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Associations Between Serum Lipids and Causes of Mortality in a Cohort of 3499 Urban Thais: The Electricity Generating Authority of Thailand (EGAT) Study

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The association between serum lipids and mortality has not previously been established in Thailand. Baseline data from the Electricity Generating Authority of Thailand (EGAT) cohort study, plus a resurvey of the cohort 15 years later were analyzed. Participants were employees of EGAT: 2702 men and 797 women. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were taken as predictive variables; age, sex, hypertension, diabetes, cigarette smoking, alcohol drinking, and body mass index were taken as confounders. Dependent variables were all-causes and specific causes of mortality over 17 years of follow-up. The major cause of death among men was cardiovascular disease (CVD); among women, it was cancer. Relative risks (RR) for specific causes of death, for a mmol/L increase in each lipid, were estimated after adjustment for confounding factors using Cox proportional hazards regression. TC and LDL-C were negatively associated with liver cirrhosis mortality, although it was likely that the low cholesterol concentration was a consequence of the disease. HDL-C was negatively associated with CVD mortality (RR = 0.59; 95% confidence interval [CI], 0.39-0.93), coronary heart disease (CHD) mortality (RR = 0.36; 95% CI, 0.17-0.75) and all cause-mortality (RR = 0.68; 95% CI, 0.54-0.87). TG was not associated with mortality. HDL-C is an important risk factor for CVD in middle-class urban Thais. Health promotion programs to improve lipid profiles, such as effective exercise campaigns and dietary advice, are required to increase HDL-C and to help prevent CVD and premature death in Thailand.

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Introduction

In Thailand, diseases of the circulatory system are the most common cause of death. The mortality rate for coronary heart disease (CHD) increased between 1991 and 1996, and, although it then decreased in 1997, it remained the major cause of death.¹ Other common forms of vascular disease were stroke and peripheral arterial disease; these conditions and CHD have a common underlying condition of atherosclerosis. This finding is associated with evaluated

values of total cholesterol (TC), triglycerides (TG), and low density lipoprotein cholesterol (LDL-C) and low values of high density lipoprotein cholesterol (HDL-C).²⁻⁵ However, low serum cholesterol has sometimes been associated with an increased risk of cancer mortality, which has led to uncertainty regarding the overall benefit of lowering blood cholesterol.^{6,7} To date, this issue has not been explored in Thailand, where TC tends to be relatively low compared with typical Western populations. Lipid profile levels in people from different countries may vary because of differences in socioeconomic status, genetics, and lifestyle (including exercise, smoking, and diet). In this study, we address the possibility that benefits of certain lipid profiles with respect to cardiovascular disease (CVD) mortality might be offset by an increase in mortality from cancer and other diseases using data from the Electricity Generating Authority of Thailand (EGAT) Study.

Methods

In 1985, all 7824 eligible employees, between 35 and 54 years of age, of the Electricity Generating Authority of Thailand (EGAT) based at the company's headquarters in Bangkok were invited, by means of a letter, to take part in a cross-sectional study of cardiovascular risk factors⁸⁻¹⁰; 3499 (2702 men and 797 women) agreed to participate. Subjects completed a self-administered cardiovascular risk factor questionnaire, underwent an oral glucose tolerance test and a physical examination, and gave blood samples. These examinations were repeated in 1997 and 2002. In 2002, the mortality status of participants was ascertained by post, telephone, or personal contact, and causes of death were verified using all available information.

Statistical Analysis

Baseline CVD risk factors were compared between the sexes using Mann-Whitney (continuous variables) and χ^2 (categorical variables) tests. Standardized mortality ratios were calculated using the 1993 world population¹¹ as the standard population. The association between lipid levels and causes of mortality were analyzed using Cox survival models.¹² Hazard ratios (HR) were calculated for a 1 SD (mmol/L) increase in each lipid, adjusted for sex and age, and also

Table I. Summary statistics for lipid variables and other cardiovascular risk factors at baseline, by sex^a

| Variable | Total (n = 3499) | Men (n = 2702) | Women (n = 797) |
|---|---------------------|-------------------|--------------------|
| Age (y) | 43.01 (5.10) | 43.37 (5.20) | 41.74 (4.53) |
| Total cholesterol (mg/dL) | 5.77 (1.12) | 5.80 (1.12) | 5.67 (1.11) |
| LDL-C (mg/dL) | 3.80 (1.06) | 3.81 (1.07) | 3.75 (1.05) |
| HDL-C (mg/dL) | 1.22 (0.30) | 1.18 (0.29) | 1.36 (0.30) |
| Triglycerides (mg/dL) | 1.72 (1.31) | 1.87 (1.41) | 1.22 (0.64) |
| Body mass index (kg/m ²) | 23.08 (3.14) | 23.17 (3.10) | 22.78 (3.25) |
| Diabetes: n (%) | 239 (6.8) | 203 (7.5) | 36 (4.5) |
| Hypertension ^b : n (%) | 706 (20.2) | 606 (22.4) | 100 (12.5) |
| Current cigarette smoking: n (%) | 1515 (43.3) | 1465 (54.3) | 50 (6.3) |
| Current alcohol drinking: n (%) | 2284 (65.3) | 1996 (73.9) | 288 (36.2) |

Abbreviations: LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

^aValues shown are mean (standard deviation) unless otherwise specified. Numbers of participants shown in parentheses.

