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Association between serum high-density lipoprotein cholesterol and hypertension: results of Kanagawa Investigation of Total Checkup Data from the National Database-9 (KITCHEN-9)

Running title: HDL-C and hypertension: results of KITCHEN-9

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Abstract

Background

Although high-density lipoprotein has cardioprotective effects, the association between serum high-density lipoprotein cholesterol (HDL-C) and hypertension is poorly understood.

Objective

We investigated whether low and high concentrations of HDL-C are associated with hypertension using a large healthcare dataset.

Methods

In a community-based cross-sectional study of 1,493,152 Japanese people aged 40–74 years who underwent a health checkup, blood pressures and clinical parameters, including nine HDL-C concentrations (20–110 mg/dL or over) were investigated.

Results

A crude U-shaped relationship was observed between the nine HDL-C concentrations and blood pressure in males (n = 830,669), while a left-to-right inverted J-shaped relationship was observed in females(n = 662,483). An age-adjusted logistic regression analysis showed J-shaped relationships (left-to-right inversion in females) between HDL-C and odds ratios for hypertension (≥140/90 mmHg), with lower limits of 60–79 mg/dL in males and 90–99 mg/dL in females, which were unchanged after adjusting for smoking, habitual exercise, alcohol consumption, and pharmacotherapy for hypertension, dyslipidemia, and diabetes. However, further adjustment for body mass index and serum triglyceride concentration revealed latent positive linear associations between HDL-C and hypertension, although the association between extremely high HDL-C (≥100 mg/dL) and hypertension was attenuated in non-alcohol drinkers.

Conclusion

Both low and extremely high HDL-C concentrations are associated with hypertension. The former association may be dependent on excess fat mass, which is often concomitant with low HDL-C, whereas the latter association may be dependent on frequent alcohol consumption.

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Keywords: high-density lipoprotein cholesterol; hypertension; blood pressure; low high-density lipoprotein cholesterol; extremely high high-density lipoprotein cholesterol; body mass index; big data

Abbreviations

BMI, body mass index; CETP, cholesteryl ester transfer protein; CVD, cardiovascular disease; HDL-C, High-density lipoprotein; MHLW, Ministry of Health, Labour, and Welfare; TG, triglyceride

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Introduction

High-density lipoprotein (HDL) is considered to have cardioprotective effects, which have been confirmed repeatedly in molecular, cellular, animal, and human studies [1-5]. Therefore, individuals with a high serum HDL cholesterol (HDL-C) concentration are considered to be at a lower risk of cardiovascular disease (CVD) and mortality according to the concepts of "the higher, the better" and "longevity syndrome" [2,6,7]. However, in the past decade, several studies have shown a U-shaped relationship between HDL-C and CVD, non-CVD, and all-cause mortality [8-14], which suggests that, like low HDL-C, very or extremely high HDL-C is not beneficial for overall health. Moreover, increasing HDL-C with pharmacotherapy, including cholesteryl ester transfer protein (CETP) inhibitors, has not shown protective effects against CVD and mortality [15-18]. Among the plausible causes of adverse reactions with CETP inhibitors (torcetrapib and evacetrapib), a slight increase in blood pressure [19,20] and vasoactive effects [21] have been observed and may have been considered as markers of profound adverse reactions due to neuroendocrine or vasomotor effects [15], although the underlying mechanisms remain unknown.

Hypertension is a leading cause of CVD and mortality worldwide. However, to date, the fundamental relationship between serum HDL-C concentration and blood pressure has been poorly argued, probably because an inverse relationship has been observed between serum HDL-C and CVD and its risk factors [4,5].

Unexpectedly, however, instead of an inverse relationship, a slight U-shaped relationship, a left-to-right inverted J-shaped relationship [9,11,13], or a positive linear relationship [12,14] between circulating HDL-C and blood pressure or hypertension have been observed in several studies. Despite these relationships being noted, authors have not particularly addressed them; hence, their statistical significance is unclear.

To date, three studies have addressed the association between HDL-C concentration and

hypertension [22-24]. Additionally, we recently showed an association between extremely high HDL-C (≥110 mg/dL) and hypertensive retinopathy in a general population who underwent fundus examinations [25]. Our results suggested a positive association between HDL-C concentration and blood pressure/hypertension-related pathology. However, these four studies [22-25], which examined the pathophysiology of very low and high HDL-C concentrations (e.g., <30 mg/dL and ≥90 mg/dL), consisted of relatively small sample sizes (<5,000 participants in total). Actually, the number of subjects with hypertension was only 16 in the extremely high HDL-C group in our previous study [25]. Consequently, it was difficult to conduct an appropriate statistical analysis with proper adjustment for relevant confounding factors (covariates) in the low and very high HDL-C groups, which hampered disclosure of a latent overall association between HDL-C concentration and hypertension. Adjustment of concomitant background factors, such as sex, weight, alcohol consumption, smoking, exercise, and pharmacotherapy, may be crucial for statistical analysis, because all are likely to influence both serum HDL-C concentration and blood pressure.

In this context, we investigated the apparent (age- and sex-adjusted) and latent (adjusted for multiple background factors) associations between serum HDL-C concentration and blood pressure in a community-based cross-sectional study using a big healthcare dataset of 1.5 million general Japanese people [26]. This enabled us to identify complicated associations with appropriate adjustment for confounders and classifications, such as sex and alcohol consumption.

Methods

Study Design and Subjects

We performed a composite multidisciplinary study involving secondary use of annual health checkup data in Japan (Kanagawa Investigation of the Total Checkup Data from the National Database [KITCHEN]) to investigate clinical factors primarily associated with cardiometabolic disease. Details of the study concept and design have been published elsewhere [26]. Since 2008, all Japanese people aged 40–74 years are supposed to undergo a yearly itemized health checkup

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managed by the Ministry of Health, Labour, and Welfare (MHLW) [26,27]. The present study included all individuals who underwent these specific health checkups and who were living in Kanagawa Prefecture. The study protocol was approved by the Ethics Committee of Kanagawa University of Human Services (10–43) and the MHLW of Japan (No. 121).

