血圧の脳卒中などに及ぼす健康影響(NIPPON DATA80)

NIPPON DATA80 Research Group ： J.Human Hypertens. 17:851-857,2003

１．研究目的と方法

血圧が脳卒中をはじめとする循環器疾患の重要な危険因子であることは広く知られているが、第６次改訂の高血圧区分と循環器疾患死亡や総死亡との関連に関する研究は我が国ではほとんど行われていない。我々は1980年の循環器疾患基礎調査受診者を対象としたコホート研究（NIPPON DATA80）のデータセットを用いて、血圧の健康影響を高血圧区分別に高血圧の循環器疾患や総死亡に及ぼす影響の強さについて検討した。

本研究は遡りコホート研究の手法を用いて1994年に追跡調査を実施し、対象者の92%の生命予後と死因を明らかにして解析したものである。対象者の観察人年は男性で53948人年、女性で70932人年で、観察期間中の死亡者数は1327名であった。対象者を高血圧区分に区分する際、降圧剤を服用していないものは血圧成績をそのまま用いて分類した。降圧剤服用中のものは検診受診時の最大最小血圧が140/90未満の場合には軽症高血圧区分としてあつかい、それ以上の血圧値を持つ服用者はそれぞれの高血圧区分に含めて解析を行った。

２．結果

表に高血圧区分別の脳卒中、心疾患、循環器疾患、総死亡の年齢を調整した相対危険度を示した。男性では高血圧区分が高くなるほど、脳卒中、心疾患、循環器疾患および総死亡の相対危険度が有意に高くなった。女性でも心疾患死亡をのぞいて有意に相対危険度が高くなった。以上から、血圧が高いことは脳卒中や心疾患などの循環器疾患の危険因子であることが確認されたとともに、総死亡にも強く影響する因子であることが明らかとなった。表には示さないが、関連が有意となった疾患への高血圧の影響はcoxの比例ハザードモデルを用いた重回帰分析（肥満度、飲酒習慣、喫煙、総コレステロール値、随時血糖値を調整）の結果でも有意であったことから、多の危険因子とは独立して寄与していると考えられる。

Coxの比例ハザードモデルによる他の循環器疾患危険因子を調整した高血圧区分の回帰係数を用いて、最適血圧を基準とし高血圧区分別の脳卒中の相対危険度を求め、当該区分の有病率から脳卒中による過剰死亡割合を求めた。過剰死亡割合とはその高血圧区分に属することによる脳卒中死亡の最適血圧に比較した増加割合を計算によって求めたものである。最適血圧区分でないことによる脳卒中の過剰死亡割合は男性で130%、女性で42%であり男性の方が多く観察された。この理由として男性の血圧が女性より高いことを反映していると考えられた。

高血圧区分がもっとも高い群で脳卒中の多因子調整相対危険度はもっとも高くなったが、対象者にしめる割合（有病率）が少ないために、過剰死亡割合は男性で22%、女性で7%に

とどまった。逆に軽症高血圧区分では脳卒中死亡の相対危険度は比較的小さくなるが、有病率が各区分でもっとも高くために、過剰死亡率も男性では48%、女性でも18%ともっとも高い値を示した。

3. 考察と結論

我が国では1970年以降、高血圧治療の普及や生活環境条件などの改善により脳卒中の年齢調整死亡率は著しい改善を認め、先進国の中でもほぼ中程度の死亡率にまで改善している。今後我が国が更に脳卒中死亡率の改善を図るには、脳卒中死亡の危険度の高い患者に対する適切な治療を行うとともに、軽症高血圧や、正常高値血圧に対して積極的な対策が必要と考えられる。

日本人の代表集団における HDL コレステロールと総死亡の関連；NIPPON DATA90 における 10 年間の追跡による検討

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[目的] HDL（high density lipoprotein）コレステロール（HDL-C）は虚血性心疾患の発症や死亡と負の関連を示し、米国やニュージーランド、ポーランドでは総死亡とも直線的な負の関連を示すことが指摘されている。一方、北欧やロシアなどでは HDL-C と総死亡の関連はU字型を示すことが報告されており、大量飲酒による交絡が指摘されている。しかしながら HDL-C と総死亡の関連について本邦での知見は少ない。
[方法] 全国から無作為に選ばれた 300 地区の住民 8,384 人のうち、循環器疾患の既往歴がなく、高脂血症で治療中の者を除く 7,175 人を 2000 年まで約 10 年間追跡した (NIPPON DATA90)。ベースラインの HDL-C（mg/dl）値により、35 未満、35-39、40-59、60-69、70 以上の５群に分けて、40-59 mg/dl を基準として総死亡のハザード比（HR）を Cox の比例ハザードモデルで求めた。その際、年齢、性別、Non-HDL コレステロール、トリグリセリド、高血圧、糖尿病、BMI、喫煙、飲酒は統計学的に調整した。

[結果] 追跡期間中に 636 人が死亡し、174 人が循環器疾患（虚血性心疾患 25 人、脳血管疾患 70 人）、243 人が悪性新生物であった。総死亡の HR は、35 未満、35-39、60-69、70 以上の各群で、1.13 (0.85-1.50)、1.11 (0.85-1.44)、0.81 (0.64-1.03)、0.70 (0.53-0.93)で、70 以上群で有意に低かった（線形モデルによる trend 検定: p= 0.02)。この傾向は男女別に分けても同様であった。疾病別に見ると、循環器疾患、がん、非がん非循環器疾患いずれの死亡も、HDL-C が 60-69mg/dl または 70mg/dl 以上群で最も低いことが観察された。HDL-C が 80mg/dl または 100mg/dl の区分からの死亡者について死因および死亡時年齢を確認したが、動脈硬化性疾患による死亡は認めず、死亡時年齢も高齢であった。

[結論] 日本人の代表集団における HDL-C と総死亡の関連は、北欧のようなU字型の関連を示さず、米国と同様、ほぼ直線的な負の関連を示した。総死亡の観点からも HDL-C は高いことが望ましい。また「高過ぎる」HDL-C が逆に動脈硬化性疾患死亡や短命化の要因である証拠は示されなかった。したがって集団としてみた場合、HDL-C は高いほうが望ましいと考えられる。

表1. HDLコレステロールと総死亡の関連(NIPPON DATA90)

HDLコレステロール (mg/dl)	人年	総死亡			
		死亡者数	ハザード比 (95% 信頼区間.)	有意性	有意性(線形)
<35	4943	65	1.13 (0.85, 1.50)	0.39	
35-39	5982	73	1.11 (0.85, 1.44)	0.45	
40-59	34783	344	1.00		0.02
60-69	12136	92	0.81 (0.64 1.03)	0.09	
70≦	10833	62	0.70 (0.53, 0.93)	0.01	

注)性別、年齢、BMI、中性脂肪、non-HDLコレステロール、高血圧、糖尿病、喫煙、飲酒を調整

(研究成果の公表)

Okamura T, Hayakawa T, Kadowaki T, et al. The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population. Atherosclerosis 2006; 184: 143-150.