^bBlood pressure \geq 140/90 or current use of blood pressure lowering therapy.

additionally adjusted for systolic blood pressure, diabetes (yes/no), current cigarette smoking (yes/no), current alcohol drinking (yes/no), and body mass index (BMI; kg/m²). For grouped analysis, individuals were classified according to approximately equal thirds of each lipid variable, as assessed at baseline. Cox proportional hazard models were used to estimate the hazard ratio of the different causes of mortality, with corresponding 95% confidence intervals (CI) calculated using the "floating absolute risk" method.⁹ Information on repeat measures of blood pressure and fasting TC, HDL, LDL, and TG were available for 2770 individuals that participated in the 1997 survey and for 2329 individuals that underwent the 2002 survey. These repeat measures were used to estimate, for each lipid variable, an attenuation coefficient using a linear mixed regression model¹² that accounted for the within-subject correlation and the varying time intervals between measurements. Regression attenuation coefficients¹² were calculated in this

Table II. Adjusted hazard ratios (95% confidence intervals) for 1 standard deviation increase in each lipid variable (triglycerides was log transformed), by specific causes of death^a

| Variable/ Adjustments | All Causes (n = 355) | Coronary Heart Disease (n = 50) | Stroke (n = 44) | Total Vascular ^b (n = 109) | Cancer (n = 109) | GI and Liver Diseases (n = 35) | External Causes (n = 54) | Other Causes ^c (n = 48) |
|-----------------------------|-------------------------|---------------------------------------|---------------------|---|---------------------|--------------------------------------|--------------------------------|--|
| TC (mmol/L) | | | | | | | | |
| Age and sex | 0.81 (0.65-1.02) | 1.21 (0.68-2.15) | 0.62 (0.32-1.19) | 1.03 (0.69-1.53) | 0.87 (0.58-1.32) | 0.26 (0.12-0.57) | 0.67 (0.36-1.25) | 0.98 (0.55-1.76) |
| All covariates ^d | 0.79 (0.63-1.00) | 1.07 (0.59-1.93) | 0.53 (0.27-1.02) | 0.89 (0.59-1.33) | 0.90 (0.59-1.38) | 0.27 (0.12-0.60) | 0.73 (0.39-1.38) | 1.01 (0.56-1.81) |
| LDL-C (mmol/L) | | | | | | | | |
| Age and sex | 0.82 (0.63-1.06) | 1.50 (0.79-2.83) | 0.63 (0.29-1.36) | 1.13 (0.72-1.78) | 0.95 (0.60-1.49) | 0.23 (0.10-0.54) | 0.55 (0.28-1.12) | 0.90 (0.47-1.73) |
| All covariates ^d | 0.86 (0.67-1.11) | 1.40 (0.72-2.70) | 0.60 (0.28-1.30) | 1.06 (0.67-1.68) | 1.01 (0.64-1.59) | 0.28 (0.12-0.66) | 0.64 (0.32-1.28) | 1.01 (0.52-1.95) |
| HDL-C (mmol/L) | | | | | | | | |
| Age and sex | 0.73 (0.57-0.93) | 0.27 (0.13-0.56) | 0.60 (0.30-1.19) | 0.53 (0.33-0.83) | 0.65 (0.42-1.01) | 0.86 (0.42-1.79) | 1.56 (0.90-2.70) | 0.72 (0.39-1.33) |
| All covariates ^d | 0.68 (0.54-0.87) | 0.36 (0.17-0.75) | 0.61 (0.32-1.19) | 0.60 (0.39-0.93) | 0.59 (0.37-0.93) | 0.72 (0.34-1.49) | 1.19 (0.66-2.12) | 0.67 (0.36-1.23) |
| TG (mmol/L) | | | | | | | | |
| Age and sex | 1.23 (0.98-1.56) | 1.29 (0.71-2.34) | 2.18 (1.24-3.85) | 1.63 (1.11-2.40) | 0.97 (0.63-1.51) | 0.98 (0.47-2.06) | 0.89 (0.47-1.70) | 1.63 (0.91-2.93) |
| All covariates ^d | 1.06 (0.84-1.33) | 0.87 (0.47-1.61) | 1.51 (0.86-2.66) | 1.11 (0.76-1.64) | 0.96 (0.61-1.51) | 0.84 (0.41-1.74) | 1.11 (0.57-2.14) | 1.32 (0.74-2.35) |

Abbreviations: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; GI, gastrointestinal.

