were added successively to the null model (Model 1): age (Model 2), municipality population size (medium and small population sizes compared with large population size) (Model 3), and body mass index, serum total cholesterol, diabetes (serum glucose of 11.1 mmol/l or higher, history of diabetes, or both), hypertension (systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or antihypertensive drug use), current smoking, and daily alcohol consumption (Model 4). All probability values were two tailed with significance level of $p < 0.05$.

Results

Table 2 shows the baseline characteristics of the subjects by municipality population size. The subjects in the small population size were significantly older, both for men and women ($p < 0.001$). Percentages of hypertension were significantly higher among the subjects in the small population size, both for men ($p = 0.01$) and women ($p < 0.001$). On the other hand, serum total cholesterol was significantly higher among the subjects in the large population size, both for men ($p < 0.001$) and women ($p = 0.001$). As for obesity, a divergent pattern was observed between men and women, wherein body mass index was significantly higher in men ($p = 0.001$) but significantly lower in women ($p = 0.01$), among the subjects in the large population size. Percentages of current smokers and daily alcohol drinkers were significantly higher among the subjects in the large population size for women ($p < 0.001$), whereas current smokers occupied a higher percentage among the subjects in the medium population size and daily alcohol drinkers exhibited no significant difference in percentage by municipality population size in men.

Table 3 shows the numbers of persons, person-years, and numbers of deaths and mortality rate from total stroke as well as the percentages of cerebral infarction and cerebral hemorrhage by municipality population size. Crude mortality rates were higher in municipalities with large population size both in men and women, but this tendency was not observed for age-adjusted mortality rate in men. Age-adjusted mortality rate from total stroke was highest in the large municipalities in men because

Table 2

Baseline characteristics of subjects by municipality population size (Japanese men and women aged 30 years and older in 1980, NIPPON DATA80)

	Municipality population size			
	Large	Medium	Small	p
Men				
Number of subjects	1082	1570	1428	
Age (years)	49.0 (12.6)	49.5 (12.9)	52.1 (13.6)	<0.001
Body mass index (kg/m^2)	22.8 (3.0)	22.5 (2.9)	22.3 (2.7)	0.001
Serum total cholesterol (mmol/l)	5.0 (0.8)	4.8 (0.9)	4.7 (0.8)	<0.001
Diabetes (%)	7.1	6.1	7.7	0.22
Hypertension (%)	47.0	49.2	52.9	0.01
Current smoker (%)	60.4	65.7	62.7	0.02
Daily alcohol drinker (%)	48.0	47.1	49.5	0.41
Women				
Number of subjects	1459	1992	1778	
Age (years)	48.8 (12.8)	50.2 (13.1)	53.0 (13.6)	<0.001
Body mass index (kg/m^2)	22.7 (3.3)	22.8 (3.5)	23.0 (3.3)	0.01
Serum total cholesterol (mmol/l)	5.0 (0.9)	4.9 (0.9)	4.9 (0.9)	0.001
Diabetes (%)	3.8	4.5	4.0	0.52
Hypertension (%)	37.6	40.8	44.7	<0.001
Current smoker (%)	11.7	9.4	5.7	<0.001
Daily alcohol drinker (%)	4.2	2.7	1.9	<0.001

Note. Numbers in parentheses indicate standard deviation. p values were calculated by ANOVA for continuous variables and by chi square test for categorical variables. Municipality population size: Large ($\geqslant 300,000$); Medium ($30,000–<300,000$); Small ($<30,000$). Diabetes was defined as serum glucose of 11.1 mmol/l or higher, history of diabetes, or both. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, or antihypertensive drug use.

Table 3
Numbers of persons and person-years, numbers of deaths and crude and age-adjusted mortality rates from total stroke, and percentages of cerebral infarction and cerebral hemorrhage for total stroke by municipality population size in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

Municipality population size	No. of persons	No. of person-years	No. of deaths from total stroke	Mortality rate from total stroke (per 1000)		Stroke type (%)		
				Crude	Age-adjusted	Total stroke	Cerebral infarction	Cerebral hemorrhage
Men								
Large	1082	18,719	30	1.6	2.4	100	70	13
Medium	1570	26,869	59	2.2	1.4	100	58	24
Small	1428	23,502	73	3.1	1.7	100	60	27
Women								
Large	1459	26,086	25	1.0	0.9	100	44	24
Medium	1992	35,196	52	1.5	1.1	100	58	19
Small	1778	30,464	73	2.4	1.3	100	53	16

Note. Municipality population size: Large ($\geqslant 300{,}000$); Medium ($30{,}000-<300{,}000$); Small ($<30{,}000$). Age-adjusted mortality rate was standardized in accordance with the world population.

the age-specific mortality rate in the oldest age group comprised of those 85 years and older contributed to a marked rise in the overall age-adjusted mortality rate (only one person belonged to the oldest age group, and he died of a stroke after a relatively short time). Among deaths from total stroke, the percentage of deaths from cerebral infarction was consistently higher than deaths from cerebral hemorrhage by municipality population size, both in men and women.

