表8. 2000年循環器疾患基礎調査に於ける最大血圧、最小血圧の平均値

	最大血圧		最小血圧	
	男性	女性	男性	女性
年齢階級	平均値 (SD)	平均値 (SD)	平均値 (SD)	平均値 (SD)
30-39 歳	123.7 (13.0)	113.5 (13.8)	78.5 (10.4)	71.3 (10.4)
40-49 歳	130.3 (15.9)	123.4 (17.0)	84.1 (11.5)	80.0 (11.7)
50-59 歳	137.5 (19.8)	132.5 (19.5)	85.4 (12.0)	83.0 (12.1)
60-69 歳	142.0 (17.9)	140.3 (19.8)	84.1 (12.0)	82.8 (11.3)
70歳以上	146.2 (19.0)	144.7 (19.0)	80.0 (11.4)	78.5 (11.4)

最大血圧は男女ともに年齢区分が高くなり 30 歳代と比較すると 70 歳以上では男性では 23mmHg。女性では 33mmHg 高いことがわかる。これに対して最小血圧では男女ともに 50 歳代が最も高く 60 歳代、70 歳以上ではむしろ低い傾向が認められる。この背景として、高齢者では血管壁の硬化が進んで弾性が低下すると同じ血液量が低下する場合でも最大血圧は高く逆に最小血圧はむしろ低下する。高齢になっても最大血圧に比較して最小血圧が高い傾向を示す場合にはむしろ血管の弾性が高く保たれていると考えることも出来る。従って高齢者での最小血圧の高値が循環器疾患の予測因子として適切なのかどうかを明らかにする必要がある。

表9. 重回帰分析による1標準偏差あたりの最大血圧、最小血圧の循環器疾患死亡に対するハザード比*

	最大血圧		最小血圧	
年齢階級	ﾊｻﾞｰﾄﾞ比	(95% CI)	ﾊｻﾞｰﾄﾞ比	(95% CI)
30-64 歳	1.53	(1.19- 1.96)	1.52	(1.12- 2.06)
65-74 歳	1.70	(1.31- 2.20)	1.60	(1.21- 2.10)
75 歳以上	1.23	(1.03- 1.48)	1.10	(0.94- 1.28)
全年齢	1.31	(1.17- 1.47)	1.27	(1.10- 1.46)

*: 年齢、血清総コレステロール値、随時血糖、喫煙習慣、飲酒習慣を調整

しかし我が国では中高年と高齢者で血圧と循環器疾患の関係が同様にみられるか詳細な検討はなされていなかった。そこで高齢者の循環器疾患リスクの意義を最大血圧と最小血圧を比較して、高齢者の最小血圧の意義を NIPPON DATA80 の 19 年追跡データセットを用いて、降圧剤を服用していない男性について分析を行った。表 7 には男性について全年齢及び 30－64 歳、65－74 歳、75 歳以上の最大血圧と最小血圧各区分別の相対危険度を示した。最大血圧では最も若年齢層で相対危険度の変化が大きくなったが、各カテゴリーの死亡数が少ないため信頼区間が大きく相対危険度の上昇は 160mmHg 以上の区分で有意となった。65－74 歳でもほぼ同様でありその結果、最大血圧と最小血圧では年齢区分により影響が異なることが明らかとなった。年齢調整値でみると最大血圧

が最も低い群で死亡率が最も低かった。最小血圧区分でも同様であった。表 9 に最大血圧と最小血圧のそれぞれの平均的な寄与を比較するために循環器疾患死亡率の多変量調整標準化ハザード比を年齢階級別および全年齢で示した。最大血圧では、75 歳以上でやや相対危険度は小さくなるが、すべての年齢階級において最大血圧が高くなるほど循環器疾患死亡が有意に高くなることが示された。これに対して最小血圧では、75 歳未満の年齢層ではハザード比がほぼ最高血圧のそれと同じであり、この年齢層では最高血圧と最小血圧の循環器疾患への影響度はほぼ同じであることが示された。しかし高齢者では最小血圧と循環器疾患死亡の関連は明らかではなかった。これらの結果は脳卒中単独で解析した場合でもほぼ同様であったが、発症例数が少ないため十分な検討は出来ていない。

以上をまとめると 75 歳未満の対象者での循環器疾患死亡の最大血圧と最小血圧の標準化ハザード比はほぼ同じであるが、75 歳以上では最大血圧では有意にとどまったにもかかわらず、最小血圧はほとんど寄与しないことが明らかとなった。日本人においても高齢者における危険指標としては最大血圧がよりよい指標であると考えられる。循環器疾患予防のためには高齢者を含むすべての年齢層で、最大血圧をコントロールすることが重要と考えられた。女性でも同様な解析を実施したが、若年者の死亡率が低く十分な検討は出来なかった。

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日本語要約

（邦題）

日本人の代表集団における総コレステロールと死因別死亡、総死亡の関連：NIPPON DATA80 による 19 年間の追跡調査から

【背景】

既に NIPPON DATA80 の 14 年追跡により、本邦の男性の高コレステロール血症と心筋梗塞死亡の関連は明らかにされている（Okamura T, et al. J Intern Med 2003)。しかしながら女性における高コレステロール血症と心筋梗塞の関連、日本人集団における高コレステロール血症と総死亡の関連は明らかにされていない。

【方法】

全国から層化無作為抽出された日本人の代表集団である NIPPON DATA80 の 19 年追跡のデータを用いて、血清総コレステロールと総死亡、死因別死亡の関連を検討した。1980 年の循環器疾患基礎調査受検者 10,546 人のうち、循環器疾患の既往歴のある 280 人、データ欠損のある 180 人、追跡不能の 870 人を除外した 9,216 人（男性 4,035 人、女性 5,181 人)、平均年齢 50.0±13.2 歳を 1999 年まで追跡した。総コレステロールの区分は 160 未満、160-179、180-199、200-219、220-239、240-259、260mg/dl 以上の 7 つに分けて、160-179mg/dl を基準とした各疾患、総死亡の相対危険度を男女別、男女計で求めた。高血圧や糖尿病などの交絡要因を調整し、Cox の比例ハザードモデルを用いて解析した。

【結果】

男性では総コレステロールの区分が高くなるに従い段階的に虚血性心疾患死亡リスクが上昇しており、有意差はないが 200mg/dl 以上で相対危険度は 2 倍を超え、240～259 mg/dl、260mg/dl 以上の両群で有意な上昇を認めた(相対危険度はそれぞれ 3.7 と 3.8)。一方、女性では 260 mg/dl まではほぼフラットでリスクの上昇を認めず、260mg/dl 以上の群のみ有意なリスク上昇を示した(3.8)。本研究の結果から高コレステロール血症の危険因子としての意義は男女で異なることが示された。また総コレステロールと脳卒中の間に一定の傾向は認められなかった。唯一、病型別の解析でむしろ低コレステロール血症（＜160mg/dL）が脳出血のリスクであった（ハザード比 3.77、95%信頼区間 1.02-13.90)。一方、男女とも低コレステロール群（160 mg/dl 未満）群の肝臓病（肝臓がん、肝硬変、急性および慢性肝炎）死亡率は、160～199 mg/dl の群に比し有意に

