体格指数と総死亡の関連- NIPPON DATA80 の検討から

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背景

アジア人の体型が西欧人と異なることは知られており、西欧人とアジア人では健康な体格指数（Body mass index, 体重/（身長の２乗））の基準値(西欧人では25kg/m^2)が異なる可能性がある。そこで、本研究ではNIPPON DATA80のデータを用いて体格指数と総死亡率の関連を分析した。

方法

対象は循環器疾患既往のない日本人男性・女性8,924名であり、追跡期間は19年間である。体格指数レベルによるリスクの推定にはコックス比例ハザードモデルを用い、年齢、性、喫煙習慣、飲酒習慣の調整を行った。

結果

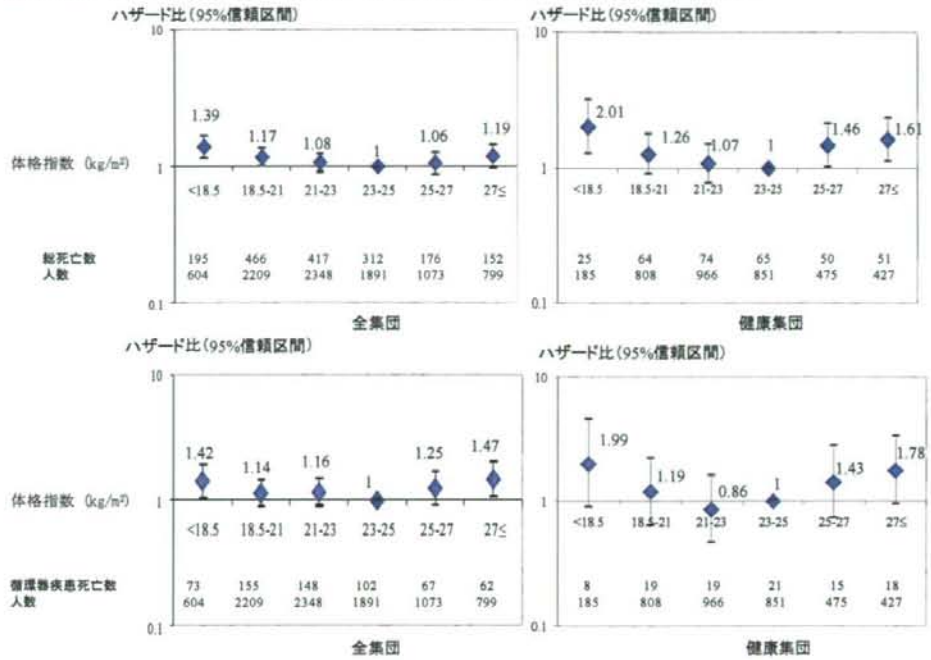
図に示すとおり、体格指数と総死亡はU型関連を示した。総死亡リスクが最大となるのは体格指数 18.5kg/m^2 の群（ハザード比 1.39; 95%信頼区間=1.16-1.67)で、体格指数23-24.9kg/m^2 の群で総死亡リスクが最小であった。やせの者で死亡リスクが高いことは、やせている者に低栄養者・喫煙者・何らかの既往歴を持つ者・高齢者が多く含まれる影響もあると考えたため、70歳未満の非喫煙者で追跡開始後5年以上生存していた健康者(3712名）に絞った分析も行った。しかし、この分析でも結果の傾向は変わらず、全体集団でも健康者集団でも体格指数 21-22.9kg/m^{2}の群と 23.0-24.9 kg/m^{2}の群のリスクに差はなかった。

また循環器疾患をエンドポイントとした分析も実施したが結果は同様であった。

結論

我々の検討からはアジア人で体格指数の正常域を西欧人より低めに設定する必要性を認めなかった。アジア人の至適体格指数について今後さらなる検討が必要である。

図、体格指数と総死亡、循環器疾患死亡の関連、全集団、健康集団別の検討,NIPPON DATA80, 1980-1999.



Relationship between body mass index and all-cause mortality in Japan: NIPPON DATA80

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Running head: Optimal BMI among entire and healthy Japanese
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Abstract
Background: Since body composition in Asian populations is largely different from Western populations, a healthy BMI could also differ. Thus, further study is needed to determine if a healthy BMI in Asians should be lower than Western populations, as recommended by the World Health Organization (WHO).
Methods: We investigated the relationship between BMI and mortality in a sample of 8924 Japanese male and female without stroke or heart disease.
Results: During 19 years of follow-up, 1718 deaths were observed. We found a U-shaped relationship between BMI and fatal events. Risk of total mortality was highest in participants with BMI < 18.5 kg/m2 and lowest in participants with BMI 23.0-24.9 kg/m2. These findings persisted after excluding the first 5 years of follow-up with a focus on healthy participants who never smoked, were aged <70 years, and had total cholesterol levels ≥4.1 mmol/L (N=3712). For both the full sample and healthy participants, all-cause mortality risk did not differ between BMI ranges from 21.0-22.9 and 23.0-24.9 kg/m2.
Conclusion: Our findings do not support the recent WHO implications that BMI's < 23.0 kg/m2 is healthy for Asians. Further studies are needed to identify an optimal BMI range for Asia.
Word counts: 195 words.
Key words, body mass index, cardiovascular diseases, mortality, prospective studies, Japan

INTRODUCTION

Body composition in Asia is different from Western populations. Some reports have indicated that Asian populations tend to have a higher ratio of body fat at any given body mass index (BMI) (1, 2). Furthermore, recent studies have suggested that the area of visceral fat is wider among Japanese than in Western individuals with a similar girth (3). Thus, whether it is appropriate to apply Western guidelines to define obesity in Asian populations is uncertain. The World Health Organization (WHO) recommends that optimal BMI should be lower in Asian versus Western populations (4).

On the other hand, several prospective studies conducted in Japan and in other Asian countries have suggested that not only obese, but also underweight individuals have a high risk of all-cause mortality

(5-9). Several explanations have been proposed to explain how being underweight is associated with all-cause mortality, such as (1) the effect of heavy smoking on weight loss (5, 10-12); (2) the effect of age (older participants are relatively leaner than those who are middle-aged) (10, 12, 13); (3) total cholesterol (TC) is lower in leaner individuals and low TC affects hemorrhagic stroke, cancer and liver diseases (14-17); (4) weight loss is often associated with subclinical diseases (5-15, 17, 18).

