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Association between extremely high high-density lipoprotein-cholesterol and hypertensive retinopathy: results of a cross-sectional study from Kanagawa Investigation of Total Checkup Data from the National Database-6 (KITCHEN-6)

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ABSTRACT

Objectives Doubt has been cast on the atheroprotective effect of very high high-density lipoprotein cholesterol (HDL-C). Hypertensive retinopathy (HR) is caused by persistent systemic hypertension. Therefore, we aimed to investigate the association between extremely high HDL-C (EH-HDL) and HR.

Design A cross-sectional study.

Participants A total of 4072 general Japanese population aged 40–74 years who underwent regular medical check-ups including fundus examinations.

Outcome measures HR and clinical parameters including serum HDL-C were investigated. HR was determined by the Keith-Wagener classification and the Scheie classifications for Hypertension and Atherosclerosis (n=4054 available). Serum HDL-C was divided into five categories: 30–49, 50–69, 70–89, 90–109 and ≥110 mg/dL.

Results Overall, 828 (20.3%) subjects had Keith-Wagener-HR, 578 (14.3%) had hypertension-HR, and 628 (15.5%) had atherosclerosis-HR. Blood pressure decreased as HDL-C level increased, whereas the prevalences of HRs showed U-shaped curves against HDL-C with minimum values for HDL-C 90–109 mg/dL. In logistic regression analyses, EH-HDL ≥110 mg/dL was significantly associated with Keith-Wagener-HR and atherosclerosis-HR, compared with HDL-C 90–109 mg/dL after adjustments for age, sex and systolic blood pressure (OR 3.01, 95% CI 1.45 to 6.27 and OR 2.23, 95% CI 1.03 to 4.86). The hypertension-HR was not significantly associated with EH-HDL regardless of adjustment for the confounding factors (p=0.05–0.08). Although serum HDL-C as a continuous variable was inversely associated with three HRs, which disappeared after adjustment for the confounding factors.

Conclusion EH-HDL may be associated with HR independently of blood pressure, suggesting that EH-HDL reflects a special atherosclerotic condition.

Strengths and limitations of this study

► Hypertensive retinopathy was evaluated by three different methods.
► Each assessment for hypertensive retinopathy was graded into five or six classifications.
► There may be a selection bias for the eligible subjects who underwent a fundus examination.
► The numbers of cases for hypertensive retinopathy were very small (n=10–16) in the extremely high high-density lipoprotein cholesterol (HDL-C) group, which may lower the reliability of outcomes.
► The association between hypertensive retinopathy and extremely high HDL-C may be indirect, although minimum confounding factors were adjusted in the model.

INTRODUCTION

During the last decade, doubt has been cast on the atheroprotective effect of very high high-density lipoprotein cholesterol (HDL-C) against cardiovascular disease (CVD).[1–3] Consistently, cohort studies in recent years have shown that higher mortality rates associated with CVD are observed in individuals with HDL-C levels above 80–100 mg/dL.[4–7] In addition, we recently demonstrated that people with extremely high HDL-C (EH-HDL; ≥110 mg/dL) have increased risks for diabetes[8] and impaired glucose metabolism equivalent to pre-diabetes,[9] compared with HDL-C 80–89 and 70–79 mg/dL, respectively, which showed a J-shaped or U-shaped association between the levels of HDL-C and impaired glucose metabolism.

Besides diabetes, hypertension is a strong risk factor for the development and

aggravation of CVD, including ischaemic heart disease and stroke. Therefore, it is important for health professionals to detect early signs of organ damage caused by chronic hypertension.[10] Traditionally, assessment of the retinal vasculature by fundus examinations has been used to evaluate the condition of the systemic microcirculation and risk factors for CVD.[11] Hypertensive retinopathy (HR) assessed by the Keith-Wagener-Barker[12] and Scheie[13] classifications was found to be associated with cardiovascular events and cardiovascular mortality.[14]

We aimed to investigate the association between EH-HDL and HR in a cross-sectional study of the general Japanese population. Simultaneously, because the optimal level of HDL-C in the field of CVD remains unknown, we addressed this issue from the viewpoint of HR.

METHODS

Study design and participants

We conducted a composite multidisciplinary study involving secondary use of mandatory health check data in Japan (Kanagawa Investigation of the Total Checkup Data from the National Database) to elucidate the factors primarily associated with cardiometabolic diseases. The overall study concept and design were described elsewhere.[15] The present study included all individuals who underwent these specific health checks and were living in Kanagawa Prefecture.