In the three-level model where six regions of Japan were entered at level 3, no variance was observed at level 3, and the parameters at level 2 (areas) and level 1 (individuals) differed only slightly from the two-level model (individuals at level 1 nested within areas at level 2). The results of the two-level multilevel analyses are therefore shown in Table 4. In Model 1 (null model), statistically significant variance between areas was not observed in men ($p = 0.12$) but was in women ($p = 0.04$). Intraclass correlation coefficients were 7.3% for men and 10.6% for women. In Model 2, age had statistically significant effects ($p<0.001$), and variance between areas was no longer statistically significant. In the age-adjusted model (Model 3) and the multivariate-adjusted model (Model 4), women had higher regression coefficients for municipality population sizes. Odds ratios and 95% CIs were calculated in Models 3 and 4, and significantly elevated odds ratio for the small population size compared with the large population size was observed for women in Model 4. In multivariate analyses, we used a dichotomous

variable for hypertension. We then analyzed the data using instead a continuous variable for systolic and diastolic blood pressure, but similar results were obtained.

The results of two-level multilevel analyses for cerebral infarction, which was a dominant stroke type in our cohort as indicated in Table 3, are shown in Table 5. In Model 1 (null model), statistically significant variance between areas was not observed in men ($p = 0.41$) but was in women ($p = 0.04$). Intraclass correlation coefficients were 5.6% for men and 18.6% for women. In Model 2, age had statistically significant effects ($p<0.001$), and variance between areas was no longer statistically significant. In the age-adjusted model (Model 3) and the multivariate-adjusted model (Model 4), odds ratios and 95% CIs were calculated. Significantly elevated odds ratios for the small population size compared with the large population size were not observed for men or women, but odds ratios were higher for women than for men both in Models 3 and 4. In multivariate analyses, we used a dichotomous variable for hypertension. We then analyzed the data using instead a continuous variable for systolic and diastolic blood pressure, but similar results were obtained.

Discussion

In our study, we discovered a tendency for stroke mortality to be higher in rural areas than in urban areas, especially in women, using municipality population size as an indicator of urban and rural.

Table 4

Regression coefficients and odds ratios of deaths from total stroke for municipality population size by two-level multilevel logistic regression analysis in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

	Regression coefficients (SE)				Odds ratios (95%CI)	
	Model 1	Model 2	Model 3	Model 4	Model 3	Model 4
Men						
Fixed parameters						
Constant	−3.21 (0.09)	−9.16 (0.48)	−9.35 (0.51)	−9.81 (1.10)		
Individual level						
Age		0.10 (0.01)	0.10 (0.01)	0.10 (0.01)	1.11 (1.09–1.12)	1.11 (1.09–1.12)
Area level						
Municipality population size						
Medium			0.27 (0.25)	0.26 (0.25)	1.31 (0.81–2.13)	1.29 (0.80–2.10)
Small			0.33 (0.24)	0.30 (0.24)	1.40 (0.87–2.24)	1.36 (0.84–2.18)
Random parameters						
Between areas	0.26 (0.17)	0.16 (0.15)	0.15 (0.15)	0.12 (0.15)		
Women						
Fixed parameters						
Constant	−3.55 (0.09)	−10.05 (0.52)	−10.25 (0.54)	−11.28 (0.95)		
Individual level						
Age		0.11 (0.01)	0.11 (0.01)	0.10 (0.01)	1.11 (1.10–1.13)	1.11 (1.09–1.12)
Area level						
Municipality population size						
Medium			0.28 (0.26)	0.29 (0.26)	1.32 (0.79–2.20)	1.34 (0.80–2.23)
Small			0.48 (0.25)	0.52 (0.25)	1.62 (0.99–2.65)	1.68 (1.02–2.77)
Random parameters						
Between areas	0.39 (0.19)	0.12 (0.15)	0.09 (0.15)	0.10 (0.15)		

Note. Model 1, null model; Model 2, age-adjusted; Model 3, adjusted for age and municipality population size; Model 4, adjusted for age, municipality population size, body mass index, serum total cholesterol, diabetes, hypertension, current smoking, and daily alcohol drinking. Municipality population size: Large (⩾300,000); Medium (30,000–<300,000); Small (<30,000).

As our study areas were randomly selected from throughout Japan, the results are considered to reflect a general urban–rural difference in stroke mortality in Japan. As no variance was found between regions (level 3) in the three-level model, the geographical variation in stroke mortality reported a few decades ago in several ecological studies (Takahashi et al., 1957; Tamashiro et al., 1981; Ueshima et al., 1986) might have been partly a reflection of unbalanced distribution of urban and rural areas by region. This is a plausible explanation because distributions of municipalities by population size were significantly different (Table 1), and the northeastern part of Japan in particular was characterized as the region with a higher proportion of municipalities with small population size, that is, rural areas.

The urban–rural difference was more pronounced in women than in men for total stroke. To examine these results in further detail, we also showed the results for cerebral infarction, which is a dominant stroke type in our cohort. Although statistically

significant variance in the two-level null model was observed only for women, the odds ratios of deaths from cerebral infarction for the medium and small municipality population sizes compared with the large population size were higher than unity only for women. This contrast between men and women in urban–rural difference of cerebral infarction deaths seems to have contributed to the gender difference in urban–rural gradient.