約３倍高かった。病理学的機序を含めて考察すると、採血時に既に存在していた肝臓病による肝機能の低下が低コレステロール血症の原因と考えられる。肝硬変による肝臓の線維化（fibrosis）は肝臓におけるコレステロールの合成を障害する。肝臓は臓器としての予備力が高いため、自覚症状がないまま生活している人も多くそれとは気がつかないまま健診等を受診している人も多いと考えられた。総コレステロール値と総死亡の関連は、基準群（160～179 mg/dl）に比して 260mg/dl 以上と 160mg/dl 未満の両端の群でのみ有意に高いU字型の関連を示した。これは既存の国内の多くの研究と同様である。そこで“因果の逆転”の主役をなしていると考えられる肝臓病による死亡および採血から５年以内の早期死亡（採血に重症のがんなどを患っていた人の影響を除くため）を除外すると 160 mg/dl 未満の総死亡の上昇は消失した。

【結論】

本邦において男女とも高コレステロール血症は心筋梗塞の危険因子であるが、カットオフポイントは女性のほうが高めと考えられた。また総死亡はコレステロールが高い群と低い群の両方で上昇していたが、低い群での上昇には潜在的な肝臓疾患による“因果の逆転”が関与しており、低いコレステロールが肝臓病の原因とは考えにくい。日本人集団においても高コレステロール血症は総死亡を高めるリスクであると考えられる。

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The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort

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Abstract

No study has shown a positive relationship between hypercholesterolemia and all-cause mortality in the Japanese population. Therefore, a cohort study of 17.3 years' duration was conducted on 9216 participants aged 30 years or older, selected randomly from throughout Japan. In both the lowest (<4.14 mmol/L, 160 mg/dl) and highest (≥6.71 mmol/L, 260 mg/dl) total cholesterol (TC) groups, there was a positive association between TC and risk of all-cause mortality (hazard ratio (HR) 1.19; 95% confidence interval (CI), 1.03–1.37 and 1.36 (95% CI, 1.05–1.77), respectively). The lowest TC group had an increased risk of liver disease (HR 3.03; 95% CI, 1.70–5.43), whereas the highest TC group had an increased risk of coronary heart disease (HR 3.81; 95% CI, 1.70–5.43). After exclusion of deaths due to liver disease during the entire follow-up period and all-cause deaths within the first 5 years of follow-up, the increased HR in the lowest TC group disappeared (HR 1.05; 95% CI, 0.89–1.24). Although the cut-off point seemed to be higher than that for Western populations, hypercholesterolemia was shown to be positively associated with all-cause mortality in Japan.

Keywords: Cholesterol; All-cause mortality; Liver disease; Cohort studies; Risk factors

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1. Introduction

The causal relationship between high levels of serum total cholesterol (TC) and coronary heart disease is well established. Several studies in Western populations have shown clearly that a high cholesterol concentration contributes to an increased risk of all-cause mortality [1–4]. However, to our knowledge, a positive relationship between high serum levels of TC and all-cause mortality has not been reported in Asian populations [5–8].

Recent prospective studies in Japan have shown, however, that low serum TC is a predictive marker for deaths due to liver cancer in community residents [8] and for liver cancer in blood donor who are positive for antibodies to the hepatitis C virus [9]. Accordingly, the relationship between TC and all-cause mortality may be affected by liver diseases in the Japanese population, which is known to have a higher mortality from chronic liver diseases and liver cancer compared with Western populations [10].

Therefore, our a priori hypothesis was that serum TC may be associated positively with all-cause mortality in Japanese residents, but that this relationship may be modified by mortality from liver disease. In order to investigate the validity of this hypothesis, we carried out a 17.3-year cohort study to investigate the relationship between serum TC and all-cause and/or liver disease mortality.

2. Methods

2.1. Populations

A total of 10,546 community dwellers (4640 men and 5906 women), aged 30 years and over, from 300 districts participated in the National Cardiovascular Survey in 1980. These districts were randomly selected throughout Japan to avoid regional bias. In other words, this survey covered all 47 prefectures of Japan according to census population in 1980.

These participants were followed until 1999. As the overall population aged ≥30 in the surveyed districts numbered 13,771, the number of participants was 10,546 (participation rate) 76.6%). The present study extended the follow-up period of NIPPON DATA80 (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980), the details of which have been reported previously [8,11–16]. Of the 10,546 participants, a total of 1330 were excluded for the following reasons: past history of coronary heart disease or stroke ($n=280$), missing information at the baseline survey ($n=180$), and lost to follow-up ($n=870$). We then analyzed the data from the remaining 9216 participants (4035 men and 5181 women). There was no significant difference in the mean TC between the participants lost to follow-up and those in the study.

2.2. Endpoint determination

As reported previously, [8,11–16] we confirmed those participants who had died in each area by computer matching of data from the National Vital Statistics, using the area, gender, date of birth and death as key codes. In order to clarify the cause of death, we used the National Vital Statistics. In Japan, all death certificates issued by medical doctors are forwarded centrally to the Ministry of Health and Welfare via the public health centers in the area of residency. The underlying cause of death for the National Vital Statistics was coded according to the Ninth International Classification of Disease (ICD-9) until the end of 1994 and from the beginning of 1995 by the 10th International Classification of Disease (ICD-10) by specialists for coding in the Ministry of Health and Welfare. In our analyses, liver cancer (ICD-9 code: 155, 199.1; ICD-10 code: C22) and non-cancer liver disease (ICD-9 code: 70, 570–573; ICD-10 code: B15–B19, K70–K77) were combined into a single category (death due to liver disease).

Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, Japan. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (Nos. 12–18, 2000).

2.3. Baseline examination

Non-fasting blood samples were drawn and centrifuged within 60 min of collection. Serum total cholesterol and albumin were analyzed using an auto analyzer (SMA12/60; Technicon, Tarrytown, USA) at one central laboratory (Present name: Osaka Medical Center for Health Science and Promotion). Since April 1975, the precision and accuracy of the cholesterol measurements in the laboratory have been certified by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (CDC), Atlanta, Georgia [17].

Baseline blood pressures were measured on the right arm of seated participants by trained observers using a standard mercury sphygmomanometer. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, the use of antihypertensive agents, or any combination of these findings. Serum glucose was measured by the cupric-neocuproine method. Diabetes was defined as a non-fasting serum glucose ≥11.1 mmol/L, a history of diabetes, or both. Height in stocking feet and weight in light clothing were measured. Public health nurses obtained information on smoking, drinking and medical history.

2.4. Statistical analysis

We set the cut-off points for serum TC based on the combination of clinical criteria. First, we defined 4.14 mmol/L (160 mg/dl), 5.18 mmol/L (200 mg/dl) and 6.21 mmol/L (240 mg/dl) of serum TC as cut-off points according to the

adult treatment panel III [18] and international conference of low blood cholesterol [4]. The Japan Atherosclerotic Association also defined 5.69 mmol/L (220 mg/dl) or greater as a threshold criterion for hypercholesterolemia; [19] on the other hand, the manual of Health and Medical Service Law in Japan recommends medication for hypercholesterolemia when serum TC is 6.71 mmol/L (260 mg/dl) or greater [20]. Finally, we added "4.66 mmol/L (180 mg/dl)" as an additional cut-off point because there was a large number of participants with TC levels between 4.14 and 5.17 mmol/L. Consequently, the relationship between serum TC and mortality was determined in the following seven groups with 0.51 mmol/L (20 mg/dl) increments: <4.14 mmol/L (<160 mg/dl), 4.14–4.65 (160–179), 4.66–5.17 (180–199), 5.18–5.68 (200–219), 5.69–6.20 (220–240), 6.21–6.70 (240–259) and ≥6.71 mmol/L (≥260). We used the participants with TC levels between 4.14 and 4.65 mmol/L as a reference group because this was the largest of the seven TC groups. We also used quintiles of serum TC to group the participants (<4.16, 4.16–4.59, 4.60–5.03, 5.04–5.60, ≥5.61 mmol/L).

