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High-density lipoprotein cholesterol, a protective or a risk factor for developing coronary heart disease? Tehran Lipid and Glucose Study

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BACKGROUND: Recently, there are controversial findings on protective effect of high-density lipoprotein cholesterol (HDL-C) against coronary heart disease (CHD) in some population.
OBJECTIVE: We aim to determine the effect of HDL-C on CHD in premenopausal and postmenopausal women.
METHODS: Between February 1999 and August 2001, 3778 women aged 30 to 74 y, free of clinical cardiovascular diseases, were recruited and followed up to March 2010. HDL-C and other CHD risk factors were measured at baseline. Using multivariable Cox proportional hazard model, the adjusted hazard ratio was calculated.
RESULTS: During a median follow-up of 9.6 y, a total of 228 new CHD events occurred. In postmenopausal women, the adjusted hazard ratio for each standard deviation increase in HDL-C was 0.76 (95% confidence interval, 0.63–0.92). Among premenopausal women, a time varying model was fitted; the adjusted hazard ratio for each standard deviation increase of HDL-C among 30-year-old women was 2.67 (95% confidence interval, 0.98–7.29) but decreased by 5% for each year increase of age.
CONCLUSIONS: Different effects of HDL-C in premenopausal and postmenopausal women were identified. During premenopausal period, the hazard of CHD increased by any increase of HDL-C level, but the amount of this increment gradually decreased over time, whereas during postmenopausal period, the hazard of CHD was inversely associated with HDL-C level.
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Introduction

The role of lipid profiles as risk factors of coronary heart disease (CHD) has long been studied, with a general consensus that elevated levels of high-density lipoprotein cholesterol (HDL-C) provide a cardioprotective effect, whereas a high level of low-density lipoprotein cholesterol is atherogenic.[1]

However, new findings challenge the concept that rising plasma HDL-C is associated with reduction in risk of myocardial infarction. Two major groups of recent research strongly favor the notion that HDL-C is not always associated with lower risk of CHD. The first is genetically based studies that refute a causal role of HDL-C in reducing risk of CHD,[2–4] and the second group of studies are trials of drugs with the aim of increasing HDL cholesterol, which have not consistently shown decreases in CHD.[5–7] These findings are leading to the hypothesis that HDL-C may contain both protective and nonprotective components. Recent research declares that HDL functionality that is mainly related to HDL sub classes is a better therapeutic target and protection against CHD than HDL quantity.[8–10] Recent evidence suggests that some factors such as inflammation, uremia, psoriasis, and aging may alter the function and composition of HDL-C.[11–14] Some of these alterations are partly attributed to the content of apolipoproteins. Despite valuable knowledge on HDL structure and functionality in biomedical research, there is still limited evidence in epidemiologic studies revealing its controversial effects on CHD.[15] Previous study in Tehran Lipid and Glucose Study (TLGS) reported no protective effect of HDL-C against CVD in women.[16] In this study, we aim to investigate the effect of HDL-C on CHD in a population-based cohort of women. Because natural menopause has an unfavorable effect on lipid metabolism, we specifically stratified our population into premenopausal and postmenopausal women.

Materials and methods

Study population

This study is a part of TLGS, a population-based cohort that was initiated in 1999 to 2001.[17] Of 4482 women, aged 30 to 74 y, we selected those (n = 4278) without a history of cardiovascular disease (CVD). Further excluding subjects with missing data, resulted in 3778 individuals eligible to enter the study. They were followed until March 2010 with median follow-up of 9.6 y. This study has been approved by the ethical committee of Research Institute for Endocrine Sciences, and all participants gave informed written consent.

Clinical and laboratory measurements

The details of the measurements have been published elsewhere[18]; briefly, at baseline examination, for all partici- pants, medical history, physical measurements (including systolic and diastolic blood pressure and anthropometry), and overnight fasting blood sampling were done. Blood samples were measured for total cholesterol, triglycerides, and HDL-C as described previously.[18] Independent predictor variables were considered as diabetes mellitus (fasting plasma glucose ≥7 mmol/L, 2-h plasma glucose ≥11.1 mmol/L, or current use of antidiabetic drugs); family history of CVD (any prior CVD diagnosed by a physician in first-degree relatives aged under 65 y for women and under 55 y for men); smoking status (current regular or occasional use of cigarettes); menopause (absence of spontaneous menstrual bleeding for more than 12 mo after age 50 y)[19]; and hypertension (mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medications).

Follow-up and outcome event

The follow-up period for present study was defined from the baseline examination up to March 20, 2010; details of outcome collection have been described previously.[17] The first CHD event was the outcome of this study and included any one of the following: definite myocardial infarction, probable myocardial infarction, unstable angina, angiographic-proven CHD, and death due to CHD.

