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Research

Longitudinal Change in The Cumulative Incidence and Maintenance Rate of Metabolic Syndrome among Participants of the Specific Health Check and Guidance System in Japan

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Abstract

Background: The trends in cumulative incidence and maintenance rate of metabolic syndrome (MetS) are not yet available in Japan. Methods: Data of the Tokutei-Kensin from 2008 to 2014 were used in this study. The total number of participants was 3,809,853. Among them, we identified 933,490 individuals who have screened at least twice during the study period. The mean number of visits was 3.4 times per person. Cumulative incidence of MetS was defined among those who were free of MetS at the first screening. The maintenance rate of MetS was defined among those who were diagnosed with MetS at both the first and the second screening. Kaplan Meier curves were obtained for both the incidence and maintenance rate of MetS.Results: The cumulative incidence of MetS was 5.7%, 9.6%, 3.5% (1 year), 8.0%, 12.4%, 5.3% (2 years), 8.5%, 12.8%, 5.8% (3 years), 8.0%, 12.3%, 5.4% (4 years), 9.6%,16.2%, 5.4% (5 years), and 7.0%, 14.7%, 3.0% (6 years), in total, men, and women, respectively. The maintenance rate of MetS was 47.4%, 49.7%, 43.4% (1 year), 44.6%, 46.9%, 39.8% (2 years), 42.7%, 44.5%, 39.8% (3 years), 42.4%, 45.1%, 38.5% (4 years), 38.9%, 38.1%, 40.1% (5 years), and 40.0%, 35.3%, 46.2% (6 years), in total, men, and women, respectively. Incidence of MetS was higher in men than that of women. However, the maintenance rate of MetS was similar between men and women. Conclusions: Maintenance rate of MetS has decreased substantially in both genders who were diagnosed with MetS at the initial screening. However, the actual number of MetS has increased as the higher numbers of subjects developed MetS after the screening.

Key words: metabolic syndrome, cumulative incidence, maintenance rate, gender difference, life expectancy

Introduction

Metabolic syndrome (MetS) and obesity have been known as related to cardiovascular disease in western countries [1, 2]. Obesity was not so common among Japanese, in particular women, Also, the incidence of cardiovascular disease is relatively low among Japanese [3]. A recent literature review supports the positive relationship between MetS and cardiovascular disease [4].

A specific nationwide health check-up and guidance system, called Tokutei-Kenshin, was initiated in April 2008 in Japan [5]. This project aims to detect metabolic syndrome (MetS) and if confirmed, to provide individual instruction to modify lifestyle and the necessary treatment. The target population comprises Japanese citizens between the ages of 40–74 years. We have been focused mostly on chronic kidney disease (CKD) [6, 7, 8], diabetes mellitus (DM) [9, 10], and mortality [11-14]. Lifestyle is a significant modifier of CKD [15], cardiovascular disease (CVD) [16], and mortality [16, 17]. We recently confirmed that MetS was a significant risk factor for mortality [18].

Intervention through this screening program was shown to be very effective for the reversal of MetS [19]. However, the proportion of people attending the intervention program is as low as 11%. The trends in the cumulative incidence and maintenance rate of MetS have not been well studied. Such information would be helpful for the future modification of the protocol of screening among the Japanese population. However, lifestyle modification should be carefully performed such as educational attainment and marital status [20], gender difference [21], uric-acid level [22], and smoking habit [23].

In the present study, we examined the MetS in both cumulative incidence and maintenance rate among the subjects who have participated, in at least twice the nationwide screening.