Age-adjusted mean values and the prevalence of baseline characteristics were estimated using analysis of covariance or the chi-square test. The multivariable adjusted hazard ratio (HR) for all-cause or cause-specific mortality was calculated using a Cox's proportional hazards model adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking and alcohol intake. We used three dummy variables to classify subjects based on their smoking habit (never-smoked; ex-smoker; current smoker ≤20 and >20 cigarettes/day, with never-smoked being defined as the reference group) and their alcohol intake (never-drank; ex-drinker; occasional drinker and daily drinker, with never-drank being defined as the reference group). Gender-specific analyses were also carried out.

The analyses were repeated excluding all-cause deaths within the first 5 years of follow-up and/or deaths due to liver disease during the entire follow-up period.

All confidence intervals were estimated at the 95% level and significance was assumed at a P-value of <0.05. The Statistical Package for the Social Sciences (SPSS Japan Inc. version 13.0J, Tokyo, Japan) was used for all the analyses.

3. Results

The mean age in our entire study population was 50.0 ± 13.2 years (mean ± S.D.), 49.7 ± 13.1 years in men and 50.1 ± 13.3 years in women. The mean serum TC was 4.88 ± 0.87 mmol/L (188.6 ± 33.6 mg/dl), 4.81 ± 0.85 mmol/L (186.0 ± 32.9 mg/dl) in men and 4.93 ± 0.88 mmol/L (190.7 ± 34.0 mg/dl) in women.

Table 1 shows the age-adjusted means and prevalence of the baseline characteristics of all the participants in each

Table 1
Age and age-adjusted mean value and prevalences of baseline characteristics stratified by cholesterol level at the baseline survey in 1980, NIPPON DATA80

Risk characteristics	Baseline serum total cholesterol level (mmol/L)							P-values[a]
	<4.14	4.14–4.65	4.66–5.17	5.18–5.68	5.69–6.20	6.21–6.70	6.71-	
Men								
TC, stratum mean (mmol/L)	3.74	4.39	4.91	5.41	5.90	6.41	7.30	
No. of persons	851	1000	937	648	354	167	78	
Age (years)	51.0 (14.0)	50.0 (13.4)	49.3 (13.1)	48.8 (12.6)	48.9 (11.8)	50.2 (12.2)	49.3 (11.0)	<0.001
Albumin (g/L)	43.0 (0.10)	44.1 (0.09)	44.4 (0.09)	45.0 (0.10)	45.4 (0.13)	45.6 (0.22)	45.7 (0.31)	<0.001
BMI (kg/m^2)	21.7 (0.13)	22.0 (0.09)	22.6 (0.09)	23.2 (0.11)	23.5 (0.14)	23.9 (0.21)	24.1 (0.29)	0.030
Hypertension (%)	44.9	46.3	50.3	50.3	55.4	57.5	62.8	<0.001
Diabetes (%)	1.2	0.8	1.2	1.7	1.2	0.6	2.6	0.603
Daily drinker (%)	46.7	49.5	48.9	49.4	48.3	36.5	50	0.081
Current smoker (%)	66.9	66.4	63.9	56.3	59.3	57.5	53.8	<0.001
Heavy smoker (>20 cigarettes day^{-1}) (%)	21.2	24.6	25.1	23.3	30.5	29.3	28.2	0.017
Women								
TC, stratum mean (mmol/L)	3.78	4.40	4.91	5.40	5.91	6.40	7.20	
No. of persons	952	1183	1142	925	528	275	176	
Age (years)	44.7 (12.9)	47.3 (13.0)	50.6 (12.8)	53.1 (12.9)	54.8 (12.0)	56.3 (11.5)	56.9 (11.6)	<0.001
Albumin (g/L)	43.1 (0.08)	43.3 (0.07)	43.6 (0.07)	43.9 (0.08)	44.0 (0.10)	44.0 (0.17)	44.3 (0.19)	<0.001
BMI (kg/m^2)	22.1 (0.10)	22.4 (0.10)	22.8 (0.10)	23.2 (0.11)	23.6 (0.15)	23.8 (0.20)	24.4 (0.30)	<0.001
Hypertension (%)	27.0	32.7	37.5	46.8	54.0	56.4	58.5	<0.001
Diabetes (%)	0.2	0.6	0.6	1.2	1.5	2.2	3.4	<0.001
Daily drinker (%)	3.2	2.6	3.0	2.7	3.2	1.8	2.8	0.920
Current smoker (%)	7.9	7.9	10.1	9.2	11.0	5.5	9.1	0.068
Heavy smoker (>20 cigarettes day^{-1}) (%)	0.7	0.3	0.8	0.6	1.5	0.7	0.6	0.291

[a] Analysis of covariance for continuous variables, chi-square test for categorical variables. The null hypothesis is that each mean or prevalence among all TC categories was equal. Numbers in parentheses are standard deviations for age and standard errors for other variables.

cholesterol category. The mean age in each TC group was similar in men although analysis of covariance showed statistical significance. For women, there was a trend of increasing age with increasing cholesterol levels. There were significant differences in the mean values for albumin and BMI, with these being greatest in the higher cholesterol group in both genders. There were also significant differences in the prevalence of hypertension in both genders and in the prevalence of diabetes in women. In men, the highest TC group had the highest prevalence of diabetes and current drinker; however, they did not reach statistical significance by chi-square test because of small sample size of the highest TC group. The lowest TC group had the highest prevalence of smoking in men.

The total person-years studied were 159,293 with a mean follow-up period of 17.3 years. During the follow-up period there were 1841 deaths (992 males and 849 females). Of these, 36% ($N=666$) were due to cardiovascular disease that included 128 coronary heart disease deaths and 306 stroke deaths (intra-cerebral hemorrhage, $n=65$; cerebral infarction, $n=174$; others, $n=67$).

Among the total deaths, 30% ($n=558$) were due to cancer. The three major causes of cancer death were stomach cancer ($n=131$), lung cancer ($n=107$) and liver cancer ($n=50$), a total that represented 52% of deaths due to cancer. Of all the deaths, 34% ($n=617$) were due to non-cardiovascular or non-cancer diseases. There were 35 deaths due to non-cancer liver disease (liver cirrhosis, $n=26$), which represented approximately 5% of all-cause deaths when deaths due to liver cancer were included ($n=85$).

Table 2 shows the number of deaths and multivariable-adjusted HR for the major causes of death except for cardiovascular disease according to TC stratification. Mortality from cancer was not associated with TC levels in either gender although it was highest in the lowest TC group. The mortality from non-cancer or non-cardiovascular disease was also not associated with the TC level. We found there was a positive association between the lowest TC group and increased risk for all-cause mortality in men (HR = 1.21 (95% CI, 1.01–1.45), women (HR = 1.26; 95% CI, 0.99–1.60) and in the combined data from both genders (HR = 1.19; 95% CI, 1.03–1.37). The highest TC group also had an increased risk for all-cause mortality in men (HR = 1.44; 95% CI, 0.90–2.31), women (HR = 1.24; 95% CI, 0.90–1.71) and in the combined data from both genders (HR = 1.36; 95% CI, 1.05–1.77).