This cross-sectional study used data collected from 1 681 513 people who attended health checks between April 2012 and March 2013. After exclusion of subjects who did not undergo fundus examinations (n=1 677 433) and those with incomplete data (n=8), 4072 subjects (0.24% of original sample) remained for analysis in the study. Although undergoing a health check-up is an enforced matter for most of the company workers, an additional fundus examination was not mandatory for eligible individuals undergoing annual check-ups, which depends on the personal intention, consequently resulting in the lower rate of participants. However, subjects with hypertension and diabetes are usually recommended to undergo this examination in Japan.

We received digitally recorded anonymous data from the Ministry of Health, Labour and Welfare of Japan, as part of its nationwide programme, involving the provision of medical data to third parties.[15] To protect against the identification of specific individuals, their ages had been categorised as 40–44, 45–49, 50–54, 55–59, 60–64, 65–69 or 70–74 years. In this study, however, to evaluate subject age as a single numeric value, we transformed the age groups into substituted ages (s-age), corresponding to the median for each age group (42, 47, 52, 57, 62, 67 and 72 years, respectively).

Patient and public involvement

There was no patients and public involvement in this study.

Measurements

Anthropometric and laboratory measurements were obtained in the morning following an overnight fast. Serum HDL-C was divided into five categories with intervals of 20 mg/dL: 30–49, 50–69, 70–89, 90–109 and ≥110 mg/dL. After 5 min resting in the sitting position, blood pressure was mostly determined using an automated sphygmomanometer utilising one measurement (around 70%), first among two measurements (around 20%) and second among two measurements (around 10%) in the healthcare institute holding the check-ups.[15]

Bilateral fundus examinations were performed by funduscopy. HR grading for the saved fundus photo was conducted by ophthalmologists using a modified Keith-Wagener classification.[16] The six Keith-Wagener grades were as follows: (1) normal; (2) mild narrowing and crossing of retinal arterioles; (3) moderate narrowing and crossing of retinal arterioles; (4) grade 3 plus atherosclerotic retinopathy or retinal vein occlusion; (5) severe narrowing and crossing of retinal arterioles and (6) grade 5 plus papilledema. HR was also assessed using the Scheie classification, which was subdivided into two classifications: Hypertension and Atherosclerosis[17] (n=4054 available for both). The five Hypertension grades were as follows[13 17] =: (1) normal; (2) barely detectable arterial narrowing; (3) obvious arterial narrowing with focal irregularities plus light reflex changes; (4) grade 3 plus retinal haemorrhages and/or exudate and (5) grade 4 plus papilledema. The five Atherosclerosis grades were as follows[13 17]: (1) normal; (2) broadening of the light reflex from arterioles, with minimal or no arteriovenous compression; (3) light reflex changes and more prominent crossing changes; (4) copper wire appearance of arterioles and more arteriovenous compression; (5) silver wire appearance of arterioles and most severe arteriovenous crossing changes. Presence of HR in each classification was determined as any abnormal findings for grade ≥2, except for normal findings.

The low-density lipoprotein cholesterol (LDL-C) to HDL-C ratio (LDL-C/HDL-C) was also calculated because it has been shown that increased LDL-C/HDL-C may be associated with initiation of atherosclerosis.[18 19]

Statistical analysis

Data were expressed as mean±SD or median (IQR). Differences in continuous and categorical variables among the five HDL-C groups were evaluated by analysis of variance (ANOVA) and the χ^2 test, respectively. A logistic regression model was used to evaluate the associations between HDL-C category or HDL-C as a continuous variable and HR, with adjustment for potential confounding factors (age, sex and systolic blood pressure), and yielded adjusted ORs and 95% CIs. Other factors were not adjusted because of the small sample size in EH-HDL group. The same analysis was conducted after the subjects were restricted to those without diabetes, and those without pharmacotherapy for hypertension, diabetes or dyslipidaemia, to exclude the effects of diabetes and these

pharmacotherapies. All statistical analyses above were performed using SAS-Enterprise Guide (SAS-EG V.7.1) in SAS software, V.9.4 (SAS Institute). Cut-off points of HDL-C for Keith-Wagener-HR, hypertension-HR and Aatherosclerosis-HR were also calculated by receiver operating characteristic (ROC) curve analysis based on an assumption that the higher HDL-C the lower rate of HR. ROC curve analysis was conducted using a statistical software 'EZR' (Easy R) based on R and R commander.[20] Values of p<0.05 were considered to represent statistical significance. When differences in HR prevalence among the five HDL-C groups were evaluated by the χ^2 test, values of p<0.005 were considered to represent statistical significance, based on the Bonferroni test.

