を解析するときのもっとも一般的に使用されている生存解析法の一方法である．Cox 比例ハザードモデルではベースライン時の要因 $x$ と死亡確率との関連を，瞬間的な死亡の強さ(ハザード)という概念を介して結びつけている．つまり，ベースライン時に要因 $x$ をもっているヒトの，ベースラインからの追跡時間 $t$ での死亡ハザードを $\lambda(t:x)$ とすると，$\lambda(t:x)=\lambda_0(t)\times e^{\beta x}$ としてモデル化しているのである．ここで，$\lambda_0(t)$ は基準ハザードであり，$\beta$ は要因 $x$ の回帰係数である．つまり，ベースライン時の要因 $x$ は，基準ハザードを“基準”にすれば，追跡時間 $t$ とは無関係に(比例的に)死亡ハザードに影響しているということである．

この比例ハザードモデルの下で，生存関数を求めると，要因 $x$ をもっているヒトの時間における生存確率 $S(t:x)$ は，$S(t:x)=[S_0(t)]^{\exp(\beta x)}$，となる．ここで，$S_0(t)$ は基準ハザード $\lambda_0(t)$ に対応する生存率である．さらに，集団での要因の平均 $\bar{x}$ を用いて，$S(t:x)$ をすこし変形すると，$S(t:x)=\{[S_0(t)]^{\exp(\beta\bar{x})}\}^{\exp(\beta(x-\bar{x}))}$ である．右辺の $[S_0(t)]^{\exp(\beta\bar{x})}$ は，対象集団での要因の平均 $\bar{x}$ をもっているヒトの時間 t における生存率になっている．したがって，要因の平均 $\bar{x}$ の生存確率 $[S_0(t)]^{\exp(\beta\bar{x})}$ を求めれば，それを $\exp(\beta(x-\bar{x}))$ 乗した形で，要因 $x$ に対応した生存確率 $S(t:x)$ が推定されることになる．死亡確率はしたがって，$1-S(t:x)$ である．

このようにして要因 $x$ に対応した死亡確率が推定される．しかし，手計算は無理であり，統計ソフトを利用することになる．

## 統計解析ソフト SAS の利用

実際に，NIPPON DATA 80 に基づいて死亡確率を推定し，それをチャートの形で色づけ示したものがすでに述べた図 1 である．このチャートを作成するための SAS プログラムを示す．エンドポイント評価指標である冠動脈疾患死亡に影響を与える要因としてベースライン時年齢，収縮期血圧，総コレステロール，随時血糖，喫煙を考慮し，Cox 比例ハザードモデルに必要なデータがファイル名 nippon80. dat に入っているものとする．

表 1 に示しているように，データはベースライン時年齢(AGE)，収縮期血圧(SBP)，総コレステロール(TC)，随時血糖値(BS)，喫煙(SMK)，冠動脈疾患死亡の有無(CHD)，追跡年(PYEAR)の並びであるとする．冠動脈疾患死亡は，変数名 CHD で，0 は生存，1 は死亡である．

表 1　ファイル名 nippon80.dat のデータ

| | | | | | | |
|---|---|---|---|---|---|---|
| 69.3 | 166 | 149 | 115 | 1 | 0 | 19 |
| 74.8 | 138 | 196 | 134 | 1 | 1 | 0.57 |
| 82.1 | 132 | 185 | 119 | 1 | 1 | 2.82 |
| 69.1 | 222 | 252 | 139 | 1 | 0 | 19 |
| 52.3 | 150 | 191 | 142 | 2 | 0 | 14 |
| 63.6 | 140 | 166 | 115 | 1 | 0 | 19 |
| ・ | ・ | ・ | ・ | ・ | ・ | ・ |
| ・ | ・ | ・ | ・ | ・ | ・ | ・ |

表 2 は SAS に nippon80. dat からデータを入力し，つぎに Cox モデルを走らせ，回帰係数，および要因の平均値に対応する生存率を求めるための SAS プログラムを示している．なお，SAS データステップのなかで，随時血糖および喫煙は 0-1 データに変換している．

実際に SAS を走らせると表 3 のような結果が出力される．要因(age, sbp, tc, bsc, smkc)の回帰係数 $\beta$ は，Parameter Estimate の欄をみれば，$\beta=(0.100,\ 0.011,\ 0.012,\ 0.852,\ 0.333)$ と推定さ

**サイドメモ**

### NIPPON DATA

循環器疾患基礎調査は，わが国における循環器疾患およびその危険因子の実態を知り循環器疾患の予防と治療に資することを目的として，ほぼ 10 年おきに行われている．層化無作為抽出により選択された日本を代表する 30 歳以上を対象とする横断調査である．NIPPON DATA は，この循環器疾患基礎調査を断面調査のみに終わらせることなく，対象者を追跡調査したものである[1,2]．この追跡調査によって，わが国を代表する若年者から高齢者にわたる広い範囲の年齢層において循環器疾患の危険因子を明らかにすることができ，循環器疾患の疫学・予防研究にとって有用な情報源となった．なお，NIPPON DATA は National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged の略称であり，1980 年の循環器基礎調査対象者の追跡調査である NIPPON DATA 80 と 1990 年の循環器基礎調査対象者の追跡調査である NIPPON DATA 90 とがある．

表 2　回帰係数，および要因の平均値に対応する生存率を求めるための SAS プログラム

```
data death ;      (data から run までで作成されるデータを SAS データとしてファイル名 death に格納する)
infile 'nippon80.dat' ;      (SAS に input するデータの元ファイルは nippon80.dat にあることの意味)
input age sbp tc bs smk chd pyear ;      (input する変数名を定義する)
bsc=0 ;                                  (随時血糖 bs が 200 未満は bsc=0200 以上は bsc=1
if bs>=200 then bsc=1 ;                        とする 0-1 ダミー変数 bsc を定義する)
smkc=0 ;                                 (喫煙 smk が 2 以上のとき喫煙者，1 のとき非喫煙者
if smk>=2 then smkc=1 ;                        とする 0-1 ダミー変数 smkc を定義する)
run ;
proc phreg data=death ;      (上で作成された SAS データ death を使って比例ハザード回帰分析をする)
model pyear*chd(0)=age sbp tc bsc smkc ;      (追跡時間 pyear と評価指標 chd とを＊で結びつけ，chd が 0 のとき
                                               センサード(生存)である．回帰係数を求める要因を＝の後に列記)
baseline out=abcd survival=s ;      (baseline コマンドを使って要因の平均に対応する生存率を求める．その生存率
                                     をファイル名 abcd に出力し，生存率 survival は s という変数名にする)
run ;
proc print data=abcd ;      (上で出力された abcd のファイルを書き出す)
run ;
```

