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ORIGINAL ARTICLE

Increased high-density lipoprotein cholesterol is associated with a high prevalence of pre-hypertension and hypertension in community-dwelling persons

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Abstract The aim of this article was that high-density lipoprotein cholesterol (HDL-C) reduces blood vessel injury through its antioxidant and anti-inflammatory functions. However, the effect of HDL-C on blood pressure may be controversial. Therefore, the aim of this study was to address whether HDL-C level is associated with blood pressure, and we examined cross-sectional data from community-dwelling persons. A total of 859 men [58 ± 15 (mean ± standard deviation); 20–89 (range) (years) and 1,169 women (61 ± 13; 19–88 years)] participants not on medication for hypertension were recruited from a single community at the time of their annual health examination. We examined the relationship between cardiovascular risk factors and blood pressure status. Multiple linear regression analysis using systolic blood pressure (SBP) and diastolic blood pressure (DBP) as an objective variable showed that HDL-C was significantly and independently associated with both SBP ($\beta = 0.138$), and DBP ($\beta = 0.144$). Compared to normotensive participants with the lowest quartile of HDL-C, multivariate-adjusted odds ratio (OR) for pre-hypertension was 1.72 (1.22–2.45) for the second quartile, 1.51 (1.07–2.15) for the third quartile, and 1.52 (1.04–2.22) for the highest quartile. Moreover, compared with normotensive participants with the lowest quartile, the multivariate-adjusted ORs for hypertension were 2.37 (1.63–3.45), 2.24 (1.54–3.28), 3.15 (2.10–4.74), respectively. There were no interactions between the two groups stratified by gender, age, BMI, drinking status, TG, FPG, and medication. Therefore, we concluded that HDL-C levels were positively associated with blood pressure in Japanese dwelling-community persons.

Keywords HDL cholesterol · Risk factor · Blood pressure · Pre-hypertension · Hypertension

List of abbreviations

T-C	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol

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Introduction

High-density lipoprotein (HDL) is able to remove cholesterol present within an artery atheroma and transport it back to the liver for elimination through the gastrointestinal tract, which is the main reason why cholesterol transported within HDL particles (HDL-C) is called "good cholesterol" [1]. HDL-C also reduces blood vessel injury through its antioxidant and anti-inflammatory functions [1]. Individuals with higher HDL-C levels seem to have decreased risks for developing cardiovascular disease (CVD), while those with lower HDL-C levels (less than 40 mg/dL) have increased rates for CVD [1]. On the other hand, higher HDL-C levels are correlated with cardiovascular health, however, no incremental increase in HDL-C has been demonstrated to improve health and in some conditions, it paradoxically enhances the process of atherosclerosis [2].

High blood pressure is a component of the metabolic syndrome (MetS), which is defined as the combination of visceral obesity, hypertension, increased triglycerides (TG) level, decreased HDL-C, and impaired fasting plasma glucose (FPG), and is most prevalent among the Japanese population [3]. Insulin resistance is associated with the underlying mechanisms of these abnormalities [4–7], and visceral obesity, increased TG and impaired FPG are independent predictors of prevalent hypertension [8, 9]. These conditions cause endothelial dysfunction, inadequate vasodilation and/or paradoxical vasoconstriction in peripheral arteries in response to stimuli that release nitric oxide (NO) [10, 11]. However, among the five components of MetS, HDL-C is unique because it does not significantly correlate with blood pressure [12]. Oda et al. [12] demonstrated a positive correlation of HDL-C levels with systolic blood pressure (SBP) and diastolic blood pressure (DBP) even after multiple linear regression analysis in apparently healthy Japanese men and women. These positive associations have not been reported previously in Caucasian population. The effect of HDL-C on blood pressure may be controversial.

Thus, the aim of this study was to address whether there is an association between HDL-C level and blood pressure; we examined cross-sectional data from community-dwelling persons.