To diminish the impact of these effects on the relationship between BMI and mortality and to understand whether or not Japanese should have a lower optimal BMI than Westerners as proposed by the WHO, we examined the association between BMI and death from all causes and from cardiovascular disease (CVD) in a restricted sample of healthy Japanese individuals who were <70 years in age, who had never smoked, whose total cholesterol (TC) levels were not particularly low, and who survived for at least 5 years. To our knowledge, the association between BMI and mortality in such a restricted healthy sample has not been described.

MATERIALS AND METHODS

The subjects in this cohort study were participants in the Japanese National Cardiovascular Survey of 1980, which was conducted together with the annual National Nutrition Survey that uses a similar methodology and questionnaire. The standardized procedures used in this survey have been described elsewhere (14, 15). All household members aged 30 years or older (up to 92 years) (N = 13,771) were surveyed in 300 randomly selected census tracts throughout Japan.

A total of 10,546 individuals (76.6 percent of 13,771) aged 30 years or older completed the 1980 baseline examination (NIPPON DATA80) (14, 15). Among these, we excluded 2 individuals for whom information about height was not available, 755 participants with a history of CVD, 16 who did not have complete information about confounding factors, and 849 participants who could not be followed up because of incomplete residential access information after the first survey. Consequently, we analyzed 8,924 participants (3,969 male and 4,955 female).

As previously reported (14, 15), we identified the participants who had died by computer matching data from Japanese National Vital Statistics records, using area, gender, date of birth, and death as key codes. We obtained permission to use the National Vital Statistics records from the Management and Coordination Agency of the Government of Japan. Approval was further granted from the Institutional Review Board of Shiga University of Medical Science (Nos. 12–18, 2000).

To examine the relationship between BMI and death due to all causes and CVD, participants were divided into seven BMI categories: BMI <18.5 kg/m2, 18.5-20.9 kg/m2, 21.0-22.9 kg/m2, 23.0-24.9 kg/m2, 25.0-26.9 kg/m2, 27.0-29.9 kg/m2, and ≥30 kg/m2. The distributions of baseline characteristics across BMI groups were gender and age-adjusted using analysis of covariance and logistic regression.

We estimated the relative hazards (RH) and the 95% confidence intervals (CI) for all-cause and CVD mortality between the BMI strata using the Cox proportional hazards regression model. There were no apparent reasons to suggest that the proportionality assumption was inappropriate. We regarded the group with BMI 23.0-24.9 kg/m2 as a reference. For the entire cohort, we used 2 models to estimate the RH: (1) adjusted for age, gender, smoking, and alcohol consumption, and (2) adjusted for the same factors, plus systolic BP, use of antihypertensive medication, TC, and diabetes. Diabetes was defined as a non-fasting glucose value ≥ 11.1 mmol/L (≥200 mg/dL) or a self-reported history of diabetes (19).

To diminish the effects of confounding due to age, smoking, TC, and pre- or co-existing disease on mortality, we analyzed the data after removing the first 5 years of follow-up among those who had never smoked, who were aged <70 years, and who had TC ≥4.1 mmol/L (15). All p-values were based on a 2-sided level of significance. Data were analyzed using SAS software (version 9.1).

RESULTS

Table 1 shows the age- and gender-adjusted relationship between BMI and several CVD risk factors. Systolic BP, diastolic BP, and TC were increased with increasing BMI. Similarly, adjusted percentages for antihypertensive medication or having diabetes also increased with increasing BMI. In contrast, the age-adjusted percent of current smokers declined as BMI increased. These findings were similar in both males and females (data not shown).

After 19 years of follow-up, there were 1,718 deaths, among which 607 were due to CVD. Because of the limited number of obese individuals, we combined BMI: 27.0-29.9 kg/m2 and BMI ≥30 kg/m2 into

one group for the following analyses.

Figure 1A shows the RH of all-cause mortality across the BMI groups, in which a U-shaped relationship between BMI and fatal events is apparent after adjusting for age, gender, smoking, and alcohol consumption status (Model 1). The RH for all-cause mortality was higher in the underweight (Model 1, RH=1.39; 95%CI=1.16-1.67), compared with the reference group. Adjustment for BP, antihypertensive medication, TC, and diabetes did not alter this finding (data not shown). The RH for all-cause and CVD mortality (Figure 1 (B)) was the lowest in the participants with BMI between 23 and 25 kg/m2. Since the relationship between BMI and all-cause and CVD mortality was similar between male and female (data not shown), we analyzed male and female together in the following analyses.

Figure 1 also shows the results after excluding the first 5 years of follow-up and restricting the sample to those who never smoked, were aged <70 years, and whose TC level was ≥4.1 mmol/L. Risk for both all-cause (Figure 1 (C)) and CVD mortality (Figure 1 (D)) was not attenuated in underweight individuals. The risk increased in participants with BMI ≥25 kg/m2 and seemed more apparent in this restricted sample of healthy participants than in the entire population. For all-cause mortality, even in this restricted sample of healthy participants, those with BMI between 23 and 25 kg/m2 had the lowest risk of all-cause mortality. The risk of death due to CVD was also similar in this group to that of the group whose BMI was between 21 and 22.9 kg/m2.

DISCUSSION

The results of the present study show that the lowest relative risk for all-cause mortality was associated with a BMI between 23.0 to 24.9 kg/m2. This range was also unchanged when analyses were limited to participants who had never smoked, were aged <70 years, had TC ≧4.1 mmol/L, and who could be followed up for at least 5 years.

Several factors might modify the relationship between BMI and all-cause mortality, especially for lower BMI levels. The effect of weight loss due to smoking (5, 10-12), higher age (10, 12, 13), low TC (14-16, 20), and subclinical conditions which can co-exist in underweight individuals (5-15, 17, 18) might explain the higher mortality in lean participants. However, when we restricted our analyses to participants younger than 70 years, who never smoked, had TC ≥4.1 mmol/L, and who could be followed up for at least 5 years, the relationship between higher all-cause mortality and being underweight persisted. The data also show that those with a BMI between 23 and 25 kg/m2 in this restricted sample of healthy individuals had the lowest risk of all-cause mortality. Thus, we conclude that higher mortality among lean participants can not be fully explained by the above mentioned factors. The relationship between BMI and CVD mortality was also similar to associations with all-cause mortality. This was consistent with a recent study of Korean men and women who did not have self-reported atherosclerotic CVD, cancer, liver disease, diabetes, or respiratory diseases at baseline (5).