上記のプログラム中の下線部は SAS の規定コマンドである．また，記号；は必要である．

表 3　SAS による計算結果のアウトプット

Analysis of Maximum Likelihood Estimates

| Variable | DF | Parameter Estimate | Standard Error | Wald Chi-Square | Pr> Chi-Square | Risk Ratio |
|---|---|---|---|---|---|---|
| AGE | 1 | 0.100162 | 0.01195 | 70.2539 | 0.0001 | 1.105 |
| SBP | 1 | 0.011279 | 0.00552 | 4.17003 | 0.0411 | 1.011 |
| TC | 1 | 0.011802 | 0.00333 | 12.5253 | 0.0004 | 1.012 |
| BSC | 1 | 0.852447 | 0.36884 | 5.34148 | 0.0208 | 2.345 |
| SMKC | 1 | 0.332785 | 0.25457 | 1.70883 | 0.1911 | 1.395 |

| OBS | AGE | SBP | TC | BSC | SMKC | PYEAR | S |
|---|---|---|---|---|---|---|---|
| 1 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 0 | 1 |
| 2 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 0.91 | 0.99992 |
| 3 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 1.56 | 0.99984 |
| ・ | ・ | ・ | ・ | ・ | ・ | ・ | ・ |
| 27 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 9.43 | 0.99742 |
| 28 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 9.62 | 0.99730 |
| 29 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 10.09 | 0.99718 |
| ・ | ・ | ・ | ・ | ・ | ・ | ・ | ・ |
| 68 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 18.27 | 0.99034 |
| 69 | 50.6439 | 138.556 | 186.021 | 0.038835 | 0.62965 | 18.29 | 0.99011 |

れた．さらに，対象集団での要因の平均(下段の表の AGE，SBP，TC，BSC，SMKC の各欄の値)をみると，$(\overline{age}, \overline{sbp}, \overline{tc}, \overline{bsc}, \overline{smkc})=(50.64, 138.6, 186.0, 0.039, 0.630)$であり，この集団平均に対応する生存確率は PYEAR の欄の追跡 10 年時点(ここでは 10.09)での生存率 S をみると 0.997 と推定された．したがって，ある与えられた要因 $x=(age, sbp, tc, bsc, smkc)$をもつヒトの 10 年時点の生存率は，

$$S(10:x)=(0.997)^{[\exp(0.100(age-50.64)+0.011(sbp-138.6)+0.012(tc-186.0)+0.852(bsc-0.039)+0.333(smkc-0.630)]}$$

を計算すれば求められる．追跡 10 年内での死亡率はしたがって，$1-S(10:x)$である．

たとえば，収縮期血圧 170，総コレステロール

230，随時血糖 200 以上，非喫煙，年齢 65 歳のヒトの 10 年生存率を求めるならば，$age=65$，$sbp=170$，$tc=230$，$bsc=1$，$smkc=0$ を代入すると，$S(10:x)=(0.997)^{[\exp(0.100(65-50.64)+0.011(170-138.6)+0.012(230-186.0)+0.852(1-0.039)+0.333(0-0.630)]}=0.967$，したがって，10 年以内の死亡率 $1-S(10:x)$ は 3.27%となる．

このようにしてベースライン時年齢，収縮期血圧，総コレステロール，随時血糖区分，喫煙区分，のあらゆる組合せで 10 年以内の死亡率が計算でき，その計算された死亡率をレベルに応じて適当に分割し色づけすれば，リスク評価チャートが作成される．死亡率をどのように分割して色づけするかは，このチャートを用いる場面を念頭に入れて作成する必要がある．

## おわりに

個人個人の危険因子のレベルに応じた予後発症確率を定量的に表す危険度評価チャートの作成方法について解説した．Cox 比例ハザードモデルを用いて，各危険因子の回帰係数および集団の平均的な危険因子レベルに対応する基準生存率を算出する手続きを踏んでおけば，あらゆる危険因子レベルに応じた予後発症確率を計算でき，それに基づいて危険度評価チャートが作成される．SAS プログラムについても解説しているので，研究者が各自の追跡調査に基づいて独自のリスク評価チャートを作成することができるものと思われる．

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研究成果の要約

# 日本人代表集団におけるBMI別の脳梗塞死亡および脳出血死亡に対する血圧の影響

**Miyamatsu N, Kadowaki T,Okamura T et al. Different Effects of Blood Pressure on Mortality from Stroke Subtypes Depending on BMI Levels: a 19-year Cohort Study in the Japanese General Population - NIPPON DATA80 – J of Human Hypertension 2005, Volume 19, Number 4, Pages 285-291.**

【研究の目的】高血圧が脳卒中の最も重要な危険因子のひとつであることは数多くの研究で示されてきたが、肥満が脳卒中に及ぼす影響については報告により異なる。これは、肥満が血圧と脳卒中との関連に影響を与えていること、次に同じ脳卒中であっても脳出血と脳梗塞とでは病態や発症機序が異なっており病型別の検討が必要であることを示している。また、欧米人と日本人では脳卒中の病型分布や肥満度が大きく異なっており、日本における脳卒中予防対策のためには日本人対象の調査に基づいた上記の危険度評価が必要である。

【研究方法】全国から無作為抽出された300地区に居住する1980年の循環器疾患基礎調査受診者10546人を19年間追跡した(NIPPON DATA80)。このうち、脳卒中の既往がなく、かつ情報に欠損のない9338人を解析対象とした。1980年当時のBMI値で3分し、各BMI階級別に収縮期・拡張期血圧10mmHg上昇による総脳卒中死亡・脳梗塞死亡・脳出欠死亡の相対危険度を性・年齢・血清総コレステロール値、血清アルブミン値、血糖値、BMI、喫煙習慣、飲酒習慣、降圧剤内服、糖尿病の既往を統計学的に補正し算出した。

