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Association of high-density lipoprotein cholesterol concentration with different types of stroke and coronary heart disease: The Japan Public Health Center-based prospective (JPHC) study

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ABSTRACT

Background and aims: Although low high-density lipoprotein (HDL) cholesterol concentration is an established risk factor for coronary heart disease (CHD), information regarding subtypes of stroke is very limited, especially in Asian populations.
Methods: A prospective study was conducted among 30,736 individuals aged 40–69 years, who lived in nine communities in Japan and did not have a history of cardiovascular disease (CVD). CHD and stroke, including its subtypes, were assessed, and sex-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for outcomes were estimated according to quintiles of HDL cholesterol using Cox proportional models adjusted for other CVD risk factors.
Results: We identified 296 CHD and 1712 stroke events over a median 15 yr of follow-up. HDL cholesterol concentration showed an inverse association with CHD in men and women. A low HDL cholesterol concentration slightly raised the risk for total strokes in men, but not in women. When analyzed by subtypes, we observed an inverse relationship between HDL cholesterol concentration and the incidence of lacunar infarction, with an adjusted HR for the lowest quintile of HDL cholesterol concentration compared with the highest quintile of 1.63 (95% CI, 1.00–2.66) in men and 1.97 (95% CI, 1.19–3.26) in women. HDL cholesterol concentration was positively associated with the risk of intracerebral hemorrhage (ICH) in a linear manner in women (p for trend = 0.028), but not in men.
Conclusions: The associations of HDL cholesterol concentration with lacunar infarction and ICH may be related to different functional properties of HDL rather than to its protective function against lipid-rich atherosclerosis.

1. Introduction

Several prospective studies have confirmed that high-density lipoprotein (HDL) cholesterol concentration is inversely associated with atherosclerotic diseases; however, its mechanistic role in the prevention of atherosclerosis is not fully understood [1,2]. Despite the fact that a low HDL cholesterol concentration is an established risk factor for coronary heart disease (CHD), its association with stroke and stroke subtypes remains to be elucidated [3]. Addressing this question in Asian populations is of particular interest as they have a unique CVD case mix characterized by low CHD and high stroke incidence rates [4]. Although a few prospective studies have demonstrated an association between HDL cholesterol concentration and CVD incidence or mortality in Japan

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[5–8], evidence regarding stroke and stroke subtypes is very limited.

Several mechanisms for HDL's anti-atherosclerotic effect have been proposed, including its function in promoting cholesterol efflux from peripheral cells by reverse cholesterol transport [9]. In contrast to the unequivocal inverse relationship between HDL cholesterol concentration and CHD events [5,10,11], some studies have reported a significant inverse relationship between HDL cholesterol and incident stroke [12–15], whereas others did not [8,16,17]. In particular, the association between HDL cholesterol concentration and hemorrhagic stroke remains uncertain [18–20]. These inconsistent results suggest that HDL may have a different role in stroke development separate from its anti-atherosclerotic function.

We therefore, conducted a prospective study in approximately 31,000 individuals in nine population-based cohorts. The relationships between the incidence rates of CHD concentration, stroke, and stroke subtypes and baseline blood HDL cholesterol concentration were investigated over a median follow-up period of 15 yr.

2. Materials and methods

2.1. Study population

We conducted the Japan Public Health Center-based Prospective (JPHC) Study since 1990 (Cohort I) and 1993–1994 (Cohort II) in 11 public health-center areas that have information on CVD mortality or incidence [21]. The total population size was 140,420 Japanese residents aged 40–59 yr (Cohort I) or 40–69 yr (Cohort II). The participants completed questionnaires on lifestyle 5 and 10 yr after the baseline examinations. For the present study, we selected participants after five yr in Cohort I (n = 45,019) and at baseline in Cohort II (n = 63,216), as HDL cholesterol was not measured in all subjects at baseline in Cohort I. After excluding two communities without CVD registration, we selected individuals who had blood examinations at baseline (n = 31,296). After exclusion of those with a history of CVD, 30,736 individuals were included in the analyses.

The study protocol, including the procedure for obtaining informed consent in the JPHC study, was approved by the Human Ethics Review Committees of the National Cancer Center, Ehime University Graduate School of Medicine, and by each registered hospital.