RESULTS

The mean HDL-C levels were 58.2 mg/dL in men and 72.0 mg/dL in women, and 130 (3.2%) subjects had HDL-C ≥100 mg/dL. Overall, 828 (20.3%) subjects had Keith-Wagener-HR, 578 (14.3%) had hypertension-HR and 628 (15.5%) had Atherosclerosis-HR.

The means of s-age, HDL-C and prevalence of women and pharmacotherapy were significantly lower in included subjects in this study (50.0±6.3 years, 62.7±17.3 mg/dL, 33.3% and 19.9%) than those excluded (n=1,677,433) (54.4±9.9 years, 63.5±16.9 mg/dL, 42.9% and 25.0%), whereas no difference was observed in systolic blood pressure and prevalence of daily alcohol drinkers between included subjects (123±17.0 mm Hg and 27.0%) and excluded (123±17.1 mm Hg and 28.3%).

Table 1 shows the characteristics of the included subjects according to the five HDL-C categories. Most of the parameters, including body mass index, systolic blood pressure, diastolic blood pressure and LDL-C/HDL-C, and the prevalence of current smokers, diabetes and pharmacotherapy decreased with increasing HDL-C level (ANOVA and χ^2 test, all p<0.001). However, female sex and daily alcohol drinkers increased with increasing HDL-C level (χ^2 test, p<0.001). No significant difference in s-age was observed among the five groups.

Table 2 shows the prevalence of HR grades according to HDL-C groups. Although statistical analysis was not conducted due to none in many cells, grade 1 was prevalent in the highest HDL-C group, regardless of types of HR. In contrast, grades of ≥2 seemed to be more prevalent in lower HDL-C groups. ROC curve analysis showed cut-off points of HDL-C 64.0 mg/dL for Keith-Wagener-HR, 63.0 mg/dL for hypertension-HR, and 52.0 mg/dL for atherosclerosis-HR, with area under curve (95% CI) of 0.55 (0.53–0.57), 0.53 (0.51–0.56) and 0.54 (0.52–0.57), respectively (data are not depicted).

Table 1	Characteristics of the study participants (n=4072)					
HDL-C category (mg/dL)	30–49	50–69	70–89	90–109	≥110	P value
N (% of total)	959 (23.6)	1847 (45.4)	958 (23.5)	250 (6.1)	58 (1.4)	
s-age (years)	50.3±6.3	49.8±6.3	50.0±6.3	50.5±6.4	50.3±5.3	0.26
Women, n (%)	108 (11.3)	539 (29.2)	512 (53.4)	156 (62.4)	42 (72.4)	<0.0001
BMI (kg/m^2)	25.7±3.4	23.6±3.2	21.8±2.8	20.8±2.5	19.9±2.4	<0.0001
SBP (mm Hg)	127±16.9	123±17.2	119±16.0	120±16.9	115±17.4	<0.0001
DBP (mm Hg)	80.3±12.7	77.4±12.9	73.8±12.5	74.6±12.4	70.7±12.7	<0.0001
HDL-C (mg/dL)	43.0±4.6	58.9±5.6	78.0±5.7	96.4±5.1	118±7.9	
LDL-C (mg/dL)	133±32.5	131±32.0	121±30.6	115±27.6	117±36.3	<0.0001
LDL-C/HDL-C*	3.13±0.79	2.25±0.61	1.56±0.42	1.19±0.29	0.99±0.30	<0.0001
Triglyceride, IQ (mg/dL)	161 (113-161)	99 (71-142)	71 (53-97)	60 (47-85)	59 (47-75)	<0.0001
FPG (mg/dL)	103±24.3	97.3±18.3	94.6±15.0	93.0±10.8	91.0±10.3	<0.0001
Diabetes, n (%) †	90 (9.4)	90 (4.9)	34 (3.6)	−‡	−‡	<0.0001
Pharmacotherapy, n (%) §	253 (26.4)	383 (20.7)	134 (14.0)	32 (12.8)	10 (17.4)	<0.0001
CVD, n (%)	29 (3.0)	54 (2.9)	18 (1.9)	−‡	−‡	0.39
Current smoking, n (%)	385 (40.2)	430 (23.3)	116 (12.1)	22 (8.8)	−‡	<0.0001
Habitual exercise, n (%) ¶	266 (27.7)	550 (29.8)	278 (29.0)	79 (31.6)	12 (20.7)	0.52
Daily alcohol drinking, n (%)	201 (21.0)	469 (25.4)	322 (33.6)	86 (34.4)	20 (34.5)	<0.0001

Differences in continuous and categorical variables were evaluated by analysis of variance and the χ^2 test, respectively.
*LDL-C/HDL-C was calculated as LDL-C divided by HDL-C.
†Diabetes was defined as FPG≥126 mg/dL and/or pharmacotherapy for diabetes.
‡Not expressed because of the small number of participants (<10), which could affect confidentiality.
§Pharmacotherapy for hypertension, diabetes or dyslipidaemia.
¶Habitual exercise to a light sweat for over 30 min per session twice weekly.
BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; LDL-C/HDL-C, ratio of LDL-C to HDL-C; s-Age, substituted age; SBP, systolic blood pressure.