Methods

Study subjects and baseline characteristics

Details of the dataset of the nationwide screening program of the Specific Health Check-up and Guidance System (Tokutei-Kensin) in Japan have been previously published [6-18]. From 2008 to 2014, we collected individual records of 3,809,853 participants from 192 municipals of 27 prefectures. The process for the database construction is summarized in Figure 1. From the total number of subjects who participated (about 3.8 million), we selected those who visited at least twice during the study visit. Finally, we used the dataset of 933,490 participants for the analysis. During the study period, the mean number of visits was 3.4 times per subject. MetS was defined as waist circumference (men≥85cm, women≥90cm) plus two or three abnormal values in blood sugar metabolism (fasting blood glucose≥100mg/dL or HbA1c≥5.2% by 2012 (JDS), HbA1c≥5.6% by NGSP since 2013), lipid (triglyceride≥150mg/dL, or HDL cholesterol<40mg/dL), and blood pressure (systolic≥130mmHg, or diastolic≥85mmHg) [18]. The original database was solely used and managed by Okinawa Heart and Renal Association (OHRA). Furthermore, the preliminary dataset was verified and confirmed independently by Dr. Tsuneo Konta. Afterward, further analyses were done by using a standard analysis file (SAF) without any personal identifier. We used data from 2008-2014; for Multivariate Cox regression analysis with MetS new-onset and MetS maintenance at 1 year as the outcome, the baseline subjects were those who were first seen in 2008-2013, and the outcome was the new-onset of MetS and the maintenance of MetS at 1 year.

All procedures performed in studies involving human participants were performed following the ethical standards of the institutional and/or national research committee at which the studies were conducted (Fukushima Medical University; IRB approval number #1485, #2771) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was performed according to Ethical Guidelines for Medical and Health Research Involving Human Subjects enacted by MHLW of Japan

http://www.mhlw.go.jp/file/06-Seisakujo-uhou-10600000-Daijinkanboukouseikagakuka/0000069410.pdf and

http://www.mhlw.go.jp/file/06-Seisakujo-uhou-10600000-Daijinkanboukouseikagakuka/0000080278.pdf].

In the context of the guideline, the investigators shall not necessarily be required to obtain informed consent, but we made public information concerning this study on the web [http://www.fmu.ac.jp/univ/sangaku/data/koukai_2/2771.pdf] and ensured the opportunities for the research subjects to refuse to utilize their personal information.

Calculation of cumulative incidence of MetS

The denominator is the number of people in each year group between the first and second checkup among those with MetS (-) at the first checkup (the number in the 1-year group is the number of people whose interval between the first and second checkups was 1 year), and the numerator is the number of new cases of MetS among them.

Calculation of the maintenance rate of MetS

Among the subjects with MetS (+) at the first checkup, and the rate of maintenance of MetS (+) at the time of the next checkup. The denominator is the number of people who were MetS (+) at the first checkup and the number of people in each year group between the first and second checkups (the number of people in the 1-year group is the number of people whose interval between the first and second checkups was 1 year), and the numerator is the number of people who maintained MetS (+) at the second

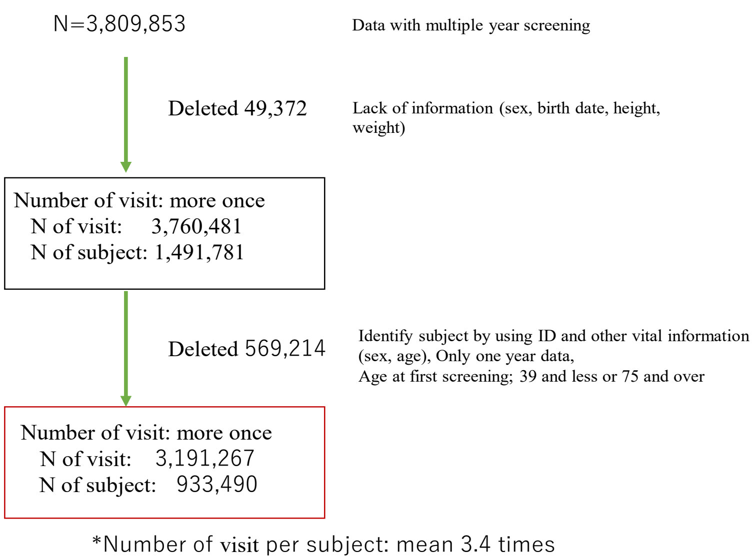

Figure 1.