Since the WHO defines a healthy BMI as <23 kg/m2 in Asian individuals (4), data regarding optimal BMI for all-cause mortality in Asia is of interest. For Western populations, a healthy BMI is defined as <25 kg/m2. Our study does not support the notion that a lower BMI cut-off value in Asian versus Western populations is warranted because all-cause mortality risk does not appear to differ between BMI ranges from 18.5-22.9 and 23.0-24.9 kg/m2.. Findings further suggest that risk of death may be highest in individuals with a BMI <18.5 kg/m2, even for those who fell in our restricted healthy sample. We believe that additional studies are needed to properly identify an optimal BMI range for Asian populations that is associated with maximum longevity.

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Appendix

NIPPON DATA80, 90: "National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged."

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Consultant: Osamu Iimura (Hokkaido JR Sapporo Hospital, Sapporo, Hokkaido), Teruo Omae (Health C&C Center, Hisayama, Kasuya, Fukuoka), Kazuo Ueda (Murakami Memorial Hospital, Nakatsu, Oita), Hiroshi Yanagawa (Saitama Prefectural University, Koshigaya, Saitama), Hiroshi Horibe (Aichi Medical University, Nagakute, Aichi).

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Participating Research Associates: Toshihiro Takeuchi, Mitsuru Hasebe, Fumitsugu Kusano, Takahisa Kawamoto and members of 300 Public Health Centers in Japan, Masumi Minowa (Faculty of Humanities, Seitoku University, Matsudo, Chiba), Minoru Iida (Kansai University of Welfare Sciences, Kashiwara, Osaka), Tsutomu Hashimoto (Kinugasa General Hospital, Yokosuka, Kanagawa), Shigemichi Tanaka (Department of Cardiology, Cardiovascular Center, Teine Keijinkai, Sapporo, Hokkaido), Atsushi Terao (Health Promotion Division, Department of Public Health and Welfare, Shiga Prefecture, Otsu, Shiga), Katsuhiko Kawaminami (Department of Public Health Policy, National Institute of Public Health, Wako, Saitama), Koryo Sawai (The Japanese Association for Cerebro-cardiovascular Disease Control, Tokyo), Shigeo Shibata (Clinical Nutrition, Kagawa Nutrition University, Sakado, Saitama).

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Figure legend

Figure 1.
Relationship of body mass index (BMI) with death from all causes and cardiovascular disease (CVD) in the unrestricted and restricted sample of healthy individuals.

(A) Relationship between BMI categories and all cause mortality in the unrestricted sample.
(B) Relationship between BMI categories and CVD mortality in the unrestricted sample.
(C) Relationship between BMI categories and all cause mortality in the restricted sample of healthy individuals.
(D) Relationship between BMI categories and all cause mortality in the restricted sample of healthy individuals.

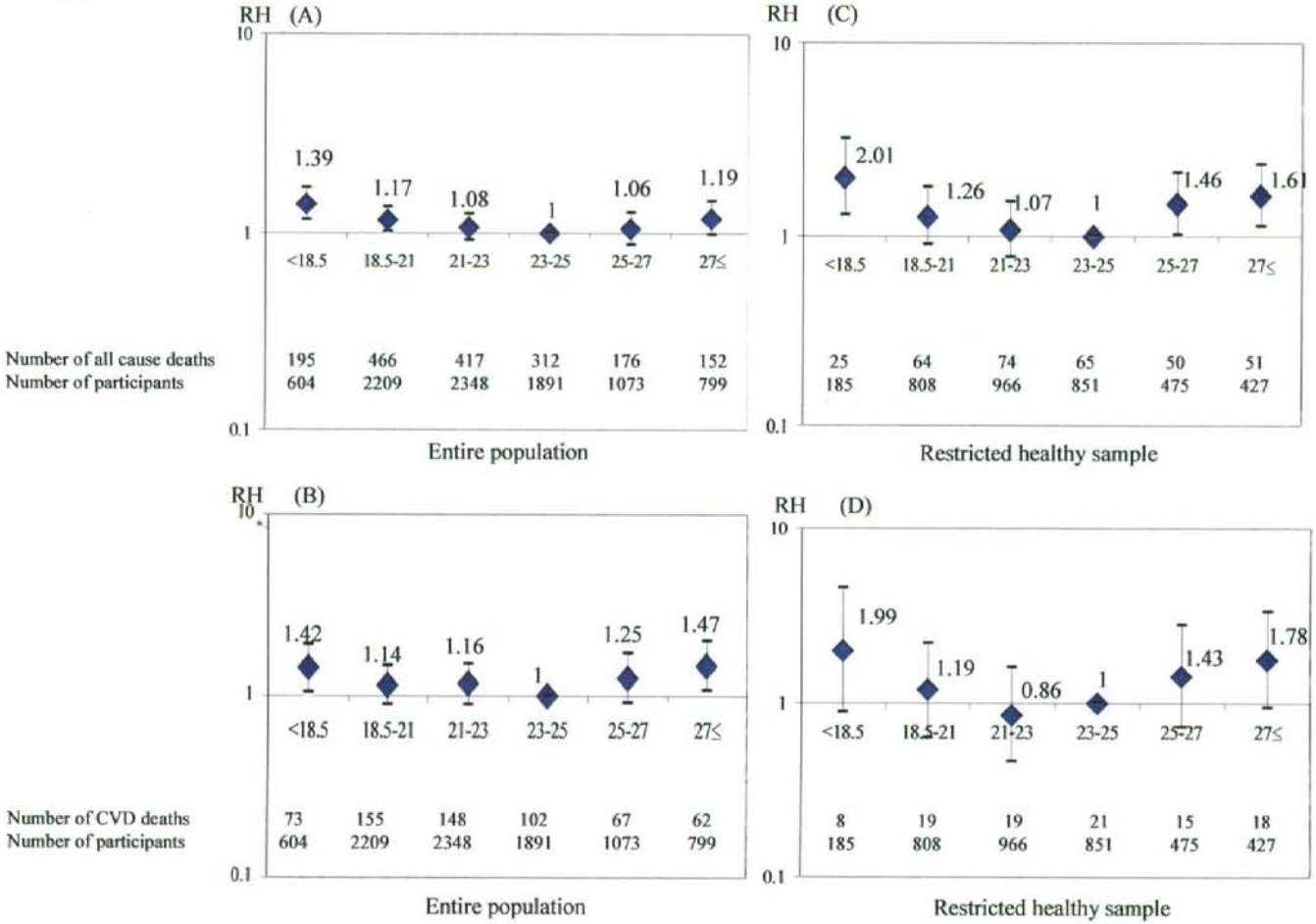
RH: relative hazards are adjusted for age, gender, smoking (never, past, current; 1-20, 21-40, or 41+-cigarettes per day), and alcohol consumption (never, past, occasional and daily). The BMI range from ≥23 to <25 kg/m2 is used as a reference for comparison with other BMI strata.
Diamonds and numbers above diamonds represented RH.
Bars represent 95% confidence intervals for the corresponding RH.
The restricted sample of a healthy individuals is defined as participants who had never smoked, were aged <70 years, had TC ≧4.1 mmol/L, and who could be followed up for more than 5 years.

