ORIGINAL RESEARCH

Dyslipidemia and the Risk of Developing Hypertension in a Working-Age Male Population

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***Background*—**Hypertension is one of the main comorbidities associated with dyslipidemia. This study aimed to examine the extent to which dyslipidemia increases the risk of developing hypertension in a Japanese working-age male population.

***Methods and Results*—**We analyzed data from 14 215 nonhypertensive male workers (age 38±9 years) who underwent annual medical checkups. Subjects were followed up for a median of 4 years to determine new-onset hypertension, defined as blood pressure (BP) ≥140/90 mm Hg or use of antihypertensive medication. The associations between serum lipid levels and development of hypertension were examined. During the follow-up period, 1483 subjects developed hypertension. After adjusting for age, body mass index, impaired fasting glucose/diabetes, baseline BP category, alcohol intake, smoking, exercise, and parental history of hypertension, subjects with a total cholesterol (TC) level ≥222 mg/dL were at a significantly increased risk of developing hypertension (hazard ratio: 1.28; 95% CI: 1.06–1.56) compared to subjects with a TC level ≤167 mg/dL. Similar results were observed for subjects with high low-density lipoprotein cholesterol (LDLC) and non-high-density lipoprotein cholesterol (HDLC) levels. A U-shaped relationship was found between HDLC level and risk of hypertension; compared to the third quintile, the multiadjusted hazard ratio was 1.22 (95% CI: 1.03–1.43) in the lowest quintile and 1.34 (95% CI: 1.12–1.60) in the highest quintile.

***Conclusions*—**Elevated serum levels of TC, LDLC, and non-HDLC were associated with an increased risk of hypertension in working-age Japanese men. For HDLC, risk of hypertension was increased at both low and high levels. **(*J Am Heart Assoc*. 2016;5:e003053 doi: 10.1161/JAHA.115.003053)**

Key Words: cohort study • hypertension • lipids • prediction • risk factor

Hypertension and dyslipidemia are important risk factors for cardiovascular disease. Coexistence of hypertension and dyslipidemia is often observed in daily clinical practice, and this empirical observation is consistent with baseline characteristics of clinical study participants.[1–4] Population-based epidemiological studies have also reported that gradual increases in blood pressure (BP) or prevalence of hypertension are associated with increases in blood lipid levels.[5–8] One possible explanation for these relationships is that hypertension and dyslipidemia share common pathophysiological etiologies, such as obesity and the resulting dysregulation of adipocytokine release from adipose tissue.[9] Furthermore, dyslipidemia adversely affects functional and structural arterial properties and promotes atherosclerosis.[10–12] These changes may impair BP regulation, which, in turn, predisposes individuals with dyslipidemia to development of hypertension.

From an epidemiological perspective, a number of cohort studies have strongly indicated a causal relationship between dyslipidemia and risk of future development of hypertension.[13–20] However, with a single exception,[14] all of these studies have been conducted in non-Asian populations. Therefore, to accumulate further evidence in Asian populations, this study was designed to examine whether risk of hypertension is increased in individuals with dyslipidemia in working-age Japanese men.

Methods

Study Population

This study was conducted at an electrical equipment manufacturing company in Japan. Under the Industrial Safety and

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Health Law of Japan, all employers are required to conduct medical checkups of all employees at least once a year. We analyzed data from the company's medical checkup database. This study was approved by the Ethics Committee of Nippon Medical School (Tokyo, Japan) and was conducted in accord with the principles of the Declaration of Helsinki. Because there was no personal information in the database, the requirement for informed consent was waived by the ethics committee.

A total of 17 885 male workers underwent an annual medical checkup in 2008 (baseline examination). Among them, subjects with hypertension (n=2043), defined as a systolic BP ≥140 mm Hg, a diastolic BP ≥90 mm Hg, or use of antihypertensive medication, those with a history of cardiovascular disease (n=109) or malignancy (n=113), those who had received medication for dyslipidemia (n=348), and those who did not provide the full amount of information required (n=460) were excluded from the analysis. Subjects who underwent baseline examinations but who did not undergo any follow-up medical checkups (between 2009 and 2012) were also excluded (n=133). Additionally, subjects who initiated medication for dyslipidemia during the follow-up period were excluded (n=464) because this might have affected BP levels.[21] Finally, 14 215 subjects (age range: 19–63 years) were included in the analysis.

Baseline Examinations

All participants underwent anthropometric and BP measurements, as well as blood sampling. Subjects' height and weight were measured, and body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Obesity was defined as a BMI ≥25.0 kg/m^2.

