mass index and smoking by age in women in Göteborg 1980–1995

	Year	Number	Age						All (age-adjusted)
			39–44		45–54		55–64		
Serum cholesterol, mmol/l									
	1980	426	5.50 (0.94)	601	6.23 (1.09)	345	6.84 (1.34)	1372	6.21
	1985	117	5.82 (1.31)	198	6.21 (1.21)	168	6.77 (1.25)	483	6.27
	1990	151	5.26 (0.87)	217	5.83 (1.15)	215	6.53 (1.12)	583	5.90
	1995	169	5.14 (1.01)	241	5.61 (1.08)	225	6.05 (0.98)	635	5.58
p for trend			<0.0001		<0.0001		<0.0001		<0.0001
Serum cholesterol <6%									
	1980		71		46		24		49
	1985		62		48		24		47
	1990		83		60		35		61
	1995		82		69		50		68
Serum cholesterol ≥7%									
	1980		6		21		45		22
	1985		17		22		41		25
	1990		3		15		35		16
	1995		4		10		17		10
Serum triglycerides mmol/l									
	1980	426	0.95 (0.48)	601	1.07 (0.54)	346	1.39 (0.77)	1372	1.13
	1985	117	0.99 (0.61)	198	1.18 (0.68)	168	1.33 (0.86)	483	1.18
	1990	151	1.07 (0.47)	217	1.27 (0.51)	214	1.47 (0.59)	583	1.28
	1995	169	1.17 (0.54)	241	1.39 (0.75)	225	1.48 (0.76)	635	1.34
p for trend			<0.0001		<0.0001		0.12		<0.0001
Serum triglycerides <1%									
	1980		73		62		35		59
	1985		62		51		36		51
	1990		55		33		22		37
	1995		49		34		24		36
Serum triglycerides ≥1.5%									
	1980		9		14		30		16
	1985		10		20		31		19
	1990		13		29		41		27
	1995		23		33		39		31
Body mass index									
	1980	426	23.7 (3.6)	601	24.7 (3.9)	345	25.5 (4.1)	1372	24.6
	1985	117	24.1 (3.7)	198	24.2 (3.9)	168	25.6 (4.3)	483	24.6
	1990	151	23.9 (3.5)	217	24.9 (4.5)	215	26.0 (4.4)	583	25.0
	1995	169	24.0 (3.5)	241	25.1 (4.2)	225	26.3 (4.5)	635	25.2
p for trend			0.25		0.12		0.017		0.003
Current smokers									
	1980	426	41	601	34	345	31	1372	35
	1985	117	41	198	35	168	28	483	35
	1990	151	29	217	31	215	26	583	29
	1995	169	33	241	25	225	23	635	27
p for trend			0.013		0.018		0.027		<0.0001

6.20 mmol/l or higher as compared to women with cholesterol less than 5.17 mmol/l.[7] Data summarised from the Framingham and the Donolo-Tel Aviv studies showed that women with cholesterol exceeding 265 mg/dl (6.85 mmol/l) had incidence rates of MI/definite coronary events more than three times that of women having the lowest cholesterol values.[6] The risk of coronary disease in women with cholesterol below 264 did not substantially vary in either population. From the same time period two prospective studies performed in Scandinavia with baseline examinations done in the 1960s, found no significant association between cholesterol and subsequent MI, coronary deaths

or total mortality.[8–10] However, in a recent publication on an extended follow-up, serum cholesterol was significantly associated with total mortality in women aged 38 years at baseline but not among older women.[11]

Studies from the 1970s consistently found a strong association of cholesterol and CHD mortality in middle-aged women. In the Renfrew and Paisley survey the relative risk of coronary death during 15 years of follow-up adjusted for non-lipid risk factors was 1.77 (1.45–2.16) in women aged 45–64 years with cholesterol above 7.2 mmol/l as compared to women with cholesterol below 5.5 mmol/l.[20] No association was found with all cause mortality.[21] A Dutch study in subjects aged 30–54 years and with a 12 year follow-up found a three- to fourfold increase in risk of CHD deaths in women with cholesterol equal to or above 6 mmol/l, based, however, on 38 deaths only.[22] The relative risk for all cause mortality ($N=501$) was increased 1.5 (1.1–1.9). Stensvold et al.[15] observed an independent association of non-fasting cholesterol and coronary mortality in 35–49 years old women followed-up for 15 years, relative risk 1.3 (1.1–1.6) per unit increase of cholesterol.

