図2　BMIの年齢調整平均値の都道府県別順位と95%信頼区間：男性20～74歳　(2001-05年国民健康・栄養調査)

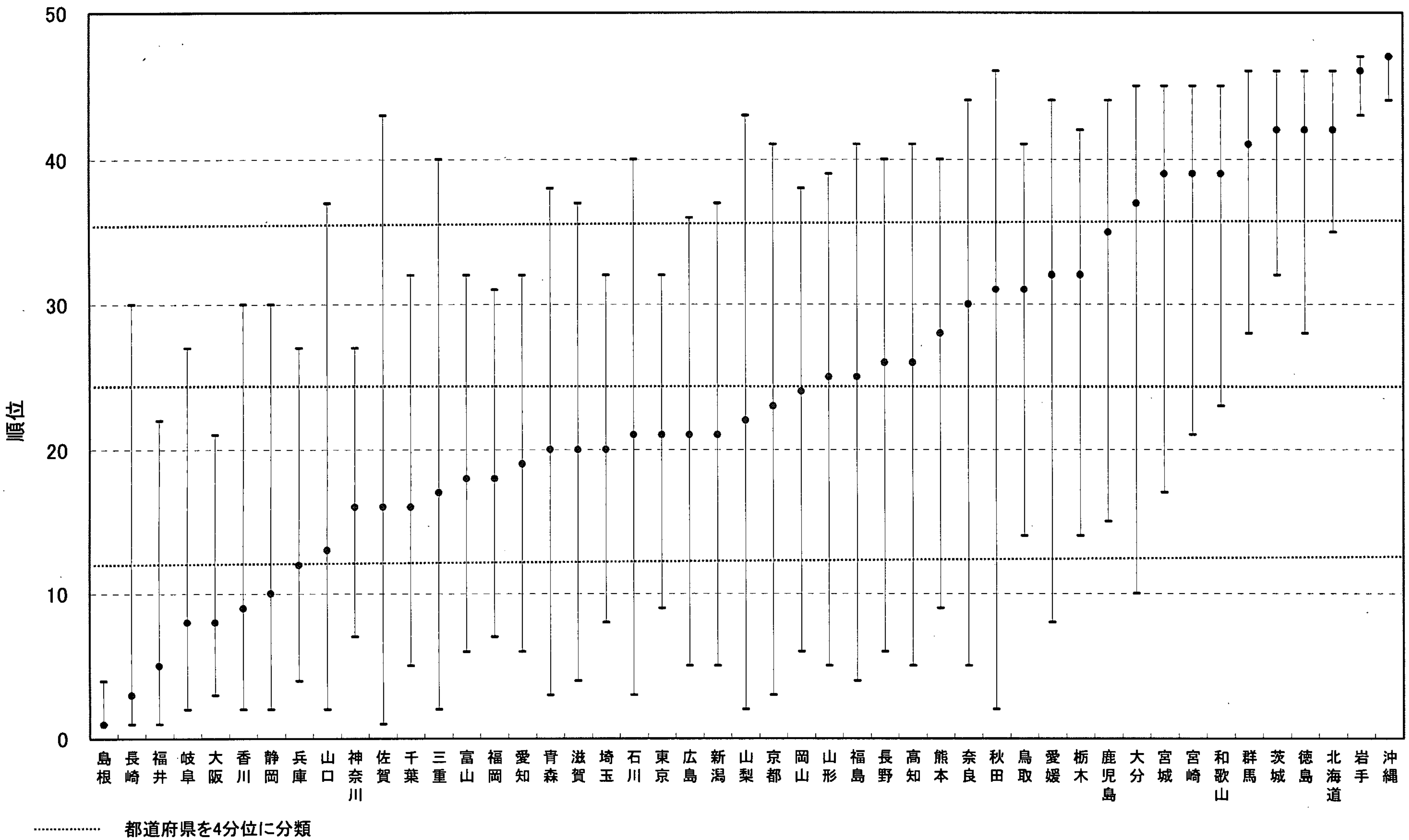
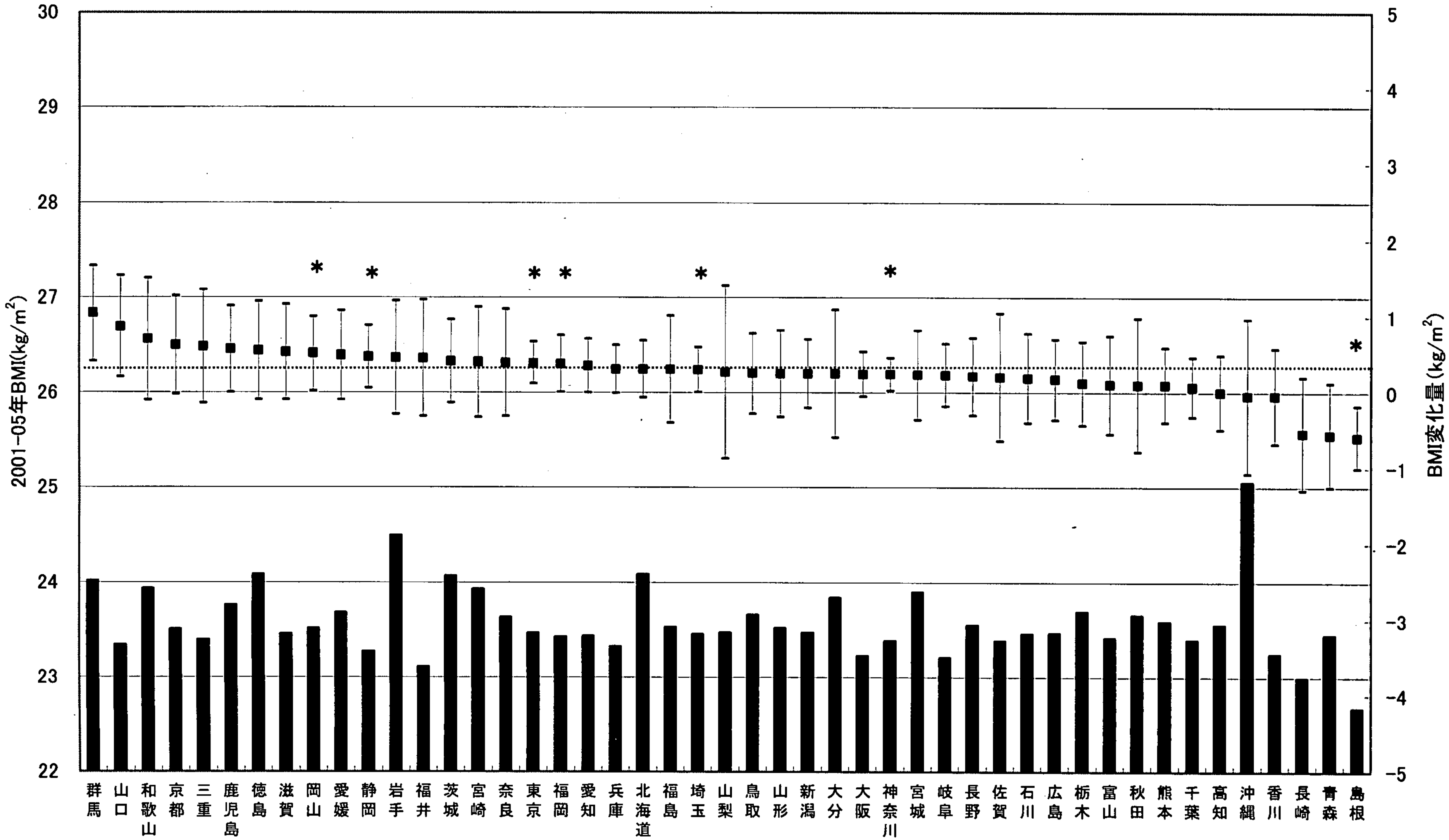