Materials and methods

Subjects

The present study is designed as a part of the Nomura study [13]. Participants were recruited at the time of their annual health examination in a rural town: Nomura-cho, Seiyo-City, which has a total population of 11,136 (as of April 2002) and located in Ehime prefecture, Japan, in 2002. Among 9,133 adults aged 19–90 years in this population, 3,164 (34.6%) took part in the program and agreed to participate in the study. Information on medical history, present conditions, and drug usage was obtained by interview. Other characteristics, such as smoking and alcohol habit were investigated by individual interviews using a structured questionnaire. Subjects taking medications for hypertension were excluded. The final study sample included 859 men and 1,169 women. This study was approved by the ethics committee of Ehime University School of Medicine, and written informed consent was obtained from each subject.

Evaluation of risk factors

Information on the demographic characteristics and risk factors was collected using clinical files. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured blood pressure in the right upper arm of participants in the sedentary position using an automatic oscillometric blood pressure recorder (BP-103i; Colin, Aichi, Japan) while they were seated after having rested for at least 5 min. Appropriate cuff bladder size was determined at each visit based on arm circumference. Normotension was defined as having SBP <120 mmHg and DBP <80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg and/or DBP of 80–89 mmHg. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg [14]. Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack·year), and the participants were classified into non-smoker and current smoker. Daily alcohol consumption was measured using the Japanese liquor unit in which a unit corresponds to 22.9 g of ethanol, and the participants were classified into never drinkers, occasional drinkers (<1 unit/day), light drinkers (1–1.9 unit/day), and heavy drinkers (≥2 unit/day). Total cholesterol (T-C), TG, HDL-C, FPG, and creatinine (enzymatic method) were measured during fasting. Low-density lipoprotein cholesterol (LDL-C) level was calculated by the Friedewald formula [15]. Participants with TG levels ≥400 mg/dL were excluded. Estimated glomerular filtration rate (eGFR) was calculated using the following equation: $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ (if female) [16].

Statistical analysis

Statistical analyzes were performed using SPSS 17.0 J (Statistical Package for Social Science Japan, Inc., Tokyo, Japan). All values are expressed as mean ± standard deviation (SD), unless otherwise specified. Data for TG and

FPG were skewed, and log-transformed for analysis. The differences among groups categorized by quartile of HDL-C level were analyzed by Student's *t*-test for continuous variables or the χ^2-test for categorical variables. Correlations between various characteristics and blood pressure status were determined using simple linear correlation (Pearson *r*) and partial correlation. Subjects were divided into four groups based on quartile of HDL-C within gender and then combined to avoid gender differences (men: quartile-1, 23–48; quartile-2, 49–56; quartile-3, 57–67; quartile-4, 68–126 mg/dL and women: quartile-1, 26–53; quartile-2, 54–63; quartile-3, 64–73; quartile-4, 74–128 mg/dL). Multiple linear regression analysis was used to evaluate the contribution of risk factors for SBP or DBP, and logistic regression analyzes were used to test significant determinants of pre-hypertension or hypertension status serving as the dichotomous outcome variable. To examine the consistency of the observed association between serum HDL-C levels and blood pressure status (hypertension versus pre-hypertension), we performed subgroup analyzes by gender (men, women), age (<65, ≥65 years), BMI (<25, ≥25 kg/m^2), drinking status (absent, present), TG (<150, ≥150 mg/dL), FPG (≥100, <100 mg/dL), and medication (absent, present), and interaction between the HDL-C category and the subgroups was analyzed by a general linear model. A value of $P < 0.05$ was considered significant.

Results

Table 1 shows the characteristics of each subject's background factors categorized according to quartile of HDL-C level. The subjects comprised 859 men aged 58 ± 15 (mean ± SD) (range 20–89) years and 1,169 women aged 61 ± 13 (19–88) years. Alcohol drinking status, HDL-C, and eGFR were significantly higher but BMI, TG, and LDL-C were significantly lower with increased HDL-C levels. FPG was V-shaped. There were no inter-group differences regarding gender, age, current smoker status, SBP, DBP, presence of anti-lipidemic and antidiabetic medication, and prevalence of CVD.

