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Does self-reported history of hypertension predict cardiovascular death? Comparison with blood pressure measurement in a 19-year prospective study

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Objectives **Hypertension as assessed by blood pressure (BP) measurement is one of the most important risk factors for cardiovascular diseases (CVD). Self-reported history of hypertension (self-reported HT) is an easy way to obtain information on BP and is known to have a certain sensitivity and high specificity for hypertension confirmed by BP measurement (confirmative HT). Thus, it might predict CVD mortality, but few studies have reported on this relationship.**

Methods **We followed 6427 participants aged 30–59 years without a history of CVD for 19 years. The multivariate-adjusted hazard ratio (HR) of CVD mortality was estimated by the Cox proportional hazard model.**

Results **The sensitivity and specificity of self-reported HT for confirmative HT were 52–65% and 95%, respectively. The multivariate-adjusted HR of self-reported HT for CVD death was 2.49 [95% confidence interval (CI) = 1.72–3.61]. Compared to participants with neither self-reported HT nor confirmative HT, those with confirmative HT showed a consistently higher HR for CVD mortality. Self-reported HT without confirmative HT was also significantly related to CVD mortality (HR = 2.10, 95% CI = 1.04–4.26). These tendencies were unchanged when we further adjusted for systolic BP (SBP) level. The age-adjusted mortality rate of individuals with self-reported HT corresponded to the age-adjusted mortality rate of individuals whose SBP was 160–179 mmHg.**

Conclusion **Self-reported HT could screen one-half of the participants for confirmative HT and was significantly associated with CVD mortality. These results indicate that self-reported HT can be a useful tool to screen for individuals with high BP if it is difficult to perform BP measurements continuously among all members of a community. *J Hypertens* 25:959–964 © 2007 Lippincott Williams & Wilkins.**

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Keywords: cardiovascular diseases, cohort study, hazard ratio, self-reported history of hypertension

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Introduction

Hypertension is one of the most important risk factors for cardiovascular diseases (CVD) [2–9]. Blood pressure (BP) strongly predicts mortality from CVD, and screening for high BP is recommended according to the US Preventive Service Task Force to identify people at increased risk for CVD [10].

However, it is hard to perform BP measurements continuously for all members of a community. On the other hand, a self-reported history of hypertension (self-reported HT) obtained, for example, by self-administered questionnaires is easier to obtain and may identify people at high risk for CVD.

Several studies have reported that self-reported HT has a certain sensitivity and high specificity in screening for HT as defined by measured BP [11–13]. Thus, self-reported HT could be a predictive marker for CVD. However, there is little evidence as to whether self-reported HT can predict CVD mortality.

To investigate the relationship between self-reported HT and CVD mortality, we analysed the database from a 19-year prospective study of 6427 Japanese citizens under 60 years of age. The study hypothesis was that

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self-reported HT obtained by self-administered questionnaire can predict CVD mortality.

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 [14–19]. 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 representative of the Japanese population. As the percentage of people taking medication for HT was high among those aged 60 years and older, we enrolled 6427 individuals (2862 men and 3565 women, mean age = 44.4 years) who were under 60 years of age and free from CVD in our study (percentage on medication: < 60 years, 5.3% versus ≥ 60 years, 24.2%).

Case identification

To determine causes of death, 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 Ninth International Classification of Disease (ICD-9) up to the end of 1994 and the Tenth International Classification of Disease (ICD-10) from the beginning of 1995. The disease classification in the present study was previously reported [14,19].

Baseline examination

Information on self-reported HT and diabetes, and the habits of smoking and drinking were obtained from interviews by public health nurses. BP was measured after 5 min of rest by trained public health nurses at each public health centre using a standard mercury sphygmomanometer. Serum total cholesterol levels were determined in a laboratory under the quality control program of the Centre for Disease Control and Prevention in the USA [20].

Definition of self-reported hypertension and confirmed hypertension

We considered that a participant had self-reported HT when the participant answered that he or she had been diagnosed with the condition. Conversely, participants who answered that they had never been diagnosed with high BP were considered self-reported normotensives. Confirmative HT assessed by measured BP was defined as SBP ≥ 160 mmHg and/or diastolic blood pressure (DBP) ≥ 95 mmHg (JNC-2), and/or taking antihypertensive medication. Otherwise, we defined participants as confirmed normotensives.

Statistical analysis

To compare baseline characteristics between the participants with and without self-reported HT, we used *t*-test for continuous variables and the chi-squared test for dichotomous variables.

To calculate the sensitivity and the specificity of self-reported HT, we observed the distribution of true and false positives and negatives in the sampled population, based on the measurement of BP by sphygmomanometer.

We used the Cox proportional hazard model for estimating the hazard ratios (HR) of the presence of self-reported HT for CVD mortality and its subtypes. In the model, we included age at study entry, sex, body mass index (BMI), serum total cholesterol, smoking habit (current or non-current smoker), drinking habit (current or non-current drinker), and history of diabetes mellitus as confounding factors.

We divided the source population into four groups according to the combination of self-reported HT and confirmative HT as assessed by BP measurement. We used two Cox proportional hazard models for estimating HRs of the combination for CVD mortality. In model 1, we included age at study entry, sex, BMI, serum total cholesterol, smoking habit (current or non-current smoker), drinking habit (current or non-current drinker), and history of diabetes mellitus to adjust for confounding factors. We also included SBP in the second model (model 2).

To compare the absolute risk of self-reported HT with that of measured SBP for CVD mortality, we calculated the age-adjusted mortality rate of the population subdivided by the presence of self-reported HT and categories of SBP (every 20 mmHg) in direct standardization. All participants of the study were selected as the reference population.

All statistical analyses were performed using SPSS statistical software, version 11.0J (SPSS, Tokyo, Japan). $P < 0.05$ (two-tailed) was considered statistically significant.

Results

In our study population, 611 out of the 879 individuals with self-reported HT had confirmed HT (true positives) and 268 were confirmed as normotensives (false positives). Similarly, among 5548 participants who reported that they had never been diagnosed with high BP, the number of confirmative normotensives (true negatives) was 5104 and 444 had confirmed HT (false negatives). Accordingly, the sensitivity of self-reported HT was 52% in men and 65% in women. The specificity of self-reported HT was 95% in both sexes.

Table 1 Characteristics of the baseline survey in 1980 of 6427 participants according to sex and self-reported hypertension (HT): NIPPON DATA80, 1980–99, Japan

	Men ($n=2862$)		Women ($n=3565$)	
	Self-reported HT		Self-reported HT	
	Absent ($n=2459$)	Present ($n=403$)	Absent ($n=3089$)	Present ($n=476$)
Age (years)†	43.6 ± 8.3	48.9 ± 7.3*	43.6 ± 8.4	49.9 ± 7.3*
Systolic blood pressure (mmHg)†	130.8 ± 15.5	155.8 ± 20.7*	125.5 ± 15.9	152.6 ± 21.6*
Diastolic blood pressure (mmHg)†	80.9 ± 10.8	95.8 ± 12.3*	76.5 ± 10.3	90.7 ± 12.3*
Serum total cholesterol (mg/dl)†	186.8 ± 32.6	193.4 ± 35.6*	185.4 ± 32.7	197.0 ± 34.2*
Bofy mass index (kg/m^2)†	22.6 ± 2.8	23.6 ± 2.8*	22.6 ± 3.2	24.4 ± 3.7*
History of diabetes (%)‡	3.0	8.0*	1.0	2.0*
Current smoker (%)‡	66.0	66.0	8.0	9.0
Current drinker (%)‡	78.0	81.0	22.0	20.0
Medication for hypertension (%)	0.0	33.5	0.0	43.3

Data are presented as mean ± SD. *Statistically significant difference between two groups ($P<0.05$). † *t*-test. ‡ Chi-squared test.

The baseline characteristics of the participants with and without self-reported HT for both sexes are shown in Table 1. The number of study participants with self-reported HT comprised 403 (14%) men and 476 (13%) women. Age, SBP and DBP, serum total cholesterol, BMI and history of diabetes were significantly higher in those with self-reported HT for both sexes. The percentages of current smokers and drinkers were not significantly different between the two groups.

The follow-up time for the 6427 participants in the present study was 117 738 person-years. There were 524 deaths among all of the participants, including 132 deaths due to CVD, 60 deaths due to all stroke and 30 deaths due to coronary heart diseases.