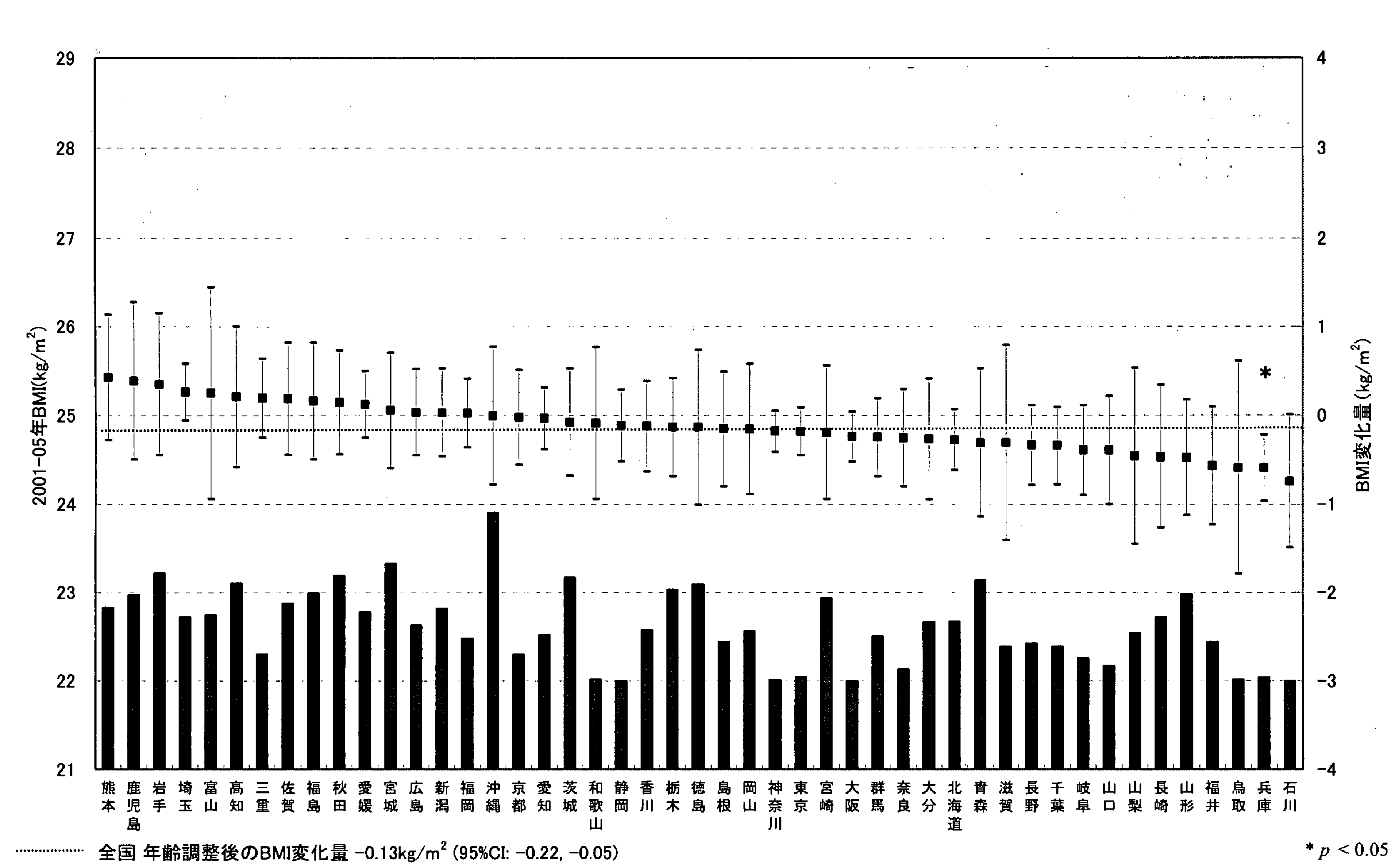
図3　BMIの年齢調整平均値（2001-05年の現状値＝棒グラフ）と5年間の変化（誤差線付き）［増加の大きい順］：男性20〜74歳（国民健康・栄養調査）



………… 全国 年齢調整後のBMI変化量 0.31kg/m² (95%CI: 0.23, 0.39)

* $p < 0.05$

図４　BMI の年齢調整平均値（2001-05 年の現状値＝棒グラフ）と５年間の変化（誤差線付き）［増加の大きい順］：女性 20～74 歳（国民健康・栄養調査）



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Is the measurement of glycated hemoglobin A1c alone an efficient screening test for undiagnosed diabetes? Japan National Diabetes Survey

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Abstract

The aim of the study was to assess the screening test properties of HbA1c for undiagnosed diabetes (DM) according to the 1999-WHO criteria and its relevance of the Japan National Diabetes Survey Cut-off points for possible and probable DM: HbA1c ≥5.6 and 6.1%. Screening properties of HbA1c predicting undiagnosed DM was examined and compared with that of fasting plasma glucose (FPG) in 1904 Funagata-town inhabitants aged 35–89 years old. The prevalence of previous DM, undiagnosed DM, and impaired glucose regulation (IGR) were 5.5, 6.0, and 18.6%, while the prevalence of probable and possible DM were 7.7 and 5.4%. The area under the receiver operating characteristic curve for undiagnosed DM was similar between HbA1c (0.856 [95% CI: 0.812–0.899]) and FPG (0.902 [0.869–0.936]). HbA1c of 5.6% gave a sensitivity of 56.5%, a specificity of 95.1%, positive and negative predictive values of 44.2 and 97.0%, and a proportion of people above the cut-off point of 8.2%. True positive tests were significantly higher with mean levels of BMI, fasting, and 2-h plasma glucose, and HbA1c, but lower with mean levels of high-density-lipoprotein cholesterol than in false negative tests. The measurement of HbA1c alone may be efficient to screen undiagnosed DM and the cut-off point of 5.6% might be proper with respect to screening tests properties for undiagnosed DM, and prediction of vascular complications in Japan.

Keywords: Hemoglobin A1c; Diabetes; Screening; Japan

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; 2-h PG, 2-h plasma glucose; HDL, high-density-lipoprotein; IFG, impaired fasting glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance; NPV, negative predictive value; OGTT, oral glucose tolerance test; JDS, Japan Diabetes Society; JNDS, Japan National Diabetes Survey; PPV, positive predictive value; ROC, receiver operating characteristic; WHO, World Health Organization

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1. Introduction

In Japan, stable glycated hemoglobin (HbA1c) was standardized in the mid 1990s by the Japan Diabetes Society (JDS) [1] and has been used to estimate the number of people with possible and probable diabetes (DM) in the Japan National Diabetes Survey (JNDS) [2]. In this survey, probable DM was defined as HbA1c over 6.1% or under treatment for DM, and possible DM was defined as HbA1c between 5.6 and 6.0% among those without treatment for DM [2]. These cut-off points for HbA1c were chosen with respect to equivalent diagnostic cut-off points for fasting plasma glucose (FPG) and 2-h plasma glucose (2-h PG) in an oral glucose tolerance test (OGTT) for undiagnosed DM in health-check examination data [2]: HbA1c of 6.1% corresponded to the diabetic 2-h PG value in an OGTT in the linear regression analysis [3], whereas an HbA1c range between 5.6 and 6.1% showed a sensitivity of 80% and a specificity of 70% for undiagnosed DM (Sasaki, unpublished data). Then, according to the JNDS performed in 2002, the total number of people having probable and possible DM has been estimated as 7.4 and 8.8 million among the Japanese general population over 20 years old [2]. However, it is unknown to what extent these cut-off points for HbA1c accurately estimate the number of people with full DM based on glucose cut-offs according to the World Health Organization (WHO) criteria [4]. Thus, we assess the screening test properties of HbA1c for undiagnosed DM and the relevance of the JNDS cut-off points, in the general population-based data from the Funagata study.

2. Subjects and methods

Details of the Funagata study have been published elsewhere [5]. Briefly, the Funagata study is a population-based study designed to clarify risk factors, related conditions, and consequences of Type 2 DM. In Funagata, an agricultural area 400 km north of Tokyo, the population aged 35–89 years was 4644 in 2001. From 2000 to 2002, 3972 inhabitants aged 35–89 years registered in the study and 1918 inhabitants (participation rate: 48.3%) participated. Of those, 1904 inhabitants (men: 43.3%, age: 61 ± 12 years old (mean ± S.D.)) over 35 years were analysed for this study.

After overnight fast, all subjects had blood samples drawn from the antecubital vein for measurement of FPG and 2-h PG on a standard 75 g OGTT (Trelan-G®, Shimizu Pharmaceutical, Shimizu), HbA1c, and other biochemical tests from 16th June 2000 to 7th July 2002. Blood samples were assayed at the laboratory in Yamagata University Hospital. Blood was transferred to fluoride-heparin tubes and kept cold until centrifugation and separation of plasma at 2500 rpm (within 6 h). Plasma was frozen immediately, stored at −20 °C, and subjected to automated glucose analysis by the glucose dehydrogenase method (GA1160; Arkray, Kyoto). Intra-assay coefficient of variation for glucose was 0.8% at 72 mg/dl and 0.6% at 238 mg/dl. Sample aliquots for HbA1c analysis were placed in EDTA tubes, kept cold until processing (within 6 h) and measured by the high-performance liquid chromatography (HPLC) method (HA-8150; Arkray, Kyoto [manufactured reference range: 2–16%]) after the standardized calibration from the JDS [1]. Intra-assay coefficient of variation for HbA1c was 1.0% at values 5.2 and 10.5%. The JDS assigned HbA1c values are converted to the National Glycoprotein Standardization Program (NGSP) assigned values by following the formula [6]: NGSP value (%) = JDS value (%) + 0.3 (%). Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2), and systolic and diastolic blood pressures were measured in the sitting position after a 5-min rest using a mercury sphyngomanometer. Total cholesterol, triglyceride, and high-density-lipoprotein (HDL) cholesterol were measured by cholesterol oxidase method, enzymatic method, and direct method, respectively.

In this study, subjects who were previously diagnosed as DM or undiagnosed DM who had FPG ≥126 mg/dl and/or 2-h PG ≥200 mg/dl on an OGTT by the WHO criteria [4] were considered as DM, whereas those who had FPG 110–125 mg/dl and/or 2-h PG 140–199 mg/dl on an OGTT by the WHO criteria [4] were considered as impaired glucose regulation (IGR). Subsequently, people were classified according to glucose categories based on cut-off points of HbA1c applied by the JNDS [2]: probable DM, people under treatment for DM, or those with HbA1c ≥6.1% without treatment for DM; possible DM, people with HbA1c 5.6–6.0% in those without treatment for DM; not abnormal, people with HbA1c <5.6% in those without treatment for DM.