Table 1. Age-, gender- adjusted baseline characteristics of several risk factors across body mass index (BMI) categories.NIPPON DATA80,1980.

			BMI<18.5	18.5 ≤ BMI<21	21≤BMI<23	23≤BMI<25	25≤BMI<27	27≤BMI<30	30≤BMI	P for trend
Male +Female	N		604	2209	2348	1891	1073	615	184	
	Age (years)	mean (SD)	54.1 (15.5)	49.6(13.8)	49.7(12.8)	49.7(12.5)	50.1(11.8)	50.8(12.2)	52.5(12.4)	0.36
	Gender (% female)	% (N)	58.3% (352)	53.9% (1191)	53.7% (1261)	55.2% (1043)	53.3% (572)	62.8% (386)	81.5% (150)	<0.01
	Systolic BP (mmHg)	mean*(SD)	129.0(22.2)	131.2(20.8)	134.9(20.6)	137.1(20.3)	140.4(20.1)	142.4(22.2)	145.0(23.1)	<0.01*
	Diastolic BP (mmHg)	mean*(SD)	76.4(12.0)	78.0(11.7)	80.8(11.9)	82.5(11.7)	84.7(11.3)	86.4(12.8)	89.3(13.8	<0.01*
	Total cholesterol (mmol/L)	mean*(SD)	4.51(0.72)	4.63(0.81)	4.81(0.83)	4.94(0.88)	5.07(0.86)	5.09(0.88)	5.24(0.91)	<0.01*
	Hypertensive drugs	%* (N of yes)	4.3% (39)	5.3% (118)	9.1% (205)	11.3% (201)	15.6% (159)	15.1% (93)	24.4% (50)	<0.01*
	Diabetes	%* (N of yes)	5.1% (38)	4.4% (99)	4.3% (98)	5.8% (105)	6.0% (62)	8.4% (49)	10.7% (18)	<0.01*
	Current smoking	%* (N of yes)	40.9% (233)	35.6% (805)	32.7% (794)	31.7% (605)	29.0% (325)	31.1% (168)	26.4% (26)	<0.01*
	Current alcohol drinking	%* (N of yes)	19.2% (109)	23.2% (527)	25.2% (614)	24.5% (468)	20.6% (231)	19.0% (100)	17.1% (15)	0.09*

N: numbers of participants;
*: adjusted for age and gender.

Figure 1


RH (A)
10
1
0.1
1.39
1.17
1.08
1
1.06
1.19
<18.5
18.5-21
21-23
23-25
25-27
27≤
Number of all cause deaths
Number of participants
195 466 417 312 176 152
604 2209 2348 1891 1073 799
Entire population
RH (C)
10
1
0.1
2.01
1.26
1.07
1
1.46
1.61
<18.5
18.5-21
21-23
23-25
25-27
27≤
25 64 74 65 50 51
185 808 966 851 475 427
Restricted healthy sample
RH (B)
10
1
0.1
1.42
1.14
1.16
1
1.25
1.47
<18.5
18.5-21
21-23
23-25
25-27
27≤
Number of CVD deaths
Number of participants
73 155 148 102 67 62
604 2209 2348 1891 1073 799
Entire population
RH (D)
10
1
0.1
1.99
1.19
0.86
1
1.43
1.78
<18.5
18.5-21
21-23
23-25
25-27
27≤
8 19 19 21 15 18
185 808 966 851 475 427
Restricted healthy sample

白血球数と病型別心血管疾患死亡との関連

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はじめに

白血球数は炎症マーカーとして広く周知されており、健診や臨床の場で日常的に用いられている検査である。白血球数が正常範囲を超える場合に「炎症あり」と診断されるが、正常範囲での白血球数の高低が持つ病態意義については未だ確立されておらず、保健・医療現場においてもそのような観点からの判断には至っていない。我々は、NIPPON DATA90の10年間を追跡した研究で、白血球数の増加は総死亡と心血管疾患死亡の独立した予測因子であり、その関連は女性において顕著であったと報告した（Tamakoshi K, Toyoshima H, Yatsuya H, Matsushita K, Okamura T, Hayakawa T, Okayama A, Ueshima H; NIPPON DATA90 Research Group. White blood cell count and risk of all-cause and cardiovascular mortality in nationwide sample of Japanese--results from the NIPPON DATA90. Circ J. 2007;71(4):479-85.）。しかしながら、先の研究では、死亡症例が少なく、病型別に心血管疾患死亡と白血球数との関連を検討することはできなかった。そこで、今回、追跡期間が15年間に延長したNIPPON DATA90のデータを用いて、白血球数と心血管疾患死亡及び冠動脈性心疾患、脳卒中死亡との関連について検討した。

方法

NIPPON DATA90に登録された30歳以上の男女10,956名のうち、健診成績、血液検査成績、生活習慣のアンケートが得られ、15年間追跡された人は、8,383名（男性3,504名、女性4,879名）であった。先の報告と同様に解析の際には、白血球数が4,000個/mm^3未満の者と臨床的に明らかに炎症が存在すると考えられる白血球数が10,000個/mm^3を超える者は除外した後、対象者を白血球数4,000-4,900個/mm^3、5,000-5,900個/mm^3、6,000-6,900個/mm^3、7,000-7,900個/mm^3、8,000-8,900個/mm^3、9,000-10,000個/mm^3、の6群に分けた。次いで、全対象者に対して、コックスの比例ハザードモデルを用いて、年齢、性、BMI、喫煙状況、飲酒状況、運動習慣、収縮期血圧、血清コレステロール値、血清HDLコレステロール値、ヘモグロビンA1c値を調整した後の4,000-4,900個/mm^3群を基準とした心血管疾患死亡、冠動脈性心疾患死亡、脳卒中死亡に対するRRと95%CIを算出した。さらに、性別に同様の解析を行った。