After religious review of our research project by the MHLW of Japan, our protocol was accepted in December 2016. We received digitally recorded anonymous data from the MHLW of Japan in September 2017, as part of its nationwide program involving the provision of medical data to third parties [28]. To conceal the identity of specific individuals, their ages were categorized 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 corresponding to the median of each age group (42, 47, 52, 57, 62, 67, and 72 years).

We initially reviewed data collected from 1,819,173 people aged 40–74 years who attended health checkups between April 2013 and March 2014. After excluding subjects with at least one missing continuous or categorical data point, 1,493,152 subjects were included in the study analysis (830,669 males and 662,483 females).

Measurements

Anthropometric and laboratory measurements were obtained on the morning following an overnight fast. Body weight and height were objectively measured by trained institutional staff members. Body mass index (BMI) was calculated as mass (in kg) divided by the square of height (m^2). Biochemical measurements were performed automatically using standard methods. Serum low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride (TG) concentrations were measured automatically, mainly spectrophotometrically (in ~85% of samples) using a direct, non-precipitation method, and the remainder were measured using other methods following rigorous instructions from the MHLW [26].

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After five minutes of resting in the sitting position, blood pressure at the upper arm was determined using an automated sphygmomanometer at the healthcare institute performing the checkups [26]. Blood pressure was measured once in 70% of patients and twice in 30% of patients. Of patients who underwent two blood pressure measurements, the first result was used in 20% of patients, while the second result was used in 10% of patients.

Hypertension was defined as a systolic and/or diastolic blood pressure of ≥140 mmHg and/or ≥90 mmHg, respectively, regardless of self-reported pharmacotherapy for hypertension. Pharmacotherapy for hypertension (the contents of which were unknown) was considered as a confounding factor in the analysis model. Pulse pressure was calculated as systolic minus diastolic blood pressure. Subjects were classified into nine categories at 10-mg/dL HDL-C concentration intervals: 20–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, 100–109, and ≥110 mg/dL.

Because serum HDL-C concentration and blood pressure are elevated in people who frequently consume alcohol [29,30], to eliminate the effect of alcohol consumption on serum HDL-C and blood pressure, we investigated the association between these variables in a subgroup of subjects who answered “hardly drink (including cannot drink)” when asked “How often do you drink alcohol (sake, distilled spirits, beer, liquor and so)?” [26].

Additionally, to further investigate blood pressure and pulse pressure in the HDL-C concentration categories specified above, both ends of the HDL-C concentration spectrum (20–39 and ≥110 mg/dL) were further divided into 20–29 and 30–39 mg/dL and 110–119, 120–129, and ≥130 mg/dL, respectively (Supplementary Figure 1), because the proportion of subjects with these HDL-C concentrations was very low (0.16% and 0.2% in total, respectively).

Statistical Analysis

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Data are expressed as mean ± standard deviation or median (interquartile range). Differences in continuous and categorical variables were evaluated by analysis of variance (ANOVA) and the χ^2 test, respectively. Trends in the prevalence of dichotomized categorical variables across the increasing HDL-C strata were evaluated by Cochran–Armitage tests. A logistic regression model was used to evaluate the associations between the nine HDL-C concentration categories and hypertension with adjustment for potential confounding factors (age, sex, BMI, TG, LDL-C, glycated hemoglobin [HbA1c] [National Glycohemoglobin Standardization Program value], history of cardiovascular disease, pharmacotherapy for hypertension, diabetes mellitus, dyslipidemia, smoking, frequency of alcohol consumption, and habitual exercise), and yielded adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Trends for linear associations between HDL-C concentration categories and their ORs for hypertension were examined with Pearson's correlation test after coding HDL-C concentration categories from 1 to 9. All statistical analyses were performed using SAS-Enterprise Guide (SAS-EG 7.1) in SAS software, version 9.4 (SAS Institute, Cary, NC, USA). P values of <0.05 were considered statistically significant.

Results

Table 1 shows the characteristics of subjects according to the nine HDL-C concentration categories. There were 50,064 subjects with an HDL-C concentration of ≥100 mg/dL (3.4% of the total), and nearly 75% of these were female. Overall, all continuous variables (blood pressure, pulse pressure, BMI, TG, LDL-C, and HbA1c), except age, were lower in the higher HDL-C groups compared with the lower HDL-C groups (ANOVA, all $P < 0.0001$). The prevalence of pharmacotherapy (for hypertension, diabetes mellitus, and dyslipidemia), CVD history, and current smoking were also lower (Cochran–Armitage test, all $P < 0.0001$). However, the prevalence of the female sex, daily alcohol consumption, and habitual exercise was higher in the higher HDL-C groups compared with the lower HDL-C groups (all $P < 0.0001$).

A U-shaped relationship was observed between systolic and diastolic blood pressure and the nine

HDL-C concentration categories in males (***Figure 1A***), while a left-to-right inverted J-shaped relationship was observed in females (***Figure 1B***). In ***Supplementary Figure 1***, where the minimum and maximum HDL-C concentration categories were further divided, higher blood pressure was observed in the highest HDL-C group (HDL-C: 120–129 and ≥130 mg/dL). Similarly, as shown in ***Supplementary Figure 2***, higher pulse pressures were observed in males.

Table 2 shows the prevalence of hypertension and the results of the logistic regression analysis. Overall, hypertension was more common in the higher HDL-C groups in males (Cochran–Armitage test, $P = 0.007$), whereas it was less common in females ($P < 0.0001$).