Individuals with previously diagnosed DM were included in total DM estimate but excluded from the analyses of screening properties. The area under the receiver operating characteristic (ROC) curve [7] for HbA1c and FPG predicting undiagnosed DM was compared. The performance of HbA1c and FPG in relation to identify undiagnosed DM included sensitivity: percentage of individuals with undiagnosed diabetes who had a positive screening test; specificity: percentage of individuals without undiagnosed diabetes who had a negative screening test; predictive values for positive (PPV): percentage of individuals with screening test positive who had undiagnosed diabetes; and negative (NPV): percentage of individuals with screening test negative who had non diabetes, and the proportion of people with above the cut-off value.

Sum total number was estimated and compared between people with possible plus probable DM applied by the JNDS, and those previously diagnosed plus undiagnosed DM defined by the WHO criteria [4], after age-adjusting for the projected Japanese population on 1st October 2002 [8].

Cardiovascular disease (CVD) risk profiles were compared between true positive tests (HbA1c ≥5.6% in those with undiagnosed DM) and false negative tests (HbA1c <5.6% in those with undiagnosed DM) by Student's *T*-test.

The study was approved by the International Review Board of Yamagata University and informed consent to participate was obtained from the participants.

SPSS for Windows Version 14.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. p-Values were based on two-sided tests and the cut-off point for statistical significance was $p < 0.05$.

3. Results

3.1. Distribution of people according to glucose categories applied by the JNDS and the 1999-WHO criteria

The crude prevalence of previously diagnosed DM, undiagnosed DM, and IGR according to the 1999 WHO criteria were: 5.5% (105/1904), 6.0% (115/1904), and 18.6% (354/1904) among 1904 inhabitants aged 35–89 years (Table 1). Whereas the crude proportion of people classified as possible and probable DM according to the glucose categories applied by the JNDS were: 5.4% (103/1904) and 7.7% (146/1904) (Table 1). The prevalence of all DM increased with deterioration of glucose categories applied by the JNDS (Table 1) while the prevalence of IGR was highest in possible DM (35.0%) and lowest in probable DM (4.8%). Forty-four percent of people with undiagnosed DM and the 88% with IGR were included in the glucose category of not abnormal applied by the JNDS.

3.2. ROC curve analysis for HbA1c predicting undiagnosed DM

Fig. 1 shows the ROC curve for HbA1c and FPG predicting undiagnosed DM among 1799 individuals without previously diagnosed DM. The AUC of the ROC curve for HbA1c (0.856 [95% confidence interval; 0.812–0.899]) predicting undiagnosed DM was similar to that for FPG (0.902 [0.869–0.936]). FPG gave a sensitivity of 64.3% (74/115), a specificity of 95.3% (1605/1684), and the proportion of people above the cut-off of 8.5% (153/1799) with a cut-off value ≥110 mg/dl (IFG level) (Fig. 1). A similar sensitivity (62.6%) and specificity (92.5%) for HbA1c corresponded to HbA1c of 5.5%, where 2S.D. above the mean HbA1c for people with normal glucose by the WHO criteria (4.9 ± 0.3%) (Fig. 2).

3.3. Performance characteristics of HbA1c for undiagnosed DM

The JNDS cut-off point of HbA1c ≥5.6% gave a sensitivity of 56.5% (65/115), a specificity of 95.1% (1602/1684), a PPV of 44.2% (65/147), a NPV of 97.0% (1602/1652), and the proportion of people above the cut-off point of 8.2% (147/1799) (Table 1 and Fig. 2). At HbA1c value of 5.3% where maximizing sensitivity plus specificity, the sensitivity, specificity, PPV, NPV, and the proportion of people above the cut-off point were: 77.4% (89/115), 82.1% (1382/1684), 22.8% (89/391), 98.2% (1382/1408), and 21.7% (391/1799) (Figs. 1 and 2). The PPV, 100 − NPV, and the proportion of people above the cut-off level increased with higher HbA1c (Fig. 2).

3.4. Estimated number of people with DM based on the JNDS cut-off points in the Funagata study

After age-adjusting for the projected Japanese population in 1st October 2002, the respective numbers

Table 1
Distribution of people according to glucose categories defined by the JNDS and the 1999-WHO criteria among 1904 inhabitants aged 35–89 years in the Funagata-town inhabitants during the period between year 2000 and 2002

Glucose category by JNDS	Glucose category according to the 1999 WHO criteria					
	Plasma glucose (mg/dl) On a 75 g OGTT	Normal, FPG < 110 and 2-h PG < 140	IGR, FPG 110–125 or 2-h PG 140–199	Undiagnosed DM, FPG ≥ 126 or 2-h PG ≥ 200	Previously diagnosed DM	Overall
HbA1c (%)						
Not abnormal	<5.6	1291	311	50	3	1655
Possible DM	5.6–6.0	35	36	30	2	103
Probable DM	≥6.1	4	7	35	1	47
Probable DM	Treated DM	0	0	0	99	99
	Overall	1330	354	115	105	1904

Possible DM: HbA1c 5.6–6.0% in people without treatment for diabetes. Probable DM: people under treatment for diabetes and/or those with HbA1c ≥6.1% in people without treatment for diabetes.

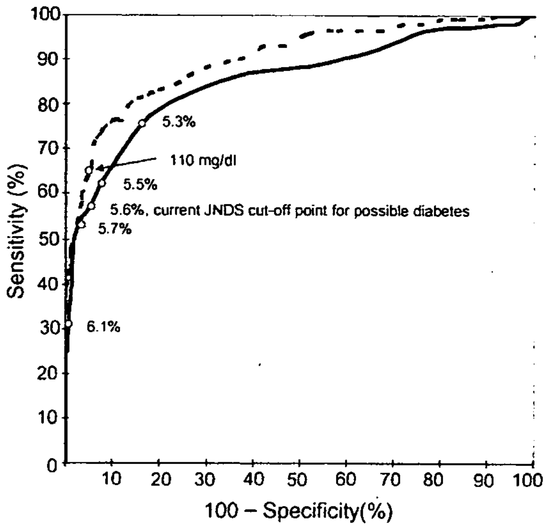

Fig. 1. Receiver-operating characteristic curves for HbA1c and FPG corresponding undiagnosed diabetes defined 1997-WHO criteria among 1799 Funagata-town inhabitants. Straight line: AUC for HbA1c predicting newly diagnosed diabetes. Dotted line: AUC for FPG predicting newly diagnosed diabetes.

of people with probable and possible DM have been estimated as 4.8 and 3.4 million, and the sum total of 8.2 million was larger than the 7.4 million who actually had DM by the WHO criteria. When the cut-off point of HbA1c for possible DM was raised from 5.6 to 5.7%, the total number of people with all DM was estimated as 7.2 million.

3.5. Comparison of CVD risk profiles between true positive tests and false negative tests

Undiagnosed DM identified at HbA1c ≥5.6% (true positive tests) were significantly higher with mean levels of BMI (25.7 kg/m^2 versus 24.4 kg/m^2, $p < 0.05$), FPG (136 mg/dl versus 107 mg/dl, $p < 0.005$), 2-h PG (263 mg/dl versus 224 mg/dl, $p < 0.005$), and HbA1c (6.5% versus 5.2%, $p < 0.005$) but lower with mean levels of HDL cholesterol (53 mg/dl versus 60 mg/dl, $p < 0.05$) than undiagnosed DM unidentified at HbA1c ≥5.6% (false negative tests).

4. Discussion

HbA1c is a reliable index of glucose metabolism over the 1–2 months before testing [9–11], and the prevalence of diabetic retinopathy in relation with HbA1c has a similar pattern to the relation with FPG and 2-h PG on a 75 g OGTT [12–14]. However, its use as a screening test for undiagnosed DM remains inconclusive [15–18]. Since the measurement of HbA1c does not require fasting, the JNDS is currently using HbA1c for an estimation of number of people with DM [2]. In the Funagata study, the predictability of HbA1c for undiagnosed DM defined by the WHO criteria [4] was almost the same as FPG. However, the glucose categories of probable DM and possible DM based on HbA1c applied by the JNDS were not identical to the glucose categories of diabetes and IGR based on plasma