Table 3 shows the number of deaths and multivariable-adjusted HRs for cardiovascular and liver disease. Mortality from cardiovascular disease was the highest in the highest TC group in both genders, with significantly higher HR in

Table 2
The number of deaths and multivariable-adjusted HRs (95% CIs) for cancer, non-cardiovascular, non-cancer and all-cause mortality; according to serum total cholesterol level in a 17.3-year follow-up study, NIPPON DATA80

Baseline serum total cholesterol level (stratum mean), mmol/L	No. of persons	Person-years	Cancer		Non-cardiovascular, non-cancer		All-cause	
			No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)
Men								
<4.14 (3.74)	851	13768	92	1.22 (0.90, 1.64)	90	1.28 (0.94, 1.74)	259	1.21 (1.01, 1.45)
4.14–4.65 (4.39)	1000	17000	84	1.00	78	1.00	241	1.00
4.66–5.17 (4.91)	937	16057	74	1.08 (0.79, 1.47)	75	1.26 (0.92, 1.74)	223	1.18 (0.98, 1.42)
5.18–5.68 (5.41)	648	11113	44	1.01 (0.67, 1.46)	44	1.32 (0.90, 1.93)	140	1.25 (1.01, 1.55)
5.69–6.20 (5.90)	354	6192	22	0.88 (0.54, 1.41)	26	1.21 (0.77, 1.89)	76	1.08 (0.83, 1.41)
6.21–6.70 (6.41)	167	2872	13	1.12 (0.62, 2.03)	5	0.49 (0.20, 1.21)	34	1.02 (0.71, 1.47)
6.71– (7.30)	78	1365	6	1.20 (0.52, 2.76)	6	1.57 (0.67, 3.64)	19	1.44 (0.90, 2.31)
Women								
<4.14 (3.78)	952	16784	34	1.19 (0.76, 1.86)	42	1.34 (0.89, 2.00)	118	1.26 (0.99, 1.60)
4.14–4.65 (4.40)	1183	21011	47	1.00	56	1.00	165	1.00
4.66–5.17 (4.91)	1142	20011	53	0.96 (0.64, 1.43)	62	1.02 (0.71, 1.47)	185	0.98 (0.79, 1.21)
5.18–5.68 (5.40)	925	16155	46	0.88 (0.58, 1.33)	61	1.00 (0.69, 1.45)	171	0.92 (0.74, 1.21)
5.69–6.20 (5.91)	528	9252	23	0.68 (0.41, 1.14)	36	0.92 (0.60, 1.41)	106	0.92 (0.74, 1.14)
6.21–6.70 (6.40)	275	4751	10	0.58 (0.29, 1.16)	23	1.19 (0.73, 1.95)	54	0.88 (0.68, 1.12)
6.71– (7.20)	176	2960	10	0.88 (0.44, 1.77)	13	1.01 (0.55, 1.88)	50	1.24 (0.90, 1.71)
Men and women combined								
<4.14 (3.76)	1803	30552	126	1.21 (0.95, 1.55)	132	1.26 (0.99, 1.61)	377	1.19 (1.03, 1.37)
4.14–4.65 (4.39)	2183	38011	131	1.00	134	1.00	406	1.00
4.66–5.17 (4.91)	2079	36068	127	1.03 (0.80, 1.31)	137	1.16 (0.91, 1.48)	408	1.09 (0.95, 1.26)
5.18–5.68 (5.40)	1573	27268	90	0.96 (0.73, 1.26)	105	1.15 (0.89, 1.50)	311	1.07 (0.92, 1.25)
5.69–6.20 (5.91)	882	15444	45	0.78 (0.55, 1.10)	62	1.05 (0.77, 1.43)	182	0.98 (0.82, 1.17)
6.21–6.70 (6.40)	442	7623	23	0.89 (0.52, 1.27)	28	0.97 (0.64, 1.47)	88	0.96 (0.76, 1.22)
6.71– (7.23)	254	4325	16	1.01 (0.60, 1.72)	19	1.19 (0.73, 1.95)	69	1.36 (1.05, 1.77)

HR, hazard ratio; 95% CI, 95% confidence interval. HR was adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking category and alcohol intake category. Gender was also adjusted while a sex-combined analysis was performed.

Table 3
The number of deaths and multivariable-adjusted hazard ratios for cardiovascular and liver disease mortality according to serum total cholesterol level, NIPPON DATA80

Baseline serum total cholesterol level (stratum mean), mmol/L	No. of persons	Person-years	Cardiovascular						Liver disease	
			All		Coronary heart disease		Stroke		No. of deaths	HR (95% CI)
			No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)	No. of deaths	HR (95% CI)		
Men										
<4.14 (3.74)	851	13768	77	1.15 (0.84, 1.58)	10	1.07 (0.46, 2.51)	43	1.21 (0.78, 1.89)	32	2.74 (1.36, 5.52)
4.14–4.65 (4.39)	1000	17000	79	1.00	12	1.00	40	1.00	11	1.00
4.66–5.17 (4.91)	937	16057	74	1.24 (0.90, 1.71)	12	1.21 (0.54, 2.71)	32	1.08 (0.68, 1.73)	10	1.07 (0.45, 2.52)
5.18–5.68 (5.41)	648	11113	52	1.51 (1.05, 2.17)	12	2.11 (0.92, 4.84)	27	1.53 (0.92, 2.54)	3	0.59 (0.16, 2.15)
5.69–6.20 (5.90)	354	6192	28	1.19 (0.77, 1.85)	9	2.17 (0.89, 5.25)	11	0.97 (0.49, 1.90)	2	0.59 (0.13, 2.68)
6.21–6.70 (6.41)	167	2872	16	1.44 (0.83, 2.48)	7	3.74 (1.44, 9.76)	3	0.53 (0.16, 1.73)	0	–
6.71– (7.30)	78	1365	7	1.68 (0.77, 3.69)	3	3.77 (1.02, 13.9)	2	0.97 (0.23, 4.07)	0	–
Women										
<4.14 (3.78)	952	16784	42	1.21 (0.81, 1.79)	7	0.94 (0.36, 2.45)	17	1.05 (0.58, 1.92)	9	3.13 (1.04, 9.42)
4.14–4.65 (4.40)	1183	21011	62	1.00	12	1.00	30	1.00	5	1.00
4.66–5.17 (4.91)	1142	20011	70	1.00 (0.71, 1.42)	10	0.73 (0.31, 1.71)	28	0.77 (0.46, 1.30)	5	0.90 (0.26, 3.12)
5.18–5.68 (5.40)	925	16155	64	0.91 (0.64, 1.30)	12	0.92 (0.41, 2.08)	31	0.80 (0.48, 1.33)	2	0.35 (0.07, 1.83)
5.69–6.20 (5.91)	528	9252	47	1.03 (0.70, 1.52)	10	1.14 (0.48, 2.70)	22	0.85 (0.58, 1.49)	4	1.07 (0.28, 4.10)
6.21–6.70 (6.40)	275	4751	21	0.95 (0.58, 1.57)	3	0.74 (0.20, 2.68)	9	0.70 (0.33, 1.50)	2	1.25 (0.24, 6.61)
6.71– (7.20)	176	2960	27	1.84 (1.15, 2.93)	9	3.33 (1.35, 8.18)	11	1.31 (0.65, 2.67)	0	–
Men and women combined										
<4.14 (3.76)	1803	30552	119	1.11 (0.86, 1.42)	17	0.91 (0.49, 1.71)	60	1.14 (0.80, 1.62)	41	3.03 (1.70, 5.43)
4.14–4.65 (4.39)	2183	38011	141	1.00	24	1.00	70	1.00	16	1.00
4.66–5.17 (4.91)	2079	36068	144	1.12 (0.89, 1.42)	22	1.01 (0.56, 1.81)	60	0.92 (0.65, 1.30)	15	1.02 (0.50, 2.06)
5.18–5.68 (5.40)	1573	27268	116	1.13 (0.88, 1.46)	24	1.42 (0.79, 2.56)	58	1.06 (0.74, 1.52)	5	0.53 (0.19, 1.45)
5.69–6.20 (5.91)	882	15444	75	1.12 (0.84, 1.49)	19	1.67 (0.90, 3.11)	33	0.94 (0.61, 1.43)	6	0.97 (0.38, 2.51)
6.21–6.70 (6.40)	442	7623	37	1.14 (0.79, 1.65)	10	1.84 (0.86, 3.91)	12	0.69 (0.37, 1.29)	2	0.62 (0.14, 2.71)
6.71– (7.23)	254	4325	34	1.90 (1.29, 2.79)	12	3.81 (1.84, 7.91)	13	1.38 (0.75, 2.54)	0	–