Table 2 Prevalence of HR according to the grades and types of HR

HDL-C (mg/dL) group	30–49	50–69	70–89	90–109	≥110
Grades of Keith-Wagener-HR					
0 (normal)	75.1	79.6	83.4	85.2	72.4
1	21.3	18.0	14.6	12.4	25.9
2	3.6	2.3	2.0	2.0	1.7
3	0.0	0.1	0.0	0.0	0.0
4	0.1	0.1	0.0	0.0	0.0
5	0.0	0.0	0.0	0.4	0.0
Grades of hypertension-HR					
0 (normal)	84.2	85.0	88.0	89.5	84.5
1	13.3	13.4	10.9	8.5	13.8
2	2.3	1.6	1.1	2.0	1.7
3	0.2	0.1	0.0	0.0	0.0
4	0.0	0.0	0.0	0.0	0.0
Grades of atherosclerosis-HR					
0 (normal)	81.8	84.5	86.9	87.5	79.3
1	15.6	13.9	11.4	10.9	19.0
2	2.5	1.6	1.6	1.2	1.7
3	0.1	0.1	0.1	0.0	0.0
4	0.0	0.0	0.0	0.4	0.0

The number in the grades of each HR is explained in the methods section.
Statistical analysis was not conducted because the small number and absence are observed in many cells.
HDL-C, high-density lipoprotein cholesterol; HR, hypertensive retinopathy.

As shown in table 3, the prevalence of the three HRs decreased with increasing HDL-C level (χ^2 test, p<0.001). Although the prevalence of Keith-Wagener-HR was significantly higher in the lowest group of HDL-C 30–49 mg/dL compared with the reference group of HDL-C 90–109 mg/dL (χ^2 test, p=0.0009), no significant difference was observed between the subjects with the reference HDL-C and those with EH-HDL (p=0.03). However, logistic regression analysis showed that EH-HDL ≥110 mg/dL was significantly associated with Keith-Wagener-HR, compared with HDL-C 90–109 mg/dL (model 1). The association was strengthened by further adjustments for confounders including age, sex and systolic blood pressure (model 2, OR 3.01, 95% CI 1.45 to 6.27, p<0.01). Association of EH-HDL with atherosclerosis-HR was observed after adjustment for age, sex and BMI (model 2), whereas association of EH-HDL with hypertension-HR was not. The associations of EH-HDL with Keith-Wagener-HR and atherosclerosis-HR remained when subjects were restricted to those without diabetes (model 3) or those without pharmacotherapy for hypertension, dyslipidaemia and diabetes (model 4).

By contrast, although the lowest group of HDL-C 30–49 mg/dL was significantly associated with all HRs (model 1 for all), the statistical significance completely disappeared after adjustment for age, sex and BMI (model 2 for all).

Meanwhile, when HDL-C was treated as a continuous variable in the analysis model, significant inverse associations between HRs and HDL-C were observed (model 1), which disappeared after adjustment for confounding factors. Unexpectedly, HDL-C was positively associated with Hypertension-HR when subjects were restricted to those without pharmacotherapy for hypertension, dyslipidaemia and diabetes (model 4).

DISCUSSION

In this study, we found that EH-HDL ≥110 mg/dL was significantly associated with HR assessed by the Keith-Wagener classification and Scheie atherosclerosis classification, and that the associations were independent of blood pressure, age and sex. However, the grades of HR in the EH-HDL group may be mild (mostly grade 1) compared with lower HDL-C groups.

In contrast, in the crude model (model 1 in table 3), HDL-C as a continuous variable was inversely associated with all three HRs, although the inverse associations disappeared after adjustment for confounding factors. These results may be consistent with the provisional cut-off points (52–64 mg/dL) of HDL-C for HRs obtained from ROC curve analysis, although area under curves were low, which is based on the traditional assumption that the cardioprotective effect of HDL increases with increasing level of HDL-C.