In the logistic regression analysis, inverse associations were observed between the nine HDL-C concentration categories and their crude ORs for hypertension in overall subjects ($r = -0.83$, $P = 0.006$) and in females ($r = -0.86$, $P = 0.003$), whereas a positive association was observed in males ($r = 0.73$, $P = 0.03$) (***Model 1***). An age-adjusted logistic regression analysis showed J-shaped relationships (left-to-right inversion in females) between HDL-C concentration categories and their ORs for hypertension, with a lower limit of 60–79 mg/dL in males and 90–99 mg/dL in females (***Table 2, Model 2***), which were not largely altered after adjustment for smoking; habitual exercise; alcohol consumption; and pharmacotherapy for hypertension, dyslipidemia, and diabetes mellitus (***Model 3***). However, after further adjustment for BMI and serum TG, the relationships between HDL-C concentration categories and hypertension transformed into positive linear relationships in both males and females (***Model 4***), which remained after adjustment for LDL-C and HbA1c (***Model 5***) and when restricted to no pharmacotherapy for hypertension, diabetes mellitus, and dyslipidemia (***Model 6***).

In the subgroup of non-drinkers (n = 595,268), an age-adjusted logistic regression analysis showed strong inverse linear associations between HDL-C concentration categories and hypertension in the overall cohort ($r = -0.94$, $P = 0.001$) and in females ($r = -0.95$, $P < 0.001$) (***Table 3, Model 2***). This inverse association was also observed in males, although the strength was attenuated ($r = -0.77$, P

= 0.02). These trends were not altered after adjustment for smoking; habitual exercise; and pharmacotherapy for hypertension, dyslipidemia, and diabetes mellitus (***Model 3***). However, after further adjustment for BMI and serum TG, the relationships transformed into positive linear relationships in both males and females (***Model 4***). These associations did not change after additional adjustment for LDL-C and HbA1c (***Model 5***) and when restricted to no pharmacotherapy (***Model 6***).

Discussion

Using a large healthcare dataset of 1.5 million general people, our study investigated complicated associations between serum HDL-C concentration and blood pressure, both of which are pivotal to the incidence of CVD and mortality and are simultaneously influenced by genetic background, comorbidities, and lifestyle factors, such as alcohol consumption, exercise, smoking, and body weight.

At first, our study demonstrated apparent U- or J-shaped crude associations between serum HDL-C concentration and hypertension. Similar relationships were also observed between serum HDL-C concentration and pulse pressure, which is a marker of atherosclerosis and a hyperdynamic circulation [31,32]. However, the positive association between a low HDL-C concentration and hypertension, which was more marked in females compared with males, disappeared after adjusting for BMI and serum TG. Because a high BMI and serum TG concentration usually reflect obesity, such apparent associations might be dependent on an excess body fat mass.

An apparent association between an extremely high serum HDL-C concentration (≥100 mg/dL) and hypertension, which was more common in males, was also observed. However, this positive association was attenuated when subjects were restricted to the subgroup of non-drinkers, suggesting that this association may be largely dependent on frequent alcohol consumption, which has been shown to raise serum HDL-C via inhibition of CETP activity and activation of lipoprotein

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lipase [33,34].

In the U- or J-shaped relationships between HDL-C concentrations and hypertension, the reference ranges of HDL-C in this study (60–79 mg/dL for males and 90–99 mg/dL for females; *Table 2*) were consistent with previous studies [9,10], although the value in females was slightly higher in our study.

After full consideration of covariates (confounders), among which BMI and serum TG were the most influential factors, positive linear associations between serum HDL-C concentration categories and hypertension were observed in both males and females, regardless of alcohol consumption and pharmacotherapy for hypertension, diabetes mellitus, and dyslipidemia.

The underlying mechanism behind these fundamental positive linear associations is unknown. Unmeasured factors, such as heart rate; endocrine disorders accompanied by elevated catecholamines, cortisol, aldosterone, thyroid hormones, and apolipoprotein A1; CETP inactivity; and sodium consumption, might contribute to these associations.

Meanwhile, a low HDL-C concentration is often observed in patients with malnutrition [35,36], who usually have a low body weight and blood pressure. The small reduction in blood pressure in the lowest HDL-C group (20–29 mg/dL; Supplementary Figure 1) might reflect a glimpse of this phenomenon. Adjustment for BMI may disclose this pathophysiology by eliminating the effect of excess body weight. Because BMI and serum TG were normal or low on average in the very and extremely high HDL-C groups (≥100 mg/dL), adjustment for BMI and TG did not change the association between high HDL-C concentration and hypertension. Taken together, adjustment for BMI and TG had a greater impact in the low HDL-C groups compared with the extremely high HDL-C group, which may have resulted in transformation into a positive linear association.

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As shown in ***Figure 1*** and ***Supplementary Figure 1***, in ordinary clinical practice, healthcare professionals may identify hypertension in patients with obesity (who are likely to have a low serum HDL-C concentration) and a normal blood pressure in those without obesity (who are likely to have normal or high serum HDL-C). Therefore, healthcare professionals are likely to observe an inverse relationship between HDL-C and blood pressure.

However, healthcare professionals who encounter patients with very high HDL-C concentrations, particularly male patients, may be aware of a specific U- or J-shaped relationship between HDL-C and blood pressure. Of note, since very high serum HDL-C concentrations are less prevalent, most healthcare professionals are likely to overlook such rare cases and conclude that high blood pressure is observed exclusively in patients with low HDL-C.