Table 1. Baseline Characteristics of the Study Population, Overall and According to the Quintile of Serum TC Levels

Variables	Overall (n=14 215)	Quintile of TC					*P* Value*
		First (n=2889)	Second (n=2863)	Third (n=2830)	Fourth (n=2879)	Fifth (n=2754)	
TC range, mg/dL	76 to 369	76 to 167	168 to 185	186 to 201	202 to 221	222 to 369	
Age, y	38±9	34±8	37±9	39±9	41±8	42±8	<0.001
Body mass index, kg/m^2	22.7±2.9	21.6±2.6	22.3±2.8	22.6±2.8	23.2±2.8	23.6±2.9	<0.001
Obesity, n (%)	2550 (17.9)	257 (8.9)	414 (14.5)	489 (17.3)	638 (22.2)	752 (27.3)	<0.001
Systolic BP, mm Hg	118±11	113±11	115±11	115±11	117±11	118±11	<0.001
Diastolic BP, mm Hg	70±9	67±8	69±9	70±9	71±9	73±9	<0.001
Optimal BP, n (%)	8626 (60.7)	2101 (72.7)	1805 (63.0)	1749 (61.8)	1606 (55.8)	1365 (49.6)	<0.001
Normal BP, n (%)	3375 (23.7)	548 (19.0)	668 (23.3)	670 (23.7)	739 (25.7)	750 (27.2)	
High-normal BP, n (%)	2214 (15.6)	240 (8.3)	390 (13.6)	411 (14.5)	534 (18.5)	639 (23.2)	
TC, mg/dL	195±32	152±12	177±5	193±5	211±6	242±18	<0.001
TG†, mg/dL	82 (58, 121)	61 (46, 83)	72 (54, 99)	84 (61, 117)	94 (68, 133)	115 (82, 165)	<0.001
LDLC‡, mg/dL	114±29	80±14	99±12	112±13	127±14	153±21	<0.001
HDLC, mg/dL	62±16	58±11	61±13	62±14	62±15	62±16	<0.001
Non-HDLC, mg/dL	134±34	95±15	116±14	132±15	149±16	180±25	<0.001
Fasting plasma glucose, mg/dL	92±14	87±8	89±8	90±10	91±11	92±14	<0.001
HbA1c, %	5.3±0.5	5.2±0.3	5.2±0.4	5.3±0.4	5.3±0.4	5.4±0.5	<0.001
Medication for diabetes, n (%)	54 (0.4)	8 (0.3)	10 (0.3)	12 (0.4)	7 (0.2)	17 (0.6)	0.16
Impaired fasting glucose/diabetes, n (%)	394 (2.8)	40 (1.4)	46 (1.6)	79 (2.8)	97 (3.4)	132 (4.8)	<0.001
Current smoker, n (%)	4313 (30.3)	892 (30.9)	870 (30.4)	819 (28.9)	845 (29.4)	887 (32.2)	0.064
Excess alcohol intake, n (%)	2321 (16.3)	360 (12.5)	440 (15.4)	476 (16.8)	510 (17.7)	535 (19.4)	<0.001
Regular exercise, n (%)	3334 (23.5)	658 (22.8)	701 (24.5)	638 (22.5)	688 (23.9)	649 (23.6)	0.40
Parental history of hypertension, n (%)	3040 (21.4)	529 (18.3)	571 (19.9)	624 (22.0)	674 (23.4)	642 (23.3)	<0.001

BP indicates blood pressure; HbA1c, glycated hemoglobin; HDLC indicates high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

*ANOVA or chi-square test, as appropriate, among the quintile of serum TC levels.

†Median (interquartile range).

‡Calculated using Friedewald's formula in 14 102 subjects with the TG level <400 mg/dL.

Right brachial BP was measured by well-trained staff members while the subject was seated, after at least 5 minutes of rest, using a mercury sphygmomanometer with a cuff selected in accord with right-arm circumference. The first and fifth Korotkoff sounds were recorded to determine systolic and diastolic BP, respectively. BP was measured twice with a 1-minute interval between measurements. BP was categorized as optimal (systolic BP <120 mm Hg and diastolic BP <80 mm Hg), normal (systolic BP 120–129 mm Hg or diastolic BP 80–84 mm Hg), and high normal (systolic BP 130–139 mm Hg or diastolic BP 85–89 mm Hg), according to the guidelines for the management of hypertension in Japan and in Europe.[22,23] The measurement that provided the lower BP category was used for analysis. If the BP category was the same for both measurements, the recording that showed the lower systolic BP was used.