Table 2 shows the relationship between participant characteristics and blood pressure status. Pearson's correlation coefficient showed that age, BMI, TG, LDL-C, presence of anti-lipidemic medication, and FPG correlated

Table 1 Characteristics of subjects categorized by quartile of HDL cholesterol level

HDL cholesterol level Men Women Characteristics	Quartile-1 23–48 mg/dL 26–53 mg/dL $N = 534$	Quartile-2 49–56 mg/dL 54–63 mg/dL $N = 485$	Quartile-3 57–67 mg/dL 64–73 mg/dL $N = 510$	Quartile-4 68–126 mg/dL 74–128 mg/dL $N = 499$	*P* value*
Gender (men) (%)	43.1	41.4	43.3	41.5	0.889
Age (years)	60 ± 13	60 ± 14	59 ± 14	59 ± 14	0.198
Body mass index[a] (kg/m^2)	24.3 ± 3.1	23.2 ± 3.2	22.8 ± 2.9	21.8 ± 2.8	<0.001
Drinking status[b] (never/light/moderate/heavy)	48.7/31.6/12.7/6.9	44.9/30.1/16.3/8.7	39.2/30.6/18.6/11.6	34.1/31.5/21.2/13.2	<0.001
Current smoking status (%)	21.7	18.6	20.4	16.2	0.133
Systolic blood pressure (mmHg)	133 ± 20	134 ± 20	133 ± 21	133 ± 22	0.566
Diastolic blood pressure (mmHg)	79 ± 11	80 ± 12	79 ± 11	79 ± 12	0.392
Triglycerides (mg/dL)	128 (94–181)	101 (76–137)	83 (65–109)	74 (55–94)	<0.001
HDL cholesterol (mg/dL)	44 ± 6	56 ± 4	65 ± 4	82 ± 10	<0.001
LDL cholesterol (mg/dL)	120 ± 35	119 ± 33	115 ± 31	111 ± 28	<0.001
Anti-lipidemic medication (%)	5.2	4.3	3.5	4.6	0.603
Fasting plasma glucose (mg/dL)	94 (88–103)	82 (87–99)	93 (87–101)	92 (87–100)	0.046
Antidiabetic medication (%)	3.9	2.5	2.2	2.6	0.316
eGFR[c] (mL/min/1.73 m^2)	80.8 ± 17.4	82.4 ± 18.3	82.3 ± 16.4	85.1 ± 16.1	0.001
Cardiovascular disease (%)	6.6	6.4	5.3	3.4	0.103

Subjects were divided into four groups based on the quartile of high-density lipoprotein cholesterol within the genders and then combined to avoid gender differences. *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *eGFR* estimated glomerular filtration rate. Data presented are mean ± SD. Data for TG and FPG were skewed and presented as median (interquartile range) values, and were log-transformed for analysis

* *P* value Student's *t*-test for continuous variables or the χ^2-test for categorical variables

[a] Body mass index was calculated using weight in kilograms divided by the square of the height in meters

[b] Alcohol consumption was measured using a Japanese liquor unit where 1 unit corresponds to 22.9 g of ethanol (never drinkers, light drinkers (<1 unit/day), moderate-drinkers (1–2 unit/day)/heavy drinkers (≥2 unit/day))

[c] $\text{eGFR} = 194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287} \times 0.739$ (if female)

positively with SBP, while female sex, current smoker status, and eGFR correlated negatively with DBP. Age, BMI, drinking status, TG, LDL-C, and FPG correlated significantly with DBP, while female sex and eGFR correlated negatively with DBP.