結果

最終的に上記の解析を行うことができた対象者は、7,219名（男性2,973、女性4,246）であり、総観察人年は98,520人年（男性39,700人年、女性58,820人年）、平均観察期間は13.6年（男性13.4年、女性13.9年）であった。観察期間中、341（男性179、女性162）の心血管疾患死亡が確認され、そのうち、冠動脈性心疾患死亡は75（男性49、女性29）、脳卒中死亡は151（男性79、女性72）であった。

1．白血球数と心血管疾患死亡リスク（Table 1）

対象者全体では、白血球数の少ない順に各群の相対危険度RR（95%CI）を示すと、1.00（基準）、1.03（0.72-1.45）、1.10（0.78-1.55）、1.03（0.71-1.50）、1.22（0.79-1.89）、1.86（1.13-3.05）であり、白血球数が最も多い群（9,00-10,000個/mm^3）は最も低い群（4,000-4,900個/mm^3）に比して有意に高いリスクを有していた。性別では、男性においては全体の結果と同様に白血球数が最も多い群は最も低い群に比して有意に高いリスクを有していた〔RR:1.66（1.16-4.15）〕。女性においては、白血球数が増加するほど心血管疾患死亡リスクが有意に増加する傾向がみられ、白血球数が最も低い群に対する最も高い群のRRは2.31（1.05-5.11）であった。（傾向性p値＝0.026）

2.白血球数と冠動脈性心疾患死亡リスクとの関連（Table 2）

対象者全体では、白血球数が最も多い群（9,00-10,000個/mm^3）は最も低い群（4,000-4,900個/mm^3）に比して、統計学的には有意ではないものの高いリスク〔RR:2.11（0.86-5.19）〕を有していた。性別に分析した結果でも、同様に男性ではRR：95%信頼区間が1.76：0.58-5.37、女性では3.23：0.62-17.0と白血球数が最も多い群は最も低い群に比して、統計学的には有意ではないものの高いリスクを有していた。いずれの分析においてもRRに統計学的に有意な傾向性は認められなかった。

3．白血球数と脳卒中死亡リスクとの関連（Table 3）

対象者全体では、白血球数の少ない順に各群の相対危険度RR（95%CI）を示すと、1.00（基準）、1.27（0.76-2.14）、1.16（0.67-2.01）、1.42（0.81-2.50）、1.63（0.84-3.16）、2.27（1.05-4.92）であり、白血球数が増加するほど脳卒中死亡リスクが有意に増加する傾向がみられた。（傾向性p値＝0.044）性別の分析では、男性においては白血球数と脳卒中死亡との間に関連は認められなかったが、女性において白血球数の少ない順に各群の相対危険度RR（95%CI）は、1.00（基準）、1.41（0.67-2.98）、1.54（0.69-3.401）、2.04（0.90-4.62）、3.00（1.21-7.40）、2.83（0.77-10.4）と白血球数が増加するほど脳卒中死亡リスクが有意に増加する傾向がみられた。（傾向性p値＝0.008）

結果のまとめ

心血管疾患死亡リスクに関して、性別の分析により、新たに男性においても白血球数が最も多い群（9,00-10,000 個/mm³）は最も低い群（4,000-4,900 個/mm³）に比して有意に高いリスクを有することが分かった。女性においては先の 10 年追跡の研究で報告した白血球数と心血管疾患死亡リスクとの正の関連をさらに強く示唆する結果が得られた。病型別の分析では、白血球数と冠動脈性心疾患死亡リスクとの間には白血球数が 9,000 個/mm³以上の群で高いリスクが観察されたものの統計学的に有意な関連は認められなかった。一方、脳卒中死亡リスクとの間には統計学的に有意な正の関連が認められ、この関連は、女性において顕著であった。

結語

NIPPON DATA90 の平均 13.6 年に及ぶ追跡結果の検討では、白血球数の増加は、心血管疾患に対する既知の危険因子とは独立した予測因子であった。病型別の検討では、白血球数は冠動脈性心疾患よりも脳卒中において死亡との間に強い関連が認められた。性別では、女性において正の関連が顕著であった。

白血球が心血管疾患発症の病態に直接関与しているのか、あるいは原因となる要因の単なるマーカーであるのかは定かではない。しかしながら、本研究において、多くの既知の危険因子とは独立してその関連が認められたことは、因果関係を示唆するものである。白血球数は測定系も標準化されており、費用も安価であり、広く健診や臨床の場で用いられている。それ故に、炎症の有無を判断する指標としての役割に加えて、予防や臨床分野で心血管疾患の予測因子としての可能性を探るべきである。そのためには、カットオフ値の設定や長期に亘る変動との関連を検討する必要がある。

Table 1 Adjusted relative risk (RR) for death from cardiovascular disease according to white blood cell count, NIPPON DATA90

Baseline WBC count (cells/mm^3)	*No. of deaths*	*Person-years*	*Age, sex-adjusted RR (95% CI)*	*Multivariate-adjusted RR* (95% CI)*
Overall				
4,000-4,900	*58*	*13155*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*86*	*23987*	*1.12 (0.80-1.56)*	*1.03 (0.72-1.45)*
6,000-6,900	*82*	*25000*	*1.20 (0.86-1.68)*	*1.10 (0.78-1.55)*
7,000-7,900	*57*	*19474*	*1.16 (0.80-1.67)*	*1.03 (0.71-1.50)*
8,000-8,900	*34*	*11180*	*1.48 (0.90-2.27)*	*1.22 (0.79-1.89)*
9,000-10,000	*24*	*5723*	*2.40 (1.48-3.90)***	*1.86 (1.13-3.05)***
p-value for trend			*0.003*	*0.074*
Men				
4,000-4,900	*26*	*3859*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*43*	*7824*	*1.26 (0.77-2.06)*	*1.20 (0.73-1.98)*
6,000-6,900	*46*	*9959*	*1.23 (0.76-1.99)*	*1.11 (0.68-1.83)*
7,000-7,900	*29*	*8522*	*0.98 (0.57-1.67)*	*0.90 (0.52-1.55)*
8,000-8,900	*19*	*6070*	*1.28 (0.70-2.34)*	*1.02 (0.70-2.34)*
9,000-10,000	*16*	*3466*	*2.19 (1.16-4.15)***	*1.66 (1.16-4.15)***
p-value for trend			*0.185*	*0.710*
Women				
4,000-4,900	*32*	*9296*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*43*	*16163*	*1.00 (0.63-1.58)*	*0.96 (0.60-1.53)*
6,000-6,900	*36*	*15041*	*1.17 (0.72-1.88)*	*1.13 (0.70-1.85)*
7,000-7,900	*28*	*10952*	*1.40 (0.84-2.34)*	*1.26 (0.74-2.13)*
8,000-8,900	*15*	*5111*	*1.74 (0.94-3.21)*	*1.50 (0.80-2.82)*
9,000-10,000	*8*	*2257*	*2.67 (1.22-5.92)***	*2.31 (1.05-5.11)***
p-value for trend			*0.005*	*0.026*