Statistical analysis

Baseline characteristics between subjects with and without CHD were compared by Student t test for continuous variables, Mann–Whitney test for skewed variables, and chi-square test for categorical variables.

We analyzed the data splitting for menopausal status, and used Cox proportional hazard (PH) model to study the adjusted effect of HDL-C and other lipid measures on occurrence of CHD outcome. Because we found a nonproportionality of the hazard ratio (HR) for HDL-C before menopause, we used a time varying model.

To account for left truncated survival time and as the individual's true survival time is underestimated by the time-on-study information (obtained from study entry), we used age as the time scale, and the outcome variable is age at event or censorship.[20] Because the age of entry to the study was 30 y, we subtracted age at event from age 30 y.

The likelihood ratio χ^2 statistic was assessed as an indicator of global goodness of fit of predictive models. For choosing the better model, a higher value indicates a better model fit. The PH assumption was evaluated for categorical variables with both graphical approaches by comparing log–log survival curves and also interaction with time. For continuous variables, we used just interaction with time to assess PH assumption. In case of rejecting the assumption, a time varying model was used. All continuous variables were standardized, and HRs and their 95% confidence intervals (CIs) were estimated for one standard

Table 1   Baseline characteristics of participants according to menopausal statues

Covariates	Premenopause N = 2427	Postmenopause N = 1351
Age, y, mean (SD)	39.4 (6.5)	58.3 (7.6)
Hypertension, n (%)	384 (15.8)	642 (47.5)
Diabetes mellitus, n (%)	207 (8.5)	315 (23.3)
Smoking, n (%)	116 (4.7)	48 (3.5)
Family history of cardiovascular disease, n (%)	446 (18.4)	246 (18.1)
Waist-to-hip ratio, cm, mean (SD)	0.83 (0.1)	0.9 (0.1)
Body mass index, kg/m^2, mean (SD)	28.1 (5.1)	29.02 (4.5)
Lipid-lowering medication, n (%)	52 (2.1)	134 (9.9)
Lipid profile, mg/dL, median (25th–75th percentile)		
Total cholesterol	204 (178–232)	242 (213–274)
Triglycerides	136 (94–199)	175 (128–247)
HDL cholesterol	42 (35–49)	46 (39–53)

HDL, high-density lipoprotein; SD, standard deviation.

deviation (SD) increment of continuous variables. Data analysis was performed using Stata 12.

Results

This study consisted of 3778 women, mean age 46.2 y (SD, 11.4; range, 30–74). There was no significant difference between followed and nonfollowed participants regarding age, lipid markers, and major risk factors for CHD (data not shown). A total of 36,322 person-years were followed, during which 228 new CHD events including 59 cases in premenopausal and 166 cases in postmenopausal women occurred. The median duration of follow-up was 9.6 y, and the incidence rate of CHD was 62.77 per 10,000 person-years.

Thirty-six percent of participants (N = 1351) were in postmenopausal period. Baseline characteristics of participants including anthropometric measures, CHD risk factors, and lipid profiles in premenopausal and postmenopausal women are illustrated in Table 1. Except for smoking status and family history of CVD, there were significant differences between the 2 groups in all other variables. A total of 186 women (4.92%) were on lipid-lowering drugs.

Tables 2 and 3 illustrate the result from Cox PH analyses examining lipid measures and other risk factors as predictors of CHD in premenopausal and postmenopausal women, respectively. In the multivariable-adjusted model for premenopausal women, there was a strong positive association among hypertension, diabetes mellitus, family history of CVD, and total cholesterol. Body mass index and lipid-lowering medication did not show a significant effect in multivariable-adjusted model and ignored in final analysis. In Cox model, PH assumption was not met for HDL-C; therefore, a time varying model was used. Increasing HDL-C was associated with increasing risk of CHD (HR, 2.67; CI, 0.98–7.29) and there was a negative significant interaction between time and HDL-C (HR, 0.95;

Table 2   Hazard ratio estimate of risk factors for coronary heart disease in premenopausal women

Covariates	Univariable model HR (95% CI)*	P value	Multivariable-adjusted model HR (95% CI)*	P value
Hypertension	1.87 (1.34–2.61)	.001	2.71 (1.59–4.62)	.001
Diabetes mellitus	17.39 (3.79–79.7)	.001	2.68 (1.53–4.72)	.001
Current smoking	1.44 (0.67–3.07)	.35	1.12 (0.27–4.67)	.87
Family history of CVD	1.82 (1.29–2.57)	.001	2.28 (1.32–3.94)	.003
Waist-to-hip ratio	1.38 (1.17–1.63)*	.001	1.13 (0.83–1.54)	.44
Total cholesterol	1.19 (1.04–1.37)*	.01	1.48 (1.06–2.05)	.03
TG	1.13 (1.04–1.23)*	.004	0.91 (0.7–1.18)	.48
HDL-C	0.74 (0.63–0.87)*	.001	2.67 (0.98–7.29)	.05
HDL-C × time†			0.95 (0.91–0.99)	.036

CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation; TG, triglyceride.