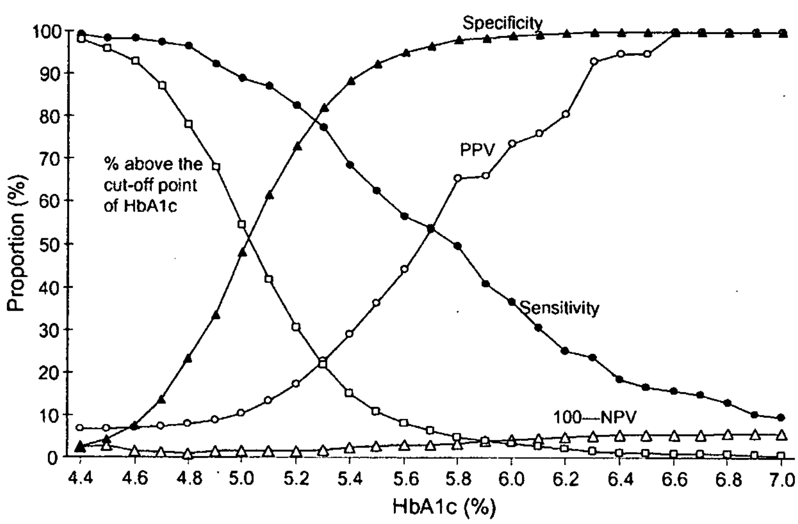

Fig. 2. Sensitivity, specificity, positive predictive value (PPV), 100 – negative predictive value (NPV), and the proportion of people above the cut-off point of HbA1c for undiagnosed diabetes, according to different HbA1c concentrations among 1799 Funagata-town inhabitants without previously diagnosed diabetes. Black circle: sensitivity. Black triangle: specificity. While circle: PPV. While triangle: 100 – NPV. White square: % of people above the cut-off point of HbA1c.

glucose according to the WHO criteria [2]. The cut-off point of HbA1c ≥5.6% as possible plus probable DM gave a very high specificity (95%) and a moderate sensitivity (57%), and PPV (44%) for undiagnosed DM. Identified cases of DM using this cut-off point had worse glucose metabolism and lipid profile than those unidentified. Thus, using the current cut-off point of possible DM in the JNDS might be relevant for the identification of the higher risk of vascular complications among those with undiagnosed DM in Japan.

The appropriate cut-off of HbA1c for defining the true prevalence of DM in a population is important for pubic health planning and action. In the Funagata study, the glucose categories of possible and probable DM applied by the JNDS did not correctly estimate the number of people with IGR and DM in Japan. Because the glucose categories of probable and possible DM based on HbA1c are not identical to the glucose categories of DM and IGR based on plasma glucose on an OGTT, respectively. However, the cut-off point of HbA1c for possible DM could be used to estimate number of people with undiagnosed plus diagnosed diabetes.

In terms of agreement about diagnosis of DM, the maximum agreement was found at HbA1c of 5.3%, with a sensitivity of 77% and a specificity of 82%, in our study. Whereas HbA1c of 5.6% gave a sensitivity of 57% and a specificity of 95%, and thus, not surprisingly, total agreement of diagnosis was different from that found at HbA1c of 5.3%. Moreover, the predictability of DM given positive test result (i.e. PPV) at HbA1c of 5.3% was half of that at HbA1c of 5.6%. Since total agreement of diagnosis of DM was similar at HbA1c of 5.6 and 5.7, the former cut-off point gave 3% higher sensitivity (57% versus 54%) and 9% lower PPV (44% versus 53%) than the latter cut-off point. However, the PPV at HbA1c of 5.6% seemed to be still moderate. Thus, the choice of HbA1c of 5.6% as a cut-off point may be reasonable to detect more people with undiagnosed DM in Japan.

The diagnostic screening cut-off points should be decided by their relevance for likelihood of complications. The Hisayama study [19] has reported that HbA1c had a similar predictability of future retinopathy to 2-h PG or FPG, and the optimal HbA1c associated with future retinopathy was 5.7% with a sensitivity of 87% and a specificity of 90%. This study also identified the threshold of mean HbA1c associated with prevalence of retinopathy at a range between 5.5 and 5.8%. However, a longitudinal study of Pima Indians [12] has shown a clear cut-off for mean HbA1c of 7.0% (6.7% in our country), above which the incidence of retinopathy steeply increased. In the cross-sectional data from the Third National Health and Nutrition Examination Survey [14], prevalence of retinopathy started to increase at a range of mean HbA1c between 5.9 and 6.2% (5.6–5.9% in our country), which has an almost similar level to the Hisayama study. Thus, our results, together with findings of others, suggest that the current JNDS cut-off point may be reasonable with respect to the prediction of retinopathy in Japanese living in Japan.

A recent population-based study from the U.K. [20] has demonstrated a graded increase in all-cause and CVD mortality across the population range of HbA1c, independent of other CVD risk factors. The same holds true with FPG and 2-h PG [21]. So far, there is no available data confirming the continuous relationship between the population range of HbA1c and CVD in our country. However, the cut-off point of HbA1c associated with CVD risk might be lower in comparison to microvascular complications, as even lesser impairments of glucose regulation are already associated with an increased CVD risk [22].

The treatment goal of HbA1c is practically important as a screening cut-off when the disease is present and identified. In Japan, the upper limit of good control of HbA1c in diabetic patients was less than 6.5% [23] because the Kumamoto study showed that diabetic retinopathy and nephropathy rarely occurred among diabetic patients with lower than this cut-off point [24]. However, those subjects were all previously diagnosed cases with mean duration of diabetes of 6.5–6.6 years [24] and the treatment target among newly diagnosed cases has not yet been identified.

HbA1c has been established as a strongest risk factor for microvascular complications in patients with DM [25], and FPG, 2-h PG, and HbA1c are continuous risk factors for developing CVD [20–22]. Thus, people with DM identified by the JNDS cut-off point for possible DM were at higher risk for vascular complications than those unidentified, since the former group had worse glucose and HDL cholesterol profiles than the latter group.

In conclusion, measurement of HbA1c seems to be as efficient as measuring FPG to screen people with undiagnosed DM. The current screening cut-off point of HbA1c of 5.6% may be reasonable, with respect to screening properties of undiagnosed DM, as well as prediction and prevention of vascular complications in Japan.

Competing interests

None declared.

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Prevalence of metabolic syndrome and optimal waist circumference cut-off values in Japan

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Abstract

The present study examined the prevalence of metabolic syndrome (MetS) when the Japanese diagnostic criteria was used, the prevalence of each component in the criteria, and also the validity of the waist circumference cut-off value measured at the navel level, using the results obtained from the Japanese National Health and Nutrition Survey (NHNS) in 2003.

The prevalence of MetS in 2113 subjects according to the Japanese diagnostic criteria was 22.8% (95% CI: 20.2–25.5) for males and 8.7% (7.1–10.4) for females. The prevalence for high blood pressure (HBP), dyslipidemia (DLP), high fasting blood glucose (HFG) and central obesity for males/females were 59.1% (56.0–62.2)/47.2% (44.3–50.1), 40.5% (37.3–43.6)/27.9% (25.4–30.5), 19.1% (16.6–21.6)/16.2% (14.0–18.3) and 45.9% (42.7–49.0)/17.4% (15.3–19.5), respectively. The low prevalence of MetS for females was attributed to a larger waist circumference cut-off value for females (90 cm) than for males (85 cm). Optimal waist circumference cut-off values of subjects, who fulfil at least two of HBP, DLP or HFG, estimated from the receiver operating characteristic curve were subsequently found to be 85 cm for males and 80 cm for females. Based on the new values, the prevalence of MetS was found to be 22.8% for males and 19.2% for females.

The present study revealed that optimal waist circumference cut-off value was much shorter than that previously proposed in females.

Keywords: Metabolic syndrome; Waist circumference; Prevalence; Diagnostic criteria

1. Introduction

According to a 2003 World Health Organization (WHO) report, 29.2% of the total annual deaths in the world (16.7 million deaths) are caused by cardiovascular disease (CVD) [1]. Multiple overlapping risk factors, such as obesity, high blood pressure (HBP), dyslipidemia (DLP), and glucose intolerance contribute to the onset of CVD. Moreover, these risk factors are considered to be inherently closely linked. This notion was reported by Reaven as syndrome X [2]. Similar types of notions were reported thereafter, including a 'deadly quartet' [3].

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In 2001, the US Adult Treatment Panel (ATP) III published diagnostic criteria for metabolic syndrome (MetS) in order to clearly define these conditions. The new criteria define MetS as fulfilment of at least three of the following: a waist circumference equal to or greater than the cut-off value, low high density lipoprotein (HDL) cholesterol levels, high triglyceride (TG) levels, HBP levels, and high fasting blood glucose (HFG) levels [4].

In Japan, diagnostic criteria for MetS that focused on central obesity according to waist circumference were reported in 2005 [5]. This meant that MetS was defined as a waist circumference value (85 cm for males and 90 cm for females) equivalent to at least 100 cm^2 of intraperitoneal visceral fat area at the height of the navel, and any two of the following: dyslipidemia, HFG levels, and HBP levels. The International Diabetes Federation (IDF) published its own diagnostic criteria later the same year, focusing on waist circumference as the parameter of visceral obesity, similar to the diagnostic criteria from Japan HFG [6]. In the IDF report, the waist circumference cut-off value for Asians was 90 cm for males and 80 cm for females.

Using the results obtained from participants in the Japanese National Health and Nutrition Survey (NHNS) in 2003, the present study examined the prevalence of MetS when the Japanese diagnostic criteria was used, the prevalence of each parameter in the Japanese diagnostic criteria and the validity of the waist circumference cut-off value in the Japanese diagnostic criteria based on an accumulation of these parameters.

2. Research design and methods

2.1. Subjects

The present study targeted participants in the 2003 NHNS [7] who met the conditions listed below.