Blood samples were obtained from the antecubital vein after ≥8 hours of fasting. Standard enzymatic methods were used to measure serum total cholesterol (TC), triglycerides (TG), and plasma glucose levels. Serum high-density lipoprotein (HDL) cholesterol (HDLC) levels were measured using the direct method. Serum low-density lipoprotein cholesterol (LDLC) levels were calculated using the Friedewald formula in subjects with TG levels <400 mg/dL (n=14 102). Serum non-HDLC levels were calculated as TC minus HDLC levels. Glycated hemoglobin (HbA1c) levels were measured using the latex coagulating method. HbA1c levels were recorded in the form used by the Japan Diabetic Society (JDS) and were converted to National Glycohemoglobin Standardization Program (NGSP) values in accord with the following equation[24]: NGSP HbA1c (%)=1.02×JDS HbA1c (%)+0.25. Impaired fasting glucose/diabetes was defined as a fasting plasma glucose level of ≥110 mg/dL, an HbA1c level of ≥6.5%, or the current use of glucose-lowering medication.

A self-reported questionnaire was used to collect data regarding subjects' parental history of hypertension and lifestyle factors, including smoking status, exercise habits, and alcohol intake. Smoking status was categorized as either current smoking or nonsmoking. Current smoking was defined as cigarette consumption on a regular basis (at least once-daily) at the time of the examination. Regular exercise was defined as the performance of continuous

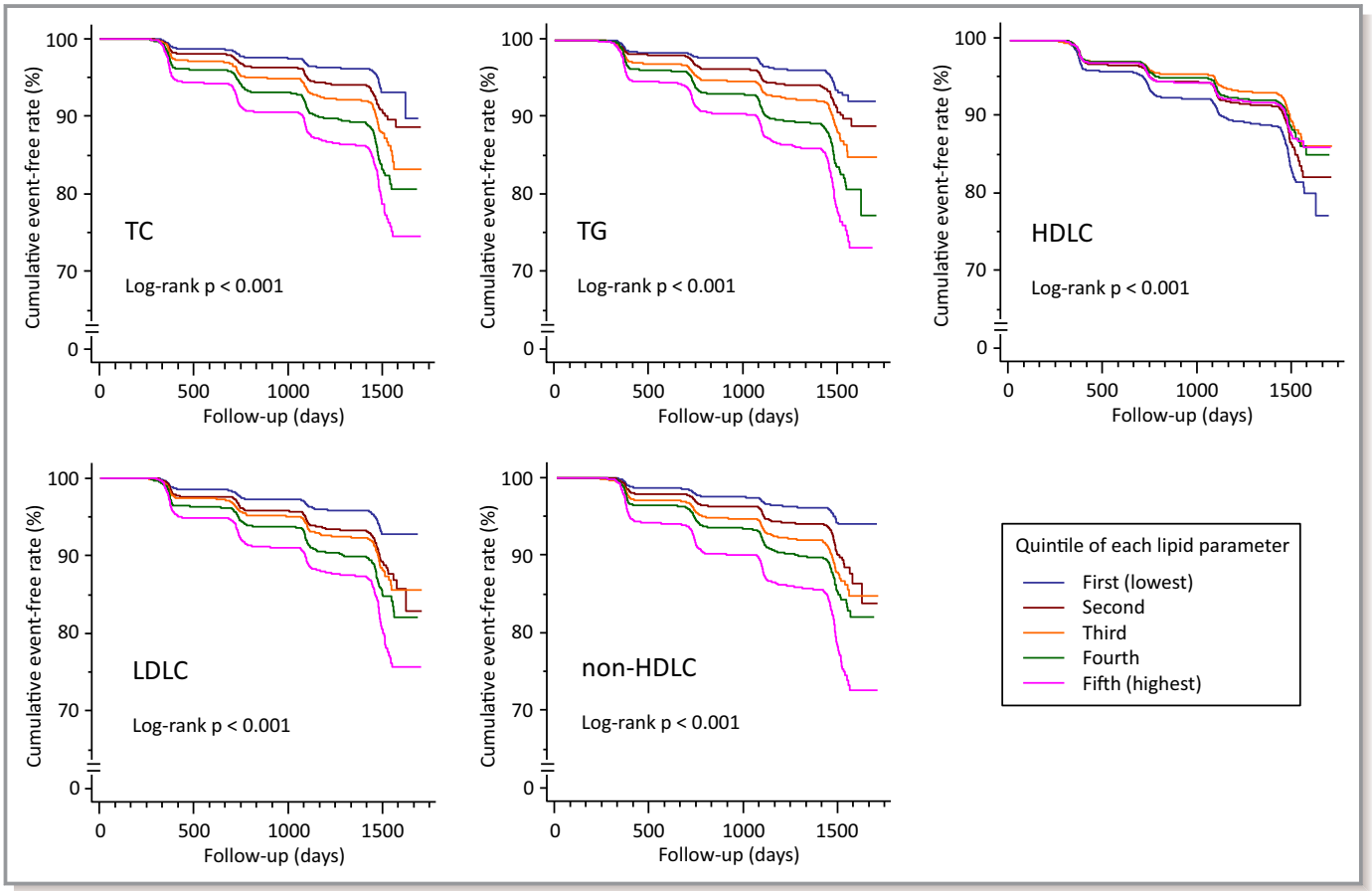

Figure 1. Kaplan–Meier curve for cumulative hypertension-free survival rate by quintile for each lipid parameter. HDLC indicates high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