Table 2 Relationship between various characteristics and blood pressure status by simple linear correlation

Characteristics	SBP (mmHg) r (P value)	DBP (mmHg) r (P value)
Gender (men = 0, women = 1)	−0.057 (0.010)	−0.169 (<0.001)
Age (years)	0.367 (<0.001)	0.207 (<0.001)
Body mass index (kg/m^2)	0.206 (<0.001)	0.242 (<0.001)
Current smoking status (no = 0, yes = 1)	−0.057 (0.010)	0.027 (0.227)
Drinking status (never = 0/sometimes = 1/light = 2/heavy = 3)	0.042 (0.056)	0.164 (<0.001)
Triglycerides (mg/dL)	0.173 (<0.001)	0.217 (<0.001)
HDL cholesterol (mg/dL)	−0.019 (0.403)	−0.037 (0.093)
LDL cholesterol (mg/dL)	0.060 (0.007)	0.072 (0.001)
Anti-lipidemic medication (nNo = 0, yes = 1)	0.045 (0.044)	0.028 (0.200)
Fasting plasma glucose (mg/dL)	0.222 (<0.001)	0.159 (<0.001)
Antidiabetic medication (no = 0, yes = 1)	0.021 (0.354)	−0.020 (0.378)
Estimated GFR (mL/min/1.73 m^2)	−0.141 (<0.001)	−0.127 (<0.001)

Data for TG and FPG were skewed and log-transformed for analysis

r Pearson's correlation coefficient

To find independently confounding factors for SBP and DBP, multiple linear regression analysis using SBP and DBP as an objective variable, adjusted for confounding factors as explanatory variables, showed that HDL-C ($\beta = 0.138$) as well as age ($\beta = 0.403$), BMI ($\beta = 0.212$), drinking status ($\beta = 0.052$), TG ($\beta = 0.149$), LDL-C ($\beta = -0.049$), FPG ($\beta = 0.119$), and presence of antidiabetic medication ($\beta = -0.048$) were significantly and independently associated with SBP, and HDL-C ($\beta = 0.144$) as well as female sex ($\beta = -0.109$), age ($\beta = 0.235$), BMI ($\beta = 0.217$), drinking status ($\beta = 0.119$), TG ($\beta = 0.178$), FPG ($\beta = 0.066$), and antidiabetic medication ($\beta = -0.057$) were also independently associated with DBP (Table 3).

We decided to test the influence of the quartiles of HDL-C levels on SBP and DBP, taking into account the influence of confounding factors (Table 4). Compared with normotensive participants with the lowest quartile of HDL-C, multivariate-adjusted odds ratio (OR) for pre-hypertension was 1.72 (95% CI, 1.22–2.45) for the second quartile, 1.51 (1.07–2.15) for the third quartile, and 1.52 (1.04–2.22) for the highest quartile. Moreover, compared with the normotensive participants with the lowest quartile, the gender, age and BMI-adjusted OR for hypertension was 1.91 (1.34–2.73) for the second quartile, 1.57 (1.11–2.22) for the third quartile, and 2.08 (1.46–2.98) for the highest quartile, and the multivariate-adjusted ORs for hypertension were 2.37 (1.63–3.45), 2.24 (1.54–3.28), and 3.15 (2.10–4.74), respectively. Compared with the pre-hypertensive participants with the lowest quartile, the gender, age and BMI-adjusted OR for hypertension was 1.87 (1.36–2.58) for the highest quartile, and the multivariate-adjusted ORs for

Table 3 Relationship between various characteristics and blood pressure status by multivariate linear regression analysis