Gender difference was also observed in the change of odds ratios from age-adjusted model to multivariate-adjusted model for total stroke. Multivariate analyses revealed that the urban–rural difference in stroke mortality remained after adjustment for such risk factors as hypertension and cigarette smoking. However, the odds ratios of the multivariate-adjusted model by municipality population size were slightly lower in men and slightly higher in women. This result may have been because the baseline characteristics were differently associated with municipality population size between men and women. In the multivariate-adjusted

Table 5

Regression coefficients and odds ratios of deaths from cerebral infarction for municipality population size by two-level multilevel logistic regression analysis in 19-year follow-up of Japanese men and women aged 30 years and older in 1980 (NIPPON DATA80)

	Regression coefficients (SE)				Odds ratios (95%CI)	
	Model 1	Model 2	Model 3	Model 4	Model 3	Model 4
Men						
Fixed parameters						
Constant	−3.71 (0.11)	−10.56 (0.66)	−10.59 (0.68)	−10.93 (1.43)		
Individual level						
Age		0.12 (0.01)	0.11 (0.01)	0.12 (0.01)	1.12 (1.10–1.14)	1.12 (1.10–1.15)
Area level						
Municipality population size						
Medium			0.05 (0.30)	0.03 (0.30)	1.05 (0.58–1.89)	1.03 (0.57–1.86)
Small			0.10 (0.29)	0.07 (0.29)	1.10 (0.62–1.96)	1.07 (0.60–1.91)
Random parameters						
Between areas	0.20 (0.24)	0.18 (0.23)	0.18 (0.23)	0.13 (0.22)		
Women						
Fixed parameters						
Constant	−4.19 (0.13)	−12.22 (0.80)	−12.54 (0.83)	−13.96 (1.37)		
Individual level						
Age		0.13 (0.01)	0.13 (0.01)	0.13 (0.01)	1.14 (1.11–1.16)	1.13 (1.11–1.16)
Area level						
Municipality population size						
Medium			0.52 (0.37)	0.54 (0.37)	1.68 (0.81–3.47)	1.71 (0.83–3.53)
Small			0.56 (0.36)	0.56 (0.36)	1.75 (0.86–3.57)	1.76 (0.86–3.58)
Random parameters						
Between areas	0.75 (0.36)	0.23 (0.27)	0.18 (0.26)	0.10 (0.25)		

Note. Model 1, null model; Model 2, age-adjusted; Model 3, adjusted for age and municipality population size; Model 4, adjusted for age, municipality population size, body mass index, serum total cholesterol, diabetes, hypertension, current smoking, and daily alcohol drinking. Municipality population size: Large ($\geqslant$300,000); Medium (30,000–<300,000); Small (<30,000).

model, statistically significant risk factors other than age were hypertension and current smoking for men and hypertension for women. For hypertension, the larger the municipality population size was, the lower the percentage of hypertension both in men and women. On the other hand, for current smoking in women, though it was not significant in the multivariate-adjusted model, the larger the municipality population size was, the higher the percentage of current smokers in women. For current smoking in men, no consistent trend with municipality population size was found.

We used population size of a municipality to define whether a given area was urban or rural. The questionnaire of the 1980 survey asked subjects whether the type of location of their residence was "urban" or "rural," with the latter defined as farming and fishing villages. According to this survey, percentages of subjects indicating that the location of their residence was rural were 79%, 29%, and 14% for municipalities with small, medium, and large population sizes, respectively.

This is further evidence that municipality population size is a valid indicator of the definition.

The reasons for the geographical variation of stroke mortality investigated in several ecological studies (Takahashi et al., 1957; Tamashiro et al., 1981; Ueshima et al., 1986) could be associated with urban–rural difference by area. These research groups observed that excess intake of sodium and insufficient intake of animal protein were related to high stroke mortality. Ueshima et al. (1986) examined the relationship between alcohol consumption and stroke mortality in an ecological study with prefectures as units of analysis, and found that stroke mortality was higher in the areas with high alcohol consumption. Our analyses have included several risk factors, such as hypertension and daily consumption of alcohol in multivariate models, but there remained an urban–rural gradient even after adjustment for these factors. Therefore, the gradient we observed could be related to dietary factors, such as animal protein intake. This possibility is partly explained in a pooled data analysis by

Okayama et al. (1995), which revealed that changes in serum cholesterol levels among middle-aged Japanese were consistent with the increase in meat consumption per day per capita from 23.9 to 66.2 g in rural populations and from 51.2 to 77.6 g in urban populations, based on Japan's National Nutrition Surveys conducted in 1966 and 1990.

Differences in medical resources might also have affected the urban–rural difference in stroke mortality in the study. For many years rural areas faced a lack of medical resources, and to remedy this shortage, many medical schools were founded throughout Japan in the 1980s. However, Kobayashi and Takaki (1992) revealed that a doubling of the number of physicians due to the increased number of medical schools failed to improve the disproportionate urban–rural distribution of physicians. It is no wonder that areas with fewer medical resources are disadvantaged with respect to the early detection and treatment of stroke.

Stroke incidence and mortality have been compared between urban and rural areas in several countries (Correia et al., 2004; Hong et al., 1994; Powles, Kirov, Feschieva, Stanoev, & Atanasova, 2002; Walker et al., 2000; Yiannakoulias et al., 2004). Some studies have reported higher rates in rural areas (Correia et al., 2004; Hong et al., 1994; Powles et al., 2002). Others have reported similar rates in the two areas (Yiannakoulias et al., 2004), or even lower rates in rural areas (Walker et al., 2000). Correia et al. (2004) reported higher stroke incidence among a rural population compared with an urban population in northern Portugal. In China, incidence among rural men and mortality rate among rural men and women aged 65–74 years were higher than those of their urban counterparts from 1984 to 1991 in Shanghai (Hong et al., 1994). As our data only involved stroke mortality, it is necessary to further investigate difference in stroke incidence and case fatality between urban and rural areas.