Table 2 shows person-years of follow-up, the number of deaths, the crude mortality rates per 1000 person-years for CVD death, and cause-specific mortality according to

Table 2 Risk of self-reported hypertension (HT) for cardiovascular disease mortality and its subtypes: NIPPON DATA80, 1980–99, Japan

	Overall		Men		Women	
	Self-reported HT		Self-reported HT		Self-reported HT	
	Absent ($n=5548$)	Present ($n=879$)	Absent ($n=2459$)	Present ($n=403$)	Absent ($n=3089$)	Present ($n=476$)
Person-years of follow-up period	101 989	15 749	644 765	7063	57 224	8686
Death due to cardiovascular diseases						
Cases	80	52	50	32	30	20
Mortality rate (per 1000 person-years)	0.78	3.30	0.08	4.53	0.52	2.30
Age-adjusted hazard ratio	1.00	2.57 (1.80–3.68)*	1.00	2.54 (1.61–4.00)*	1.00	2.62 (1.46–4.71)*
Multivariate-adjusted hazard ratio	1.00	2.49 (1.72–3.61)*	1.00	2.37 (1.48–3.80)*	1.00	2.73 (1.50–4.96)*
Death due to all stroke						
Cases	33	27	19	15	14	12
Mortality rate (per 1000 person-years)	0.32	1.71	0.03	2.12	0.24	1.38
Age-adjusted hazard ratio	1.00	3.22 (1.91–5.43)*	1.00	2.94 (1.47–5.85)*	1.00	3.71 (1.66–8.29)*
Multivariate-adjusted hazard ratio	1.00	3.22 (1.88–5.53)*	1.00	2.85 (1.40–5.82)*	1.00	3.84 (1.66–8.88)*
Death due to cerebral infarction						
Cases	13	14	7	8	6	6
Mortality rate (per 1000 person-years)	0.13	0.89	0.01	1.13	0.10	0.69
Age-adjusted hazard ratio	1.00	3.55 (1.65–7.63)*	1.00	3.72 (1.33–10.4)*	1.00	3.34 (1.05–10.6)*
Multivariate-adjusted hazard ratio	1.00	3.50 (1.56–7.87)*	1.00	3.31 (1.12–9.77)*	1.00	3.63 (1.04–12.70)*
Death due to cerebral hemorrhage						
Cases	9	7	6	4	3	3
Mortality rate (per 1000 person-years)	0.09	0.44	0.01	0.57	0.05	0.35
Age-adjusted hazard ratio	1.00	3.09 (1.12–8.53)*	1.00	2.39 (0.66–8.67)	1.00	5.01 (0.92–27.3)
Multivariate-adjusted hazard ratio	1.00	3.20 (1.13–9.06)*	1.00	2.57 (0.69–9.63)	1.00	4.68 (0.82–26.70)
Death due to coronary heart diseases						
Cases	21	9	15	7	6	2
Mortality rate (per 1000 person-years)	0.21	0.57	0.02	0.99	0.10	0.23
Age-adjusted hazard ratio	1.00	1.81 (0.81–4.03)	1.00	2.11 (0.84–5.31)	1.00	1.14 (0.22–5.80)
Multivariate-adjusted hazard ratio	1.00	1.53 (0.67–3.47)	1.00	1.65 (0.64–4.27)	1.00	1.23 (0.24–6.42)

Values in parentheses indicate 95% confidence interval of hazard ratios. *Statisitically significant difference between two groups. The age-adjusted hazard ratio = the presence of history of hypertension and age at study entry was entered in the model. Sex was also included in the model when we estimated overall hazard ratio. The multivariate-adjusted hazard ratio = the presence of history of hypertension, age at study entry, body mass index, serum total cholesterol, smoking habit, drinking habit, and the presence of history of diabetes were entered in the model. Sex was also included in the model when we estimated overall hazard ratio.

the presence of self-reported HT. For both sexes, the mortality rates from CVD, all stroke, cerebral infarction, cerebral hemorrhage and coronary heart diseases were higher in the participants with self-reported HT than in those without self-reported HT.

Table 2 also 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. The multivariate-adjusted HR of CVD death compared to those without self-reported HT was 2.37 [95% confidence interval (CI) = 1.48–3.80] in men and 2.73 (95% CI = 1.50–4.96) in women. As there was no apparent interaction between men and women for CVD mortality or its subtypes, we combined men and women in the following analysis. For overall participants, the HR was 2.49 (95% CI = 1.72–3.61) for death from CVD, 3.22 (95% CI = 1.88–5.53) from all stroke, 3.50 (95% CI = 1.56–7.87) from cerebral infarction, 3.20 (95% CI = 1.13–9.06) from cerebral hemorrhage and 1.53 (95% CI = 0.67–3.47) from coronary heart diseases. When the participants with antihypertensive agents were excluded from the data, the results were almost similar: HR for CVD mortality was 1.98 (95% CI = 1.25–3.16).

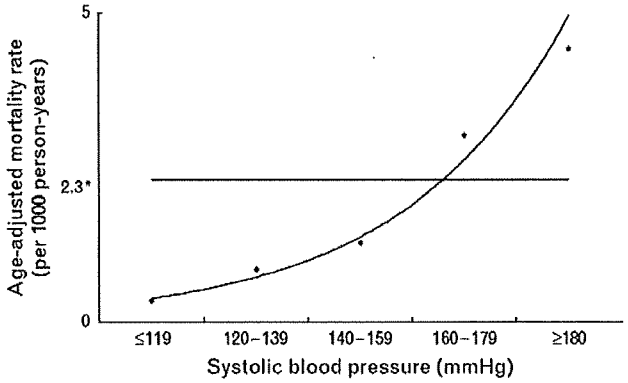
Table 3 shows the multivariate-adjusted HRs of the combination of those with self-reported HT and those with confirmative HT for CVD death. The multivariate-adjusted HRs were 3.42 (95% CI = 2.24–5.20) for confirmative HT with self-reported HT, 2.78 (95% CI = 1.66–4.67) for confirmative HT without self-reported HT, and 2.10 (95% CI = 1.04–4.26) for confirmative normotensives with self-reported HT compared to confirmative normotensives without self-reported HT. When we included SBP in the models as a confounder, these tendencies were unchanged. When we excluded the participants under medication for HT, the results were also similar; HR for CVD mortality was 2.69 (95% CI = 1.60–4.54) among confirmative HT without self-reported HT, 2.68 (95% CI = 1.50–4.76) among confirmative HT with self-reported HT, and 2.09 (95% CI = 1.03–4.24) among confirmative normotensive with self-reported HT. These tendencies were unchanged when we further adjusted for SBP.

Table 3 Risk of combination of self-reported hypertension (HT) and confirmative HT for cardiovascular disease (CVD) mortality: NIPPON DATA80, 1980–99, Japan

	Self-reported HT	
	Present	Absent
Confirmative hypertension		
n	611	444
Person-years of follow-up	10858.78	8014.76
Mean ± SD systolic blood pressure (mmHg)	161 ± 20	158 ± 15
CVD event	43	20
CVD mortality (per 1000 person-years)	3.96	2.50
Multivariate-adjusted hazard ratio†	3.42 (2.24–5.20)	2.78 (1.66–4.67)
Multivariate-adjusted hazard ratio‡	1.68 (0.94–3.00)	1.52 (0.82–2.79)
Confirmative normotension		
N	268	5104
Person-years of follow-up	4890.42	93974.04
Mean ± SD systolic blood pressure (mmHg)	138 ± 12	125 ± 13
CVD event	9	60
CVD mortality (per 1000 person-years)	1.84	0.64
Multivariate-adjusted hazard ratio†	2.10 (1.04–4.26)	1.00
Multivariate-adjusted hazard ratio‡	1.72 (0.84–3.50)	1.00

Data are presented as mean ± SD. † The multivariate-adjusted hazard ratio : the presence of history of hypertension, age at the study entry, sex, body mass index, serum total cholesterol, smoking habit, drinking habit, and the presence of history of diabetes were entered in the model. ‡ The multivariate-adjusted hazard ratio : the presence of history of hypertension, age at the study entry, sex, body mass index, serum total cholesterol, smoking habit, drinking habit, the presence of history of diabetes, and systolic blood pressure (BP) were entered in the model. Confirmative HT assessed by measured BP was defined as systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 95 mmHg, and/or taking antihypertensive medication.

Fig. 1



Age-adjusted mortality rate per 1000 person-years according to systolic blood pressure: NIPPON DATA80, 1980–99, Japan. *Age-adjusted mortality rate per 1000 person-years for participants with self-reported hypertension. All participants of the study were used for the age-adjusted reference population (direct standardization).

Figure 1 shows the age-adjusted mortality rate for CVD mortality per 1000 person-years according to the categories of SBP. The age-adjusted mortality rate was 2.30 for participants with self-reported HT and 0.85 for those without self-reported HT. The corresponding age-adjusted CVD mortality rate for those with self-reported HT was observed around the SBP category of 160–179 mmHg.

Discussion

Our study is the first report to present the risk of self-reported HT for CVD mortality and that of its subtypes. A significant increase of CVD death among people with self-reported HT was observed in this study.

Because we had data on both self-reported HT from questionnaires and SBP from BP measurement, we

reconfirmed the risk of confirmative HT irrespective of self-reported HT and found that self-reported HT without confirmative HT also increased the risk for CVD mortality.

The participants of this study were from a nationwide cohort study, and they were selected by a stratified random sampling method. Accordingly, the results of the present study would apply to the general Japanese population. Furthermore, the participants in our study were observed for 19 years, which is a long follow-up period and increases the value of our study substantially.

The sensitivity (52–65%) and the specificity (95%) of self-reported HT for confirmative HT in our study correspond to the results of previous studies [21–23]. For example, in the National Health and Nutritional Examination Survey III, the sensitivity for self-reported diagnosis of HT was 71% and the specificity was 90% [24]. These results suggest that self-reported HT could screen more than one-half of the cases with confirmative HT.