2.2. Baseline surveys

The self-administered questionnaire included questions about medical history, smoking and alcohol-drinking habits, sports during leisure time, menopause (for women), and time since the last meal (≥8 h or not). We asked the participants about sports during leisure time, i.e., "How many times did you participate in sports and physical activity other than during working hours," with 5 predefined categories of, almost never exercise, 1–3 days per month, 1–2 days per week, 3–4 days per week, and almost daily. This question represented leisure-time physical activity and was validated [22,23]. A trained technician measured blood pressure in the right arm using a standard mercury sphygmomanometer, with the patient in the sitting position after having rested for at least five minutes. Body mass index (BMI, kg/m^2) was calculated as weight divided by the square of height. Hypertension was defined as systolic and diastolic blood pressures ≥140/90 mmHg, or the use of medication to treat hypertension. Diabetes was defined as a fasting plasma glucose ≥7.0 mmol/L, a non-fasting glucose ≥11.0 mmol/L, or the use of medication to treat diabetes. The concentrations of total cholesterol, HDL cholesterol, triglycerides, and glucose in the blood were measured by conventional enzyme methods. External quality control for the measurement of serum lipids and plasma glucose was provided by the Standardization Program of the Japan Medical Association. For international quality control, the laboratories joined the program of the Osaka Medical Center for Health Science and Promotion, a member of the Cholesterol Reference Method Laboratory Network (CRMLN) to standardize total and HDL cholesterol [24].

2.3. Ascertainment of stroke and CHD incidence rates

The subjects were followed-up for a median of 15.0 yr from 1995 to December 31, 2009 (Cohort I) and from 1993 to December 31, 2012 (Cohort II). Person-yr were calculated from the date of entry to that of the first endpoint (death, emigration, or lost to follow-up) or to each end day.

We identified CVD occurrences in our communities as described previously [4]. In brief, the medical records of possible stroke hospitalizations in 81 major hospitals located in the communities were reviewed systematically by physicians. Strokes were defined as a definite diagnosis based on computed tomography scans, magnetic resonance images, or autopsy [25]. We classified strokes into subarachnoid hemorrhage, intracerebral hemorrhage (ICH), and ischemic strokes which included lacunar infarction, large-artery occlusive infarction, embolic infarction, and unclassified [26].

Myocardial infarction was confirmed from medical records according to the criteria of the MONICA project, which requires typical chest pain and evidence from an electrocardiogram, cardiac enzymes, and/or autopsy records [27]. Sudden cardiac death was defined as a death of unknown cause that occurred within one hour of the onset of the event. We classified myocardial infarction and sudden cardiac death as CHD.

2.4. Statistical analysis

A Cox proportional hazards model was used to calculate sex-specific hazard ratios (HRs) and 95% confidence intervals (CI) using data grouped according to quintiles of HDL cholesterol, with the highest quintile serving as a reference stratified by study community. Model 1 was adjusted for age (continuous). Model 2 was additionally adjusted for smoking status (current smoker or not), alcohol intake (≥1 day/week alcohol or not), sports at leisure time (rarely, 1–2, 3–4 times/week, and almost every day), BMI, menopause in women (yes/no), systolic blood pressure (continuous), use of antihypertensive agents (yes/no), diabetes (yes/no), use of antilipemic agents (yes/no), and non-HDL cholesterol. When analyzed for CHD and stroke occurrences, we created two models with or without non-HDL cholesterol. The penalized spline (P-spline) method adjusted for age and stratified by study community was used in the Cox regression models to examine dose-response relationships between log-transformed HDL cholesterol concentration and the hazard ratios for CHD, ICH, ischemic stroke, and lacunar infarction, [28]. The degrees of freedom in the P-spline terms were automatically selected based on the Akaike information criteria [29]. The p value for non-linear trend was used to determine the significance of the P-spline term. A linear trend was examined using median values of HDL cholesterol in each quintile in the Cox regression models. Competing risk analyses were also conducted as a sensitivity analysis by modeling the cumulative incidence function described by Fine and Gray [30]. Analyses stratified according to the presence of hypertension and overweight, and analyses excluding those with high total cholesterol or those taking antilipemic medications were also carried out as additional analyses of sensitivity. Statistical significance was