There were some limitations in our study. First, individual socioeconomic factors were not taken into account because data for income and level of education were not available and data for occupation were limited to working subjects. Second, use of Japan's National Vital Statistics for stroke deaths where stroke subtypes may generally be misclassified on death certificates is considered to be one possible shortcoming. However, most stroke cases in Japan are referred to hospitals. Moreover, computerized tomography scanning was performed

in over 85% of stroke patients in the 1980s, even in rural areas throughout Japan (Kita et al., 1999). Finally, we used a multilevel logistic regression model that did not take observation period into consideration. When we applied a frailty model of Cox regression (Therneau & Grambsch, 2000), hazard ratios for the medium and small population sizes compared with the large population size were slightly higher than the respective odds ratios from the present study, but the results did not change materially.

In conclusion, in a cohort established in 1980 and followed-up until 1999, mortality from stroke was higher in rural areas than in urban areas, especially in women. This gradient remained even after adjustment for traditional risk factors. Therefore, we next need to investigate difference in stroke incidence and case fatality between urban and rural areas.

Acknowledgements

Appendix A

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血糖値の脳出血死亡への影響に関する研究：NIPPON DATA 80

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　高血糖は脳梗塞の危険因子としてよく知られているが、高血糖と脳出血との関係はいまだ明らかではない。我々はNIPPON DATA (the National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged) 80 を用いて血糖値が脳出血死亡に及ぼす影響について前向きに検討し、血糖値が高いほど年齢調整脳出血死亡率が高いことを報告した。今回、同一の集団において、脳出血の主要な危険因子の有無別に血糖値と脳出血の関連について検討した。

対象と方法
　1980 年、全国から無作為抽出して行われた循環器疾患基礎調査の受検者に対してその後追跡調査を行って設定した集団 NIPPON DATA 80 のうち、脳卒中の既往がなく、血糖値が測定された男女 9,403 人（観察開始時 30〜92 歳）を対象とした。
　対象を血糖値の四分位別に分割し、血糖値の四分位別に脳出血の粗死亡率および全体の対象を基準として年齢調整した死亡率を求めた。さらに Cox の比例ハザードにより、血糖値の第 1 四分位を基準として他の群についてそれぞれ性、年齢、BMI、最大血圧、総コレステロール、アルブミン、降圧薬の服用、喫煙および飲酒について調整した相対ハザード比および95%信頼区間を求めた。それぞれの検討において群間の傾向はトレンド検定によって確認した。
　開始時調査で降圧薬を毎日または時々服用していると答えた者あるいは最大血圧が140mmHg 以上または最小血圧が 90mmHg 以上の者を高血圧群として、高血圧の有無別に同様の計算を行った。また、総コレステロール値が 160mg/dL 未満の者を総コレステロール低値群、現在喫煙していると答えた者を喫煙群、現在毎日あるいは時々飲酒すると答えた者を飲酒群として、それぞれの要因の有無別に同様に計算を行った。

結果と考察
　9,403 人の 19 年の観察（164,079 人年、観察期間平均 17.4 年、男 70,449 人年、女 93,630 人年）により、65 例（男 35 例、女 30 例）の脳出血による死亡が確認された。
　表1に血糖値の四分位階級別に脳出血の粗死亡率と年齢調整死亡率および第 1 四分位を基準として各群についてそれぞれ Cox の比例ハザードモデルで算出した調整ハザード比を示す。血糖値が高いほど粗死亡率、年齢調整死亡率ともに高かった。血糖値の第 1 四分位を基準とした調整ハザード比は第 2 四分位で 1.0(95%CI 0.4, 2.7)、第 3 四分位で 1.4(0.6, 3.4)、第 4 四分位で 2.2(1.0, 5.0)と血糖値が高い群ほど有意に高くなった。
　表2に高血圧の有無別にみた血糖値の四分位階級別の脳出血粗死亡率、年齢調整死亡率および調整ハザード比を示す。高血圧群では血糖値が高いほど死亡率、ハザード比ともに有意に高くなった。一方、非高血圧群においても血糖値が高いほどそれぞれが高い傾向にあった

が有意ではなかった。

表3に総コレステロール低値の有無別にみた脳出血の死亡率および調整ハザード比を示す。総コレステロール低値群では非低値群に比べ全体に死亡率が高かったが、血糖値との関連は明らかではなかった。一方、総コレステロール非低値群では、血糖値が高いほど死亡率、ハザード比ともに有意に高くなった。

表4に喫煙の有無別にみた脳出血の死亡率および調整ハザード比を示す。喫煙群、非喫煙群ともに血糖値が高いほど脳出血死亡が増加する傾向にあったが、喫煙群では有意ではなかった。

表5に飲酒の有無別にみた脳出血の死亡率および調整ハザード比を示す。喫煙と同様に、飲酒群、非飲酒群ともに血糖値が高いほど脳出血死亡が増加する傾向にあったが、飲酒群では有意ではなかった。