^aNumbers of deaths shown in parentheses.

^bTotal vascular includes all coronary heart disease and stroke plus 16 others.

^cRespiratory (n = 14); infectious (n = 10); renal (n = 5); diabetes (n = 3); unknown (n = 16).

^dAdjusted for sex, age, systolic blood pressure, diabetes, current cigarette smoking, current alcohol drinking, and body mass index.

way for TC (2.3), TG (2.1), HDL (2.1), and LDL (2.4). For the grouped analyses by thirds, the hazard ratios were plotted against the *usual* mean values, rather than the baseline mean values, of each lipid variable.

Results

Baseline Values

Table I shows summary statistics at baseline for all lipid variables and for the other cardiovascular risk factors taken as confounding variables in further analyses of lipids. There were significant differences between men and women for all variables ($P < .05$). Men had higher mean age, TC, LDL-C, TG, and BMI, a higher prevalence of diabetes and hypertension, and a much higher

prevalence of smoking and drinking than women. Women had higher values of HDL-C than men.

Mortality Follow-up

During the follow-up from 1985 to 2002, there were 56 389 person-years of observation. In 2002, the vital status of 244 (7%) persons (194 men and 50 women) could not be determined, whereas 355 (10%) deaths were identified with 307 deaths (11%) among men and 48 (6%) among women. Of all deaths, 109 (31%) were caused by CVD: 50 (14%) by CHD, 44 (12%) by stroke, and 15 (4%) by other vascular diseases. Another 109 deaths (31%) were attributable to cancer, mainly due to lung cancer and hepatocholangiocarcinoma; 35 (10%) were caused by gastrointestinal (GI) and liver disease, mainly liver cirrhosis; 54 (15%) were caused by external causes, mainly traffic accidents; and 48 (14%) were due to other causes.

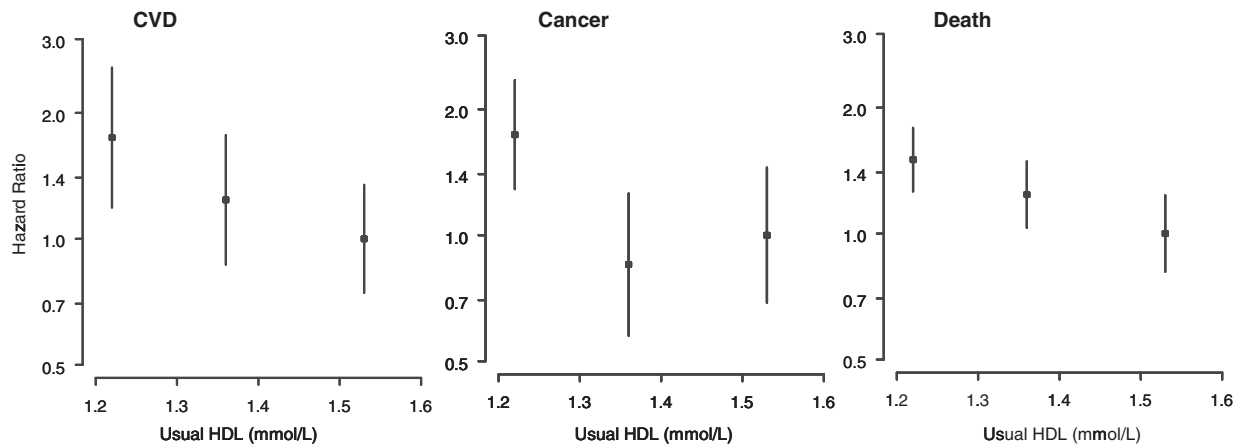


Figure 1. The adjusted relationships between usual values of high density lipoprotein cholesterol (HDL) and the 2 major causes of death and all-causes of death, demonstrating the linearity of the effects for vascular causes and total mortality, whereas the relationship with cancer suggests an excess risk only at relatively low HDL-C. CVD, cardiovascular disease.

Associations Between Serum Lipids and Mortality

Table II shows results by several broad causes of death and for all causes combined, after adjustment for other major CVD risk factors. Serum TC had a negative association with death from GI and liver disease (HR for a unit [mmol/L] increase = 0.27; 95% CI, 0.12-0.60). Serum LDL-C had a negative association with death from GI and liver disease (HR = 0.28; 95% CI, 0.12-0.66), similar to serum TC. Serum HDL-C had a negative association with CVD (HR = 0.59; 95% CI, 0.39-0.93), CHD (HR = 0.36; 95% CI, 0.17-0.75), cancer (HR = 0.59; 95% CI, 0.37-0.93), and all-cause mortality (HR = 0.68; 95% CI, 0.54-0.87). The age- and sex-adjusted associations between serum TG and CVD and CHD were significant, but these effects were substantially attenuated after taking into account the confounding effect of the other major confounders.