2.1.1. The National Health and Nutrition Survey

The objective of this survey was to acquire fundamental data to elucidate the physical condition, nutritional intake and dietary habits of the nation's population, and promote overall enhancement of the health of the population, based on the Health Promotion Law (Law No. 103 of 2002).

Survey subjects were individuals aged 1 or older as of November 1, 2003 living in a household in a unit ward established in the 2003 National Livelihood Survey. The survey targeted households and household members from among 300 unit wards selected by random stratification. From the 300 unit wards randomly assigned, 4160 households cooperated in the survey. The survey comprised the following three sub surveys: physical condition survey, nutritional intake survey, and lifestyle survey.

The physical condition survey was conducted on one day during November 2003. Physicians, public health nurses, and medical technologists were in charge of the survey. The physical condition survey targeted household members of the targeted households, who were gathered in a convenient location to participate. Height, body weight, and waist circumference at the navel level at the end of expiration under normal breathing in a standing position, were measured. Measurements were read in units of 0.5 cm. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken basically from the upper right arm when the subject was sitting in a chair. The subject was asked to extend their elbow during measurement so the measured site was at the height of the heart. Measuring was performed using a Riva-Rocci sphygmomanometer and a JIS standard manchette. Blood pressure readings were taken twice, with the second reading adopted as the value for the current study.

Blood was taken from the cubital vein with the assistance of a tourniquet. Triglyceride levels were measured by enzymatic method using L-type Wako TG/H reagent, HDL cholesterol was measured by direct method using Choletest-NHDL reagent, plasma glucose levels were measured by enzymatic method using a CicaLiquid GLU reagent, and the measuring device was an H7170.

An interview was conducted on subjects to determine if they were on any medication. Subjects who were currently taking anti hypertensive drugs, insulin injections or glucose lowering drugs, and drugs to lower lipids were defined as subjects 'on medication'.

2.1.2. Number of participants

The total number of participants in the 2003 NHNS was 11,105 (5263 males and 5842 females). Of these, 9391 people (4243 males and 5148 females) participated in the physical condition survey and 5307 of these subjects (2112 males and 3195 females) in turn underwent blood testing.

2.1.3. Final number of subjects

A diagnostic criterion for MetS required that blood be sampled during fasting. However, not all subjects in the present study had their blood sampled during fasting, so of the above 5307 subjects, we examined 2113 subjects (955 males and 1158 females) who declared they had fasted for at least 5 h.

2.2. Diagnostic criteria for MetS [5]

The diagnostic criteria for MetS used were those of the Japanese Society of Internal Medicine.

MetS was defined as a waist circumference of at least 85 cm for males and at least 90 cm for females, which was considered the essential marker of visceral fat accumulation (which corresponds to at least a 100 cm^2 area of intraperitoneal visceral fat area at the height of the navel), as well as at least two of the following three items: (1) serum dyslipidemia (TG value of 150 mg/dL or above or HDL cholesterol of less than 40 mg/dL); (2) HBP (SBP of 130 mmHg or more or DBP of 85 mmHg or more), and; (3) HFG levels (fasting blood glucose of 110 mg/dL or above). If an individual was receiving drug therapy for hypertriglyceridemia, low HDL cholesterol, high blood pressure or diabetes mellitus, each item was recorded as a positive finding regardless of the test data.

2.3. Analysis

2.3.1. Prevalence of MetS and its each component

We examined the prevalence of MetS according to the Japanese diagnostic criteria. Next, the prevalence of subjects who were found to have serum dyslipidemia, HBP, and HFG levels, and the ratio of subjects found to meet the criterion for waist circumference, which make up the diagnostic criteria for MetS, were shown according to 10-year age groups from age 20.

2.3.2. Validity of waist circumference cut-off value in the Japanese diagnostic criteria

To investigate the validity of the waist circumference cut-off value in the Japanese diagnostic criteria, the optimal waist circumference cut-off value of subjects who fulfil at least two of the following factors was estimated from the receiver operating characteristic (ROC) curve analysis: (1) serum dyslipidemia (TG value of 150 mg/dL or above or HDL cholesterol of less than 40 mg/dL); (2) HBP (SBP of 130 mmHg or more or DBP of 85 mmHg or more), and; (3) HFG levels (fasting blood glucose of 110 mg/dL or above).

2.3.3. Prevalence of MetS when the waist circumference cut-off value was changed

We further investigated in what way the prevalence of MetS changed when an optimal waist circumference cut-off value calculated from the ROC curve analysis was used.

SPSS was used for the statistical analysis. The Chi-square test was employed to test the difference in ratios. The *t*-test was used to assess the difference in the means of the continuous variables. The present survey was one of the government approved statistical surveys, and the Japanese Ministry of Internal Affairs and Communications reviewed the survey plan overall including ethical considerations. The data, which was made anonymous, was analyzed for secondary use only after approval was obtained from the relevant authorities in the Ministry of Health, Labour, and Welfare.

3. Results

3.1. Demographic information of subjects

Table 1 shows the number of people in each age group among the 2113 (955 males and 1158 females) subjects who were targeted for analysis. There was no significant difference between the number of males and females across all age groups (Chi-square test: $p = 0.733$) and no difference at all in the mean age (±S.D.) of males (51.7 ± 15.9) and females (51.7 ± 15.7, $p = 0.971$) (Table 1). The mean ± S.D. of TG (male: 148 ± 113, female: 126 ± 316 mg/dL, $p = 0.036$), SBP (male: 132 ± 19, female: 126 ± 21 mmHg, $p < 0.001$) and DBP (male: 82 ± 12, female: 76 ± 11 mmHg, $p < 0.001$) in males were significantly higher than those in females, and the mean ± S.D. of HDL was significantly lower in males than that in females (male: 57 ± 15, female: 66 ± 16 mg/dL, $p < 0.001$). There was no significant difference in the

Table 1
Number of analyzed subjects by age group and sex, and mean age by sex in the Japanese National Health and Nutrition Survey in 2003

Age groups	Male *N* (%*)	Female *N* (%*)	Total *N* (%**)
20–29	100 (46.7)	114 (53.3)	214 (10.1)
30–39	145 (45.0)	177 (55.0)	322 (15.2)
40–49	155 (42.2)	212 (57.8)	367 (17.4)
50–59	225 (45.2)	273 (54.8)	498 (23.6)
60–69	199 (47.8)	217 (52.2)	416 (19.7)
>70	131 (44.3)	165 (55.7)	296 (14.0)
Total	955 (45.2)	1158 (54.8)	2113 (100.0)
Mean age (±S.D.)***	51.7 ± 15.9	51.7 ± 15.7	51.7 ± 15.8

Chi-square test of male and female comparison across all age groups ($p = 0.733$).
* Percentage for each age group by sex.
** Percentage of this entire population (2113 people).
*** *t*-Test comparison of mean age according to sex ($p = 0.971$).

mean glucose level between males and females (male: 102 ± 28, female: 100 ± 25 mg/dL, $p = 0.586$).

3.2. Prevalence rate of MetS

The overall prevalence of MetS according to the Japanese diagnostic criteria was 22.8% (95% CI: 20.2–25.5%) for males and 8.7% (95% CI: 7.1–10.4%) for females ($p < 0.001$). The prevalence of MetS for males aged 40 or older exceeded 20%. However, the prevalence for females up to the 50–59 year age group was less than 5%. It dramatically increased, however, to more than 20% in females aged 60 or older (Fig. 1A).

3.3. Prevalence rates of factors comprising the MetS diagnostic criteria

3.3.1. Blood pressure

The overall prevalence for HBP was 59.1% (95% CI: 56.0–62.2%) for males and 47.2% (95% CI: 44.3–50.1%) for females ($p < 0.001$). The number of people with positive findings increased with age; prevalence was higher in males up to the 50–59 year group, but it was about equal between males and females aged 60 or older. At least 80% of both males and females aged 70 or older showed HBP levels (Fig. 2A).

3.3.2. Dyslipidemia

The overall prevalence for subjects found to fulfil the criteria for dyslipidemia was 40.5% (95% CI: 37.3–43.6%) for males and 27.9% (95% CI: 25.4–30.5%) for females ($p < 0.001$). Clear sex differences were seen: nearly 40% of males aged 30 or older were diagnosed with dyslipidemia, while a rate of more than 40% among females was seen only in subjects aged 60 and older (Fig. 2B).

3.3.3. High fasting blood glucose

The overall prevalence for subjects found to have a blood glucose level of 110 mg/dL or more was 19.1% (95% CI: 16.6–21.6%) for males and 16.2% (95% CI: 14.0–18.3%) for females ($p = 0.046$). There were no clear sex differences in the prevalence for high blood glucose according to the different age groups (Fig. 2C).

3.3.4. Waist circumference

The overall prevalence for subjects who had a waist circumference of at least 85 cm for males and at least 90 cm for females was 45.9% (95% CI: 42.7–49.0%) for males and 17.4% (95% CI: 15.3–19.5%) for females ($p < 0.001$). Across all age groups, the prevalence of males were extremely higher than those of females (Fig. 3A).