【結果】解析対象者の平均観察年数は17.3年であり、追跡期間中に観察された脳卒中死亡は311人、うち脳梗塞死亡は176人、脳出血死亡は68人であった。BMI3分位による肥満度別の分析では、中～高BMI階級で収縮期血圧上昇が総脳卒中死亡と関連していたのに対し、低BMI階級では有意な関連を認めなかった。しかし病型別の検討では、収縮期血圧上昇は低～中BMI階級で脳出血死亡を、中～高BMI階級では脳梗塞死亡を有意に上昇させた(下表参照)。この結果は拡張期血圧についても同様であった。

**表. BMI別にみた収縮期血圧と総脳卒中死亡、脳卒中病型別死亡との関連**

| | 総脳卒中死亡 | | | 脳梗塞死亡 | | | 脳出血死亡 | | |
|---|---|---|---|---|---|---|---|---|---|
| BMI | RR | 95%CI | p value | RR | 95%CI | p value | RR | 95%CI | p value |
| -21.2 | 1.09 | (1.00-1.18) | 0.06 | 0.96 | (0.85-1.07) | 0.42 | 1.38 | (1.17-1.62) | <0.001 |
| 21.3-23.8 | 1.15 | (1.06-1.26) | <0.01 | 1.19 | (1.06-1.33) | <0.001 | 1.23 | (1.03-1.47) | 0.02 |
| 23.9- | 1.20 | (1.09-1.33) | <0.001 | 1.21 | (106-1.38) | 0.01 | 1.23 | (0.99-1.52) | 0.07 |

注) RRは収縮期血圧10mmHG上昇による相対危険度。

【メッセージ】血圧上昇が関連する脳卒中死亡は肥満度によって病型が異なるものの、脳卒中死亡の予防のためには全ての肥満度において血圧管理が重要である。

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ORIGINAL ARTICLE

# Different effects of blood pressure on mortality from stroke subtypes depending on BMI levels: a 19-year cohort study in the Japanese general population—NIPPON DATA80

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**To evaluate the relationship between blood pressure and cerebrovascular death depending on body mass index (BMI) levels, we analysed a database of 9338 subjects from the National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, which was originally conducted a baseline survey in 1980 and followed up in 1999. Relative risk (RR) and a 95% confidence interval (CI) of death from total stroke, cerebral infarction, and intracerebral haemorrhage after adjusting for age, sex, serum cholesterol, albumin, glucose, the use of antihypertensive agents, a past history of diabetes, BMI, smoking, and drinking were estimated with the Cox-proportional hazard model in the BMI tertile groups of a representative Japanese population. Cutoff points of BMI tertiles are 21.2 and 23.8 kg/m$^2$. The results indicated that a 10 mmHg systolic blood pressure (SBP) increase was associated with mortality from intracerebral haemorrhage at low and middle BMI groups (RR = 1.38 and 1.23; 95% CI = 1.17–1.62 and 1.03–1.47, respectively). SBP was positively associated with mortality from cerebral infarction in middle and high BMI groups (RR = 1.19 and 1.21; 95% CI = 1.06–1.33 and 1.06–1.38, respectively). The effects of diastolic blood pressure on intracerebral haemorrhage and infarction had the same tendency as those of SBP. These results suggested that the causal effect of blood pressure on stroke subtypes might be modified by BMI.**
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**Keywords:** stroke; body mass index; intracerebral haemorrhage; cerebral infarction; cohort study

## Introduction

Stroke was a leading cause of death in Japan until 1980, and is still one of the three major causes of deaths, although mortality from stroke has decreased considerably for several decades.[1–3] An above-mentioned decrease has especially been observed in mortality from cerebral haemorrhage.[2] Many studies have reported that hypertension is one of the most important risk factors in total strokes and a risk factor for all subtypes, such as intracerebral haemorrhage and cerebral infarction.[4–9]

It has been well elucidated that body mass index (BMI) is positively associated with blood pressure.[10] However, the relationship between BMI and stroke mortality or morbidity is still controversial.[11–15] Recently, there have been no significant differences in mean blood pressures between Japanese and Caucasian populations.[16] However, the proportions of stroke subtypes in Japanese and Caucasians are quite different; there is a much higher prevalence of cerebral haemorrhage in Japan than in Caucasians.[17] Furthermore, the mean BMI of the Japanese is much lower than that of Western populations.[16]

Our *a priori* hypothesis was therefore that increased blood pressure is a risk factor in stroke and

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the combination of blood pressure and BMI would be a predictable marker of stroke subtypes in the Japanese general population. To investigate this hypothesis, we analysed the database from a 19-year prospective study of 9338 participants in the National Survey on Circulatory Disorders conducted by the Ministry of Health and Welfare in 1980.

## Methods

### Population

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 which have previously been reported elsewhere.[18–22] Briefly, a total of 10 546 community dwellers (4640 men and 5906 women) aged 30 years and over from 300 randomly selected districts participated in the survey, and were followed up until November, 1999. Of the 10 546 participants, 1208 were excluded for the following reasons: failure to follow-up ($n = 908$), past history of stroke ($n = 110$), and some missing information in the baseline survey ($n = 190$). This left 9338 participants (4081 men and 5257 women) for inclusion in the analysis.

### End point determination

The procedure for end point determination has been reported elsewhere.[19–21] Briefly, the underlying causes of death for Japan's National Vital Statistics were to be coded according to the 9th International Classification of Disease (ICD-9) by the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. Codes of 430–438 in ICD-9 and I60–I69 in ICD-10 were defined as death from total strokes, which included death from cerebral infarction (codes of 433, 434, 437.7a, 7b in ICD-9, I61 and I69.1 in ICD-10) and from cerebral haemorrhage (codes of 431–432 in ICD-9, I63 and I69.3 in ICD-10).