Table 1. Number of subjects used for the incidence curve by Kaplan Meier analysis

MS Incidence	Men	Women	Men, Age≥65	Men, Age<65	Women, Age≥65	Women, Age<65
Baseline	278123	474686	146415	131708	229630	245056
1-year	278123	474686	146415	131708	229630	245056
2-years	186095	337062	94440	91655	155254	181808
3-years	125851	247816	62404	63447	110515	137301
4-years	76203	163106	36923	39280	70241	92865
5-years	26544	60865	13096	13448	26003	34862
9-years	3464	8388	1710	1754	3434	4954

Table 2. Number of subjects used for the maintenance rate curve by Kaplan Meier analysis

MS Maintenance	Men	Women	Men, Age≥65	Men, Age<65	Women, Age≥65	Women, Age<65
Baseline	54980	32827	29019	25961	18937	13890
1-year	54980	32827	29019	25961	18937	13890
2-years	26043	14723	13359	12684	8155	6568
3-years	12494	6876	6259	6235	3714	3162
4-years	5421	2941	2644	2777	1542	1399
5-years	1473	804	704	769	403	401
6-years	97	41	53	44	23	18

checkup.

Statistical analyses

Data were analyzed with SAS/STAT software (version 6.03, SAS Institute, Tokyo, Japan). The student's t-test and the Chi-squared test were performed to compare the significance of discrete variables. Multivariate Cox regression analysis was performed to evaluate the risks for the changes in the trend of the cumulative incidence and maintenance rate of MetS. Factors used for the adjustment were body mass index, systolic and diastolic blood pressure, fasting blood glucose, HbA1c, triglyceride, HDL cholesterol, LDL cholesterol, eGFR, proteinuria, alcohol intake, smoking, history of stroke, acute myocardial infarction renal failure, dialysis, and drug use for hypertension, diabetes mellitus, and hyperlipidemia and were based on self-reported information in the medical questionnaire. The hazard ratio and 95% confidence interval were obtained. A P value of less than 0.05 was considered statistically significant in all analyses. We also examined the Kaplan Meier curves for the cumulative incidence of MetS and maintenance rate of MetS. The number of subjects used for the Kaplan Meier curves were shown in Tables 1 and 2.

Results

The cumulative incidence of MetS

As a whole, the cumulative incidence of MetS was 6.2% (total), 10.1% (men), and 3.9% (women), respectively. The relationship between the cumulative incidence of MetS and the interval of screening was shown up to 6 years (Figure 2), it was gradually increased. In particular, the cumulative incidence in men was higher than that of women. Baseline characteristics of subjects who remained without MetS and developed MetS were summarized in (Supplementary Table 1). Those who developed MetS were a significantly higher proportion of men of older age. Other variables except renal failure/ dialysis were also significantly different as the number of subjects was large.

The maintenance rate of MetS

It was 46.6% (total), 48.9% (men), and 38.5% (women), respectively. Similar to the changes in cumulative incidence, the relationship between the maintenance rate of MetS and the interval of screening is shown up to 6 years (Figure 3). After the initial screening, the maintenance rate of MetS gradually declined. Baseline characteristics of subjects who remained MetS and disappeared MetS were summarized in (Supplementary Table 2). Those who remained MetS were a significantly higher proportion of men of older age. Other variables except for current smokers and history were also significantly different.

Effect of gender and age on the cumulative incidence and maintenance rate of MetS

By using a multivariate Cox hazard analysis, the multivariate-adjusted hazard ratio (HR) of cumulative incidence of MetS was significantly higher in men; HR was 2.38 (95% confidence interval 2.29-2.47), and elderly (age≥65 years); HR was 1.35 (95% confidence interval 1.31-1.39), respectively (Table 3). The cumulative incidence of MetS was 5.7% (age< 65 years) and 6.6% (age≥65 years). The multivariate-adjusted hazard ratio (HR) of the maintenance rate of MetS was significantly higher in men; HR was 1.43 (95% confidence interval 1.37-1.51), and

Table 3. The association of age, gender with the cumulative incidence and maintenance rate of MetS status at 1-year