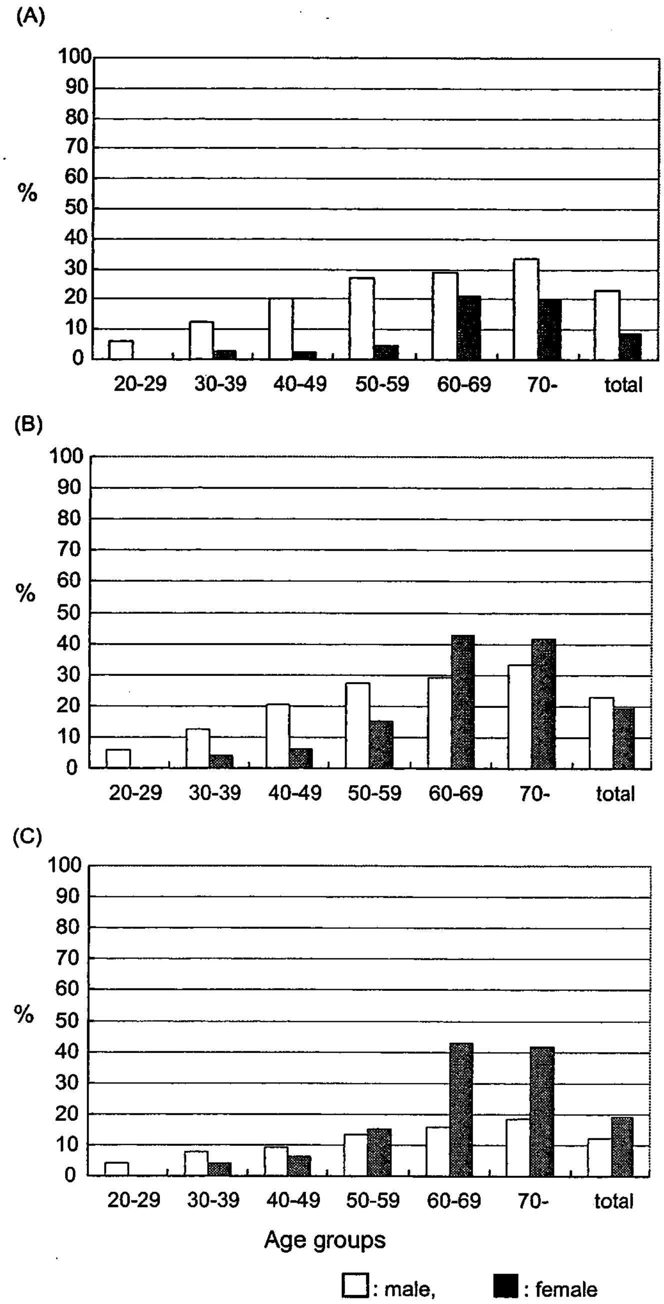

Fig. 1. Prevalence rate of metabolic syndrome by age and sex according to several waist circumference cut-off values in the Japanese National Health and Nutrition Survey in 2003: (A) 85 cm for males and 90 cm for females; (B) 85 cm for males and 80 cm for females; (C) 90 cm for males and 80 cm for females. Male: □; female: ■.

3.4. Estimation of optimal waist circumference cut-off value

The optimal waist circumference cut-off value was estimated by the ROC curve analysis based on subjects who fulfil at least two of the MetS diagnostic criteria.

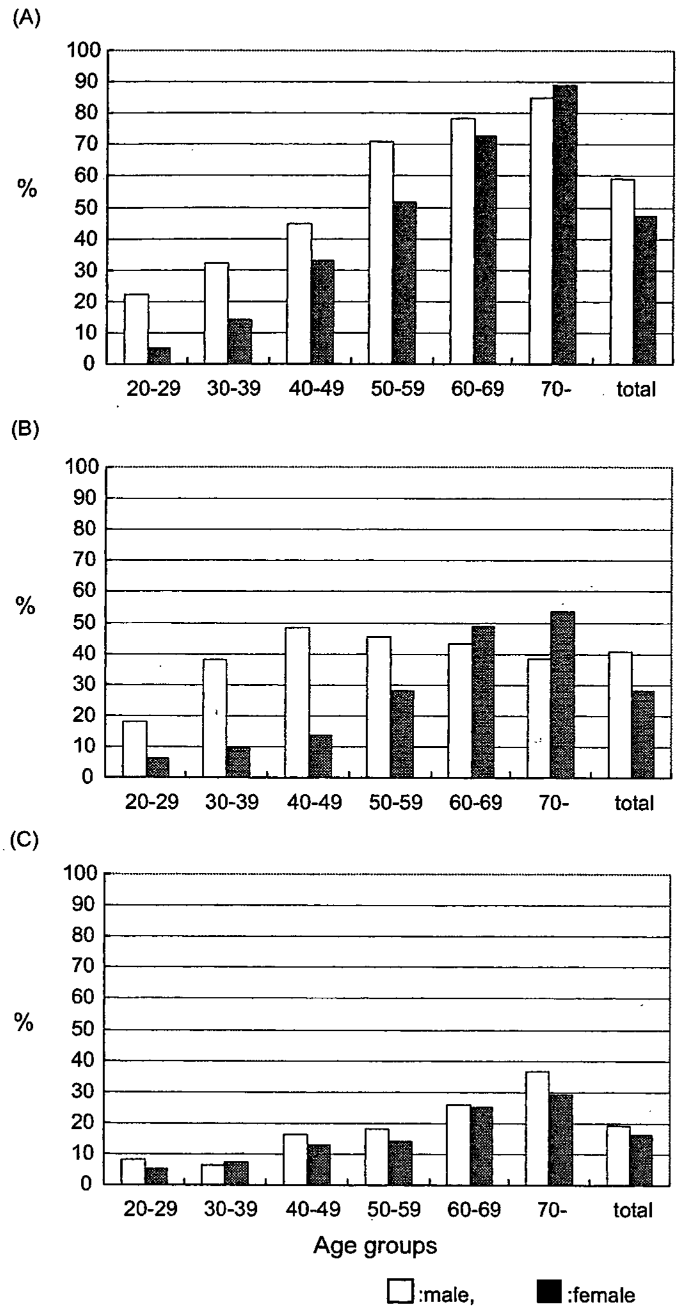

Fig. 2. Prevalence rate of subjects meeting the criteria for each component of metabolic syndrome by age and sex in the Japanese National Health and Nutrition Survey in 2003. (A) High blood pressure: systolic ≥130 mmHg or diastolic ≥85 mmHg; (B) dyslipidemia (triglyceride ≥150 mg/dL or HDL-cholesterol <40 mg/dL); (C) high fasting blood glucose (fasting plasma glucose ≥110 mg/dL). Male: □; female: ■.

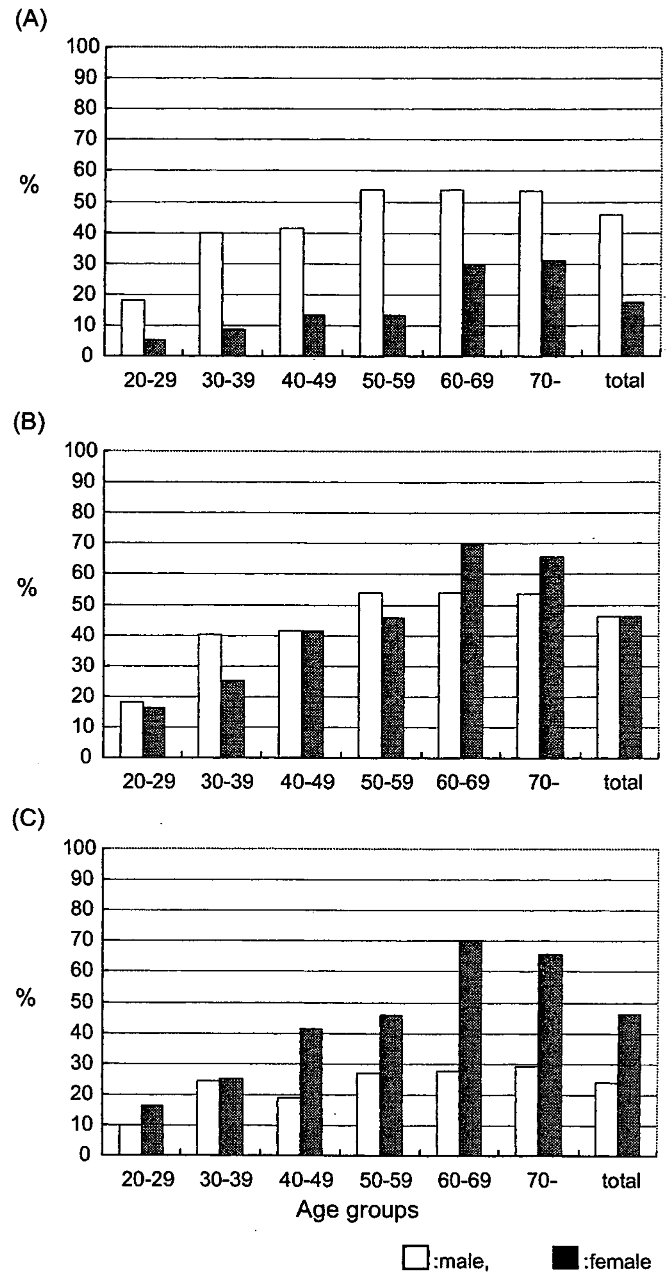

Fig. 3. Prevalence rate of subjects according to several waist circumference cut-off values by age and sex in the Japanese National Health and Nutrition Survey in 2003: (A) 85 cm for males and 90 cm for females; (B) 85 cm for males and 80 cm for females; (C) 90 cm for males and 80 cm for females. Male: □; female: ■.