*Values are HRs (95% CI) from Cox proportional hazard analysis for 1-SD change.

†Interaction with time (age).

Table 3   Hazard ratio estimate of risk factors for coronary heart disease in postmenopausal women

	Univariate model		Multivariate-adjusted model	
Covariates	HR (95% CI)[*]	P value	HR (95% CI)[*]	P value
Hypertension	3.18 (1.88–5.37)	.001	1.46 (1.03–2.06)	.03
Diabetes mellitus	3.64 (2.14–6.22)	.001	2.43 (1.74–3.38)	.001
Current smoking	0.82 (0.2–3.38)	.79	1.59 (0.70–3.65)	.26
Family history of CVD	2.06 (1.2–3.54)	.009	1.71 (1.21–2.43)	.003
Waist–to-hip ratio	1.33 (1.00–1.78)[*]	.049	1.18 (0.99–1.42)	.06
Total cholesterol	1.54 (1.22–1.94)[*]	.001	1.18 (1.00–1.38)	.05
TG	1.20 (1.03–1.39)[*]	.01	0.96 (0.81–1.14)	.66
HDL-C	0.99 (0.78–1.28)[*]	.99	0.76 (0.63–0.92)	.005

CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; SD, standard deviation; TG, triglyceride.

*Values are HRs (95% CI) from Cox proportional hazard analysis for a 1-SD increase.

CI, 0.91–0.99), that is, the HR of one SD increase in HDL-C at the age of 30 y was 2.67 but with each increasing year of age, this HR decreased by 5% (Fig. 1).

Among postmenopausal women in the multivariable model, PH assumption was met for all variables and positive associations were found for hypertension, diabetes mellitus, total cholesterol, and family history of CVD with CHD. In this model, HDL-C was a protective factor for CHD. The risk of CHD was decreased by 24% with 1-SD increment of HDL-C.

We also evaluated the interaction among HDL-C and diabetes, hypertension, family history of CVD, and total cholesterol in premenopausal and postmenopausal women, which was not significant in either group.

Discussion

In this population-based cohort study of women, we concentrated on the role of HDL-C in developing CHD.

Increasing HDL-C was a protective factor only for postmenopausal women but in premenopausal women, the effect of HDL-C was not constant at different ages. Increasing HDL-C acted as a risk factor for 30-year-old women, and its hazard decreased with increasing age.

Similar findings have been reported about impaired protection of HDL-C against CHD in women. In another study on TLGS data, HDL-C did not have a protective effect for incident CVD among women and had a protective effect only among nondiabetic men.[16] Onat et al[21] showed that in the general Turkish adult population, HDL-C did not protect against the development of CHD in women, whereas a 12 mg/dL increase of HDL-C in men, decreased the risk of CHD by 20%. Recent interventional and genetic-based studies failed to establish a causal role between HDL-C and risk of myocardial infarction.[2–7,22] Although this study found a negative result for HDL-C against CHD in terms of HDL quantity, biomedical research addresses the issue of dysfunctional HDL-C in terms of
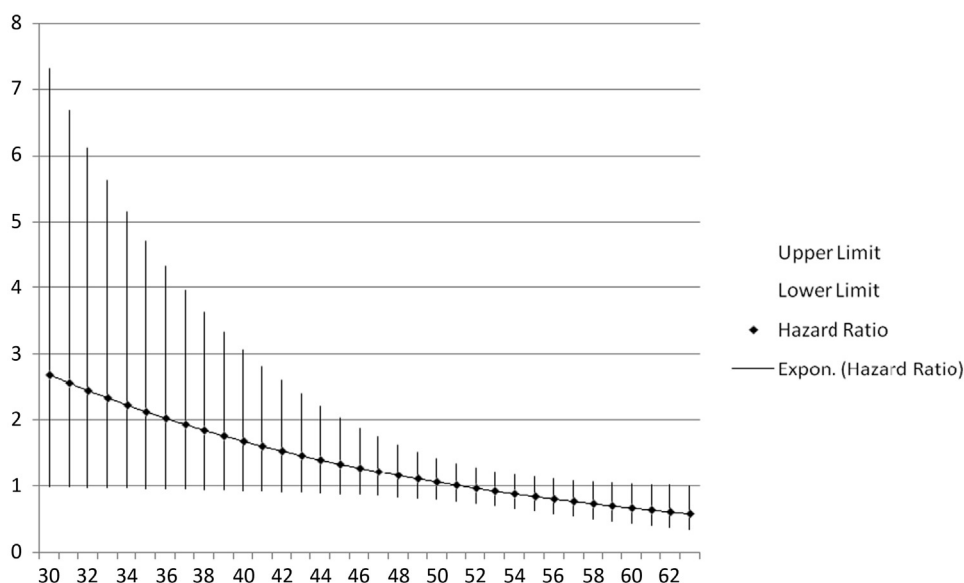

Figure 1   Trend of changes in hazard ratio of high-density lipoprotein cholesterol for coronary heart disease by increasing age in premenopausal women.