Characteristics	SBP (mmHg)		DBP (mmHg)	
	r (P value)	β (P value)	r (P value)	β (P value)
Gender (men = 0, women = 1)	–	−0.022 (0.420)	–	−0.109 (<0.001)
Age (years)	–	0.403 (<0.001)	–	0.235 (<0.001)
Body mass index (kg/m^2)	–	0.212 (<0.001)	–	0.217 (<0.001)
Current smoking status (no = 0, yes = 1)	0.017 (0.457)	0.018 (0.452)	0.007 (0.762)	0.000 (0.987)
Drinking status (never = 0/occasional = 1/light = 2/heavy = 3)	0.077 (<0.001)	0.052 (0.043)	0.121 (<0.001)	0.119 (<0.001)
Triglycerides (mg/dL)	0.093 (<0.001)	0.149 (<0.001)	0.122 (<0.001)	0.178 (<0.001)
HDL cholesterol (mg/dL)	0.092 (<0.001)	0.138 (<0.001)	0.091 (<0.001)	0.144 (<0.001)
LDL cholesterol (mg/dL)	−0.040 (0.070)	−0.049 (0.022)	0.031 (0.168)	0.025 (0.265)
Anti-lipidemic medication (no = 0, yes = 1)	−0.018 (0.429)	−0.024 (0.224)	−0.007 (0.748)	−0.020 (0.328)
Fasting plasma glucose (mg/dL)	0.121 (<0.001)	0.119 (<0.001)	0.059 (0.008)	0.066 (0.003)
Antidiabetic medication (no = 0, yes = 1)	−0.017 (0.439)	−0.048 (0.019)	−0.045 (0.044)	−0.057 (0.008)
Estimated GFR (mL/min/1.73 m^2)	0.046 (0.038)	0.030 (0.174)	−0.014 (0.515)	−0.019 (0.399)
r^2	–	0.234 (<0.001)	–	0.188 (<0.001)

Data for TG and FPG were skewed and log-transformed for analysis

r gender, age, and BMI-adjusted partial correlation coefficient; β standardized coefficient

Table 4 Association between HDL cholesterol levels and blood pressure status

Characteristics	*N*	Non-adjusted		Gender, age and BMI-adjusted		Multivariate analysis[a]	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Pre-hypertension vs. normotension	708/542						
Quartile-1	198/142	1 (reference)		1 (reference)		1 (reference)	
Quartile-2	179/108	1.19 (0.86–1.64)	0.292	1.48 (1.06–2.08)	0.023	1.72 (1.22–2.45)	0.002
Quartile-3	178/141	0.91 (0.67–1.23)	0.528	1.17 (0.84–1.62)	0.348	1.51 (1.07–2.15)	0.021
Quartile-4	153/151	0.73 (0.53–0.99)	0.045	1.14 (0.81–1.61)	0.446	1.52 (1.04–2.22)	0.032
Hypertension vs. normotension	778/542						
Quartile-1	194/142	1 (reference)		1 (reference)		1 (reference)	
Quartile-2	198/108	1.34 (0.98–1.85)	0.071	1.91 (1.34–2.73)	<0.001	2.37 (1.63–3.45)	<0.001
Quartile-3	191/141	0.99 (0.73–1.35)	0.957	1.57 (1.11–2.22)	0.011	2.24 (1.54–3.28)	<0.001
Quartile-4	195/151	0.95 (0.70–1.28)	0.716	2.08 (1.46–2.98)	<0.001	3.15 (2.10–4.74)	<0.001
Hypertension vs. pre-hypertension	778/708						
Quartile-1	194/198	1 (reference)		1 (reference)		1 (reference)	
Quartile-2	198/179	1.13 (0.85–1.50)	0.401	1.27 (0.94–1.71)	0.116	1.35 (0.99–1.83)	0.060
Quartile-3	191/178	1.10 (0.82–1.46)	0.531	1.30 (0.96–1.76)	0.088	1.44 (1.04–2.00)	0.028
Quartile-4	195/153	1.30 (0.97–1.74)	0.075	1.87 (1.36–2.58)	<0.001	2.12 (1.48–3.04)	<0.001

OR odds ratio, *CI* confidence interval

* *P* value versus tertile-1

[a] Multivariate-adjusted for gender, age, body mass index, current smoking status, drinking status, TG, LDL cholesterol, anti-lipidemic medication, FPG, antidiabetic medication, and estimated GFR. Data for TG and FPG were skewed and log-transformed for analysis

hypertension were 1.44 (1.04–2.00) for the third quartile and 2.14 (1.48–3.04) for the highest quartile.