In recent years, several studies have shown that extremely high serum HDL-C may not be protective against CVD development [8-14]. Some of these studies presented U-shaped or positive linear relationships between HDL-C concentration categories and blood pressure [9,11,13], although the authors did not particularly argue them in their articles. Furthermore, none of these studies investigated pulse pressure in terms of HDL-C concentration categories.

In addition, clinical trials evaluating the effects of CETP inhibitors, which do not show a protective effect against CVD events, demonstrated a slightly increase in systolic blood pressure of 1.2–5.4 mmHg after intervention, concomitant with a substantial increase in HDL-C concentration [15,16]. Likewise, in our study, the difference in systolic blood pressure between the reference HDL-C concentration group and the extremely high HDL-C concentration group was small (6 mmHg at most in males) (Supplementary Figure 1), which is coincidently equivalent to the increase in blood pressure caused by CETP inhibitors, as outlined above. However, it is unknown whether there is a common mechanism underpinning the pathophysiology between a naturally high HDL-C concentration and HDL-C raised by pharmacotherapy. Further study will be needed to confirm whether this small increase in blood pressure has clinical significance in patients with atherosclerosis and CVD.

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Limitations

This study has some limitations that should be noted. First, the causality between HDL-C concentration and hypertension could not be identified, since this study adopted a cross-sectional design. Second, because subjects in this study were general people who underwent a health checkup, most were healthy and free from CVD and hypertension. Therefore, the results may not be applicable to other populations or patients with CVD and hypertension. Third, data on sodium consumption and other nutrients, including potassium and fiber, and the menopausal state in women (postmenopausal or not) were unavailable in this study. These factors influence blood pressure and HDL-C concentration and thus should be considered in future studies. Fourth, secondary hypertension and dyslipidemia were not excluded in this study. Furthermore, because blood pressure was measured at a healthcare institute, blood pressure measurements at home/at night and during physical exertion were not utilized.

Conclusions

The association between HDL-C concentration and blood pressure is complicated and differs between males and females and between people who consume alcohol and those who do not. In clinical practice, an apparent inverse association between HDL-C concentration (30–70 mg/dL, which is the frequently observed range) and hypertension may be observed, although this association can depend on body fat mass. The robust association between an extremely high HDL-C concentration and hypertension, particularly in males, and the fundamental positive linear association between HDL-C concentration and hypertension may challenge the traditional concept of “the higher, the better” and the high HDL-C concentration caused by CETP inhibitors. Further studies, including long-term prospective studies and clinical trials, on pharmacotherapy intervention are needed to confirm our results.

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Figure legends

Figure 1

Blood pressure in males and females according to nine HDL-C concentration categories.

With HDL-C concentrations of 20–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90–99, 100–109, and ≥110 mg/dL, n = 57,052, 193,722, 235,749, 171,612, 95,359, 45,195, 19,204, 7,624, and 5,152 for males and 6,800, 44,379, 112,421, 160,350, 148,963, 99,424, 52,858, 22,886, and 14,402 for females, respectively.

Supplementary Figure S1

Blood pressure in males and females according to 12 HDL-C concentration categories.

With HDL-C concentrations of 20–29, 20–39, 110–119, 120–129, and ≥130 mg/dL, n = 2,134,

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54,918, 3,019, 1,200, and 933 for males and 213, 6,587, 9,044, 3,302, and 2,056 for females. The number of subjects in other HDL-C concentration categories is the same as described in Figure 1.

Supplementary Figure S2

Pulse pressure in males and females according to 12 HDL-C concentration categories.

The number of subjects in each HDL-C concentration category is the same as described in Supplementary Figure 1.

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Table 1. Clinical characteristics of subjects

Data are presented as mean ± standard deviation, median (interquartile range) [triglyceride], or n (%).