ELSEVIER

Atherosclerosis 184 (2006) 143–150

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

The inverse relationship between serum high-density lipoprotein cholesterol level and all-cause mortality in a 9.6-year follow-up study in the Japanese general population

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Received 22 September 2004; received in revised form 13 March 2005; accepted 28 March 2005
Available online 23 May 2005

Abstract

In populations with higher high-density lipoprotein cholesterol (HDL-C) levels and lower coronary mortality than Western populations, such as in Japan, the beneficial effect of HDL-C on all-cause mortality may be different. Furthermore, prior studies have not focused on very high level of HDL-C. A total of 7175 community Japanese residents without a past history of cardiovascular disease in 300 randomly selected districts were followed for 9.6 years. During follow-up, there were 636 deaths. The multivariate adjusted hazard ratio (HR) of HDL-C for all-cause or cause-specific mortality was calculated using a Cox proportional hazard model adjusted for other cardiovascular risk factors. The all-cause mortality suggested an inverse, graded relation with HDL-C categories; HR for the very high HDL-C category (≥1.82 mmol/L), compared with the reference group (1.04–1.55 mmol/L), was 0.73 (95% confidence interval, C.I., 0.50–1.06) for men, 0.63 (95% C.I., 0.41–0.94) for women and 0.70 (95% C.I., 0.53–0.93) when men and women were combined. Serum HDL-C as a continuous variable showed a significant inverse association with all-cause mortality. The cardiovascular mortality indicated a non-significant but inverse graded relation with HDL-C categories. As in the many Western populations, serum HDL-C levels were inversely associated with all-cause mortality in the Japanese general population.

Keywords: High-density lipoprotein cholesterol; Mortality; Cohort studies; Risk factors

1. Introduction

Serum high-density lipoprotein cholesterol (HDL-C) levels are known to be inversely associated with the risk of coronary heart disease (CHD) [1–6]. Serum HDL-C levels are also inversely associated with all-cause mortality in New Zealand, US and Polish populations. [5,7–9]. However, a U-shaped or positive relationship between HDL-C and all-cause mortality has been found in northern European populations [9–11].

In populations with a higher HDL-C level and lower coronary mortality, such as in Japan [12–15], the effect of HDL-C on all-cause mortality has not yet been evaluated. To our knowledge, there are few previous cohort studies that investigated the relationship between HDL-C and all-cause mortality in Non-Western populations. [16,17] Furthermore, prior studies did not focus on very high levels of HDL-C, which is more common in Japanese individuals. [18]

Our a priori hypothesis is that high serum levels of HDL-C are inversely associated with all-cause mortality

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doi:10.1016/j.atherosclerosis.2005.03.042

in a representative sample of the Japanese population. We examined this hypothesis using 9.6 years of follow-up data from the National Survey on Circulatory Disorders, Japan, which was initiated in 1990.

2. Methods and population

2.1. Population

Cohort studies of the National Survey on Circulatory Disorders, Japan, were called NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged). NIPPON DATA included two cohort studies. The baseline surveys were performed in 1980 and 1990 (NIPPON DATA80 and NIPPON DATA90). The details of these cohorts have been previously reported [14,19–21]. In the present study, we analysed data from NIPPON DATA90 because the baseline survey of NIPPON DATA80 did not include the measurement of serum HDL-C.

A total of 8384 community residents (3504 men and 4880 women, ≥30 years old) from 300 randomly selected districts participated in the survey and were followed until November 15, 2000. The overall population aged 30 and greater in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population. Of the 8384 participants, 1209 were excluded for the following reasons: past history of coronary heart disease or stroke ($n=165$), the use of lipid-lowering agents ($n=252$), information missing at the baseline survey ($n=637$), and failure to access due to incomplete residential access information at the first survey ($n=155$). The remaining 7175 participants (3014 men and 4161 women) were included in the analysis.

2.2. Follow-up survey

The underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) for deaths occurring to the end of 1994 and the 10th International Classification of Disease (ICD-10) for deaths occurring from the beginning of 1995. The details of the classification in the present study were described elsewhere [14,19–21].

Permission to use National Vital Statistics was obtained from the Management and Coordination Agency, Government of Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were obtained and the serum was separated and centrifuged soon after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. These samples were shipped to one laboratory (SRL, Tokyo) for blood measurements.

Serum total cholesterol and triglycerides (TG) were measured enzymatically. HDL-C was measured by the precipitation method using heparin-calcium. Lipid measurements were standardized by the CDC-NHLBI (Centers for Disease Control/National Heart, Lung, and Blood Institute) Lipids Standardization Program [22]. We calculated non-HDL cholesterol as serum total cholesterol minus serum HDL-C [23]. Plasma glucose was also measured enzymatically. Diabetes was defined as serum glucose ≥11.1 mmol/L, a history of diabetes or both.

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated subjects. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents, or any combination of these. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on smoking, drinking, and medical histories.

2.4. Statistical analysis

First, we divided participants into three categories of HDL-C according to cut off points clinically regarded to be important (HDL-C < 1.04, 1.04–1.55 and ≥1.56 mmol/L; HDL-C < 40, 40–59 and ≥60 mg/dL)[1], and the median HDL-C level in each low (<1.04) and high (≥ 1.56) HDL-C group was used for cut-off values between moderately low and very low, or moderately high and very high groups (0.91 and 1.82 mmol/L, 35 and 70 mg/dL, respectively). Consequently, the relation between HDL-C and risk characteristics at the baseline survey or cause-specific mortality was described by dividing participants into five categories (HDL-C < 0.91, 0.91–1.03, 1.04–1.55, 1.56–1.81 and ≥1.82 mmol/L; HDL-C < 35, 36–39, 40–59, 60–69 and ≥70 mg/dL).

Analysis of variance was used for comparisons of multiple group means and the χ^2-test was used to compare frequencies. We computed geometric mean (antilogarithm of the log-transformed mean) for TG, because the distribution of this blood measurement was positively skewed.

The multivariate adjusted hazard ratio (HR) of each HDL-C category for all-cause or cause-specific mortality was calculated using a Cox proportional hazard model adjusted for age, non-HDL cholesterol, TG (log-transformed), body mass index, hypertension, diabetes, smoking category (never-smoked; ex-smoker; current smoker, ≤20 and ≥21 cigarettes/day) and drinking category (never-drank, ex-drinker, current drinker). We also adjusted for sex when we performed sex-combined analyses. Wald's tests were used to test for significance of the HR in each HDL-category compared to the reference category [24]. The category with HDL-C level of 1.04–1.55 mmol/L was defined as the

reference group. The model with continuous serum HDL-C value instead of HDL-C categories was also examined to clarify the linear trend between HDL-C and mortality. The HR was calculated again excluding deaths within the first 3 years of follow-up because subjects who had a severe but sub-clinical disease might have affected the relationship between mortality and serum HDL-C levels.