Simultaneously, the present results suggest that the optimal HDL-C level is approximately 90–109 mg/dL, which is a little higher than the finding in our previous studies (70–89 mg/dL),[8 9] and much higher than

Table 3 ORs of HDL-C for hypertension retinopathy

HDL-C category (mg/dL)	30–49	50–69	70–89	90–109	≥110	HDL-C as a continuous variable
Keith-Wagener-HR, case, n (% in each group)	239 (24.9)†	377 (20.4)	159 (16.6)	37 (14.8)	16 (27.6)	
Model 1	1.91 (1.31–2.79)***	1.48 (1.02–2.13)*	1.15 (0.78–1.69)	1	2.19 (1.12–4.30)*	0.991 (0.986–0.995)***
Model 2	1.48 (0.98–2.23)	1.34 (0.91–1.99)	1.21 (0.80–1.83)	1	3.01 (1.45–6.27)**	0.998 (0.993–1.003)
Model 3	1.36 (0.90–2.07)	1.31 (0.88–1.95)	1.16 (0.76–1.76)	1	3.01 (1.44–6.31)**	0.999 (0.994–1.005)
Model 4	1.33 (0.83–2.16)	1.33 (0.84–2.09)	1.18 (0.74–1.90)	1	3.23 (1.39–7.49)**	1.000 (0.994–1.007)
Hypertension-HR, n‡ case, n (% in each group)	955	1840	953	248	58	
	151 (15.8)	277 (15.1)	114 (12.0)	26 (10.5)	10 (17.2)	
Model 1	1.61 (1.04–2.50)*	1.52 (0.99–2.32)	1.16 (0.74–1.83)	1	1.79 (0.81–3.97)	0.993 (0.988–0.999)*
Model 2	1.08 (0.67–1.75)	1.29 (0.81–2.04)	1.21 (0.75–1.96)	1	2.36 (0.99–5.63)	1.003 (0.997–1.009)
Model 3	0.97 (0.59–1.58)	1.27 (0.80–2.01)	1.16 (0.71–1.88)	1	2.36 (0.98–5.68)	1.004 (0.998–1.010)
Model 4	0.86 (0.47–1.55)	1.26 (0.73–2.20)	1.21 (0.68–2.16)	1	2.63 (0.90–7.65)	1.008 (1.000–1.015)*
Atherosclerosis-HR, n‡ case, n (% in each group)	955	1840	953	248	58	
	174 (18.2)	286 (15.5)	125 (13.1)	31 (12.5)	12 (20.7)	
Model 1	1.56 (1.03–2.35)*	1.29 (0.87–1.92)	1.06 (0.69–1.61)	1	1.83 (0.87–3.82)	0.992 (0.987–0.997)**
Model 2	1.27 (0.82–1.96)	1.20 (0.79–1.82)	1.09 (0.70–1.69)	1	2.23 (1.03–4.86)*	0.998 (0.992–1.003)
Model 3	1.15 (0.74–1.80)	1.14 (0.75–1.74)	1.00 (0.64–1.56)	1	2.21 (1.01–4.83)*	0.999 (0.993–1.005)
Model 4	1.08 (0.65–1.81)	1.11 (0.69–1.79)	1.01 (0.61–1.67)	1	2.57 (1.07–6.20)*	1.001 (0.995–1.008)

Model 1: Unadjusted.
Model 2: Adjusted for age, sex, and systolic blood pressure.
Model 3: Model two when subjects were restricted to those without diabetes (no pharmacotherapy for diabetes and fasting plasma glucose less than 126 126 mg/dL) (available n=3853).
Model 4: Model two when subjects were restricted to those without pharmacotherapy (for hypertension, diabetes, or dyslipidaemia) (available n=3260).
*P<0.05, **p<0.01, ***p<0.001.
†P=0.0009 vs reference HDL-C group of 90–109 mg/dL by the χ^2 test.
‡Total available: n=4054.
§Habitual exercise to a light sweat for over 30 min per session twice weekly.
HDL-C, high-density lipoprotein cholesterol; HR, hypertensive retinopathy.

traditionally thought (60–70 mg/dL).[15] A plausible explanation for this discrepancy is that the present analysis was not conducted according to male and female sex because of the small sample size in the high HDL-C groups and thus the high prevalence of women, who have higher HDL-C level than men,[4–6] in the high HDL-C groups may have raised the optimal HDL-C level to a higher level as a whole. In this study, the mean HDL-C level in women was 72.0 mg/dL, which is already beyond the traditionally established high level (60–70 mg/dL).[15] Moreover, the higher HDL-C level and gradual increase in the Japanese population compared with populations in other countries[21 22] may have contributed to the higher optimal HDL-C level in the present study.