The merits of the collection of past history by questionnaire include convenience and a high response rate. For example, in the Japan Public Health Center-based Prospective Study (the JPHC Study), which is a large-scale cohort study in Japan, the participation rate of self-administered questionnaire was 78.8%, whereas the participation rate of BP measurement was only 34.1% [25]. Obviously, measuring BP for all members in worksites or communities is preferable. As we showed the data, confirmed HT as assessed by BP measurement had significantly higher risk for CVD mortality irrespective of self-reported HT. However, measuring BP continuously among all community members is hard to perform. For community members who do not attend the BP measurements, screening for individuals with high BP by self-report can be a useful tool. If those who do not attend BP measurements claim that they have been diagnosed with high BP, their risk for CVD death could be considered as high if their SBP is in the 160–179 mmHg range.

We have to note that participants with self-reported HT without confirmative HT also had a significantly higher CVD risk in our study. Although the relationship was not statistically significant after adjusting for SBP in the model, the same tendency still remained. These results suggest that a single screening measurement of BP might misclassify the participants with high BP. If participants with confirmative normotension claimed that they had been diagnosed with HT previously, it might be better for health care providers to recheck the measurement or have the measurement performed in another setting such as at home, which is known to have better predictive value for CVD mortality [26], to confirm whether or not the participant's BP is high.

Our study also supports the legitimacy of self-reported HT as one of the confounders in the large-scale studies previously published [27,28]. In several large cohort studies, such as the Nurses' Health Study, the Physicians' Health Study, the JPHC Study and the Japan Collaborative Cohort Study (the JACC Study), self-administered questionnaires including the history of HT were often used for confounders.

One of the limitations of our study is that confirmative HT was defined as SBP $\geq$ 160 mmHg and/or DBP $\geq$ 95 mmHg, because we followed the definition of HT at the time when the baseline survey was performed. Therefore, further studies are needed to confirm that self-reported HT as a predictive marker for CVD mortality can be applied under the new definition of hypertension (SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg) by a prospective cohort study. However, it might be hard to confirm the risk of self-reported HT under the new guidelines with a prospective cohort study because it has been only 10 years since the new guidelines for HT were established. Thus, we consider that our study includes the best available data for the time being. Second, confirmative HT in our study was defined by the single BP measurement in the baseline survey, although repeated measurements are required to confirm HT. Thus, the prevalence of confirmative HT could be overestimated in our study.

In conclusion, self-reported HT is a predictive marker of CVD death in the Japanese population. As self-reported HT could identify more than one-half of the cases with confirmed HT, it may be a useful tool for screening. To identify individuals at high cardiovascular risk and to improve their health outcomes, assessment of self-reported HT by questionnaire may screen many people with HT who would not otherwise seek appropriate treatment.

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There are no conflicts of interest.

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White Blood Cell Count and Risk of All-Cause and Cardiovascular Mortality in Nationwide Sample of Japanese

— Results From the NIPPON DATA90 —

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Background The association of white blood cell (WBC) count with all-cause and cardiovascular disease (CVD) mortality were examined in the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged (NIPPON DATA) 90.
Methods and Results A total of 6,756 Japanese residents (2,773 men and 3,983 women) throughout Japan without a history of CVD were followed for 9.6 years. A Cox proportional hazards regression model was used to estimate the relative risk (RR) and 95% confidence interval (CI). We documented 576 deaths with 161 deaths from CVD. Overall, after adjusting for several confounders including age, sex, body mass index at baseline, smoking status, alcohol consumption, regular exercise, diastlic blood pressure, total cholesterol, high-density lipoprotein-cholesterol and hemoglobin A1c, a graded association between WBC count and higher risk of all-cause mortality was observed (WBC of 9,000–10,000 cells/mm^3 vs WBC of 4,000–4,900: RR=1.61, 95% CI: 1.07–2.40, p for trend=0.02). Elevated WBC count was almost significantly associated with high risk of CVD mortality (WBC of 9,000–10,000 vs WBC of 4,000–4,900: RR=1.79, 95% CI: 0.97–3.71). These associations strengthened among women. Stratified by smoking status, never-smokers with WBC counts of 9,000–10,000 had a 3.2 fold elevated risk for CVD death compared with those with WBC counts of 4,000–4,900.
Conclusions The WBC count may have potential as a predictor for all-cause mortality, particularly CVD mortality. (*Circ J* 2007; **71:** 479–485)

Key Words: Cardiovascular disease; Mortality; White blood cell count

Recently, evidence has been put forward indicating that chronic inflammation is associated with cardiovascular disease (CVD).[1–4] The white blood cell (WBC) is recognized as an important cellular marker of systemic inflammation. An elevated WBC count has been associated with cardiovascular risk factors such as cigarette smoking, obesity and metabolic disorders including hypertension, diabetes mellitus and dyslipidemia.[5,6] Several studies have also shown an increased risk of coronary heart disease (CHD),[7–11] stroke[11–14] and all-cause mortality among persons with a high WBC count.[15,16] However, these findings could not be generalized since most of them come from studies on occidental populations. They may not be true of Asian people, particularly among Japanese men who have a higher rate of smoking and Japanese women who have a lower rate than people in other developed countries (smoking rate of men and women: 52.8% and 13.4% in Japan, 25.7% and 21.5% in United States of America, 27.0% and 26.0% in United Kingdom, and 38.6% and 30.3% in France, respectively).[17] Moreover, the WBC count is known to be positively associated with body mass index (BMI),[6] and Japanese people are much leaner than occidental people.[18]

One purpose of the present study is to examine the relationship of the WBC count with all-cause and CVD mortality in a cohort study of representative Japanese men and women randomly selected throughout Japan.

Methods

Study Population

NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged) 80 and 90 are nationwide Japanese

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studies to evaluate prospectively the various risks and/or protective factors regarding circulatory disease mortality among the adult population for use in the development of future preventive measures. The study methods and ethical issues have been described in detail elsewhere![19–21] In the present study, data from NIPPON DATA90 were analyzed because the WBC count was not measured in NIPPON DATA80. Briefly, the baseline survey in NIPPON DATA90 was performed in 1990 for all household members aged 30 years or older in 300 districts randomly selected throughout Japan. Of 10,956 enrolled in this survey, a total of 8,384 community residents (3,504 men and 4,880 women) provided the data from medical examinations, blood tests and self-administered questionnaires about lifestyle, and were followed until 15 November 2000. The survey response rate was 76.5%. Of the 8,384 participants, we excluded subjects with any of the following criteria: past history of stroke (n=159), past history of CHD (n=230), missing information on lifestyle factors or body size (n=113), no available data to evaluate a vital criteria during the follow-up period (n=182), missing information on WBC count at baseline or metabolic parameters (n=550), subjects with WBC counts of less than 4,000 cells/mm^3 indicating clinical leucopenia (n=217) and subjects with WBC counts of more than 10,000 cells/mm^3 indicating clinically relevant inflammatory conditions (n=306). We limited WBC count from 4,000 to 10,000 cells/mm^3 to minimize the potential influences of several factors related to elevated or decreased WBC counts beyond normal limits. In all, 1,628 subjects were excluded, and the remaining 6,756 (2,773 men and 3,983 women) were included in the present study.

Follow-up Survey

Vital statistics for determining causes of death were obtained from the Management and Coordination Agency, Government of Japan. The underlying causes of death for the National Vital Statistics were coded according to the 9th International Classification of Disease (ICD-9) until 1994 and the 10th International Classification of Disease (ICD-10) from 1995.

The present study protocol was approved by the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Baseline Examination

Non-fasting blood samples were collected in the tubes containing anticoagulant. These tubes were stored at room temperature and collected during the morning of the day after blood collection by a commercial hematological laboratory (SRL, Tokyo, Japan). The WBC counts were measured with an automatic hematology analyzer (E-3000, Toa Medical Electronics, Kobe, Japan) and expressed as 100 cells/mm^3. Hemoglobin (Hb) A1c was measured using the latex agglutination method. The serum was separated and centrifuged soon after coagulation. Serum total cholesterol (TC) was measured enzymatically and high-density lipoprotein-cholesterol (HDL-C) was measured using the precipitation method using heparin-calcium. Systolic and diastolic blood pressures (SBP and DBP) were measured by trained observers using a standard mercury sphygmomanometer. BMI was calculated as weight (kg) divided by the square of height (m). Information on smoking status, drinking habits and medical histories was obtained by public health nurses.

Statistical Analysis

Subjects were divided into 6 categories according to WBC count (cells/mm^3) as follows: 4,000–4,900, 5,000–5,900, 6,000–6,900, 7,000–7,900, 8,000–8,900, and 9,000–10,000. We speculated a threshold effect of elevated WBC count on mortality. So we divided WBC counts into 6 categories by 1,000.

First, to elucidate the differences in potential confounding variables among WBC categories, we calculated proportions, means and standard deviations by sex. Chi-square test or analysis of variance was performed to explore the potential association between WBC count and potential confounding variables.

Second, the Cox proportional hazards regression model was used to estimate, by means of the hazard ratio, the relative risk (RR) and 95% confidence interval (CI) of each WBC category for all-cause or cause-specific mortality in the age and multivariate model. Persons who died of other causes in cause-specific analysis were measured at the date of death. Survivors were measured at the date of the last follow-up. RRs of mortality in individual WBC categories were computed with the WBC category of 4,000–4,900 cells/mm^3 considered as the reference. Multivariate models were adjusted for age (continuous), BMI (continuous), smoking status (never, former, current: dummy code), alcohol consumption (current, former, never: dummy code), regular exercise (yes, no), DBP, TC, HDL-C and HbA1c (continuous). The model including SBP instead of DBP showed the same results. A linear trend of association was assessed by the regression model assigning score (0, 1, 2, ...) to the levels of the WBC category. We checked the assumption of proportional hazards by the log-minus-log (LML) plot. Each categorical covariate remained intact and each continuous covariate was categorized into the quartiles, and the LML plots were examined. For each covariate, the plots were parallel, indicating that the proportional hazard assumption was not violated.