All confidence intervals were estimated at the 95% level. A P-value of <0.05 was considered significant. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 11.0J, Tokyo, Japan) was used for the analyses.

3. Results

The age at the baseline survey was 52.8 ± 13.5 (mean ± S.D.) for men and 51.8 ± 13.8 for women. The range of HDL-C was 0.40–3.65 mmol/L for men (mean ± S.D.: 1.30 ± 0.39) and 0.42–3.18 mmol/L (mean ± S.D.: 1.48 ± 0.39) for women.

Table 1 shows the baseline characteristics of the subjects. There were significant differences in the mean values for body mass index (BMI), non-HDL cholesterol and TG, and in the prevalence of diabetes; these variables were lower in

Table 1
Means (±S.D.) and prevalences of baseline characteristics stratified by HDL cholesterol level at the baseline survey in 1990, NIPPON DATA90

Risk characteristics	Baseline HDL-C range, mmol/L (mg/dL)					P-values
	Very low <0.91 (35)	Low 0.91–1.03 (35–39)	Reference 1.04–1.55 (40–59)	High 1.56–1.81 (60–69)	Very high 1.82+ (70+)	
Men						
Number of subjects (proportion, %)	346 (11.5)	374 (12.4)	1590 (52.8)	373 (12.4)	331 (11.0)	
HDL-cholesrerol, stratum mean (mmol/L)	0.78 ± 0.09	0.96 ± 0.04	1.25 ± 0.14	1.65 ± 0.07	2.08 ± 0.28	<0.001
Age (years)	53.2 ± 13.8	52.3 ± 13.8	52.8 ± 13.5	53.3 ± 13.4	53.2 ± 13.2	0.78
BMI (kg/m^2)	24.3 ± 2.9	24.1 ± 2.9	22.9 ± 3.0	21.8 ± 2.5	21.5 ± 2.6	<0.001
Total cholesterol (mmol/L)	5.10 ± 1.03	5.15 ± 1.06	5.05 ± 0.92	5.12 ± 0.85	5.42 ± 0.89	<0.001
Non-HDL cholesterol (mmol/L)	4.32 ± 1.03	4.19 ± 1.05	3.80 ± 0.93	3.46 ± 0.85	3.33 ± 0.93	<0.001
Triglyceride (mmol/L)[a]	2.38	1.84	1.34	1.06	0.97	<0.001
Hypertension (%)	50.9	43.9	49.9	48.0	47.1	0.24
Diabetes (%)	6.9	5.1	3.5	3.5	3.9	0.04
Smoking						
Never-smoker (%)	15.0	24.9	20.2	20.1	24.5	
Ex-smoker (%)	19.4	20.3	24.1	24.9	25.1	
Current smoker (≤20 cigarettes/day) (%)	37.6	31.8	36.8	39.4	37.8	<0.001
Current smoker (≥21 cigarettes/day) (%)	28.0	23.0	18.9	15.5	12.7	
Drinking						
Never-drinker (%)	53.8	51.1	32.5	25.2	19.9	
Ex-drinker (%)	9.2	7.5	5.7	3.8	4.2	<0.001
Current drinker (%)	37.0	41.4	61.8	71.0	75.8	
Women						
Number of subjects (proportion, %)	177 (4.3)	260 (6.2)	2055 (49.4)	886 (21.3)	783 (18.8)	
HDL-cholesrerol, stratum mean (mmol/L)	0.78 ± 0.09	0.96 ± 0.03	1.30 ± 0.15	1.66 ± 0.07	2.06 ± 0.24	<0.001
Age (years)	59.1 ± 13.5	57.0 ± 14.1	52.5 ± 13.9	50.0 ± 13.4	48.8 ± 12.7	<0.001
BMI (kg/m^2)	24.6 ± 3.0	24.2 ± 3.1	23.3 ± 3.3	22.0 ± 3.1	21.6 ± 2.9	<0.001
Total cholesterol (mmol/L)	5.09 ± 1.04	5.41 ± 1.23	5.25 ± 1.00	5.32 ± 0.90	5.51 ± 0.88	<0.001
Non-HDL cholesterol (mmol/L)	4.31 ± 1.05	4.44 ± 1.23	3.95 ± 1.01	3.66 ± 0.90	3.45 ± 0.85	<0.001
Triglyceride (mmol/L)[a]	2.20	1.89	1.25	0.98	0.82	<0.001
Hypertension (%)	58.8	57.7	42.6	36.6	31.7	<0.001
Diabetes (%)	5.1	5.8	3.6	2.0	0.5	<0.001
Smoking						
Never-smoker (%)	85.9	84.6	88.3	90.2	89.1	
Ex-smoker (%)	1.7	2.3	2.4	2.5	2.9	0.03
Current smoker (≤20 cigarettes/day) (%)	9.6	11.2	8.5	7.0	7.3	
Current smoker (≥21 cigarettes/day) (%)	2.8	1.9	0.8	0.3	0.6	
Drinking						
Never-drinker (%)	96.6	94.2	93.9	92.6	87.1	
Ex-drinker (%)	1.1	1.2	0.8	1.4	0.8	<0.001
Current drinker (%)	2.3	4.6	5.3	6.1	12.1	

HDL means "high-density lipoprotein". S.D. means standard deviations. Analysis of variance was used for comparisons of multiple group means and the χ^2-test was used to compare frequencies.

[a] Geometric mean.

the higher HDL-C groups in both sexes. The prevalence of current drinkers for both sexes was higher in the higher HDL-C groups. The prevalence of current smokers for both sexes was low in the moderately high or in the very high HDL-C groups. The mean values of age and the prevalence of hypertension for women were also lower in the groups with higher levels of HDL-C.

Total person-years were 68,678 (28,419 for men and 40,259 for women) and the mean follow-up period was 9.6 years. During follow-up, there were 636 deaths (352 for men and 284 for women), of which 27% ($n=174$) were due to cardiovascular disease. There were 25 deaths due to coronary heart disease, 50 due to heart failure, and 70 due to stroke (42 cerebral infarction, 12 cerebral haemorrhage and 16 others). Among the total deaths, 38% ($n=243$) were due to cancer and 35% ($n=219$) were due to non-cancer, non-cardiovascular disease.

Table 2 shows the number of deaths and multivariate-adjusted HRs for all-cause mortality. The all-cause mortality suggested an inverse, graded relation with HDL-C categories; the HR for the very high HDL-C category (≥ 1.82 mmol/L) was 0.73 (95% C.I., 0.50–1.06) for men, 0.63 (95% C.I., 0.41–0.94) for women and 0.70 (95% C.I., 0.53–0.93) when men and women were combined. In contrast, the HR for the very low HDL-C category (<0.91 mmol/L) was 1.14 (95% C.I., 0.80–1.62) for men and 1.17 (95% C.I., 0.72–1.92) for women, although these HR values did not reach statistical significance. As a continuous variable, the serum HDL-C showed a significant inverse association with all-cause mortality for women ($P=0.04$), an inverse association for men with borderline statistical significance ($P=0.05$), and a significant inverse association when men and women were combined ($P=0.02$).