Variables	Cumulative Incidence of MetS		Maintenance rate of MetS	
	Unadjusted HR (95%CI)	Adjusted HR (95%CI)*	Unadjusted HR (95%CI)	Adjusted HR (95%CI)*
Men (vs. Women)	2.90 (2.83-2.96)	2.38 (2.29-2.47)	1.29 (1.25-1.33)	1.43 (1.37-1.51)
≧65 years (vs. <65 years)	1.17 (1.15-1.20)	1.35 (1.31-1.39)	1.09 (1.06-1.12)	1.10 (1.05-1.14)

*Factors used for adjustment; body mass index, SBP, DBP, FBS, HbA1c, TG, HDL-C, LDL-C, eGFR, proteinuria, alcohol intake, smoking, past history of stroke, acute myocardial infarction renal failure, dialysis, and drug use for hypertension, diabetes mellitus, and hyperlipidemia.

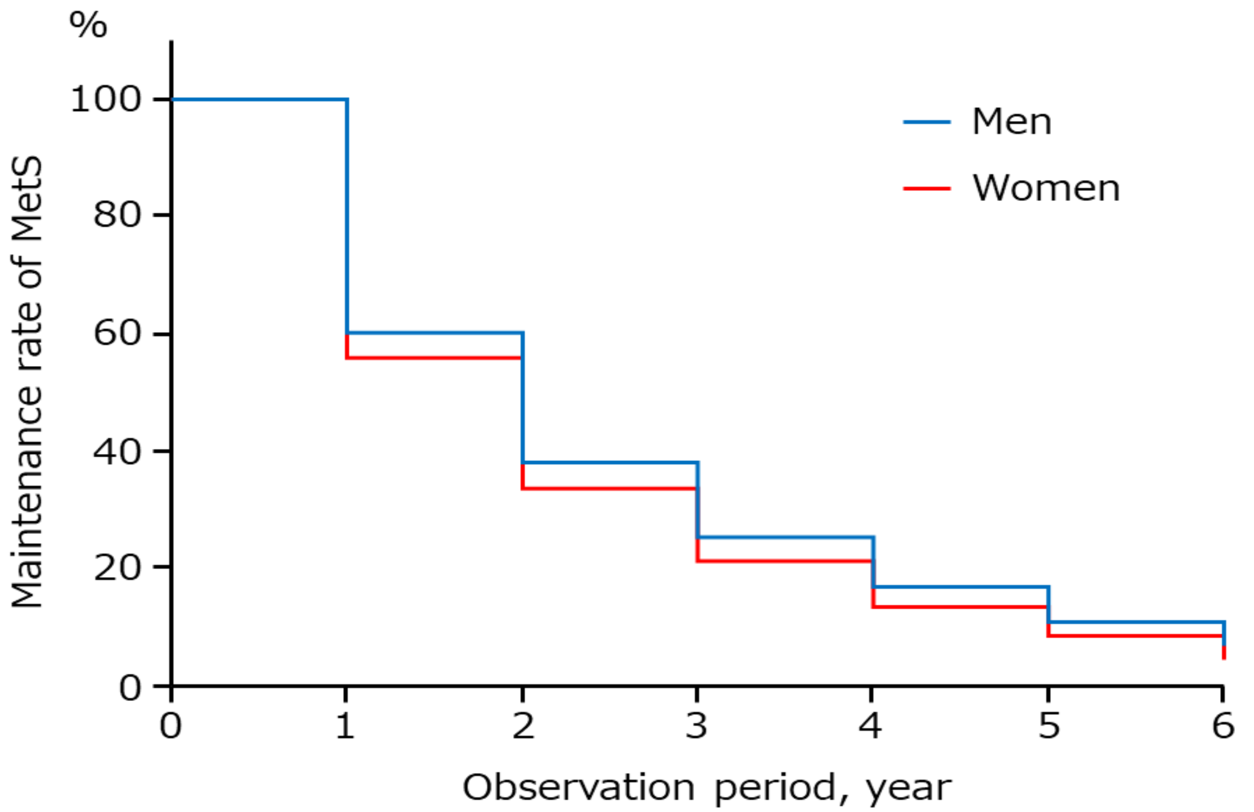

Figure 2. Kaplan-Meier curve: Incidence of metabolic syndrome among those who were free of metabolic syndrome at the first screening

elderly (age≥65 years); HR was 1.10 (95% confidence interval 1.05-1.14), respectively. Maintenance rate of MetS was 45.5% (age< 65 years) and 47.5% (age≥65 years). Kaplan Meier curves were shown in Supplementary Figures 1 and 2.