To elucidate the modification of the effects of WBC count by smoking status, subjects were stratified into 3 subgroups (never, former, current). In addition, we estimated the multivariate RR of each WBC category. We also stratified the subjects into 2 subgroups by BMI of 25 kg/m^2 according to criteria recommended by the Japan Society for the Study of Obesity[22] and thereafter performed the same analysis.

All analyses were performed using the SPSS 11.0 statistical package. $P<0.05$ was considered statistically significant.

Results

The mean (standard deviation (SD)) of age at baseline was 52.3 (13.6) years (53.0 (13.4) for men and 51.9 (13.7) for women). Mean (SD) and median values of WBC (cells/mm^3) were significantly higher among men (mean (SD), 6,821 (1,427); median, 6,700) than women (6,330 (1,326); 6,200) ($p<0.001$).

The baseline characteristics of the subjects according to WBC category are shown in Table 1. Compared with those in lower WBC categories, subjects in higher WBC categories were likely to be young, obese and current smokers among both men and women. DBP, TC, HDL-C and HbA1c were significantly different among the WBC categories. The WBC counts were positively associated with DBP, TC and HbA1c and negatively with HDL-C.

Total person-years were 64,788 (26,245 for men and

Table 1 Baseline Characteristics by Sex According to WBC Count, NIPPON DATA90, 1990–2000

	WBC conut (cells/mm³)						p for difference
	4,000–4,900	5,000–5,900	6,000–6,900	7,000–7,900	8,000–8,900	9,000–10,000	
Men							
Number of subjects	281	555	691	579	427	240	
*Age**	59.0±14.4	54.1±13.8	53.2±13.4	52.3±12.6	50.4±12.7	48.7±12.2	<0.001
*BMI (kg/m²)**	22.0±2.97	22.7±2.85	23.0±2.88	23.2±3.08	23.3±3.19	23.3±3.03	<0.001
*SBP (mmHg)**	136.4±21.0	136.1±19.9	138.4±20.6	137.8±19.8	138.6±20.3	138.8±19.5	0.2
*DBP (mmHg)**	81.9±11.2	82.6±11.8	84.4±11.8	84.2±11.4	84.3±11.6	84.8±11.7	<0.01
*TC (mg/dl)**	188.6±34.9	192.9±35.5	199.2±34.6	199.4±36.1	203.4±38.0	202.1±36.3	<0.001
*HDL-C (mg/dl)**	53.4±15.3	51.6±14.7	51.6±15.6	49.9±14.3	49.4±15.6	48.0±14.4	<0.001
*Hemoglobin A1c (%)**	4.97±0.77	4.95±0.67	5.00±0.86	4.99±0.61	5.00±0.61	5.15±0.87	<0.05
Smoking status							
Never-smoker (%)	35.2	27.7	22.6	18.8	12.6	8.8	<0.001
Former-smoker (%)	33.5	28.5	27.4	21.8	17.8	11.3	
Current smoker (%)	31.3	43.8	50.1	59.4	69.6	80.0	
Alcohol consumption							
Never-drinker (%)	32.0	37.1	34.4	34.5	36.1	30.0	0.10
Former-drinker (%)	7.5	8.1	4.9	5.2	4.9	4.6	
Current drinker (%)	60.5	54.8	60.6	60.3	59.0	65.4	
Regular exercise (%)	29.5	24.1	23.0	22.5	16.6	22.9	<0.01
Medical history							
Hypertension (%)	20.6	19.6	23.2	19.9	20.1	23.3	0.5
Diabetes (%)	5.7	6.5	7.5	5.7	5.2	5.4	0.3
Dyslipidemia (%)	4.3	4.0	8.0	7.3	5.4	6.3	<0.05
Women							
Number of subjects	625	1,099	1,013	745	350	151	
*Age**	55.1±13.9	53.0±13.6	51.3±13.7	50.4±13.3	49.4±13.3	48.0±13.0	<0.001
*BMI (kg/m²)**	22.3±3.16	22.7±3.18	22.8±3.14	23.2±3.42	23.2±3.43	23.3±3.58	<0.001
*SBP (mmHg)**	132.8±20.2	132.9±20.5	133.2±21.1	133.5±21.1	133.9±19.7	135.6±21.7	0.7
*DBP (mmHg)**	78.5±11.4	79.4±11.3	79.4±12.1	79.5±11.7	80.8±12.0	80.9±12.2	<0.05
*TC (mg/dl)**	200.2±37.2	206.7±37.7	208.9±38.3	208.3±36.4	210.7±39.7	206.3±40.5	<0.001
*HDL-C (mg/dl)**	57.9±15.2	58.1±15.4	57.4±14.8	55.5±14.5	55.0±14.3	53.7±12.6	<0.001
*Hemoglobin A1c (%)**	4.82±0.57	4.89±0.69	4.88±0.65	4.93±0.80	4.93±0.78	5.09±0.92	<0.001
Smoking status							
Never-smoker (%)	93.4	90.9	89.4	86.0	80.3	79.5	<0.001
Former-smoker (%)	1.9	3.0	2.3	3.1	2.3	1.3	
Current smoker (%)	4.6	6.1	8.3	10.9	17.4	19.2	
Alcohol consumption							
Never-drinker (%)	92.6	92.7	92.8	92.3	90.9	93.4	0.5
Former-drinker (%)	1.6	0.8	0.5	1.2	1.4	0.0	
Current drinker (%)	5.8	6.5	6.7	6.4	7.7	6.6	
Regular exercise (%)	19.4	18.5	18.3	18.7	17.7	21.9	0.9
Medical history							
Hypertension (%)	22.2	19.6	19.4	22.6	18.3	19.2	0.4
Diabetes (%)	3.4	4.5	3.1	3.4	1.7	6.0	0.09
Dyslipidemia (%)	8.2	6.9	7.7	8.2	3.7	6.0	0.1

**mean±standard deviation.*
WBC, white blood cell; NIPPON DATA, National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged; BMI, body mass index; SBP, systolic blood pressure; DBP, diastlic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol.

38,543 for women), the mean follow-up period was 9.6 years (9.5 for men and 9.7 for women) and the range of follow-up period was 1.6–10.0 years (1.6–10.0 for men and 1.8–10.0 for women). During follow-up, there were 576 deaths (307 among men and 269 among women). Of them, 161 deaths (28%) were due to CVD.

Table 2 shows the association between WBC and all-cause mortality. Overall, after multivariate-adjustment, a graded association between WBC count and higher risk of all-cause mortality was observed (p for trend=0.02; WBC of 9,000–10,000 cells/mm³ vs WBC of 4,000–4,900 cells/mm³: RR=1.61, 95% CI: 1.07–2.40). Stratified by sex, this graded association was observed only among women (p for trend=0.03).

Table 3 presents the association between WBC and CVD mortality. For the entire sample, subjects in the highest category were likely to have a higher risk of death from CVD (RR=1.79, 0.97–3.71), but the estimates showed no significant trend. Sex-specific multivariate-adjusted analyses showed borderline significant increases in RR for CVD mortality only among women, with RR and 95% CIs for the lowest, 2nd, 3rd, 4th, 5th, highest categories of 1.00 (referent), 1.02 (0.53–1.96), 1.12 (0.56–2.24), 0.88 (0.39–1.97), 2.04 (0.90–4.64) and 2.66 (0.95–7.45), respectively (p for trend=0.08). Since similar RRs for lowest to 4th and 5th to highest were observed, these categories were analyzed in combination. Women with WBC counts of 8,000–10,000 cells/mm³ had over a 2-fold elevated risk of CVD (RR=2.18, 1.23–3.88) compared with those with WBC counts of 4,000–7,900 cells/mm³. Additionally, in the context of public health practice, women with WBC counts of 8,000–10,000 cells/mm³ had a 1.5-fold borderline significantly higher risk for all-cause mortality (RR=1.50, 0.95–2.37) and a 2.2-fold significantly higher risk for CVD mortality (RR=2.22, 1.06–4.62) compared to those with WBC counts of 4,000–4,900 cells/mm³. No significant association was

Table 2 Adjusted RR for All-Cause Mortality According to the WBC Count, NIPPON DATA90, 1990–2000