Table 3 shows the number of deaths and multivariate-adjusted HRs for the major causes of death. The cardiovascular mortality indicated an inverse, graded relation with HDL-C categories when men and women were combined, although no HDL-C category reached statistical significance. The cardiovascular mortality was highest in very low HDL-C category and lowest in very high HDL-C category in both men and women. The very low HDL-C group showed a significant increase in HR for all-cause (HR: 1.62, 95% C.I., 1.10–2.37) or cardiovascular mortality (HR: 2.70, 95% C.I., 1.28–5.68) when we defined the very high HDL-C group (≥1.82 mmol/L) as the reference group in the sex-combined Cox analysis (data not shown in the table).

The serum HDL-C value showed an inverse association with cardiovascular mortality when men and women were combined, and for women, both with borderline statistical significance ($P=0.07$ and $P=0.07$). The very high HDL-C category also showed the lowest cancer mortality and the second lowest non-cancer, non-cardiovascular mortality without statistical significance.

Table 4 shows the number of deaths and multivariate-adjusted HRs of mortality due to stroke, coronary heart disease and heart failure. We only show the sex-combined analysis because the number of deaths due to each subtype of cardiovascular disease was too small to permit valid

Table 2
The number of deaths and multivariate-adjusted HRs[a] (95% C.I.s) for all-cause deaths according to serum HDL cholesterol level

Baseline HDL cholesterol level, mmol/L (mg/dl)	No. of persons	Person-years	All-cause deaths			
			No. of deaths	HR[a] (95% C.I.)	P	P^b
Men						
<0.91 (35)	346	3259	45	1.14 (0.80, 1.62)	0.47	
0.91–1.03 (35–39)	374	3500	46	1.20 (0.86, 1.69)	0.29	
1.04–1.55 (40–59)	1590	14,996	184	1.00		0.05
1.56–1.81 (60–69)	373	3512	44	0.84 (0.61, 1.18)	0.32	
1.82+ (70+)	331	3152	33	0.73 (0.50, 1.06)	0.10	
Women						
<0.91 (35)	177	1684	20	1.17 (0.72, 1.92)	0.53	
0.91–1.03 (35–39)	260	2482	27	1.06 (0.70, 1.61)	0.79	
1.04–1.55 (40–59)	2055	19,787	160	1.00		0.04
1.56–1.81 (60–69)	886	8624	48	0.76 (0.54 1,.06)	0.10	
1.82+(70+)	783	7681	29	0.63 (0.41, 0.94)	0.03	
Men and women combined						
<0.91 (35)	523	4943	65	1.13 (0.85, 1.50)	0.39	
0.91–1.03 (35–39)	634	5982	73	1.11 (0.85, 1.44)	0.45	
1.04–1.55 (40–59)	3645	34,783	344	1.00		0.02
1.56–1.81 (60–69)	1259	12,136	92	0.81 (0.64, 1.03)	0.09	
1.82+ (70+)	1114	10,833	62	0.70 (0.53, 0.93)	0.01	

HDL means "high-density lipoprotein".

[a] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, trigfyceride (log-transformed), non-HDL cholesterol, hypertension, diabetes, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group. Sex was also adjusted in the men and women combined model.

[b] Continuous serum HDL-C value was used in the proportinal hazard model.

Table 3
The number of deaths and multivariate-adjusted HRs[a] (95% C.I.s) for major causes of death according to serum HDL cholesterol level

Baseline HDL cholesterol level, mmol/L (mg/dl)	Person-years	Cardiovascular				cancer				Non-cancer, non-cardiovascular			
		No. of deaths	HR[b] (95% C.I.)	P	P^a	No. of deaths	HR[b] (95% C.I.)	P	P^a	No. of deaths	HR[b] (95% C.I.)	P	P^a
Men													
<0.91 (35)	3259	15	1.53 (0.81,2.90)	0.19		12	0.72 (0.38, 1.38)	0.32		18	1.41 (0.79, 2.50)	0.24	
0.91–1.03 (35–39)	3500	9	0.90 (0.43, 1.88)	0.77		20	1.38 (0.82, 2.32)	0.23		17	1.24 (0.70, 2.19)	0.46	
1.04–1.55 (40–59)	14,996	48	1.00		0.51	73	1.00		0.21	63	1.00		0.16
1.56–1.81 (60–69)	3512	14	1.01 (0.55, 1.85)	0.97		21	1.08 (0.66, 1.78)	0.76		9	0.48 (0.24, 1.00)	0.05	
1.82+ (70+)	3152	7	0.65 (0.29, 1.45)	0.29		10	0.56 (0.28, 1.10)	0.09		16	0.98(0.56, 1.72)	0.95	
Women													
<0.91 (35)	1684	8	1.43 (0.64, 3.17)	0.38		8	1.30 (0.60, 2.82)	0.51		4	0.76 (0.27, 2.19)	0.62	
0.91–1.03 (35–39)	2482	10	1.20 (0.59, 2.43)	0.62		11	1.18 (0.61, 2.29)	0.63		6	0.76 (0.32, 1.80)	0.53	
1.04–1.55 (40–59)	19,787	47	1.00		0.07	60	1.00		0.10	53	1.00		0.88
1.56–1.81 (60–69)	8624	10	0.54 (0.27, 1.08)	0.08		15	0.65 (0.36, 1.16)	0.14		23	1.09 (0.66, 1.82)	0.73	
1.82+ (70+)	7681	6	0.48 (0.20, 1.15)	0.10		13	0.73 (0.39, 1.37)	0.33		10	0.69 (0.34, 1.39)	0.30	
Men and women combined													
<0.91 (35)	4943	23	1.50 (0.92, 2.46)	0.11		20	0.85 (0.52, 1.40)	0.53		22	1.20 (0.73, 1.95)	0.47	
0.91–1.03 (35–39)	5982	19	1.04 (0.63, 1.74)	0.87		31	1.21 (0.81, 1.82)	0.36		23	1.03 (0.65, 1.64)	0.91	
1.04–1.55 (40–59)	34,783	95	1.00		0.07	133	1.00		0.12	116	1.00		0.45
1.56–1.81 (60–69)	12,136	24	0.74 (0.47, 1.17)	0.20		36	0.88 (0.60, 1.28)	0.49		32	0.81 (0.54 1.20)	0.30	
1.82+(70+)	10,833	13	0.56 (0.31, 1.01)	0.05		23	0.69 (0.44, 1.08)	0.11		26	0.85 (0.55, 1.31)	0.45	

HDL means "high-density lipoprotein".

[a] Continuous serum HDL-C value was used in the proportinal hazard model.

[b] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, triglyceride(log-transformed), non-HDL cholesterol, hypertension, diabetes, cigarette smoking category and alcohol intake category by a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group. Sex was also adjusted in the men and women combined model.