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

### Baseline examination

Baseline blood pressures were measured by trained observers with a standard mercury sphygmomanometer on the right arm of seated subjects after a 5-min rest. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or higher, a diastolic blood pressure (DBP) of 90 mmHg or higher, the use of antihypertensive agents, or any combination of these. Height in stocking feet and weight in light clothing were measured. The BMI was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on smoking and drinking, and medical history.

Nonfasting blood samples were drawn and centrifuged within 60 min of collection. Serum total cholesterol and albumin were analysed in an auto analyzer (SMA12/60; Technicon, Tarrytown, USA) at one specific laboratory (Center for Adult Diseases, Osaka). The laboratory has been certified since April 1975 by the CDC-NHLBI Lipid Standardization Program of the Center for Disease Control and Prevention (CDC), Atlanta, regarding the precision and accuracy of its cholesterol measurements.[23] Serum glucose was measured by the cupric-neocuproine method with some auto analyzer.[24]

### Statistical analysis

Mean values and the prevalence of baseline characteristics were calculated in each group according to BMI tertiles, and the differences were tested by analysis of covariance with adjustment for age and sex or $\chi^2$ tests. The cutoff points for BMI tertiles were 21.2 and 23.8. We computed geometric means (antilogarithms of the log-transformed mean) for serum glucose because the distribution of this variable was positively skewed.

Multivariate-adjusted RRs and a 95% CI for a 10 mmHg increment of SBP or DBP on mortality from cerebral infarction, intracerebral haemorrhage and total stroke were calculated using the Cox-proportional hazard model adjusting for age, sex, serum cholesterol, albumin, glucose (log-transformed), the use of antihypertensive agents, a past history of diabetes, BMI, smoking (current smoker or not), and drinking (current drinker or not). We also did sex-specific analysis. RRs associated with a 10 mmHg increase in SBP or DBP were calculated.

The Statistical Package for Social Science (SPSS Japan Inc. Version 11.0J, Tokyo, Japan) was used for the analyses. All probability values were two-tailed with a significance level of $P < 0.05$, and all CIs were estimated at the 95% level.

## Results

Table 1 lists the characteristics of the participants according to BMI tertiles in the baseline survey. Mean values of SBP, DBP, serum cholesterol, albumin, glucose, and the prevalence of hypertension, antihypertensive medication, past history of diabetes were higher in higher BMI tertiles. On the other hand, prevalence of current smoker was higher in lower BMI tertiles.

Table 2 shows the crude mortality from total stroke, cerebral infarction, and cerebral haemorrhage. Mean follow-up period of this study was

**Table 1** Age- and sex-adjusted means (standard errors) and prevalence of risk characteristics in study participants according to BMI tertiles in 19-year follow-up of NIPPON DATA80 database

| *BMI tertiles* | *Low (n = 3116)* | *Middle (n = 3111)* | *High (n = 3111)* | P *value** |
|---|---|---|---|---|
| Men (%) | 44.3 | 45.5 | 41.4 | 0.04 |
| BMI stratum mean (kg/m$^2$) | 19.5 (0.03) | 22.5 (0.03) | 26.2 (0.03) | <0.01 |
| Age[a] | 50.9 (14.4) | 50.3 (13.0) | 50.6 (12.1) | 0.19 |
| SBP (mmHg) | 131.4 (0.33) | 135.7 (0.33) | 140.5 (0.33) | <0.01 |
| DBP (mmHg) | 77.9 (0.05) | 81.2 (0.05) | 84.9 (0.05) | <0.01 |
| Serum cholesterol (mmol/l) | 4.7 (0.02) | 4.9 (0.02) | 5.1 (0.02) | <0.01 |
| Serum albumin (g/l) | 43.6 (0.04) | 44.0 (0.04) | 44.2 (0.04) | <0.01 |
| Serum glucose (mmol/l)[b] | 7.0 | 7.0 | 7.2 | <0.01 |
| Current smokers (%) | 35.8 | 33.5 | 28.5 | <0.01 |
| Current drinkers (%) | 42.9 | 47.0 | 41.6 | <0.01 |
| Hypertension (%) | 29.0 | 38.0 | 48.6 | <0.01 |
| Antihypertensive medication (%) | 6.7 | 10.3 | 15.3 | <0.01 |
| Past history of diabetes (%) | 2.4 | 2.6 | 4.1 | 0.01 |

BMI: body mass index (kg/m$^2$).
Cutoff points of BMI tertiles are 21.2 and 23.8.
Hypertension was defined as a SBP of 140 mmHg or higher or a DBP of 90 mmHg or higher or current use of antihypertensive agentes, regardless of blood pressure.
NIPPON DATA80: National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980.*ANOVA for continuous variables and $\chi^2$ test for dichotomous variables.
[a]Mean and standard deviation.
[b]Geometric mean value.

**Table 2** Crude mortality from total stroke, cerebral infarction, and intracerebral haemorrhage by body mass index levels in 19-year follow-up of NIPPON DATA80 database

| | | | *Total stroke* | | *Cerebral infarction* | | *Intracerebral haemorrhage* | |
|---|---|---|---|---|---|---|---|---|
| *BMI tertiles* | *No. of person* | *Person-year* | *No. of death* | *Rate (per 1000 person-years)* | *No. of death* | *Rate (per 1000 person-years)* | *No. of death* | *Rate (per 1000 person-years)* |
| Low | 3116 | 52 331 | 114 | 2.1 | 69 | 1.3 | 26 | 0.5 |
| Middle | 3111 | 54 325 | 108 | 2.0 | 58 | 1.1 | 24 | 0.4 |
| High | 3111 | 54 658 | 89 | 1.7 | 49 | 0.9 | 18 | 0.3 |

BMI: body mass index (kg/m$^2$).
Cutoff points of BMI tertiles are 21.2 and 23.8.
NIPPON DATA80: National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980.