Discussion

Death Rates and Causes of Death

During the 17-year follow-up period, 355 deaths were identified among this cohort, giving a crude death rate from all causes of 6.3 per 1000 person-years. This rate is lower than anticipated from

national statistics, but the EGAT population is probably representative of a middle-class urban Thai population. As is typical in many Western countries, CVD was the leading cause of death among both men (31% of all deaths) and women (11%). These percentages are lower than those in the European Union, in which nearly half (42%) of all deaths are caused by CVD (43% in men and 55% in women).¹¹ They are also lower than found in urban areas of China, India, and Africa,¹³ although higher than reported among Korean men.¹⁴ CHD was more common than stroke among both men and women, consistent with other world populations, especially those of Western countries,¹⁵ but not with certain countries in Asia where stroke is more widespread.^{13,16,17} The age-standardized mortality rate¹⁸ among this study population for CHD death was 0.95 for men and 0.11 per 1000 for women. These values are lower than all WHO MONICA¹⁹ centers except Beijing,²⁰ which had rates of 43 and 24 per 100 000 among men and women, respectively. The ratio of age-standardized mortality rates, men to women, caused by CVD death was 9.0, by CHD was 8.6, and by stroke was 8.8; these ratios were higher than most countries in the WHO MONICA project,¹⁹ possibly explained by the very low smoking rates among women in EGAT.

Cardiovascular Mortality

In this study, there was no evidence of an association between TC and the risk of CVD mortality,

consistent with the 3 Chicago epidemiological studies,²¹ but in contrast to many other studies.^{14,21–25} Differences may be the result of disparities in cardiovascular diseases by race/ethnicity, socioeconomic status, lifestyle, and geography; trends in cardiovascular disease prevention and treatment services; and strategies to reduce overall cardiovascular diseases and disparities among subpopulations.

The Framingham Study²⁶ has suggested that a low serum HDL-C level is a major risk factor for CHD. In this cohort, HDL-C was inversely associated with CVD and CHD deaths, consistent with many studies in Western countries^{27–33} and in Asia,^{14,24,34} but were not associated with stroke death. For every 1 SD decrease in HDL-C, there was a 67% increase in the incidence of CVD death and nearly a 3-fold increase in the incidence of CHD death.

Cancer Mortality

Some studies have shown an inverse relationship between TC and the risk of cancer,^{14,23,35–37} but other studies were inconsistent.^{6,20,38,39} In the Honolulu and Framingham studies,^{6,21} there was an inverse association, which is unlikely to be explained by a preclinical cancer effect, because the first years of follow-up were excluded from the analysis. In this study, no association was found between cholesterol and risk of cancer. The Heart Protection Study has shown that lowering total cholesterol by more than 1 mmol/L is not associated with an increase of cancer, even among those participants who had cholesterol lowered to very low levels.⁴⁰

Liver Disease Mortality

Many studies^{35,41,42} have reported an association between a low TC level and subsequent nonatherosclerotic disease incidence or death, as found here. The Yugoslavia Cardiovascular Disease Study⁴³ showed no association between TC and liver cirrhosis. The question of whether low TC is a true risk factor or alternatively a consequence of occult disease at the time of TC measurement still remains unanswered.⁷ Excluding the first 5 years of mortality data in EGAT made no substantive difference to the results, in contrast to the Honolulu Heart Program, which reported a weaker relationship when the first year of follow-up was excluded.⁴⁴ LDL-C was also inversely related with cirrhosis death in

EGAT, and, again, excluding the first 5 years of deaths had no real effect on the results.

External Causes

There was no evidence of an association between serum lipids and external causes of mortality (traffic accidents, homicides, suicide, and violence). Other studies have reported a nonsignificant⁴³ or a negative association.^{20,35,45} One study showed that the relationship was confounded by alcohol consumption.⁴⁶

All Cause Mortality

Epidemiological studies have often reported a U-shaped relationship between TC and all-cause mortality.^{14,21,27,47} However, here the relationship was flat. There was no statistically significant association between TC and all-cause mortality, in contrast to some other studies.^{14,22,36} On the other hand, there was a statistically significant association between HDL-C and all-cause mortality, consistent with Polish and US data.²⁷

Some health behaviors and treatments of participants during the long period of follow-up may have affected survival probability, as well as study factors measured at baseline. Accessibility to health care, change in lifestyle, and economic status may improve or worsen, both at early and late stages of the study period. Unknown reasons for loss to follow-up also threaten the validity of the results. Finally, the study population here is not typical of Thais in general. Nevertheless, the EGAT study provides some of the best information to date of the effects of lipids and death by cause among middle-class urban Thais.

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