Because HRs assessed by the Keith-Wagener-Barker[12] and Scheie[17] classifications were associated with cardiovascular events, the present results suggest that EH-HDL may reflect a certain atherosclerotic condition, possibly beyond blood pressure. Consist with this notion, previous studies[14 23 24] showed associations of HR with cardiovascular events and mortality that were independent of blood pressure. Uncommon hypertension not disclosed by typical measurements, such as microartery hypertension, and paroxysmal and nocturnal hypertension, may contribute to the underlying mechanism.

Meanwhile, the associations between HRs and lowest group of HDL-C 30–49 mg/dL were considered reasonable, because BMI, blood pressure, current smokers and pharmacotherapy for hypertension, dyslipidaemia or diabetes were highest in this group among the five HDL-C groups. However, the associations appeared to be influenced by these confounding factors because they disappeared after adjustment for age, sex and systolic blood pressure. Thus, the underlying mechanisms for the HRs may differ between the extremes of HDL-C: lowest HDL-C and EH-HDL.

Notably, the cardiometabolic profile appeared to be most preferable in the EH-HDL-C group because abnormal values of parameters were hardly observed in this group. Therefore, it is strange that the highest ORs for HRs were observed in the EH-HDL group (table 3), and the underlying mechanisms are unknown.

In recent years, we have demonstrated associations between EH-HDL and incidences of diabetes and prediabetes.[8 9] Coincidently, Wong et al[25] showed an independent association between retinal arteriolar narrowing, a specific feature of HR, and risk of diabetes in middle-aged people. Therefore, a possible link between HR and EH-HDL may exist through a pathophysiology related to diabetes. Unfortunately, the incidence of diabetes was very low (less than 10) in the EH-HDL group, which prevented us to analyse the prevalence of diabetes properly. However, several studies have shown that age-related macular degeneration, a leading cause of irreversible vision loss, is positively associated with HDL-C, although conflicting results have remained.[26–28] A forest plot in the meta-analysis by Wang et al[26] showed a significant association between HDL-C and age-related macular degeneration, suggesting that people with high HDL-C levels may be at increased risk for age-related macular degeneration.

Alternatively, as we previously proposed,[9] another mechanism may exist for the association. Catecholamines, which are over-secreted in pheochromocytoma and paragangliomas, can cause hypertension, diabetes and weight loss.[29] Some of their features, such as diabetes and low BMI, were applicable to the features of subjects with EH-HDL in our previous studies.[9 10] Consistently, Gosk-Przybyłek et al[30] recently showed that excessive secretion of catecholamine was related to retinal artery thickening, independently of blood pressure. However, elevated blood pressure, including paroxysmal hypertension, is often difficult to detect in patients with pheochromocytoma,[31] which may hamper clarification of the characteristics of individuals with latent hypertension. Nevertheless, some common pathophysiology to pheochromocytoma may exist in the pathophysiology of individuals with EH-HDL.

Besides specific genetic factors, such as *CETP*, *APOA1* and *LCAT*,[32 33] regular exercise and daily alcohol drinking can raise the level of HDL-C[34 35] and may partly contribute to the underlying mechanism of HR, although these factors were considered as relevant confounding factors in the present study. It is also possible that the function of HDL may be modified or impaired in subjects with EH-HDL, resulting in a proatherogenic property, and so-called dysfunctional HDL.[36 37] To estimate the atherogenic property of HDL, Apo A-I and Apo A-I/Apo B ratio may be more appropriate than HDL-C and HDL-C/LDL ratio.[38 39] Furthermore, the currently observed association between EH-HDL and HR may be indirect and complicated due to other lipids such as triglyceride and LDL-C[40 41] and risk factors.[42 43]

Limitations

Several limitations should be mentioned. First, among the subjects who underwent the regular checkups, few subjects underwent fundus examinations (0.24% in this study). Moreover, subjects treated with pharmacotherapy for diabetes or hypertension usually undergo fundus examinations by primary ophthalmologists at regular intervals, and such patients are likely to refrain from extra tests at check-ups, although they are highly likely to have HR. Therefore, there may be a selection bias for the eligible subjects in this study. However, as shown in the results, the overall characteristics of this study did not seem abnormal or special, if compared with excluded subjects, although significant differences were observed in some parameters. In addition, the proportion of subjects with very high HDL-C in the present study, such as ≥100 mg/dL, was almost the same (3.2%) as that in our previous study on 388 000 people (3.3%).[8] Second, the small number of cases (n=10–16 in the EH-HDL group), which may lower the reliability of outcomes, hampered the classification into men and women, and the controlling for restricted confounding factors (age,