17.3 years (161 315 person-years). During the follow-up period, 311 deaths from stroke were observed, including 176 cerebral infarctions, 68 intracerebral haemorrhages, and 67 other types of stroke (subarachnoidal haemorrhage and unclassified). A 10 mmHg increase in SBP was positively associated with death due to total stroke, cerebral infarction, and intracerebral haemorrhage (RR = 1.14, 1.10, and 1.26; 95% CI = 1.08–1.20, 1.02–1.18, and 1.14–1.40, respectively) after adjustment for age, sex, serum cholesterol, albumin and logarithmic-transformed glucose levels, BMI, smoking and drinking status, current use of antihypertensive agents, and a past history of diabetes. The increase in DBP was also positively associated with total stroke, cerebral infarction and cerebral haemorrhage (RR = 1.29, 1.15, and 1.66; 95% CI = 1.17–1.42, 1.01–1.31, and 1.37–2.01, respectively). Cox-proportional hazard model did not show any relation between BMI and stroke mortality (data not shown in the table).

Table 3 shows the RRs for a 10 mmHg increase in SBP on mortality from total stroke, cerebral infarction, and intracerebral haemorrhage stratified by BMI tertiles. SBP was an independent risk factor for total stroke and cerebral infarction only in the middle and high BMI tertiles. This relation was not observed in the low BMI tertile. Concerning the mortality due to cerebral haemorrhage, it was clarified that an increase in SBP was an independent risk for mortality only in the low and middle BMI tertiles. These results were not substantially affected when DBP instead of SBP was included as an independent risk factor in the Cox-proportional hazard models (Table 4). Results on sex-specific analysis were essentially on a par with the above-mentioned results that were described in Tables 3 and 4.

**Table 3** Relative risks and 95% CIs of 10 mmHg increase in SBP for total stroke, cerebral infarction, and haemorrhage mortality by BMI tertiles in Cox analyses in 19-year follow-up of NIPPON DATA80 database

| | *Total stroke* | | | *Cerebral infarction* | | | *Intracerebral haemorrhage* | | |
|---|---|---|---|---|---|---|---|---|---|
| *BMI tertiles* | *RR* | *95% CI* | P-*value* | *RR* | *95% CI* | P-*value* | *RR* | *95% CI* | P-*value* |
| Low | 1.09 | (1.00–1.18) | 0.06 | 0.96 | (0.85–1.07) | 0.42 | 1.38 | (1.17–1.62) | <0.001 |
| Middle | 1.15 | (1.06–1.26) | <0.01 | 1.19 | (1.06–1.33) | <0.001 | 1.23 | (1.03–1.47) | 0.02 |
| High | 1.20 | (1.09–1.33) | <0.001 | 1.21 | (1.06–1.38) | 0.01 | 1.23 | (0.99–1.52) | 0.07 |

The multivariate-RR was calculated adjusting for age, sex, serum cholesterol, serum albumin, logarithmic transformed serum glucose, BMI, cigarette smoking (current smoker or not), drinking (current drinker or not), current use of antihypertensive medication, and past history of diabetes.
BMI: body mass index (kg/m$^2$).
Cutoff points of BMI tertiles are 21.2 and 23.8.
NIPPON DATA80: National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980.

**Table 4** Relative risks and 95% CIs of 10 mmHg increase in DBP for total stroke, cerebral infarction, and haemorrhage mortality by BMI tertiles in Cox analyses in 19-year follow-up of NIPPON DATA80 database

| | *Total stroke* | | | *Cerebral infarction* | | | *Intracerebral haemorrhage* | | |
|---|---|---|---|---|---|---|---|---|---|
| *BMI tertiles* | *RR* | *95% CI* | P-*value* | *RR* | *95% CI* | P-*value* | *RR* | *95% CI* | P-*value* |
| Low | 1.15 | (0.97–1.35) | 0.10 | 0.89 | (0.72–1.10) | 0.28 | 1.93 | (1.39–2.68) | <0.001 |
| Middle | 1.40 | (1.19–1.64) | <0.001 | 1.36 | (1.09–1.70) | 0.01 | 1.75 | (1.29–2.37) | <0.001 |
| High | 1.34 | (1.12–1.59) | 0.001 | 1.30 | (1.02–1.67) | 0.04 | 1.46 | (0.99–2.15) | 0.06 |

The multivariate-RR was calculated adjusting for age, sex, serum cholesterol, serum albumin, logarithmic transformed serum glucose, BMI, cigarette smoking (current smoker or not), drinking (current drinker or not), current use of antihypertensive medication, and past history of diabetes.
BMI: body mass index (kg/m$^2$).
Cutoff points of BMI tertiles are 21.2 and 23.8.
NIPPON DATA80: National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980.

## Discussion

We clarified that increased blood pressure was associated with intracerebral haemorrhage mortality among participants with lower BMI levels, whereas it was associated with cerebral infarction mortality among participants with higher BMI levels. These results suggest that the causal effect of blood pressure on stroke subtypes may be influenced by BMI levels.

The present study revealed that blood pressure was a better predictable marker of cerebral infarction in the high BMI group than in the low BMI group. It has been well established that the metabolic syndrome due to visceral fat accumulation is a strong risk factor for coronary heart disease or nonhaemorrhagic stroke.[25–27] High BMI group showed higher serum cholesterol and glucose levels than other groups, adding to higher prevalence of past history of diabetes. Furthermore, participants with higher BMI levels may have more risk factors, which were not included in the baseline survey, compared to participants with lower BMI levels. For example, a large proportion of obese people have visceral fat accumulation, affecting insulin resistance, HDL-cholesterol, triglyceride, and HOMA index which is a key factor in the metabolic syndrome.[28,29] We assumed that the impact of blood pressure on cerebral infarction would be emphasized by the influence of these risk factors in participants with higher BMI levels. This multiplied impact of blood pressure is a well-known cumulative effect in the metabolic syndrome.

Some previous studies have reported that serum cholesterol is inversely associated with a risk of intracerebral haemorrhage.[20,30] Participants with low BMI levels in the present study had lower serum cholesterol levels than those with high BMI levels (the difference; about 0.4 mmol/l). Although we did multivariate adjustments for serum cholesterol levels in the BMI category for specific analysis, participants in the lowest BMI group may have been affected by low serum cholesterol levels, one of the possible predictive marker for intracerebral haemorrhage.[31] The number of participants with low serum cholesterol level, for example less than 4.14 mmol/l,[20,30] was 224 (24.8%) from 904-hypertensives in the low BMI group and 171 (11.2%) from 1531-hypertensives in the high BMI group. Previous studies suggested a combined enhance effect, between

hypertension and serum low cholesterol level on mortality or morbidity of intracerebral haemorrhage.[30,32] Accordingly, more combinations of increased blood pressure and lower serum cholesterol might be observed in the low BMI group than other groups. This may partially explain why the relation between blood pressure and mortality from cerebral haemorrhage was intensive in lean people and weak in relatively obese people.