Next, to control potential confounding factors by gender, age, BMI, drinking status, TG, FPG, and medication, the data were further stratified by their values (Table 5). Compared with the pre-hypertensive participants, multivariate-adjusted OR for hypertension increased significantly and similarly with increase in HDL-C levels, and there were no interaction between the two groups.

Discussion

In this cross-sectional, population-based study, we set out to determine the prevalence of pre-hypertension and hypertension, as defined by the JNC-7 criteria, and examine the potential confounding factors [14]. This study demonstrated that pre-hypertension and hypertension are common, affecting more than half of men (77.1%) and women (70.4%). We have confirmed a positive association between HDL-C and blood pressure status. In addition, we found a significantly positive association between quartiles of HDL-C levels and pre-hypertension, and hypertension. Little data is available on the association between HDL-C levels and the prevalence of pre-hypertension and hypertension among community-dwelling persons in Japan, and the reason for this association is unknown [12].

Several prospective epidemiological studies have found that high HDL-C levels constitute an independent protective factor for CVD risk [17]. Halperin et al. [18] demonstrated that men in the highest quintile of HDL-C had a 32% decrease in the risk of developing hypertension compared with those in the lowest quintile during a 14.1 years follow-up of 3,110 men free of hypertension. Sesso et al. [19] also reported that the relative risks of developing hypertension from the lowest (reference) to the highest quintile of the baseline HDL-C level were 1.00, 0.93, 0.87, 0.87, and 0.81 ($P < 0.001$ for trend) during 10.8 years of follow-up of 16,130 middle-aged and older women free of hypertension. In addition, in 17,527 initially healthy women without baseline hypertension during 8 years of follow-up, increased HDL-C was associated with a lower risk of hypertension [OR for quintile 5 vs. 1: 0.79 (0.70–0.89)] [20]. Many different factors affect both CVD risk as well as HDL-C levels. Such adjustments, however, do not guarantee the absence of residual confounding factors [21], and one may ask what the meaning of statistical outcomes is when the adjustments concern parameters that are intrinsically related to HDL metabolism [22]. It is apparent that many patients with normal or even elevated HDL experience clinical events [23]. Furthermore, in a cross-sectional study of 1,803 apparently healthy Japanese persons, Oda et al. [12] demonstrated that the OR (95% CI) of a 1 mg/dL increment of HDL-C for hypertension control by age, BMI, FPG, TG, high sensitivity

Table 5 Association between HDL cholesterol levels and blood pressure within selected subgroups

Stratified subgroups	*N*	HT vs. PHT	Multivariate-adjusted		
		Cases (%)	OR (95% CI)	*P* value	*P* interaction
All	1,486	778/708	1.26 (1.12–1.41)	<0.001	–
Gender					0.879
Men	663	344/319	1.23 (1.04–1.47)	0.017	
Women	823	434/389	1.28 (1.09–1.50)	0.002	
Age (years)					0.741
< 65 years	755	320/435	1.30 (1.10–1.53)	0.002	
≥65 years	731	458/273	1.21 (1.03–1.42)	0.019	
Body mass index					0.850
<25 kg/m^2	1,066	528/538	1.23 (1.08–1.41)	0.002	
≥25 kg/m^2	420	250/170	1.33 (1.05–1.67)	0.016	
Drinking status					0.628
Absent	632	349/283	1.26 (1.08–1.47)	0.003	
Present	854	429/425	1.22 (1.02–1.46)	0.026	
Triglycerides					0.361
<150 mg/dL	1,178	612/566	1.22 (1.08–1.38)	0.002	
≥150 mg/dL	308	166/142	1.44 (1.06–1.96)	0.019	
Fasting plasma glucose					0.941
<100 mg/dL	1,014	481/533	1.26 (1.10–1.45)	0.001	
≥ 100 mg/dL	472	297/175	1.23 (1.00–1.50)	0.049	
Medication					0.716
Absent	1,365	717/648	1.26 (1.11–1.42)	<0.001	
Present	121	61/60	1.34 (0.91–1.97)	0.142	