** Adjusted for age, sex, BMI at baseline, smoking status (never, former, current), alcohol consumption (never, former, current), regular exercise (yes, no), systolic blood pressure, total cholesterol, HDL.cholesterol, and hemoglobin A1c. ** $p < 0.05$.*

Table 2 Adjusted relative risk (RR) for death from coronary heart disease according to white blood cell count, NIPPON DATA90

Baseline WBC count (cells/mm^3)	*No. of deaths*	*Person-years*	*Age, sex-adjusted RR (95% CI)*	*Multivariate-adjusted RR* (95% CI)*
Overall				
4,000-4,900	*14*	*13155*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*17*	*23987*	*0.89 (0.44-1.80)*	*0.88 (0.43-1.80)*
6,000-6,900	*18*	*25000*	*0.98 (0.48-1.97)*	*0.89 (0.43-1.83)*
7,000-7,900	*9*	*19474*	*0.65 (0.28-1.52)*	*0.60 (0.25-1.41)*
8,000-8,900	*8*	*11180*	*1.18 (0.49-2.87)*	*1.00 (0.40-2.49)*
9,000-10,000	*9*	*5723*	*2.83 (1.19-6.71)***	*2.11 (0.86-5.19)*
p-value for trend			*0.164*	*0.445*
Men				
4,000-4,900	*8*	*3859*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*10*	*7824*	*0.90 (0.36-2.30)*	*0.92 (0.35-2.40)*
6,000-6,900	*12*	*9959*	*0.95 (0.39-2.34)*	*0.81 (0.32-2.06)*
7,000-7,900	*7*	*8522*	*0.69 (0.25-1.93)*	*0.63 (0.22-1.81)*
8,000-8,900	*5*	*6070*	*0.94 (0.30-2.92)*	*0.75 (0.23-2.44)*
9,000-10,000	*7*	*3466*	*2.56 (0.90-7.29)*	*1.76 (0.58-5.37)*
p-value for trend			*0.321*	*0.751*
Women				
4,000-4,900	*6*	*9296*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*7*	*16163*	*0.86 (0.29-2.55)*	*0.92 (0.30-2.81)*
6,000-6,900	*6*	*15041*	*0.99 (0.32-3.10)*	*1.07 (0.33-3.43)*
7,000-7,900	*2*	*10952*	*0.51 (0.10-2.55)*	*0.52 (0.10-2.64)*
8,000-8,900	*3*	*5111*	*1.80 (0.45-7.22)*	*1.74 (0.42-7.32)*
9,000-10,000	*2*	*2257*	*3.25 (0.66-16.1)*	*3.23 (0.62-17.0)*
p-value for trend			*0.365*	*0.405*

* *Adjusted for age, sex, BMI at baseline, smoking status (never, former, current), alcohol consumption (never, former, current), regular exercise (yes, no), systolic blood pressure, total cholesterol, HDL.cholesterol, and hemoglobin A1c.*

Table 3 Adjusted relative risk (RR) for death from stroke according to white blood cell count, NIPPON DATA90

Baseline WBC count (cells/mm^3)	*No. of deaths*	*Person-years*	*Age, sex-adjusted RR (95% CI)*	*Multivariate-adjusted RR* (95% CI)*
Overall				
4,000-4,900	*23*	*13155*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*41*	*23987*	*1.36 (0.82-2.27)*	*1.27 (0.76-2.14)*
6,000-6,900	*32*	*25000*	*1.22 (0.71-2.10)*	*1.16 (0.67-2.01)*
7,000-7,900	*29*	*19474*	*1.54 (0.89-2.68)*	*1.42 (0.81-2.50)*
8,000-8,900	*16*	*11180*	*1.85 (0.97-3.53)*	*1.63 (0.84-3.16)*
9,000-10,000	*10*	*5723*	*2.73 (1.28-5.83)***	*2.27 (1.05-4.92)***
p-value for trend			*0.011*	*0.044*
Men				
4,000-4,900	*12*	*3859*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*21*	*7824*	*1.36 (0.67-2.76)*	*1.24 (0.60-2.57)*
6,000-6,900	*17*	*9959*	*1.01 (0.48-2.14)*	*0.92 (0.43-1.97)*
7,000-7,900	*15*	*8522*	*1.13 (0.53-2.44)*	*1.01 (0.46-2.22)*
8,000-8,900	*7*	*6070*	*1.07 (0.42-2.77)*	*0.87 (0.33-2.31)*
9,000-10,000	*7*	*3466*	*2.23 (0.86-5.79)*	*1.71 (0.64-4.59)*
p-value for trend			*0.465*	*0.846*
Women				
4,000-4,900	*11*	*9296*	*1.00* (referent)	*1.00* (referent)
5,000-5,900	*20*	*16163*	*1.36 (0.65-2.85)*	*1.41 (0.67-2.98)*
6,000-6,900	*15*	*15041*	*1.47 (0.67-3.21)*	*1.54 (0.69-3.40)*
7,000-7,900	*14*	*10952*	*2.10 (0.95-4.65)*	*2.04 (0.90-4.62)*
8,000-8,900	*9*	*5111*	*3.12 (1.29-7.51)***	*3.00 (1.21-7.40)***
9,000-10,000	*3*	*2257*	*3.06 (0.85-11.1)*	*2.83 (0.77-10.4)*
p-value for trend			*0.004*	*0.008*

* *Adjusted for age, sex, BMI at baseline, smoking status (never, former, current), alcohol consumption (never, former, current), regular exercise (yes, no), systolic blood pressure, total cholesterol, HDL.cholesterol, and hemoglobin A1c.* ** *$p < 0.05$.*

検診における安静時心電図のq波は循環器疾患死亡を予測するか
日本人代表集団の19年追跡による結果より

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【研究の背景】安静時心電図においてミネソタコードによるq波異常を有する場合、循環器疾患死亡のリスクが約2倍になることが海外における検討により報告されている。しかし本邦では地域住民を対象とした検診ベースで、循環器疾患既往のない場合のq波異常についてその意義は検討されていない。またミネソタコードにより分類されたq波異常の段階により循環器疾患死亡リスクが異なるか、ST-T異常や高R波を有さない場合のq波も循環器疾患死亡を予測するかについては、内外の研究においてほとんど行われていない。