Baseline WBC count (cells/mm³)	No. of deaths	Person-years	Age, (sex)-adjusted RR (95%CI)	Multivariate-adjusted RR* (95%CI)
Overall				
4,000–4,900	97	8,563	1.00 (referent)	1.00 (referent)
5,000–5,900	146	15,852	1.09 (0.84–1.40)	1.06 (0.81–1.37)
6,000–6,900	135	16,374	1.09 (0.84–1.41)	1.08 (0.82–1.41)
7,000–7,900	100	12,824	1.14 (0.86–1.51)	1.12 (0.84–1.50)
8,000–8,900	63	7,419	1.43 (1.04–1.98)†	1.32 (0.95–1.84)
9,000–10,000	35	3,756	1.82 (1.23–2.70)**	1.61 (1.07–2.40)†
p value for trend			<0.01	0.02
Men				
4,000–4,900	49	2,555	1.00 (referent)	1.00 (referent)
5,000–5,900	72	5,191	1.12 (0.78–1.61)	1.08 (0.75–1.57)
6,000–6,900	69	6,569	0.95 (0.65–1.37)	0.98 (0.67–1.43)
7,000–7,900	52	5,585	0.98 (0.66–1.45)	0.99 (0.66–1.48)
8,000–8,900	41	4,047	1.35 (0.89–2.06)	1.30 (0.84–2.02)
9,000–10,000	24	2,299	1.68 (1.02–2.76)†	1.48 (0.89–2.48)
p value for trend			0.1	0.2
Women				
4,000–4,900	48	6,008	1.00 (referent)	1.00 (referent)
5,000–5,900	74	10,661	1.07 (0.74–1.53)	1.03 (0.72–1.49)
6,000–6,900	66	9,805	1.26 (0.87–1.83)	1.23 (0.84–1.80)
7,000–7,900	48	7,239	1.36 (0.91–2.03)	1.32 (0.87–1.98)
8,000–8,900	22	3,372	1.52 (0.92–2.52)	1.38 (0.82–2.32)
9,000–10,000	11	1,457	2.03 (1.05–3.93)†	1.78 (0.92–3.47)
p value for trend			0.01	0.03

*Adjusted for age, sex, BMI at baseline, smoking status (never, former, current), alcohol consumption (never, former, current), regular exercise (yes, no), DBP, TC, HDL-C, and hemoglobin A1c.
**p<0.01. †p<0.05.
RR, relative risk; CI, confidence interval. Other abbreviations see in Table 1.

Table 3 Adjusted RR for Death From Cardiovascular Disease According to WBC Count, NIPPON DATA90, 1990–2000

Baseline WBC count (cells/mm³)	No. of deaths	Person-years	Age, (sex)-adjusted RR (95%CI)	Multivariate-adjusted RR* (95%CI)
Overall				
4,000–4,900	29	8,563	1.00 (referent)	1.00 (referent)
5,000–5,900	43	15,852	1.09 (0.68–1.75)	1.05 (0.65–1.69)
6,000–6,900	37	16,374	1.05 (0.64–1.71)	1.00 (0.61–1.66)
7,000–7,900	21	12,824	0.87 (0.49–1.52)	0.82 (0.46–1.45)
8,000–8,900	20	7,419	1.69 (0.95–3.00)	1.46 (0.80–2.65)
9,000–10,000	11	3,756	2.19 (1.08–4.45)**	1.79 (0.97–3.71)
p value for trend			0.08	0.2
Men				
4,000–4,900	13	2,555	1.00 (referent)	1.00 (referent)
5,000–5,900	20	5,191	1.17 (0.58–2.36)	1.09 (0.53–2.23)
6,000–6,900	19	6,569	0.99 (0.49–2.01)	0.93 (0.45–1.93)
7,000–7,900	11	5,585	0.79 (0.35–1.78)	0.72 (0.31–1.64)
8,000–8,900	10	4,047	1.27 (0.55–2.93)	1.04 (0.44–2.49)
9,000–10,000	6	2,299	1.62 (0.60–4.34)	1.23 (0.44–3.40)
p value for trend			0.7	0.9
Women				
4,000–4,900	16	6,008	1.00 (referent)	1.00 (referent)
5,000–5,900	23	10,661	1.03 (0.54–1.95)	1.02 (0.53–1.96)
6,000–6,900	18	9,805	1.10 (0.56–2.17)	1.12 (0.56–2.24)
7,000–7,900	10	7,239	0.92 (0.42–2.03)	0.88 (0.39–1.97)
8,000–8,900	10	3,372	2.24 (1.01–4.95)**	2.04 (0.90–4.64)
9,000–10,000	5	1,457	3.10 (1.13–8.50)**	2.66 (0.95–7.45)
p value for trend			0.04	0.08

*Adjusted for age, sex, BMI at baseline, smoking status (never, former, current), alcohol consumption (never, former, current), regular exercise (yes, no), DBP, TC, HDL-C, and hemoglobin A1c.
**p<0.05.
Abbreviations see in Tables 1,2.

observed in men.

The effect of modification of smoking status on the associations between WBC count and all-cause and CVD mortality was assessed (Table 4). The associations of WBC count with all-cause and CVD mortality were pronounced in never-smokers. Elevated WBC count was borderline significantly associated with increased risk of all-cause mortality in a graded manner (p for trend=0.07). Never-smokers with WBC counts of 9,000–10,000 cells/mm³ had over a 3-fold elevated risk for CVD death compared with those with WBC counts of 4,000–4,900 cells/mm³ (RR= 3.20, 1.25–8.24). When 6 categories were combined into

Table 4 Multivariable-Adjusted RR and 95% CI for All-Cause Mortality and Death From Cardiovascular Disease According to WBC Count by Smoking Status Among Overall Subjects, NIPPON DATA90, 1990–2000

Baseline WBC count (cells/mm³)	Person-years	All-cause			Cardiovascular disease		
		No. of deaths	RR*	95%CI	No. of deaths	RR*	95%CI
Never-smoker							
4,000–4,900	6,529	59	1.00	(referent)	20	1.00	(referent)
5,000–5,900	11,169	78	1.03	(0.73–0.146)	25	1.03	(0.56–1.88)
6,000–6,900	10,286	63	1.14	(0.79–1.64)	15	0.88	(0.44–1.75)
7,000–7,900	7,292	49	1.28	(0.87–1.88)	11	0.89	(0.42–1.89)
8,000–8,900	3,241	19	1.25	(0.74–2.12)	7	1.49	(0.62–3.59)
9,000–10,000	1,365	10	1.67	(0.85–3.32)	6	3.20	(1.25–8.24)**
	p value for trend		0.07			0.2	
Former-smoker							
4,000–4,900	992	15	1.00	(referent)	4	1.00	(referent)
5,000–5,900	1,774	29	1.87	(0.73–2.65)	8	1.24	(0.36–4.31)
6,000–6,900	2,003	25	1.19	(0.61–2.29)	3	0.47	(0.10–2.15)
7,000–7,900	1,427	15	1.17	(0.56–2.44)	4	1.03	(0.25–4.28)
8,000–8,900	795	9	1.46	(0.62–3.48)	4	1.62	(0.37–6.98)
9,000–10,000	266	4	1.99	(0.62–6.35)	0	–	
	p value for trend		0.5			0.9	
Current smoker							
4,000–4,900	1,041	23	1.00	(referent)	5	1.00	(referent)
5,000–5,900	2,909	39	0.81	(0.48–1.37)	10	0.95	(0.32–2.86)
6,000–6,900	4,085	47	0.88	(0.53–1.47)	19	1.52	(0.55–4.21)
7,000–7,900	4,105	36	0.80	(0.47–1.38)	6	0.56	(0.17–1.90)
8,000–8,900	3,383	35	1.09	(0.63–1.89)	9	1.23	(0.39–3.86)
9,000–10,000	2,125	21	1.24	(0.67–2.29)	5	1.35	(0.37–4.91)
	p value for trend		0.3			0.9	

*Adjusted for age, sex, BMI at baseline, alcohol consumption (never, former, current), regular exercise (yes, no), DBP, TC, HDL-C, and hemoglobin A1c.
**p<0.05.
Abbreviations see in Tables 1,2.

Table 5 Multivariable-Adjusted RR and 95% CI for All-Cause Mortality and Death From Cardiovascular Disease According to WBC Count by BMI of 25 kg/m² Among Overall Subjects, NIPPON DATA90, 1990–2000

Baseline WBC count (cells/mm³)	Person-years	All-cause			Cardiovascular disease		
		No. of deaths	RR*	95%CI	No. of deaths	RR*	95%CI
BMI: <25 kg/m²							
4,000–4,900	7,009	82	1.00	(referent)	23	1.00	(referent)
5,000–5,900	12,334	112	1.02	(0.77–1.37)	33	1.28	(0.69–2.40)
6,000–6,900	12,591	108	1.13	(0.84–1.52)	32	1.05	(0.54–2.01)
7,000–7,900	9,459	79	1.15	(0.84–1.58)	16	1.08	(0.54–2.16)
8,000–8,900	5,354	44	1.19	(0.81–1.73)	15	1.87	(0.89–3.92)
9,000–10,000	2,759	25	1.48	(0.93–2.35)	7	2.38	(0.99–5.76)
	p value for trend		0.08			0.09	
BMI: ≥25 kg/m²							
4,000–4,900	1,554	15	1.00	(referent)	6	1.00	(referent)
5,000–5,900	3,518	34	1.11	(0.65–1.91)	10	0.98	(0.34–2.81)
6,000–6,900	3,784	27	1.24	(0.71–2.14)	5	0.51	(0.15–1.77)
7,000–7,900	3,365	21	0.87	(0.45–1.66)	5	0.68	(0.19–2.40)
8,000–8,900	2,065	19	1.55	(0.79–3.05)	5	1.12	(0.29–4.26)
9,000–10,000	997	10	1.62	(0.68–3.87)	4	2.56	(0.58–11.2)
	p value for trend		0.3			0.5	

*Adjusted for age, sex, BMI at baseline, alcohol consumption (never, former, current), regular exercise (yes, no), DBP, TC, HDL-C, and hemoglobin A1c.
Abbreviations see in Tables 1,2.