sex and systolic blood pressure). Third, the contents and purpose of pharmacotherapy (hypertension, diabetes or dyslipidaemia) is unknown in this study, which can influence the outcomes. Among them, statin therapy, a most common pharmacotherapy for atherosclerosis, may influence the outcomes. However, similar results were observed in the sub-analysis of subjects without such pharmacotherapy (table 3), suggesting the slight contribution of pharmacotherapy to the currently observed associations. Fourth, although history of eye treatments such as laser treatment may influence the assessment of HRs, such information is unavailable in this study. Finally, the study had a cross-sectional design, which does not allow us to speculate on the causality between EH-HDL and HR. Taken together, caution should be exercised in the interpretation of the present results particularly because of the small cases in the EH-HDL and larger and well-designed prospective studies including HR data are needed to confirm the present findings and to elucidate the underlying mechanisms.

CONCLUSION

Compared with relatively high HDL-C, EH-HDL ≥110 mg/dL was significantly associated with HR independently of confounding factors such as blood pressure, suggesting that EH-HDL may reflect a certain atherosclerotic condition. However, it may be also important to confirm the overall relationship between HDL-C and HR.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics Committee of Kanagawa University of Human Services (10–43) and the Ministry of Health, Labour and Welfare of Japan (No. 121). We received the digitally recorded non-distinguishing anonymous data from the MHLW in August 2017. We have opened the protocol of our study to the public on our university homepage, which was updated in October 2017.

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REFERENCES

1. Masuda D, Yamashita S. Very high levels of high-density lipoprotein cholesterol and cardiovascular events in Japanese population. *J Atheroscler Thromb* 2016;23:771–2.
2. Madsen CM, Nordestgaard BG. Is it time for new thinking about high-density lipoprotein? *Arterioscler Thromb Vasc Biol* 2018;38:484–6.
3. Singh K, Rohatgi A. Examining the paradox of high high-density lipoprotein and elevated cardiovascular risk. *J Thorac Dis* 2018;10:109–12.
4. Sharif S, van der Graaf Y, Nathoe HM, et al. HDL cholesterol as a residual risk factor for vascular events and all-cause mortality in patients with type 2 diabetes. *Diabetes Care* 2016;39:1424–30.
5. Ko DT, Alter DA, Guo H, et al. High-density lipoprotein cholesterol and cause-specific mortality in individuals without previous cardiovascular conditions: the CANHEART study. *J Am Coll Cardiol* 2016;68:2073–83.
6. Madsen CM, Varbo A, Nordestgaard BG. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur Heart J* 2017;38:2478–86.
7. Hirata A, Sugiyama D, Watanabe M, et al. Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: the EPOCH-JAPAN study. *J Clin Lipidol* 2018;12:674–84.
8. Nakajima K, Higuchi R, Iwane T, et al. High incidence of diabetes in people with extremely high high-density lipoprotein cholesterol: results of the Kanagawa investigation of total checkup data from the National Database-1 (KITCHEN-1). *J Clin Med* 2019;8:381.
9. Nakajima K, Higuchi R. Impaired glucose metabolism in people with extremely elevated high-density lipoprotein cholesterol and low alcohol consumption: results of the Kanagawa investigation of total checkup data from the National Database-3 (KITCHEN-3). *J Clin Med* 2019;8:1825.
10. Luo BP, Brown GC. Update on the ocular manifestations of systemic arterial hypertension. *Curr Opin Ophthalmol* 2004;15:203–10.
11. Grosso A. Detection and management of vascular hypertension. *Compr Ophthalmol Update* 2007;8:145–54.
12. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1974;268:336–45.
13. Nokiba H, Takei T, Suto C, et al. Association between Ophthalmological changes and cardiovascular diseases in patients with chronic kidney disease undergoing hemodialysis. *J Atheroscler Thromb* 2015;22:1248–54.
14. Sairenchi T, Iso H, Yamagishi K, et al. Mild retinopathy is a risk factor for cardiovascular mortality in Japanese with and without hypertension: the Ibaraki Prefectural health study. *Circulation* 2011;124:2502–11.
15. Nakajima K, Iwane T, Higuchi R, et al. Kanagawa investigation of the total Check-up data from the National database (kitchen): protocol for data-driven population-based repeated cross-sectional and 6-year cohort studies. *BMJ Open* 2019;9:e023323..
16. Keith NM, Wagener HP, Barker NW. Some different types of essential hypertension: their course and prognosis. *Am J Med Sci* 1939;191:332–43.
17. Scheie HG. Evaluation of ophthalmoscopic changes of hypertension and arteriolar sclerosis. *AMA Arch Ophthalmol* 1953;49:117–38.
18. Tamada M, Makita S, Abiko A, et al. Low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a useful marker for early-stage carotid atherosclerosis. *Metabolism* 2010;59:653–7.
19. Enomoto M, Adachi H, Hirai Y, et al. LDL-C/HDL-C ratio predicts carotid intima-media thickness progression better than HDL-C or LDL-C alone. *J Lipids* 2011;2011:1–6.
20. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013;48:452–8.
21. Ueshima H, Iida M, Shimamoto T, et al. High-density lipoprotein-cholesterol levels in Japan. *JAMA* 1982;247:1985–7.
22. Yokoyama S, Ueshima H, Miida T, et al. High-density lipoprotein levels have markedly increased over the past twenty years in Japan. *J Atheroscler Thromb* 2014;21:151–60.