HDL quality instead of quantity.[23,24] Various methods have been proposed to measure dysfunctional HDL-C including analyzing anti-inflammatory and antioxidant properties of HDL-C attributed to apolipoprotein levels.[23] Some mechanisms have been suggested for reverse atheroprotective effects of HDL-C, most of which attributed to the role of apolipoproteins. Recently, a new study by Jensen et al[25] highlighted the role of apolipoprotein C-III (apo C-III) as a component involved in CHD pathogenesis and identified 2 types of HDL-C according to the presence or the absence of apo C-III, which result in the nonprotective and protective effects on the risk of CHD, respectively. In quantification of serum apolipoprotein in Japan, Noma et al found that Apo C-II, C-III, and E tended to decrease after 60 y of age.[26] The result of this study with respect to the varying effect of HDL-C over time may support the role of changing concentrations of different apolipoproteins and alteration of HDL quality with aging. Race and/or ethnicity differences of apo C-III have also been reported by recent studies.[27] Moreover, available evidence suggests a high probability of dysfunctional HDL-C in Asian Indians. At identical levels of HDL-C, Asian Indians have a higher proportion of less cardioprotective small HDL particles and a lower proportion of more cardioprotective large HDL particles compared with whites.[28,30] A recent study performed on an Asian population may support the idea of different lipid profile characteristics compared with Western communities[29]

We considered major risk factors of CHD including hypertension, diabetes, smoking, and family history of premature CVD as covariates in the models. Smoking did not show any association with CHD because of the very low prevalence of this trait in our women; more adjustment with passive smoking feature did not change the results (data not shown). The effect of waist-to-hip ratio, as a good index for central obesity, disappeared after multivariable adjustment because other covariates especially diabetes, hypertension, and lipids are its intermediate factors; neither did more adjustment with general obesity (data not shown). Considering lipid medication as an additional covariate attenuated the effect of total cholesterol on CHD but did not change the effect of HDL-C (data available on request).

There are some limitations that should be taken into consideration. First, the number of CHD events in premenopausal women was too small; this yielded a loss of power to detect a significant result. Second, in this study, the lipid markers were measured only once at baseline, so the intraindividual variation and potential bias resulting from regression dilution of lipid markers cannot be ignored, but according to the study by Clarke on the impact of regression dilution for blood pressure and blood cholesterol,[31] the uncorrected associations of cardiovascular outcomes with baseline measurements underestimate the strength of the real associations with usual levels of these risk factors. Unfortunately, there was no detailed data about the kind of lipid-lowering drugs and the intensity of treatment at the baseline and during follow-up. However,

because lower than 10% of participants used lipid-lowering medication at the baseline, it seems that these lacking data would yield a negligible effect on the results. And third, we did not measure inflammatory parameters including C-reactive protein, fibrinogen, and Apo A-1. We lacked a precise measurement of physical activity and energy expenditure either; however, the results did not change after more adjustment for an exercise variable defined as exercise ≥3 times a week (data not shown).

As expected, there was a large heterogeneity between premenopausal and postmenopausal women with respect to conventional risk factors of CHD. In postmenopausal women, the prevalence of nearly all risk factors was greater than that in premenopausal women. This heterogeneity may modify the effect of HDL-C on CHD. Although we reported HRs adjusted for conventional risk factors, determining the role of each risk factor in this effect modification needs more complicated analysis with much more sample size. In addition, the population of this cohort may be somewhat different from Western communities especially in lower prevalence of smoking habit, low use of lipid-lowering drugs, and high prevalence of diabetes mellitus. Our primary analysis revealed no interaction among smoking habit, lipid-lowering drugs, and diabetes with HDL-C on which the result may be extrapolated to other population regarding these variables; however, still some other unmeasured lifestyle characteristics, like nutrition habits, may modify the effect of HDL-C on CHD in different populations.

The strengths of this study include its prospective design on a large representative sample of a general population. This study also evaluated the time varying nature of HDL-C in data analysis and age as the time scale, which have never been considered previously. In this study, we found violation of PH assumption for HDL-C.

In conclusion, this study found disproportional assumption for HDL-C and opposite role for protective effect of HDL-C on CHD in women during their premenopausal and postmenopausal periods, which revealed an interaction between HDL-C and age and menopause. To estimate the overall effect of HDL-C on CVD identifying HDL-C quality served as dysfunctional HDL, and its quantity is strongly recommended.

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