HDL-C categories (mg/dL)	30-39	40-49	50-59	60-69	70-79	80-89	90-99	100-109	≥ 110
N (% of total)	63,852 (4.3)	238,101 (16.0)	348,170 (23.3)	331,962 (22.2)	244,322 (16.4)	144,619 (9.7)	72,062 (4.8)	30,510 (2.0)	19,554 (1.3)
s-Age	54.0 ± 10.0	54.2 ± 10.0	54.8 ± 10.1	55.1 ± 10.2	55.1 ± 10.1	55.2 ± 10.0	55.4 ± 9.7	55.6 ± 9.4	55.8 ± 9.2
Women, n (%)	6,800 (10.7)	44,379 (18.6)	112,421 (32.3)	160,350 (48.3)	148,963 (61.0)	99,424 (68.8)	52,858 (73.4)	22,886 (75.0)	14,402 (73.7)
BMI (kg/m^2)	25.9 ± 3.7	25.0 ± 3.6	23.9 ± 3.4	22.8 ± 3.2	21.8 ± 3.0	21.1 ± 2.8	20.7 ± 2.7	20.4 ± 2.6	20.1 ± 2.6
SBP (mmHg)	126 ± 16.4	125 ± 16.4	124 ± 16.8	122 ± 17.2	121 ± 17.5	120 ± 17.6	120 ± 17.6	120 ± 17.9	121 ± 18.2
DBP (mmHg)	78.4 ± 11.5	78.1 ± 11.5	77.0 ± 11.6	75.4 ± 11.7	74.3 ± 11.7	73.7 ± 11.7	73.6 ± 11.6	73.9 ± 11.8	74.7 ± 12.0
PP (mmHg)	47.3 ± 11.1	47.0 ± 11.0	47.1 ± 11.2	47.0 ± 11.3	46.6 ± 11.4	46.4 ± 11.4	46.3 ± 11.4	46.4 ± 11.5	46.7 ± 11.6
Triglyceride (mg/dl)	185 (130–270)	138 (99–193)	106 (77–146)	85 (64–117)	73 (56–98)	66 (51–87)	62 (49–81)	59 (47–76)	58 (46–75)
LDL-C (mg/dl)*	121 ± 33.4	130 ± 32.4	130 ± 32.2	126 ± 31.6	122 ± 30.8	120 ± 30.2	118 ± 30.3	117 ± 30.8	112 ± 32.6
HDL-C (mg/dl)	36.0 ± 2.9	45.1 ± 2.8	54.6 ± 2.9	64.3 ± 2.9	74.2 ± 2.8	84.0 ± 2.8	93.8 ± 2.8	103.8 ± 2.8	120.4 ± 11.9
HbA1c (NGSP, %)**	5.9 ± 0.9	5.7 ± 0.8	5.6 ± 0.7	5.5 ± 0.5	5.5 ± 0.5	5.5 ± 0.4	5.4 ± 0.4	5.4 ± 0.4	5.4 ± 0.5
Pharmacotherapy for hypertension, n (%)	16,700 (26.2)	56,096 (23.6)	73,636 (21.2)	59,303 (17.9)	36,521 (15.0)	19,188 (13.3)	8,810 (12.2)	3,677 (12.1)	2,533 (13.0)
diabetes, n (%)	5,974 (9.4)	16,629 (7.0)	17,094 (4.9)	11,105 (3.4)	5,720 (2.3)	2,675 (1.9)	1,123 (1.6)	490 (1.6)	343 (1.8)
dyslipidemia, n (%)	91,03 (14.3)	34,431 (14.5)	49,956 (14.4)	42,471 (12.8)	26,229 (10.7)	13,417 (9.3)	6,005 (8.3)	2,345 (7.7)	1,410 (7.2)
Cardiovascular disease, n (%)	3,293 (5.2)	9,747 (4.1)	12,237 (3.5)	9,867 (3.0)	6,100 (2.5)	3,327 (2.3)	1,532 (2.1)	597 (2.0)	349 (1.8)
Current smokers, n (%)	28,658 (44.9)	81,543 (34.3)	89,236 (25.6)	63,958 (19.3)	37,275 (15.3)	18,864 (13.0)	8,550 (11.9)	3,667 (12.0)	2,629 (13.4)
Alcohol drinkers, n (%)***	11,580 (18.1)	55,642 (23.4)	96,004 (27.6)	96,149 (29.0)	72,192 (29.6)	44,524 (30.8)	23,825 (33.1)	11,156 (36.6)	8,577 (43.9)
Regular exercisers, n (%)****	14,582 (22.8)	60,875 (25.6)	99,252 (28.5)	102,162 (30.8)	78,890 (32.3)	48,424 (33.5)	25,094 (34.8)	10,874 (35.6)	7,300 (37.3)

*Available n = 1,448,907.

** Available n = 1,260,117.

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***Drinkers who consume alcohol every day.
***Regular exercise defined as ≥30 min at least twice a week.
All continuous and categorical variables show significant differences with an ANOVA or χ^2 test, with $P < 0.0001$ across the nine HDL-C concentration categories.
s-Age, substituted age; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

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Table 2. Odds ratios of nine HDL-C concentration categories for hypertension

HDL-C category (mg/dL)	20–39	40–49	50–59	60–69	70–79	80–89	90–99	100-109	≥ 110	Correlation coefficients and P values
Whole subjects (n = 1,493,152)										
Case of Hypertension, n (% in each group)	14,945 (23.4)	54,614 (22.9)	73,451 (21.1)	62,374 (18.8)	41,429 (17.0)	23,369 (16.2)	11,364 (15.8)	5,060 (16.6)	3,590 (18.4)	a
Model 1	1.63 (1.59-1.68)	1.59 (1.56-1.63)	1.43 (1.40-1.46)	1.24 (1.21-1.26)	1.09 (1.07-1.12)	1.03 (1.01-1.06)	1	1.06 (1.02-1.10)	1.20 (1.15-1.25)	-0.83 0.006
Model 2	1.26 (1.22-1.29)	1.27 (1.24-1.30)	1.18 (1.16-1.21)	1.09 (1.07-1.12)	1.03 (1.00-1.05)	1.01 (0.98-1.03)	1	1.07 (1.03-1.11)	1.20 (1.15-1.25)	-0.55 0.12
Model 3	1.31 (1.28-1.35)	1.30 (1.27-1.33)	1.20 (1.17-1.23)	1.10 (1.08-1.13)	1.03 (1.01-1.06)	1.01 (0.99-1.04)	1	1.06 (1.02-1.10)	1.15 (1.11-1.20)	-0.71 0.03
Model 4	0.49 (0.47-0.50)	0.63 (0.62-0.65)	0.73 (0.71-0.75)	0.80 (0.78-0.82)	0.87 (0.85-0.89)	0.94 (0.92-0.97)	1	1.12 (1.08-1.16)	1.27 (1.22-1.33)	0.99 <0.001
Model 5	0.50 (0.48-0.52)	0.62 (0.61-0.64)	0.71 (0.70-0.73)	0.79 (0.77-0.81)	0.86 (0.84-0.88)	0.94 (0.91-0.97)	1	1.10 (1.06-1.15)	1.27 (1.21-1.34)	0.99 <0.001
Model 6	0.46 (0.44-0.48)	0.59 (0.57-0.61)	0.70 (0.67-0.72)	0.77 (0.75-0.80)	0.85 (0.82-0.87)	0.93 (0.90-0.96)	1	1.14 (1.08-1.19)	1.30 (1.23-1.38)	0.99 <0.001
Men (n = 830,669)										
Case of Hypertension, n (% in each group)	13,447 (23.6)	45,228 (23.4)	53,195 (22.6)	37,934 (22.1)	21,306 (22.3)	10,480 (23.2)	4,684 (24.4)	2,095 (27.5)	1,551 (30.1)	b
Model 1	1.09 (1.06-1.11)	1.07 (1.06-1.09)	1.03 (1.01-1.04)	1	1.01 (1.00-1.03)	1.06 (1.04-1.09)	1.14 (1.10-1.18)	1.34 (1.27-1.41)	1.52 (1.43-1.61)	0.73 0.03
Model 2	1.12 (1.09-1.14)	1.11 (1.09-1.12)	1.04 (1.03-1.06)	1.00 (0.98-1.02)	1	1.04 (1.01-1.06)	1.10 (1.06-1.14)	1.28 (1.22-1.35)	1.45 (1.36-1.54)	0.61 0.08
Model 3	1.22 (1.19-1.26)	1.18 (1.16-1.21)	1.09 (1.07-1.11)	1.02 (1.00-1.04)	1	1.02 (0.99-1.05)	1.07 (1.03-1.11)	1.23 (1.16-1.30)	1.36 (1.28-1.45)	0.25 0.52