This was found to be 84.9 cm for males and 81.1 cm for females (Fig. 4).

3.5. Prevalence of MetS using the estimated waist circumference cut-off value

We again calculated the rates of subjects found to meet the criterion for waist circumference and the prevalence of MetS, using 85 cm for males and 80 cm for females—which is a value estimated as optimal waist circumference cut-off. The percentage of subjects found to meet the waist circumference criterion was 45.9% (95% CI: 42.7–49.0%) for males and 46.3% (95% CI: 43.4–49.2%) for females ($p = 0.465$), which showed that the rates between males and females according to age group was almost identical (Fig. 3B).

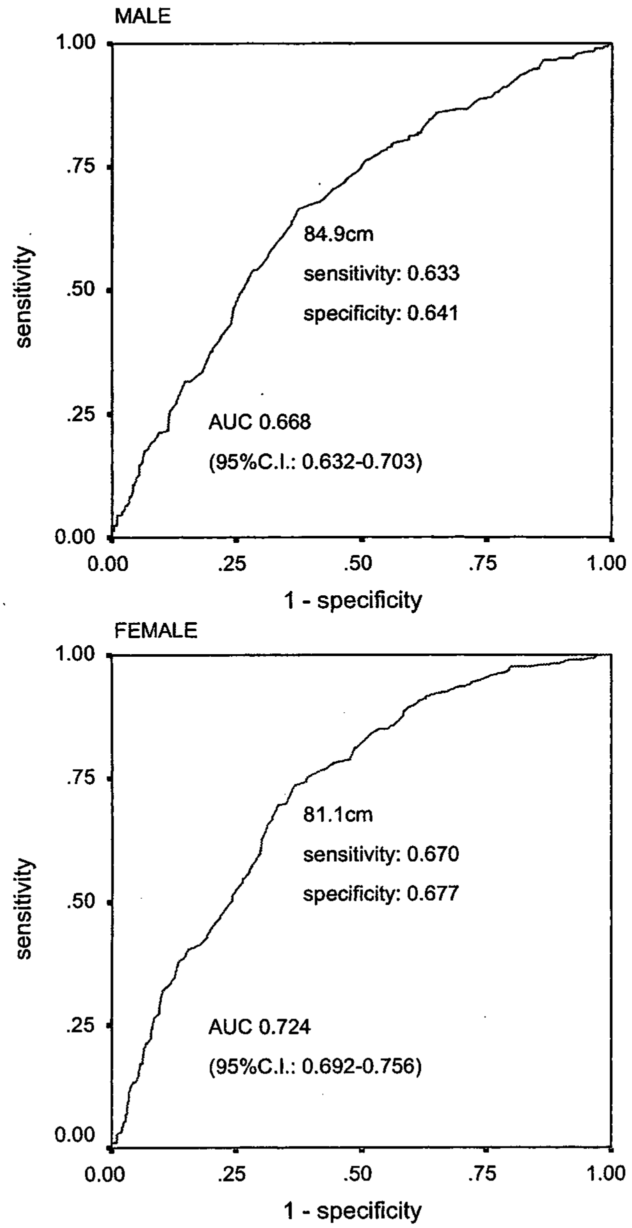

Fig. 4. Estimation by ROC curve analysis of the waist circumference cut-off values for males and females in order to find people with at least two of the following: high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg), dyslipidemia (triglyceride ≥150 mg/dL or HDL cholesterol <40 mg/dL), and fasting blood glucose ≥110 mg/dL, in the Japanese National Health and Nutrition Survey in 2003.

Based on these findings, the prevalence of MetS were estimated to be 22.8% (95% CI: 20.2–25.5%) for males and 19.2% (95% CI: 17.0–21.5%) for females ($p = 0.025$), which were comparatively close values between the two sexes. By age group, the prevalence among females was lower than that among male up to the 50–59 year age group, but it increased from the age of 60. This is suggestive of an increased risk of CVD after menopause (Fig. 1B).

3.6. *Prevalence of MetS using the Asian waist circumference cut-off values in the IDF diagnostic criteria*

The waist circumference cut-off values in Asians other than Japanese in the IDF metabolic syndrome diagnostic criteria are 90 cm for males and 80 cm for females [6]. Using these, we calculated the rates of subjects found to meet the criterion for waist circumference and the prevalence of MetS. The percentage of subjects found to meet the waist circumference criterion was 23.8% (95% CI: 21.1–26.5%) for males and 46.3% (95% CI: 43.4–49.2%) for females ($p < 0.001$). The rates were therefore almost identical for the 30–39 year age group, but in all other age groups the rates of females were higher (Fig. 3C). Based on these findings, the prevalence of MetS were estimated to be 12.1% (95% CI: 10.0–14.1%) for males and 19.2% (95% CI: 17.0–21.5%) for females, so the rate was higher among females ($p < 0.001$). By age group, the prevalence among males was slightly high up to the 40–49 year age group and almost equivalent in the 50–59 year age group. From age 60, the prevalence among females was about twice that of males (Fig. 1C).

4. Discussion

MetS is defined around the world as a cluster of conditions that can lead to CVD, so a campaign has begun to prevent CVD by intervening in people who are diagnosed with MetS.

In Japan, the waist circumference cut-off value in diagnostic criteria for MetS was adopted as 85 cm for males and 90 cm for females which correspond to 100 cm^2 of intraperitoneal visceral fat in a cross section at the height of the navel as revealed by CT [5]. In contrast, the IDF has adopted as its diagnostic criteria for Asians a waist circumference cut-off value of 90 cm for males and 80 cm for females, but for Japanese, it has taken the values indicated by the Japanese Society of Internal Medicine—85 cm for males and 90 cm for females [6]. However, there have been a very few epidemiological studies in Japan on the prevalence of MetS using these unique Japanese criteria. Moreover, there have also been virtually no studies examining the validity of this cut-off value.

In the present study, the prevalence of MetS under the Japanese criteria was 22.8% for males and 8.7% for females. If the IDF criteria [6] was used to define MetS in the current study, the prevalence was increased to be 27.7% in males and 10.9% in females. The prevalence under the IDF criteria was higher than that under the Japanese criteria due to difference in definition, lower cut-off value for blood glucose and higher cut-off value for HDL cholesterol in females (data not shown in the results section). Under both criteria, the prevalence of Mets among females was less than half that of males. These findings were largely influenced by the higher waist circumference cut-off value of 90 cm adopted for females than for males based on the Japanese MetS diagnostic criteria (Figs. 2 and 3).

There have been several reports on the prevalence of MetS among Asians. One study on 40,698 South Koreans (26,528 males and 14,170 females), which adopted the ATPIII diagnostic criteria and a waist circumference cut-off value of 90 cm for males and 80 cm for females, found the prevalence to be higher among females (12.4%) than males (9.8%), similar to the present study [8]. In contrast, a study in Singapore on 4723 subjects, which also used the ATPIII diagnostic criteria and a waist circumference cut-off value of 90 cm for males and 80 cm for females, found that the prevalence was higher among males (18.1%) than females (12.5%) of Chinese descent [9]. A study on 15,540 Chinese which adopted the ATPIII diagnostic criteria and defined obesity as a BMI of at least 25.0 kg/m^2 found that the prevalence was higher among females (17.8%) than males (9.8%) [10].

In general, Japanese are genetically similar in comparative terms to South Koreans and Chinese. However, even among North-Eastern Asians, the MetS prevalence and male-to-female ratio differ considerably. It is therefore necessary to establish specific waist circumference cut-off values for each Asian country, region and ethnic group.

The optimal waist circumference cut-off value maximizing sensitivity and specificity for diagnosing MetS in the present study population, which was representative of the overall Japanese population, was found to be 85 cm for males and 81 cm for females. In Japan, there have been two previous reports that estimated the waist circumference cut-off value for diagnosing MetS. The first was a study on 3574 employees of a telephone company and their family members (2947 males and 627 females). It estimated the valid cut-off value for the intraperitoneal visceral fat area at the height of the navel, as determined by CT, to be 100 cm^2 for males and 65 cm^2 for females. Based on these figures, it then estimated the optimal waist circumference cut-off value to be 86 cm for males and 77 cm for females [11]. The other report calculated the optimal cut-off value for waist circumference among 692 healthy subjects (408 males and 284 females) who fulfilled at least two of the criteria in the ATP III diagnostic criteria. The results were 85 cm for males and 78 cm for females [12]. These reports differed to the present report in that they either targeted employees and family members of one company or participants of physical check-up. The percentage of females was also low in these reports. It is therefore possible that their results were biased compared to the present study which was based on a national survey using accurately sampled population. However, although the methodology differed, the optimal waist circumference cut-off values were still shown to be almost the same as those in the present study—85 cm for males and 81 cm for females. Taken together, the three studies suggest that the ideal waist circumference cut-off values for diagnosing MetS in Japan are 85 cm for males and 80 cm for females. In other words, the optimal value for males might be the current value for diagnosing MetS in Japan, but the female value should be changed to 80 cm, which is the value adopted by the IDF in their diagnostic criteria for Asian females.