In two recently reported studies from Finland and Norway, conducted from the late 1970s and early 1980s and thus more comparable to our study in terms of study period as well as geographical setting, total cholesterol was a highly significant predictor for subsequent CHD incidence and mortality in middle-aged women (as in men).[13,14] A 1 mmol/l increase in cholesterol was associated with a 38% increase in risk of incident MI in the study by Njølstad et al.[13] after adjustment for coronary risk factors including triglycerides and HDL cholesterol. In addition, it was observed that only at cholesterol levels of 7.4 mmol/l or above did the incidence rise in women and the association was significant in smokers only. In the study by Jousilahti et al.[14] a 1 mmol increase in cholesterol was associated with a 21% increase both in CHD incidence and CHD mortality. The strong association with high cholesterol levels and CHD incidence and mortality is in agreement with our results showing 51% increase in MI, 30% increase in CHD hospitalisations and 18% increase in mortality per 1 mmol increase in cholesterol after adjustment for non-lipid variables and triglycerides. HDL cholesterol was not measured in our study but as reported in other studies in women a correction including HDL cholesterol would probably have had only a marginal impact on the magnitude of the associations observed.[13]

In the present study, women with triglycerides equal to or above 1.5 mmol/l had a three- to sixfold increased risk of MI, a threefold increase in risk of being hospitalised with CHD and a doubling in risk of all cause mortality as compared to women with triglycerides below 1.0 mmol/l. Although triglycerides were strongly related to systolic blood pressure, smoking, BMI, diabetes and physical activity, adjustment for these and other non-lipid factors did not materially alter the risk estimates. The association between triglyceride and CHD remained also after adjustment for cholesterol. However, it could be argued that correction for total cholesterol may represent an overcorrection as a proportion of the cholesterol is transported by triglyceride rich particles.[23,24]

Our data are consistent with earlier reports showing that fasting elevated triglyceride levels are strongly associated with CHD in women. In a meta analysis including five population-based prospective studies in women of triglycerides and cardiovascular disease relative risk estimates in individual studies for triglyceride varied between 1.69 and 2.05 and the summary univariate RR was 1.79 (1.50–2.07).[24] After adjustment for HDL cholesterol and other risk factors, the risk was decreased to 44% in women but remained statistically significant. Corresponding estimate for MI in our study, adjusted for total cholesterol and other non-lipid risk factor was 49%. As HDL cholesterol was not measured in our study and as adjustment for HDL substantially attenuates the association of triglycerides with the risk of CHD[23,25,26] the relative risks in our study may be overestimated. However, the strong inverse correlation between triglyceride and HDL cholesterol and the considerable differences in the variation of these measurements may result in a consistent underestimation of the association triglyceride-disease in multivariate analyses.[26]

Interestingly, it has been noted that triglycerides seemed to be a more potent risk factor for cardiovascular disease in Scandinavian than in other countries.[26] In the meta analysis, mentioned earlier, the crude relative risk estimates were higher in studies conducted in Sweden[8–10] than in studies from the US (2.02 vs 1,71).[7] A similar difference between geographical regions was also observed among men. In more recent studies from Scandinavia, started in the 1970s or 1980s and with at least 10 years follow-up of middle-aged women, Njølstad et al.[13] found no association of triglycerides and CHD incidence in multivariate analysis including lipids. Other studies from the US reported triglycerides to provide substantial CHD prediction

also after adjustment for LDL-C and HDL-C and Lp(a).[27] Triglycerides were also associated with much greater top quintile relative risk in women (4.7) than in men (2.1).[27]

There are several limitations with respect to the finding of the present study. There were a limited number of end-points, which is often the case in studies on CHD in women. This means that the confidence intervals in some instances are wide. The end-point data were derived from official registers and not specifically validated for this study. However, the registers used in the present study have been used to create the National AMI register in Sweden which has been validated by comparing data from register with a random sample of medical records from patients discharged with a diagnosis of either acute MI or other ischemic heart disease.[28] The predefined criteria for definite MI was met in 86%, with a further 9% classified as 'probable MI'.

During the past 20 years CHD incidence and mortality has declined in middle-aged women in Sweden and the cardiovascular risk factor pattern has changed.[2,29] Data from this study including information from the MONICA surveys (1985–1995), where the laboratory methods were standardised, show decreasing serum cholesterol and smoking rates while BMI and triglycerides increased in women. During this time period body weight increased, particularly among young women, despite no decrease of reported physical activity.[2] In another study of Göteborg women there have been increases in waist to hip ratio from the late 1960s to early 1990s whereas BMI remained stable.[30] It is likely that an imbalance between calorie intake, content and composition of diet, and a sedentary life style is an important explanatory factor for the increasing levels of triglycerides and BMI observed in this study. Thus, a pattern of risk factors mainly characterised by metabolic disturbances is emerging in women. In view of the fact that several studies have shown that the development of the declining trends in CHD incidence and mortality have been less favourable in women than in men[31–33] and the findings that triglycerides, diabetes and HDL cholesterol seem to assert a greater impact on CHD risk in women than in men[4,5] preventive measures to correct metabolic aberrations seem particularly warranted in women.

In conclusion, elevated fasting cholesterol and fasting triglycerides are associated with a high risk of developing CHD in middle-aged women. The favourable declining trend in cholesterol and smoking in the population was offset by an appreciable increase in serum triglycerides and a moderate increase in BMI suggesting that interventional strategies directed to correct metabolic aberrations may be specifically warranted in women.

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