exercise at an intensity sufficient to break a sweat for at least 30 minutes ≥2 days per week for at least 1 year. Excessive alcohol intake was defined as alcohol intake of ≥6 days per week.

Follow-up Examinations

The outcome measure of this study was the time until the development of hypertension. Subjects were followed up for a median of 4.0 years (range, 0.3–4.7) using annual medical checkup data, including BP values and information regarding initiation of antihypertensive medication, collected between 2009 and 2012. During a total follow-up of 53 285 person-years, 1483 subjects developed hypertension. Of the remaining subjects, 12 004 were censored at completion of the 4-year follow-up period, and 728 were censored before completion of the 4-year follow-up period. Approximately 93% of subjects (n=13 262) completed BP measurements at each annual medical checkup until they were censored or developed hypertension.

Statistical Analysis

All statistical tests were performed using IBM SPSS Statistics software (version 22; IBM Japan, Tokyo, Japan). Continuous variables with or without a skewed distribution are expressed as the median (interquartile range) or mean±SD, respectively. Categorical variables are expressed as the number (%). Between-group comparisons were conducted using analysis of variance, the χ^2 test, or the Kruskal–Wallis test, as appropriate. To examine risk of developing hypertension associated with each lipid parameter, age- and multiadjusted Cox proportional hazards models were used to calculate the hazard ratio (HR) and the corresponding 95% CI. For Cox analyses, each lipid parameter was divided into quintiles and dichotomized according to the clinical cut-off points defined by the Japan Atherosclerosis Society[25]: high TC (≥220 mg/dL); high LDLC (≥140 mg/dL); high TG (≥150 mg/dL); low HDLC (<40 mg/dL); and high non-HDLC (≥170 mg/dL). The covariates used in the multiadjusted Cox analysis were

Table 2. Association Between Quintile of Each Lipid Parameter and the Risk of Developing Hypertension

Lipid Parameters and Models	Quintile of Each Lipid Parameter					*P* Value for Trend
	Lowest	Second	Third	Fourth	Highest	
TC, mg/dL	76 to 167	168 to 185	186 to 201	202 to 221	222 to 369	
No. of cases/at risk	139/2889	215/2863	278/2830	384/2879	467/2754	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.29 (1.04–1.60)	1.52 (1.24–1.87)	1.87 (1.53–2.28)	2.20 (1.81–2.68)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.00 (0.81–1.24)	1.16 (0.95–1.43)	1.19 (0.97–1.45)	1.28 (1.06–1.56)	0.001
TG, mg/dL	14 to 54	55 to 72	73 to 95	96 to 133	134 to 1321	
No. of cases/at risk	142/2917	199/2775	276/2924	368/2768	498/2831	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.36 (1.10–1.69)	1.62 (1.32–1.98)	2.15 (1.77–2.62)	2.72 (2.25–3.28)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.08 (0.87–1.34)	1.17 (0.96–1.44)	1.25 (1.03–1.53)	1.22 (0.99–1.49)	0.027
HDLC, mg/dL	23 to 49	50 to 56	57 to 63	64 to 72	73 to 162	
No. of cases/at risk	411/3060	310/2889	246/2884	253/2710	263/2672	
Age-adjusted HR (95% CI)	1.00 (Reference)	0.84 (0.73–0.98)	0.67 (0.57–0.78)	0.74 (0.63–0.86)	0.74 (0.63–0.86)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	0.99 (0.85–1.15)	0.82 (0.70–0.97)	0.99 (0.84–1.17)	1.10 (0.92–1.30)	0.52
LDLC†, mg/dL	20 to 89	90 to 105	106 to 119	120 to 137	138 to 301	
No. of cases/at risk	151/2853	254/2952	254/2689	341/2794	445/2814	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.43 (1.17–1.75)	1.35 (1.10–1.65)	1.63 (1.34–1.97)	1.97 (1.63–2.38)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.17 (0.96–1.44)	1.06 (0.86–1.30)	1.16 (0.95–1.41)	1.27 (1.05–1.53)	0.022
Non-HDLC, mg/dL	25 to 105	106 to 123	124 to 140	141 to 162	163 to 334	
No. of cases/at risk	134/2955	217/2850	278/2738	359/2924	495/2748	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.42 (1.15–1.77)	1.65 (1.34–2.03)	1.84 (1.50–2.25)	2.56 (2.11–3.11)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.23 (0.99–1.52)	1.18 (0.96–1.46)	1.17 (0.96–1.44)	1.33 (1.09–1.63)	0.018