HR, hazard ratio; 95% CI, 95% confidence interval. HR was adjusted for age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking category and alcohol intake category. Gender was also adjusted while a sex-combined analysis was performed.

women and when the gender data were combined. The mortality for coronary heart disease suggested a positive graded relationship with TC when the gender data were combined. For men, the HR in the second highest TC group was 3.74 (95% CI, 1.44–9.76), while the HR in the highest TC group was 3.77 (95% CI, 1.02–13.9). For women, although a graded relationship was not observed, the highest TC group had a significantly increased risk of death from coronary heart disease. Mortality from stroke was not associated with TC levels in either gender. The mortality from cerebral hemorrhage was the highest in the lowest TC group in men (HR = 3.77; 95% CI, 1.35–10.5), while the mortality from cerebral infarction was not associated with TC levels in either gender (data not shown). The lowest TC group was positively associated with an increased risk for death from liver disease in men, women and the combined gender data.

The association between TC group and cause-specific mortality after excluding deaths within the first 5 years of follow-up was essentially similar to those shown in Table 2 and 3 (data not shown).

When all-cause mortality was calculated after exclusion of liver disease (Fig. 1), the increased HR in the lowest TC group disappeared (HR = 1.10, 95% CI, 0.95–1.28, for combined data of men and women). In contrast, in the combined data, the positive relationship between the highest TC group and all-cause mortality remained significant with an increase in HR (HR = 1.41, 95% CI, 1.12–1.38). After further excluding deaths within the first 5 years of follow-up, the magnitude of the HR in the lowest TC group decreased (HR = 1.05; 95% CI, 0.89–1.24), whereas the HR in the highest TC group increased even further (HR = 1.48; 95% CI, 1.12–1.96). Repeating these analyses on data grouped according to gender showed nearly identical results (data not shown).

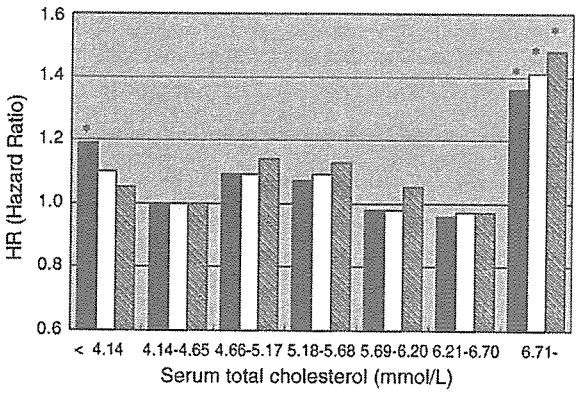

Fig. 1. Multivariable-adjusted hazard ratios (HR) for all-cause mortality grouped according to serum total cholesterol after adjustment for gender, age, serum albumin, body mass index, hypertension, diabetes, cigarette smoking and alcohol intake. Black bars show HR for all-cause mortality among all participants. White bars show HR for all-cause mortality after exclusion of deaths due to liver disease during the entire follow-up period. Hatched bars show HR for all-cause mortality after further exclusion of all-cause deaths within the first 5 years of follow-up. ($^{*}P < 0.05$).

In addition to stratifying participants based on clinical TC cut-off values, we also grouped all participants according to the quintile of serum TC. When we used the second quintile (4.16–4.59 mmol/L) as a reference group, we observed a significant increase in all-cause (HR = 1.21, 95% CI, 1.05–1.40) and liver disease mortality (HR = 2.91, 95% CI, 1.58–5.35) in the lowest TC quintile (<4.16 mmol/L, 161 mg/dl). This was similar to the results obtained in the lowest TC group (<4.14 mmol/L, 160 mg/dl) when clinical TC cut-off values were used to group the participants. However, the highest TC quintile (≥5.61 mmol/L, 217 mg/dl) was not associated with an increase in all-cause or any cause-specific mortality except for coronary heart disease (HR = 2.01; 95% CI, 1.16–3.51). When HR for all-cause mortality was calculated after exclusion of liver disease, the increased HR in the lowest TC quintile disappeared. Gender-specific analysis also showed similar results (data not shown).

4. Discussion

This 17.3-year cohort study of the Japanese population showed a positive association between the lowest (<4.14 mmol/L) or highest (≥6.71 mmol/L) TC levels and an increased risk of all-cause mortality. However, the relationship between low TC and all-cause mortality disappeared when deaths due to liver disease were excluded, with only the highest TC group showing a significant increase in all-cause mortality. The strengths of the present study were a high response rate in the baseline survey at which time several biological markers were measured and a long duration of follow-up of randomly selected subjects. The large number of person-years in the study also allowed us to use multivariable analysis to examine the relationship between high serum TC and all-cause mortality using cut-off points set higher than previous studies in Asian populations [5–8].

The prevalence of hepatitis C virus (HCV) infection in Japanese residents born before World War II has been estimated to be approximately 5–7%, [21,22] a level considerably higher than in Western countries [23–25]. Because the majority of our study participants belonged to the pre-World War II generation, the prevalence of HCV infection in our study cohort would be expected to be relatively high. It has recently been revealed that a low serum cholesterol level in individuals with chronic HCV infection is a predictor of both liver fibrosis [26] and liver cancer [9] Another study indicated that subjects with genotype 1b hepatitis C viral infection (the most common genotype of the HCV in Japan) had significantly lower serum cholesterol levels than those infected with hepatitis B virus or genotype 2a HCV, even in the pre-cirrhosis period [27].

These results suggest that hypocholesterolemia in Japan is associated with the prevalence of persistent infection with HCV. Low serum TC may be a response to liver dysfunction caused by progressive fibrotic changes rather than a primary cause of liver fibrosis. We believe these findings may partly

explain the relationship we observed between low TC and all-cause death in Japan. An epidemic of HCV infection occurred mainly in the pre-war generation of the Japanese population as a result of commercial blood transfusions carried out during the two decades after World War II [28]. This interpretation is also supported by our previous finding that a history of earlier blood transfusion was associated with hypocholesterolemia in a rural Japanese community [29].