Baseline characteristics by gender

They were shown in Supplementary Table 3. In men, the prevalence of smokers, DM, and history of CVD and stroke were more than twice as high compared to women. However, the current smoker was less in the elder-age group (≥65 years) than in men (Supplementary Table 4). In women, the current smoker was also higher among the younger age group (<65 years) (Supplementary Table 5).

Discussion

This study examined the cumulative incidence and maintenance rate of MetS among the nationwide screening program from the fiscal year 2008 to 2014 (6 years). Men and the elderly group (age≥65) population were at risk of higher cumulative incidence and maintenance rate of MetS. According to the abridged life table from the Ministry of Health, Labour and Welfare, the life expectancy was78.4 years in men and 85.3 years in women in 2002, and it increased to 81.4 in men and 87.5 years in 2019, respectively. The gender discrepancy in life expectancy remains high at 6 years, yet the reasons are not clear. Early detection of MetS and lifestyle modification may improve life expectancy in men.

Subjects with MetS have a significant impact on the incidence of CKD [6, 7, 8], diabetes mellitus (DM) [9, 10], and mortality [11-14]. Accordingly, when diagnosed MetS, they are entitled to further examination and lifestyle intervention. Lifestyle per se is a significant modifier of CKD [15], CVD [16], and mortality [16-17]. Recently, we confirmed that MetS was a significant risk