【方法】1980年第3次循環器疾患基礎調査の参加者（NIPPON DATA80）のうち、循環器疾患の既往がなく、ベースライン調査の安静時心電図において心房細動・WPW症候群・完全左脚ブロックがない8341人（男性3695人、女性4646人）を対象とした。心電図のq波をミネソタコードにより分類し、対象者を以下の3群に分け（正常群、軽度異常群（ミネソタコード1-3-）、中等度～重度異常群（ミネソタコード1-2-,1-1-））19年間追跡した。追跡のエンドポイントは、循環器疾患、脳卒中、心疾患による死亡とした。コックス比例ハザードモデルを用い、循環器疾患の危険因子を調整して正常群に対する軽度異常群、中等度～重度異常群の循環器疾患・脳卒中・心疾患による死亡についてのハザード比を算出した。更にST低下、T波異常、高R波を有する対象者を除いて同様の解析を行った。また高血圧、高血糖、高脂血症の有無により対象者を各々2群に分け軽度異常群、中等度～重度異常群の循環器疾患・脳卒中・心疾患による死亡についてのハザード比を算出した。

【結果】中等度～重度異常群におけるハザード比は、循環器疾患死亡に対し1.75（95%信頼区間（CI）:0.97-3.17）、心疾患死亡に対し2.97(95%CI:1.43-6.16)であった。同様に軽度異常群のハザード比は、心疾患死亡に対し1.95(95%CI:1.00-3.81)であった。ST低下、T波異常、高R波例を除いた場合も、高血圧・高血糖・高脂血症の有無で対象者を分けた場合も、同様の解

析を行ったが傾向は変わらなかった。q 波と脳卒中の間には関連はみられなかった。

【結論】循環器疾患の既往がない地域住民を対象とした場合、検診における安静時心電図において指摘された中等度以上の q 波異常は、循環器疾患、特に心疾患による死亡と強い関連があった。一般住民において q 波異常を有する頻度は高くはないが、循環器疾患死亡、特に心疾患に対する予測能を有することから、心電図によるスクリーニングの有用性が示唆された。

Title: Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population

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Abstract
Aim: Little is known about the prognostic value of q wave abnormality for cardiovascular disease (CVD) in resting electrocardiogram (ECG) of Japanese general population with extremely low incidence of myocardial infarction.
Methods: We followed 8,339 participants without past and present history of CVD for 19 years. The multivariate-adjusted hazard ratio (HR) of q wave abnormality for CVD mortality was estimated by the Cox proportional hazards model.
Results: The multivariate-adjusted HR of composite findings of moderate or severe q wave abnormality was 1.75 (95% confidence interval (CI):0.97-3.17) for mortality due to CVD and 2.97 (95%CI: 1.43-6.16) due to heart diseases. The multivariate-adjusted HR of mild abnormality for mortality from heart diseases was 1.95 (95%CI: 1.00−3.81). The relationship between moderate and severe abnormalities and mortality from CVD was unchanged when the participants with ST-T changes and high amplitude R waves were excluded and when the participants were divided by the presence of major CVD risk factors such as hypertension. Q wave abnormality was not associated with the risk of stroke.
Conclusion: Moderate or severe q wave abnormalities are prominent and important predictor for mortality due to CVD and heart disease in Japanese general population without CVD history.
Key words: hazard ratio, cardiovascular diseases, heart diseases, cohort study
Running title: Prognostic value of q wave for CVD mortality

Introduction

The resting electrocardiogram (ECG) abnormalities such as q or ST-T wave abnormality classified by Minnesota code (MC) have consistently been associated with an increased risk of all cause mortality and CVD death, with most studies reporting a doubled relative risk [1-3].

Q wave in resting ECG is considered as a sign of old myocardial infarction[4]. Previous studies assessed the risk of q wave abnormality among the general population [1,2,5,6], however, little is known about the prevalence or prognostic value of q wave abnormality in the non-Western general population such as Japanese with extremely low incidence of myocardial infarction.

In the previous studies performed in the community, abnormality of q, ST, and T wave, left bundle branch block (LBBB) and high amplitude R waves were categorized into major or minor abnormalities to assess the risk for CVD or coronary heart disease (CHD) [7,8], and only a few study assessed q wave abnormality by grade of MC respectively [1,5]. The assessment of q wave by grade is necessary to determine whether even a small q wave of the individual in the community without history of cardiac event would be a predictor for CVD. Moreover, a question remains whether the risk of q wave abnormality on CVD and its subtypes are independent from ST-T abnormality and high amplitude R waves or not.

To investigate the independent prognostic value of q wave for mortality due to CVD and its subtypes, we analyzed the data from 19-year prospective study of 8,339 Japanese citizens free from CVD history at baseline.

Subjects and Methods

Study participants

We used data from the National Integrated Project for Prospective Observation of Non-communicable Diseases and its Trends in the Aged, 1980 (NIPPON DATA80). Details of the study have been described elsewhere [9-15]. In this survey, 300 areas were selected by stratified random sampling based on the national census in 1975. All residents aged 30 years or older in these areas were enrolled, and a total of 10,546 people participated in the survey (response rate: 76.6%). Accordingly, these participants were considered to be reasonably representative of the Japanese population.

In this study, we enrolled 8,339 participants (3,694 male and 4,645 female) who were free from CVD history, atrial fibrillation (Minnesota Code (MC),8-3), Wolff-Parkinson-White syndrome (MC, 6-4-1), and complete LBBB (MC, 7-1).

Case identification

To determine causes of death after 19 years follow up, we used the National Vital Statistics database of Japan with permission of the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and the 10th International Classification of Disease (ICD-10) from the beginning of 1995. The details of the disease classification in the present study was previously reported [16,17], and the name of the diseases according to the classification of ICD-9 and -10 are shown in Table-1. CVD (ICD 9 code: 393 to 459), stroke (ICD 9 code: 430 to 438), and heart disease (ICD 9 code: 393 to 398, 410 to 414, 415 to 429) were identified. Approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Baseline examination

Information on history of CVD, diabetes, medication for hypertension, and the habits of smoking and drinking were obtained from interviews by public health nurses. Blood pressure was measured after five minutes' rest by trained public health nurses at each public health center using a standard mercury sphygmomanometer. Serum total cholesterol levels were determined in a laboratory (Osaka Medical Center for Health Science and Promotion) under the quality control program of the Center for Disease Control and Prevention in the United States [18]. Casual glucose concentration was measured by the cupric-neocuproine method [19]. Original glucose values obtained by the cupric-neocuproine method were converted to those of the glucose-oxidase method, which is currently the standard, by use of an equation reported by the same laboratory [20].