Another possible explanation for the evident effect of blood pressure on deaths due to intracerebral haemorrhage in the low BMI group was case fatality. Kurth *et al*,[15] reported that 25.3% of intracerebral haemorrhages were fatal whereas only 2.4% of ischaemic strokes were fatal. Furthermore, case fatalities due to haemorrhagic stroke were higher in the lower BMI group, although case fatalities due to ischaemic stroke were not affected by BMI levels.[15] These results suggested that fatal haemorrhagic stroke occurred more often in lean people. This may also explain the phenomenon we observed because the end point outcomes were only mortality in the present study. In addition, since the number of intracerebral haemorrhage death in the highest BMI group in the present study was lower than that in the other BMI group, the power might not be intensive enough. This may also explain why the relation between blood pressure and intracerebral haemorrhage in the high BMI group was not significant.

There are some drawbacks to the present study. First, we used National Vital Statistics based on death certificates issued by medical practitioners on the underlying causes of death. Stroke subtypes may generally be misclassified on death certificates. However, most stroke cases in Japan are referred to hospitals and computerized tomography (CT) scanning was performed on over 85% of stroke patients in the 1980s, even in rural areas throughout Japan.[33] Therefore, we believe that basing our analyses on the National Vital Statistics was sufficiently reliable. Second, since the present study was based on blood pressure and BMI measurements on the baseline survey only, the results might include regression dilution bias. Finally, we found blood pressure was not related to mortality from cerebral infarction in lean participants in the present study, although blood pressure has been regarded as the most important risk factor for stroke worldwide.[4–9] A possible reason for this result in this study is the outcome criterion. We did not obtain any information on the incidence of stroke in this study, because the end point outcomes were evaluated based on death certificates. In addition, we were unable to estimate ischaemic stroke subtypes more precisely such as large-artery occlusive, lacunar, or cardioembolic infarction. Further studies by accurately diagnosing cerebral infarction, which is confirmed through imaging studies or autopsy, will be needed because case fatalities from these ischaemic subtypes might be varied.[34]

In conclusion, the combination of high BMI and increased blood pressure might be a better predictive marker of cerebral infarction than blood pressure alone, whereas the combination of low BMI and high blood pressure might foresee cerebral haemorrhage well. Although it is important to control hypertension to prevent deaths due to stroke regardless of BMI, we should pay more attention to the relationship between blood pressure and BMI for the stroke subtypes at risk.

## Acknowledgements

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## Appendix

## List of the NIPPON DATA80 Research group

*NIPPON DATA80*: 'National Integrated Projects for Prospective Observation of Non-communicable Diseases And its Trends in the Aged'.

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研究成果の要約

心電図ミネソタコードと総死亡の関連

**Horibe H., Kasagi F., Kagaya M et al. A Nineteen-Year Cohort Study of the Relationship of Electrocardiographic Findings to All Cause Mortality Among Subjects in The National Survey on Circulatory Disorders, NIPPON DATA80.**

【研究の目的】 日本の代表集団について、ミネソタコードによる客観的な心電図所見を有する者の19年間にわたる長期生命予後を明らかにする。
【研究の方法】 旧厚生省による1980年に実施した循環器基礎調査の受診者のうち心電図検査を受けた9，629人を研究対象とした。心電図所見はミネソタコードにより客観的に把握し、1980年から1999年にわたる19年間生死の追跡調査を実施した。生命予後は、年齢、収縮期血圧、血糖、喫煙習慣を同時に考慮し、コックス比例ハザード比として計算により求めた。対照は主な心電図所見のいずれもない者とした。
【結果】 心電図上Q･QS所見を有する者の死亡危険は、対照者の1．57倍(コード1－3)から3．71倍(コード1－1)であった。電気軸については、1．37(コード2－1)倍から4．16(コード2－5)、左R波増高については、1．34(コード3－1)倍から1．35(コード3－3)倍であった。ST下降については、1．63(コード4－3)倍から、2．59(コード4－1)倍、T異常については、1．54(コード4—3)倍から2．33(コード5－1)倍であった(表参照)。
【メッセージ】 心電図異常は総死亡上昇を予測する因子であり、各ミネソタコードごとの19年間の総死亡危険度を、他の因子も同時に考慮しながら数量的に明確に示した。

表　一例として、T異常を示す者の総死亡との関連をコックスハザード比として示す。
(括弧内は９５%信頼限界、*** p<0.001　** p<0.01　* p<0.05　+ p<0.10)

| ミネソタコード | | 男＋女 | 男 | 女 |
|---|---|---|---|---|
| T | 5-1 | 2.33 (1.51-3.61) *** | 2.27 (1.24-4.16) ** | 2.53 (1.34-4.78) ** |
| T | 5-2 | 1.82 (1.49-2.22) *** | 2.52 (1.86-3.42) *** | 1.43 (1.09-1.87) ** |
| T | 5-3 | 1.54 (1.24-1.91) *** | 1.62 (1.14-2.31) ** | 1.56 (1.18-2.05) ** |
| T | 5-4 | 1.35 (0.96-1.88) + | 1.45 (0.90-2.32) | 1.26 (0.78-2.03) |
| T | 5-5 | 1.06 (0.84-1.34) | 1.02 (0.68-1.52) | 1.05 (0.79-1.41) |

**A Nineteen-Year Cohort Study on the Relationship of Electrocardiographic Findings to All Cause Mortality Among Subjects in The National Survey on Circulatory Disorders, NIPPON DATA80.**

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Running title: ECG and mortality in NIPPON DATA80

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*Abstract*

BACKGROUND: Electrocardiogram (ECG) is one of the most popular tools for daily clinics and health checkup and has been used for the National Survey on Circulatory Disorders to assess the health status in Japanese people. The significance to predict mortality from all causes among people with ECG abnormality is to be clarified using national samples.