Table 4
The number of deaths and multivariate-adjusted HRs [a] (95% C.I.s) for the subgroups of cardiovascular death according to serum HDL cholesterol level

Baseline HDL cholesterol level, mmol/L (mg/dl)	Person-years	Stroke				Coronary heart disease				Heart failure			
		No. of deaths	HR[b] (95% C.I.)	P	P^a	No. of deaths	HR[b] (95% C.I.)	P	P^a	No. of deaths	HR[b] (95% C.I.)	P-values	P-values
Men and women combined													
<0.91 (35)	4943	8	1.51 (0.66, 3.44)	0.33		2	0.83 (0.18, 3.92)	0.81		10	2.28 (0.99, 5.22)	0.05	
0.91–1.03 (35–39)	5982	10	1.60 (0.77, 3.32)	0.21		2	0.77 (0.17, 3.55)	0.74		5	0.89 (0.33, 2.39)	0.81	
1.04–1.55 (40–59)	34,783	36	1.00		0.04	15	1.00		0.14	25	1.00		0.06
1.56–1.81 (60–69)	12,136	12	0.94 (0.48, 1.84)	0.87		1	0.19 (0.02, 1.43)	0.11		8	0.94 (0.42, 2.12)	0.88	
1.82+ (70+)	10,833	4	0.43 (0.15, 1.22)	0.11		5	1.24 (0.43, 3.58)	0.70		2	0.35 (0.08, 1.49)	0.15	

HDL means "high-density lipoprotein".
[a] Continuous serum HDL-C value was used in the proportinal hazard model.
[b] HR means hazard ratio and 95% C.I. means 95% confidence interval. The HR was adjusted for age, body mass index, triglyceride(log-transformed), non-HDL cholesterol, hypertension, diabetes, cigarette smoking, category and alcohol intake category by a Cox proportional hazard model. The Wald's test was used to examine the difference in the HR of each HDL-C category compared with the reference group. Sex was also adjusted in the men and women combined model.

sex-specific multivariate analysis. We did not observe any significant differences in the HR for each subtype of cardiovascular disease amongst the five HDL-C categories. However, as a continuous variable, the serum HDL-C showed a significant inverse association with stroke mortality ($P = 0.04$), and an inverse association with heart failure mortality with borderline significance ($P = 0.06$).

The mortality results were not substantially affected after excluding deaths within the first 3 years of follow-up (data not shown).

4. Discussion

In the present study, serum levels of HDL-C were inversely associated with all-cause death in the Japanese general population. The very high HDL-C group (≥ 1.82 mmol/L) showed lowest HR for all-cause mortality. In contrast, a positive relationship between low HDL-C category and all-cause mortality did not reach statistical significance, although the HRs were highest in the low (0.91–1.03 mmol/L) or very low (<0.91 mmol/L) HDL-C groups.

An inverse relationship between HDL-C and all-cause mortality has been reported in US [5,8,9], New Zealand [7] and Polish [8] populations. On the other hand, a U-shaped or a positive relationship between HDL-C and all-cause mortality has been found in Russian [9] Norwegian [10] and Finnish [11] populations. In the Norwegian [10] and Finnish studies [11], total mortality was higher in the highest HDL-C group (>1.75 mmol/L and >1.61 mmol/L, respectively) than in the group with the second highest HDL-C category. These exceptional findings were explained by alcohol-related excess mortality due to heavy alcohol consumption or alcoholism in these Northern European countries [9–11]. Paunio et al. suggested that the beneficial effect of HDL-C might be underestimated by the confounding effect of a heavy alcohol intake [11].

Although the prevalence of current drinkers was highest in the high HDL-C group in the present study, we believe potential confounding by alcohol consumption for the inverse association between HDL-C and all-cause mortality may be small. One reason is the lower prevalence of alcoholism in the Japanese population, partly due to the high prevalence of genetic defective low-Km human mitochondrial aldehyde dehydrogenase, which was not observed in Caucasians [25,26]. Furthermore, a similar pattern concerning the relationship between HDL-C and all-cause mortality was observed in both men and women, although the prevalence of current drinkers was quite different.

We observed a positive but non-significant relation between low serum HDL-C and all-cause or cardiovascular mortality. A 10-year cohort study of community-dwelling Japanese showed that participants with serum HDL-C < 0.78 mmol/L (30 mg/dL) had a remarkably increased risk of stroke, although participants with an HDL-C of 0.78–1.03 mmol/L (30–39 mg/dL) did not have an increased

risk [27]. Stroke mortality in Japan is much higher than coronary heart disease mortality [14]. Accordingly, we may have failed to detect a higher risk of cardiovascular or all-cause mortality when we used the criteria of <0.91 mmol/L or <1.04 mmol/L to define the low HDL-C group. Furthermore, because the mean levels of total and non-HDL cholesterol in the present study were lower than in the Western population [13,23], the atherogenic effect of low HDL-C due to low reverse cholesterol transport may be masked. However, the very low HDL-C group (<0.91 mmol/L) showed a 13% increases in all-cause and 50% increase in cardiovascular mortality compared with the reference group (1.04–1.55 mmol/L), which showed a 62% increase in HR for all-cause mortality and about triple higher HR for cardiovascular mortality when we defined the very high HDL-C group (≥1.82 mmol/L) as the reference group in the Cox model. These results indicate that a low serum level of HDL-C is an important predictive marker for all-cause or cardiovascular death in this population.

There are several explanations for the high serum HDL-C level in Japan. Compared to Caucasians, Japanese have a much lower body mass index and a higher prevalence of genetic cholesteryl ester transfer protein (CETP) deficiency [18,28]. It is controversial whether very high levels of serum HDL-C are protective against coronary heart disease. There are few epidemiologic studies that have investigated the relationship between high HDL-C levels or CETP deficiency and coronary heart disease [18,28,29]. There is only one prospective study, which showed a low risk of coronary heart disease in participants with high HDL-C (≥ 1.56 mmol/L) in Japanese descendants in Hawaii [29], irrespective of CETP deficiency. A large cross-sectional study in a southwest Japanese community with detection of genetic CETP deficiency also showed a low prevalence of coronary heart disease in participants with very high HDL-C (≥ 2.07 mmol/L, 80 mg/dL) [18]. These studies suggest that an increased level of serum HDL-C may be protective against coronary heart disease mortality in Japan, irrespective of the cause for the HDL-C increase.

There are some limitations in the present study. First, we used mortality as an endpoint, which may have led to misclassification of the cause of death. Mortality statistics for coronary heart disease may have been underestimated because deaths coded as "heart failure" may have hidden some coronary events [30]. A graded inverse relation between HDL-C categories and heart failure mortality suggests the existence of this misclassification. However, the death-certificate diagnosis of stroke in Japan has been reported to be accurate [20], and the present study focused mainly on all-cause mortality. Second, major results of the present study were based on a relatively small number of deaths in each HDL-C category. Further studies with a larger sample size or longer follow-up period are needed in other non-Western populations.