Most cohort studies in non-Western populations have failed to demonstrate a positive relationship between high serum TC and all-cause mortality [5–8]. We found participants with a TC level ≥6.71 mmol/L, a higher level than US criteria (≥6.21 mmol/L), had an increased risk of all-cause mortality, mainly as a consequence of coronary heart disease. It was reported in the 1960 and 1970s that a cohort of Japanese people born before World War II had markedly lower serum TC levels [30]. Although subjects may have had elevated TC at the baseline survey, it was not possible to determine the duration of elevated TC levels prior to the baseline measurement. A "lag time" between exposure to high serum TC levels and the occurrence of coronary heart disease may provide an explanation of the higher cut-off value for TC in the Japanese population. Accordingly, the effect of high serum TC on both coronary heart disease and all-cause mortality may be attenuated.

Similar to previous studies in Japan, we found no positive relationship between cholesterol levels and stroke [31,32]. In fact, we observed the highest mortality for cerebral hemorrhage in the lowest TC group in men. Some studies, [8,31] but not all, [33] reported that hypocholesterolemia was associated with a higher risk of cerebral hemorrhage. However, we were unable to determine if this was a causal relationship.

The present study had some limitations. First, a single cholesterol measurement at the baseline survey may have underestimated the relationship between TC and mortality due to regression dilution effects [34]. Second, we divided the population into seven TC groups with an unbalanced number of participants based on the combination of clinical criteria because the prevalence of hypercholesterolemia (6.71 mmol/L or greater) was very small in this population. Third, we did not measure antibodies against the hepatitis C virus, and non-fasting blood collection might have affected serum glucose levels. Fourth, the change in the ICD coding from version 9 to version 10 during follow-up period may have been a confounding factor in the diagnosis of the cause of death. However, ICD coding was done by specialists in the Ministry of Health and Welfare, not by researchers. Furthermore, mortality from stroke and cancer is known to be accurately reported on death certificates in Japan [35,36]. Although underestimation of coronary heart disease deaths during the use of ICD 9 is possible, [37] this should make it more difficult to show a positive association between high TC and death due to coronary heart disease. Thus, the positive association that we observed may be conservative.

In conclusion, as in the Western populations, we showed that high serum levels of TC in the Japanese general population were positively associated with all-cause mortality, although the cut-off point appeared to be higher in Japanese residents than Westerners. Furthermore, the relationship between hypocholesterolemia and liver diseases, such as liver cancer, liver cirrhosis and hepatitis, may increase all-cause mortality in hypocholesterolemic Japanese residents.

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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：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。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。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、コックスの比例ハザードモデル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。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。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。

結果：脳梗塞死亡でU字型の関連が見られた。男女合わせた解析では最も高いBMIカテゴリ（=30kg/m^2)でハザード比の上昇(ハザード比 2.46, 95%信頼区間 1.01-5.99)が認められた。男女別の解析では、統計学的に有意差は認められなかったがそれぞれ最も高いハザード比を示した。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。

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。

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Body Mass Index and Risk of Stroke Mortality among a Random Sample of Japanese Adults: 19-Year Follow-Up of NIPPON DATA80

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Key Words
Body mass index · Stroke mortality · Cerebral infarction · Intracerebral hemorrhage · Obesity

Abstract
Background: The relationship between body mass index (BMI) and stroke mortality remains unclear. The aim of the present study was to elucidate the relationship between BMI and stroke death in a representative cohort of Japanese men and women. ***Methods:*** We analyzed a database of 9,526 men and women aged 30 years and older who were randomly selected throughout Japan in 1980. These individuals had no history of stroke and were followed for 19 years. Hazard ratios (HR) and their 95% confidence intervals (CI) of deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage were examined using Cox's proportional hazards regression models of BMI levels. ***Results:*** A U-shaped association between BMI and cerebral infarction mortality was observed. Participants with the highest BMI category (BMI ≥ 30.0) showed a significantly highest HR for cerebral infarction (HR 2.46, 95% CI 1.01–5.99). The excess risk at the lower extreme of the BMI was confined to men. These associations did not change after excluding deaths occurring in the first 2 years of follow-up. ***Conclusions:*** In the Japanese general population, a U-shaped association between BMI and cerebral infarction mortality was found and the excess risk at the lower extreme of the BMI was confined to men.

Members of the NIPPON DATA80 Research Group are listed in the appendix.

Introduction

Although high body mass index (BMI) is well recognized as a risk factor for coronary heart disease, data on the association between BMI and stroke mortality remain limited. Obesity was categorized as a 'less well documented or potentially modifiable risk factor' in the guideline statement for health professionals from the Stroke Council of the American Heart Association [1]. Several studies have found a positive association between obesity and the risk of fatal and nonfatal stroke, particularly ischemic stroke [2–8]. Others have suggested a U-

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shaped association, with individuals at either extreme of the BMI distribution at high risk [9, 10].

Most large-scale epidemiological studies have been conducted on western populations in which the criteria for obesity are different from those for Asian populations. Furthermore, few long-term follow-up studies have been conducted on Asian populations. Among Japanese men and women, the mean BMI is much lower than that of western countries [11]. However, Asian populations tend to have a higher percentage of body fat at any given BMI [12]. In Japan, the mean BMI has increased steadily over the last several decades [13, 14]. Clearly, the obesity epidemic is not restricted to western countries, and increases in mean BMI often occur at a faster rate in Asian countries than in western countries.

In the present study, we examined the relationship between BMI and deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage during 19 years of follow-up of men and women in a nationally representative cohort of the Japanese population.

Subjects and Methods

Populations

The present study was based on the National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged conducted in 1980 (NIPPON DATA80). The details of the NIPPON DATA80 have been reported previously [15, 16].

The subjects of this cohort were participants in the National Survey on Circulatory Disorders in 1980. A total of 10,546 community-dwelling individuals (4,640 men and 5,906 women) aged 30 years and over from 300 randomly selected districts participated in the survey in 1980. This cohort of subjects was followed until 1999. As the overall population aged 30 years and over was 13,771 in the surveyed districts, the participation rate in the study was 76.6%. From the total of 10,546 participants, 1,020 were excluded for the following reasons: failure to follow-up (n = 870), past history of stroke (n = 117), and some missing data in survey (n = 33). Finally, data from 9,526 participants (4,171 men and 5,355 women) were used for the analyses.

Baseline Variables

The standardized procedures used in the National Survey on Circulatory Disorders in 1980 have been described elsewhere [15–17]. Staff members of the local public health centers in the respective districts carried out the examinations in community centers. Body weight was measured with participants wearing light clothes without shoes. The height of each participant was measured without shoes by a stadiometer. Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Nonfasting blood samples were drawn and centrifuged within 60 min of collection. Frozen serum was sent to the Osaka Medical Center for Health Science and Promotion, Osaka, Japan. At the laboratory, serum total cholesterol was measured using the Lieberman-Burchard direct method. Blood sugar was measured using a cupric-neocuproine method. A Technicon SMA 1260 (Technicon Instruments, Tarrytown, N.Y., USA) was used for these measurements.

Baseline information on hypertension, history of stroke and coronary heart disease, and smoking and alcohol drinking habits were obtained from a self-administered questionnaire. Individuals who indicated a history of hypertension were asked whether they were using antihypertensive agents or not. Subjects were asked to indicate whether they were current smokers, had quit smoking, or had never smoked. For alcohol drinking habits, subjects were asked to indicate whether they were nondrinkers, ex-drinkers, occasional drinkers, or everyday drinkers. Subjects were qualified as current drinkers if the response was occasional drinker or everyday drinker.

Follow-Up and Outcome Definitions

Subjects who died during the follow-up period were identified by local public health centers. Vital statistics for determining causes of death were obtained from the Management and Coordination Agency of the Government of Japan. The underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Diseases for data regarding deaths until the end of 1994 and the 10th International Classification of Diseases for data regarding deaths from the beginning of 1995 [16].