2 categories, never-smokers with WBC counts of 8,000–10,000 cells/mm³ had a 2-fold high risk of CVD (RR=2.05, 1.12–3.76) compared with those with WBC counts of 4,000–7,900 cells/mm³.

Table 5 shows the effect of modification of BMI on the associations between WBC count and all-cause and CVD mortality. Among the subjects with BMI of <25 kg/m², WBC count was borderline significantly and positively associated with all-cause mortality risk and CVD mortality risk in a dose-dependent manner (p for trend=0.08, 0.09, respectively). In contrast, among the subjects with a BMI of ≥25 kg/m², those with a WBC count of ≥8,000 cells/mm³ seemed have high RRs for all-cause and CVD mortality although statistically not significant.

Discussion

In the present study of a nationally representative cohort of Japanese men and women, WBC count was significantly and positively associated with increased risk of all-cause

mortality among all subjects, even after adjustment for well-known confounding factors including age, BMI, smoking status, alcohol consumption, regular exercise, DBP, TC, HDL-C and HbA1c (p value for trend=0.02). After stratification by sex, this association was obvious among women (p value for trend=0.03). Moreover, as for CVD mortality, the subjects, especially women, with a WBC count of ≥8,000 cells/mm^3 were likely to have increased risk. In addition, when stratified by smoking status, we found associations between elevated WBC count and all-cause and CVD mortality in never-smokers.

First, the gender difference observed in the present study requires consideration. The present study showed a significant association of WBC count with all-cause mortality and CVD mortality among women but not among men. These findings may in part be explained by the difference in smoking status between men and women since the WBC count increases with the amount smoked. In the present study, the proportions of current smokers were 54.2% and 8.7% among men and women, respectively, and the smoking rate of men was higher than those of other studies conducted in occidental countries, which demonstrated the usefulness of the WBC count as a strong predictor of mortality[12,15] In a study of Koreans whose smoking status was similar to that of Japanese, the strong association of elevated WBC with mortality was observed among never smokers rather than smokers![10] In the present study, overall, the associations of WBC count with all-cause and CVD mortality were observed in never-smokers though analyses by sex could not be performed because of an insufficient sample size. Smoking may conceal the true association. To confirm the sex difference of the effect of WBC count on mortality in Japan, it is necessary to examine this issue among non-smoking men and women in much larger prospective studies.

The present study showed that an elevated WBC count predicted all-cause mortality among all subjects and especially among women. A few earlier studies have presented data stratified by sex or included only women. Only 3 studies found a positive association between the WBC count and all-cause mortality in women![10,11,21] The WBC count broadly indicates the level of host response to stressors and provides an index of acute and chronic inflammatory processes. Although this association remained after adjustment for clinical diagnosis of major chronic diseases, subclinical diseases may have affected the observed association. The association may be in part a consequence of the association between WBC count and CVD mortality, as mentioned below.

We found that an elevated WBC count was an independent predictor of CVD mortality among Japanese women. Several studies have assessed the WBC count as a predictor of CVD in women though there is far less research for women than for men?[,9–11,13,14] Of them, the Women's Health Initiative Observational Study (WHI-OS) provided some interesting findings![11] The WHI-OS reported that the RR of CHD, stroke, and CVD were 2.36 (95%CI: 1.51–3.68), 1.46 (95%CI: 1.17–1.81) and 1.47 (95%CI: 1.26–1.72) among women in the upper quartile of WBC counts (6,710–15,000 cells/mm^3) compared with those in the lowest quartile (2,500–4,700 cells/mm^3) although several causes that lead to elevated or decreased WBC counts beyond normal limits need to be considered in the interpretation of the results. WHI-OS also showed that the upper quartile was a threshold for elevated risk and was approximated by a WBC count of greater than 6,700 cells/mm^3 (RR of CVD mortality: 1.00 (lowest quartile: referent), 1.01 (second quartile), 1.12 (third quartile), 1.47 (upper quartile)). Such a threshold effect was also observed in the present study (RR of CVD mortality: 1.00 (WBC of 4,000–4,900 cells/mm^3: referent), 1.02 (WBC of 5,000–5,900 cells/mm^3), 1.12 (WBC of 6,000–6,900 cells/mm^3: referent), 0.88 (WBC of 7,000–7,900 cells/mm^3), 2.04 (WBC of 8,000–8,900 cells/mm^3), 2.66 (WBC of 9,000–10,000 cells/mm^3); WBC of 8,000–10,000 vs WBC of 4,000–7,900: RR=2.18, 1.23–3.88). This finding may be relevant to the underlying mechanisms between elevated WBC and CVD mortality risk. In addition, the WHI-OS conducted the nested case-control study to evaluate the association between WBC and CHD mortality under consideration of high sensitive C-reactive protein (hsCRP), which is widely recognized not only as inflammatory indicator but also as cardiovascular risk factor. The WBC count was still an independent predictor of CHD risk, comparable in magnitude to hsCRP, although adjustment for hsCRP attenuated the association between WBC count and CHD death. Unfortunately, information on hsCRP was not available in the present study.

We also examined whether BMI modified the association between WBC count and mortality risk. There were the borderline significant and positive associations between WBC count and all-cause and CVD mortality risk among the subjects with a BMI of <25 kg/m^2. Among the subjects with a BMI of ≥25 kg/m^2, the RR for those with WBC count of ≥8,000 cells/mm^3 were also likely to be high although statistically not significant. The number of obese subjects was too small to judge the modification by BMI in the present study. Speculatively, together with the results in previous studies on occidentals with high BMI, BMI may not modify the association between WBC count and mortality risk?[–9,11–15]

It is not known whether WBC is involved directly in the pathogenesis of CVD events or is merely a risk marker for other factors causing CVD. The association of elevated WBC count with CVD risk remained after adjusting for other CVD risk factors, suggesting a causal relationship. A number of pathogenetic mechanisms have been postulated to help explain the association. WBC influence blood rheology and adhesive properties, and have a role in endothelial injury by adhering to endothelium and damaging it with toxic oxygen compounds and proteolytic enzymes?[3] It is possible that the WBC count in healthy persons is a sign of active atherogenesis and helps to identify high-risk candidates for CVD.

The present study has several important strengths. First, these data are from a large nationally representative cohort and, thus, our findings can be generalized to the Japanese population. Second, we excluded participants with WBC counts below and above the clinically defined normal range to remove potential contributions from reduced immune function and infections, particularly chronic infections, respectively. The present study has several potential limitations. First, only one measurement of WBC count was performed. Therefore, WBC counts that were available in the present study may differ from the usual WBC counts in individuals since WBC counts fluctuate easily. Multiple WBC measurements over time may provide more accurate and detailed information to predict future mortality. If this proves true, the present study may underestimate the true association between WBC and mortality. In future, we

would like to investigate individual variation of WBC count to examine the validity of WBC count by one measurement and the usefulness of multiple WBC measurements. Second, a few previous studies provided the positive associations of neutrophils with all-cause and CVD mortality[8,16] Unfortunately, we had no data on differential WBC counts. Third, the sample was too small to study the associations between WBC counts and specific sites of CVD. Finally, unfortunately, hsCRP was not measured in the present study. Therefore, we may overestimate the association between WBC count and mortality because we could not use hsCRP as a covariate.

In conclusion, our results suggest an association of elevated WBC count with all-cause and CVD mortality among Japanese people, especially among women and among never-smokers. It is necessary to pay further attention to the potentiality of WBC count as a predictor of mortality.

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Appendix 1

List of the NIPPON DATA90 Research group:
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Relationship Between Metabolic Risk Factor Clustering and Cardiovascular Mortality Stratified by High Blood Glucose and Obesity

NIPPON DATA90, 1990–2000

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OBJECTIVE — Metabolic syndrome is diagnosed according to several criteria. Of these, some require glucose intolerance and others require obesity for the diagnosis. We investigated the relationship between metabolic risk factor clustering and cardiovascular disease (CVD) mortality stratified by high blood glucose or obesity.

RESEARCH DESIGN AND METHODS — We followed 7,219 Japanese men and women without a history of CVD for 9.6 years. We defined high blood pressure, high blood glucose, high triglycerides, low HDL cholesterol, and obesity as metabolic factors. The multivariate adjusted hazard ratio (HR) for CVD mortality according to the number of clustering metabolic factors was calculated using the Cox proportional hazards model.

RESULTS — During follow-up, 173 participants died of CVD. The numbers of metabolic risk factors and CVD mortality were positively correlated (P_{trend} = 0.07). The HR was obviously higher among participants with than among those without high blood glucose and clustering of ≥2 other metabolic risk factors (HR 3.67 [95% CI 1.49–9.03]). However, the risk increase was only modest in participants without high blood glucose even if they had ≥2 other metabolic risk factors (1.99 [0.93–4.28]). Conversely, metabolic risk factor clustering was related to CVD mortality irrespective of obesity.

CONCLUSIONS — Our findings suggest that glucose tolerance plays an important role in CVD mortality. Because the prevalence of nonobese participants with several metabolic risk factors was quite high and their CVD risk was high, excluding them from the diagnosis of metabolic syndrome because of the absence of obesity might overlook their risk.

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Members of the NIPPON DATA Research Group can be found in an online appendix at http://dx.doi.org/10.2337/dc06-2074.