HT hypertension, *PTN* pre-hypertension

[a] Multivariate-adjusted for gender, age, body mass index, drinking status, smoking status, TG, LDL cholesterol, anti-lipidemic medication, FPG, antidiabetic medication, and eGFR. Data for TG and FPG were skewed and log-transformed for analysis

C-reactive protein, LDL-C, MetS, diabetes, exercise status, drinking status, and smoking status was 1.03 (1.02–1.04; $P < 0.001$) in men and 1.03 (1.01–1.05; $P = 0.002$) in women. Also in our study, similar results were obtained.

The mechanisms by which HDL-C reflects the risk for pre-hypertension or hypertension are not completely understood. However, a recent study demonstrated that HDL particle size, in addition to the actual level of HDL-C, also appears to be an important predictor of hypertension risk. Interestingly, increased concentrations of HDL particles (as assessed by, e.g., nuclear magnetic resonance or 1- and 2D gel electrophoresis), posed a greater risk, in particular small HDL (HDL3) particles, whereas large HDL (HDL2) particles posed a lower risk [20]. Conflicting results were obtained, with evidence that either HDL2 constitutes a strong predictor of CVD risk factors [24]. In addition, the increased HDL-C in hypertensive individuals might be associated with an increased rate of deficient HDL function [25]. The HDL subclasses appear to have a differential effect on lipoprotein oxidative protection [26]. Furthermore, factors that induce hypertension such as inflammation and oxidative stress may contribute to disturbances in HDL metabolism and thus reduced recycling and renovation of HDL [27]. Thus, HDL structure and function may be more important than HDL cholesterol level in predicting risks for CVD [28].

On the other hand, alcohol consumption increases HDL-C levels [29] and heavy drinking may increase blood pressure [30, 31]. In this study, the prevalence of heavy drinkers (≥2 unit/day) was 14.3% in men with normotension, 19.4% in men with pre-hypertension, and 31.4% in men with hypertension. HDL-C levels were significantly higher with increased alcohol drinking status ($P < 0.001$). However, the positive association between HDL-C and blood pressure was observed in both groups stratified by drinking status (e.g., drinker and non-drinker), and remained independent after adjustment for drinking status. Therefore, it is not likely that the positive association between HDL-C and pre-hypertension or hypertension results from heavy drinking.

Some limitations of this study must be considered. First, the response rate was as low as 35%, which is commonly the case in other conventional community studies in Japan. However, the relatively large sample size enabled the assessment of an extensive array of HDL-Cs in relation to blood pressure. Second, the cross-sectional study design is limited in its ability to eliminate causal relationships between HDL-C and blood pressure. Third, SBP and DBP

are based on a single assessment of blood pressure, which may introduce a misclassification bias. Fourth, we could not rule out one-time hypertension and white-coat hypertension. Fifth, we could not eliminate the possible effects of underlying diseases on the results. We also could not eliminate the possible effects of medications for diabetes, and dyslipidemia on the present findings. Therefore, the demographics and referral source may limit generalizability.

Conclusion

This study showed that increased HDL-C was significantly associated with elevated blood pressure in community-dwelling persons. The underlying mechanism behind this relationship is unknown, and seems to be independent of traditional confounding factors, such as age, BMI, drinking status, current smoking status, TG, LDL-C, FPG, and eGFR. Further investigation of the longitudinal data from our study will provide more definitive answers to this issue.

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Competing interests The authors declare that they have no competing interests.

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