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

*Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

†Calculated using Friedewald's formula in 14 102 subjects with the TG level <400 mg/dL.

age, BMI, baseline BP category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension, in addition to each lipid parameter. To ensure that subjects with hypertension were excluded at the baseline examination, the multiadjusted Cox analysis was repeated according to the quintile of each lipid parameter after excluding 439 subjects who developed hypertension by the first annual follow-up. Finally, multiadjusted Cox analyses stratified by age (<40 or ≥40 years), systolic BP (<120 or ≥120 mm Hg), diastolic BP (<80 or ≥80 mm Hg), impaired fasting glucose/diabetes (yes or no), and obesity (yes or no) were performed for the clinical cut-off points for each lipid parameter. We visually examined the plot of log-minus-log survival versus log of survival time and confirmed that the proportional hazard assumption was valid. All statistical tests were 2-sided, and $P<0.05$ was considered statistically significant.

Results

Overall, the mean age of the study population was 38±9 years. Baseline characteristics in the entire population and for the quintiles of serum TC level are presented in Table 1. All variables, except for prevalence of medication for diabetes, current smoking, and regular exercise, were significantly different among the quintiles of TC.

Figure 1 shows the Kaplan–Meier curve for the cumulative hypertension-free survival rate during the follow-up period by quintile for each lipid parameter. Subjects in the highest quintile of all lipid parameters, except HDLC, had the lowest cumulative hypertension-free survival rate. On the other hand, subjects in the lowest quintile of HDLC had the lowest cumulative hypertension-free survival rate.

Table 2 shows the HRs for developing hypertension associated with each lipid parameter. In the age-adjusted model, compared to subjects in the lowest quintiles, those

Table 3. Association Between Quintile of Each Lipid Parameter and the Risk of Developing Hypertension After Excluding Subjects Who Developed Hypertension by the First Annual Follow-up

Lipid Parameters and Models	Quintile of Each Lipid Parameter					*P* Value for Trend
	Lowest	Second	Third	Fourth	Highest	
TC, mg/dL	76 to 167	168 to 185	186 to 201	202 to 220	221 to 369	
No. of cases/at risk	103/2853	160/2808	199/2751	261/2654	321/2710	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.32 (1.03–1.69)	1.51 (1.19–1.92)	1.85 (1.47–2.33)	2.04 (1.63–2.57)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.03 (0.80–1.32)	1.17 (0.92–1.49)	1.19 (0.94–1.51)	1.24 (0.82–1.55)	0.025
TG, mg/dL	14 to 54	55 to 72	73 to 94	95 to 132	133 to 1321	
No. of cases/at risk	98/2873	148/2724	182/2740	263/2712	353/2727	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.48 (1.15–1.92)	1.63 (1.28–2.09)	2.24 (1.77–2.83)	2.85 (2.28–3.57)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.20 (0.93–1.55)	1.20 (0.94–1.54)	1.35 (1.06–1.71)	1.32 (1.04–1.68)	0.021
HDLC, mg/dL	23 to 49	50 to 56	57 to 63	64 to 72	73 to 162	
No. of cases/at risk	291/2940	221/2800	166/2804	180/2637	186/2595	
Age-adjusted HR (95% CI)	1.00 (Reference)	0.84 (0.71–1.00)	0.62 (0.52–0.76)	0.74 (0.61–0.89)	0.73 (0.61–0.88)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	0.99 (0.83–1.18)	0.77 (0.63–0.93)	0.98 (0.83–1.18)	1.10 (0.90–1.35)	0.66
LDLC†, mg/dL	20 to 89	90 to 104	105 to 119	120 to 137	138 to 301	
No. of cases/at risk	110/2812	168/2704	201/2798	239/2692	302/2671	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.41 (1.11–1.79)	1.41 (1.12–1.78)	1.61 (1.28–2.02)	1.91 (1.53–2.38)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.16 (0.91–1.48)	1.12 (0.89–1.42)	1.17 (0.93–1.47)	1.26 (1.004–1.58)	0.068
Non-HDLC, mg/dL	25 to 104	105 to 122	123 to 140	141 to 161	162 to 334	
No. of cases/at risk	85/2782	158/2766	210/2819	247/2709	344/2700	
Age-adjusted HR (95% CI)	1.00 (Reference)	1.59 (1.22–2.07)	1.82 (1.41–2.35)	2.04 (1.59–2.62)	2.66 (2.09–3.40)	<0.001
Multiadjusted* HR (95% CI)	1.00 (Reference)	1.34 (1.02–1.74)	1.30 (1.01–1.68)	1.30 (1.01–1.68)	1.40 (1.09–1.80)	0.046