The research protocol of the present study was approved by the Ethics Committee of Shiga University of Medical Science, Japan.

Statistical Analysis

Cox's proportional hazards regression models were used to examine the relationships between BMI and mortality. To determine the relationship between BMI and stroke mortality, BMI was entered as a categorical variable [11, 18]. Increasing levels of BMI were investigated using five BMI categories: <18.5, 18.5–22.9, 23.0–24.9, 25.0–29.9, and ≥30.0. These categories mirror WHO categories except normal category. The WHO normal category (18.5–24.9) was divided into two because the majority of the study population and events fell into that particular category. We selected the third category (23.0–24.9) as a reference. Furthermore, Cox's proportional hazard analyses were performed after excluding subjects who died within the initial 2 years of the follow-up period in order to rule out the possibility that subjects with subclinical diseases, such as cancer and chronic inflammatory disease, might have affected baseline BMI and the relationship with final outcome. Men and women were analyzed comprehensively. Smoking status, alcohol drinking can be confounded in BMI and mortality association; these variables were included in the model as well as age and sex. Blood pressure, serum total cholesterol, and glucose are considered in part to be a biological consequence of obesity, these variables were also adjusted in further analysis. Stratified analyses were performed by sex. All analyses were carried out using SAS version 8.02 for Windows (SAS Institute, Cary, N.C., USA).

Table 1. Baseline characteristics by category of BMI of 9,526 Japanese men and women aged 30 years and over in 1980, NIPPON DATA80

	BMI				
	<18.5	18.5–22.9	23.0–24.9	25.0–29.9	≥30.0
Men					
Number	273	2,194	902	765	37
Age, years	57.0 ± 16.0	50.7 ± 13.3	49.3 ± 12.4	48.5 ± 11.5	49.7 ± 12.6
Systolic blood pressure, mm Hg	137.3 ± 24.7	136.8 ± 21.0	139.6 ± 19.9	141.6 ± 19.4	143.1 ± 23.2
Diastolic blood pressure, mm Hg	79.5 ± 11.2	81.9 ± 12.2	84.8 ± 11.6	87.6 ± 12.2	91.2 ± 13.9
Serum total cholesterol, mmol/l	4.5 ± 0.7	4.7 ± 0.8	4.9 ± 0.9	5.1 ± 0.9	5.3 ± 1.0
Serum glucose, mmol/l	7.3 ± 2.0	7.2 ± 2.1	7.3 ± 2.3	7.3 ± 1.9	8.3 ± 2.5
Medication (antihypertension), %	9.2	8.0	10.2	13.6	16.2
Current smoker, %	68.9	65.5	61.8	56.3	48.7
Current drinker, %	63.0	75.0	77.1	75.0	62.2
Deaths from total stroke, n (n/TPY)	20 (5.02)	97 (2.63)	22 (1.41)	24 (1.78)	2 (3.26)
Deaths from cerebral infarction, n (n/TPY)	17 (4.26)	58 (1.57)	11 (0.70)	14 (1.04)	1 (1.63)
Deaths from intracerebral hemorrhage, n (n/TPY)	3 (0.75)	23 (0.62)	6 (0.38)	6 (0.45)	1 (1.63)
Women					
Number	381	2,620	1,135	1,056	163
Age, years	53.3 ± 15.0	49.6 ± 13.6	51.0 ± 12.9	52.4 ± 12.1	53.4 ± 12.2
Systolic blood pressure, mm Hg	128.7 ± 20.4	130.3 ± 20.5	135.3 ± 20.7	141.4 ± 21.9	146.7 ± 22.6
Diastolic blood pressure, mm Hg	75.6 ± 12.1	77.5 ± 11.3	80.6 ± 11.4	83.8 ± 11.4	88.5 ± 13.5
Serum total cholesterol, mmol/l	4.7 ± 0.8	4.8 ± 0.9	5.0 ± 0.9	5.1 ± 0.9	5.4 ± 0.9
Serum glucose, mmol/l	7.2 ± 1.9	7.0 ± 1.7	7.2 ± 1.8	7.4 ± 2.2	7.6 ± 1.8
Medication (antihypertension), %	5.8	7.9	12.6	18.8	31.9
Current smoker, %	16.3	8.5	7.7	8.7	5.5
Current drinker, %	16.3	21.8	19.9	16.7	17.2
Deaths from total stroke, n (n/TPY)	12 (1.91)	70 (1.52)	33 (1.65)	31 (1.67)	8 (2.82)
Deaths from cerebral infarction, n (n/TPY)	7 (1.11)	35 (0.76)	17 (0.85)	17 (0.92)	5 (1.76)
Deaths from intracerebral hemorrhage, n (n/TPY)	3 (0.48)	15 (0.32)	7 (0.35)	4 (0.22)	2 (0.70)

TPY = Total person-years follow-up (/1,000 person-years).

Results

The mean (± standard deviation) baseline BMI in our entire study population was 22.7 (± 3.2), with means of 22.5 (± 2.9) observed for men and 22.9 (± 3.4) for women. Table 1 shows the mean and prevalence of the baseline characteristics and unadjusted numbers of deaths due to stroke by BMI categories. Death rates are shown per 1,000 person-years. Mean values for systolic blood pressure, diastolic blood pressure, serum total cholesterol, and use of antihypertension agents in both sexes were higher in higher BMI categories. In contrast, the proportion of current smokers was higher in lower BMI categories.

Total population time observed was 164,457 person-years, and the mean follow-up period was 17.3 years. During the follow-up period, 319 deaths due to stroke were observed, including 182 cerebral infarctions, 70 intracerebral hemorrhages and 67 other types of stroke (subarachnoid hemorrhage and unclassified). The relationships among baseline BMI categories and deaths due to total stroke, cerebral infarction, and intracerebral hemorrhage are shown in table 2. A U-shaped association between BMI and cerebral infarction mortality was observed. In both men and women, the highest BMI category (≥30.0) showed the highest hazard ratio, although it did not reach statistical significance. We observed statistically significant elevation when men and women were combined. The excess risk in the lower extreme of the BMI distribution was confined to men. For total stroke mortality, pattern of association was similar to that of cerebral infarction; however, no statistically significant association was observed in the model adjusted for age, smoking, and alcohol drinking.

To exclude the influence of preexisting disease, deaths during the first 2 years of the follow-up period were excluded from the analysis. There were 25 deaths due to total stroke, including 10 cerebral infarctions and 5 intracerebral hemorrhages during the first 2-year follow-up period. After excluding such deaths, similar trends were observed.

Discussion

We found a U-shaped association between BMI and cerebral infarction mortality, the excess risk in the lower extreme of the BMI distribution was confined to men. The U-shaped association did not change after excluding deaths in the first 2 years of follow-up. The strengths of the present study are as follows: (1) the analysis of randomly selected subjects representative of the Japanese population; (2) a high participation rate (76.6%); (3) the direct collection of height, weight and biological markers from all participants; (4) a long follow-up period (19 years). Although previous cohort studies have been conducted in selected geographic areas of Japan, no follow-up studies have been conducted on a randomly selected sample throughout Japanese population. Furthermore, while several large cohort studies [10] have collected data by means of interviews, in the present study, staff members of local public health centers measured height and weight, and blood samples received from all participants were accurately measured. In Japan, a national prevention program for all Japanese residents (examination of health care under the health care law for the aged) has been in place since 1983; thus, the baseline data in the present study was not influenced by that intervention.