非高血圧群では血糖値と脳出血死亡の間に関連を認めず、高血圧群では関連を認めたことから、脳出血死亡に対して高血圧と血糖は効果を強める方向の交互作用があるものと考えられた。一方、総コレステロール低値群、喫煙群、飲酒群はそれぞれ、そうでない群と比較して脳出血の死亡率が高い傾向にあったが、それぞれの群のなかでは血糖値と脳出血の死亡率の間に有意な関連は認められなかった。これらの要因を持つ者では血糖値が低くても脳出血の死亡率が高く、結果として血糖の影響が認められにくくなったものと思われた。

本集団において、血糖値が高いほど脳出血の年齢調整死亡率が高くなることを報告したが、今回の検討において高血圧の多い集団において糖尿病への対策が重要であることが確認された。我が国は諸外国に比べて脳出血が多く、現在増え続けている糖尿病への対策が今後、より一層重要であると考えられた。

表1 血糖値階級別にみた脳出血死亡の粗、年齢調整率およびハザード比

血糖値階級	脳出血死亡率(/10万人年)		ハザード比†
(mg/dL)	粗死亡率	年齢調整死亡率	(95%CI)
1st(-113)	1.9 (8 /2372)‡	2.5	1
2nd(113-122)	2.2 (9 /2338)	2.5	1.0 (0.4, 2.7)
3rd(123-138)	4.1 (17 /2375)	3.8	1.4 (0.6, 3.4)
4th(139-)	8.0 (31 /2318)	6.0	2.2 (1.0, 5.0)
P for trend	p<0.001	p=0.010	p=0.015

†性、年齢、BMI、最大血圧、総コレステロール、アルブミン、喫煙および飲酒習慣で調整

‡死亡数/観察人数

表2　高血圧の有無別にみた血糖値階級別脳出血死亡の粗、年齢調整率およびハザード比

高血圧群(最大血圧140mmHgまたは最小血圧90mmHg以上または降圧薬服用中の者)

| 血糖値階級 | 脳出血死亡率(/10万人年) | | ハザード比† |
(mg/dL)	粗死亡率	年齢調整死亡率	(95%CI)
1st(-113)	4.4　(6 / 789)‡	3.6	1
2nd(113-122)	3.7　(6 / 967)	3.1	1.0 (0.3, 3.1)
3rd(123-138)	7.2　(14 /1146)	4.6	1.4 (0.5, 3.7)
4th(139-)	12.8　(27 /1328)	9.2	2.5 (1.0, 6.2)
P for trend	p=0.002	p=0.021	p=0.012

非高血圧群

| 血糖値階級 | 脳出血死亡率(/10万人年) | | ハザード比† |
(mg/dL)	粗死亡率	年齢調整死亡率	(95%CI)
1st(-113)	0.7　(2 /1583)‡	1.5	1
2nd(113-122)	1.2　(3 /1371)	1.3	1.2 (0.2, 9.0)
3rd(123-138)	1.3　(3 /1229)	1.9	1.5 (0.2, 9.7)
4th(139-)	2.3　(4 / 990)	2.8	1.8 (0.3,10.6)
P for trend	p=0.170	p=0.594	p=0.482

†性、年齢、BMI、総コレステロール、アルブミン、喫煙および飲酒習慣で調整

‡死亡数/観察人数

表3 総コレステロール低値の有無別にみた血糖値階級別脳出血死亡の粗、年齢調整率およびハザード比

総コレステロール低値群(160mg/dL未満)

血糖値階級 (mg/dL)	脳出血死亡率(/10万人年)		ハザード比†
	粗死亡率	年齢調整死亡率	(95%CI)
1st(-113)	3.4 (3 / 494)‡	5.4	1
2nd(113-122)	3.6 (3 / 470)	6.3	0.6 (0.1, 3.7)
3rd(123-138)	6.4 (5 / 448)	7.6	1.5 (0.3, 6.3)
4th(139-)	9.4 (6 / 396)	7.1	1.3 (0.3, 5.7)
P for trend	p=0.124	p=0.720	p=0.673

総コレステロール非低値群

血糖値階級 (mg/dL)	脳出血死亡率(/10万人年)		ハザード比†
	粗死亡率	年齢調整死亡率	(95%CI)
1st(-113)	1.5 (5 /1878)‡	2.0	1
2nd(113-122)	1.8 (6 /1868)	1.8	1.4 (0.3, 3.4)
3rd(123-138)	3.5 (12 /1927)	3.1	1.4 (0.5, 4.2)
4th(139-)	7.8 (25 /1922)	5.9	2.6 (1.0, 6.9)
P for trend	p<0.001	p=0.004	p=0.008

†性、年齢、BMI、最大血圧、アルブミン、喫煙および飲酒習慣で調整

‡死亡数/観察人数

表4　喫煙の有無別にみた血糖値階級別脳出血死亡の粗、年齢調整率およびハザード比

喫煙群（喫煙すると答えた者）

| 血糖値階級 | 脳出血死亡率(/10万人年) | | ハザード比† |
(mg/dL)	粗死亡率	年齢調整死亡率	(95%CI)
1^{st}(-113)	2.1　(3 / 804)‡	2.9	1
2^{nd}(113-122)	3.7　(5 / 760)	4.9	1.7 (0.4, 7.2)
3^{rd}(123-138)	2.4　(3 / 723)	2.9	0.9 (0.2, 4.7)
4^{th}(139-)	8.7　(11 / 776)	7.4	2.6 (0.7, 9.9)
P for trend	p=0.031	p=0.130	p=0.236