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

*Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

†Calculated using Friedewald's formula in 13 677 subjects with the TG level <400 mg/dL.

with higher TC, TG, LDLC, and non-HDLC levels showed a significantly increased risk of hypertension. For HDLC, higher serum levels were associated with a significantly reduced risk of hypertension. In the multiadjusted model, subjects with TC levels in the highest quintile had a significantly higher HR (1.28; 95% CI: 1.06–1.56) compared to those in the lowest quintile. Similar results were observed for subjects in the highest quintiles of LDLC (HR, 1.27; 95% CI: 1.05–1.53) and non-HDLC (HR, 1.33; 95% CI: 1.09–1.63). Subjects in the fourth quintile of TG had a significantly higher HR compared to those in the lowest quintile, but those in the highest quintile did not. Intriguingly, the HR for subjects in the third quintile of HDLC was significantly lower than those in the lowest quintile, but the HR for subjects in the highest quintile appeared to be higher than both groups, suggesting a U-shaped relationship. The results of the sensitivity analyses after excluding subjects who developed hypertension by the first annual follow-up are presented in Table 3. The results were similar to those obtained in the overall analyses.

To investigate the U-shaped relationship between HDLC levels and the risk of hypertension further, the multiadjusted Cox analysis was performed using the third quintile of HDLC as the reference group. As shown in Figure 2, a clear U-shaped relationship was found between the HDLC level and risk of developing hypertension, with significantly increased HRs for subjects in all 4 quintiles compared to the reference group. Even after excluding subjects who developed hypertension by the first annual follow-up, the U-shaped relationship remained significant (ie, when compared to the third quintile, the HR [95% CI] in the lowest, second, fourth, and highest quintile of HDLC was 1.31 [1.07–1.59], 1.29 [1.06–1.58], 1.29 [1.04–1.59], and 1.44 [1.16–1.78], respectively).

Table 4 shows the age- and multiadjusted HRs for developing hypertension when subjects were dichotomized according to the clinical cut-off point for each lipid parameter. In the age-adjusted model, all of the lipid parameters were associated with a significantly increased risk of hypertension. In the multiadjusted model, high TC, high LDLC, and high non-HDLC increased the risk of hypertension with an HR (95% CI) of 1.16 (1.04–1.30), 1.13 (1.01–1.27), and 1.20 (1.06–1.35), respectively.

Results of the subgroup analysis are shown in Table 5. High TC, high LDLC, and high non-HDLC levels were generally associated with an increased risk of hypertension in subjects age <40 years, those with systolic BP ≥120 mm Hg, those without impaired fasting glucose/diabetes, and those with obesity. In contrast, when subjects were stratified by diastolic BP, the association of high TC, high LDLC, and high non-HDLC levels with hypertension was not consistent. Low HDLC levels were only associated with an increased risk of hypertension in subjects with impaired fasting glucose/diabetes. High TG was not associated with a significant risk of hypertension in any of the subgroup analyses.

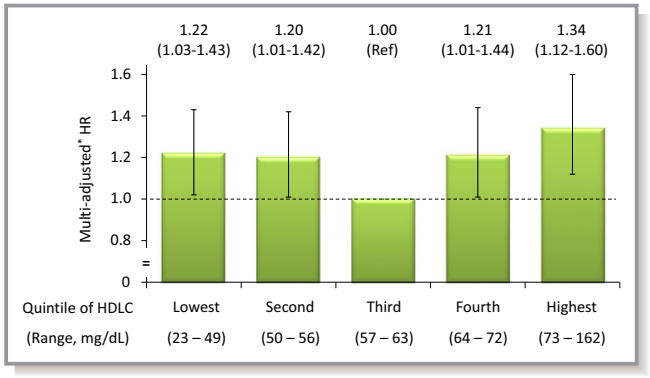

Figure 2. Relationship between high-density lipoprotein cholesterol (HDLC) levels and risk of hypertension. The third quintile of HDLC is set as the reference category. The hazard ratio (HR) was significantly higher at both low and high HDLC levels. *Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