A limitation of the present study was that blood was sampled from subjects after food intake. However, according to a report by Ceriello et al., the TG level after fat loading decreases almost back to the pre-loading level in healthy individuals after 4 h. In the present study, we only selected and analyzed subjects who had fasted for at least 5 h, so it is considered extremely unlikely that the sampling of blood after food intake affected the results [13].

In addition, the waist circumference in the present study was measured at the height of the navel, but in the diagnostic criteria of the IDF it was measured at the midpoint between the subcostal margin and the margin of the supracristal plane. There have been little reports to date that have examined the differences between the two measurement sites. Several paper reported that there was considerable difference between the two especially in females [14,15]. Therefore, this should also be examined in the future.

The present study investigated the waist circumference cut-off value that is related to risk factors for CVD. It is important to note that the waist circumference cut-off value was not estimated as a predictive factor of cardiovascular events. To determine whether or not the waist circumference cut-off values proposed here really do predict cardiovascular events would require further testing by tracking the cohorts in the present study.

We estimated the prevalence of MetS in Japan using data of participants in the 2003 Japanese National Health and Nutrition Survey. Results based on current diagnostic criteria revealed a prevalence of 22.8% for males and 8.7% for females. The extremely low prevalence for females was attributed to the setting of a larger waist circumference cut-off value for females (90 cm) than for males (85 cm). Appropriate waist circumference cut-off values were subsequently found to be 85 cm for males and 80 cm for females. Based on the new values, the prevalence of MetS was found to be 22.8% for males and 19.2% for females. Further investigation will be needed to determine if the cases diagnosed under these criteria fall into a true high-risk group for future CVD.

Conflict of interest

All the authors have no conflict of interest.

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Original Article

Establishment of External Quality Control Program for hs-CRP and Three-Year Follow-Up of the Performance for Precision and Accuracy

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Aim: We established an external quality control (QC) program for high-sensitivity C-reactive protein (hs-CRP) for a collaborative epidemiological study.
Methods: External QC was performed 3 times in 3 years to follow hs-CRP performance for precision and accuracy.
Results: For precision, the mean coefficient of variation (CV) of the internal QC by 9 laboratories was 2.2% and 1.9% in the 1st and 2nd tests, respectively. The mean CV of the external QC by 4 laboratories was 2.7% in the three tests. The CV of both the internal and external QC satisfied the acceptable range specified by the AHA/CDC Scientific Statement, CV <10%. For accuracy, the mean values of the 1st external QC by 9 laboratories were set as the consensus value and the acceptable range was set to within ±10% from it. The mean accuracy by 9 laboratories was 0.51% in the 2nd external QC. The mean accuracy by 4 laboratories was −0.37% in the 3rd external QC. These findings demonstrated that the initial consensus value was valid in the continued external QC, and hs-CRP was stable for 3 years.
Conclusion: We demonstrated both the precision and accuracy of hs-CRP by an external QC program applied for 3 years in a collaborative epidemiological study.

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Key words; hs-CRP, CRM470, Accuracy, Precision

Introduction

According to epidemiological studies and clinical trials, arteriosclerosis is vascular tissue inflammation that progresses in a chronic course, and a slight persistent elevation of the hs-CRP level, an inflammatory reaction index, reflects the degree of functional impairment of vascular endothelium, serving as a predictive factor of cardiovascular events[1, 2]. Epidemiological studies are significant with regard to whether these findings are applicable to the Japanese population[3, 4]. The Japan National Cardiovascular Center (NCVC)–collaborative Inflammation Cohort (JNIC) Study investigated the association of hs-CRP and arteriosclerosis in 5,213 men and 7,071 women aged 40 years or older in 7 communities of Japan, and was a collaborative epidemiological study in which 9 analytical laboratories participated[5]. Although there have been many reports of hs-CRP performance in the short term in clinical laboratories, the precision and accuracy of hs-CRP measured by multiple analytical laboratories have not been assessed for 3 years from the viewpoint of an epidemiological study. Thus, we newly established an external QC program for hs-CRP that covered a 3-year period to clarify the precision and accuracy of values measured in this large population-based study.

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Materials and Methods

External QC Program of hs-CRP

The external QC program of hs-CRP was designed for this study by partial revision of the "Proposal of hs-CRP standardized measurement method by BN system (January 2003)" proposed by Dade Behring Co., Ltd in Tokyo. As the distribution of the logarithm of hs-CRP has a normal distribution, the CV, statistic power, and 2-sided significance level were set to 2%, 80%, and 0.05, respectively, as suggested by the statistically analytical group, and the program was designed to clarify the precision, accuracy and acceptable range of accuracy for the study[6,7]. Samples that covered ranks 1 to 5 of the baseline CRP cut-off value of the 5-step categories proposed by Ridker were selected for the external QC program[2]. According to the "Distribution of hs-CRP among apparently healthy American men and women" by Ridker, quintiles 1, 2, 3, 4 and 5 are in the range 10 to 70 μg/dL of hs-CRP with low risk estimate, range 70 to 110 μg/dL with mild risk estimate, range 120 to 190 μg/dL with moderate risk estimate, 200 to 380 μg/dL with high risk estimate and 380 to 1,500 μg/dL with highest risk estimate, respectively.

The measurement procedure was as follows: Taking sera containing hs-CRP at 5 concentrations (samples 1 to 5) (serum volume of 1 mL per 2-mL cryogenic vial of Sumitomo Bakelite Co., Ltd.) as one set, samples were randomly subjected to quadruplicate measurement using routine samples from examinees for 5 days. Accordingly, 100 measured values (20 × 5) were obtained from a single serum sample set of the external QC.

Analytical Laboratories Participating in the External QC Program

Nine analytical laboratories, including the Osaka Medical Center for Health Science and Promotion (OMC), participated in the external QC program. The 9 analytical laboratories performed the 1st test of the external QC in May 2003, and the 2nd test 6 months later, in November 2003. Four of the 9 analytical laboratories, including the OMC, performed the 3rd test in January-May 2006, 3 years after the 1st test. Sera at 5 concentrations of identical lots were measured by all analytical laboratories in all 3 external QC tests. Information regarding the distribution of identical lots in all 3 tests was not disclosed to any analytical laboratory before analysis.

Sera for Internal QC and External QC

Internal QC: Including the 5 days on which sera for external QC were measured, serum for internal QC was measured for 20 days. One measured value ($n = 1$) was reported per day, and the CV of values measured by internal QC was calculated. Serum for internal QC was selected by each analytical laboratory.

External QC: Serum samples from examinees who gave informed consent were selected from residual fresh sera collected at the OMC. The sera were classified into 5 groups based on the hs-CRP concentration[2], and defatted as follows: A defatting agent (Aerosil) provided by Dade Behring Co., Ltd. (Tokyo, Japan) was slowly added to and mixed with the original serum for about 30 minutes to adjust the concentration to 2-3%, followed by stirring at laboratory temperature for 30 minutes, and centrifuged at 10,000 × G for 15 minutes. The supernatant was used for external QC. The defatted sera were stored at −70℃ after confirming that the vials were tightly sealed. All sera for external QC were negative for HBs and HIV antigens.

Measurement Conditions of Analytical Laboratories

All participating laboratories measured hs-CRP using a nephelometer (BN ProSpec or BN II), N Latex CRP II as the reagent and N CRP reference material calibrated with CRM 470 as the standard. They were all products of Dade Behring Co., Ltd. (Tokyo, Japan)[8].

Statistical Processing and Assessment Criteria

The results obtained by external QC were analyzed by one-way layout analysis of variance[9]. Precision was presented as the CV, and assessed based on the acceptable range specified in the AHA/CDC Scientific Statement[1], CV <10%. The mean of the outlier-processed 1st test values measured by the 9 analytical laboratories was regarded as the consensus value for accuracy[9]. Outliers were defined as points more than 3 SD from the subject's mean score. Accuracy was presented as %bias from the consensus value. The %bias represents a systematic error, defined as %deviation from the consensus value. The acceptable range of accuracy was set to within ±10% of the consensus value, and the results of the 2nd and 3rd external QC were evaluated under these criteria.

It was prescribed in the external QC protocol that, when a mean deviated by ±15% or more from the consensus value, the analytical laboratory was required to revise the procedure. For the revision, a supply of the international plasma protein reference material (CRM 470)[8] was prepared, with comprehensive consultation with Dade Behring Co., Ltd. on instruments, reagents, measurement conditions, samples, procedure, and maintenance.

Results

Precision

The precisions of the 1st and 2nd tests of the internal QC by each analytical laboratory are shown in **Table 1**. When the precision of the internal QC in the short term of 20 days was investigated, the CV of the