A standard 12-lead ECG was recorded in the supine position. Each ECG was coded independently by two researchers according to the Minnesota Code, which was developed to document significant ECG pattern change using objective comparison rules [21]. Codes in agreement were accepted, whereas codes in disagreement were adjusted by a panel of epidemiologists and cardiologists[16]. Participants were divided into three categories according to q wave abnormality grade as follows: q wave normal, mild q wave abnormality (MC, 1-3), and moderate or severe abnormality (MC, 1-1 and 1-2). Moderate and severe abnormalities were included in one group because the number of participants with moderate or severe abnormality was small.

Diagnosis for the presence of hypertension was systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or current medication for hypertension [22]. Because the most of the participants were not fasted when the baseline survey was conducted, we defined hyperglycemia as casual glucose level $\geq$ 140 mg/dl or the presence of history of diabetes mellitus[23]. Diagnosis for the presence of hyperlipidemia was defined as serum total cholesterol $\geq$ 200 mg/dl [24].

Statistical Analysis

To compare baseline characteristics between the participants with and without q wave abnormality, we used analysis of variance or the chi-square test. Age-adjustment was performed by analysis of covariance for continuous variables.

We used the Cox proportional hazards model for estimating the hazard ratios (HR) of the presence of q wave abnormality for CVD mortality and its subtypes (stroke or heart disease). In the model, we included age at study entry, sex, body mass index (BMI), systolic blood pressure, serum total cholesterol, smoking (current or non-current), alcohol drinking (current or non-current), and the presence of hyperglycemia as confounding factors.

Further analysis was performed after exclusion for ST depression (MC, 4-1 to 4-4), T wave abnormality (MC, 5-1

to 5-4), and high amplitude R waves (MC, 3-1 to 3-3) from the source population[3,25].

When we divided the participants according to the presence of hypertension, hyperglycemia, and hyperlipidemia, similar analysis was performed.

Results

Baseline Characteristics

The baseline characteristics of the participants with and without q wave abnormality for both sexes are shown in Table 2. The number of study participants with mild q wave abnormality comprised 62 (1.7 %) men and 46 (1.0 %) women. The number of study participants with moderate or severe q wave abnormality comprised 23 (0.6 %) men (moderate: 14, severe: 9) and 13 (0.3 %) women (moderate: 10, severe: 3). Age and the percentages of the presence of history of diabetes and hyperglycemia were significantly higher in those with q wave abnormality for both sexes. Systolic blood pressure, the percentages of hypertension and medication for hypertension, and serum total cholesterol were higher in those with q wave abnormality in men. Casual glucose level was higher in those with q wave abnormality in women. Although age-adjustment slightly attenuated these relations, most relations remained statistically significant.

Risk of q wave abnormality for CVD mortality and its subtypes

There were 1578 deaths among all of the participants, including 544 deaths due to CVD, 257 deaths due to all stroke and 257 deaths due to heart diseases.

Table 3 shows age-adjusted and multivariate-adjusted HRs for CVD death and cause-specific mortality. On the whole, the age-adjusted and multivariate- adjusted HRs were almost the same as death from CVD and its subtypes. Among the participants with moderate or severe q wave abnormality, the multivariate-adjusted HR for CVD death compared to those without q wave abnormality was 1.79 (95%CI: 0.87-3.65) in men and 1.69 (95%CI: 0.54-5.29) in women. Since there was no apparent interaction between sex for CVD mortality or its subtypes, we combined men and women. For overall participants, the HR of moderate or severe q wave abnormality was 1.75 (95%CI: 0.97-3.17) for death due to CVD, 0.48 (95%CI: 0.12-2.00) due to stroke, 2.97 (95%CI: 1.43-6.16) due to heart diseases.

The multivariate-adjusted HR of the participants with mild q wave abnormality for CVD death compared to those without q wave abnormality was 1.27 (95%CI: 0.60-2.71) in men and 1.87 (95%CI: 0.92-3.80) in women. For overall participants, the HR of mild q wave abnormality was 1.50 (95%CI: 0.90-2.51) for death due to CVD, 1.05 (95%CI: 0.43-2.56) due to stroke, 1.95 (95%CI: 1.00-3.81) due to heart diseases.

For all-cause mortality, the multivariate-adjusted HRs of moderate or severe q wave abnormality and mild q wave abnormality were 1.62 (95%CI: 1.05-2.50), and 1.28 (95%CI: 0.92-1.80) respectively.

After we additionally excluded the participants with complete A-V block (MC, 6-1), right bundle branch block (MC, 7-2), and persistent ventricular rhythm (MC, 8-2), the HRs and 95%CIs of moderate and severe q wave abnormality was 1.87 (95%CI: 1.03-3.38) for CVD mortality, and 3.20 (95%CI: 1.55-6.63) for heart disease mortality. Similarly, the HRs of mild q wave abnormality for CVD and heart disease mortality was 1.47 (95%CI: 0.86-2.51) and 1.82 (95%CI: 0.90-3.70), respectively.

Risk of q wave abnormality after exclusion of other ECG abnormalities

As shown in the Table 4, the multivariate-adjusted HRs of moderate or severe q wave abnormality for mortality from CVD and heart diseases were significantly elevated even when the participants with ST depression, T wave abnormality and high amplitude R waves were excluded. In the similar analysis, the multivariate-adjusted HRs of mild q wave abnormality were almost the same, however, the relationship was not statistically significant.

Risk of q wave abnormality according to the presence of major CVD risk factors

Table 5 shows age-adjusted and multivariate-adjusted HRs for CVD death and heart disease mortality according to the q wave abnormality when the participants were divided by the presence of hypertension, hyperglycemia, and hyperlipidemia, respectively. For mortality from stroke, we did not perform the further analysis because there was no significant relationship between q wave abnormality and mortality from stroke after the multivariate adjustment as shown in Table 3 and 4. Among most of these subgroups, the HRs of moderate or severe q wave abnormality for mortality from CVD and heart diseases were significantly elevated, and those of mild abnormality were elevated although the relationship did not reach to statistically significance.