Discussion

This cohort study found that subjects in the highest quintiles of TC, LDLC, and non-HDLC significantly increased the risk of developing hypertension in working-age Japanese men. These significant associations were retained when clinical cut-off points were used for the diagnosis of high TC, high LDLC, and high non-HDLC. In the subgroup analysis, the associated risk appeared to be most pronounced in subjects age <40 years, those with systolic BP ≥120 mm Hg, those with obesity, or those without impaired fasting glucose/diabetes. Intriguingly, the U-shaped relationship was found between HDLC levels

Table 4. Association Between Clinical Cut-off Point of Each Lipid Parameter and Risk of Developing Hypertension in the Overall Study Population

Lipid Parameters	Age-Adjusted HR (95% CI)	Multiadjusted* HR (95% CI)
High TC (≥220 mg/dL)	1.49 (1.34–1.66)	1.16 (1.04–1.30)
High TG (≥150 mg/dL)	1.77 (1.57–1.98)	1.11 (0.98–1.25)
Low HDLC (<40 mg/dL)	1.30 (1.03–1.65)	1.01 (0.80–1.29)
High LDLC (≥140 mg/dL)	1.40 (1.25–1.57)	1.13 (1.01–1.27)
High non-HDLC (≥170 mg/dL)	1.70 (1.52–1.92)	1.20 (1.06–1.35)

HDLC indicates high-density lipoprotein cholesterol; HR, hazard ratio; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
*Adjusted for age, body mass index, baseline blood pressure category, impaired fasting glucose/diabetes, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

Table 5. Association Between Clinical Cut-off Point of Each Lipid Parameter and the Risk of Developing Hypertension, Stratified by Age, Systolic BP, Diastolic BP, IFG/DM, or Obesity

	High TC		High TG		Low HDLC		High LDLC		High non-HDLC	
	HR*	95% CI	HR*	95% CI	HR*	95% CI	HR*	95% CI	HR*	95% CI
Age, y										
<40	1.36	1.08 to 1.71	1.13	0.87 to 1.45	0.84	0.53 to 1.35	1.30	1.02 to 1.66	1.38	1.08 to 1.77
≥40	1.09	0.96 to 1.23	1.09	0.95 to 1.25	1.05	0.79 to 1.39	1.07	0.93 to 1.22	1.13	0.99 to 1.30
Systolic BP, mm Hg										
<120	1.10	0.85 to 1.44	1.23	0.92 to 1.65	0.68	0.36 to 1.29	1.10	0.83 to 1.46	1.17	0.87 to 1.56
≥120	1.17	1.04 to 1.32	1.08	0.95 to 1.24	1.09	0.84 to 1.41	1.14	1.001 to 1.29	1.20	1.06 to 1.37
Diastolic BP, mm Hg										
<80	1.20	1.01 to 1.44	1.20	0.98 to 1.46	0.85	0.55 to 1.30	1.19	0.99 to 1.44	1.15	0.94 to 1.40
≥80	1.10	0.96 to 1.27	1.03	0.89 to 1.20	1.05	0.78 to 1.40	1.08	0.93 to 1.25	1.20	1.04 to 1.39
IFG/DM†										
No	1.18	1.05 to 1.32	1.07	0.94 to 1.21	0.87	0.66 to 1.13	1.17	1.04 to 1.32	1.20	1.07 to 1.36
Yes	1.02	0.67 to 1.54	1.45	0.97 to 2.18	2.64	1.44 to 4.84	0.76	0.48 to 1.20	1.14	0.75 to 1.74
Obesity‡										
No	1.10	0.95 to 1.27	1.13	0.96 to 1.33	1.01	0.67 to 1.52	1.09	0.93 to 1.27	1.10	0.93 to 1.29
Yes	1.24	1.04 to 1.47	1.08	0.91 to 1.29	0.99	0.74 to 1.34	1.18	0.99 to 1.41	1.32	1.11 to 1.57

BP indicates blood pressure; HbA1c, glycated hemoglobin; HDLC, high-density lipoprotein cholesterol; HR, hazard ratio; IFG/DM, impaired fasting glucose/diabetes; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

*Adjusted for age, body mass index, baseline BP category, IFG/DM, excessive alcohol intake, current smoking, regular exercise, and parental history of hypertension.

†Defined as fasting plasma glucose ≥110 mg/dL, HbA1c ≥6.5%, or current use of glucose-lowering medication.

‡Defined as body mass index ≥25.0 kg/m^2.

and the risk of developing hypertension. With the exception of 1 study conducted in China,[14] all of the previous studies that have reported a longitudinal association between lipid parameters and the risk of developing hypertension were conducted in non-Asian populations.[13,15–20] Therefore, our study provides important evidence that dyslipidemia is significantly associated with an increased risk of developing hypertension in an Asian population.