In conclusion, serum HDL-C levels were inversely associated with all-cause mortality in a representative sample of the Japanese population. Furthermore, very high serum HDL-C (≥ 1.82 mmol/L) might be associated with decreased risk for all-cause mortality. It may be beneficial to increase serum HDL-C levels by lifestyle modification [18] or some therapeutic measures, such as weight reduction, smoking cessation, increased physical activity, frequent fish consumption [31] and CETP inhibition [32].

Acknowledgements

This study was supported by a research grant from Ministry of Health, Labor and Welfare, H14-16-Chouju-003.

Appendix A

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Body Mass Index (BMI)と脳卒中死亡について
－NIPPON DATA80：19年間の追跡－

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【要旨】
目的：Body Mass Index(BMI) と脳卒中死亡の関係は議論の残るところである。本研究は、日本を代表する集団であるNIPPON DATA80の19年間の追跡によってBMIと脳卒中死亡の関係を明らかにする目的で行った。
方法：1980年に全国から無作為抽出によって選ばれた30歳以上の成人男女を19年間追跡し、脳卒中既往のない9526人を対象に解析を行った。コックスの比例ハザードモデルを用いて、BMIの全脳卒中、脳梗塞、脳出血死亡のハザード比と95%信頼区間を求めた。
結果：脳梗塞死亡でU字型の関連が見られた。最も高いBMIカテゴリ(≥30kg/m^2)で、統計学的に有意に高いハザード比(ハザード比2.46, 95%信頼区間1.01-5.99)が観察された。低いBMIのハザード比の上昇は男に限ってみられた。これらの関係は追跡最初の2年間を除いた解析でも大きな違いはなかった。
結論：日本の一般集団では、BMIと脳梗塞死亡の間にU字の関係が見られた。低いBMIのハザード比の上昇は男に限って観察された。

【はじめに】

高いBody Mass Index (BMI)は冠動脈疾患の危険因子として知られているが、脳卒中死亡との関連については議論の残るところである。Stroke Council of the American Heart Associationのガイドラインの中では、肥満は"less well documented or potentially modifiable risk factors"に分類されている[1]。いくつかの先行研究では特に脳梗塞において[2-8]、肥満と脳卒中の関連は正であると認めているが、U字型を示すとの報告もある[9,10]。

わが国において脳卒中の年齢調整死亡率は年々減少しているものの、今日でも主な死亡原因疾患の一つであり、寝たきりの原因の第1位である。さらに今後高齢化が加速すれば、脳卒中の問題は量、質ともに大きくなると考えられる。

大規模な疫学研究は、欧米で行われていることが多いが、欧米の肥満の基準とアジア地域の肥満の基準は異なっている[11,12]。さらに、長期の追跡研究においてアジアの集団を対象に実施されているものはたいへん少ない。アジア地域の成人男女において、

BMI の平均値は欧米の BMI と比較して低い[11]が、アジアの民族は欧米の同じ値の BMI の人より、脂肪の割合が高いことが知られている[13]。

わが国において BMI の平均値は年々上昇しており、特に男性と 50 歳以上の女性にその傾向が著しい[14,15]。このように、肥満の及ぼす影響は欧米諸国のみの問題ではなく、わが国を含むアジアの諸国においても同様に深刻である。

本研究では、BMI と脳卒中（全脳卒中、脳梗塞、脳出血）死亡の関係を明らかにするために、日本を代表する集団である NIPPON DATA80 の 19 年間の追跡結果に基づいて解析をおこなった。

【方法】

対象集団

本コホート調査の対象者は、1980 年の循環器疾患基礎調査[16]を受けたもので、日本全国から層化無作為抽出された 300 地区に居住する 30 歳以上の男女 10546 人（男 4640 人、女 5906 人）を 19 年間追跡した（NIPPON DATA80）。該当地域に居住する 30 歳以上の男女は 13771 人であり、参加率は 76.6%であった。10546 人のうち、追跡できなかった者、脳卒中の既往があった者、欠損データがあった者を除いた合計 9526 人（男 4171 人、女 5355 人）を解析対象とした。

ベースライン調査

1980 年の循環器疾患基礎調査は詳しくは文献[16-19]に記載されているが、対象地区を管轄する保健所長が班長となり医師、臨床検査技師又は衛生検査技師、保健師及び事務担当者等の調査員によって編成された。身長・体重、および血圧は国民栄養調査の手技により[20]、身長は裸足にて単位を cm として小数点以下 1 位まで測定し、体重は裸体に近い状態で小数点以下 1 位まで測定した。衣服を着たまま測定した場合はあらかじめ家庭で測定した衣服の重さを差し引いた。血圧測定は訓練された保健婦が標準水銀血圧計を用いて行い 5 分安静の後、椅座位にて右腕の上腕部で測定した。採血時間は規定しなかった。血液化学検査は、総コレステロール値はリーバーマン・バーチャッド直接法で血糖値はネオカプロン銅法を用い、測定はテクニコン SMA12/60 で実施した。

ベースラインにおける高血圧、循環器疾患の既往歴、喫煙や飲酒習慣の情報は、調査票を用いて集収した。調査票で、高血圧既往ありは、高血圧薬の服用の有無を問い、喫煙習慣は、「以前からほとんどすわない」「今すっている」「今はやめているが以前すった」のいずれかを選び、飲酒習慣は「以前からほとんど飲まない」「毎日飲む」「ときどき飲む」「今はやめているが以前飲んだ」のいずれかを選択させた。

追跡調査

1980 年の循環器疾患基礎調査受検者について調査を担当した 300 地区の保健所の協力により、生死と現住所を明らかにした。死亡例は総務省の許可を得て人口動態テープと照合し、1994 年までは ICD9、1995 年以降は ICD10 の分類による死因分類を得た。1994 年までは ICD9 の簡単分類に従い、脳血管疾患（全脳卒中）(58-60)、脳出血(58)、脳梗塞(59)、その他の脳血管疾患(60)に分類した。1995 年以降は ICD10 の分類に従い、脳血管疾患（全脳卒中）(I60-I69)、脳出血(I61, I69.1)、脳梗塞(I63, I69.3)、その他の脳血管疾患（I60-I69 の残り）に分類した。

本研究は、主任研究者の所属する滋賀医科大学の倫理審査委員会にて承認されている。

統計解析

BMI が年齢およびその他の因子を調整した全脳卒中、脳梗塞、脳出血死亡に及ぼす影響について、Cox Proportional hazard regression model を用いてハザード比と 95%信頼区間を求めた。BMI は、<18.5, 18.5-22.9, 23.0-24.9, 25.0-29.9, ≥30kg/m^2 のカテゴリに分けて解析した。カテゴリは WHO 基準[11]に従ったが、ほとんどの対象者が含まれてしまう Normal range（普通体重）のカテゴリは二分し、23.0-24.9kg/m^2 を基準とした。さらに、悪性腫瘍や慢性炎症性疾患の影響や因果の逆転を考慮して、追跡開始最初の 2 年間を除いて同様の解析を行った。男女合わせて、性、年齢、喫煙習慣、飲酒習慣を調整した解析と、それらに収縮期血圧、総血清コレステロール値、血糖値といった肥満に biological な結果として影響する変数を加えて調整した解析を行った。男女別にも同様にそれぞれ観察した。すべての解析は SAS version 8.02 for Windows 統計ソフトを用いた。