非喫煙群

| 血糖値階級 | 脳出血死亡率(/10万人年) | | ハザード比† |
(mg/dL)	粗死亡率	年齢調整死亡率	(95%CI)
1^{st}(-113)	1.8　(5 /1568)‡	2.4	1
2^{nd}(113-122)	1.4　(4 /1578)	1.5	0.7 (0.1,2.9)
3^{rd}(123-138)	4.8　(14 /1652)	4.0	1.6 (0.6, 4.6)
4^{th}(139-)	7.7　(20 /1542)	5.3	2.1 (0.8, 5.8)
P for trend	p<0.001	p=0.034	p=0.029

†性、年齢、BMI、最大血圧、総コレステロール、アルブミンおよび飲酒習慣で調整

‡死亡数/観察人数

表5 飲酒の有無別にみた血糖値階級別脳出血死亡の粗、年齢調整率およびハザード比

飲酒群（毎日または時々飲酒すると答えた者）

血糖値階級 (mg/dL)	脳出血死亡率(/10万人年)		ハザード比†
	粗死亡率	年齢調整死亡率	(95%CI)
1^{st}(-113)	2.6　(5 /1087)‡	4.1	1
2^{nd}(113-122)	3.2　(6 /1059)	4.9	1.2 (0.4, 4.1)
3^{rd}(123-138)	2.7　(5 /1029)	3.5	0.8 (0.2, 2.7)
4^{th}(139-)	8.8　(14 / 951)	7.6	2.0 (0.7, 5.9)
P for trend	p=0.016	p=0.197	p=0.278

非飲酒者群

血糖値階級 (mg/dL)	脳出血死亡率(/10万人年)		ハザード比†
	粗死亡率	年齢調整死亡率	(95%CI)
1^{st}(-113)	1.3　(3 /1285)‡	1.6	1
2^{nd}(113-122)	1.3　(3 /1279)	1.4	0.5 (0.7,3.6)
3^{rd}(123-138)	5.1　(12 /1346)	4.0	2.4 (0.7, 8.5)
4^{th}(139-)	7.5　(17 /1367)	5.0	2.8 (0.8, 9.6)
P for trend	p<0.001	p=0.018	p=0.023

†性、年齢、BMI、最大血圧、総コレステロール、アルブミンおよび喫煙習慣で調整

‡死亡数/観察人数

各脂質項目と予後の関連－特に循環器系疾患に着目して－

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はじめに

　脂質異常症が心筋梗塞に代表される動脈硬化性心血管系疾患の危険因子であることは広く知られている。とりわけ、低比重リポ蛋白（LDL）コレステロール高値が動脈硬化性心血管系疾患の発症と強く関連することが、多くの研究で示されている。ところが、最近一部の欧米における研究が、他の脂質項目（例えば、高比重リポ蛋白［HDL］コレステロールや非 HDL コレステロール）の方が将来の動脈硬化性心血管系疾患の予測という観点において、LDL コレステロールよりも優れていると報告している。適切かつ効率的な心血管系疾患の予防を考える上で、どの脂質項目が最も心血管系疾患の発症と関連があるかを明らかにすることは極めて重要と考えられる。

　しかしながら、日本では、このような観点で複数の脂質項目を比較検討し、どの脂質項目が動脈硬化性心血管系疾患の発症予測において最も優れているかを調べた研究は皆無である。日本における冠動脈疾患発生率が欧米と比して約 5 分の 1 であり、依然脳卒中による死亡率が冠動脈疾患による死亡率を上回っていることなどからも、欧米のデータを日本における心血管系疾患の予防戦略に用いることは適切でないかもしれない。

　そこで、我々は NIPPON DATA 90 を用いて、総コレステロール、HDL コレステロール、非 HDL コレステロール、総コレステロール／HDL コレステロール比と全死亡、癌による死亡、循環器疾患による死亡の関連について調査した。

方法

　NIPPON DATA 90 に参加した 8,384 名のうち、以下の条件に該当する対象者を除外した：フォローアップなし（214 名）、採血結果なし（643 名）、脳卒中または心筋梗塞の既往あり（216 名）、身長または体重の記録なし（4 名）、高脂血症のため通院中（221 名）。結果的に 7,086 名(男性 2,970 名、女性 4,116 名)が本研究の対象となった。平均観察期間は 9．6 年であった。Cox 比例ハザード回帰モデルを用いて、各脂質項目の五分位の全死亡、癌および循環器疾患による死亡に対する相対リスクならびにその 95％信頼区間を求めた。第 3 五分位を基準とした。本研究における採血結果は随時採血であったため、食事の影響を受けにくいとされる総コレステロールと HDL コレステロールに絞って検討した。また、これら 2 項目より計算され、心血管系疾患の発症との関連が強いという報告もある非 HDL コレステロール、総コレステロール／HDL コレステロール比も検討に加えた。全解析において、年齢、性別、喫煙を調整変数とした。