Some prospective studies have shown an increased risk for stroke with increasing BMI, particularly cerebral infarction [2–8]. Several studies also suggested that abdominal obesity, rather than general obesity, is associated

Table 2. Relationship between BMI and death due to total stroke, cerebral infarction, and intracerebral hemorrhage in 9,526 Japanese men and women aged 30 years and over, as determined at the 19-year follow-up of NIPPON DATA80

BMI	Stroke				Cerebral infarction			
	adjusted for age, smoking and alcohol		fully adjusted[a]		adjusted for age, smoking and alcohol		fully adjusted[a]	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Men and women[b]								
<18.5	1.14 (0.73, 1.77)	0.56	1.36 (0.87, 2.12)	0.18	1.57 (0.90, 2.73)	0.11	1.85 (1.05, 3.26)	0.03
18.5–22.9	1.21 (0.89, 1.64)	0.23	1.28 (0.94, 1.74)	0.12	1.28 (0.84, 1.96)	0.25	1.36 (0.88, 2.09)	0.17
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	1.22 (0.84, 1.78)	0.29	1.17 (0.80, 1.71)	0.41	1.43 (0.86, 2.39)	0.17	1.41 (0.84, 2.36)	0.20
≥30.0	1.94 (0.98, 3.82)	0.06	1.87 (0.95, 3.69)	0.07	2.46 (1.01, 5.99)	0.05	2.49 (1.02, 6.10)	0.05
Men								
<18.5	1.64 (0.89, 3.03)	0.11	1.90 (1.02, 3.53)	0.04	2.64 (1.22, 5.70)	0.01	3.07 (1.41, 6.68)	<0.01
18.5–22.9	1.58 (0.99, 2.51)	0.05	1.61 (1.01, 2.57)	0.05	1.85 (0.97, 3.53)	0.06	1.87 (0.98, 3.58)	0.06
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	1.62 (0.91, 2.90)	0.10	1.57 (0.88, 2.80)	0.13	2.02 (0.91, 4.45)	0.08	1.91 (0.86, 4.22)	0.11
≥30.0	3.60 (0.84, 15.36)	0.08	3.71 (0.87, 15.88)	0.08	4.59 (0.59, 35.75)	0.15	4.73 (0.61, 36.94)	0.14
Women								
<18.5	0.79 (0.40, 1.55)	0.50	0.99 (0.50, 1.96)	0.98	0.92 (0.37, 2.26)	0.85	1.12 (0.45, 2.81)	0.81
18.5–22.9	0.95 (0.63, 1.44)	0.81	1.06 (0.70, 1.62)	0.79	0.91 (0.51, 1.63)	0.76	1.03 (0.57, 1.88)	0.92
23.0–24.9	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
25.0–29.9	0.97 (0.59, 1.58)	0.89	0.93 (0.56, 1.52)	0.76	1.04 (0.53, 2.05)	0.90	1.05 (0.53, 2.09)	0.88
≥30.0	1.47 (0.68, 3.17)	0.33	1.44 (0.66, 3.13)	0.36	1.72 (0.63, 4.68)	0.29	1.85 (0.68, 5.09)	0.23

HR = Hazard ratio; CI = confidence interval.
[a] Adjusted for, age, smoking, alcohol, systolic blood pressure, serum cholesterol level, and serum glucose level.
[b] Adjusted for sex.

with an increased risk for stroke [19]. Obesity is a strong risk factor for the development of hypertension [20], diabetes [21], and hypercholesteremia [22]. It has been well established that metabolic syndrome, due to visceral fat accumulation, is a strong risk factor in ischemic stroke [22, 23]. In the present study, participants in the highest BMI group may have had more risk factors related to metabolic syndrome but were not included in the baseline survey. For example, a large proportion of obese individuals have higher visceral fat accumulation than nonobese individuals, which is a key factor of metabolic syndrome [22]. As we did not measure serum high-density lipoprotein cholesterol, triglyceride levels, or the homeostasis model assessment index, we need to adjust for or assess these factors in a further study.

One of the possible explanations for excess risk in men in the lower extreme of the BMI distribution was due to case fatality. Mortality was the only endpoint outcome in the present study; thus, results were not affected by non-fatal cerebral infarction. Kimura et al. [24], reported that the case fatality rate was 6.9% in patients with ischemic stroke and transient ischemic attack. Also Kiyohara et al. [25], reported that lower BMI was a significant risk factor for death after stroke.

Observational studies of body weight and mortality are susceptible to methodological problems, including failure to control for weight loss due to subclinical disease and the unhealthy biological effects of heavy smoking [26]. For deaths due to cerebral infarction, a U-shaped association was observed between BMI and hazard ratio among men; however no such association was observed among women. Mean BMI among women increased with increasing age. In contrast, among men, mean BMI increased in the 40s and 50s, but decreased with increasing age. The effect of age may have influenced the pattern of association even after adjusting the models for age. It is difficult to control the above-mentioned 'reverse-causal' effect and confounding factors in a cohort study. Thus, the relation between low BMI and mortality should be interpreted with caution.

The present study has several limitations. First, for detecting statistically significant relationships between BMI and mortality, especially for BMI $\geq$ 30.0, the sample size was not large enough. The prevalence of obesity (BMI $\geq$ 30.0) in Japanese adults is quite low compared with data from western populations [11]. In the present study, subjects with BMI $\geq$ 30.0 account for only 0.9% of men and 3.0% of women. Second, we used National Vital Statistics on the underlying causes of death, which are based on death certificates issued by medical practitioners, as endpoints. Stroke subtypes may lead to misclassification on death certificates. However, since the 1980s, the use of CT scans on stroke patients has been widespread among local Japanese hospitals [27]. Therefore, we believe the diagnoses of stroke subtypes on death certificates to be sufficiently accurate.

In conclusion, a U-shaped association between BMI and cerebral infarction mortality was found. The excess risk at the lower extreme of the BMI distribution was confined to men.

Intracerebral hemorrhage			
adjusted for age, smoking and alcohol		fully adjusted[a]	
HR (95% CI)	p value	HR (95% CI)	p value
1.02 (0.38, 2.72)	0.97	1.23 (0.46, 3.29)	0.69
1.19 (0.63, 2.24)	0.58	1.26 (0.67, 2.37)	0.48
1.00 (reference)		1.00 (reference)	
0.91 (0.40, 2.08)	0.83	0.83 (0.36, 1.91)	0.66
2.57 (0.72, 9.13)	0.14	2.31 (0.65, 8.26)	0.20
0.92 (0.23, 3.74)	0.91	1.00 (0.24, 4.12)	1.00
1.40 (0.57, 3.44)	0.47	1.37 (0.55, 3.40)	0.50
1.00 (reference)		1.00 (reference)	
1.39 (0.45, 4.34)	0.57	1.36 (0.44, 4.23)	0.60
5.75 (0.69, 48.10)	0.11	6.61 (0.79, 55.65)	0.08
1.06 (0.27, 4.18)	0.94	1.55 (0.39, 6.24)	0.54
0.99 (0.40, 2.42)	0.97	1.19 (0.48, 2.95)	0.71
1.00 (reference)		1.00 (reference)	
0.58 (0.17, 1.99)	0.39	0.50 (0.15, 1.72)	0.27
1.79 (0.37, 8.63)	0.47	1.47 (0.30, 7.25)	0.63

Appendix

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