【結果】

対象者の開始時調査(1980 年) 時点の BMI 平均（±標準偏差）は、22.7(±3.2)kg/m^2 で、男は 22.5(±3.2)kg/m^2、女は 22.9(±3.4)kg/m^2 であった。表 1 に性別・BMI カテゴリ別にみた開始時調査における年齢、収縮期および拡張期血圧、総コレステロール値、血糖値（平均値±標準偏差）、高血圧治療率、喫煙・飲酒習慣（割合）を示した。収縮期血圧、拡張期血圧、総コレステロール値、そして高血圧治療率は男女ともに高い BMI カテゴリで高い傾向を示した。その反対に、喫煙ありの割合は低い BMI で高い傾向を示した。

集団の総観察人年は、164457 人年で平均の追跡期間は 17.3 年であった。追跡期間中 319 人の全脳卒中死亡が観察された。そのうち 182 人は脳梗塞、70 人は脳出血で 67 人はその他の脳卒中（くも膜下出血およびその他の脳卒中）であった。表 2 に、BMI カテゴリ別の粗死亡率（/1000 人年）を示した。

BMIカテゴリ別にみた全脳卒中、脳梗塞、脳出血死亡のハザード比と95%信頼区間を表3に示した。U字型の関連がBMIと脳梗塞死亡で観察された。男女別の解析では、それぞれ最も高いBMIカテゴリ（≥30kg/m²)で、統計学的に有意差は認められなかったが最も高いハザード比を示した。男女合わせた解析ではハザード比の上昇に統計学的有意差が認められた。低いBMIでハザード比が上昇する傾向は男にのみ限って見られた。

全脳卒中死亡のハザード比は、脳梗塞と同じような傾向を示したが、年齢、喫煙、飲酒習慣といった交絡因子のみを調整したモデルでは有意差は認められなかった。

追跡開始最初の2年間を除いた解析においても、同じような結果が観察された。

【考察】

本研究では、BMIと脳梗塞死亡ではハザード比がU字の関連で、低い部分のBMIについては男にだけ限られて上昇が観察された。また、この傾向は追跡開始最初の2年間を除いた解析でも変わらなかった。

本研究の長所は（1）無作為抽出による、日本国民を代表するサンプルを解析対象としている　（2）高い参加率である　（3）身長・体重、血圧、血液化学検査が質問紙ではなく直接対象者から測定された　（4）長期間の追跡（19年間）があげられる。いくつかの疫学研究では、地域や対象者を限定したものであって、無作為抽出による日本を代表する集団での追跡研究はない。また、大規模疫学研究の多くは、身体所見（身長・体重、血圧）や血液検査データを問診や調査票などの自己申告で収集しているのに対して、本研究では管轄する保健所スタッフが直接、全員に対して測定を行った。

わが国では老人保健法が1982年に成立し、その後、保健事業で健康診査をはじめ、大きな介入がなされたが、本研究の開始時である1980年はその影響をまだ受けていない状態であった。

いくつかの追跡研究は脳卒中、特に脳梗塞ではBMIが高くなるとリスクが高くなると報告している[2-8]。また、研究は腹部の肥満が全身の肥満よりリスクの上昇と関連する[21]としているものもある。肥満は高血圧[22]、糖尿病[23]、高コレステロール血症[24,25]と強く関連していることが知られており、メタボリックシンドロームが脳梗塞のリスクになっているということも確立している。しかし、HDLコレステロール値や中性脂肪、HOMA indexなどメタボリックシンドロームの鍵となる因子を測定していないためこれ以上の評価が困難で今後の課題と考える。

男の低いBMIレベルで高いハザード比が観察された理由のひとつとして致死率が考えられる。本研究ではエンドポイントが死亡のみを扱っているため、死亡以外の転帰をとったものの影響が含まれない。清原ら[26]は30日以内の脳梗塞致死率は久山町の研究で9.0%としており、低BMIが脳卒中発症後死亡に対して統計学的有意なリス

クであると報告している。

観察研究で体重と死亡率を観察する際、いくつかの方法論的な問題がある。一つはもともと疾患があるために体重が減少しているということと（因果の逆転）と、喫煙による交絡、それから高血圧、高コレステロール血症、高血糖などといったBiological consequenceによって本来の結果が薄められてしまうということである[27]。

脳梗塞死亡のハザード比に関して男でU字が観察されたが、女では観察されなかった。BMIの平均は女では年齢が高くなるにつれて高くなる傾向があったのに対し、男では、BMIの平均は40代、50代で高くなり、その後年齢が高くなるに従って低くなるので、年齢の影響がモデルで調整しても完全に取り除けないのではないかと推測される。このように因果の逆転と、交絡の影響をコホート研究から完全に調整することは難しい。従って、低BMIと死亡のリスクを評価、考察する際は十分な注意が必要である。

本研究の欠点は、脳卒中死亡とBMIの関係を観察する上で統計学的に有意な関係を示すには、特にBMI≥30kg/m^{2}の集団においてサンプル数が少ないことがあげられる。しかし、日本における肥満者（BMI≥30kg/m^2）の割合はたいへん低く、対象集団中男で0.9%、女で3.0%であった。もう一つは、エンドポイントとして死亡を確定するために人口動態統計テープに基づいてそれを行ったため（死亡個票は医師の診断）、死亡原因についてmisclassificationが含まれる可能性を否定できない。しかし、1980年代からわが国にはCTスキャンが急速に普及[28]したため、脳卒中の型の診断に関しても正確であると考えられる。

結論として、U字の関連がBMIと脳梗塞死亡の間で観察された。低い部分のBMIのハザード比上昇については、男のみに限られた。

表1. 性別・BMIカテゴリ別にみたベースライン調査の年齢、血圧、総コレステロール、血糖値（平均値±標準偏差）、高血圧治療率と生活習慣(%)