Abbreviations: CVD, cardiovascular disease; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

The World Health Organization (WHO) states that individual risk factors for cardiovascular disease (CVD) convey greater CVD risk. Furthermore, even though each one of these risk factors alone is not serious, the risk becomes more "powerful" when they are combined (1). Metabolic syndrome is the concept of clustering risk factors comprising insulin resistance, abdominal fat distribution, dyslipidemia, and hypertension (2–5).

Several institutions have established their own diagnostic criteria for metabolic syndrome. The National Cholesterol Education Program (NCEP) considers that each metabolic factor has the same importance (6), whereas the WHO requires impaired glucose tolerance among its criteria to diagnose metabolic syndrome (7). Finally, the International Diabetes Federation (IDF) and the Japanese guidelines require central obesity defined by waist circumference to diagnose metabolic syndrome (8,9). Thus, whether a relationship between metabolic risk factor clustering and CVD mortality differs according to obesity or impaired glucose tolerance, which are both required for a diagnosis of metabolic syndrome, should be determined. Thus, in the present study, we investigated the association between metabolic factor clustering and CVD mortality stratified according to obesity or impaired glucose tolerance in a population-based cohort study in the Japanese general population.

RESEARCH DESIGN AND METHODS

— Cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease and Its Trends in the Aged). NIPPON DATA includes two cohort studies. Baseline data were surveyed in 1980 and in 1990 (NIPPON DATA80 and NIPPON DATA90), and

Table 1—*Means and prevalence of baseline characteristics of 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990)*

Baseline risk characteristics	Number of metabolic factors					
	0	1	2	3	4	5
n	1,604	2,657	1,643	942	336	37
Women (%)	67.3	54.3	59.4	55.4	56.9	56.0
Age (years)	44.1 ± 11.0	52.7 ± 13.6	56.0 ± 13.4	56.1 ± 12.5	58.0 ± 13.2	58.6 ± 11.2
BMI (kg/m^2)	20.9 ± 2.0	21.9 ± 2.4	24.1 ± 3.2	25.5 ± 3.1	26.7 ± 2.4	27.8 ± 2.0
Systolic blood pressure (mmHg)	114.9 ± 8.8	137.2 ± 19.7	141.8 ± 19.0	145.8 ± 17.4	149.2 ± 16.4	154.3 ± 18.4
Diastolic blood pressure (mmHg)	71.7 ± 7.5	82.1 ± 11.4	84.3 ± 11.4	86.7 ± 10.8	88.1 ± 11.5	89.7 ± 12.0
Total cholesterol (mg/dl)	194.2 ± 32.0	198.6 ± 36.2	206.0 ± 37.9	217.3 ± 40.8	224.6 ± 42.7	237.8 ± 43.7
Triglycerides (mg/dl)	78 (57–106)	95 (70–127)	127 (91–176)	192 (131–252)	255 (205–346)	269 (214–363)
HDL cholesterol (mg/dl)	63.5 ± 12.8	58.2 ± 14.6	49.5 ± 13.2	42.4 ± 10.9	37.5 ± 7.8	36.2 ± 6.8
Blood glucose (mg/dl)	92.6 ± 13.5	98.4 ± 22.5	105.5 ± 33.0	114.4 ± 45.9	126.5 ± 51.3	196.7 ± 69.7
High blood pressure (%)	0.0	72.1	82.8	93.7	99.4	100
High triglycerides (%)	0.0	2.8	20.0	55.1	89.3	100
Low HDL cholesterol (%)	0.0	16.1	46.0	73.5	93.2	100
High blood glucose (%)	0.0	2.1	11.7	19.2	33.3	100
Drinking						
Never drinker (%)	73.8	64.0	70.9	66.8	73.8	73.0
Ex-drinker (%)	2.3	2.7	3.4	3.8	3.3	10.8
Current drinker (%)	23.9	33.3	25.7	29.4	22.9	16.2
Smoking						
Never smoker (%)	65.8	58.2	61.6	58.1	54.2	56.8
Ex-smoker (%)	8.6	11.2	11.8	12.3	13.7	10.8
Current smoker (%)	25.6	30.6	26.6	29.6	32.1	32.4
Physical activity						
Yes (%)	18.9	20.3	20.6	21.2	19.3	24.3
No for physical problems (%)	3.4	5.3	6.8	7.1	9.0	10.8
No for other reasons (%)	77.7	74.4	72.6	71.8	71.7	64.9

Data are %, mean ± SD, or median (interquartile range). Metabolic factors were defined as follows: obesity as BMI ≥25 kg/m^2, high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high blood glucose as nonfasting blood glucose ≥140 mg/dl and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 md/dl for men or ≤50 mg/dl for women.

the details of these cohorts have been reported (10–15). Here, we analyzed data from NIPPON DATA90 because the baseline survey of NIPPON DATA80 does not include some important metabolic factors such as HDL cholesterol.

A total of 8,384 residents (3,504 men and 4,880 women, aged ≥30 years) from 300 randomly selected districts participated in the survey and were followed until 15 November 2000. The participation rate in this survey was 76.5%. Of the 8,384 participants, 1,165 were excluded because of a history of coronary heart disease or stroke (n = 371), information missing at the baseline survey (n = 636), and failure to access because of incomplete residential access information at the first survey (n = 158). The remaining 7,219 participants (2,999 men and 4,220 women) were included in the analysis.

Table 2—*Multiple adjusted HRs and 95% CIs according to the individual components of metabolic risk factor in 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990–2000)*

Component of metabolic factor	*n*	HR (95% CI)
Obesity	1,706	0.87 (0.60–1.27)
High blood glucose	579	1.45 (0.99–2.14)
High blood pressure	4,530	2.07 (1.21–3.52)
High triglycerides	1,259	1.42 (0.95–2.11)
Low HDL cholesterol	2,224	0.79 (0.56–1.12)

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, physical activity, and other components of metabolic factors. Metabolic factors were defined as in the footnote to Table 1. *n* is the number of participants who had the conditions.

Follow-up survey

The underlying causes of death in the National Vital Statistics were coded according to the ICD-9 until the end of 1994 and according to the ICD-10 from the start of 1995 until the end of 2000. Details of these classifications are described elsewhere (10–15). The Institutional Review Board of Shiga University of Medical Science (No. 12–18, 2000) approved this study.

Baseline examination

Nonfasting blood samples were obtained at the baseline survey. The serum was separated and centrifuged soon after blood coagulation. Plasma samples were collected in siliconized tubes containing sodium fluoride and shipped to one laboratory (SRL, Tokyo, Japan) for blood measurements. Plasma glucose was measured enzymatically. Serum triglycerides

Table 3—*Multiple adjusted HRs and 95% CIs according to number of metabolic factors in 2,999 men and 4,220 women ≥30 years (NIPPON DATA90, 1990–2000)*

Number of metabolic factors	*n*	Person-years	Cardiovascular deaths	HR (95% CI)
0	1,604	15,740	8	1.00 (—)
1	2,657	25,398	67	1.93 (0.92–4.05)
2	1,643	15,526	52	1.94 (0.91–4.13)
3	942	8,999	29	2.12 (0.96–4.70)
4	336	3,167	15	2.44 (1.02–5.84)
5	37	361	2	3.27 (0.69–15.50)
				P_{trend} 0.074

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, and physical activity. Metabolic factors were defined as in the footnote to Table 1.

and total cholesterol were also measured enzymatically, and HDL cholesterol was measured after heparin-calcium precipitation (16).

BMI was calculated as weight in kilograms divided by the square of height in meters. Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants. Public health nurses obtained information on smoking, alcohol consumption, physical activity, and medical history. We divided participants into four categories of smokers (never-smoked, ex-smoker, and current smoker <20 or ≥20 cigarettes/day) and six categories of drinking (never-drinker; ex-drinker; and current drinker of 1, 2, 3, and 4 gou of sake/day; 1 gou [180 ml] is equivalent to 23 g of alcohol) (11). We divided participants into three categories of physical activity (yes or no for physical problems, and no for any other reason).

We defined metabolic factors as follows: obesity, BMI ≥25 kg/m^2; high blood pressure, systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, administration of antihypertensive agents, or any combination of these; and high blood glucose, serum glucose ≥140 mg/dl, medication for diabetes, or both. Because our samples were nonfasting, the postload blood glucose level for diagnosis of impaired glucose tolerance was ≥140 mg/dl (17). We defined high triglycerides as nonfasting serum triglyceride ≥200 mg/dl and also as taking medication for dyslipidemia. Low HDL cholesterol was defined as serum HDL cholesterol ≤40 mg/dl for men and ≤50 mg/dl for women.

Statistical analysis

Continuous variables were compared using ANOVA, and the χ^2 test was used to compare the dichotomized variables to examine differences in baseline characteristics of participants according to the numbers of clustering metabolic factors.

The multivariate adjusted hazard ratio (HR) of all CVD mortality for each group was calculated using the Cox proportional hazards model adjusted for age, sex, total cholesterol, smoking, drinking, and physical activity category. When we calculated HR for an individual component of a metabolic factor, we further adjusted for other components of the metabolic factor. We used nonobese participants without any metabolic factor or participants with neither a metabolic factor nor high blood glucose as references in analyses stratified by obesity or high blood glucose (required component by the IDF and WHO, respectively). Because leaner participants also have a higher CVD mortality risk in Japan, we further analyzed a data subset excluding leaner participants (BMI <18.5 kg/m^2) (18,19).