METHODS: ECG findings recorded among 9,629 subjects for National Survey on Circulatory Disorders 1980 in Japan, were classified using the Minnesota Codes (mc). Their relationships to all cause mortality over 19 years were examined using a Cox proportional hazard model adjusted for sex, age, systolic blood pressure, blood glucose, and smoking habits.

RESULTS: Subjects with abnormal Q-QS findings showed significant high death hazard ratios (to 3.71(mc1-1) to 1.57 (mc1-3)) to the subjects who were free from any major ECG findings. Hazard ratios were 1.37 (mc2-1) to 4.16 (mc2-5) for axis deviation, and 1.34 (mc3-1) to 1.35 (mc3-3) for left high R waves. Those were 1.63 (mc4-3) to 2.59 (mc4-1) for ST depression, and 1.54 (mc5-3) to 2.33 (mc5-1) for T abnormality. The lower the second number of the Minnesota Codes was, the higher hazard ratio was observed in the Q-QS, ST, T codes. The hazard ratios of junction-type ST depression (mc4-4), and low T waves (mc5-4, 5-5) were not significant.

CONCLUSIONS: Electrocardiographic findings defined by the Minnesota Codes were useful to predict the risk for mortality from all causes even after adjusting for the other major risk factors, and the results supported a usefulness of the electrocardiogram for health check-ups.

*Key words*: Electrocardiographic findings, Minnesota codes, Epidemiology, Cohort study, Mortality

## Introduction

The major causes of death has been neoplasm, cerebrovascular disease, and ischemic heart disease in these years, Japan. The electrocadiographic examination is one of the most efficient and non-invasive methods used to check a condition of the heart. In order to decrease those deaths, Japanese government had worked hard to implement a series of multiphasic health check-ups throughout the country, including ECG examination [1]. The relevant medical staffs and the participants must be interested in the implications of a specific ECG finding for the participant's prognosis.

For an epidemiological purpose, the Minnesota Code system was developed by Henry Blackburn and others in 1960 [2], and revised by Ronald Prineas and others in 1982 [3]. Recently the revised code system was used worldwide to confirm the objectivity of ECG findings.

The Japanese Government performed a series of National Surveys on the Circulatory Disorders almost every ten years [1]. A research group had been organized to follow-up those participants to clarify the relation of risk factors, such as obesity [4], smoking [5], serum uric acid [6], total cholesterol [7], blood pressure [8], resting heart rate [9] and so forth [10]-[11]. These participants were from a national stratified random sample throughout the country, not merely nation-wide pooled samples by relevant researchers. It was an epoch making achievement to follow these nationally sampled participants and to evaluate their ECG findings objectively with the by Minnesota Code system. The attempt could be achieved by support of Ministry of Health and Welfare (presently new Ministry of Health, Labor, and Welfare) and extensive cooperation of nearly 300 local Health Centers along with collaborators listed in Appendix I and II. Similar type national samples were available in the United States for National Health and Nutrition Surveys 1971-75, 1976-80, and 1988-94, and many valuable reports presenting year-by-year [12]~[17], but not yet for extensive ECG

findings.

The purpose of this study was to investigate the relationship of ECG findings coded by the Minnesota code system to deaths of all cause by following-up 19 years of national samples participated in the National Survey on Circulatory Disorders done in 1980.

## Materials and Methods

The Japanese Ministry of Health and Welfare carried out the National Survey on Circulatory Disorders in order to clarify the recent status of Japanese people by examining all residents resided in the 300 stratified random sample areas selected throughout the country in 1980. A Working Committee charged local health centers on health check-up in the assigned areas under the guidance for the National Survey (the details described in an Official Report by the Ministry [1] ). In 1980, 10,546 people participated in the Survey (Response rate was 79.1%), and the Cohort Study Group on Activity in Daily Living and Prevention of Degradation in Quality of Life among the Elderly followed them up to 1999.

The Cohort Study Group identified 9,629 (4,103 males and 5,535 females) alive or dead people with ECG record successfully by 15th September 1999. Among them, 118 were lost after the date of moving, but they were definitely alive till the time of moving out according to their official records, "residence registration record" kept in any one of local administrative offices throughout the country. The number of deaths was 1,327 (13.8%), in which 711 deaths were males (16.8%) and 616 deaths were females (11.4%). The detail cause of deaths among this cohort appeared in the previous papers [6][7][8] and a series of annual research reports [11]. The frequency distribution of deaths did not differ from the national figures in 1980-90. A Working Group of ECG Coding for the National Survey on Circulatory Disorders carefully coded their electrocardiograms twice by independent coders who belonged to the different university or institution in 1980 (Appendix II). If there were any discrepancy

in their codes, the third well-experienced coder (one of the authors, HH) made final decision strictly applying the original coding rule (Minnesota Codes 1982 [3]).

Major ECG findings were abnormal Q-QS (mc1-1 to 1-3), axis deviation (mc2-1 to 2-5), high R (mc3-1 to 3-4), ST depression (mc4-1 to 4-4), T abnormality (mc5-1 to 5-5), atrio-ventricular conduction defect (mc6-1 to 6-8), intra-ventricular conduction defect (mc7-1 to 7-8), arrhythmia (mc8-1 to 8-9-1), and miscellaneous findings (mc9-1 to 9-3, 9-5). The code 5-5 was one of additional Japanese finding for minor T abnormality (T amplitude less than one tenth but over one twentieth of the R amplitude)[18]. The code 8-9-1 was assigned to ectopic beats less than 10 % of recorded beats defined for the Survey. A defined control group was free not only from the relevant code to be analyzed, but also free from any major ECG codes. An abnormal electrocardiogram (ECG) group consisted of subjects with any of major ECG codes, and it was used to analyze the over-all abnormal ECG findings.

In order to apply a multivariate analysis, the Cox proportional hazard model [19], the authors considered the major confounding factors, which were sex, age as of 1980, body mass index, and systolic blood pressure, total serum cholesterol, blood glucose, smoking and drinking habits. However, the hazard ratios of body mass index, drinking habits, and total serum cholesterol did not show statistical significance by a series of pretests and were excluded from further analyses. The number of cigarettes divided smoking habits into 4 levels, such as 3 for over 40 cigarettes /day, 2 for 21 to 40, 1 for 1 to 20 cigarettes /day, and 0 for non-smoker, the last of which included ex-smokers.