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Model 4	0.55 (0.53-0.57)	0.69 (0.68-0.71)	0.80 (0.78-0.81)	0.89 (0.87-0.91)	1	1.12 (1.09-1.15)	1.25 (1.20-1.30)	1.52 (1.44-1.60)	1.72 (1.62-1.84)	0.99 <0.001
Model 5	0.56 (0.54-0.58)	0.69 (0.67-0.71)	0.79 (0.77-0.81)	0.89 (0.87-0.91)	1	1.12 (1.08-1.15)	1.26 (1.21-1.32)	1.52 (1.43-1.62)	1.75 (1.63-1.88)	0.98 <0.001
Model 5 [d]	0.44 (0.42-0.46)	0.55 (0.52-0.57)	0.62 (0.60-0.65)	0.70 (0.68-0.73)	0.79 (0.76-0.83)	0.89 (0.85-0.93)	1	1.21 (1.12-1.29)	1.38 (1.28-1.50)	0.98 <0.001
Model 6	0.42 (0.39-0.44)	0.53 (0.50-0.56)	0.62 (0.59-0.65)	0.70 (0.67-0.74)	0.79 (0.75-0.83)	0.89 (0.84-0.94)	1	1.21 (1.12-1.32)	1.40 (1.28-1.54)	0.98 <0.001
Women (n = 662,483)										
Case of Hypertension, n (% in each group)	1,498 (22.0)	9,386 (21.2)	20,256 (18.0)	24,440 (15.2)	20,123 (13.5)	12,889 (13.0)	6,680 (12.6)	2,965 (13.0)	2,039 (14.2)	c
Model 1	1.95 (1.83-2.08)	1.85 (1.79-1.92)	1.52 (1.48-1.57)	1.24 (1.21-1.28)	1.08 (1.05-1.11)	1.03 (1.00-1.06)	1	1.03 (0.98-1.08)	1.14 (1.08-1.20)	-0.86 0.003
Model 2	1.66 (1.55-1.77)	1.62 (1.57-1.68)	1.37 (1.33-1.42)	1.18 (1.15-1.22)	1.06 (1.03-1.10)	1.03 (1.00-1.06)	1	1.03 (0.98-1.08)	1.14 (1.08-1.21)	-0.84 0.005
Model 3	1.49 (1.39-1.59)	1.50 (1.45-1.56)	1.31 (1.27-1.35)	1.16 (1.12-1.19)	1.06 (1.03-1.09)	1.03 (1.00-1.06)	1	1.02 (0.97-1.07)	1.11 (1.05-1.17)	-0.85 0.004
Model 4	0.57 (0.53-0.61)	0.72 (0.70-0.75)	0.79 (0.76-0.81)	0.84 (0.81-0.87)	0.89 (0.86-0.91)	0.96 (0.93-0.99)	1	1.08 (1.03-1.13)	1.22 (1.16-1.29)	0.99 <0.001
Model 5	0.62 (0.58-0.67)	0.73 (0.70-0.76)	0.78 (0.76-0.81)	0.84 (0.81-0.86)	0.88 (0.85-0.91)	0.96 (0.93-1.00)	1	1.06 (1.00-1.11)	1.22 (1.15-1.30)	0.99 <0.001
Model 6	0.63 (0.57-0.69)	0.70 (0.66-0.74)	0.77 (0.74-0.81)	0.81 (0.78-0.85)	0.86 (0.83-0.90)	0.95 (0.91-0.99)	1	1.10 (1.04-1.18)	1.26 (1.17-1.35)	0.98 <0.001

Hypertension was defined as a blood pressure of ≥140/90 mmHg.
The lowest odds ratio was determined as the reference category in Models 1–3.
The correlation coefficients (r) between coded numbers for HDL-C groups (1–9) and their odds ratios were examined by Pearson's correlation test.

Model 1: Unadjusted.
Model 2: Adjusted for age and sex (whole subjects).

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Model 3: Model 2 plus adjustment for smoking, pharmacotherapy (for hypertension, diabetes mellitus, or dyslipidemia), smoking, habitual exercise [e], and daily alcohol consumption.
Model 4: Model 3 plus adjustment for body mass index and serum triglyceride concentration.
Model 5: Model 4 plus adjustment for serum low-density lipoprotein cholesterol and HbA1c. Available *n* = 1,221,930 (668,297 males and 553,633 females).
Model 6: Model 5 when restricted to those without pharmacotherapy for hypertension, diabetes mellitus, or dyslipidemia.
Available *n* = 898,722 (481,257 males and 417,465 females).

[a] $P < 0.0001$, [b] $P = 0.007$, and [c] $P < 0.0001$ for the trend using the Cochran–Armitage test.
[d] Reference HDL-C concentration was replaced with 90–99 mg/dL to compare with females.
[e] Habitual exercise to a light sweat for over 30 min per session twice weekly.