Body mass index (BMI)	<18.5kg/m^2	18.5-22.9kg/m^2	23.0-24.9kg/m^2	25.0-29.9kg/m^2	≥30.0kg/m^2
男					
人数（人）	273	2194	902	765	37
年齢（歳）	57.0±16.0	50.7±13.3	49.3±12.4	48.5±11.5	49.7±12.6
収縮期血圧 (mmHg)	137.3±24.7	136.8±21.0	139.6±19.9	141.6±19.4	143.1±23.2
拡張期血圧 (mmHg)	79.5±11.2	81.9±12.2	84.8±11.6	87.6±12.2	91.2±13.9
総コレステロール値(mg/dl)	173.3±26.3	180.8±31.1	191.3±33.8	198.8±33.0	203.5±38.4
血糖値 (mgl/dl)	131.8±36.3	129.7±38.1	132.1±41.3	131.5±34.4	148.6±45.8
高血圧治療あり(%)	9.2	8.0	10.2	13.6	16.2
喫煙あり(%)	68.9	65.5	61.8	56.3	48.7
飲酒あり(%)	63.0	75.0	77.1	75.0	62.2
女					
人数（人）	381	2620	1135	1056	163
年齢（歳）	53.3±15.0	49.6±13.6	51.0±12.9	52.4±12.1	53.4±12.2
収縮期血圧 (mmHg)	128.7±20.4	130.3±20.5	135.3±20.7	141.4±21.9	146.7±22.6
拡張期血圧 (mmHg)	75.6±12.1	77.5±11.3	80.6±11.4	83.8±11.4	88.5±13.5
総コレステロール値(mg/dl)	182.1±30.1	187.0±32.9	193.8±34.9	198.2±34.5	207.8±35.1
血糖値 (mg/dl)	129.0±34.1	126.6±31.3	130.2±32.2	133.8±40.1	137.3±32.1
高血圧治療あり(%)	5.8	7.9	12.6	18.8	31.9
喫煙あり(%)	16.3	8.5	7.7	8.7	5.5
飲酒あり(%)	16.3	21.8	19.9	16.7	17.2

表2. 性別・BMIカテゴリ別にみた観察人年、全脳卒中・脳梗塞・脳出血別死亡数と粗死亡率 （対1000人年）

	総数	<18.5kg/m^2	18.5-22.9kg/m^2	23.0-24.9kg/m^2	25.0-29.9kg/m^2	≥30.0kg/m^2
男						
人数:人	4171	273	2194	902	765	37
観察人年:人年	70584	3986	36869	15637	13478	614
全脳卒中死亡:人(粗死亡率 /1000人年)	165 (2.34)	20 (5.02)	97 (2.63)	22 (1.41)	24 (1.78)	2 (3.26)
脳梗塞死亡:人(粗死亡率 /1000人年)	101 (1.43)	17 (4.26)	58 (1.57)	11 (0.70)	14 (1.04)	1 (1.63)
脳出血死亡:人(粗死亡率 /1000人年)	39 (0.55)	3 (0.75)	23 (0.62)	6 (0.38)	6 (0.45)	1 (1.63)
女						
人数:人	5355	381	2620	1135	1056	163
観察人年:人年	93873	6280	46185	20054	18515	2839
全脳卒中死亡:人(粗死亡率 /1000人年)	154 (1.64)	12 (1.91)	70 (1.52)	33 (1.65)	31 (1.67)	8 (2.82)
脳梗塞死亡:人(粗死亡率 /1000人年)	81 (0.86)	7 (1.11)	35 (0.76)	17 (0.85)	17 (0.92)	5 (1.76)
脳出血死亡:人(粗死亡率 /1000人年)	31 (0.33)	3 (0.48)	15 (0.32)	7 (0.35)	4 (0.22)	2 (0.70)

表3. BMIカテゴリ別にみた全脳卒中、脳梗塞、脳出血別のハザード比と95% 信頼区間

Body mass index	全脳卒中		脳梗塞		脳出血	
	ハザード比 (95% 信頼区間)		ハザード比 (95% 信頼区間)		ハザード比 (95% 信頼区間)	
(kg/m^2)	年齢・喫煙・飲酒で調整	多変量調整*	年齢・喫煙・飲酒で調整	多変量調整*	年齢・喫煙・飲酒で調整	多変量調整*
男女合計†						
<18.5	1.14 (0.73 , 1.77)	1.36 (0.87 , 2.12)	1.57 (0.90 , 2.73)	1.85 (1.05 , 3.26)	1.02 (0.38 , 2.72)	1.23 (0.46 , 3.29)
18.5-22.9	1.21 (0.89 , 1.64)	1.28 (0.94 , 1.74)	1.28 (0.84 , 1.96)	1.36 (0.88 , 2.09)	1.19 (0.63 , 2.24)	1.26 (0.67 , 2.37)
23.0-24.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25.0-29.9	1.22 (0.84 , 1.78)	1.17 (0.80 , 1.71)	1.43 (0.86 , 2.39)	1.41 (0.84 , 2.36)	0.91 (0.40 , 2.08)	0.83 (0.36 , 1.91)
≥30.0	1.94 (0.98 , 3.82)	1.87 (0.95 , 3.69)	2.46 (1.01 , 5.99)	2.49 (1.02 , 6.10)	2.57 (0.72 , 9.13)	2.31 (0.65 , 8.26)
男						
<18.5	1.64 (0.89 , 3.03)	1.90 (1.02 , 3.53)	2.64 (1.22 , 5.7)	3.07 (1.41 , 6.68)	0.92 (0.23 , 3.74)	1.00 (0.24 , 4.12)
18.5-22.9	1.58 (0.99 , 2.51)	1.61 (1.01 , 2.57)	1.85 (0.97 , 3.53)	1.87 (0.98 , 3.58)	1.40 (0.57 , 3.44)	1.37 (0.55 , 3.40)
23.0-24.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25.0-29.9	1.62 (0.91 , 2.9)	1.57 (0.88 , 2.80)	2.02 (0.91 , 4.45)	1.91 (0.86 , 4.22)	1.39 (0.45 , 4.34)	1.36 (0.44 , 4.23)
≥30.0	3.60 (0.84 , 15.36)	3.71 (0.87 , 15.88)	4.59 (0.59 , 35.75)	4.73 (0.61 , 36.94)	5.75 (0.69 , 48.1)	6.61 (0.79 , 55.65)
女						
<18.5	0.79 (0.40 , 1.55)	0.99 (0.50 , 1.96)	0.92 (0.37 , 2.26)	1.12 (0.45 , 2.81)	1.06 (0.27 , 4.18)	1.55 (0.39 , 6.24)
18.5-22.9	0.95 (0.63 , 1.44)	1.06 (0.70 , 1.62)	0.91 (0.51 , 1.63)	1.03 (0.57 , 1.88)	0.99 (0.40 , 2.42)	1.19 (0.48 , 2.95)
23.0-24.9	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
25.0-29.9	0.97 (0.59 , 1.58)	0.93 (0.56 , 1.52)	1.04 (0.53 , 2.05)	1.05 (0.53 , 2.09)	0.58 (0.17 , 1.99)	0.50 (0.15 , 1.72)
≥30.0	1.47 (0.68 , 3.17)	1.44 (0.66 , 3.13)	1.72 (0.63 , 4.68)	1.85 (0.68 , 5.09)	1.79 (0.37 , 8.63)	1.47 (0.30 , 7.25)

*：年齢、喫煙、飲酒、収縮期血圧、総コレステロール値、血糖値で調整

†：性別で調整