In order to clarify the effect of deaths close to the date of examination, the Cox death hazard ratios were calculated for deaths in 1980 to 1999, in 1983 to 1999, and in1985 to 1999. A statistical package, Dr' SPSS II (which was a subset of the SPSS sets) was used for this analysis [20]. The hazard ratios described in the result section were all statistically significant ($p<0.05$), besides otherwise specified.

## Results

The number of subjects with ECG findings and deaths of all cause showed in Table 1, along with the death percentages in 19 years. Number of subjects in the reference group was 5,535 and the deaths were 836 (15.1%) during the follow-up period. Number of subjects with any major ECG code was 4,103, and the number of deaths was 1,174 deaths (28.6%)

***The hazard ratios of 5 risk factors among subjects along with any one of major ECG codes*** (Table 2)

With analysis using Cox proportional hazard model, the death hazard ratio of subjects with any one of major ECG findings were formulated in Table 2, adjusted for sex, age, systolic blood pressure, blood glucose, and smoking habits.

The hazard ratio of females to males was 0.65. By separate analysis by sex, the hazard ratio of subjects with abnormal ECG among males was 1.34, and tended to be higher than those (1.19) in females. The hazard ratio tended to be higher in females than those in males for smoking habits (1.29 vs 1.18).

***The effect by exclusion of the deaths close to the date of examination*** (Table 3)

The Cox hazard ratios of mortality from all causes were essentially similar for the subjects with abnormal ECG finding before (1.28) and after excluding the deaths within 5 years after the examination (1.21). Those of sex, systolic blood pressure, blood glucose, or smoking did not change appreciably.

Based on these results, the further analysis by Cox proportional hazard model was performed with all deaths throughout the follow-up period.

***The hazard ratio of subjects with any one of Q-QS, axis deviation, and high R codes*** (Table 4)

*1) Q-QS codes:* The Cox death hazard ratios of subjects with each Minnesota code adjusted for age, systolic blood pressure, blood glucose, smoking habits, and sex if applicable, were shown in Table 4. The ratios for Q-QS code 1-1 were significantly high in both sexes. The ratio for minor Q-QS code 1-3 also showed a significant elevation.

*2) Axis deviation codes:* The hazard ratio for axis code 2-1 (left axis deviation) was 1.37 for male and female combined. The ratio was not significant in males (1.19), contrary to that in females (1.81).

The ratios of subjects with axis code 2-3 (minor right axis deviation) were significantly high among males and females combined and among males. The hazard ratio for axis code 2-4 (extreme axis deviation, 2.85) and 2-5 (4.16) was significantly high among the sex combined and among males, and tended to be higher than those codes for 2-1, 2-2, or 2-3.

*3) High R codes:* The hazard ratios for codes 3-1 and 3-3 (left high R codes) were significantly high at the same levels. The hazard ratio for code 3-2 was significantly high only in males. The ratio for code 3-2 tended to be higher than those for code 3-1 and code 3-3 in males.

***The hazard ratio of subjects with any one of ST depression and T abnormality codes*** (Table 4)

*1) ST depression codes:* Among the hazard ratios for code 4-1, 4-2, 4-3, and 4-4 (ST depression), those for code 4-1 and code 4-2 were significantly high in the sex combined, in males and in females. The hazard ratios of subjects with ST depression were ordered inversely by the second code numbers in the sex combined, in males and in females.

*2) T abnormality codes:* Among the hazard ratios of subjects with T abnormality, that for code 5-1 was the highest in females and in the sex combined. The ratio of code 5-2 was the highest in males. The hazard ratios for code 5-4 and for code 5-5 were not statistically significant.

***The hazard ratio of subjects with any one of atrio-ventricular and ventricular conduction defect codes*** (Table 4)

*1) Atrio-ventricular codes:* Among the death hazard ratios of subjects with incomplete atrio-ventricular block, that of code 6-2 was the highest in males and in females. The hazard ratio for code 6-5 (short PQ interval) was also significantly high in males or females. The ratio for code 6-3 (PQ prolongation) was significantly high only in males.

*2) Ventricular codes:* Among the death hazard ratios of subjects with intraventricular block code (code 7-1,7-2,7-3,7-4 and 7-5), those for code 7-1 and 7-2 were significantly high. Although the ratio for code 7-4 was also high but not significant in males and in the sexes combined. The hazard ratio of subjects with complete right bundle branch block (code 7-2) was significant only in females and in the sexes combined

***The hazard ratio of subjects with any one of arrhythmia and miscellaneous codes (Table 4)***

*1) Ectopic beats:* The death hazard ratio of subjects with frequent ectopic beats (code 8-1) was over double but not significant in males and close to double in the sex combined. The hazard ratio with less frequent ectopic beats (code 8-9-1, An optional code for the National Survey) was also over double and significant in males.

*2) Atrial fibrillation or flutter:* Among the hazard ratios of subjects with arrhythmia, code 8-3 (atrial fibrillation or flutter) was the highest in females and in the sexes combined. The hazard ratios for code 8-7(sinus tachycardia) and code 8-8 were significantly high only in males, but not in females at all.

*3) Miscellaneous codes:* The death hazard ratio of subjects with low voltage (code 9-1) was significantly high only in the sex combined. The hazard ratio of subjects with ST elevation (code 9-2) was significantly high in the sexes combined and in males, but not in females.

The hazard ratio of subjects with counter clockwise rotation (code 9-4-1) was significantly high only in males, and that with clockwise rotation (code 9-4-2) was significantly high in each sex and in both sexes combined.

The ratio with high T wave (code 9-5) was significantly high in males and in the sexes combined.

***The deaths from heart disease among the subjects with ECG codes*** (Table 5)

1) *Abnormal ECG group:* The proportion of heart disease death in the abnormal ECG group in females tended to be higher than that in males (21.9 vs 17.2 %).

2) *By each ECG code groups*