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Table 3. Odds ratios of nine HDL-C concentration categories for hypertension in subjects who hardly consumed alcohol

HDL-C category (mg/dL)	30–39	40–49	50–59	60–69	70–79	80–89	90–99	100-109	≥ 110	Correlation coefficients and P values
Whole subjects, n (% in total n = 595,268)	30,758 (5.2)	100,349 (16.9)	137,781 (23.1)	131,843 (22.1)	96,651 (16.2)	55,464 (9.3)	26,373 (4.4)	10,397 (1.7)	5,652 (0.9)	
Case of Hypertension, n (% in each group)	6,911 (22.5)	21,560 (21.5)	26,542 (19.3)	21,528 (16.3)	14,153 (14.6)	7,579 (13.7)	3,411 (12.9)	1,356 (13.0)	733 (13.0)	[a]
Model 2	1.88 (1.79-1.97)	1.79 (1.72-1.87)	1.55 (1.49-1.61)	1.29 (1.24-1.34)	1.15 (1.11-1.20)	1.07 (1.02-1.12)	1	1.01 (0.94-1.08)	0.97 (0.89-1.06)	-0.94 0.001
Model 3	1.68 (1.60-1.76)	1.62 (1.56-1.69)	1.42 (1.37-1.48)	1.22 (1.17-1.27)	1.12 (1.07-1.16)	1.05 (1.01-1.10)	1	1.01 (0.95-1.09)	0.99 (0.91-1.08)	-0.92 0.001
Model 4	0.64 (0.61-0.67)	0.79 (0.75-0.82)	0.86 (0.82-0.89)	0.88 (0.84-0.91)	0.93 (0.89-0.97)	0.98 (0.94-1.02)	1	1.08 (1.01-1.16)	1.07 (0.98-1.17)	0.96 < 0.001
Model 6 [d]	0.69 (0.65-0.75)	0.79 (0.74-0.84)	0.85 (0.80-0.89)	0.85 (0.80-0.90)	0.92 (0.87-0.97)	0.96 (0.90-1.02)	1	1.10 (1.00-1.21)	1.07 (0.95-1.21)	0.98 < 0.001
Men, n (% in total n = 227,709)	25,865 (11.4)	70,200 (30.8)	66599 (29.2)	38,101 (16.7)	16,939 (7.4)	6,499 (2.9)	2,345 (1.0)	755 (0.3)	406 (0.2)	
Case of Hypertension, n (% in each group)	5,795 (22.4)	14,952 (21.3)	12,772 (19.2)	6,290 (16.5)	2,672 (15.8)	931 (14.3)	335 (14.3)	128 (17.0)	72 (17.7)	[b]
Model 2	1.83 (1.62-2.06)	1.73 (1.54-1.95)	1.50 (1.33-1.69)	1.24 (1.10-1.39)	1.16 (1.02-1.31)	1.02 (0.89-1.16)	1	1.23 (0.98-1.54)	1.27 (0.96-1.68)	-0.77 0.02
Model 3	1.72 (1.52-1.94)	1.64 (1.46-1.85)	1.44 (1.28-1.62)	1.21 (1.07-1.36)	1.14 (1.01-1.29)	1.01 (0.88-1.16)	1	1.22 (0.97-1.52)	1.26 (0.95-1.67)	-0.74 0.02
Model 4	0.65 (0.57-0.73)	0.79 (0.70-0.89)	0.87 (0.77-0.98)	0.88 (0.78-0.99)	0.97 (0.85-1.10)	0.94 (0.82-1.08)	1	1.30 (1.03-1.63)	1.25 (0.94-1.68)	0.98 < 0.001
Model 6 [d]	0.70 (0.59-0.82)	0.80 (0.68-0.94)	0.87 (0.74-1.02)	0.89 (0.76-1.05)	0.99 (0.83-1.16)	0.95 (0.79-1.14)	1	1.24 (0.92-1.69)	1.21 (0.82-1.79)	0.98 < 0.001

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Women, n (% in total n = 367,559)	4,893 (1.3)	30,149 (8.2)	71,182 (19.4)	93,742 (25.5)	79,712 (21.7)	48,965 (13.3)	24,028 (6.5)	9,642 (2.6)	5,246 (1.4)	
Case of Hypertension, n (% in each group)	1,116 (22.8)	6,608 (21.9)	13,770 (19.3)	15,238 (16.3)	11,481 (14.4)	6,648 (13.6)	3,076 (12.8)	1,228 (12.7)	661 (12.6)	[c]
Model 2	1.78 (1.65-1.93)	1.75 (1.67-1.83)	1.53 (1.46-1.59)	1.28 (1.23-1.34)	1.15 (1.10-1.20)	1.08 (1.03-1.13)	1	0.99 (0.92-1.06)	0.95 (0.86-1.04)	-0.95 < 0.001
Model 3	1.55 (1.43-1.68)	1.55 (1.48-1.63)	1.40 (1.34-1.46)	1.22 (1.17-1.27)	1.11 (1.06-1.16)	1.06 (1.01-1.11)	1	1.00 (0.93-1.07)	0.96 (0.88-1.06)	-0.96 < 0.001
Model 4	0.64 (0.59-0.70)	0.78 (0.74-0.83)	0.86 (0.82-0.90)	0.89 (0.85-0.93)	0.93 (0.89-0.98)	0.99 (0.94-1.04)	1	1.06 (0.98-1.14)	1.05 (0.95-1.15)	0.95 < 0.001
Model 6 [d]	0.78 (0.68-0.88)	0.81 (0.75-0.87)	0.85 (0.80-0.91)	0.85 (0.80-0.90)	0.91 (0.86-0.97)	0.97 (0.91-1.03)	1	1.08 (0.98-1.19)	1.04 (0.92-1.18)	0.97 < 0.001

Model 2: Adjusted for age and sex (overall cohort).
Model 3: Model 2 plus adjustment for smoking, pharmacotherapy (for hypertension, diabetes mellitus, or dyslipidemia), smoking, habitual exercise [d], and daily alcohol consumption.
Model 6: Model 3 plus adjustment for body mass index, serum triglyceride, serum low-density lipoprotein cholesterol, and HbA1c in subjects without pharmacotherapy (for hypertension, diabetes mellitus, or dyslipidemia). Total available: n = 352,981 (131,735 males and 221,246 females).