結果

　観察期間中 615 例の死亡を認めた。その内、237 例が癌による死亡、168 例が心血管系疾患によるものであった。総コレステロールおよび非 HDL コレステロールの第 1 五分位は全死亡と正の関連を認めた(Table 1、総コレステロール：RR [95% CI], 1.55 [1.22-1.99], P<0.001、非 HDL コレステロール：1.67 [1.31-2.14], P<0.001)。一方、総コレステロールおよび非 HDL コレステロールの第 5 五分位は有意な関連を認めなかった。総コレステロール、非 HDL コレステロールでは低値になるほど全死亡リスクが高くなる傾向性を認めた（共に Trend P<0.001）。HDL コレステロールでは第 5 五分位において、全死亡リスクが低い傾向を認めた(RR [95% CI], 0.78 [0.59-1.03], P=0.080). 総コレステロール／HDL コレステロール比は各五分位、傾向性の検定でも統計学的に有意な関係を認めなかった。

　より詳細に検討するため、癌による死亡（Table 2）と循環器疾患による死亡（Table 3）毎に同様の解析を行った。癌による死亡では、全死亡と同様に総コレステロールと非 HDL コレステロールにおいて、低値がリスクと関連する統計学的に有意な傾向を認めた（共に Trend P<0.05）。脂質 4 項目の各分位で統計学的に有意に癌による死亡と関連した群はなかったが、総コレステロール、非 HDL コレステロールともに第 4 五分位で癌による死亡リスクが低くなる傾向を認めた（総コレステロール：RR [95% CI], 0.68 [0.43-1.05], P=0.081、非 HDL コレステロール：0.68 [0.45-1.04], P=0.075)。

　驚くべきことに循環器疾患による死亡でも、総コレステロールおよび非 HDL コレステロールの第 1 五分位は心血管系疾患による死亡とも正の有意な関連を示した(総コレステロール：1.83 [1.12-2.98], P=0.015、非 HDL コレステロール：1.90 [1.14-3.18], P=0.014)。総コレステロールでは傾向性の検定でも、低値になるほど有意にリスクが高くなった（Trend P<0.05）。HDL コレステロールの第 5 五分位は循環器疾患による死亡リスクが低い傾向を認めた（RR 0.63 [0.37-1.09]、P=0.098）。

　コレステロール低値が肝機能低下例や悪性腫瘍など低栄養状態にある影響を反映している可能性も考え、トランスアミラーゼ上昇例（GOT または GPT≧50IU）ならびに観察後 3 年以内に死亡した症例を除外した上で同様な検討を行った（Table 4 と 5）。全死亡との関連を Table 4 に示す。いずれの脂質項目においても、各五分位で有意に全死亡と関連したものはなかった。しかし、傾向性の検定において、総コレステロールならびに非 HDL コレステロールでは低値になるほど有意にリスクが高くなった（ともに Trend P<0.05）。

　循環器疾患による死亡との関連を Table 5 に示す。肝障害、観察後 3 年以内に死亡した例を除外した場合には、総コレステロール、非 HDL コレステロールともに、心血管系死亡との間に有意な関連を認めなかった。一方、HDL コレステロールの第 5 五分位は有意に循環器疾患による死亡リスクが低かった（RR [95%CI], 0.51 [0.26-0.98], P=0.044）。

結語

　NIPPON DATA 90 の平均 9.6 年の観察期間の検討では、総コレステロール低値ならび

に非 HDL コレステロール低値は、全死亡のリスクとなるだけではなく、心血管系疾患による死亡のリスクでもあった。この結果の正確な原因は明らかでないが、肝障害例や観察後 3 年以内に死亡した例を除外すると、統計学的有意性が失われたことから、全身状態が不良な例の影響が示唆された。現時点での、循環器疾患による死亡例数が少なく、脳梗塞、脳出血、冠動脈疾患など疾患毎の分析ができないため、更なる観察ののち、より詳細な分析が必要であろう。

　しかしながら、一般健診などを想定した場合には、肝障害や全身状態に配慮した上で、総コレステロール低値（171 mg/dl 未満）、非 HDL コレステロール低値（115 mg/dl 未満）にも目を配る必要性が示唆される。

　一方、循環器疾患による死亡において、HDL コレステロール高値が発症防御的に作用することが示されたとともに、総コレステロール／HDL コレステロール比が循環器疾患による死亡の予測因子として有用でない可能性が示唆された。

Table 1. Relative risks for total death according to quintiles of each lipid parameters

Total Death

				Quintiles			Trend P
		Q1	Q2	Q3	Q4	Q5	
TC	No. of subjects	1446	1366	1420	1467	1387	
	Median (range)	158 (92–171)	181 (172–189)	199 (190–208)	220 (209–233)	252 (234–425)	
	No. of events	175	122	105	100	113	
	RR (95%CI)	1.55 (1.22–1.99)	1.25 (0.96–1.63)	1.00 reference	0.83 (0.63–1.09)	1.00 (0.76–1.31)	<0.001
	P	<0.001	0.092		0.180	0.991	
HDLC	No. of subjects	1413	1420	1423	1415	1415	
	Median (range)	36 (15–41)	45 (41–49)	53 (49–57)	61 (57–66)	75 (66–141)	
	No. of events	162	126	134	112	81	
	RR (95%CI)	0.95 (0.75–1.19)	0.87 (0.68–1.10)	1.00 reference	0.87 (0.67–1.11)	0.78 (0.59–1.03)	0.251
	P	0.644	0.242		0.264	0.080	
NonHDLC	No. of subjects	1415	1422	1414	1418	1417	
	Median (range)	102 (45–115)	125 (115–135)	144 (135–154)	166 (154–180)	199 (180–344)	
	No. of events	152	119	114	105	125	
	RR (95%CI)	1.67 (1.31–2.14)	1.20 (0.93–1.56)	1.00 reference	0.88 (0.68–1.15)	1.06 (0.82–1.36)	<0.001
	P	<0.001	0.161		0.348	0.681	
TC/HDLC	No. of subjects	1417	1417	1418	1410	1424	
	Median (range)	2.6 (1.5–2.9)	3.2 (2.9–3.4)	3.7 (3.4–4.1)	4.5 (4.1–5.0)	5.9 (5.0–17.1)	
	No. of events	110	110	134	116	145	
	RR (95%CI)	1.16 (0.90–1.49)	0.90 (0.70–1.16)	1.00 reference	0.83 (0.65–1.06)	0.92 (0.73–1.17)	0.087
	P	0.253	0.405		0.138	0.495	

TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; NonHDLC, non high-density lipoprotein cholesterol; TC/HDLC, TC to HDLC ratio

Table 2. Relative risks for cancer death according to quintiles of each lipid parameters

Cancer Death

		Quintiles				
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend P
TC	No	1446	1366	1420	1467	1387	
	Median (range)	158 (92–171)	181 (172–189)	199 (190–208)	220 (209–233)	252 (234–425)	
	No. of events	63	48	45	35	46	
	RR (95%CI)	1.32 (0.89–1.94)	1.14 (0.76–1.71)	1.00	0.68 (0.43–1.05)	0.94 (0.62–1.43)	0.010
	P	0.163	0.533	reference	0.081	0.785	
HDLC	No	1413	1420	1423	1415	1415	
	Median (range)	36 (15–41)	45 (41–49)	53 (49–57)	61 (57–66)	75 (66–141)	
	No. of events	64	52	50	43	28	
	RR (95%CI)	1.00 (0.69–1.45)	0.95 (0.64–1.40)	1.00	0.92 (0.61–1.38)	0.70 (0.44–1.11)	0.174
	P	0.989	0.781	reference	0.670	0.128	
NonHDLC	No	1415	1422	1414	1418	1417	
	Median (range)	102 (45–115)	125 (115–135)	144 (135–154)	166 (154–180)	199 (180–344)	
	No. of events	55	41	52	38	51	
	RR (95%CI)	1.30 (0.88–1.90)	0.87 (0.58–1.31)	1.00	0.68 (0.45–1.04)	0.92 (0.62–1.35)	0.049
	P	0.187	0.499	reference	0.075	0.660	
TC/HDLC	No	1417	1417	1418	1410	1424	
	Median (range)	2.6 (1.5–2.9)	3.2 (2.9–3.4)	3.7 (3.4–4.1)	4.5 (4.1–5.0)	5.9 (5.0–17.1)	
	No. of events	38	41	57	44	57	
	RR (95%CI)	0.92 (0.61–1.38)	0.79 (0.53–1.19)	1.00	0.73 (0.49–1.08)	0.84 (0.58–1.22)	0.605
	P	0.671	0.261	reference	0.111	0.361	

TC, total cholesterol; HDLC, high–density lipoprotein cholesterol; NonHDLC, non high–density lipoprotein cholesterol; TC/HDLC, TC to HDLC ratio

Table 3. Relative risks for CVD death according to quintiles of each lipid parameters

CVD Death

		Quintiles					
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Trend P
TC	No	1446	1366	1420	1467	1387	
	Median (range)	158 (92–171)	181 (172–189)	199 (190–208)	220 (209–233)	252 (234–425)	
	No. of events	49	32	25	31	31	
	RR (95%CI)	1.83 (1.12–2.98)	1.33 (0.82–2.34)	1.00	1.09 (0.64–1.84)	1.15 (0.68–1.95)	0.023
	P	0.015	0.224	reference	0.760	0.609	
HDLC	No	1413	1420	1423	1415	1415	
	Median (range)	36 (15–41)	45 (41–49)	53 (49–57)	61 (57–66)	75 (66–141)	
	No. of events	48	30	40	31	19	
	RR (95%CI)	0.95 (0.62–1.44)	0.70 (0.43–1.12)	1.00	0.78 (0.49–1.25)	0.63 (037–1.09)	0.269
	P	0.792	0.135	reference	0.306	0.098	
NonHDLC	No	1415	1422	1414	1418	1417	
	Median (range)	102 (45–115)	125 (115–135)	144 (135–154)	166 (154–180)	199 (180–344)	
	No. of events	37	39	25	31	36	
	RR (95%CI)	1.90 (1.14–3.18)	1.84 (1.13–3.09)	1.00	1.22 (0.72–2.07)	1.42 (0.85–2.37)	0.074
	P	0.014	0.016	reference	0.462	0.179	
TC/HDLC	No	1417	1417	1418	1410	1424	
	Median (range)	2.6 (1.5–2.9)	3.2 (2.9–3.4)	3.7 (3.4–4.1)	4.5 (4.1–5.0)	5.9 (5.0–17.1)	
	No. of events	25	33	35	32	43	
	RR (95%CI)	1.03 (0.62–1.72)	1.03 (0.64–1.65)	1.00	0.89 (0.55–1.44)	1.06 (0.68–1.65)	0.930
	P	0.916	0.916	reference	0.630	0.813	

CVD, cardiovascular disease; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; NonHDLC, non high-density lipoprotein cholesterol; TC/HDLC, TC to HDLC ratio