There could be several pathophysiological mechanisms involved in the association between dyslipidemia and increased risk of hypertension. First, dyslipidemia may impair endothelial function,[10,11] which may consequently disrupt production of nitric oxide and regulation of BP. Second, dyslipidemia may predispose individuals to development of hypertension by reducing baroreflex sensitivity.[26,27] The baroreflex is the regulation of BP by a negative feedback loop; baroreceptors, located in blood vessels, activate the parasympathetic nervous system, which counteracts any changes in BP. Third, dyslipidemia decreases the distensibility of large elastic arteries.[12] This decrease may reduce the windkessel effect,[28] which, in turn, increases BP, in particular, systolic BP. Last, physical inactivity and a high-fat diet promote obesity and dyslipidemia. In obese individuals, adipose tissue excessively secretes adipocytokines, such as leptin, thereby inducing insulin resistance and subsequent activation of the sympathetic nervous system and the renin-angiotensin system.[9] These biological changes may, in turn, raise BP. In the present study, the multivariate analyses were adjusted for several potential confounding factors, including BMI. However, other adiposity-related residual confounders may be involved in the association between dyslipidemia and risk of hypertension.

Our findings of an association between low HDLC levels and an increased risk of hypertension are consistent with previous reports.[14,16,18–20] However, our finding that risk of hypertension was also increased with high HDLC levels was unexpected. One possible explanation for this finding is the involvement of dysfunctional HDL in our study population. The main function of HDL is to promote reverse cholesterol transport from macrophages. A cross-sectional clinical study demonstrated an inverse relationship between the cholesterol efflux capacity of HDL, evaluated by the function of ATP-binding cassette transporters, and the intima-media thickness of the carotid artery and prevalence of coronary artery disease.[29] The Dallas Heart Study showed that a higher cholesterol efflux capacity of HDL predicts a lower risk of cardiovascular disease.[30] These results suggest that dysfunctional HDL loses its antiatherogenic action. Rather, an in vivo

and in vitro study indicated that dysfunctional HDL is proatherogenic.[31] Heritable cholesteryl ester transfer protein (CETP) deficiency is often reported in Japanese people with increased circulating HDLC levels[31,32]; CETP deficiency may account for ≈27% and 32% of subjects with HDLC ≥60 and ≥80 mg/dL, respectively.[32] In our study, the minimum HDLC level in the highest quintile was 73 mg/dL, suggesting that a certain proportion of the subjects in this group may have had CETP deficiency. Importantly, although it remains a matter of debate, the function of HDL is reportedly impaired in subjects with CETP deficiency.[33] These findings are supported by the results of the Framingham Heart Study, which showed circulating CETP activity to be inversely associated with risk of incident cardiovascular disease.[34] Taken together, we speculate that a certain number of subjects with high HDLC levels in our study had dysfunctional, proatherogenic HDL, which impairs functional and structural arterial properties and thus increases risk of hypertension.

From a clinical perspective, our findings suggest that the association between dyslipidemia and risk of cardiovascular disease may be partly explained by a gradual increase in BP over time. Therefore, health care providers should be attentive to the trajectory of BP, and professional support should be provided to prevent or delay the development of hypertension in patients with dyslipidemia.

This study has several potential limitations. First, our study population included only working-age Japanese men. Therefore, it is unknown whether our results can be extrapolated to women, the elderly, or other ethnic groups. Second, the follow-up duration in our study (median of 4 years) was short compared to previous studies (5–10 years or more).[13–20] Some of the equivocal findings in this study, such as the association between TG levels and risk of hypertension, may be attributable to this limitation. Third, because this was an observational study, the possibility of a reverse association between dyslipidemia and hypertension could not be ruled out. However, in the sensitivity analysis excluding subjects who developed hypertension by the first annual follow-up, the association between dyslipidemia and risk of developing hypertension remained significant. This would reduce the possibility of the reverse association. Fourth, although the duration of exposure for dyslipidemia, as well as other risk factors, may be associated with the risk of developing hypertension, these data were not available in this study. Finally, the serum lipid levels were measured on a single day. Therefore, the intraindividual variation of lipid profiles was not taken into consideration in this study.

In conclusion, our findings show that elevated serum TC, LDLC, and non-HDLC levels were associated with an increased risk of hypertension in working-age Japanese men. Furthermore, risk of hypertension was increased at both low and high HDLC levels. Further studies are needed to confirm this U-shaped relationship. Overall, our results may contribute to the accumulation of evidence that dyslipidemia increases risk of hypertension in Asian populations. From a clinical perspective, the importance of strict BP management in patients with dyslipidemia was indicated. Clinical trials that examine whether treatment of dyslipidemia reduces the risk of developing hypertension are needed to verify the results of this observational study.

Disclosures

None.

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