[a] $P < 0.0001$, [b] $P < 0.0001$, and [c] $P < 0.0001$ for the trend using the Cochran–Armitage test.
[d] Habitual exercise to a light sweat for over 30 min per session twice weekly.

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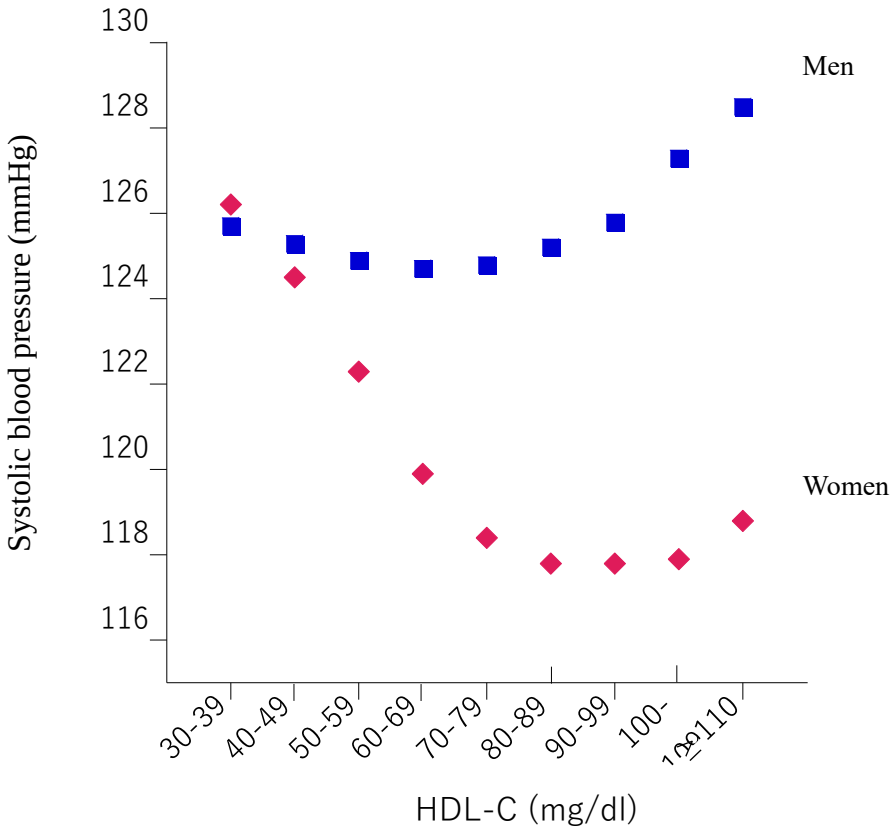
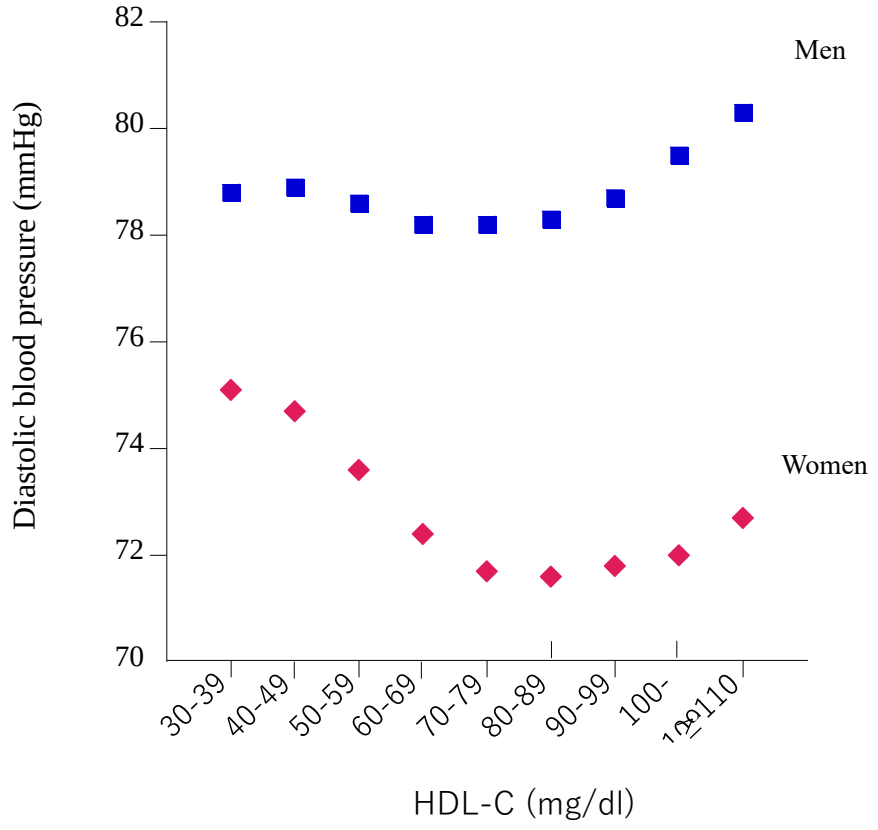
Figure 1





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