All CIs were estimated at the 95% level. $P < 0.05$ was considered significant. The Statistical Package for the Social Sciences (version 11.0J; SPSS Japan, Tokyo, Japan) was used to perform all analyses.

RESULTS — Table 1 shows the baseline characteristics of the study participants according to the numbers of metabolic factors. Total person-years were 69,170, and the mean follow-up period was 9.6 years. During follow-up, 625 participants died of all causes and 173 died of CVD. Table 2 shows the multiple adjusted HRs and 95% CIs according to individual components of metabolic risk factors.

Table 3 shows the number of deaths, multiple adjusted HRs, and 95% CIs according to various numbers of metabolic factors. The HRs for CVD mortality were higher in the group with more metabolic factors, but the trend was not statistically significant (P_{trend} = 0.074). The relationship between numbers of risk factors and CVD mortality did not differ according to sex ($P_{interaction}$ = 0.70). We therefore combined men and women in the following analyses. The tendency for HR to be higher in those with more metabolic factors was similar for heart disease (three risk factors: HR 2.08 [95%CI 0.67–6.48]; four risk factors: 3.97[1.24–12.72]; five risk factors: not applicable) and stroke (three risk factors: 2.07 [0.67–6.37]; four risk factors: 1.23 [0.30–5.05]; five risk factors: 6.26 [CI, 1.13–34.60]) mortality. The HR tendency for all-cause mortality was similar, but the number of clustering metabolic factors was not significantly related to all-cause mortality (three risk factors: 1.16 [0.81–1.65]; four risk factors: 1.18 [0.77–1.80]; five risk factors: 1.44 [0.57–3.63]).

Table 4 shows multiple adjusted HRs (95% CI) due to the number of metabolic factors except high blood glucose stratified by high blood glucose. The HRs trended to increase in both groups (with and without high blood glucose). The HR for CVD in participants with ≥3 metabolic factors but high blood glucose was modest and not statistically significant. Conversely, HRs were obviously higher for participants with high blood glucose and ≥2 other metabolic factors than those for participants with neither metabolic factors nor high blood glucose. The risk increases were statistically significant.

Table 4 also shows multiple adjusted HRs (95% CI) for CVD mortality according to the number of metabolic factors other than obesity stratified by obesity. The relationship between HRs and the numbers of metabolic factors was positive in both obese and nonobese groups. This relationship was unchanged when participants with lower BMI (≥18.5 kg/m^2) were excluded.

CONCLUSIONS — We found that metabolic factor clustering was positively associated with CVD mortality in the general Japanese population. The risk increase in participants with both high blood glucose and ≥2 metabolic factors was significantly higher than in those with neither high blood glucose nor metabolic risk factors. The risk in nonobese participants with more metabolic factors was also increased.

Although investigating the relation-

Table 4—*Blood glucose category–specific multiple-adjusted HRs and 95% CIs according to number of metabolic factors other than high blood glucose and BMI category–specific multiple-adjusted HRs and 95% CIs according to the number of metabolic factors other than obesity in 2,999 men and 4,220 women aged ≥30 years (NIPPON DATA90, 1990–1999)*

	Number of metabolic factors	*n*	Person-years	Cardiovascular deaths	HR (95% CI)	HR (95% CI)
High blood glucose						
Without	0	1,604	15,740	8	1.00 (—)	
	1	2,600	24,867	65	1.91 (0.91–4.02)	
	2	1,451	13,796	45	1.99 (0.93–4.28)	
	≥3	985	9,522	22	1.61 (0.71–3.67)	
With	0 and 1	249	2,241	9	1.78 (0.68–4.67)	
	2	181	1,638	12	3.67 (1.49–9.03)	
	≥3	149	1,267	12	3.25 (1.31–8.06)	
BMI						
<25 kg/m^2	0	1,604	15,740	8	1.00 (—)	1.00 (—)
	1	2,474	23,576	67	1.98 (0.94–4.17)	2.14 (0.85–5.43)
	2	993	9,282	37	1.95 (0.90–4.25)	2.24 (0.86–5.82)
	≥3	442	4,108	24	2.83 (1.25–6.39)	3.35 (1.25–8.95)
≥25 kg/m^2	0 and 1	833	8,045	15	1.75 (0.73–4.16)	2.12 (0.76–5.89)
	2	551	5,339	10	1.47 (0.57–3.75)	1.78 (0.59–5.19)
	≥3	322	3,080	12	2.37 (0.96–5.89)	2.84 (0.99–8.17)

HRs were estimated by a Cox proportional hazards model adjusted for sex, age, total cholesterol, smoking habits, drinking habits, and physical activity. High blood glucose was defined as nonfasting blood glucose ≥140 mg/dl and/or medication. Metabolic factors were defined as follows: obesity as BMI ≥25 kg/m^2, high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 mg/dl for men or ≤50 mg/dl for women. In the group with high blood glucose, 0 and 1 metabolic factors were combined because we found only two cardiovascular deaths in the group whose number of metabolic factors was 0. *HRs (95% CI) were analyzed for participants with BMI >18.5 kg/m^2. Metabolic factors were defined as follows: high blood pressure as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or medication, high blood glucose as nonfasting blood glucose ≥140 mg/dl and/or medication, high triglycerides as nonfasting triglycerides ≥200 mg/dl and/or medication, low HDL cholesterol as HDL cholesterol ≤40 mg/dl for men or ≤50 mg/dl for women. In the group with BMI ≥25 kg/m^2, 0 and 1 metabolic factors were combined because we found no cardiovascular death in the group whose number of metabolic factors was 0.

ship between metabolic factor clustering and CVD mortality is important, prospective studies on the topic are still scarce. On the basis of the NCEP and WHO definitions of metabolic syndrome, several investigators have reported that participants with metabolic syndrome or metabolic factor clustering have a high HR of CVD mortality (20–25). Ford (26) summarized prospective cohort studies and reported that the HRs of CVD mortality were 1.65 [5% CI 1.38–1.99] according to the NCEP definition and 1.93 [1.39–2.67] according to the WHO definition, respectively. This result is consistent with our findings that participants with more metabolic factors have a higher risk of CVD mortality. Our results were also comparable with those of a prospective study in Japan showing that the relative risk of cardiac diseases was 2.23 [1.14–4.34] in participants with ≥3 metabolic factors compared with that in participants with <3 metabolic factors (27).

The IDF definition requires obesity for diagnosis of metabolic syndrome. These guidelines explain that central (abdominal) obesity is a prerequisite for this diagnosis because it is easy to assess and independently associated with each of the other metabolic syndrome components (8). The IDF guidelines do not essentially require insulin resistance because it is difficult to measure in day-to-day clinical practice (7,8). However, although increased waist circumference is an important component of metabolic syndrome, some individuals with multiple risk factors and an increased risk of CVD mortality have normal waist circumference (28,29). For example, Katzmarzyk et al. (28) reported that waist circumference is a valuable component of metabolic syndrome, but they also raised the concern that the IDF requirement of an increased waist circumference warranted caution because a large proportion of individuals with normal waist circumference also have multiple risk factors and an increased risk of mortality.

We found here that nonobese participants with three or more metabolic factors had significantly higher HRs for CVD death and that their risk was similar to that of obese participants with the corresponding number of metabolic factors. Thus, a proportion of high-risk participants might be overlooked if obesity is a diagnostic requirement for metabolic syndrome. Waist circumference supposedly indicates visceral fat more accurately than BMI in terms of predicting diabetes (30). However, we did not have any information about waist circumference and used BMI as it closely correlates with waist circumference. Furthermore, BMI has been used to diagnose obesity in many epidemiological studies of metabolic syndrome (22,23), indicating that BMI was acceptable for our purposes. However, because of the use of BMI, we might have underestimated the impact of obesity on CVD mortality. A similar study using waist circumference should clarify the relation.

The WHO guidelines indicate that the presence of diabetes, impaired glucose tolerance, or insulin resistance is necessary for a diagnosis of metabolic syndrome because this condition is considered a special classification for those with the potential for diabetes (manifested as impaired glucose tolerance, impaired fasting glucose, or insulin resistance determined using the hyperinsulinemic-euglycemic clamp) (1,7). Here, we also stratified participants according to blood glucose level and found that the HR was higher among those with than among those without high blood glucose. These findings suggest that glucose toler-

ance plays an important role in CVD mortality. Some reports have shown higher HRs with use of the WHO rather than the NCEP definition of metabolic syndrome. This result means that the participants with impaired glucose tolerance have higher HRs, a finding that the present results support (26). However, several participants with clustering of metabolic factors other than impaired glucose tolerance also had an increased risk of CVD mortality.

Some limitations other than using BMI should be noted about the present study. First, we used nonfasting blood samples and thus we might have misclassified participants with high blood glucose or hypertriglyceridemia. Second, we did not adjust for socioeconomic status because relevant information was not available. However, all Japanese are covered by the national health insurance program and socioeconomic status does not affect access to treatment. Therefore, the impact of socioeconomic status on our findings should be minimal.

In summary, the CVD risk was obviously higher among individuals with than among those without high blood glucose and multiple metabolic risk factors, suggesting that high blood glucose plays an important role in CVD mortality. Conversely, the prevalence of nonobese participants with several metabolic factors was quite high and their CVD risk was high. Thus, metabolic factors should be carefully considered and appropriately managed even among individuals with a BMI <25.

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