23 Wong TY, Klein R, Couper DJ, *et al*. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis risk in Communities study. *Lancet* 2001;358:1134–40.

24 Wong TY, Klein R, Sharrett AR, *et al*. Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis risk in Communities study. *JAMA* 2002;287:1153–9.

25 Wong TY, Klein R, Sharrett AR, *et al*. Retinal arteriolar narrowing and risk of diabetes mellitus in middle-aged persons. *JAMA* 2002;287:2528–33.

26 Wang Y, Wang M, Zhang X, *et al*. The association between the lipids levels in blood and risk of age-related macular degeneration. *Nutrients* 2016;8:663.

27 Burgess S, Davey Smith G. Mendelian randomization implicates high-density lipoprotein cholesterol-associated mechanisms in etiology of age-related macular degeneration. *Ophthalmology* 2017;124:1165–74.

28 Betzler BK, Rim TH, Sabanayagam C, *et al*. High-density lipoprotein cholesterol in age-related ocular diseases. *Biomolecules* 2020;10:645.

29 Plouin P-F, Gimenez-Roqueplo A-P. Pheochromocytomas and secreting paragangliomas. *Orphanet J Rare Dis* 2006;1:49.

30 Gosk-Przybyłek M, Doroszko A, Dobrowolski P, *et al*. Retinal arterial remodeling in patients with pheochromocytoma or paraganglioma and its reversibility following surgical treatment. *J Hypertens* 2020;38:1551–8.

31 Roden M. How to detect pheochromocytomas?--the diagnostic relevance of plasma free metanephrines. *Wien Klin Wochenschr* 2002;114:246–51.

32 Holleboom AG, Vergeer M, Hovingh GK, *et al*. The value of HDL genetics. *Curr Opin Lipidol* 2008;19:385–94.

33 Kardassis D, Mosialou I, Kanaki M, *et al*. Metabolism of HDL and its regulation. *Curr Med Chem* 2014;21:2864–80.

34 Safeer RS, Cornell MO. The emerging role of HDL cholesterol. is it time to focus more energy on raising high-density lipoprotein levels? *Postgrad Med* 2000;108:87–98.

35 Bishop BM. Systematic review of CETP inhibitors for increasing high-density lipoprotein cholesterol: where do these agents stand in the approval process? *Am J Ther* 2015;22:147–58.

36 Feng H, Li X-A. Dysfunctional high-density lipoprotein. *Curr Opin Endocrinol Diabetes Obes* 2009;16:156–62.

37 Ossoli A, Pavanello C, Giorgio E, *et al*. Dysfunctional HDL as a therapeutic target for atherosclerosis prevention. *Curr Med Chem* 2019;26:1610–30.

38 Chait A, Montes VN. Apolipoproteins and diabetic retinopathy. *Diabetes Care* 2011;34:529–31.

39 Chang Y-C, Wu W-C. Dyslipidemia and diabetic retinopathy. *Rev Diabet Stud* 2013;10:121–32.

40 Davis MD, Fisher MR, Gangnon RE, *et al*. Risk factors for high-risk proliferative diabetic retinopathy and severe visual loss: early treatment diabetic retinopathy study report #18. *Invest Ophthalmol Vis Sci* 1998;39:233–52.

41 Emanuelsson F, Nordestgaard BG, Tybjærg-Hansen A, *et al*. Impact of LDL cholesterol on microvascular versus macrovascular disease: a Mendelian randomization study. *J Am Coll Cardiol* 2019;74:1465–76.

42 Hoekstra M, Van Berkel TJC. Functionality of high-density lipoprotein as antiatherosclerotic therapeutic target. *Arterioscler Thromb Vasc Biol* 2016;36:e87–94.

43 He Y, Kothari V, Bornfeldt KE. High-density lipoprotein function in cardiovascular disease and diabetes mellitus. *Arterioscler Thromb Vasc Biol* 2018;38:e10–16.