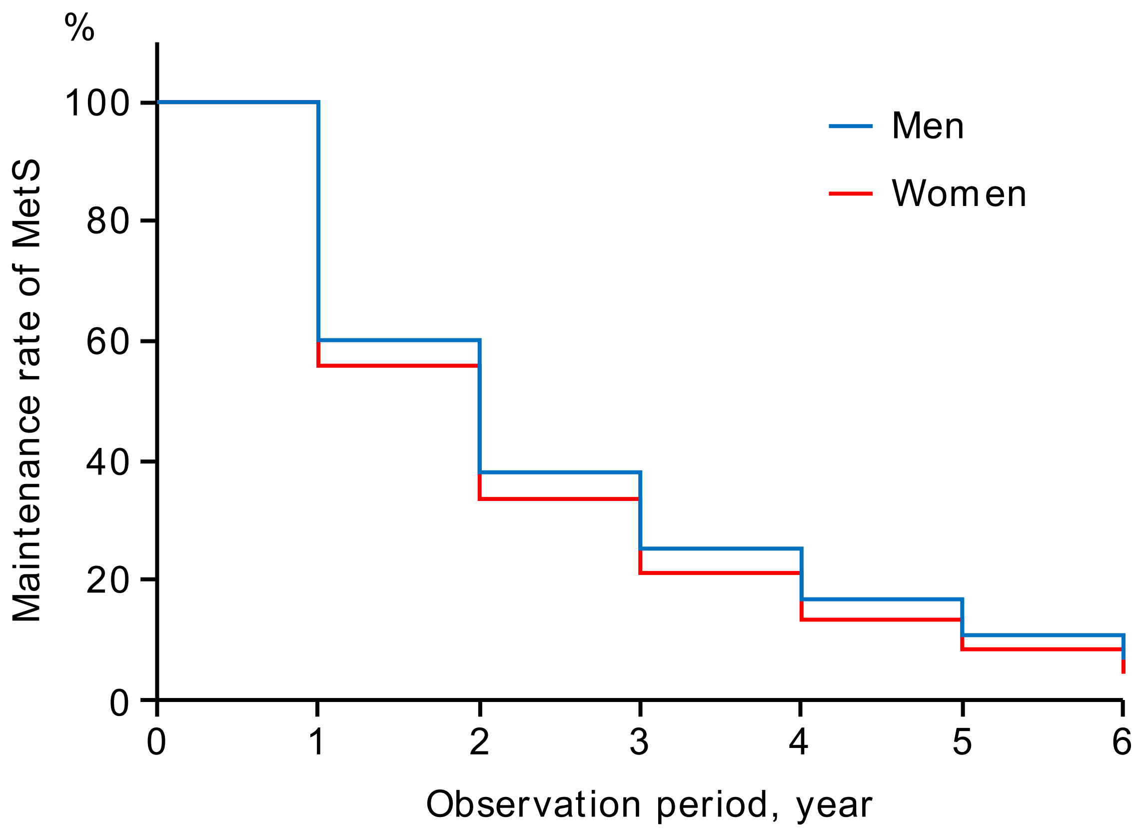

Figure 3. Kaplan-Meier curve: Maintenance rate of metabolic syndrome among those subjects who were diagnosed metabolic syndrome at the first screening

factor for mortality [18]. Therefore, early intervention in overweight/obese adults, namely MetS subjects is necessary to prevent the progression of CKD [24, 25] and death.

The dipstick proteinuria test for CKD detection was cost-effective [26, 27], but not yet shown for the diagnosis of MetS at the general screening. The key strategy for the prevention of MetS is to keep body weight within the normal range through nutritional management and adequate exercise. in particular aged populations. Intervention through this screening program was shown to be very effective for the reversal of MetS [19]. However, the proportion of people attending the program is as low as 11%. The trends in the cumulative incidence and maintenance rate of MetS have not been well studied. Such information would be helpful for the future modification of the protocol of screening among the Japanese population.

Lifestyle modification if convinced by the screened participants would prevent the overall incidence of MetS and reduce the prevalence of MetS. Other than the weight reduction in overweight and obese subjects, excess alcohol intake, in particular, men, is frequently observed with MetS. Alkerwi A et al recommended restricting alcohol consumption to less than 20 g/day among women, and less than 40 g/day among men [28]. Also, special education is needed for smokers as cessation of smoking, prevalent among men, is an independent predictor of new-onset of MetS. [23] Other lifestyles such as depression [29] and self-reported sleep duration [30] are reported to the associated with MetS. These observations need to be confirmed among the Japanese but are suggesting the importance of further questionnaires among apparently healthy people.

MetS were defined as waist circumference (men≥85cm, women≥90cm) plus two or three abnormal values in blood sugar metabolism, lipid, and blood pressure [18]. Waist circumference is a surrogate of central obesity but is often variable by body size, gender, and race. We reported the significance of “a body shape index (ABSI)” on all-cause mortality among screened subjects [14]. ABSI seemed to be a better predictor of death than the body mass index (BMI). However, the presence of CKD affected differently on mortality between men and women.

Strengths and limitations

The strength of the present study is that we have followed many participants of the nationwide screening program. We believe that this cohort represents the currently available database for the analysis of the changes in MetS status in Japan.

There are several limitations in the present study. First, participants in this analysis were those who had an interest in lifestyle and their health conditions. The participation rate was 38.9% (2008) and 51.4% (2016) of the target population. (Ministry of Health, Labor and Welfare) Therefore, it would not be representative of the whole Japanese population. We have no data on whether the MetS (+) individuals had attended the intervention program or not. A previous study showed that men and relatively younger (age<65 years) had a lower participation rate compared to their counterparts [27]. Second, other socio-economic factors related to the incidence and prevalence of MetS are unknown in this screening program. The number of family members, the presence of a spouse, and the location of residence might influence the lifestyle. Third, factors other than the differences in lifestyles and history of CVD, stroke, and renal failure at baseline may explain the results of the present study. Long-term lifestyle would be difficult to change by a single intervention, in a particular elderly population. Fourth, we have no data on those aged 75 and over. The medical care system for the elderly in the later stage of life also started in 2009 in Japan. Further studies on transition to this program may be warranted. Finally, other limitations on the diagnosis of MetS have been discussed in the previous paper [18].

Conclusions

This study showed the cumulative incidence of MetS increased steadily after the screening. In particular, subjects aged (≥65) men were at risk of developing MetS. However, the maintenance rate of MetS has declined steadily even after 3 years after the screening.

Conflict of Interest

The authors state they have no Conflict of Interest (COI).

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